NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Roche Products**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Spinal Muscular Atrophy UK-Muscular Dystrophy UK
      i. Spinal Muscular Atrophy UK-Muscular Dystrophy UK organisation submission
      ii. SMA UK - Appendix 4
      iii. SMA UK - Appendix 5
      iv. SMA UK - Appendix 6
      v. SMA UK - Appendix 7
   b. TreatSMA
      i. TreatSMA organisation submission
   c. Association of British Neurologists
   d. SMA REACH UK
   e. NHS England

4. **Expert personal perspectives** from:
   a. Ayesha Ali - NHS Commissioning expert, nominated by NHS England

5. **Evidence Review Group report** prepared by the School of Health and Related Research (ScHARR)

6. **Evidence Review Group – factual accuracy check**

7. **Technical engagement response** from **Roche Products**

8. **Technical engagement responses from experts:**
   a. Anne-Marie Childs – clinical expert, nominated by Muscular Dystrophy UK and Roche Products
   b. Satvinder Mahal – clinical expert, nominated by the Neonatal and Paediatric Pharmacists Group (NPPG)
   c. Andi Thornton – patient expert, nominated by TreatSMA
   d. Liz Ryburn – patient expert, nominated by Muscular Dystrophy UK-Spinal Muscular Atrophy UK

e. Lucy Frost – patient expert, nominated by TreatSMA

9. Technical engagement response from consultees and commentators:

a. Spinal Muscular Atrophy UK-Muscular Dystrophy UK
b. TreatSMA
c. Association of British Neurologists
d. SMA REACH UK

10. Evidence Review Group critique of company response to technical engagement prepared by the School of Health and Related Research (ScHARR)

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID1631: Risdiplam for treating spinal muscular atrophy in children and adults

Document B

Company evidence submission

October 2020

File name	Version	Contains confidential information	Date
ID1631_Risdiplam SMA_ACIC_Document B	1	Yes	30 October 2020

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Abbreviations

ADL	Activities of daily living
AFO	Ankle-foot orthosis
AIC	Akaike information criterion
AUC	Area under the curve
BADLS	Basic activities of daily living
BIC	Bayesian information criterion
Bi-PAP	Bilevel positive airway pressure
BSC	Best supportive care
BSID-III	Bayley Scales of Infant and Toddler Development III
BURQOL	Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe
CAD	Canadian dollars
CADTH	The Canadian Agency for Drugs and Technologies in Health
CCOD	Clinical cutoff date
CEA	Cost-effectiveness analysis
CHMP	Committee for
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP	Compound muscle action potential
CNS	Central nervous system
CSR	Clinical Study Report
DMD	Duchenne muscular dystrophy
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECG	Electrocardiogram
EFS	Event-free survival
EMA	European Medicines Agency
EQ-5D-3L	European Quality of Life-5 Dimensions-3 levels
ERG	Evidence Review Group
FDA	US Food and Drugs Administration
FVC	Forced Vital Capacity
GBP	Great British Pounds
GCP	Good Clinical Practice
HCP	Health care professional
HCRU	Health care resource use
HDU	High dependency unit
HES	Hospital Episode Statistics
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE-2	Hammersmith Infant Neurological Examination Module 2
HR	Hazard ratio
HRQOL	Health-related quality of life
HST	Highly specialized technology
HSUV	Health-state utility values
HTA	Health Technology Appraisal

IADL	Instrumental activities of daily living
ICER	Incremental cost-effectiveness ratio
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
ITC	Indirect Treatment Comparison
ITQOL	Infant Toddler quality of life
ITT	Intention-to-treat
KAFOS	Knee-ankle-foot-orthosis
LOCF	Last observation carried forward
LYG	Life years gained
MAA	Managed access agreement
MAIC	Match-adjusted indirect comparison
MD	Muscular dystrophy
MFM32	32 Item Motor Function Measure
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed model repeated measure
NHS	National Health Service
NOCB	Next observation carried forward
NR	Not reported
OLE	Open-label extension
ONS	Office for National Statistics
PAS	Patient Access Scheme
PASLU	Patient Access Schemes Liaison Unit
PICU	Paediatric intensive care unit
PIM	Promising Innovative Medicine
PSA	Probabilistic sensitivity analysis
PY	Patient-years
QALY	Quality-adjusted life year
RCT	Randomised clinical trial
RULM	Revised Upper Limb Module
RWC	Real world care
SAP	Statistical analysis plan
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMAIS	SMA Independence Scale
SMN2	Survival motor neuron 2
SOC	Standard of care
STA	Single Technology Appraisal
USD	US Dollars

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

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 spinal muscular atrophy	As per NICE final scope and in line with NICE reference case	N/A
Intervention	Risdiplam	As per NICE final scope and in line with NICE reference case	N/A
Comparator(s)	Best supportive care	As per NICE final scope and in line with NICE reference case	N/A
Outcomes	• Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life	The company submission broadly aligns with the final scope issued by NICE. Not all outcomes listed in the final scope are however explicitly used in the economic models. • Type 1 SMA: Health state occupancy in the economic model was based on motor milestone achievement using HINE-2, similarly to TA588. A separate health state for patients on permanent ventilation was included, as permanent ventilation is associated with additional costs and a more severe prognosis for patients with SMA type 1. Additional clinical outcomes from the FIREFISH study will also be used to inform the economic model, such as event-free survival and respiratory outcomes. • Type 2/3 SMA: Health state occupancy in the economic model was based on motor milestone	Effort to simplify the model structure – based on previous economic models and clinical expert opinion - and avoid the use of additional assumptions where possible.

		achievement using MFM, the primary endpoint of the SUNFISH study. The MFM was selected as a primary endpoint on the basis that it can offer sufficient gradation in the assessment of functional abilities, to fully enable assessment of treatment efficacy in a broad population of type 2 or 3 SMA patients, like the one included in SUNFISH. Additional clinical outcomes from the SUNFISH study will also be used to inform the economic model.	
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per NICE final scope and in line with NICE reference case	N/A

B.1.2 Description of the technology being appraised

The technology being appraised is described in Table 2. See Appendix C for details of the draft summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 2: Description of the technology

UK approved name and brand name	UK approved name (brand name): • Risdiplam (Evrysdi®)
Mechanism of action	Risdiplam is a survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Functional SMN protein deficiency is the pathophysiological mechanism of all SMA types. Risdiplam corrects the splicing of SMN2 to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to an increased production in functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels (1).
Marketing authorisation/CE mark status	An application for marketing authorisation for risdiplam was submitted to the European Medicines Agency (EMA) in [redacted] for the following indication: [redacted] Committee for Medicinal Products for Human Use (CHMP) opinion is expected by [redacted], and the European Commission (EC) decision by [redacted]. [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication in the UK is as per the marketing authorisation from the EMA. Please refer to the Summary of Product Characteristics for full details (1).
Method of administration and dosage	Risdiplam is taken orally once a day using the re-usable oral syringe provided, at approximately the same time each day. The recommended once daily dose of risdiplam is determined by age and body weight. • 2 months to < 2 years of age: 0.20 mg/kg • ≥2 years of age (<20 kg): 0.25 mg/kg • ≥2 years of age (≥20 kg): 5 mg
Additional tests or investigations	No additional tests or investigations are required to identify patients eligible for risdiplam.
List price and average cost of a course of treatment	£[redacted] per 60 mg/80 ml vial Treatment with risdiplam is continuous as SMA is a life-long chronic disease, therefore the average cost of a course of treatment is N/A.

Patient access scheme (if applicable)	A patient access scheme (PAS) with a simple discount of [redacted] has been submitted to PASLU. The resulting net price per 60 mg/80 ml vial is [redacted]

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

B.1.3.1 Disease overview

Pathophysiology

SMA is a neuromuscular disorder resulting in severe weakness of the limbs, trunk, bulbar and respiratory muscles secondary to failure to gain and maintain functional motor nerve innervation of skeletal muscles (2). SMA is characterised by the dysfunction of alpha motor neurons within the anterior horn of the spinal cord, leading to skeletal muscle weakness and atrophy (3-5). Respiratory failure accounts for the majority of deaths in people with SMA (6).

SMA is an autosomal recessive disorder secondary to loss-of-function mutations in both alleles of the survival motor neuron 1 (SMN1) gene with subsequent loss of SMN protein expression. In humans, there are two SMN genes, the SMN1 gene and its paralog SMN2. The SMN2 pre messenger ribonucleic acid (mRNA) undergoes alternative splicing that excludes exon 7 from 85–90% of mature SMN2 transcripts, which produces an unstable SMNΔ7 protein that is rapidly degraded, so that full length SMN2 mRNA is generated in only 10–15% of splicing events (7, 8). Accordingly, people with SMA lacking a functioning SMN1 gene are dependent on their SMN2 gene and SMA is the consequence of decreased, insufficient levels of functional SMN protein produced by the SMN2 gene. Children born with multiple copies of the SMN2 gene have milder phenotypes, further demonstrating that the pathophysiology of the disease is due to insufficient production of functional SMN protein (9, 10).

SMA subtypes

SMA is a disease continuum with its subtypes defined by age at onset and the most advanced motor milestone achieved during development, classified as types 0 through 4, where type 1 (infantile-onset) and types 2 and 3 (later- onset) represent approximately 99% of all patients (Table 3). Type 0 (congenital SMA) is very rare and most of these patients are unable to survive beyond 6 months of age. Type 4 SMA (adult onset) accounts for only approximately 1% of all SMA cases (11). Natural history data demonstrate that clinical decline can manifest differently for each SMA type depending on functional level, age, disease duration and clinical severity (12-17). It should be noted, however, that classifying a spectrum disorder such as SMA into discrete subtypes is problematic due to overlap in diagnostic criteria between infantile-onset and later-onset patients (18).

Table 3: SMA subtypes and clinical course

Type	Onset	Highest achieved motor function	Typical symptoms	Lifespan if untreated
0	Prenatal/foetal	Nil	Severe hypotonia	< 6 months
1	<6 months	Sit with support only	Respiratory failure	<2 years
2	≥6–<18 months	Sit independently	Respiratory complications and wheelchair bound	>2 years
3	≥18–<36 months	Stand and walk	Muscle weakness	Normal

4	Adult (2nd or 3rd decade)	Walk during adulthood	Very slow progressive muscle weakness	Normal

Approximately one in every 6,000 to 10,000 babies worldwide are born with a type of SMA, with type 1 SMA accounting for approximately 60% of cases (19, 20). It is estimated that 100 children are born with SMA in the UK each year, with 1200–2500 children and adults living with SMA (21).

People with infantile onset (type 1) SMA most commonly have two SMN2 gene copies and typically present symptomatically before the age of 6 months. At diagnosis, these infants demonstrate reduced motor function compared with age matched normal infants, and will uniformly and rapidly lose motor function over time as assessed with a standard instrument for infants with SMA known as the CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (22). In addition, without an effective treatment, infants with type 1 SMA never gain major motor milestones such as sitting independently (2). They also experience progressive loss of independent swallowing and respiratory function, requiring feeding tubes and chronic ventilatory support, and will face a very high risk of death. Natural history of the disease demonstrates that 50% of infants with type 1 SMA, who only have two copies of SMN2 gene, will die or require permanent daily non-invasive ventilation support by 10.5 months of age. This statistic will reach 92% for type 1 toddlers by 20 months of age (23).

People with type 2 SMA most commonly have three SMN2 gene copies, and typically present symptomatically between the ages of 6–18 months. Consistent with all SMA subtypes, children with type 2 SMA have proximal greater than distal limb weakness and lower limb greater than upper limb weakness. These children will likely be able to sit and possibly stand but never walk independently given the greater amount of weakness in their lower limbs (2). Natural history of SMA demonstrates that without treatment these children with type 2 SMA have a progressive decline in motor function over time, most prominently during the ages of 6 to 16 years, pertaining to maintaining an upright position while performing tasks with their upper limbs as measured by the Motor Function Measure 32-item version (MFM32) (24). People with type 2 SMA may also require noninvasive ventilator support, depending on the severity of the decline in pulmonary function. Children with type 2 SMA are at risk for hypoventilation, especially during sleep, which may be exacerbated by viral respiratory infection (25). People with type 2 SMA can often have a normal life expectancy however they will remain severely disabled (26).

Type 3 SMA is a less severe phenotype compared to type 1 and type 2 SMA. People with type 3 SMA most commonly have three or four SMN2 gene copies, and typically present symptomatically between the ages of 18–36 months. Consistent with all SMA subtypes, children with type 3 SMA have proximal greater than distal limb weakness and lower limb greater than upper limb weakness. These children are able to sit, stand, and walk independently (2). Natural history of SMA demonstrates that without treatment children with type 3 SMA progressively decline in motor function over time, most prominently during the ages of 10 to 15 years. Nearly a third of these patients will lose their ability to walk between the ages of 3 to 28 years old (24). Children and adults with type 3 SMA generally have normal lung function and rarely require noninvasive ventilatory support. However, pulmonary function declines over time and adults with type 3 SMA may need noninvasive ventilatory support as they age (25).

People with type 4 SMA represent less than 1% of the overall SMA population (11). They have four to six SMN2 gene copies and present with mild symptoms in adulthood (2, 27).

Clinical measures used to assess people with SMA

Given the broad and clinically heterogeneous nature of the SMA patient population, the expectations for what determines clinical benefit will vary between patients based on age and prognosis. Several outcome measures are used in clinical practice and trials to assess and monitor people with SMA (Table 4). For instance, Hammersmith Functional Motor Scale Expanded (HFMSE) is widely used to measure clinically relevant items assessing functional skills in people with type 2 and type 3 SMA, such as sitting, rolling and standing/stepping. While the HFMSE does not assess fine motor function skills, other specific scales are available to assess upper limb function such as the Revised Upper Limb Module, with other measures utilised to assess other functions, such as respiratory performance, i.e. forced vital capacity.

However, the different clinical features related to progressed SMA may affect patients' performance on these outcome measures, therefore the most appropriate assessment scale to use will vary by patient, depending on factors such as age, SMA subtype and symptoms experienced. For instance, the HFMSE is not sensitive to capture change in people with a baseline HFMSE score <10 (28, 29), compared with the MFM32 scale, which includes items relating to distal motor function that are primarily not assessed by the HFMSE, making it a more relevant measure in those patients severely impacted by a more advanced disease (24, 28, 30). This is an important consideration since severe complications such as contractures are associated with diminished motor ability and can impact performance on the HFMSE scale, thereby limiting a person's ability to attain a functional skill and therefore the ability of the scale to detect improvement in motor function (31).

Additionally, as people with SMA will be at different stages of disease, particularly those with type 2 and type 3 SMA, given the heterogeneous nature of this group individuals will have a different definition of what is considered to be a clinically meaningful outcome. It is therefore challenging to define a single minimally clinically important difference for all people with SMA for any of the motor function measures used in the trials. However, the large majority of people with SMA and their caregivers feel that disease stabilisation would represent an important and meaningful progress (32). Moreover, a discrete choice experiment conducted by Roche identified that people with SMA placed greater value on avoiding disease progression over actual improvement of their disease (33).

Table 4: Summary of outcome measures for SMA

Outcome	Description	Clinical meaningfulness
Infantile-onset SMA (type 1 SMA)		
BSID-III	• Validated outcome measure in infants to assess attainment of motor milestones including static positioning (e.g., head control, sitting), dynamic movement including locomotion (e.g., crawling), quality of movement (e.g., kicking), balance and motor planning • 72 items scored on a 2-point scale to measures whether or not patients are able to perform the assessed items	• The natural history of the disease is well defined: per definition, untreated type 1 SMA infants never achieve sitting without support (22, 23, 34) • The achievement of sitting unsupported is dramatically different from the natural disease course, therefore the ability to achieve a sitting position unsupported at 12 months, as measured by the BSID-III, is considered a clinically meaningful and important milestone in type 1 SMA.
HINE-2	• Tool scored on a 3–5 point scale to evaluates eight developmental motor milestones (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) • Previously used to evaluate motor function in SMA natural history studies and in a clinical trial in infantile-onset SMA (23, 34)	• HINE-2 motor milestones are never fully achieved or maintained in untreated infants with type 1 SMA according to natural history (34) • Achievement of important motor milestones and higher scores on the HINE-2 scale (≥ 2-point increase in the ability to kick [or maximal score] or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking) are therefore considered to be a clinically relevant improvement for an infant with type 1 SMA (35)
CHOP-INTEND	• 16 item motor function measure, with a total score ranging from 0–64 to assess both active and elicited reflexive movement (16 items in total, each scored from 0–4), such as spontaneous movement of upper and lower extremity, hand grasping, rolling, head control, and others	• In type 1 SMA natural history studies, infants typically have a mean or median total CHOP-INTEND score of < 33 points; patients progressively lose motor function following onset of symptoms, which is confirmed by a decrease in CHOP-INTEND scores over time (22, 23, 34) • Any improvement in CHOP-INTEND scores, or achievement of a score of at least 40, is considered as a clinically meaningful improvement for infants with type 1 SMA (lower threshold estimate of a clinically meaningful improvement) (22, 23) • Change of ≥ 4 in CHOP-INTEND represents an estimate of a meaningful improvement in motor function (higher threshold estimate of a clinically meaningful improvement) (35)
Later-onset SMA (type 2 and type 3 SMA)		
MFM32	• Valid and reliable assessment of different levels of motor function ability in neuromuscular diseases, including a broad range of people with SMA, validated in individuals aged 2–6 years and older (36, 37)	• Natural history data collected on patients aged 5.7 to 59 years, demonstrated that the overall slope of decline over time using the MFM32 total score is in the range of -0.9 points/year for type 2 patients and -0.6 points/year for type 3 patients (24)

	• Contains 32 items related to everyday activities of daily living, assessing three domains of motor function: D1 (standing and transfers), D2 (axial and proximal motor function), and D3 (distal motor function) • Scored on a 0–3 scale are summed and then transformed onto a 0–100 scale to yield the MFM32 total score expressed as a percentage of the maximum score possible for the scale (the lower the total score, the more severe the functional impairment	• SMA patients and caregivers consider stabilisation in functional ability as progress (32, 38-40), therefore a change of ≥ 0 in MFM32 total score representing stabilisation or improvement of motor is clinically meaningful in this patient population • A threshold of improvement on the MFM32 scale, such as ≥3 points, should be considered as a marked improvement for patients as it may represent either the acquisition of a new function or the improvement in performance of several functions (41)
RULM	• Validated scale in SMA to assess upper limb motor performance (42) • Consists of 19 items (scored on a 0–2 scale for 18 items and 0–1 for one item) assessing the performance of shoulder, elbow, wrist, and hand function. A total score from 0–37 is calculated with higher scores indicating greater upper limb functioning	• Natural history data show that over 12 months, the mean change in RULM score is -0.4 points in type 2 and type 3 patients aged 2.7 to 49.7 years (43) • Patients and caregivers have reported that small improvements and stabilisation on the RULM have meaningful impacts on daily life (40); a change of ≥0 in RULM total score representing stabilisation or improvement of motor function is clinically meaningful. • Change of ≥ 2 in RULM represents an estimate of a meaningful improvement in motor function (higher threshold estimate of a clinically meaningful improvement) (43)
HFMSE	• Widely used in SMA type 2 and 3 (29); includes clinically relevant items assessing sitting, rolling, transitions relating to crawling and kneeling, and standing/stepping but no items to assess the fine motor function of the hand, wrist, or elbow • Assesses gross motor function in individuals aged two years or older, with type 2 and 3 SMA (44) • 33 items to assess functional abilities, including standing, transfers, ambulation, and proximal and axial function, each scored on a 0–2 scale by a clinical evaluator	• Study in type 2 and type 3 patients aged 2.5 to 55 years demonstrated that the overall slope of decline in the HFMSE total score over a 12-month period is -0.57 in non-ambulant patients (45) • Stabilisation and small improvements on the HFMSE are meaningful in daily life (40); change of ≥ 0 in HFMSE total score representing stabilisation or improvement of motor function is clinically meaningful (46) • Change of ≥3 in HFMSE represents an estimate of a meaningful improvement in motor function (higher threshold estimate of a clinically meaningful improvement) (47)

BSID-III, Bayley Scales of Infant and Toddler Development III; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Hammersmith Infant Neurological Examination Module 2; MFM32 motor function measure–32 item; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.

B.1.3.2 Burden of disease and impact on quality of life

SMA is a devastating and debilitating disease, which is life threatening in individuals with the most severe types. There are a wide range of symptoms and complications that can have detrimental effects on the day-to-day lives of people with SMA and their families (38, 48). For instance:

- People with type 1 SMA require repeated visits to hospital or medical providers in addition to prolonged use of home and palliative care such as diet provision via feeding tubes, frequent pneumonia treatment and chronic ventilatory support, which often place a significant emotional and social burden on patients and caregivers.
- Progressive orthopaedic deformity is a hallmark morbidity of type 2 SMA, resulting in severe scoliosis, thoracic deformity, large joint subluxations, dislocations and contractures. These deformities result in pain, impaired seating, transfers and mobility issues, and respiratory impairment due to mechanical impact of a collapsing, rotated and twisted thoracic cage. Invasive surgery is required to manage these complications and requires significant periods of recovery.
- Older children and adolescents with type 2 or 3 SMA often require extensive home services, while people with non-ambulatory forms of SMA require 24-hour care to assist with toilet use, transfers, changing and hygiene, feeding and turning in bed. These needs bring significant challenges for patients in fully accessing and maintaining continuity in educational and employment opportunities (39), and can also impact accessibility to available therapeutic options due to the severity of their deformities and the need to travel to a specialised centre, frequently far from home (49).
- Caring for people with SMA places a significant burden on caregivers, both from a detrimental impact on their own well-being and quality of life as well as from a financial perspective, for example loss of earnings. It should be noted that the inclusion of the impact on carers was considered appropriate in previous NICE appraisals of treatments for SMA (18).

The progressive nature of the disease with loss of function over the course of months and years requires almost constant adaptation of the environment and leads to increasing disability and handicap for people with SMA. Minor viral respiratory infections or aspiration episodes may become life threatening and require intensive care and significant pulmonary rehabilitation (50-52). Given the severity of the condition, data suggest patients will benefit greatly if treated pre-symptomatically or soon after symptoms are observed rather than months after symptom onset (53).

Overall, clinicians, people living with SMA, and their parents or caregivers repeatedly cite that small improvements can make a significant difference in the ability of a person or their family to function and thrive (40). People with SMA and caregivers fear progressive loss of function, and being able to maintain those abilities (stabilisation) is a meaningful outcome. In a recent survey conducted by SMA Europe (EUPESMA-2019) covering 18 European countries (including the UK) and including over 1300 validated responses from patients and caregivers aged from 0 to 81 years, across all SMA types, almost all participants (96.7%) considered stabilisation as progress (39), even in the current clinical environment where some patients have access to an approved treatment. Furthermore, a discrete choice

experiment conducted by Roche identified that people with SMA placed greater value on avoiding disease progression over actual improvement of their disease (33).

The inability or loss of all activities of daily living (ADL) can have a major impact on individual well-being. Independence and the ability to perform basic personal tasks has been described by patients as a priority for type 2 and 3 SMA patients (54), with the preservation of or small improvements in upper extremity function being of particular importance to maintaining independence, social participation and quality of life (55). Furthermore, the importance of ADL such as independently dressing, mobility, eating and drinking, body care, toilet, mobility in and outside the house, and communication have also been highlighted in the recent extensive SMA Europe survey (39).

B.1.3.3 Current treatment practice

There are currently only two approved disease-modifying treatments for SMA in the EU.

Nusinersen (Spinraza®), a SMN2 targeting antisense oligonucleotide drug, is approved for the treatment of 5q SMA in paediatric and adult patients. Nusinersen is intrathecally administered, thus largely limiting the effects to the central nervous system (CNS). The first 3 doses of nusinersen are administered in 2-week intervals, followed by a 4th injection after 30 days and maintenance of dosing every 4 months thereafter; hence, frequent repeats of the invasive administration (lumbar puncture) are required for this treatment. Nusinersen is available in the UK via a managed access agreement (MAA) as an option for people with pre-symptomatic SMA or people with type 1, type 2 and type 3 SMA, excluding those unsuitable for intrathecal administration, on permanent ventilation or requiring a tracheostomy at baseline, and have a diagnosis of scoliosis and/or severe contractures. Furthermore, if independent ambulation is gained before starting therapy, patients must still be independently ambulant, with the exception of paediatric patients who have lost independent ambulation in the previous 12 months (18).

Approval of nusinersen was granted based on the clinical benefit demonstrated in the ENDEAR trial in infants with SMA (56) and the CHERISH trial in people with later-onset SMA (57). Patients up to 7 months old and between 2–12 years were eligible to enrol in ENDEAR and CHERISH respectively. However, the oldest patient enrolled in CHERISH at screening was 9 years, therefore there are no controlled clinical trials of nusinersen in patients over 9 years old or in people with type 3 SMA.

Onasemnogene abeparvovec (Zolgensma®), an intravenously administered gene therapy to deliver a functional copy of the SMN1 gene, received conditional marketing authorisation in the EU in May 2020 for the treatment of patients diagnosed with type 1 SMA, or SMA people with up to 3 copies of the SMN2 gene (58). However, onasemnogene abeparvovec is not currently commercially available in the UK at the time of submission.

Best supportive care (BSC) requires a multidisciplinary approach and is tailored for individual patients. This includes the monitoring and support of patients in the absence of active disease modifying treatment and relies on the prevention and treatment of co-morbidities such as swallowing and feeding difficulties, scoliosis and thoracic deformity, contractures, and respiratory insufficiency. In the last decade, improvements in SMA care, including guidance on ventilatory and feeding support, have enabled prolonged survival in people with type 1 SMA who did not receive disease-modifying therapies. Over time, palliative management for the most severe type 1 patients has been introduced more frequently at

home with increased levels of technical supportive care such as enteral nutrition, oxygen therapy, and analgesic and sedative treatments (59). Nevertheless, these measures have very limited or no impact on motor milestone achievements, and mortality rates in this patient population are still high (22, 23, 34), and with motor function declining over time for people with type 2 and type 3 SMA receiving BSC (24), there is a need for the development of targeted therapies for all people with SMA.

B.1.3.4 Limitations of current treatments and the unmet medical need

The approval of disease-modifying treatments has been a welcome breakthrough for people with SMA. However, physicians deem there to be a continuing unmet need for those who are ineligible for nusinersen as well as the many individuals for whom they regard nusinersen as being less than ideal, based on its efficacy, route of administration, and/or safety (60, 61).

While the results of Phase 3 studies with nusinersen in infantile-onset SMA (ENDEAR) (56) and in later-onset SMA (CHERISH) (57) overall demonstrate benefit in patients receiving active drug versus sham procedure control, there is still a non-negligible proportion of patients who do not respond to the drug and, thus, for whom nusinersen may not be the best option. For instance, 49% of the treated patients in ENDEAR did not exhibit an improvement in their motor milestones and 39% did not reach event-free survival (56).

Intrathecal administration is an invasive procedure that is associated with risks and may not be feasible for all SMA patients, especially those who develop severe scoliosis, joint contractures or undergo a spinal surgery procedure (62-64). Additionally, many infants and young children with SMA require anaesthesia to undergo the lumbar puncture procedure, and sedation is known to potentiate adverse respiratory reactions (65).

Clinical experts confirmed to Roche that lumbar puncture requires visits to specialist facilities with specific medical expertise and is therefore a burden on both patients and families and healthcare resources. Situations where external factors prevent patients visiting health care facilities can also impact on consistent therapy administration; for example, the COVID-19 pandemic and the global measures applied to ensure social isolation and changes in hospital priorities has forced physicians to postpone elective procedures, affecting nusinersen-treated patients.

Moreover, nusinersen is not routinely funded on the NHS and for those eligible patients, some may not receive treatment due to constrained capacity within centres that are capable of intrathecal administration; therefore, there is a need for treatment options with alternative methods of administration to increase accessibility for disease-modifying treatments for all people with SMA.

B.1.3.5 Risdiplam for the treatment of SMA

Since SMA is caused by a deficiency in SMN protein, the need to systemically increase SMN protein is at the core of disease intervention across the continuum of SMA phenotypes. Risdiplam, an *SMN2* mRNA splicing modifier, is an efficacious small molecule disease modifying therapy for SMA. It modulates *SMN2* splicing to include exon 7 into the mRNA transcript, thereby increasing the expression of functional SMN protein from the *SMN2* gene. Risdiplam has good distribution into both the central nervous system (CNS) and systemically throughout the body, increasing levels of functional SMN protein in both the CNS and periphery to a similar magnitude (66, 67). Risdiplam is therefore hypothesised to bring

greater efficacy in people with SMA than treatments targeting increases of functional SMN protein in the CNS alone (see section B.2.12). This is particularly relevant for the respiratory complications that affect people with SMA as these are often the cause of early death. Clinical trial data of risdiplam in people with infantile-onset SMA has shown that 85% of infants were alive and not on permanent ventilation after one year of treatment, while 95% of those patients alive at this point were also able to maintain the ability to swallow, demonstrating the systemic effects of risdiplam on bulbar function (68).

Risdiplam is potentially the first to market orally administered (liquid formulation). The oral route of administration and liquid formulation present a significant advantage over intrathecal injections for people with SMA. Risdiplam is a sustainable treatment option because it will be administered at home daily by the patient or a caregiver orally or via feeding tube, without requiring hospital clinic visits, invasive procedures or concomitant use of additional medicines. Assuming approval, it will be less burdensome not only to patients and caregivers but also to the health care system, addressing an important unmet medical need in the SMA community. For example, a 2019 survey carried out by Cure SMA of adults living with SMA or caregivers of children with SMA treated with nusinersen found that on the day of administration, the mean time associated with treatment for all patients was 8.26 hours (standard deviation 11.29 hrs, median 5.0 hrs [77 respondents]), with longer mean administration times reported by caregivers of paediatric patients compared to adult patients (11.32 vs. 4.78 hours respectively) (49).

In practical terms, the availability of an orally administered drug may expand the population able to receive treatment to include those for whom other routes of administration can be challenging and even contra-indicated (e.g., severe scoliosis and spine surgery for intrathecal administration or intolerance to nusinersen). Therefore, risdiplam has the potential to be a long term, sustainable treatment option for all SMA patients, across a wide range of SMA subtypes, irrespective of the patient's age, physical status, or disease severity.

Risdiplam-specific clinical data are available to support the major contribution to patient care for this efficacious, well-tolerated oral medicine compared to other invasive routes of administration. These data are from a broad range of patients and caregivers in the ongoing open-label trial of risdiplam for SMA patients who had received prior experimental or standard-of-care therapy (JEWELFISH). Of the 77 patients who previously received nusinersen, 54 patients (46%) reported inability to continue to receive nusinersen due to treatment-related tolerability concerns, treatment–related safety concerns, injection site infrastructure accessibility difficulties, lack of or loss of efficacy (69). This means that some patients who have already had access to nusinersen are not able to receive continued nusinersen therapy for medical reasons.

In addition to the medical issues of lumbar puncture discussed above, data show that patients and caregivers would prefer an oral treatment to an intrathecal injection. Sixteen patients (21%) in the JEWELFISH study cited the inconvenience of the treatment, patient preference, or caregiver preference as the primary reason for switching from nusinersen to risdiplam (69). These data support the results of a preference study conducted in the United Kingdom in 2019, which was specifically designed to quantify caregiver and patient preferences for SMA treatment attributes. These data showed that caregivers were 2.9 times more likely to choose an oral solution administered once daily over an intrathecal injection every 4 months, with all other factors being equal, and adult patients were 2.0 times more

likely to choose the oral treatment (33). The recent SMA Europe survey (EUPESMA-2019) also demonstrated that patients are more ready to accept treatment through oral administration (91.0%) compared to intrathecal (63.1%) or intravenous (84.4%) administration (39).

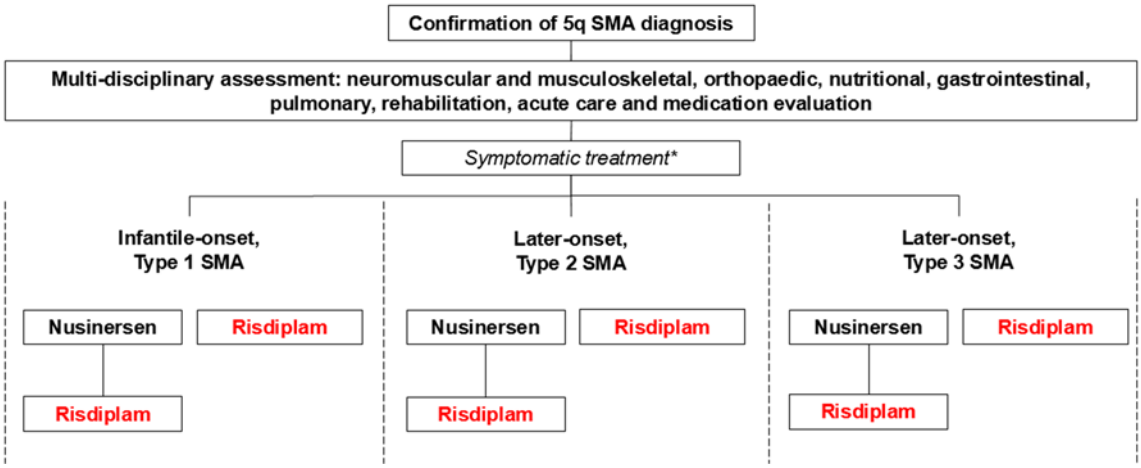
B.1.3.6 Proposed position of risdiplam in the treatment pathway

As an efficacious treatment in all people with SMA, risdiplam has the potential to significantly contribute towards addressing the continuing unmet need of people with SMA. Moreover, as an orally administered treatment, risdiplam provides a sustainable treatment option that can be administered at home and used for a life-long condition.

The eligible population for risdiplam will include those patients who choose not to receive or are unsuitable for nusinersen e.g. those with severe scoliosis or joint contractures, as well as patients who cannot tolerate and/or respond poorly to nusinersen, or are not eligible for the nusinersen MAA, i.e. non-ambulatory people with type 3 SMA. Therefore, risdiplam is anticipated to provide an additional therapeutic option for all patients across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status), but in some of those cases it will be the only available treatment option. The proposed position of risdiplam in the SMA treatment pathway is outlined below in Figure 1.

The proposed positioning of risdiplam in the clinical care pathway for SMA is supported by the broadest clinical development programme in SMA (see Section B.2.2) that has demonstrated risdiplam to be an efficacious and well tolerated treated in an SMA population as representative as possible of real-world clinical practice, ranging from infantile-onset SMA to later-onset SMA (age span: 0 to 60 years), with varied baseline characteristics.

Figure 1: Proposed position of risdiplam in the pharmacologic treatment pathway for SMA



*Symptomatic treatment will be based on individual clinical need and symptom severity following multi-disciplinary assessment

Despite the robust clinical evidence available to support a broad indication for risdiplam, it should be acknowledged that there are uncertainties and limitations within the evidence base, consistent with other currently available treatments and published data. While the treatment landscape for SMA is evolving, there is a clear need for further evidence on the efficacy and safety of long-term treatment of SMA along with information to determine appropriate treatment sequencing and identification of individual factors that can optimise treatment decisions for individual patients (70). To help address this uncertainty, registries

and observational studies will assist in collecting real world data, while the longer follow-up of clinical trials and those studies in pre-treated patients, e.g. JEWELFISH, will help to provide more robust data.

Given the uncertainties and evidence gaps outlined above, Roche considers that a MAA recommendation for risdiplam could potentially be appropriate, for the entirety or part of the population in the anticipated licence, based on:

- Uncertainties in the clinical trial evidence concerning long-term benefits
- Further data becoming available over time through our clinical trial programme (see Section B.2.11)
- Availability of UK registries SMA REACH Paediatric (already in place) and SMA Reach Adult (in development), that can serve as platforms to collect real-world evidence for people with SMA, and therefore avoid introducing any additional administration or other burdensome processes to the NHS and UK SMA community
- Risdiplam is anticipated to meet the criteria for special consideration by NICE
- Existing precedence from NICE TA588, indicating that substantial benefits might not be able to be captured by the economic models, including benefits to families and carers (18)

Consequently, Roche believes that funding through a MAA for risdiplam with additional data collection over an approximate 5 year period (similar to the TA588 MAA), or sooner depending on data availability, could potentially enable the NICE appraisal committee to make a better informed and evidence-based decision for routine funding at the end of the MAA period based on the more robust and broader evidence base that will be available at NICE re-review.

B.1.4 Equality considerations

Although risdiplam will be appraised through a single technology appraisal (STA), its assessment is anticipated to have several features that are commonly seen in the highly specialised technologies (HST) programme, therefore decision modifiers and flexibility in NICE's decision making should be taken into account.

The narrow entry criteria for NICE HST evaluation and the fact that many orphan and rare disease medicines are deemed ineligible for a HST evaluation and are routed into the STA process is recognised by the ABPI and is within the remit of the ongoing NICE Methods Review (71-73). Currently there is a significant gap between the thresholds used, evidence considered, and acceptance of different levels of uncertainty between these programmes.

The application of decision modifiers for SMA was recognised by NICE in the appraisal of nusinersen in SMA [TA588] (18), where the committee acknowledged the difficulty of appraising drugs for very rare conditions. In TA588, the committee was aware that SMA is both rare and a very serious condition, and that any treatment benefits are highly valued by patients and families. The committee was mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease (18).

In addition, the SMA patient population, for which risdiplam will be a treatment option, includes children and young people, as well as people with disabilities. This will be reflected in the clinical evidence and economic analyses and should also be considered in NICE's

decision-making, as per the precedent set in the NICE appraisal of nusinersen in SMA (TA588) (18).

In TA588, the NICE committee was mindful of the need to consider whether any adjustments to its normal considerations were needed. It discussed the need to balance the importance of improving the lives of children and their families with fairness to people of all ages. It noted NICE's social value judgements: principles for the development of NICE guidance, which emphasise the importance of considering the distribution of health resources fairly within society as a whole, as well as considering factors other than relative costs and benefits (18).

We would anticipate that the same considerations, adjustments and acknowledgements will be made to NICE's decision making in this appraisal.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Clinical evidence relevant to the decision problem of this appraisal is obtained from two pivotal studies; Study BP39056 (FIREFISH) in infants with type 1 SMA and Study BP39055 (SUNFISH) in paediatric and adult people with type 2 or 3 SMA. Both studies were conducted in two parts: a dose-finding Part 1 and a confirmatory Part 2 at the dose selected based on Part 1 data, with each part conducted in different patients of similar characteristics and with a small proportion of ambulant patients included in SUNFISH Part 1.

Results of Part 2 of each study that provide the key data confirming the efficacy and safety of risdiplam in the treatment of SMA are provided in this submission. The results of Part 1 of each study are presented as supportive data in Appendix L as they also showed clear efficacy of risdiplam in SMA, including up to 2-year data currently available for both studies.

Due to the different populations and age ranges of patients included in the two pivotal studies (as a consequence of the different age of onset of symptoms across the different SMA types), each study utilises different assessment scales for motor function and, hence, efficacy data have not been pooled across the pivotal studies. Instead, the efficacy results of each study are summarised separately.

The pivotal FIREFISH and SUNFISH studies are supported by BP39054 (JEWELFISH), an open-label, non-comparative study in people with type 1, 2 and 3 SMA (6 months to 60 years) previously enrolled in Roche Study BP29420 (MOONFISH) with the splicing modifier RO6885247 (development discontinued), or previously treated with nusinersen, onasemnogene abeparvovec or olesoxime. Since the primary objective of JEWELFISH was to assess safety, efficacy data for this study are exploratory endpoints only and are currently unavailable due to the limited treatment duration for most patients in this ongoing study at the CCOD (median treatment duration at the CCOD of 31 January 2020 was 3.0 months); however safety data from this data cut are included in the pooled safety analysis (Section B2.10).

In summary, evidence for the clinical effectiveness of risdiplam is sourced from the broadest clinical development programme in SMA, which confirms that risdiplam offers a clinical benefit to a broad and heterogeneous population of people with SMA, reflective of that seen in clinical practice, without restrictions or limitations on their physical conditions. In contrast, there are significant gaps in nusinersen clinical trial evidence concerning the benefit it offers for the real-world SMA population, considering the limited populations studied in the pivotal studies (e.g. there are no data of nusinersen in patients over 9 years old or in people with type 3 SMA) and the restrictions due to special warnings and precautions for its use.

Table 5: Clinical effectiveness evidence

Study	BP39056 (FIREFISH)	BP39055 (SUNFISH)	BP39054 (JEWELFISH)
Study design	Open-label, two-part seamless, multicentre, single-arm study. • Part 1 objectives: safety, tolerability, PK and PD, dose selection for Part 2 • Part 2 objectives: efficacy, safety and tolerability, PK and PD	Two-part seamless randomised, multicentre, placebo-controlled, double-blind study. • Part 1 objectives: safety, tolerability, PK and PD, dose selection for Part 2 • Part 2 objectives: efficacy, safety and tolerability, PK and PD	Multicentre, open label, non-comparative, single-arm, exploratory study in SMA patients previously enrolled in BP29420 (MOONFISH) or previously treated with nusinersen, onasemnogene abeparvovec or olesoxime. 24 month treatment period plus extension phase
Population	Infants with type 1 SMA aged ≥1 month and ≤7 months at the time of enrolment	People aged 2–25 years with type 2 and non-ambulant type 3 SMA.	People aged 6 months to 60 years with type 1, 2 and 3 SMA
Intervention(s)	Risdiplam	Risdiplam	Risdiplam
Comparator(s)	None (single arm)	Placebo	None (single arm)
Indicate if trial supports application for marketing authorisation	Yes ✓ / No **Indicate if trial used in the economic model** Yes ✓ / No	Yes ✓ / No **Indicate if trial used in the economic model** Yes ✓ / No	Yes ✓ / No **Indicate if trial used in the economic model** Yes / No ✓
Rationale for use/non-use in the model	FIREFISH is a Phase II/III trial providing efficacy and safety evidence for risdiplam in people with type 1 SMA. Data from Part 2 of the study were used to inform the efficacy and safety of risdiplam in the economic model.	SUNFISH is a Phase II/III trial providing efficacy and safety evidence for risdiplam in people with type 2 or 3 SMA. Data from Part 2 of the study were used to inform the efficacy and safety of risdiplam in the economic model.	Efficacy data in JEWELFISH were exploratory endpoints and are currently unavailable due to short median duration of treatment at CCOD (3.0 months), although safety data are included within the pooled analysis.
Reported outcomes specified in the decision problem	Motor function (BSID III, HINE-2, CHOP-INTEND); bulbar function; survival and ventilation-free survival; healthcare utilisation; adverse events, HRQoL	Motor function (MFM32, RULM, HFMSE); adverse events; HRQoL	Adverse events

BSID-III, Bayley Scales of Infant and Toddler Development Third Edition (BSID-III); CCOD, clinical cut-off date; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Hammersmith Infant Neurological Examination Module 2; HRQoL, health-related quality of life; MFM32, Motor Function Measure – 32 items; PD, pharmacodynamics; PK, pharmacokinetics; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

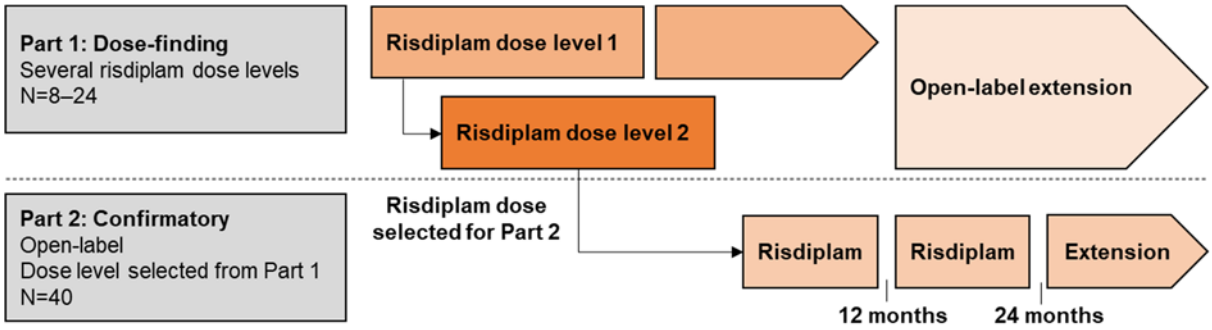
Unless otherwise stated, information on the FIREFISH and SUNFISH studies were sourced from the clinical study reports (68, 74) . Both studies were conducted in accordance with the principles of the “Declaration of Helsinki” and Good Clinical Practice (GCP).

B.2.3.1 FIREFISH study design (infantile-onset type 1 SMA)

FIREFISH is a two-part, multicentre study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in infants with infantile-onset (Type 1) SMA.

The study consists of an exploratory dose-finding part (Part 1) and an ongoing confirmatory part (Part 2) to assess the safety and efficacy of risdiplam. Following the dose selection for Part 2, patients in Part 1 were given the possibility to continue receiving risdiplam at the dose selected for Part 2, for a total treatment period of 24 months. Patients could then enter the open-label extension (OLE) phase, which would run until risdiplam is commercially available in the country of the patients who participated. In this study, both the 24-month treatment period and the OLE phase are open-label; however, the OLE has less frequent assessments than the treatment period.

Figure 2: FIREFISH study design schema (infantile-onset, type 1 SMA)



Dose Level 1includes the first three infants enrolled in the study (including the first infant who received an initial single dose of risdiplam) who all received Dose Level 1 for at least 12 months and the infant enrolled at Dose Level 1 who discontinued from the study on Study Day 19.
Dose Level 2 includes the infant enrolled at Dose Level 1 whose dose was escalated to Dose Level 2 (mean AUC0-24h,ss ≤2000 ng·h/mL) per protocol on Study Day 83 and all other infants enrolled at Dose Level 2.

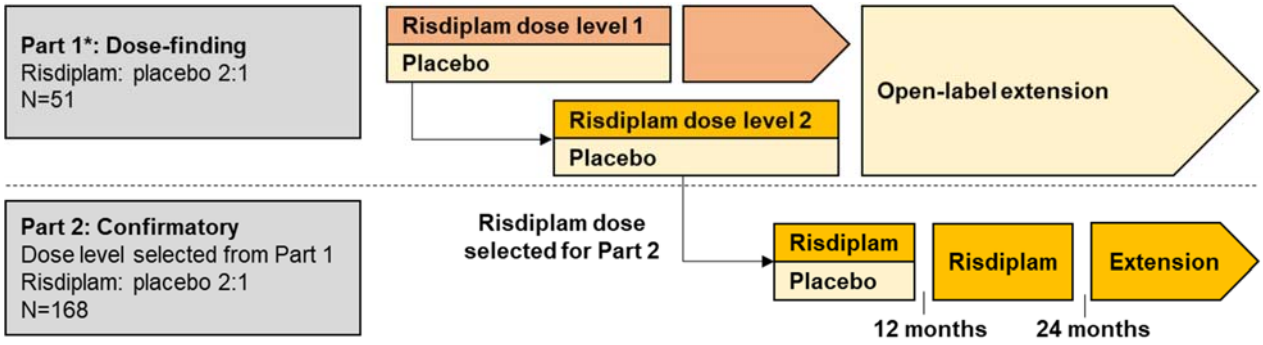
B.2.3.2 SUNFISH study design (later onset type 2 and type 3 SMA)

SUNFISH is a two-part, operationally seamless, multicentre, randomised, placebo-controlled, double-blind study designed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in people with later onset (type 2 and type 3) SMA.

Like FIREFISH, SUNFISH consisted of a dose-finding part (Part 1) and a confirmatory part (Part 2) to assess the efficacy and safety of treatment with risdiplam at the selected dose level from Part 1. After selection of the dose for Part 2, patients in Part 1 (i.e., those on placebo and on lower doses of risdiplam) were switched to the dose selected for Part 2 (the pivotal dose) as part of an OLE phase. Efficacy outcome measures overlapping with those collected in Part 2 were assessed throughout Part 1 including the OLE phase. Only people

with type 2 and non-ambulant type 3 SMA were included in Part 2 in order to minimise variability in changes in motor function and thereby increase the likelihood of detecting a treatment effect. After 12 months, patients receiving placebo in Part 2 were switched to risdiplam. Part 2 of the study is ongoing and remains blinded to the study sites.

Figure 2: SUNFISH study design schema (later onset, type 2 and type 3 SMA)



*Comprises two age groups (2–11 years and 12–25 years) with minimum of two dose-ranging cohorts per age group.

B.2.3.3 Summary of FIREFISH and SUNFISH study methodologies

Table 6: Study methodology summaries

	BP39056 – FIREFISH Infantile-onset, type 1 SMA	BP39055 – SUNFISH Later onset, type 2 and type 3 SMA
Settings and locations of data collection	Part 1: 7 investigational sites across 5 countries (Belgium [1], France [1], Italy [2], Switzerland [1], and the United States [2]). Part 2: 14 investigational sites across 10 countries (Croatia [1], France [1], Italy [4], Poland [1], Russia [1], Brazil [1], China [2], Japan [1], Turkey [1], and the United States [1]).	Part 1: 5 investigational sites across 4 countries (Italy [2], Germany [1], France [1], Belgium [1]). Part 2: 42 investigational sites across 14 countries (China [2], Belgium [3], Spain [4], France [5], Croatia [1], Italy [5], Poland [3], Russian Federation [1], Serbia [1], Japan [10], Canada [3], United States [2], Brazil [1], Turkey [1]).
Trial design	Phase II/III open-label, single arm, multicentre study to investigate the safety, tolerability, PK, PD and efficacy of risdiplam in people with type 1 SMA.	Phase II/III two-part, seamless, multicentre, randomised, double-blind, placebo-controlled study to investigate safety, tolerability, PK, PD and efficacy of risdiplam in people with type 2 and type 3 SMA
Eligibility criteria	See protocol for full details **<u>Selected inclusion criteria</u>** • Males and females aged between 28 days (1 month) of life and 210 days (7 months) (inclusive) at enrollment • Gestational age of 37 to 42 weeks • Confirmed diagnosis of 5q-autosomal recessive SMA, including: - Genetic confirmation of homozygous deletion or compound	See protocol for full details **<u>Selected inclusion criteria</u>** • For Part 1: type 2 or 3 SMA ambulant or non-ambulant. For Part 2: type 2 or 3 SMA non-ambulant • Confirmed diagnosis of 5q-autosomal recessive SMA For Part 2: 1) RULM entry item ≥2; 2) ability to sit independently as assessed by item 9 of the MFM

	heterozygosity predictive of loss of function of the SMN1 gene - Clinical history, signs or symptoms attributable to Type 1 SMA with onset after 28 days but prior to the age of 3 months • Two survival motor neuron 2 (SMN2) gene copies, as confirmed by central testing • Body weight ≥third percentile for age, using appropriate country-specific guidelines • Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the Investigator • Adequately recovered from any acute illness at the time of screening and considered well-enough to participate in the opinion of the Investigator **Selected exclusion criteria** • Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening or 5 half-lives, whichever is longer • Concomitant or previous administration of SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy study • Any history of cell therapy • Hospitalisation for pulmonary event within the last 2 months, or planned at the time of screening • Presence of clinically relevant ECG abnormalities before study drug administration • Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases • Participants requiring invasive ventilation or tracheostomy • Participants requiring awake non-invasive ventilation or with awake hypoxemia (arterial oxygen saturation less than [<] 95 percent [%]) with or without ventilator support	• Negative blood pregnancy test at screening and agreement to comply with measures to prevent pregnancy and restrictions on sperm donation **Selected exclusion criteria** • Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening or 5 half-lives, whichever is longer • Concomitant or previous administration of SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy study, either in a clinical study or as part of medical care • Any history of cell therapy • Hospitalisation for pulmonary event within the last 2 months, or planned at the time of screening • Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 month • Presence of clinically relevant ECG abnormalities before study drug administration • Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases • Participants requiring invasive ventilation or tracheostomy

	• Participants with a history of respiratory failure or severe pneumonia, and have not fully recovered their pulmonary function at the time of screening • Multiple or fixed contractures and/or hip subluxation or dislocation at birth • Presence of non-SMA related concurrent syndromes or diseases	
Trial drugs and concomitant medications	**Trial drug:** risdiplam (oral, once daily) **Part 1: Dose escalation** • Starting dose (for the first enrolled patient only): single dose at 0.00106 mg/kg • Dose Level 1: target exposure of mean area under the curve from time 0 to 24 hours at steady state ($AUC_{0\text{-}24h,ss}$) of 700 ng·h/mL • Dose Level 2: target exposure of $AUC_{0\text{-}24h,ss}$ 2000 ng·h/mL (mean) **Part 2: Starting dose levels** • Infants >1 month old and <3 months old at enrolment: 0.04 mg/kg. • Infants ≥3 months old and <5 months old at enrolment: 0.08 mg/kg. • Infants ≥5 months old at enrolment: 0.2 mg/kg. Upon review of the individual PK data for each infant enrolled in Part 1 and Part 2, the dose was adjusted to 0.2 mg/kg for all patients, in order to reach the target exposure defined in the protocol as a mean AUC of ≤2000 ng·h/mL. **<u>Selected concomitant medications</u>** Any medication, e.g., prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements, and nonmedication interventions (e.g., individual psychotherapy, cognitive behavioural therapy, smoking cessation therapy, physical therapy, and rehabilitative therapy) used by a patient within 30 days of study screening until the follow-up visit. Physiotherapy, occupational therapy, and other forms of exercise therapy were encouraged but the frequency	**Trial drugs:** risdiplam (oral, once daily) Part 1 initial doses • Part 1 initial doses: 0.02, 0.05, 0.25 mg/kg (2–11 year old patients), and 3 and 5 mg (12–25 year old patients). • Patients in Part 1 switched to the pivotal dose after the dose selection decision: 5 mg (BW ≥20 kg) and 0.25 mg/kg (BW <20 kg) Part 2: • Risdiplam administered orally at a dose of 5 mg once daily for people with BW ≥20 kg and 0.25 mg/kg once daily for people with BW <20 kg. • Matching oral placebo was administered once daily **<u>Selected concomitant medications</u>** Any medication, e.g., prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements, and non-medication interventions (e.g., individual psychotherapy, cognitive behavioural therapy, smoking cessation therapy, physical therapy, and rehabilitative therapy) used by a patient within 30 days of study screening until the follow-up visit. Physiotherapy, occupational therapy, and other forms of exercise therapy were encouraged but the frequency was to remain the same during the clinical study. See protocol for example of allowed medications **<u>Prohibited therapies</u>** – see protocol and clinical study reports

	was to remain the same during the clinical study. See protocol for example of allowed medications **<u>Prohibited therapies</u>** – see protocol and clinical study reports	
Primary outcome	**Part 1** • Safety, tolerability, PK and PD of risdiplam in infants with type 1 SMA, and to select the dose for Part 2. **Part 2** • Efficacy of risdiplam measured as the proportion of infants sitting without support after 12 months of treatment, as assessed in the gross motor scale of the Bayley Scales of Infant and Toddler Development - Third Edition (BSID-III) (defined as sitting without support for 5 seconds)	**Part 1** • Safety, tolerability, PK and PD of risdiplam in people with type 2 and type 3 (ambulant or non-ambulant) SMA, and to select the dose for Part 2 of the study. **Part 2** • Efficacy of risdiplam compared with placebo in terms of motor function in people with type 2 SMA and non-ambulant type 3 SMA, as assessed by the change from baseline in the total score of the Motor Function Measure (MFM32) at 12 months.
Other outcomes used in the economic model/specified in the scope	• Overall survival, event-free survival, motor milestone achievement as per HINE-2, respiratory support. • Outside of the clinical trial data, SMA-related patient costs and impact on patient and carer quality of life are also included in economic model	• Overall survival, motor milestone achievement as per MFM32, respiratory support. • Outside of the clinical trial data, SMA-related patient costs and impact on patient and carer quality of life are also included in economic model
Pre-planned subgroups	Following endpoints analysed by age at enrolment, sex, race, region, disease duration, and baseline CHOP-INTEND score • Proportion of patients sitting without support for 5 seconds at Month 12 • Proportion of patients who achieve a CHOP-INTEND score of 40 or higher at Month 12 • Time to death or permanent ventilation	Primary and key efficacy endpoints analysed by: • Age group (2–5, 6–11, 12–17, and 18–25 years at randomisation) • Disease severity • SMA type • SMN2 copy number

AUC, area under the curve; BSID-III, Bayley Scales of Infant and Toddler Development Third Edition (BSID-III); BW, body weight; ECG, electrocardiogram; MFM32, Motor Function Measure – 32 items; PD, pharmacodynamics; PK, pharmacokinetics; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN2, survival motor neuron 2

B.2.3.4 FIREFISH Part 2 patient demographics and baseline characteristics (infantile-onset, type 1 SMA)

Of the 41 patients enrolled in Part 2, 22 were female (53.7%), the median age at enrolment was 5.3 months (range: 2.2–6.9 months) and the majority of patients were White (22/41, 53.7%) or Asian (14/41, 34.1%).

The baseline characteristics of patients in Part 2 were typical of a symptomatic type 1 SMA population, with a median age of 1.5 months (range: 1.0–3.0 months) at symptom onset. The disease duration (time between onset of symptoms and first treatment) was <3 months in 27 patients (65.9%) and ≥3 months in 14 patients (34.1%), for a median disease duration of 3.4 months (range: 1.0–6.0 months).

Median baseline scores for CHOP-INTEND (22.0), BSID-III (2.0), HINE-2 (1.0), and CMAP amplitude (0.2 mV) were low, as expected for this symptomatic patient population. Patients' current levels of motor function at screening were also typical of this patient population, confirming that all patients had well-established disease by the time of study enrolment.

Table 7: FIREFISH Part 2 key demographic and baseline disease characteristics (infantile-onset, type 1 SMA)

	Risdiplam N=41
Median age at enrolment, months (range)	5.32 (2.2–6.9)
Median age at onset of symptoms, months (range)	1.45 (1.0–3.0)
Median age at diagnosis, months (range)	2.79 (0.9–6.1)
Sex, n (%)	
Male	19 (46.3)
Female	22 (53.7)
Race, n (%)	
White	22 (53.7)
Asian	14 (34.1)
Unknown	5 (12.2)
Region, n (%)	
Europe	24 (58.5)
North America	1 (2.4)
China	11 (26.8)
Japan	1 (2.4)
Rest of world	4 (9.8)
Median disease duration, months (range)	3.38 (1.0–6.0)
≤3 months, n (%)	14 (34.1)
>3 months, n (%)	27 (65.9)
SMN2 copy number, n (%)	
2	41 (100)
Tracheostomy, n (%)	
Yes	0
No	41 (100)
Median CHOP-INTEND score (range)	22.0 (8.0–37.0)
Median BSID-III gross motor scale total raw sore (range)	2.0 (0.0–8.0)
Median HINE-2 score (range)	1.0 (0.0–5.0)
Median CMAP negative peak amplitude, mV (range)	0.19 (0.0–0.8)
Current level of motor function, n (%)	
Head control carried upright	1 (2.4)

Head control ventral	1 (2.4)
No appropriate function listed	39 (95.1)
Highest motor function achieved, n (%)	
Controls head upright	2 (4.9)
Kicking horizontally	2 (4.9)
Kicking vertically	2 (4.9)
No appropriate function listed	35 (85.4)
Baseline level of respiratory support	
Current level of respiratory support, n (%)	
No pulmonary care	29 (70.7)
BiPAP support <16 hours per day	10 (24.4)
BiPAP support ≥16 hours per day	0
Cough assist – used daily for therapy, not illness related	3 (7.3)
Cough assist – used with an illness	1 (2.4)
Ventilation provided prophylactically, n (%)	
Yes	11 (26.8)
No	20 (73.2)
Awake assisted ventilation	0
Night-time assisted ventilation	9 (22.0)
Nap-time assisted ventilation	2 (4.9)
>16 h assisted ventilation	0
Airway clearance through cough assistance	3 (7.3)
BiPAP support ≥16h per day for >21 consecutive days, n (%)	
Yes	0
No	41 (100)
Intubation for >21 consecutive days, n (%)	
Yes	0
No	41 (100)
Baseline nutritional check up	
Able to swallow, n (%)	
Yes	40 (97.6)
No	1 (2.4)
Missing	0
Median age ability to swallow lost, months (range)	n=1 1.58 (1.6–1.6)
Primary food intake type, n (%)	
Oral fluid (milk) food intake	30 (73.7)
Mixed (fluid/pureed food) oral intake	4 (9.8)
Modified oral food intake	0
Solid food	0
Nasogastric food intake	6 (14.6)
Gastrostomy tube fed	1 (2.4)
Missing	0
Feeding route, n (%)	
Fed orally	33 (80.5)
Fed via a feeding tube	4 (9.8)
Fed via a combination of oral and tube feeding	2 (4.9)
Missing	2 (4.9)

Disease duration is the time between onset of symptoms and first treatment. Total raw score of the BSID-III gross motor scale is based on the assessment of the site clinical evaluator. Current level of motor function and highest motor function achieved reported at screening. Bi-PAP, Bilevel positive airway pressure; BSID-III, Bayley Scales of Infant Development (third edition); CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of

Neuromuscular Disorders; CMAP, compound muscle action potential; HINE-2, Hammersmith Infant Neuromuscular Examination section 2; SMA, spinal muscular atrophy; SMN2 survival motor neuron 2
Source: (68)

B.2.3.5 SUNFISH Part 2 patient demographics and baseline characteristics (later onset, type 2 and type 3 SMA)

Demographic and baseline characteristics were well balanced across treatment arms. At screening, the median patient age was 9.0 years (range: 2–25 years) in the risdiplam arm and 9.0 (range: 2–24 years) in the placebo arm. The majority of the population were White (67.2%).

Patients enrolled in SUNFISH Part 2 represent a broad range of the late-onset SMA clinical spectrum, including people with both type 2 and non-ambulant type 3 SMA, with different numbers of SMN2 copies, and with varied baseline disease characteristics including severe scoliosis. Additionally, people with contractures were not excluded from the study.

Table 8: SUNFISH Part 2 key demographic and baseline disease characteristics (later onset, type 2 and type 3 SMA)

	Risdiplam n=120	Placebo n=60
Median age at screening, years (range)	9.0 (2–25)	9.0 (2–24)
Age group, years, n (%)		
2–<6	37 (30.8)	18 (30.0)
6–11	39 (32.5)	18 (30.0)
12–17	30 (25.0)	16 (26.7)
18–25	14 (11.7)	8 (13.3)
Median age of onset of initial symptoms, months (range)	12.3 (0–57)	12.8 (6–135)
Median time between onset for initial symptoms to first treatment, months (range)	106.3 (17–275)	96.6 (1–271)
Sex, n (%)		
Male	59 (49.2)	30 (50.0)
Female	61 (50.8)	30 (50.0)
Race, n (%)		
White	80 (66.7)	41 (68.3)
Asian	23 (19.2)	12 (20.0)
Black or African American	2 (1.7)	0
Multiple	1 (0.8)	0
Unknown	14 (11.7)	7 (11.7)
Region		
Europe	81 (67.5)	43 (71.7)
North America	16 (13.3)	6 (10.0)
China	11 (9.2)	5 (8.3)
Japan	10 (8.3)	5 (8.3)
Rest of world	2 (1.7)	1 (1.7)
SMN2 copy number, n (%)		
2	3 (2.5)	1 (1.7)
3	107 (89.2)	50 (83.3)
4	10 (8.3)	8 (13.3)
Unknown	0	1 (1.7)
SMA type, n (%)		
Type II	84 (70.0)	44 (73.3)
Type III	36 (30.0)	16 (26.7)

Patients that could or could not stand, n (%)		
Standing	13 (10.8)	6 (10.0)
Could not stand	107 (89.2)	54 (90.0)
Patients that could or could not walk, n (%)		
Walking	3 (2.5)	1 (1.7)
Could not walk	117 (97.5)	59 (98.3)
No. of fractures, n (%)		
None	94 (78.3)	53 (88.3)
1–2	20 (16.7)	7 (11.7)
3–5	5 (4.2)	0
Scoliosis, n (%)		
Yes	76 (63.3)	44 (73.3)
No	44 (36.7)	16 (26.7)
Degree of curvature due to scoliosis, n (%)		
0–10	16 (13.3)	8 (13.3)
10–40	25 (20.8)	12 (20.0)
>40	34 (28.3)	23 (38.3)
Surgery for scoliosis before screening, n (%)		
Yes	29 (24.2)	17 (28.3)
No	63 (52.5)	33 (55.0)
Hip subluxation or dislocation, n (%)		
Yes	26 (21.7)	11 (18.3)
No	94 (78.3)	49 (81.7)
Hip surgery, n (%)		
Yes	4 (3.3)	3 (5.0)
No	116 (96.7)	57 (95.0)

SMA, spinal muscular atrophy; SMN2 survival motor neuron 2

The median motor function scores for the different scales at baseline were comparable across the risdiplam and placebo arms. The range of total scores at baseline for MFM32, RULM, and HFMSE was broad (i.e. MFM32: 17 to 72 points; RULM: 3 to 38 points; HFMSE: 0 to 48 points) reflecting the wide disease severity distribution of the patients in this study. The proportion of people with a HFMSE score below 10 at baseline (i.e. a baseline score that would be difficult for the HFMSE scale to detect a change from due to the insensitive nature of the assessment (28, 29)) was 41.1% across the study population, with a similar proportion in each treatment arm (risdiplam 40.8%; placebo 41.7%). Such wide range in baseline scores indicates that the patient population randomised to both treatment arms had a broad level of motor function, and that some patients were severely limited by a progressed disease by the time of study enrolment, as predicted given the natural history of SMA and the broad age range allowed by the inclusion criteria.

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

B.2.4.1 FIREFISH (infantile-onset type 1 SMA)

B.2.4.1.1 Statistical hypothesis and planned sample size

The purpose of Part 2 of FIREFISH was to estimate the proportion of infants who were sitting without support at 12 months of treatment and to test whether this proportion was higher than the pre-defined performance criterion of 5%. This was based on the well-defined

natural history of type 1 SMA, in which infants never achieve sitting without support (23, 34, 75), therefore this 5% threshold was used to define the performance criteria for success, i.e., a threshold of achievement for the risdiplam-treated infants to be assessed against within this study

The target sample size for Part 2 was 40 infants. This sample size provided at least 90% power to test the null hypothesis H_o: p≤5% versus the alternative hypothesis Ha: p>5%, if the true proportion of infants who would sit on treatment was 20%, based on an exact binomial test with a one-sided 5% significance level. With a planned sample size of 40 infants, a minimum of 5 infants sitting without support would provide a statistically significant difference from the pre-defined performance criterion (i.e., the lower limit of the two-sided 90% Clopper-Pearson [exact] confidence interval would be above 5%).

In the sample size calculations, no allowance was made for infants who withdraw early, as these infants would be classified as non-responders/non-sitters and included within the primary analysis

B.2.4.1.2 Analysis populations

The intent-to-treat (ITT) population for Part 2 was defined as all patients enrolled in Part 2 of the study, regardless of whether they received treatment or not. The ITT population was the primary analysis population for all efficacy analyses, with the exception of weight-for-age and length/height-for-age percentiles, which were analysed based on the safety population.

B.2.4.1.3 Assessment of efficacy

Efficacy results from Part 2 are compared to, and put into context with, data describing the natural history of untreated infants with type 1 SMA. These natural history data were used to define thresholds of achievement, i.e. objective performance criteria or performance goals, against which to assess the efficacy of treatment. Full details of the available sources used as the external control are provided in Appendix D. Key efficacy endpoints for FIREFISH are summarised below.

In addition to this, an indirect treatment comparison has been performed for risdiplam versus BSC in patients with type 1 SMA, aiming to inform both the clinical and the economic section of this evidence submission. More details are provided in Section B.2.9 and in Appendix M.

Table 9: Key efficacy endpoints in FIREFISH (infantile-onset type 1 SMA)

Motor function and development milestones
• Proportion of patients sitting without support for at least 5 seconds, as assessed by Item 22 of the BSID-III gross motor scale [a] • Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline • Proportion of motor milestone responders as assessed by the HINE-2[b] • Proportion of patients able to support weight or stand with support as assessed by the HINE-2 • Proportion of patients able to bounce while assessing the walking item of the HINE-2
Survival and ventilation-free survival
• Proportion of patients alive without permanent ventilation (≥16 hours of noninvasive ventilation such as BiPAP per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy) • Proportion of patients alive

Nutrition
• Proportion of people with the ability to feed orally • Proportion of people with the ability to swallow
Healthcare utilisation
• Number of hospitalisations per patient-year • Proportion of people with no hospitalisations
Patient/caregiver reported outcomes
• Change from baseline in the ITQOL-SF47 Questionnaire domains and single item scores

BiPAP, Bilevel Positive Airway Pressure; BSID-III, Bayley Scales of Infant and Toddler Development III; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Module 2; ITQOL-SF47, Infant and Toddler Quality of Life Questionnaire (47 item short form)

[a] The BSID-III gross motor scale was administered in a modified order, starting with the assessment of sitting positions (including the primary endpoint in Part 2).

[b] An infant was classified as a motor milestone responder if more HINE-2 motor milestones showed improvement than showed worsening, as defined in the SAP. Improvement was defined as at least a 2-point increase in the ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as at least a 2-point decrease in the ability to kick (or lowest score) or a 1 point decrease in the other milestones. Voluntary grasp was excluded from the definition.

The **primary endpoint** for the confirmatory Part 2 of the study was the proportion of infants who were sitting without support after 12 months of treatment. Sitting was defined as '*sits without support for at least 5 seconds'* as assessed in Item 22 of the BSID-III Gross Motor Scale. As per the scoring manual, Item 22 was not achieved if the infant sat alone for less than 5 seconds before losing balance and falling over, or if the infant used his or her arms to prop him or herself up. The assessment of the independent central readers was used for the primary analysis. Both central readers had to classify the milestone as achieved for the endpoint to be confirmed. Infants were classified as non-responders (i.e., non-sitters) for the primary analysis if they did not achieve sitting, did not maintain sitting achieved earlier, were withdrawn, died, or had a missing assessment at Month 12.

The pre-defined performance criterion for the primary endpoint was 5%.

The proportion of infants who were sitting after 12 months of treatment is presented with a two-sided 90% Clopper-Pearson (exact) confidence interval. An exact binomial test was performed to test the hypothesis that the proportion of infants who sit on treatment (p) is:

Ho: p≤5% (null) versus Ha: p>5% (alternative).

If the one-sided p-value was ≤5% (Type 1 error rate), then the null hypothesis was rejected. If the lower limit of the two-sided 90% confidence interval was above the 5% threshold, then the primary objective of the study was considered achieved.

All **secondary endpoints** (except for time-to-event) were summarised by timepoint for the ITT population using descriptive statistics.

Performance criteria were derived for some of the secondary efficacy endpoints in Part 2 using data from similar cohorts of untreated infants with type 1 SMA constructed from real world data sources/natural history studies. If multiple sources of data were available for a secondary endpoint, the cohort with the baseline characteristics most similar to those targeted by the study inclusion and exclusion criteria was used. The benchmark was based on the associated upper limit of the 90% CI from the historical data. When a pre-defined benchmark could be determined for the secondary endpoint, hypothesis testing was performed.

The tested hypothesis was that the treatment response rate (p) is:

H_0: p≤pre-defined benchmark (null) versus H_a: p>benchmark (alternative).

If the one-sided p-value was ≤5% (nominal) then the null hypothesis was rejected.

To control for multiplicity across the different endpoints, a hierarchical testing approach was implemented. The first secondary efficacy endpoint, the proportion of infants who achieve a score of 40 or higher in the CHOP-INTEND at Month 12, was tested if and only if the primary endpoint had reached the 5% significance level (i.e., p-value ≤0.05). Other secondary endpoints were tested at a 5% significance level according to the following hierarchy, as long as the p-value was ≤0.05 for endpoints higher in the hierarchy:

- Proportion of infants who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12.
- Proportion of motor milestone responders as assessed by the HINE-2 at Month 12
- Proportion of infants who are alive without permanent ventilation at Month 12
- Proportion of infants sitting without support for 30 seconds (defined as 'Sits without support for 30 seconds' as assessed in item 26 of the BSID-III gross motor scale) at Month 24
- Proportion of infants standing at Month 24 (defined as 'Stands alone' as assessed in item 40 of the BSID-III gross motor scale)
- Proportion of infants walking at Month 24 (defined as 'Walks alone' as assessed in item 42 of the BSID-III gross motor scale).

Month 24 endpoints will be analysed when all infants have reached 24 months of treatment. Any other endpoints for which hypothesis testing was performed were simultaneously tested at the 5% significance level without adjustment for multiplicity, as they were considered to provide supportive information.

B.2.4.2 SUNFISH (later-onset type 2 and type 3 SMA)

B.2.4.2.1 Statistical hypothesis and planned sample size

The target sample size for Part 2 of SUNFISH was 168 people with 112 patients randomised to risdiplam and 56 patients randomised to placebo (2:1 randomisation).

For the primary endpoint of mean change from baseline in total MFM score at Month 12, the sample size of 168 patients (allowing for a 10% dropout rate) provided at least 80% power at a two-sided 5% significance level for testing the null hypothesis (the true treatment difference is zero) versus the alternative hypothesis (the true treatment difference is 3), and assuming that the common standard deviation will be 6. This corresponds to a hypothesised effect size of 0.5. The minimal detectable treatment difference was approximately 2.03.

B.2.4.2.2 Analysis populations

The ITT population, defined as all randomised patients in Part 2, was the primary analysis population for all efficacy analyses. Patients in the ITT population were reported according to the treatment to which they were randomised. Patients not randomised but received study medication were excluded from the ITT population.

B.2.4.2.3 Assessment of efficacy

Efficacy analyses presented within this submission document are from Part 2 only. The primary efficacy estimand is based on a hypothetical treatment strategy assuming no prohibited medications intended for treatment of SMA were available and patients continued on their randomised treatment until the primary analysis timepoint. This approach facilitated the exploration of the efficacy of risdiplam in the absence of other treatments. A treatment policy strategy was also applied. For any patients who discontinued study treatment but continued in the study, all data were included regardless of initialisation of prohibited medications. Efficacy endpoints in Part 1 are considered exploratory; the results of Part 1 are presented in Appendix L as supportive data as they also showed clear efficacy of risdiplam in SMA. Key efficacy endpoints are summarised below.

Table 10: Key efficacy endpoints in SUNFISH (later onset type 2 and type 3 SMA)

Motor function and development milestones
• Change from baseline in MFM32 total score • Proportion of patients who achieved a change from baseline greater or equal to 3 points in the MFM32 total score • Proportion of patients who achieved stabilization or improvement (change from baseline greater or equal to 0 points) in the MFM32 total score • Change from baseline in RULM total score • Change from baseline in HFMSE total score
Patient/caregiver reported outcomes
• Change from baseline in the patient- and caregiver-reported SMAIS total score

HFMSE, Hammersmith Functional Motor Scale Expanded; MFM, Motor Function Measure; RULM, Revised Upper Limb Module; SMAIS, SMA independence scale.

Motor function was assessed by three different clinically relevant and validated scales in SUNFISH: the Motor Function Measure 32 (MFM32), the Revised Upper Limb Module (RULM), and the Hammersmith Functional Motor Scale Expanded (HFMSE). The clinical relevance of each motor function scale was taken into account when designing the study. Importantly, although both the MFM32 and HFMSE assess the concept of motor function, the items in the MFM32 capture a broader range of ability, including items relating to distal motor function that are primarily not assessed by the HFMSE, and therefore captures the entire breadth of the patient population within one scale. This broad range of functional ability is thus applicable, whatever the severity of the deficiencies, in non-ambulant and ambulant patients. For this reason, the MFM32 scale was chosen to evaluate the primary endpoint in SUNFISH Part 2. The primary analysis was the Mixed Model Repeated Measure (MMRM) analysis performed on the change from baseline in the total MFM32 score using all data collected in Part 2 up to 12 months.

Given the importance to people with type 2 and type 3 SMA of maintaining independence (see Section B.1.3.2.), the SMA Independence Scale (SMAIS) was developed specifically for SMA patients in order to assess function-related independence. The SMAIS contains items assessing the amount of assistance required from another individual to perform daily activities such as eating, or bathing. The SMAIS was completed by patients aged ≥12 years and caregivers of patients 2–25 years. The items in the two scales are identical. The SMAIS total score comprises 22 of the 29 items focused on upper limb ability, with each item scored on a 0-2 scale (0–44 total score). Higher scores indicate greater independence in completing activities.

The reliability, validity and responsiveness of the SMAIS has been confirmed via quantitative analysis using SUNFISH data and an independent US survey source (76). Anchor-based analyses indicated that meaningful change estimates on the SMAIS 22-item upper limb total score vary by age subgroup and that a range of 1–5 points may be meaningful. The mean score change for patients classified as 'minimally improved' on CGI-C at week 52 mean was 1.4 for the caregiver-report version (2–25 years old) and 2.8 for the patient self-report version (12-25 years old). An estimate of 2–3 points for both scales is considered a conservative meaningful change threshold in light of these data (76).

B.2.4.2.4 Adjustment for multiple testing

To control the type I error rate due to multiple testing of risdiplam versus placebo for the primary and the six key secondary efficacy endpoints in the ITT population, a gatekeeping approach was applied to the seven null hypotheses which were grouped into six families. The hypotheses to be tested were ordered hierarchically and the truncated Hochberg procedure was used in the family which contains more than one hypothesis. The following shows the seven null hypotheses and the six families of the testing for Part 2.

- Family 1 includes the hypothesis for the primary endpoint on the change from baseline total MFM32 score at Month 12 comparing risdiplam versus placebo: H_{11} (MFM32)
- Family 2 includes the hypothesis for the proportion of patients who achieve a change from baseline ≥3 on the total MFM32 score at Month 12 comparing risdiplam versus placebo: H_{21} (Prop. MFM32 ≥3)
- Family 3 includes the hypothesis for the change from baseline total score of RULM at Month 12 comparing risdiplam versus placebo: H_{31} (RULM)
- Family 4 includes the hypothesis for the change from baseline total score of HFMSE at Month 12 comparing risdiplam versus placebo: H_{41} (HFMSE)
- Family 5 includes the hypothesis for the change from baseline in total score of caregiver/parent reported SMAIS at Month 12 comparing risdiplam versus placebo: H_{51} (SMAIS)

Further information on the multiple testing approach can be found in the Primary CSR (74).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of the included randomised clinical trial was performed using established risk of bias tools recommended for HTA submissions. The complete quality assessment is presented in Appendix D. A summary is presented below.

Table 11: Clinical effectiveness evidence quality assessment

Study question	BP39055 (SUNFISH)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 FIREFISH Part 2 (infantile-onset, type 1 SMA)

Efficacy overview

- The primary efficacy endpoint for this study was met. After 12 months of treatment with risdiplam, 29.3% of patients in Part 2 were sitting without support, as assessed by Item 22 of the BSID-III gross motor scale. This proportion is significantly higher than the pre-defined performance criterion of 5% based on natural history data (p<0.0001).
- The results of the secondary and exploratory efficacy endpoints supported the primary endpoint, showing that risdiplam treatment was associated with clinically meaningful improvements in people with type 1 SMA:
  - At Month 12, 56.1% of patients achieved a CHOP-INTEND total score of 40 or higher, and 90.2% of patients achieved an increase of at least 4 points in their CHOP-INTEND score from baseline. These results are significantly higher than the pre-defined performance criteria of 17% based on natural history data (p<0.0001 for each of these endpoints).
  - At Month 12, 78.0% of patients were classified as motor milestone responders (defined as having more milestones that showed improvement from baseline than showed worsening) as assessed by the HINE-2. This proportion was significantly higher than the pre-defined performance criterion of 12% based on natural history data (p<0.0001).
  - At Month 12, 85.4% of patients were alive without permanent ventilation. This proportion is significantly higher than the pre-defined performance criterion of 42% based on natural history data (p<0.0001).
  - At Month 12, 92.7% of patients were alive. This proportion is significantly higher than the pre-defined performance criterion of 60% based on natural history data (p<0.0005).
  - At Month 12, 82.9% of patients had the ability to feed orally
  - At Month 12, a total of 9 patients (22.0%) could either stand with support (2 patients) or support weight (7 patients) when assessing the standing item, and 1 patient (2.4%) could bounce when assessing the walking item according to the HINE-2

Table 12: Clinical efficacy summary, FIREFISH Part 2

Endpoint	Risdiplam n=41	Performance criterion	p-value[a]
Primary efficacy endpoint			
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 12	12/41 29.3% (17.8–43.1%)	5%	< 0.0001
Secondary efficacy endpoints			
Motor function and development milestones			
Number / proportion (90% CI) of patients who achieve a score of 40 or higher in the CHOP-INTEND at Month 12	23/41 56.1% (42.1–69.4%)	17%	< 0.0001

Number / proportion (90% CI) of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12	37/41 90.2% (79.1–96.6%)	17%	< 0.0001
Number / proportion (90% CI) of motor milestone responders[b] as assessed by the HINE-2 at Month 12	32/41 78.0% (64.8–88.0%)	12%	< 0.0001
Number / proportion (90% CI) of patients able to support weight or stand with support[c] as assessed by the HINE-2 at Month 12	9/41 22.0% (12.0–35.2%)	NA	–
Number / proportion (90% CI) of patients able to bounce while assessing the walking item of the HINE-2 at Month 12	1/41 2.4% (0.1–11.1%)	NA	–
Survival and ventilation-free survival			
Number / proportion (90% CI) of patients alive without permanent ventilation at Month 12 (90% CI)	35/41 85.4% (73.4–92.2%)	42%	< 0.0001
Number / proportion (90% CI) of patients alive at Month 12	38/41 92.7% (82.2–97.1%)	60%	0.0005
Nutrition			
Number / proportion (90% CI) of people with the ability to feed orally[d] at Month 12	34/41 82.9% (70.3–91.7%)	NA	–
Exploratory efficacy endpoints			
Healthcare utilisation			
Number of hospitalisations[e] per patient-year at Month 12 (90% CI)	1.30 (1.02–1.65)	NA	–
Number / proportion (90% CI) of people with no hospitalisations at Month 12	20/41 48.8% (35.1–62.6%)	NA	–

[a] p-values for survival and ventilation-free survival are based on a Z-test; p-values for all other endpoints (BSID-III, CHOP-INTEND, HINE-2) are based on an exact binomial test.
[b] An improvement in a motor milestone was defined as at least a 2-point increase in the ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, or walking. Worsening was defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing or walking. Voluntary grasp was excluded from the definition. An infant was classified as a responder if more motor milestones showed improvement than showed worsening.
[c] Includes 7 patients (17.1%) who could support weight and 2 patients (4.9%) who could stand without support.
[d] Includes patients who were fed exclusively orally (28 patients overall) and those who were fed orally in combination with a feeding tube (6 patients overall) at Month 12.
[e] Hospitalisations include all hospital admissions which spanned at least two days.
BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; HINE-2, Hammersmith Infant Neurological Examination Module 2; NA, not available.
Source: (68)

B.2.6.1.1 Primary efficacy endpoint

At 12 months of treatment, 12 of 41 patients (29.3%; 90% CI: 17.8%, 43.1%) in Part 2 were sitting without support, as assessed by Item 22 of the BSID-III gross motor scale, '*sits without support for 5 seconds'*. This proportion (29.3% of patients sitting at Month 12) is significantly higher than the pre-defined performance criterion of 5% based on well-established natural history data (p<0.0001) (23, 75).

Of the 12 patients who were sitting without support for 5 seconds at Month 12, 7 patients (17.1%) had already reached this milestone after 8 months of treatment, and they maintained it at Month 12.

Table 13: Patients sitting without support for 5 seconds at Month 12 (ITT Population, FIREFISH Part 2)

Endpoint	Risdiplam n=41	Performance criterion	p-value
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 12	12/41 29.3% (17.8–43.1%)	5%	< 0.0001

BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CI, confidence interval; Source: Source: (68)

B.2.6.1.2 Secondary efficacy endpoints

Motor function and development milestones

CHOP-INTEND

At 12 months of treatment, 23 of 41 patients (56.1%; 90% CI: 42.1%, 69.4%) in Part 2 achieved a CHOP-INTEND total score of 40 or higher. This proportion is significantly higher than the pre-defined performance criterion of 17% based on natural history data (p<0.0001).

At 12 months of treatment, 37 of the 38 surviving patients in Part 2 presented motor function improvement, as measured by an increase of at least 4 points from baseline in their CHOP-INTEND score. One patient had a change of -2 at Month 12; this patient had fluctuations in the CHOP-INTEND scores during the first 12 months, with changes from baseline ranging from -2 to +3. Overall, 37 of 41 patients (90.2%; 90% CI: 79.1%, 96.6%) achieved an increase of at least 4 points from baseline, which is a significantly higher proportion than the pre-defined performance criterion of 17% based on natural history data (p<0.0001).

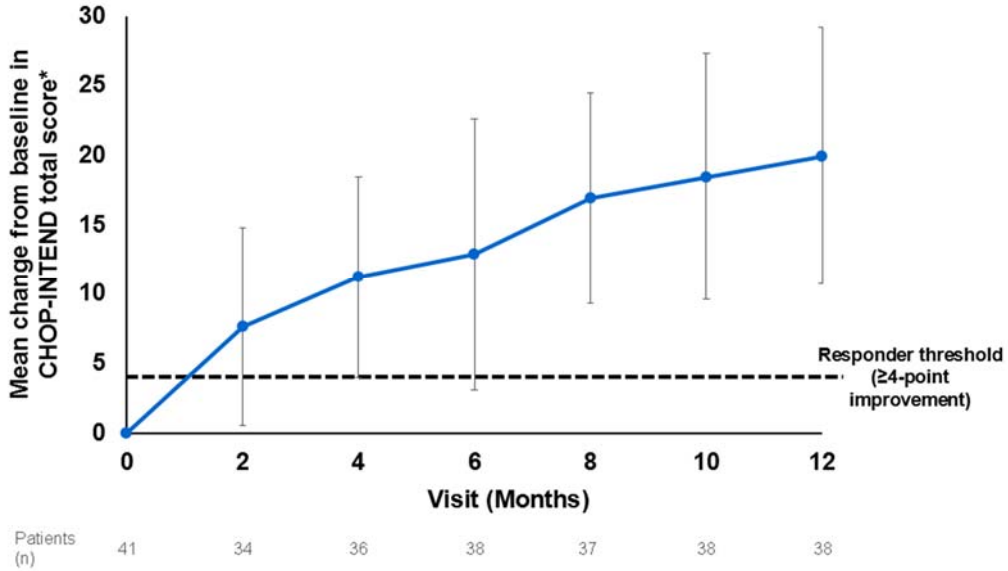
Table 14: CHOP-INTEND at Month 12, FIREFISH Part 2

Endpoint	Risdiplam n=41	Performance criterion	p-value[a]
Number / proportion (90% CI) of patients who achieve a score of 40 or higher in the CHOP-INTEND at Month 12	23/41 56.1% (42.1–69.4%)	17%	< 0.0001
Number / proportion (90% CI) of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12	37/41 90.2% (79.1–96.6%)	17%	< 0.0001

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval.
Source: (68)

The proportion of patients exhibiting head control increased over time. At baseline, 2 patients (4.9%) exhibited head control as defined by Item 12 of the CHOP-INTEND (score of ≥3; "*patient maintains the head upright for more than 15 seconds while sitting with trunk erect and support at the shoulders*"). The CHOP-INTEND score continued to improve over 12 months; the percentage of patients who achieved head control increased to 46.3% (19/41) of patients at Month 8 and 53.7% (22/41) of patients at Month 12.

Figure 2: Mean change from baseline in CHOP-INTEND total score (ITT Population, FIREFISH Part 2)



*±Standard deviation. †P<0.0001, performance criterion=17%, exact binomial test. Data cut-off: 14 Nov 2019.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
Source: (77)

HINE-2 – motor milestone responders

At 12 months of treatment, 32 of 41 patients (78.0%; 90% CI: 64.8%, 88.0%) in Part 2 were classified as motor milestone responders, as assessed by the HINE-2. This proportion is significantly higher than the pre-defined performance criterion of 12% based on natural history data (p<0.0001).

Table 15: Motor milestone responders as assessed by the HINE-2 (ITT Population, FIREFISH Part 2)

Endpoint	Risdiplam n=41	Performance criterion	p-value
Number / proportion (90% CI) of motor milestone responders[a] as assessed by the HINE-2 at Month 12	32/41 78.0% (64.8–88.0%)	12%	< 0.0001

[a] An improvement in a motor milestone was defined as at least a 2-point increase in the ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, or walking. Worsening was defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing or walking. Voluntary grasp was excluded from the definition. An infant was classified as a responder if more motor milestones showed improvement than showed worsening.
CI, confidence interval; HINE-2, Hammersmith Infant Neurological Examination Module 2; NA, not available.
Source: (68)

HINE-2 – motor milestones

The percentage of infants within the higher attainment response categories of the HINE-2 increased over time; data at Month 12 are presented below. For instance, at baseline, no patients could sit. At Month 12 of treatment, most of the patients achieved some level of sitting (61.0%): 4 patients (9.8%) were able to pivot (rotate) while sitting, 6 patients (14.6%)

achieved a stable sit, 8 patients (19.5%) sat by propping themselves up, and 7 patients (17.1%) were able to sit with support at hips.

Table 16: Summary of people within each attainment response category of the HINE-2 at Month 12 (ITT Population, FIREFISH Part 2 Patients)

n, (%)	Risdiplam n=41
Head control	
Unable to maintain head upright	7 (17.1)
Wobbles	13 (31.7)
All the time maintained upright	18 (43.9)
Sitting	
Cannot sit	13 (31.7)
Sits with support at hips	7 (17.1)
Props	8 (19.5)
Stable sit	6 (14.6)
Pivots (rotates)	4 (9.8)
Voluntary grasp	
No grasp	[redacted]
Uses whole hand	[redacted]
Index finger and thumb but immature grip	[redacted]
Pincer grip	[redacted]
Ability to kick (in supine)	
No kicking	[redacted]
Kicks horizontally, legs do not lift	[redacted]
Upward (vertically)	[redacted]
Touches leg	[redacted]
Touches toes	[redacted]
Rolling	
No rolling	[redacted]
Rolling to side	[redacted]
Prone to supine	[redacted]
Supine to prone	[redacted]
Crawling	
Does not lift head	[redacted]
On elbow	[redacted]
On outstretched hand	[redacted]
Crawling flat on abdomen	[redacted]
Crawling on hands and knees	[redacted]
Cannot test	[redacted]
Standing	
Does not support weight	25 (61.0)
Supports weight	7 (17.1)
Stands with support	2 (4.9)
Stands unaided	0
Cannot test	2 (4.9)
Not done	2 (4.9)
Walking	
Bouncing	1 (2.4)
Cruising (walks holding on)	0
Walking independently	0
Cannot test	34 (82.9)

Not done	3 (7.3)
Death	3 (7.3)
Missing	0

Patients who reached the target date for a visit but did not perform the assessment by the clinical cutoff date are counted as missing.
Source: (68)

Survival and ventilation-free survival

Time to death or permanent ventilation

The proportion of infants alive without permanent ventilation at Month 12 was 85.4% (35/41; 90% CI: 73.4%, 92.2%). Three infants died within the first 3 months following study enrolment, and 3 infants met the endpoint of permanent ventilation. The proportion of infants alive without permanent ventilation (85.4%) is significantly higher than the pre-defined performance criterion of 42% based on natural history data (p<0.0001). The median time to death or permanent ventilation was not estimable as few patients had an event.

Table 17: Time to death or permanent ventilation (ITT population, FIREFISH Part 2)

	Risdiplam n=41
People with event, n (%)	6 (14.6)
Earliest contributing event, n Death Permanent ventilation	 3 3
People without event, n (%)	35 (85.4)
Median time to event, months (90% CI)	NE (NE, NE)
12 month duration Patients remaining at risk Proportion event-free, % (90% CI)	 34 85.4 (73.4, 92.2)
Performance criterion = 42% p-value (z-test)	 <0.0001

Source: (68)

Time to death

The proportion of infants alive at Month 12 was 92.7% (38/41; 90% CI: 82.2%, 97.1%). This proportion is significantly higher than the pre-defined performance criterion of 60% based on natural history data (p<0.0005). The median time to death was not estimable as few patients had an event.

Table 18: Time to death (ITT population, FIREFISH Part 2)

	Risdiplam n=41
People with event, n (%)	3 (7.3)
Median time to event, months (90% CI)	NE (NE, NE)
12 month duration Patients remaining at risk Proportion event-free, % (90% CI)	 37 92.7 (82.2, 97.1)
Performance criterion = 60% p-value (z-test)	 0.0005

Source: (68)

Time to permanent ventilation

The proportion of infants without permanent ventilation at Month 12 was [redacted]

Table 19: Time to permanent ventilation (ITT population, FIREFISH Part 2)

	Risdiplam n=41
People with event, n (%)	[redacted]
Median time to event, months (90% CI)	[redacted]
12 month duration Patients remaining at risk Proportion event-free, % (90% CI)	 [redacted] [redacted]
Performance criterion = 60% p-value (z-test)	 [redacted]

Source: (68)

Nutrition

At Month 12, 34 patients (82.9%; 90% CI: 70.3%, 91.7%) had the ability to feed orally. Of these 34 patients, 28 (68.3%) were fed exclusively by mouth, and 6 (14.6%) were fed via a combination of oral and tube feeding.

Four patients (9.8%) were fed exclusively by feeding tube at Month 12, including 2 patients who were fed via feeding tube at baseline, 1 patient who was fed orally at baseline, and 1 patient whose feeding route at baseline was missing.

At Month 12, the primary food intake was mixed oral intake (fluid/pureed food) for 22 patients (53.7%), solid food for 7 patients (17.1%), nasogastric food intake for 5 patients (12.2%), and gastrostomy tube feeding for 4 patients (9.8%).

Table 20: Summary of patient ability to feed at Month 12 (ITT population, FIREFISH Part 2)

	Risdiplam n=41
Able to feed orally at Month 12, n (%) (90% CI)	34 (82.9) (70.3, 91.7)
Feeding route, n (%) Orally Via a feeding tube Via a combination of oral and tube feeding	 28 (68.3) 4 (9.8) 6 (14.6)
Primary food intake at Month 12, n (%) Oral fluid Mixed (fluid/pureed) oral Modified oral Solid food Nasogastric food Gastrostomy tube fed Deaths	 0 22 (53.7) 0 7 (17.1) 5 (12.2) 4 (9.8) 3 (7.3)

Source: (68)

Healthcare utilisation

Twenty of 41 patients (48.8%; 90% CI: 35.1%, 62.6%) did not require any overnight hospitalisation during the first 12 months of treatment (i.e., hospital admissions for any reason that included at least one night in the hospital. There were a total of 50 hospitalisations by Month 12, resulting in a rate of 1.30 (90% CI: 1.02, 1.65) hospitalisations per patient-year. Patients who were hospitalised were admitted for a median of 17 nights (range: 2.0–151.0) in total. These numbers also include planned / elective hospital admissions.

B.2.6.1.3 Patient/caregiver and clinician-reported outcomes

ITQOL-SF47

[redacted]

B.2.6.2 SUNFISH Part 2 (later onset, type 2 and type 3 SMA)

Efficacy overview

The primary analysis was performed at the point at which the last patient in Part 2 completed 12 months of treatment. To adjust for multiple testing in the comparison of risdiplam versus placebo for the primary and the six key secondary efficacy endpoints, a gatekeeping approach was applied and a hierarchical testing was performed (see section B.2.4.2.4). The primary and the following key secondary endpoints were met, indicating improvement or stabilisation in this broad SMA population:

- Family 1- Primary endpoint: Improvement in the MMRM analysis of the change from baseline in the MFM32 total score at Month 12 with risdiplam compared to placebo was both clinically meaningful and statistically significant for the ITT population (treatment difference: 1.55; p=0.0156).
- Family 2- Secondary endpoint: A greater proportion of patients in the risdiplam arm (38.3%) than in the placebo arm (23.7%) had a clinically meaningful and statistically significant improvement in MFM32 total score ≥3 points (odds ratio [95% CI]: 2.35 [1.01, 5.44]; unadjusted p=0.0469; adjusted p=0.0469).
- Family 3- Secondary endpoint: Improvement in the MMRM analysis of the change from baseline in the RULM total score at Month 12 with risdiplam compared to placebo was

both clinically meaningful and statistically significant (treatment difference: 1.59; unadjusted p=0.0028; adjusted p=0.0469).

In the next family of endpoints in the hierarchy (Family 4 - HFMSE scale), although a numerical improvement was demonstrated, in most cases statistical significance was not achieved, therefore, these and other subsequent secondary endpoints in the rest of the families of the hierarchy (SMAIS) are considered exploratory.

- Improvement in the MMRM analysis of the change from baseline in the HFMSE total score at Month 12 was numerically greater with risdiplam compared to placebo (treatment difference: 0.58; unadjusted p=0.3015; adjusted p=0.3902), despite low median HFMSE scores at baseline in this patient population.
- A numerically greater improvement in the MMRM analysis of the change from baseline in both caregiver-reported SMAIS (treatment difference: 2.55; unadjusted p=0.0022; adjusted p=0.3902) and patient-reported SMAIS (treatment difference: 1.45; p=0.1778) at Month 12 was observed with risdiplam compared to placebo.
- A greater proportion of patients in the risdiplam arm (69.6%) than in the placebo arm (54.2%) had an improvement in the exploratory secondary endpoint of change from baseline in MFM32 total score ≥0 points, demonstrating improvement or stabilization of disease with risdiplam treatment.

In accordance with clinical expectations, subgroup analysis showed that the greatest response in the MFM32 with risdiplam compared to placebo was observed in the youngest patients (aged 2–5 years). Importantly, improvements in RULM and disease stabilisation by the MFM32 were also achieved in the oldest patients (aged 18–25 years), an important goal of treatment in older people with SMA who had more advanced disease.

Table 21: Clinical efficacy summary, SUNFISH Part 2

Outcome	Risdiplam n=120	Placebo n=60	Difference (risdiplam minus placebo) (95% CI)	P-value
Primary endpoint				
Least squares mean change (SE) in MFM-32 Total Score from Baseline to Month 12	1.36 (0.38)	–0.19 (0.52)	1.55 (0.30, 2.81)	Unadjusted: 0.0156 Adjusted: 0.0156
Secondary endpoints				
Pts with change in MFM-32 ≥ 3 (baseline to Month 12), n (%)	44/115 (38.3)	14/59 (23.7)	OR for overall response: 2.35 (1.01, 5.44)	Unadjusted: 0.0469 Adjusted: 0.0469
People with change in MFM-32 ≥ 0 (Baseline to Month 12), n (%)	80/115 (69.6)	32/59 (54.2)	OR for overall response: 2.00 (1.02, 3.93)	0.0430
Least squares mean change (SE) in RULM Total Score from Baseline to Month 12	1.61 (0.31)	0.02 (0.43)	1.59 (0.55, 2.62)	Unadjusted: 0.0028 Adjusted: 0.0469
Least squares mean change (SE) in HFMSE	0.95 (0.33)	0.37 (0.46)	0.58 (–0.53, 1.69)	Unadjusted: 0.3015

Total Score from Baseline to Month 12				Adjusted: 0.3902
Least squares mean change (SE) in caregiver-reported SMAIS score from Baseline to Month 12	1.65 (0.50)	–0.91 (0.67)	2.55 (0.93, 4.17)	Unadjusted: 0.0022 Adjusted: 0.3902
Least squares mean change (SE) in patient-reported SMAIS Total score from Baseline to Month 12	1.04 (0.65)	–0.40 (0.86)	1.45 (–0.68, 3.57)	0.1778

CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale–Expanded; MFM-32, Motor Function Measure, 32-item version; OR, odds ratio; RULM, Revised Upper Limb Module; SE, standard error; SMAIS, Spinal Muscular Atrophy Independence Scale.
Notes: Baseline is the last measurement prior to patients first dose of risdiplam. Differences in changes from baseline were analysed using a mixed model repeated measure approach
Source:(74)

B.2.6.2.1 Primary efficacy endpoint

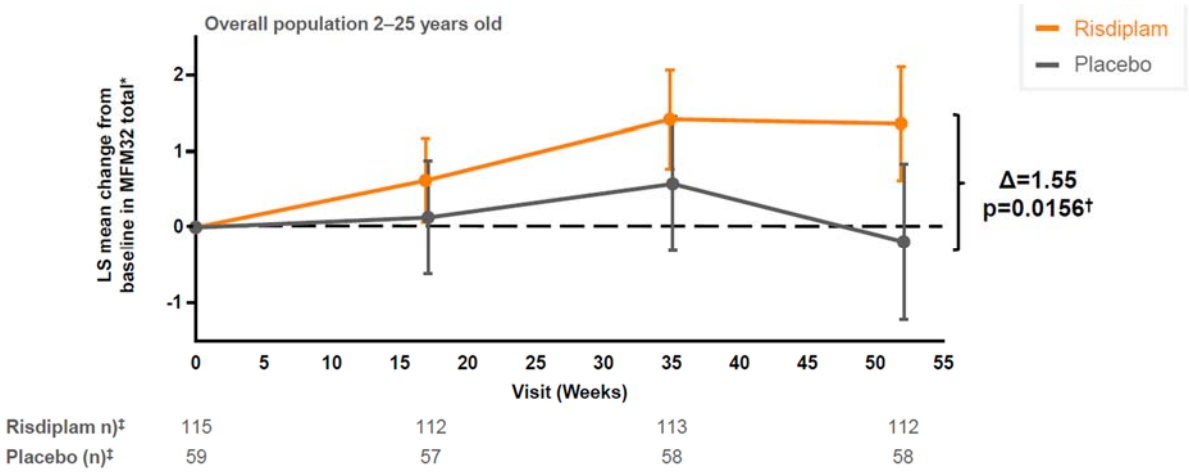
In the MMRM analysis of the MFM32 total score, the least square means (SE) change from baseline at Month 12 was 1.36 (0.38) in patients receiving risdiplam and -0.19 (0.52) in patients receiving placebo. This improvement in MFM32 total score with risdiplam treatment when compared to placebo was statistically significant and clinically meaningful (the least square difference in mean [95% CI] change from baseline in MFM32 at Month 12: 1.55 [0.30, 2.81]; p=0.0156). The least-squares mean change from baseline (95% CI) in MFM32 total score at each timepoint is presented in Figure 3.

Table 22: MMRM analysis on the change from baseline in MFM32 total score at Month 12 (SUNFISH Part 2; ITT population)

	Risdiplam n=120	**Placebo n=60**
Baseline mean MFM32 score, (SD)	n=115 45.48 (12.09)	n=59 47.35 (10.12)
LS Means change from baseline at week 52 (SE) (95% CI)	1.36 (0.38) (0.61, 2.11)	-0.19 (0.52) (-1.22, 0.84)
MMRM difference from placebo, (SE) 95% CI Unadjusted p value Adjusted p value	1.55 (0.64) (0.30, 2.81) 0.0156 0.0156	

CI, confidence interval; LS, least-squares; MFM-32, Motor Function Measure, 32-item version; SD, standard deviation; SE, standard error
Source:(74)

Figure 3: Least-squares mean change from baseline and 95% confidence interval in MFM32 total score at each timepoint up to Month 12 (SUNFISH Part 2; ITT Population)



*+/-95% confidence interval. †Mixed Model Repeated Measure, unadjusted p-value at 5% significance level. ‡Number of people with valid results = number of people with an available total score (result) at respective time points.
Intent to treat patients. Data cut-off: 6thSep 2019.
LS, least squares; MFM32, 32-item Motor Function Measure.
Source: (74, 78)

B.2.6.2.2 Secondary efficacy endpoints

MFM32 responder analysis

There was a greater proportion of responders (MFM32 total score ≥3) in the risdiplam arm (38.3%) than in the placebo arm (23.7%) at Month 12; the difference between the risdiplam arm and the placebo arm was statistically significant (odds ratio [95% CI]: 2.35 [1.01, 5.44]; unadjusted p=0.0469; adjusted p=0.0469).

The proportion of people with changes in MFM32 total score ≥0 was 69.6% in patients receiving risdiplam and 54.2% in those receiving placebo at Month 12 (odds ratio [95% CI]: 2.00 [1.02, 3.93]; p=0.0430) (Table 23). The proportion of people with a change from baseline in MFM32 of any threshold ≥0 (i.e., ≥0, ≥1, ≥2, ≥3, or ≥4), representing stabilisation or improvement in this measure, was greater in those receiving risdiplam than in those receiving placebo at all post-baseline scheduled assessment visits. The proportion of people with a change from baseline <0, representing decline in MFM32 total score, was greater in the placebo arm than in the risdiplam arm at all scheduled assessment visits.

Table 23: Change from Baseline in MFM32 Total Score at Month 12 (SUNFISH Part 2; ITT Population)

	Risdiplam n=120	Placebo n=60
Change in MFM32 total score at month 12 ≥3		
Responders, n (%) (95% CI)	44/115 (38.3) (28.94, 47.58)	14/59 (23.7) (12.03, 35.43)
Odds ratio for overall response (95% CI) p-value Adjusted p-value	2.35 (1.01, 5.44) 0.0469 0.0469	
Change in MFM32 total score at month 12 ≥0		
Responders, n (%)	80/115 (69.6)	32/59 (54.2)

(95% CI)	(60.72, 78.41)	(40.68, 67.80)
Odds ratio for overall response (95% CI) p-value	2.00 (1.02, 3.93) 0.0430	

CI, confidence interval; MFM-32, Motor Function Measure, 32-item version
Source: (74)

MFM32 domain score analysis

The MFM32 domain scores for D1 (standing and transfer), D2 (axial and proximal function), and D3 (distal function) and the combined score of D1+ D2 and D2 + D3 were summed and transformed onto a 0–100 scale (i.e., sum of all items scores within each individual domain divided by the maximum score of the corresponding domain and multiplied by 100) to yield the MFM32 domain scores, expressed as a percentage of the maximum score possible for the scale. In the MMRM analysis of the change from baseline in the individual MFM32 domains, the MMRM difference (95% CI) from placebo with risdiplam treatment was [redacted] When looking at the combined domain scores, the MMRM difference (95% CI) from placebo with risdiplam treatment was [redacted] These individual MFM32 domain results are reflective of this broad, non-ambulant population, with a high degree of disability and disease progression.

Table 24: MMRM analysis of the change from baseline in MFM32 Domains (D1, D2, D3, D1+D2 and D2+D3) score up to Month 12 (SUNFISH Part 2, ITT population)

	Risdiplam n=120	Placebo n=60
MFM32 – D1 domain total score		
Baseline mean MFM32 score, (SD)	[redacted]	[redacted]
LS Means change from baseline at week 52 (SE) (95% CI)	[redacted]	[redacted]
MMRM difference from placebo, (SE) 95% CI p value	[redacted]	
MFM32 – D2 domain total score		
Baseline mean MFM32 score, (SD)	[redacted]	[redacted]
LS Means change from baseline at week 52 (SE) (95% CI)	[redacted]	[redacted]
MMRM difference from placebo, (SE) 95% CI p value	[redacted]	
MFM32 – D3 domain total score		
Baseline mean MFM32 score, (SD)	[redacted]	[redacted]
LS Means change from baseline at week 52 (SE) (95% CI)	[redacted]	[redacted]
MMRM difference from placebo, (SE) 95% CI p value	[redacted]	
MFM32 – D1 + D2 domain total score		
Baseline mean MFM32 score, (SD)	[redacted]	[redacted]
LS Means change from baseline at week 52 (SE) (95% CI)	[redacted]	[redacted]

MMRM difference from placebo, (SE) 95% CI p value	[redacted]
MFM32 – D2 + D3 domain total score	
Baseline mean MFM32 score, (SD)	[redacted]
LS Means change from baseline at week 52 (SE) (95% CI)	[redacted]
MMRM difference from placebo, (SE) 95% CI p value	[redacted]

CI, confidence interval; LS, least-squares; MFM-32, Motor Function Measure, 32-item version; SD, standard deviation; SE, standard error
Source:(74)

Revised Upper Limb Module (RULM)

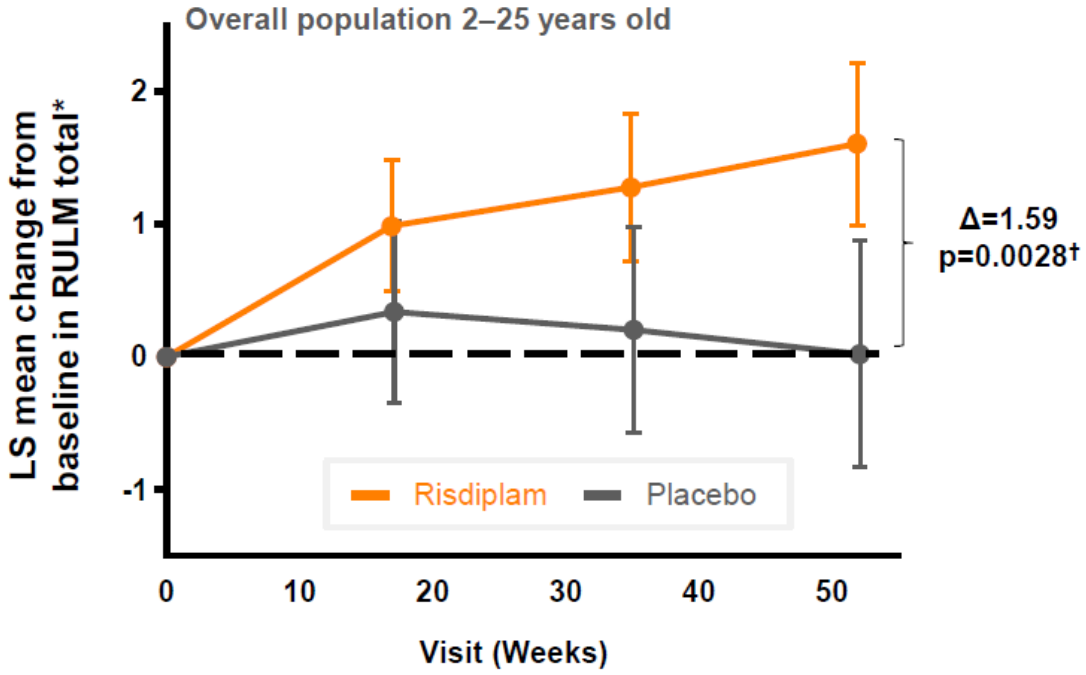
In the MMRM analysis of the RULM total score, the least-squares mean (SE) change from baseline at Month 12 was 1.61 (0.31) in patients receiving risdiplam and 0.02 (0.43) in patients receiving placebo. This improvement in RULM total score with risdiplam treatment when compared to placebo was statistically significant and clinically meaningful (least-square difference from placebo in mean [95% CI] change from baseline in RULM at Month 12: 1.59 [0.55, 2.62]; unadjusted p=0.0028; adjusted p=0.0469). The least-squares mean change from baseline (95% CI) in RULM total score at each timepoint is presented in Figure 4.

Table 25: MMRM analysis on the change from baseline in RULM total score at Month 12 (SUNFISH Part 2; ITT population)

	Risdiplam n=120	**Placebo n=60**
Baseline mean score, (SD)	n=119 19.65 (7.22)	n=58 20.91 (6.41)
LS Means change from baseline at week 52 (SE) (95% CI)	1.61 (0.31) (1.00, 2.22)	0.02 (0.43) (-0.83, 0.87)
MMRM difference from placebo, (SE) 95% CI Unadjusted p value Adjusted p value	1.59 (0.52) (0.55, 2.62) 0.0028 0.0469	

CI, confidence interval; LS, least-squares; SD, standard deviation; SE, standard error
Source:(74)

Figure 4: Least-squares mean change from baseline and 95% confidence interval on RULM total score at each timepoint up to Month 12 (SUNFISH Part 2; ITT Population)



Risdiplam (n)‡	119	118	116	112
Placebo (n)‡	58	57	56	56

*+/-95% confidence interval. †Mixed Model Repeated Measure, unadjusted p-value at 5% significance level. ‡Number of people with valid results = number of people with an available total score (result) at respective timepoints.
LS, least squares; RULM, Revised Upper Limb Module.
Source: (74, 78)

The proportion of people with a change from baseline in RULM of any threshold ≥0 (i.e., ≥0, ≥1, ≥2, ≥3, or ≥4), representing stabilisation or improvement in this measure, was [redacted] The proportion of people with a change from baseline ≤0, representing decline in RULM total score, was [redacted]

There was a [redacted] The proportion of people with changes in RULM total score ≥0 was [redacted]

Table 26: Change from Baseline in RULM Total Score at Month 12 (SUNFISH Part 2; ITT Population)

	Risdiplam n=120	Placebo n=60
Change in RULM total score ≥2 at Month 12		
Responders, n (%) (95% CI)	[redacted]	[redacted]

Odds ratio for overall response (95% CI) p-value	
Change in RULM total score ≥0 at Month 12	
Responders, n (%) (95% CI)	
Odds ratio for overall response (95% CI) p-value	

CI, confidence interval; RULM, Revised Upper Limb Module
Source: (74)

Hammersmith Functional Motor Scale Expanded (HFMSE)

In the MMRM analysis of the HFMSE total score, the mean (SE) change from baseline at Month 12 was 0.95 (0.33) in patients receiving risdiplam and 0.37 (0.46) in patients receiving placebo. This improvement in HFMSE total score with risdiplam treatment when compared to placebo was not statistically significant (least squares difference from placebo in mean [95% CI] change from baseline in HFMSE at Month 12: 0.58 [-0.53, 1.69]; unadjusted p=0.3015; adjusted p=0.3902). Of note, the median HFMSE total score at baseline was 14.0 points (min–max: 0.0–48.0) in patients receiving risdiplam and 13.0 points (min–max: 2.0–43.0) in those receiving placebo, with 41.1% of patients having a HFMSE score below 10 at baseline (risdiplam: 40.8%; placebo: 41.7%). This illustrates the advanced SMA disease in the studied patient population, and is significant because and that the HFMSE scale is not sensitive enough to detect a change in people with a baseline score <10 (28, 29).

Table 27: MMRM analysis on the change from baseline in HFMSE total score at Month 12 (SUNFISH Part 2; ITT population)

	Risdiplam n=120	**Placebo n=60**
Baseline mean score, (SD)	16.10 (12.46)	16.62 (12.09)
LS Means change from baseline at week 52 (SE) (95% CI)	0.95 (0.33) (0.29, 1.61)	0.37 (0.46) (-0.54, 1.28)
MMRM difference from placebo, (SE) 95% CI Unadjusted p value Adjusted p value	0.58 (0.56) (-0.53, 1.69) 0.3015 0.3902	

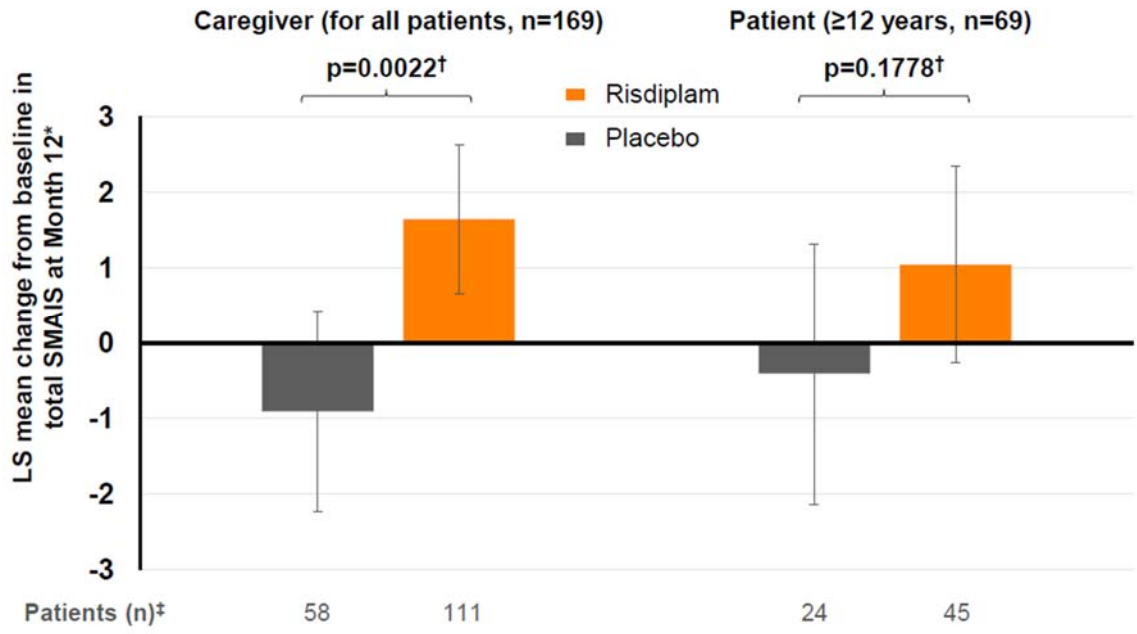
CI, confidence interval; LS, least-squares; SD, standard deviation; SE, standard error
Source:(74)

B.2.6.2.3 Patient/caregiver and clinician-reported outcomes

SMA Independence Scale (SMAIS)

The MMRM analyses of the change from baseline in SMAIS total score at Month 12 as reported by caregivers (n=176) and by patients (aged 12 or above) (n=66) are presented below. Caregivers and patients both reported gains in independence with risdiplam but losses in independence with placebo; the difference from placebo with risdiplam treatment was 2.55 (95% CI: 0.93, 4.17; unadjusted p=0.0022; adjusted p=0.3902) in the caregiver-reported assessment and 1.45 (95% CI: -0.68, 3.57; p=0.1778) in the patient-reported assessment.

Figure 5: MMRM analysis on the change from baseline in caregiver and patient-reported SMAIS total score at Month 12 (SUNFISH Part 2; ITT population)



* +/-95% confidence interval. †Mixed Model Repeated Measure, unadjusted p-value at 5% significance level. ‡Number of patients with valid results = number of patients with an available total score (result) at respective time points.
LS, least squares; SMAIS, SMA Independence Scale.

B.2.7 Subgroup analysis

B.2.7.1 FIREFISH Part 2 (infantile-onset, type 1 SMA)

Subgroup analyses were performed for the primary efficacy endpoint (proportion of patients sitting without support for 5 seconds at Month 12) and for two of the secondary efficacy endpoints (proportion of patients who achieve a CHOP-INTEND score of 40 or higher at Month 12 and time to death or permanent ventilation). Each of these endpoints was analysed by age at enrolment, sex, race, region, disease duration (i.e., time between first treatment and onset of symptoms), and baseline CHOP-INTEND score. Please refer to Appendix E for full details.

- Overall, the proportion of patients sitting without support for 5 seconds, achieving a CHOP-INTEND total score of 40 or higher, and who were alive without permanent ventilation at Month 12 was consistent among the subgroups investigated
  - Some differences were observed with subgroups based on disease duration and sex, but the numbers of patients in each subgroup are small, so the results should be interpreted with caution.

B.2.7.2 SUNFISH Part 2 (later onset, type 2 and type 3 SMA)

The consistency of the primary efficacy endpoint and key efficacy endpoints (all secondary endpoints up to Family 4 in the hierarchical testing) were explored for the following subgroups below (the SUNFISH study was not powered to demonstrate efficacy in these subgroups).

- Age group (2–5, 6–11, 12–17, and 18–25 years at randomisation)

- Disease severity (patient with MFM32 baseline total score ≤25th percentile, >25th percentile and ≤75th percentile, and >75th percentile)
- SMA type (type 2, type 3)
- SMN2 copy number (<2, 2, 3, ≥4 copies, unknown) from genotype analysis.

Subgroup analysis showed that the greatest response in the MFM32 with risdiplam compared to placebo was observed in the youngest patients (aged 2–5 years). Importantly, improvements in RULM and disease stabilisation by the MFM32 were also achieved in the oldest patients (aged 18–25 years), an important goal of treatment in older SMA patients with more advanced disease. These results confirm the effect of risdiplam treatment on motor function, which is clinically meaningful to confer benefit for patients' daily function. Please see Appendix E for full details.

An additional subgroup analysis was performed for the economic analysis of this submission, excluding patients enrolled to SUNFISH from Asia as they appear to have reported differently to patients enrolled from elsewhere (primarily Europe and North America). This subgroup includes sufficient patients (n=149) and will be powered to demonstrate an efficacy difference.

B.2.8 Meta-analysis

A meta-analysis is not necessary for patients with type 2 or type 3 SMA as head-to head comparative data for risdiplam vs. BSC are available from the SUNFISH study. However, in patients with type 1 SMA, due to the single-arm nature of the FIREFISH study, there are no relative efficacy estimates compared to BSC. A meta-analysis is however not appropriate or feasible as an approach, again due to single-arm nature of the FIREFISH study, therefore other indirect treatment comparison (ITC) methods were explored.

B.2.9 Indirect and mixed treatment comparisons

As stated in the previous Sections, a head-to head trial is available to compare risdiplam to BSC in patients with type 2 or 3 SMA (SUNFISH), therefore an ITC is not needed for this patient population. However, in the absence of head-to head evidence for risdiplam vs. BSC in patients with type 1 SMA (FIREFISH is a single-arm study), an ITC was necessary to enable a comparison for these patients, for the purposes of this evidence submission.

B.2.9.1 Systematic literature review

A SLR was conducted to identify relevant studies to inform an ITC between the interventions of interest in patients with type 1 SMA. The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design, and is outlined in Section B.1.1 and Appendix D. Of note, the scope of the SLR was broader than the ITC, with the two primary populations of interest for the SLR being patients with Type 1 (infantile-onset) SMA and patients with Type 2/3 (late-onset) SMA.

Comparators of interest

The comparators of interest considered in the decision problem for this NICE evidence submission are risdiplam and BSC (please see Section B.1.1). However, a broader patient population and additional interventions were included in the eligibility criteria for the SLR, to account for all available interventions and clinical studies in SMA. Not all these interventions are within scope of this appraisal; a broader set of criteria were taken into account in the

SLR for the purpose of informing reimbursement activities in other countries as well and to also inform potential future updates of the NMA network of evidence.

Criteria used in trial selection

The inclusion and exclusion criteria for the SLR and the study selection process are described in Appendix D.

B.2.9.2 Network meta-analysis (NMA) feasibility assessment

As a result of the clinical SLR 64 studies (26 clinical trials and 38 observational studies) were included. These are outlined according to their status (completed/ongoing) and according to SMA type in Appendix D.

In type 1 SMA, which is the population of interest for the ITC, two clinical trials were identified that assessed treatments of interest (risdiplam, BSC). The trials are: FIREFISH (risdiplam) and ENDEAR (BSC). ENDEAR was reported as a full text paper (56) at the time of writing this report.

Endpoints of interest

Endpoints of interest are those that are common across studies. For each outcome of interest, the publication must report Kaplan-Meier curves for time to event outcomes, mean/median for continuous outcomes, or the proportion of individuals for binary outcomes as per NICE DSU guidance (79, 80).

Table 28, Table 29 and

Table 30 show outcomes of interest for the analysis, and which are reported in each of the studies in patients with Type 1 SMA.

Outcomes from FIREFISH were derived from individual patient data of Part 1 (including patients from the 'High-dose' cohort on pivotal dose) and Part 2. Outcomes from ENDEAR were extracted from the primary publication (56) and, due to unavailability in the primary publication, from a presentation of interim efficacy data for the proportion of infants sitting with or without support (81).

Table 28: Motor Function Outcomes for the type 1 analysis

Outcome	Type of outcome	FIREFISH	ENDEAR*
Percentage of infants that achieve full head control (classified by HINE-2)	Binary	Yes	Yes
Percentage of infants sitting without support (classified by HINE-2)	Binary	Yes	Yes
Percentage of infants sitting with or without support (classified by HINE-2)	Binary	Yes	Yes**
Percentage of infants rolling (Classified by HINE-2)	Binary	Yes	Yes
Percentage of infants standing (Classified by HINE-2)	Binary	Yes	Yes
Motor-milestone response according to HINE-2	Binary	Yes	Yes
Percentage of infants who achieve a CHOP-INTEND score of 40 or higher	Binary	Yes	Yes
Percentage of infants with ≥ 4-point improvement in CHOP-INTEND score from baseline	Binary	Yes	Yes

* At latest available of 6-13 months for ENDEAR ** Only available interim efficacy dataset (n=51). Analysis of this outcome assumes that the baseline characteristics for the interim population are the same as for the ITT population (n=80). BSID-III: Bayley Scales of Infant and Toddler Development, version 3; HINE-2: Hammersmith Infant Neurological Examination Module; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

Table 29: Survival Endpoints for the Type 1 analysis

Outcome	Type of outcome	FIREFISH	ENDEAR
Event-free survival (death or permanent ventilation)	Time to event	Yes	Yes*
Overall survival	Time to event	Yes	Yes*

*Published Kaplan-Meier curves were digitised

Table 30: Safety Endpoints for the Type 1 analysis

Outcome	Type of outcome	FIREFISH	ENDEAR
Proportion of patients with any adverse event	Binary	Yes	Yes
Proportion of patients with any adverse event leading to discontinuation (including death)	Binary	Yes	Yes
Proportion of patients with any serious adverse event	Binary	Yes	Yes

Comparison of study characteristics

This section provides a summary of the comparison of the studies of interest for the ITC in Type 1 SMA.

Study design and inclusion/exclusion criteria

FIREFISH is an open-label, two-part, phase II/III dose-escalation/single-arm study. Part 1 is the dose-escalation part, while Part 2 is the confirmatory part at the dose selected based on the results from Part 1. ENDEAR is a double-blind phase III RCT.

FIREFISH is ongoing with a total treatment period of 24 months, followed by an open-label extension phase, while ENDEAR is complete and was terminated early. Both studies were conducted globally, across countries including Asia, Europe and the US. The number of sites that participated in the study was 31 in ENDEAR, 7 in FIREFISH Part 1 and 14 in FIREFISH Part 2.

In general, enrolment criteria were similar between the two trials, and the populations are broadly comparable. Both had similar age restrictions, genetic confirmation of disease and required infants to have two copies of the SMN2 gene. Key inclusion and exclusion criteria of the two studies are described in detail in Appendix M.

Patient characteristics

Table 31 summarises the baseline characteristics of the enrolled patients in ENDEAR and of the pooled Part 1 patients on pivotal dose and all Part 2 patients from FIREFISH. Mean age at first dose, at symptom onset and at diagnosis was higher for the BSC arm and more similar for the nusinersen arm of the ENDEAR study, compared to risdiplam in FIREFISH. Conversely, severity of disease at baseline was slightly worse in the FIREFISH patients as illustrated by the differences in baseline CHOP-INTEND (risdiplam vs sham -5.96; vs nusinersen -4.16) and HINE-2 scores (risdiplam vs sham -0.61; vs nusinersen -0.36). In general, the enrolment criteria and patient populations between the two trials can be characterised as being similar, and the populations as being broadly comparable.

Table 31: Baseline characteristics of FIREFISH and ENDEAR

Baseline characteristic	Risdiplam (FIREFISH) N=58*	Nusinersen (ENDEAR) N=80	Sham control (ENDEAR) N=41
Mean age at first dose in days (sd, [range])	163 days (44, [68-212])	163 days (NR,[52-242])	181 days (NR,[30-262])
Female gender	57%	54%	59%
Mean age at symptom onset in weeks (sd, [range])	7.2 weeks (3, [4-13.1])	7.9 weeks (NR,[2-18])	9.6 weeks (NR,[1-20])
Mean disease duration at screening in weeks (sd, [range])	13.0 weeks (5.9, [1-23.3])	13.2 weeks (NR,[0-25.9])	13.9 weeks (NR,[0-23.1])
Mean age at diagnosis in weeks (sd, [range])	12.7 weeks (6, [4-26.4])	12.6 weeks (NR, [0-29])	17.5 weeks (NR, [2-30])
Mean score on CHOP INTEND scale (sd, [range])	22.47 (6.79, [8-37])	26.63 (8.13, [NR])	28.43 (7.56, [NR])
Patients with nutritional support: Unable to swallow†/Gastrointestinal tube feeding	9%	9%	12%
Patients with ventilatory support	29%	26%	15%
Mean HINE-2 score (sd, [range])	0.93 (0.95, [0-5])	1.29 (1.07, [NR])	1.54 (1.29, [NR])
Mean CMAP negative peak amplitude (mV) - ulnar nerve (SD, [range])	0.199 (0.15, [0-0.8])	0.226 (0.19, [NR])	0.225 (0.12, [NR])

*Includes patients from the 'High-dose' (pivotal dose) cohort of Part 1 (n=17) and all patients from Part 2 (n=41) of FIREFISH

†Baseline data on gastrointestinal tube feeding was not available for most patients in Part 1, as the questionnaire was only introduced 6 months after start of the study. Ability to swallow was used as a proxy for tube feeding for these patients.

Follow-up time

The follow-up time was shorter in ENDEAR than in FIREFISH. In ENDEAR, median time on study (terminated at the interim analysis) was 280 (range: 6-442) days in the nusinersen arm and 187 (range: 20-423) days in the sham control arm.

Primary data cuts from Part 1 and Part 2 of FIREFISH with a follow-up of at least 12 months were available for this analysis. In the analyses of binary endpoints, where results are compared at specific time points, risdiplam would be favoured due to the longer follow-up duration for efficacy, and nusinersen would be favoured for safety. Therefore, a modified dataset of FIREFISH was used in the base case analyses of binary endpoints. In this dataset, any events occurring 6 months prior to data cut were not considered, resulting in a median time on study of 283 days. For analyses of time to event endpoints (event-free survival, overall survival), all available data from the 12-month data cuts were used. As survival analyses take into consideration information over all time points, these are less affected by differences in follow-up.

Endpoints and definitions

In ENDEAR, the primary study endpoint was event-free survival (time to death or permanent ventilation). Proportion of CHOP INTEND responders (≥4-point score increase from baseline at the later of day 183, 302, or 394 assessments) and overall survival rate were secondary endpoints, among others.

In FIREFISH, the primary study endpoint was the proportion of infants who were sitting without support after 12 months of treatment (defined as 'sits without support for at least 5 seconds' as assessed in Item 22 of the BSID-III Gross Motor Scale). Proportion of CHOP

INTEND responders (≥4-point score increase from baseline at Month 12), proportion of motor milestone responders as assessed by HINE-2 at Month 12, proportion of infants who achieve the attainment levels of the motor milestones as assessed in the HINE-2 (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing and walking) at Month 12, time to death or permanent ventilation and overall survival were secondary endpoints, among others.

In general, definition of endpoints were similar between the two studies. In ENDEAR, event-free survival was defined as time to death or permanent assisted ventilation. Permanent assisted ventilation was defined as tracheostomy or ≥16 hours of ventilatory support per day for >21 continuous days in the absence of an acute reversible event. In FIREFISH, the corresponding endpoints is ventilation-free survival, also defined as time to death or permanent ventilation. Permanent ventilation was defined as >16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event; or tracheostomy.

Motor-milestone response (as assessed by HINE-2) was defined as an improvement if more motor milestones show improvement than show worsening. An improvement in a motor milestone is defined as at least a 2-point increase in ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening is defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing, or walking. This definition was applied in ENDEAR and in FIREFISH. In FIREFISH, infants who die or withdraw were classified as non-responders. Infants with a totally missing HINE-2 assessment at month 12 were also classified as non-responders.

Analysis populations

In ENDEAR, the ITT set, defined as all infants who were randomized and received at least one dose of nusinersen or sham procedure, was used for event-free survival and overall survival. For the proportion of CHOP INTEND responders and proportion of motor milestone responders, an efficacy set was used. This efficacy set was 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 the first dose and the data cut-off date of the final analysis. A safety set, defined as all infants who were randomised and received at least one dose of nusinersen or sham procedure, was used for safety analyses. The same patients were included in the ITT set and the safety set, but not in the efficacy set.

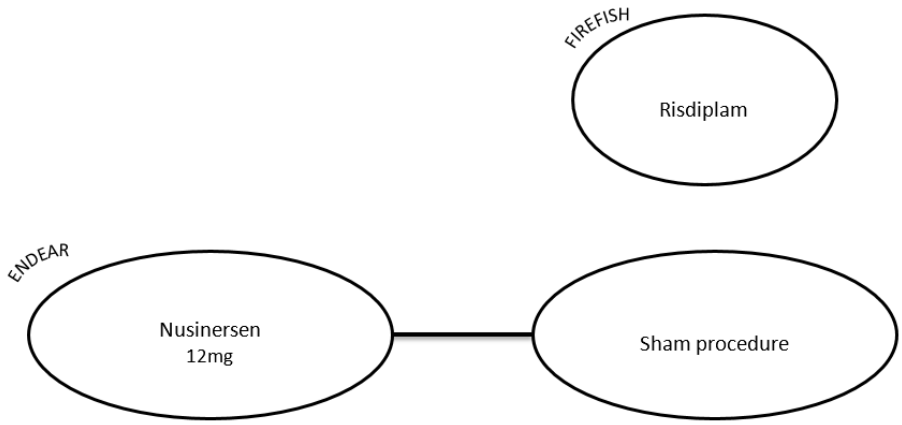
For the purpose of these analyses, an efficacy set of pooled patients from the ‘High-dose’ cohort of FIREFISH Part 1 (patients on pivotal dose selected for Part 2 of the study) and the ITT population of FIREFISH Part 2 (all infants enrolled in Part 2 of the study, regardless of whether they received treatment or not) was used for all efficacy analyses. A safety set consisting of all infants who receive at least one dose of study medication of the same pooled population were used for all safety analyses.

Network of evidence

The network of evidence for Type 1 SMA is illustrated in Figure 6. The network is disconnected; therefore, it is not possible to conduct a regular NMA. Two approaches were taken in indirectly comparing between risdiplam and BSC: naïve comparison and a comparison based on a population matching technique (unanchored MAIC) to adjust for observed differences between trial characteristics. This is to account for the fact that in

disconnected networks, analyses based on non-comparative trials could potentially be confounded by prognostic factors. The approach of implementing both a naïve and adjusted comparison is in line with NICE DSU guidance (79, 80).

Figure 6*:* Network in Type 1 SMA



B.2.9.3 Methods

The methods applied in the ITC to compare risdiplam to BSC in Type 1 SMA in the naïve comparison and the unanchored MAIC are described in Appendix M.

Predictive Factors and Effect modifiers

A literature review was undertaken to identify prognostic and predictive factors in Type 1 and Type 2/3 SMA and inform the MAIC analysis. EMBASE and Medline databases were searched for RCTs and observational studies using SMA disease terms. Two manuscripts on the results in Type 1 and Type 2/3 SMA respectively will soon be submitted for publication (82, 83).

Characteristics that were considered as matching factors for the MAIC analysis in Type 1 SMA along with the rationale for inclusion or exclusion are presented in Table 32. The selection of characteristics was based on the availability of baseline characteristics in the trials, predictive and/or prognostic factors identified in the literature review as well as feedback from the internal medical team at Roche and external medical experts.

Table 32: Covariates in Type 1 ITC analyses

Characteristic	Included/ Excluded	Justification
Mean age at first dose	Included	• Age characteristics are most commonly reported as prognostic • Age of at first dose is the most reliable measure in clinical trials. • [redacted] (82)
Duration of symptoms/disease	Included	• Flagged by internal and external medical experts • Associated with efficacy of nusinersen in subgroup analyses of the ENDEAR trial (56)

Mean baseline total CHOP INTEND score	Included	• [redacted] (82) • CHOP INTEND is seen as a stronger indicator than HINE-2 as was developed based on infants with SMA type 1 (84) and is more granular than HINE-2 (85)
Mean age at symptom onset	Excluded	• [redacted] (82) • Excluded in comparison against ENDEAR, as age at first dose and duration of symptoms were already included and considered more reliable compared to age at symptom in a trial setting.
Mean age at diagnosis	Excluded	• Age at diagnosis was not specifically flagged by the review and is subject to local accessibility of genetical analyses, hence highly variable across centers
Mean weight	Excluded	• Percentile of growth curve may be relevant, but this was not reported
Gender	Excluded	• [redacted] (82)
Race	Excluded	• Not flagged by prognostic review or medical experts
Mean HINE-2 score	Excluded	• CHOP INTEND already included as seen as a stronger indicator of motor function
Ulnar CMAP amplitude	Excluded	• CHOP INTEND already included as seen as a strong indicator of motor function
Peroneal CMAP amplitude	Excluded	• Not reported in FIREFISH

Analyses

Table 33 shows the list of analyses conducted for risdiplam versus BSC in type 1 SMA.

Table 33: List of analyses for Risdiplam vs. BSC in Type 1 SMA

Outcomes	Effect size	Timepoint	Approach	Matching factors
Event-free survival (death or permanent ventilation)	HR	- ENDEAR : All data up to data cut - FIREFISH: All data up to data cut	Unanchored MAIC	- Age at first dose in days - Duration of symptoms in weeks - Total CHOP-INTEND score at baseline
Overall survival	HR			
HINE-2, proportion of patients with motor milestone response	OR	- ENDEAR: Latest visit before data cut (median follow-up of 280 days) - FIREFISH base case: Latest visit 6 months prior to data cut (median follow-up of 283 days) - FIREFISH scenario: At 12 month visit	Unanchored MAIC	
HINE-2, proportion of patients with full head control	OR			
HINE-2, proportion of patients achieving sitting without support	OR			
HINE-2, proportion of patients achieving sitting with or without support	OR			
HINE-2, proportion of patients achieving rolling	OR			
HINE-2, proportion of patients achieving standing	OR			
CHOP-INTEND, proportion of	OR			

patients with ≥4 point improvement from baseline				
CHOP-INTEND, proportion of patients with score of ≥40	OR			
Adverse Events	OR	- ENDEAR: At data cut - FIREFISH base case: At 6 months prior to data cut - FIREFISH scenario: At data cut	Unanchored MAIC	
Adverse Events leading to discontinuation	OR			
Serious Adverse Events	OR			

B.2.9.4 Results

Both a naïve comparison and an MAIC analysis were conducted for the comparison of risdiplam to BSC in Type 1 SMA. Results from both analyses are presented in the following sections.

As noted earlier, enrolment criteria were similar between the two trials (FIREFISH and ENDEAR) and the populations are broadly comparable. However, a population-adjusted comparison was also performed for methodological completeness and for assessing the impact on results. Table 34 provides an overview over key baseline characteristics of risdiplam before and after matching, compared to the ENDEAR baseline characteristics (mean of both arms). The risdiplam baseline characteristics show that matching to the ENDEAR trial characteristics was successful. For all three selected matching factors (age at first dose, disease duration at screening and CHOP-INTEND score at baseline), risdiplam baseline characteristics post-matching were equal to the ENDEAR baseline characteristics (mean of both arms).

The ESS was reduced to 36.5 from a total sample size of 58 FIREFISH patients. Figure 7 displays the distribution of the rescaled weights. A high number of patients received weights of zero or close to zero; consistent with the reduction in sample size.

Table 34: FIREFISH baseline characteristics post ENDEAR-matching

Baseline characteristic	Pre-Matching: Risdiplam (Pooled FIREFISH)	Post-matching: Risdiplam (Pooled FIREFISH matching-adjusted to ENDEAR)	Nusinersen & BSC (ENDEAR)
Sample size (ESS)	58	[redacted]	121
Mean age at first dose in days	[redacted]	[redacted]	**169 days**
Female gender	57%	[redacted]	55%
Mean age at symptom onset in days	[redacted]	[redacted]	60 days
Mean disease duration at screening in days	[redacted]	[redacted]	**94 days**
Mean age at diagnosis in weeks	[redacted]	[redacted]	14.3 weeks
Mean score on CHOP-INTEND	[redacted]	[redacted]	**27.24**
Mean HINE-2 score	[redacted]	[redacted]	1.37
Patients with ventilatory support	[redacted]	[redacted]	22%

Figure 7: Histogram of re-scaled weights in the ENDEAR-matched FIREFISH population (total N=58)

Survival outcomes were assessed using data from the 12-months FIREFISH data cuts. Analyses of binary outcomes was conducted on two FIREFISH datasets:

i. Base case: Using FIREFISH data up until 6 months prior to datacut. This modified dataset has a similar follow-up duration (283 days) to the ENDEAR trial (ENDEAR was terminated early; median time on study in the nusinersen arm was 280 days) (56) and ensures that the populations are more comparable
ii. Scenario: Using 12-months FIREFISH data, a scenario that would be more favourable for risdiplam vs BSC

Results are provided both from a naïve comparison and from a MAIC analysis. Results of the base-case analysis are presented in the main document of this submission and the results of the scenario using 12-months FIREFISH data are presented in Appendix M.

Ventilation-free survival

Time to event analyses were conducted on the ventilation-free survival endpoints and hazard ratios were calculated based on a Cox proportional hazards model. Analyses were conducted using 12-months FIREFISH data. Differences in follow-up duration are less relevant for survival analyses as information over all time points is taken into account, unlike in analyses of binary outcomes.

The analysis results of ventilation-free survival are provided in Figure 8 and Table 35. The results of both unadjusted (naïve) analysis and MAIC are similar and suggest that risdiplam is more effective than BSC. The hazard ratio of risdiplam versus BSC is [redacted] in the naïve analysis and [redacted] in the MAIC analysis.

Figure 8: Ventilation-free survival Kaplan-Meier curves

Table 35: Ventilation-free survival hazard ratios

Comparator (STUDY)	Naïve Comparison		MAIC	
	Pre-match Number of events / Sample Size	Hazard Ratio for Risdiplam against Comparator (95%CI)	Post-match Weighted number of events / Sum of weights	Hazard Ratio for Risdiplam against Comparator (95%CI)
Risdiplam (FIREFISH)	8/58	[redacted]	5.12/44.42	[redacted]
BSC (ENDEAR)	28/41	[redacted]	28/41	[redacted]

CI, Confidence Intervals (Bootstrap; N=1000 Bootstrap samples)

Overall survival

Time to event analyses were conducted on the overall survival endpoints and hazard ratios were calculated based on a Cox proportional hazards model. Analyses were conducted

using 12-months FIREFISH data. Differences in follow-up duration are less relevant for survival analyses as information over all time points is taken into account, unlike in analyses of binary outcomes.

Analysis results of overall survival are provided in Figure 9 and Table 36. The results of both unadjusted (naïve) analysis and MAIC suggest that risdiplam is more effective than BSC. The hazard ratio of risdiplam versus BSC is [redacted] in the naïve analysis and is further reduced to [redacted] in the MAIC analysis.

Figure 9: Overall survival Kaplan-Meier curves

[redacted]

Table 36: Overall survival hazard ratios

Comparator (STUDY)	Naïve Comparison		MAIC	
	Pre-match Number of events / Sample Size	Hazard Ratio for Risdiplam against Comparator (95%CI)	Post-match Weighted number of events / Sum of weights	Hazard Ratio for Risdiplam against Comparator (95%CI)
Risdiplam (FIREFISH)	5/58	[redacted]	2.34/44.42	[redacted]
Nusinersen (ENDEAR)	13/80	[redacted]	13/80	[redacted]
BSC (ENDEAR)	16/41	[redacted]	16/41	[redacted]

CI, Confidence Intervals (Bootstrap; N=1000 Bootstrap samples)

HINE-2

ITC analyses were conducted for a list of HINE-2 endpoints, including motor milestone response and achievement of the following milestones: Full head control, rolling (supine to prone rolling), sitting without support (stable sits and pivots), sitting with and without support (sits with support at hips, props, stable sit and pivots), standing (with support and unaided).

Analyses were conducted using FIREFISH data (i) with a modified dataset using the latest visit up to 6 months prior to datacut (base case analysis) and (ii) at the 12-month visit. As ENDEAR had a shorter follow-up duration compared to FIREFISH, the analysis using 12-months data would be biased in favour of risdiplam. The modified dataset using data up to 6 months prior to data cut has a median follow-up duration of 283 days, which is similar to the follow-up of ENDEAR (280 days). Hence, analyses with the modified data set are the base case analyses.

(i) Base case analysis: Results using FIREFISH data up until 6 months prior to data cut

Results of the analysis using FIREFISH data up until 6 months prior to data cut (median follow-up of 283 days) are presented in Table 37.

MAIC results in this analysis suggest that risdiplam is more effective than BSC in terms of HINE-2 motor milestone response ([redacted]), the primary endpoint of ENDEAR. The analyses also suggest superiority on achievement of full head control ([redacted]), sitting without support ([redacted]) and sitting with and without support endpoints

([redacted]) with estimates that favour risdiplam over BSC (OR <1). For the rolling and standing motor milestones, no relative efficacy estimates (ORs) were calculated due to 0 events for both risdiplam and BSC.

The naïve analysis also produced similar results, suggesting that risdiplam is more effective than BSC on the primary endpoint of ENDEAR, HINE-2 motor milestone response ([redacted]). On the full head control, sitting without support milestones and sitting with and without support milestones, the analysis also showed improved efficacy for risdiplam vs. BSC, but with ORs of more conservative point estimate compared to the MAIC analysis (Table 37). Similarly to the MAIC analysis, for the milestones of rolling and standing no comparative efficacy estimates could be produced as no milestone achievements were recorded for either arm.

Table 37: HINE-2 motor milestones using FIREFISH data up until 6 months prior to data cut

Milestone	Comparator (STUDY)	Naïve Comparison		MAIC	
		Pre-match Number of responders / Sample size (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Post-match Weighted number of responders / Sum of weights (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)
Motor milestone response	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Full head control	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Rolling (supine to prone rolling)	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Sitting without support (stable sits and pivots)	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Sitting with and without support (sits with support at hips, props, stable sit and pivots)	Risdiplam‡ (FIREFISH)	[redacted]		[redacted]	
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]

Standing (with support and unaided)	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

‡ HINE motor milestone achievement in infants at the later of Days 0, 119, 245 and 364

§ HINE motor milestone achievement in infants at the later of Days 183, 302 and 394

* ORs calculated using half-cell correction

° Clopper-Pearson CIs

† No ORs were calculated due to 0 events in both arms.

(ii) Sensitivity analysis: HINE-2 results using FIREFISH data at 12 months

Presented in Appendix M.

CHOP-INTEND

ITC analyses were conducted for two CHOP-INTEND endpoints: CHOP-INTEND score improvement of at least 4 points and CHOP-INTEND score achievement of at least 40 points.

Analyses were conducted using FIREFISH data (i) with a modified dataset using the latest visit up to 6 months prior to data cut and (ii) at the 12-month visit. As ENDEAR had a shorter follow-up duration compared to FIREFISH, the analysis using 12-months data would be biased in favour of risdiplam. The modified dataset using data up to 6 months prior to data cut has a median follow-up duration of 283 days, which is similar to the follow-up of ENDEAR (280 days). Hence, analyses with the modified data set are the base case analyses.

(i) Base case analysis: results using FIREFISH data up until 6 months prior to data cut

Results of the analysis using FIREFISH data up until 6 months prior to data cut are presented in Table 38.

Results from both the naïve and MAIC analyses suggest risdiplam to be superior to BSC in terms of CHOP-INTEND score improvement of ≥4 points and achievement of ≥40, with the MAIC analysis demonstrating stronger signs of superior efficacy (higher ORs) for risdiplam compared to the naïve analysis.

Table 38: CHOP-INTEND results using FIREFISH data up until 6 months prior to data cut

Endpoint	Comparator (STUDY)	Naïve Comparison		MAIC	
		Pre-match Number of responders / Sample size (% Responders	Odds Ratio for Risdiplam against Comparator (95%CI)	Post-match Weighted number of responders / Sum of weights	Odds Ratio for Risdiplam against Comparator (95%CI)

		[95%CI])		(% Responders [95%CI])	
CHOP-INTEND score improvement ≥4 points	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
CHOP-INTEND score achievement ≥40 points	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

‡ CHOP-INTEND score at the later of Days 0, 119, 182, 245, 301, 364 and 427

§ CHOP-INTEND score at the later of Days 183, 302 and 394

° Clopper-Pearson CIs

(ii) Sensitivity Analysis: CHOP-INTEND results using 12 month FIREFISH data

Presented in Appendix M

Safety

Indirect treatment comparison analyses were conducted for three safety outcomes: Any AE, any AE leading to discontinuation and any serious AE.

Analyses were conducted using FIREFISH data (i) with a modified dataset using the latest visit up to 6 months prior to data cut and (ii) at the 12-month visit. As ENDEAR had a shorter follow-up duration compared to FIREFISH, the analysis using 12-months data would be biased in favour of BSC (less time to observe and record adverse events). The modified dataset using data up to 6 months prior to data cut has a median follow-up duration of 283 days, which is similar to the follow-up of ENDEAR (280 days). Hence, analyses with the modified data set are the base case analyses.

(i) Base Case Analysis: Safety results using FIREFISH data up until 6 months prior to data cut

Results of the analysis using FIREFISH data up until 6 months prior to data cut are presented in Table 39. The results suggest that risdiplam may be associated with fewer reporting of adverse events leading to discontinuation and any serious adverse event compared to BSC in both the naïve comparison and MAIC analysis. In terms of any adverse event, the analyses cannot differentiate effects between risdiplam and BSC. The point estimates indicate that risdiplam could be associated with fewer AEs compared to BSC, however the confidence intervals include ORs below and above 1.

Table 39: Safety results using FIREFISH data up until 6 months prior to data cut.

Endpoint	Comparator (STUDY)	Naïve Comparison		MAIC	
		Pre-match Number of events / Sample size	Odds Ratio for Risdiplam against Comparator	Post-match Weighted number events / Sum of	Odds Ratio for Risdiplam against Comparator

		(% with AE [95%CI])	(95%CI)	weights (% with AE [95%CI])	(95%CI)
Any adverse event	Risdiplam (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Any adverse event leading to discontinuation	Risdiplam* (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Any serious adverse event	Risdiplam (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)
*To align with the definition in ENDEAR, deaths were included as a reason for discontinuation
°Clopper-Pearson Cis

(ii) Sensitivity Analysis: Safety results using 12-month FIREFISH data

Presented in Appendix M.

B.2.9.4 Summary of Key Results

ITC analyses were conducted in the absence of head-to-head data from clinical trials to compare risdiplam to BSC in Type 1 SMA. In Type 1 SMA, a disconnected network of two studies was available: FIREFISH (risdiplam), ENDEAR (nusinersen vs BSC). As a standard NMA is not feasible in a disconnected evidence network, both a naïve comparison and a population adjustment method (MAIC) were applied, as per NICE DSU guidance (79, 80).

For the naïve analysis, an unadjusted comparison was made. For the MAIC, age at first dose, disease duration and CHOP-INTEND score were identified as predictive and/or prognostic factors and selected as the matching factors for this analysis. The matching-adjustment successfully reduced differences in mean baseline characteristics between FIREFISH and ENDEAR. However, as stated by HE experts, differences between the study populations were small and the studies were deemed as broadly comparable. Therefore, both the naïve analysis and the MAIC are potentially appropriate sources of relative efficacy estimates for risdiplam vs BSC in Type 1 SMA, with the naïve analysis providing more conservative estimates, as differences in baseline motor function are not considered.

Results from the naïve analysis were consistent with those of the MAIC analysis and suggested superior efficacy of risdiplam compared to BSC on several key endpoints, including ventilation-free survival, overall survival, HINE-2 motor milestone response and achievement of the sitting without support milestone. Results are also in line with those from a previous MAIC analyses conducted using FIREFISH Part 1 data, which also suggested superior efficacy of risdiplam compared to BSC (86).

In terms of safety, both the naïve comparison and MAIC results suggest a reduced risk of adverse events leading to discontinuation and severe adverse events, while the risk of reporting any adverse event appears to be comparable between the two treatments.

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

Strengths

There are many strengths to the ITC analyses conducted.

- The evidence networks for these analyses are based on a very comprehensive SLR looking at many endpoints and including both clinical trials and observational studies.
- Both a naïve comparison and population adjustment methodologies were used to address the challenge of having a disconnected network in Type 1 SMA, in line with NICE DSU guidance (79, 80).
- Selection of prognostic and predictive factors for the MAIC analyses was based on literature reviews (82, 83) and clinical expert opinion. Justifications for exclusion and inclusion of matching factors were clearly stated.
- A larger sample size for the comparison of treatments in Type 1 SMA was provided by pooling the 'high-dose' cohort (patients on pivotal dose) from Part 1 of FIREFISH with patients from Part 2 of FIREFISH. This decreased uncertainty of results.
- Differences between studies were addressed as much as possible. In Type 1 SMA, ENDEAR had a shorter follow up duration compared to FIREFISH due to early termination of the trial. To address this, analyses were conducted with a modified FIREFISH dataset, excluding any assessments after 6 months before data cut. Follow-up duration of this data set was similar to that of ENDEAR (~9 months of follow-up).

Limitations

Despite making as much effort as possible, the ITC analyses are also associated with some unavoidable and inherent multiple limitations.

- The disconnected evidence network in Type 1 SMA limited the choice of ITC methodologies, as standard NMA methods require common comparators (79, 80). We used both a naïve comparison and population adjustment methods (as per NICE DSU guidance (79, 80)) to assess the impact on results and to explore and attempt to reduce biases resulting from study differences.
- Although FIREFISH was successfully matched to ENDEAR in the MAIC analysis, results could still be confounded by unadjusted characteristics or unreported study differences. Improvements in survival, as observed in the results of the MAIC analyses in Type 1 SMA, could be a result of changes in standard of care around respiratory support (87, 88) and not purely an effect of treatment with risdiplam. However, trials often employ a more conservative approach, tending to use more supportive care than mandated, and would therefore be less impacted by such changes. Further, improvements with risdiplam were also seen consistently across motor function outcomes (CHOP-INTEND and HINE-2), which would not be impacted by proactive ventilatory support.
- Sham control in the ENDEAR study was assumed to reflect BSC in the UK.

- Finally, a general limitation of the MAIC approach is that by matching to the comparator trial, the target population is assumed to be that of the comparator trial. This is however expected to be less of a limitation in the comparison in Type 1 SMA, where study populations were fairly similar.

B.2.10 Adverse reactions

In order to provide a complete assessment of the safety of risdiplam in people with SMA, the available safety data were pooled and analysed. The following studies have been integrated for pooling:

- FIREFISH; Part 1 and Part 2; n=62 people with infantile-onset SMA (Type 1)
- SUNFISH; Part 1 and Part 2; n=231 people with later-onset SMA (Type 2 and 3)
- JEWELFISH; n=174 including 159 people with later-onset SMA (Type 2 and 3) and 15 people with infantile-onset SMA (Type 1)

Please refer to Appendix F for a summary of the safety results from the individual FIREFISH, SUNFISH and JEWELFISH studies, along with additional analyses from the pooled analysis not presented herein.

Out of a total of 467 patients enrolled in these 3 studies, 465 patients received at least one dose of risdiplam and are included in the safety population for the pooled safety analysis.

The pooling strategy was determined to provide an integrated safety analysis of all multiple-dose studies in SMA (All People with SMA population, N=465) and to allow a broad benefit-risk assessment by SMA type (type 1 versus type 2 and 3) to support reimbursement as a treatment for paediatric and adult people with SMA. Full details of the integrated safety analysis can be found in the Summary of Clinical Safety (2.7.4) provided in the reference pack of this submission (89).

Non-integrated safety data from the following studies are provided in Appendix F:

- Safety data from the 12-month double-blind placebo-controlled period from SUNFISH Part 2 (people with type 2 and 3 SMA) to show double-blind placebo comparison
- Studies in healthy volunteers and subjects with hepatic impairment (Studies BP39122, BP29840, NP39625, BP41361, BP40995)

The demographic characteristics of the All SMA Patients population were generally consistent with those expected for a broad population of people with type 1 and type 2 and 3 SMA. There was a higher representation of people with type 2 and 3 SMA (n=388) versus type 1 SMA (n=77) in this pooled population. Baseline demographics and disease characteristics of the integrated safety population are summarised below.

Table 40: Summary of baseline demographic and disease characteristics (integrated safety population)

	Type 1 n=77	Type 2 and Type 3 n=388	All Patients N=465
Mean age at onset of symptoms, months (SD)	1.96 (1.41)	18.85 (30.06)	16.05 (28.17)
Mean age at diagnosis, months (SD)	3.20 (1.88)	26.53 (36.14)	22.67 (34.14)
Mean age at first dose, years (SD)	1.63 (3.56)	14.00 (9.61)	11.95 (10.01)
Age group at first dose, n (%) 0 to <2 years	67 (87.0)	0	67 (14.4)

2 to <12 years	7 (9.1)	182 (46.9)	189 (40.6)
12 to <18 years	1 (1.3)	118 (30.4)	119 (25.6)
≥18 years	2 (2.6)	88 (22.7)	90 (19.4)
Gender, n (%)			
Male	33 (42.9)	200 (51.5)	233 (50.1)
Race, n (%)			
Asian	18 (23.4)	45 (11.6)	63 (13.5)
Black of African American	1 (1.3)	2 (0.5)	3 (0.6)
White	46 (59.7)	297 (76.5)	343 (73.8)
Multiple	0	2 (0.5)	2 (0.4)
Unknown	12 (15.6)	42 (10.8)	54 (11.6)
Mean baseline weight percentile (SD)	31.85 (29.50)	36.75 (35.97)	35.11 (33.97)
Mean baseline height percentile (SD)	53.90 (35.96)	35.48 (30.81)	39.18 (32.71)
SMA type, n (%)			
Type 1	77 (100)	0	77 (16.6)
Type 2	0	272 (70.1)	272 (58.5)
Type 3	0	116 (29.9)	116 (24.9)
Ambulatory status, n (%)			
Ambulatory	0	24 (6.2)	24 (5.2)
Non-ambulatory	9 (11.7)	364 (93.8)	373 (80.2)
Scoliosis, n (%)			
Yes	7 (9.1)	280 (72.2)	287 (61.7)
No	2 (2.6)	108 (27.8)	110 (23.7)
Degree of curvature due to scoliosis, n (%)			
0–10	0	42 (10.8)	42 (9.0)
10–40	3 (3.9)	95 (24.5)	98 (21.1)
>40	3 (3.9)	125 (32.2)	128 (27.5)
Number of fractures, n (%)			
None	9 (11.7)	279 (71.9)	288 (61.9)
1–2	0	85 (21.9)	85 (18.3)
3–5	0	22 (5.7)	22 (4.7)
≥6	0	1 (0.3)	1 (0.2)

SD, standard deviation; SMA, spinal muscular atrophy
Source: (89)

Extent of exposure to study treatment

In the All People with SMA population (n=465), the median duration of exposure to risdiplam was 12.68 months (range: 0.0–38.9). A total of 158 patients (34.0%) had been treated for up to 6 months, 69 patients (14.8%) for more than 6 months up to 12 months, 85 patients each (18.3%) for between 12 months and 18 months and 18 to 24 months, and 68 patients (14.6%) for more than 24 months. The overall exposure was 521.4 patient-years (PY). The overall exposure to the pivotal dose was 480.9 PY, corresponding to approximately 92% of the overall exposure time (PY).

All patients had received at least 78.5% of the total number of prescribed doses (dose intensity). Median dose intensity was 100%. An overview of exposure to risdiplam is provided below.

Table 41: Exposure to risdiplam

	Type 1 n=77	Type 2 and Type 3 n=388	All Patients N=465
Active exposure duration (months)			

Median	15.24	9.30	12.68
(range)	(0.1–34.6)	(0.0–38.9)	(0.0–38.9)
Total patient years	92.1	429.2	521.4
Pivotal dose exposure duration (months)	n=74	n=388	n=462
Median	13.98	9.13	11.98
(range)	(0.1–23.6)	(0.0–34.5)	(0.0–34.5)
Total patient years	77.9	403.0	480.9
Dose intensity, (%)			
Median	100	100	100
(range)	(91.7–100)	(78.5–100)	(78.5–100)
Exposure time in patient-years (PY)			
Total	92.1	429.2	521.4
0–≤6 months	33.6	164.2	197.8
>6–≤12 months	28.9	100.6	129.5
>12–≤18 months	19.1	87.4	106.4
>18–≤24 months	7.8	39.4	47.2
>24–≤30 months	2.1	25.7	27.8
>30–≤36 months	0.7	11.1	11.8
>36 months	0.0	0.8	0.8

Source:(89)

Overview of adverse events

The integrated analysis of adverse events (AEs) will focus mainly on rates per 100PY in order to adjust for differences in exposure time between the SMA pools

Table 42: Overview of adverse events by rates per 100PY

	Type 1 n=77 PY=92.1	**Type 2 and Type 3 n=388 PY=429.2**	**All Patients N=465 PY=521.4**
Overall total number of events			
Number of AEs	532	2479	3011
Rate per 100PY	577.37	577.53	577.50
(95% CI)	(529.34, 628.58	(555.02, 600.72)	(557.06, 598.51)
Number of fatal AEs (Grade 5)			
Number of AEs	7*	0	7
Rate per 100PY	7.60	0.00	1.34
(95% CI)	(3.05, 15.65)	NE	(0.54, 2.77)
Life-threatening AEs (Grade 4)			
Number of AEs	20	5	25
Rate per 100PY	21.71	1.16	4.79
(95% CI)	(13.26, 33.52)	(0.38, 2.72)	(3.10, 7.08)
Moderate AEs (Grade 3)			
Number of AEs	46	92	138
Rate per 100PY	49.92	21.43	26.47
(95% CI)	(36.55, 66.59)	(17.28, 26.29)	(22.24, 31.27)
Serious AEs			
Number of AEs	86	108	194
Rate per 100PY	93.33	25.16	37.21
(95% CI)	(74.66, 115.27)	(20.64, 30.38)	(32.16, 42.83)
Related AEs			
Number of AEs	15	85	100
Rate per 100PY	16. 28	19.80	19.18

(95% CI)	(9.11, 26.85)	(15.82, 24.49)	(15.61, 23.33)

* Six patients died in Study BP39056 (FIREFISH); 1 patient experienced two Grade 5 AEs leading to death (cardiac arrest and respiratory failure).
AE, adverse events; CI, confidence intervals; PY patient-years
Source: (89)

The overall AE profile for risdiplam by frequency is summarised below.

Table 43: Overview of adverse events by frequency

n, (%)	Type 1 n=77	Type 2 and Type 3 n=388	All Patients N=465
Total number of people with at least one AE	72 (93.5)	321 (82.7)	393 (84.5)
Total number of AEs, n	532	2479	3011
Total number of deaths	7 (9.1)	0	7 (1.5)
Total number of people withdrawn from study due to an AE	0	0	0
Total number of people with at least one			
AE with fatal outcome	6 (7.8)	0	6 (1.3)
Serious AE	42 (54.5)	61 (15.7)	103 (22.2)
Serious AE leading to withdrawal from treatment	1 (1.3)	0	1 (0.2)
Serious AE leading to dose modification/treatment interruption	2 (2.6)	13 (3.4)	15 (3.2)
Related serious AE	1 (1.3)	1 (0.3)	2 (0.4)
AE leading to withdrawal from treatment	1 (1.3)	0	1 (0.2)
AE leading to dose modification/interruption	3 (3.9)	30 (7.7)	33 (7.1)
Related AE	9 (11.7)	56 (14.4)	65 (14.0)
Related AE leading to withdrawal from treatment	0	0	0
Related AE leading to dose modification/interruption	0	1 (0.3)	1 (0.2)
Grade 3–5 AE	35 (45.5)	53 (13.7)	88 (18.9)

AE, adverse event
Source: (89)

Common adverse events

Overall, the AEs reported at the highest rates per 100 PY were headache (55.81 [95% CI: 49.58, 62.61]), pyrexia (43.15 [95% CI: 37.70, 49.18]), upper respiratory tract infection (41.62 [95% CI: 36.27, 47.54]), and nasopharyngitis (27.81 [95% CI: 23.47, 32.72]).

Among AEs reported at rates ≥10 per 100PY, there were higher rates of headache, nausea, and cough in people with type 2 and 3 SMA compared with type 1 SMA patients. Adverse events reported with higher rates in people with type 1 SMA were pyrexia, upper respiratory tract infection, pneumonia, constipation, respiratory tract infection, rhinitis, and teething. The differences in AE rates between type 1 SMA and type 2 and 3 SMA populations appeared to be driven mainly by differences in age; the higher rate of pneumonia in people with type 1 SMA may be associated with higher disease severity.

A summary of AEs by preferred term (PT) reported at a rate of ≥10 per 100PY in any population are summarised below.

Table 44: Adverse events reported at a rate ≥10 per 100PY by preferred term

Preferred term	Type 1	Type 2 and Type 3	All Patients

Rate per 100PY (95% CI)	n=77	n=388	N=465
Headache	0 (NE)	67.79 (60.23, 76.05)	55.81 (49.58, 62.61)
Pyrexia	91.16 (72.72, 112.87)	32.85 (27.65, 38.74)	43.15 (37.70, 49.18)
Upper respiratory tract infection	60.78 (45.91, 78.92)	37.51 (31.94, 43.77)	41.62 (36.27, 47.54)
Nasopharyngitis	21.71 (13.26, 33.52)	29.12 (24.24, 34.70)	27.81 (23.47, 32.72)
Vomiting	22.79 (14.11, 34.84)	22.83 (18.54, 27.82)	22.82 (18.91, 27.31)
Cough	8.68 (3.75, 17.11)	20.50 (16.44, 25.26)	18.41 (14.91, 22.48)
Diarrhoea	13.02 (6.73, 22.75)	16.77 (13.12, 21.12)	16.11 (12.85, 19.95)
Pneumonia	28.22 (18.43, 41.34)	9.09 (6.46, 12.42)	12.47 (9.62, 15.89)
Gastroenteritis	5.43 (1.76, 12.66)	10.02 (7.25, 13.49)	9.21 (6.79, 12.21)
Nausea	0 (NE)	10.72 (7.85, 14.29)	8.82 (6.46, 11.77)
Constipation	14.11 (7.51, 24.13)	6.99 (4.72, 9.98)	8.25 (5.97, 11.11)
Respiratory tract infection	13.02 (6.73, 22.75)	6.52 (4.33, 9.43)	7.67 (5.48, 10.45)
Rhinitis	11.94 (5.96, 21.36)	3.96 (2.31, 6.34)	5.37 (3.57, 7.76)
Teething	14.11 (7.51, 24.13)	0 (NE)	2.49 (1.33, 4.26)

Source: (89)

Treatment-related adverse events

The majority of AEs were reported as unrelated to study treatment. In the All People with SMA population, 65 patients (14.0%) had at least 1 AE that was reported as related to study treatment, and a total of 100 related AEs were reported. The rate of AEs reported as related to study treatment was 19.18 per 100PY (95% CI: 15.61, 23.33) and was comparable in both SMA populations. Overall, 3.3% of all reported AEs were reported as related. The rate of AEs reported as related to study treatment was 19.18 per 100PY (95% CI: 15.61, 23.33), and comparable between people with type 1 SMA and people with type 2 and 3 SMA.

The most frequently reported related AE by PT was diarrhoea (9 patients, 1.9%), followed by nausea (7 patients, 1.5%), rash (5 patients, 1.1%), and headache (5 patients, 1.1%). The majority of AEs resolved. The rate of AEs reported as related to study treatment decreased markedly approximately 5.5-fold over time and to a greater extent than the overall AE rate, between the 0–6 months period (40.95 per 100 PY [95% CI: 32.52, 50.90]) and the 6-12 months period (7.72 per 100PY [95% CI: 3.70, 14.20]). This decrease in rate of related AEs was comparable in both SMA populations.

Table 45: AE related to study treatment rate adjusted for patient-years at risk

	Type 1 n=77	Type 2 and Type 3 n=388	All Patients N=465
Overall			
Total patient-years at risk	92.1	429.2	521.4

No. AE	15	85	100
No. of AE per 100 PY (95% CI)	16.28 (9.11, 26.85)	19.80 (15.82, 24.49)	19.18 (15.61, 23.33)
0–≤6 months			
Total patient-years at risk	33.6	164.2	197.8
No. AE	13	68	81
No. of AE per 100 PY (95% CI)	38.64 (20.57, 66.07)	41.42 (32.17, 52.52)	40.95 (32.52, 50.90)
>6–≤12 months			
Total patient-years at risk	28.9	100.6	129.5
No. AE	2	8	10
No. of AE per 100 PY (95% CI)	6.92 (0.84, 25.01)	7.95 (3.43, 15.67)	7.72 (3.70, 14.20)
>12–≤18 months			
Total patient-years at risk	19.1	87.4	106.4
No. AE	0	5	5
No. of AE per 100 PY (95% CI)	0.00 (NE)	5.72 (1.86, 13.36)	4.70 (1.53, 10.96)
>18–≤24 months			
Total patient-years at risk	7.8	39.4	47.2
No. AE	0	2	2
No. of AE per 100 PY (95% CI)	0.00 (NE)	5.07 (0.61, 18.32)	4.24 (0.51, 15.30)

AE, adverse event; CI, confidence interval; PY, patient-year
Source: (89)

Deaths

At the time of the CCOD for each study, 6 deaths had been reported during the treatment period, all of which were infants with type 1 SMA in FIREFISH who died of SMA-related respiratory complications (3 deaths in Part 1 and 3 deaths in Part 2). One additional patient died 3.5 months after discontinuation from risdiplam therapy during the safety follow-up period.

The cause of death was classified as “progressive disease” in 6 out of 7 cases and as “adverse event” (pneumonia) for 1 patient. None of the deaths were considered by the investigator to be related to study treatment.

The deaths that occurred during the treatment period are not suspected to be due to lack of therapeutic effect of risdiplam, based on the following considerations:

- All six patients who died had advanced disease at baseline: they all had disease duration greater than 3 months at baseline and 4 patients were older than 5 months of age at first dose.
- Four out of 6 patients died within 3 months (range: 21–79 days) of starting treatment with risdiplam, prior to any efficacy assessments and in the 2 people with available post-baseline efficacy assessments, there was evidence of improved motor function, as indicated by increases from baseline in the CHOP-INTEND total score.

B.2.10.1 Summary of safety in JEWELFISH: treatment naïve vs prior treated patients

A total of 90 patients were included in the treatment-non-naive group (76 patients previously treated with nusinersen and 14 patients previously treated with onasemnogene abeparvovec [AVXS-101] in JEWELFISH). The rate of AEs per 100 PY was comparable between treatment-non-naïve patients in JEWELFISH and treatment-naïve people with SMA who were treated with risdiplam in SUNFISH (Part 1 and Part 2) and FIREFISH (Part 1 and Part 2).

Due to shorter median duration of treatment in treatment non-naïve patients compared with treatment-naïve patients (FIREFISH Part 1: 23.33 months [range: 0.6–34.6]; FIREFISH Part 2: 15.24 months [range 1.6–20.1]; JEWELFISH: 3.02 months [range: 0.0–32.8]; SUNFISH Part 1: 996.0 days [range: 287.0–1183.0 days]; SUNFISH Part 2: 540.0 days [range: 100.0–807.0]) the analysis will focus on the 0–≤6 month treatment period, where exposure times are most comparable (Naïve: type 1: 29.8 PY, type 2/3: 114.6 PY; Non-naïve: type 1: 3.1 PY, type 2/3: 22.1 PY).

In both SMA populations, the AE profile was comparable in treatment-naïve and non-naïve patients and reflective of the underlying disease. The impact of previous treatment was noticeable in the type 1 population where patients who had been on previous approved SMA therapies did not experience any Grade 4 or Grade 5 (fatal) events; however, due to the limited data in the non-naïve type 1 population, these results should be interpreted with caution.

People with type 1 SMA

During the 0–≤6 month treatment period, a total of 13 people with type 1 SMA who were previously treated with nusinersen (n=9) or AVXS-101 (n=4) had a total of 3.1 patient-years at risk (nusinersen: 2.8 PY, AVXS-101: 0.3 PY). The rate of AEs in all people with type 1 SMA was comparable between the treatment non-naive and the treatment-naïve populations (treatment non-naive: 580.27 per 100 PY [95% CI: 343.91, 917.08] vs. treatment-naïve: 681.17 per 100 PY [95% CI: 590.69, 781.60]).

In both populations, the highest rates of AEs were in the Infections and infestations SOC. At least 2 AEs were reported in treatment non-naïve patients in the SOC Infections and Infestations and Respiratory, thoracic and mediastinal disorders. While the rates in the respiratory SOC were comparable, a numerically higher rate of infections was reported in the treatment non-naive patients (treatment non-naive: 354.61 per 100 PY [95% CI: 177.02, 634.50] vs. treatment-naïve: 187.91 per 100 PY [95% CI: 141.95, 244.02]). In both populations, infections were mostly affecting the respiratory tract and generally resolved with ongoing treatment with risdiplam.

The rate of SAEs in all treatment non-naïve people with type 1 SMA during the 0–≤6 month treatment period was comparable between the treatment non-naive and the treatment-naïve populations (treatment non-naive: 193.42 per 100 PY [95% CI: 70.98, 421.00] vs. treatment-naïve: 130.87 per 100 PY [95% CI: 93.06, 178.90]). SAEs were reported in more than one treatment non-naïve patient only in the SOC Infections and infestations. In both populations the most common SAEs were in the Infections and infestations SOC driven by respiratory tract infections.

The intensity of AEs reported in both populations was reflective of the previous SMA treatment, with Grade 4 and 5 AEs reported only in treatment-naïve patients.

People with type 2 and type 3 SMA

During the 0–≤6 month treatment period, a total of 77 people with type 2 and 3 SMA who were previously treated with nusinersen (n=67) or AVXS-101 (n=10) had a total of 22.1 patient-years at risk (nusinersen: 20.4 PY, AVXS-101: 1.6 PY). The rate of AEs overall was comparable in both populations (non-naïve: 932.82 per 100 PY [95% CI: 809.78, 1069.28] vs. treatment-naïve: 773.82 per 100 PY [95% CI: 723.73, 826.47]).

AEs which occurred at the highest rates were in the SOC Infections and infestations (treatment non-naïve: 271.70 per 100 PY [95% CI: 207.33, 349.73] vs. treatment-naïve: 215.48 per 100PY [95% CI: 189.45, 244.10]), with upper respiratory tract infection being the most common preferred term in both groups, followed by Gastrointestinal disorders (172.07 per 100 PY [95% CI: 121.77, 236.19] vs. 131.73 per 100 PY [95% CI: 111.56, 154.50]), and General disorders and administrative site conditions (104.15 per 100 PY [95% CI: 66.02, 156.28] vs. 61.94 per 100PY [95% CI: 48.38, 78.13]), with the most common AE being pyrexia in both groups.

A trend for a higher rate of SAEs was observed in non-naïve patients during the 0–≤6 month treatment period (treatment non-naive: 40.75 per 100 PY [95% CI: 18.64, 77.36] vs. treatment-naïve: 22.68 per 100 PY [95% CI: 14.82, 33.24]). However, this trend was not a result of a specific type of SAEs as the most common SAEs were in the Infections and infestations SOC where the rate of SAEs was similar between the treatment-naïve (13.58 per 100PY [95% CI: 2.80, 39.70]) and treatment non-naive (14.83 per 100 PY [95% CI: 8.64, 23.75]) groups. Other SOCs with 2 or more AEs in either population were: Respiratory , thoracic and mediastinal disorders (treatment non-naïve: 9.06 [95% CI: 1.10, 32.72]; treatment-naïve: 0.87 per 100 PY [95% CI: 0.02, 4.86]); General disorders and administration site conditions (treatment non-naïve: 0.0 [NE]; treatment-naïve: 1.74 per 100 PY [95% CI: 0.21, 6.30]), and Renal and urinary disorders (treatment non-naïve: 0.0 [NE]; treatment-naïve: 1.74 per 100 PY [95% CI: 0.21, 6.30]).

No Grade 5 events were reported in either population in the entire treatment period and few patients had Grade 4 events in both populations.

B.2.11 Ongoing studies

Studies in the risdiplam clinical trial programme are currently ongoing, with anticipated timelines for final analyses for each study summarised below.

Table 46: Risdiplam clinical development programme – planned data cuts and analyses

Study	Analysis	Expected timeline
[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]

In addition to the studies listed above, a further open-label Phase II study (RAINBOWFISH, NCT03779334), investigating the efficacy and safety of risdiplam in infants with genetically diagnosed and presymptomatic SMA is currently recruiting;
[redacted]

We anticipate that the entirety of data from the risdiplam clinical trial programme would be useful and appropriate to inform a re-assessment of a potential MAA for risdiplam and a decision for routine reimbursement from NICE.

B.2.12 Innovation

Risdiplam elevates SMN levels in the CNS and periphery, improving outcomes for more patients compared to treatments that increase functional SMN protein in the CNS alone.

SMA results from mutations in the SMN1 gene leading to low levels of SMN protein expression (90). SMN protein is expressed in all cells, with motor neurons shown to be very susceptible to low levels of functional SMN protein (91); however, accumulating pre-clinical evidence indicates that SMA is a multisystem disease that also affects peripheral tissues. Reduced levels of SMN protein throughout the whole body are thought to play a vital role in disease pathophysiology (92).

Therapies for SMA aim to increase the levels of SMN protein. Effective disease intervention for SMA may therefore require a body-wide correction of SMN protein levels to reverse or ameliorate disease progression. Risdiplam is a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier. It crosses the blood-brain barrier and is distributed throughout the body, increasing levels of functional SMN protein in both the CNS and periphery to a similar magnitude (66, 67). Therefore, treatment with risdiplam is expected to improve outcomes in many patients by preventing or delaying disease progression. Furthermore, risdiplam binds to two sites on the SMN2 pre-mRNA; this unique specificity results in increased levels of full-length SMN mRNA and protein, while also reducing the impact on splicing of other pre-mRNA and avoiding the possibility of off-target effects (93).

Risdiplam has been developed with support from the SMA community; Roche collaborated with the SMA Foundation, a US non-profit organisation which funded much of the preclinical work as well as PTC Pharmaceuticals to help develop the molecule.

Risdiplam is an effective and safe disease modifying therapy that will be available for all people with SMA.

The comprehensive clinical development programme provides robust evidence that risdiplam offers a clinical benefit to a broad and heterogeneous population of people with SMA, reflective of that seen in clinical practice, without restrictions or limitations on their physical conditions. In comparison with natural history studies, risdiplam significantly improved event-free survival and the proportion of people achieving motor function development milestones as assessed by HINE-2 and CHOP-INTEND among people with infantile-onset SMA. Moreover, in people with later-onset SMA, treatment with risdiplam resulted in significant changes from baseline in the MFM32 and RULM total score, while also significantly improving both the caregiver- and patient-reported SMA Independence Scale

total score, demonstrating that meaningful improvements in a challenging-to-treat population can be achieved with risdiplam.

While nusinersen is currently the only disease-modifying treatment available in the UK, there are significant gaps in nusinersen clinical trial evidence concerning the benefit it offers for the real-world SMA population, considering the limited populations studied in the pivotal studies and the restrictions due to special warnings and precautions for its use. For example, the oldest patient enrolled in CHERISH at screening was 9 years, therefore there are no controlled clinical trials of nusinersen in patients over 9 years old or in people with type 3 SMA.

As mentioned previously, the inclusion criteria for clinical studies of risdiplam allowed for the enrolment of older patients and those with more advanced disease, compared to nusinersen clinical trials. This is important since the concept of clinical benefit differs by age and disease severity, i.e., functional improvement in younger people with less severe disease would be expected due to greater functional reserve with more potential for functional gains, compared to older people with progressed disease, for whom functional stabilisation is a greatly important treatment benefit (39, 40). Moreover, it is more difficult to demonstrate improvement on scales and outcome measures in people with more severe baseline disease characteristics as age at symptom onset, duration of symptoms and functional score are among those factors that have been reported to influence outcomes in early-onset SMA.

Furthermore, risdiplam has been well tolerated in patients exposed to date, including 465 paediatric and adult patients exposed to risdiplam for up to 3 years in studies FIREFISH, SUNFISH and JEWELFISH. Potential risks identified from nonclinical safety findings were not observed in any patient; i.e., extensive and independent ophthalmologic monitoring has not shown any evidence in humans of the retinal findings seen in nonclinical monkey studies, haematologic parameters have remained stable over time, and no drug-induced skin findings have been observed. No risks were identified following the review of vital signs, physical examinations, ECG, ophthalmological assessments, and safety laboratory data. No drug-related AEs have led to withdrawal from treatment in any patient. Overall, AEs were generally resolved and were reflective of age and underlying SMA disease.

Risdiplam offers patients sustainable self- or caregiver-assisted treatment at home

Risdiplam's oral route of administration and liquid formulation presents a significant advantage over intrathecal injections for people with SMA, irrespective of age, physical status, or disease severity. It is a sustainable treatment option due to its daily home administration, given orally or via feeding tube by the patient or a caregiver, without requiring hospital clinic visits, invasive procedures or concomitant use of additional medicines.

As an oral treatment, risdiplam does not expose patients to the known risks of lumbar puncture and the adjunctive treatments, such as sedation, anaesthesia, and imaging agents that are required for intrathecal administration of nusinersen in many SMA patients. This should expand the population able to receive treatment to include those for whom other routes of administration can be challenging and even contra-indicated (e.g., severe scoliosis and spine surgery for intrathecal administration). Moreover, a significant proportion of patients eligible for nusinersen remain untreated in clinical practice, indicating challenges in clinical service pathways that may not be applicable with an orally administered therapy (94).

Home therapy is also less burdensome and costly for the healthcare system than other therapies that require regular hospital visits, invasive procedures, trained and highly skilled

medical staff for their administration, concomitant use of other drug therapies with associated adverse events, and availability of imaging technology to support drug administration, such as CT, leading to radiation exposure in day case patients. Moreover, homecare provision will also reduce the burden on hospital pharmacies as well as providing an alternative treatment option for those vulnerable patients who are unable to attend health care facilities for external factors. For instance, the COVID-19 pandemic and the global measures applied to ensure social isolation and changes in hospital priorities has added a greater level of anxiety for vulnerable people with SMA and their caregivers that need to attend hospital treatments, and in some cases has forced the postponement of elective procedures that has affected some nusinersen-treated patients.

Risdiplam rapidly increases functional SMN protein levels and is the only disease modifying therapy for people with SMA that can be initiated within hours of diagnosis

In infants and children weighing <20 kg, the dose of risdiplam varies according to weight. Infants aged between 2 months and <2 years receive 0.2 mg/kg/day and children aged 2 or more years weighing <20 kg receive 0.25 mg/kg/day. Adults and children weighing ≥20 kg receive a fixed dose of 5 mg/day.

The selected risdiplam dosing regimen ensures similar risdiplam exposure across the wide age and body weight range in the SMA patient population, from young infants to adults. Plasma steady-state levels of risdiplam are reached after approximately 2 weeks of treatment initiation; the effective half-life in SMA patients is about 50 hours. A >2-fold median increase in SMN protein was obtained at this dosing regimen in all studies, independent of SMA type. SMN protein increased rapidly within 4 weeks after treatment start, and the increased SMN protein level was maintained throughout treatment with risdiplam. Furthermore, as an oral formulation, risdiplam is able to be initiated immediately and with a rapid increase in functional SMN protein, people with SMA will be able to benefit from treatment as early as possible after diagnosis.

The unit price of a bottle of risdiplam is the same for all patients regardless of the disease type and age of the treated patient. Therefore, the weight-based dosing regimen is estimated to result in cost savings due to bottles lasting longer in infants and children weighing <20 kg and fewer bottles required over a year than for adults and children weighing ≥20 kg (a 60 mg bottle is expected to last up to 60 days in infants receiving 0.2 mg/kg/day, up to 20 days in children receiving 0.25 mg/kg/day and up to 12 days in adults and children receiving 5 mg/day).

Despite the availability of disease-modifying therapy, the remaining unmet need for innovative medicines for SMA and how risdiplam addresses this has been acknowledged by various regulatory bodies

The potential of risdiplam to address the high unmet need in SMA was recognised by both the US Food and Drug Administration (FDA) and the European Medicines Agency when priority review status and PRIME designation were granted in November 2019 and December 2018, respectively. Approval by the FDA for risdiplam as a treatment for SMA in adults and children 2 months of age and older followed in August 2020. Furthermore, risdiplam for the treatment of SMA was granted a Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA), indicating that this treatment has the potential to address an unmet clinical need for patients. In September 2020, the MHRA issued a Positive Final Scientific Opinion for the risdiplam

Early Access to Medicines Scheme (EAMS) for the treatment of patients 2 months of age and older with type 1 and type 2 spinal muscular atrophy (SMA) who are not suitable for authorised treatment.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Risdiplam provides a substantial treatment benefit in patients across the SMA disease continuum and represents an important advancement in the treatment of SMA. The robust efficacy results observed in the FIREFISH and SUNFISH clinical studies yield substantial divergence from the natural history of disease in people with Type 1, 2 and 3 SMA when assessing patients' survival, achievement of critical motor development milestones and improvement in motor function.

The clinical development programme demonstrates consistent efficacy across the spectrum of SMA and provides substantial evidence of effectiveness for risdiplam to a broad and heterogeneous population of people with SMA that is generally reflective of the prevalent SMA population seen in UK clinical practice. However, it would be expected that once all prevalent patients had been treated with risdiplam, the focus of treatment would be those people early in their disease course who would be expected to demonstrate a greater benefit from risdiplam. Furthermore, in the risdiplam trials, there were month long delays between diagnosis and the start of the trials, whereas clinical experts have confirmed to Roche that patients would be expected to be treated almost immediately in clinical practice, leading to a better prognosis and clinical outcomes (95). Therefore efficacy outcomes from the clinical studies could potentially be considered conservative compared to outcomes that could be achieved in clinical practice, especially since emerging data suggests that disease-modifying therapies demonstrate better efficacy when administered pre-symptomatically or soon after symptoms are observed rather than months later (53).

Infantile-onset (type 1 SMA)

Risdiplam treatment was associated with a statistically significant and clinically meaningful improvement in survival, motor milestones development and motor function compared with pre-defined criterion from natural history studies, and as shown in the indirect treatment comparison. The consistent improvement was seen across all key efficacy assessments and was in line with the sustained increase of functional SMN protein, supporting the efficacy of risdiplam in type 1 SMA.

- **A high proportion of risdiplam-treated infants with well-established disease at enrolment were alive (92.7%) at month 12 of risdiplam treatment**, and 85.4% were alive while not requiring permanent ventilation (event-free survival). Patients alive who were event-free at Month 12 had an age range of 15 to 19 months, which is markedly divergent from the natural course of this rapidly progressive disease where only approximately 25% of patients would be expected to survive without permanent ventilation beyond 13.6 months of age (23). These results have direct clinical relevance as they indicate that patients are able to maintain their respiratory muscle function and breathe independently. In contrast, untreated people with infantile-onset SMA will experience progressive weakness of respiratory muscles leading to increased risk of recurrent pulmonary infections and respiratory failure, and eventual need for chronic ventilation support. Historically, such comorbidities often lead to death before the second birthday (23, 34).

- **In regards to motor milestones development, after 12 months of treatment, 29.3% of all patients were able to sit without support for 5 seconds** as assessed by Item 22 of the BSID-III (Bayley Scale of Infant Development – III) gross motor scale, the primary endpoint of this study. This is markedly different from the natural history of the disease as, by definition, people with type 1 SMA will never be able to sit independently (23, 34, 75, 96, 97). Sitting without support is clinically meaningful, because the child can now sit in a chair and is free to use both upper limbs to reach for and grasp objects and pull them to his/her face, such as for the development of self-feeding and further development of motor and cognitive functions.
- **Patients also achieved additional key motor milestones assessed by HINE-2**, including standing (22.0% of all patients were able to support weight and stand with support) and further acquiring development milestones towards developing the walking function (2.4% bouncing), with a rate of HINE-2 motor milestones responders of 78.0% (defined as having more milestones that showed improvement than showed worsening). Achieving and maintaining motor milestones according to the HINE-2 and BSID-III scales are considered clinically meaningful, as infants gain the ability to perform the basic motor skills needed for children's development.
- **Patients also presented improvements in their motor function as measured by CHOP-INTEND**: 90.2% of patients achieved a ≥4 point improvement in their CHOP-INTEND score from baseline, and 56.1% of patients achieved a CHOP INTEND score ≥40 after 12 months of treatment. The attainment of this score (40 points or more) is particularly meaningful because it is a score expected in healthy children during the early months of development, but is never seen in symptomatic type 1 SMA patients after disease onset (22). This result on the CHOP-INTEND is therefore clearly divergent from the natural disease course.
- **Swallowing and feeding ability was maintained by the majority of infants alive at Month 12**; 95% of infants alive maintained the ability to swallow while 89% were able to feed orally after 12 months of risdiplam treatment. In a natural history cohort, all infants with type 1 SMA older than 12 months required feeding support (23).
- **Risdiplam treatment dramatically reduced healthcare utilisation and overnight hospitalisation.** During the first 12 months of treatment, 49% of patients (90% CI: 35.1%, 62.6%) did not require any overnight hospitalisation. In comparison, a natural history study of infantile-onset SMA, 91% of infants experienced ≥1 in-patient hospitalisation over a mean of 11 months after symptom onset (98).
- **Risdiplam was well tolerated in people with type 1 SMA**. No risks were identified following the review of the type and frequency of AEs as well as vital signs, physical examinations, ECG, ophthalmological assessments, and safety laboratory data. None of the nonclinical safety findings (effects on epithelial tissues, haematological effects, and retinal toxicity) were observed in these people with infantile onset SMA.
- **After 24 months of treatment, people with type 1 SMA continued to receive a benefit from risdiplam in FIREFISH Part 1 (Appendix L).** The 2-year data demonstrate that event-free survival time was improved in infants treated with risdiplam compared with natural history, with continued gains in motor milestones. There is no evidence to suggest from this later data cut that infants receiving risdiplam deteriorate over time.

ITC analyses were also conducted to compare risdiplam to BSC in type 1 SMA, in a methodologically appropriate way and in the absence of head-to-head data from clinical trials. Both a naïve comparison and a population adjustment method (MAIC) were conducted. Results from the both analyses were consistent, and suggested superior efficacy of risdiplam compared to BSC on several key endpoints, including ventilation-free survival, overall survival, HINE-2 motor milestone response and achievement of the sitting without support motor milestone. In terms of safety, both analyses also suggested risdiplam has a reduced risk of adverse events leading to discontinuation and severe adverse events, while the risk of reporting any adverse event appears to be comparable between the two treatments. More details can be found in Section B.2.9.

Later-onset (type 2 and type 3 SMA)

Risdiplam treatment was associated with a statistically significant and clinically meaningful improvement in motor function in people with type 2 and type 3 SMA. Part 2 of the SUNFISH study included the broadest patient population in a placebo-controlled double-blind study that has been studied to date, including patients aged from 2 to 25 years, with a disease progression of up to 23 years by the time they received the first dose of treatment, and very low motor function scores at baseline. There were no exclusion criteria for SMA complications such as severe scoliosis and joint contractures as in other clinical studies of active treatments for SMA, thus the recruited population resembled the global spectrum of the disease, supporting the external validity of the trial results.

For the assessment of such a heterogeneous patient population, the pre-specified hierarchy of endpoints in SUNFISH Part 2 placed MFM32-related endpoints first, followed by a RULM-related endpoint, and then a HFMSE-related endpoint. The selection of this hierarchy was based on evolving clinical research and the developing knowledge of scale performance in SMA type 2 and 3 individuals.

- When analysing the broad SUNFISH study population, combining children, teenager and adult patients, risdiplam efficacy was confirmed by the primary endpoint and the top two secondary endpoints in the statistical hierarchy. **The improvement in motor function seen in patients treated with risdiplam at Month 12 was clinically meaningful and statistically significantly better than the placebo control data** (mean difference in MFM32 total score of 1.55, 95% CI: 0.30, 2.81; p=0.0156). A greater proportion of patients in the risdiplam arm (38.3%) than in the placebo arm (23.7%) had a clinically meaningful and statistically significant improvement in MFM32 total score ≥3 points (odds ratio [95% CI]: 2.35 [1.01, 5.44]; unadjusted p=0.0469, adjusted p=0.0469), the second endpoint in the statistical analysis hierarchy.
- **The proportion of people with a change from baseline in MFM32 of any threshold ≥0, representing stabilisation or improvement in this measure, was greater in those receiving risdiplam than in those receiving placebo at all post-baseline scheduled assessment visits**. Conversely, the proportion of people with a change from baseline <0, representing decline in MFM32 total score, was greater in the placebo arm than in the risdiplam arm at all scheduled assessment visits. Importantly, avoiding deterioration (i.e. achieving disease stabilisation or improvement) was ranked as the most important treatment attribute by UK SMA patients in a recent discrete choice experiment (33).

- [redacted]

- When considering upper limb function (using RULM, an assessment specifically designed for upper limb function in SMA patients (42)), the **RULM showed a clinically meaningful and statistically significant difference between risdiplam and placebo in favour of risdiplam** (mean treatment difference in RULM total score of 1.59, 95% CI: 0.55, 2.62; unadjusted p=0.0028; adjusted p=0.0469). Thus, risdiplam efficacy was confirmed by two independent and well-established motor function scales.
- **There was a numerical improvement in favour of risdiplam in the HFMSE**, but the difference at Month 12 was not statistically significant (the mean change from baseline at Month 12 was 0.95 in patients receiving risdiplam and 0.37 in patients receiving placebo). The small change was expected in the enrolled population with significant fixed disability and very low motor function scores at baseline, given that the HFMSE is not sensitive to capture change in people with a baseline HFMSE score <10 (41% had HFMSE baseline scores below 10) (27, 28, 101). This is an important consideration since severe complications such as contractures are associated with diminished motor ability and can impact performance on the HFMSE scale, thereby limiting a person's ability to attain a functional skill and realise a benefit from treatment (31).Given the variation in age and functional range together with differences in study enrolment criteria, the SUNFISH patient population is not directly comparable with those of other studies, which included patients that were generally younger and with less SMA complications or disability (57, 102). This is the first time the HFMSE and MFM32 have been used in the same clinical trial assessing a broad range of people with type 2 and 3 SMA. Both scales have different ability to capture clinical change; the MFM32 scale includes 3 domains that capture a broad range of motor function, including items relating to distal motor function that are primarily not assessed by the HFMSE, making the MFM32 a more relevant measure in those patients severely impacted by a more advanced disease (24, 28, 30).
- **Complementary evidence of the benefit of risdiplam treatment seen in the motor function assessments was also observed by the SMAIS**. Independence and the ability to perform basic personal tasks has been described by patients as a priority for type 2 and 3 SMA patients (54). The SMAIS assesses the level of independence required to complete important daily activities as reported by caregivers of patients 2-25 years and by patients aged ≥12 years. SMAIS items focus on upper limb related activities of daily living with higher scores indicating greater independence in completing

activities such as writing, using a touchscreen, dressing and washing the upper body, particularly relevant for the recruited population who are non-ambulant and wheelchair bound. Increases in both caregiver- and patient-reported SMAIS total scores were seen in the risdiplam arm, with the greatest increases reported by the caregiver. These results indicate important improvements in patients' everyday lives with regards to increased independence.

- **Risdiplam was generally well tolerated across all age groups** and none of the nonclinical safety findings were observed in these people with later-onset SMA despite comprehensive targeted monitoring. Comprehensive ophthalmologic monitoring did not show evidence of retinal toxicity and no AEs in the SOC of eye disorders were risdiplam induced.

Risdiplam efficacy was confirmed both in younger and older patients living with later-onset SMA (see subgroup analyses Appendix E):

- **Risdiplam efficacy in younger patients (2-5 years and 6-11 years) was confirmed by marked improvements in motor function scores assessed by two independent scales.** In patients aged 2 to 5 years, consistent strong results were observed in motor function measures, with greater improvements with risdiplam treatment compared to placebo in both MFM32 (mean treatment difference [95%CI]: 3.14 [0.81, 5.46]) and RULM (mean treatment difference [95%CI]: 3.41 [1.55, 5.26]) total scores at Month 12.
- **Teenagers (12-17 years) and adult patients (18-25 years) who received risdiplam showed stabilisation and/or improvement in their motor function, illustrating risdiplam therapy prevented disease progression and further disability as compared to placebo, which is the key treatment objective for these patients** (39). Older patients enrolled in SUNFISH had progressed disease and SMA-related comorbidities, such as severe scoliosis and joint contractures. Although MFM32 and RULM are the most appropriate scales to measure different aspects of motor function in a clinical trial setting, it is acknowledged that such comorbidities may prevent the positioning of patients at the starting position of certain items in these scales, preventing certain item scoring. Despite such challenges, risdiplam efficacy was confirmed by the **higher proportion of people with a change in MFM32 total score ≥0 in those receiving risdiplam than those receiving placebo** (12-17 years: 63.3% receiving risdiplam, 50.0% receiving placebo; 18-25 years: 57.1% receiving risdiplam, 37.5% receiving placebo).
- **Improvements in the MFM32 are supported by very robust and clinically significant differences on the RULM, a scale designed to assess upper limb function.** Risdiplam efficacy in older patients was not only confirmed by a global motor function scale (MFM32), but also by the RULM, a scale designed to assess upper limb motor function, which is particularly clinically relevant for the patient population enrolled in the SUNFISH study and for older people living with SMA who are wheelchair-bound and solely rely on upper limb function for performing activities of daily living. Consistent with the MFM32 data, results from the RULM also showed stabilisation or improvement in motor function in older patients (change from baseline, risdiplam and placebo respectively: 12-17 years: -0.56, -0.61; 18-25 years: 1.06; -0.68).

Conclusions

As discussed in Section B.1.3, there remains a clear unmet medical need in the field of SMA, particularly for those patients who prefer not to receive, respond poorly to, cannot tolerate or are unsuitable for intrathecally administered treatments.

By binding to two sites on the SMN2 pre-mRNA, risdiplam increases levels of full length SMN mRNA and protein while reducing the possibility of off-target effects (93). Furthermore, by crossing the blood-brain barrier, risdiplam promotes a rapid and sustained increase in SMN protein in both the CNS and systemically throughout the body (66, 67) and is therefore hypothesised to bring greater efficacy in people with SMA than treatments targeting increases of functional SMN protein in the CNS alone.

The totality of data from studies in a heterogeneous patient population that is reflective of UK clinical practice demonstrates that risdiplam is highly effective in people with both infantile and late-onset disease, supporting the proposed broad indication for risdiplam as a treatment option for all people with SMA. Taken together with a favourable safety profile in approximately 470 paediatric and adult treatment-naïve and non-treatment naïve patients with up to 3 years exposure, the evidence demonstrates a clearly positive benefit/risk profile for risdiplam and it is therefore anticipated to provide an additional innovative disease modifying therapy for all patients across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status). Moreover, for those patients who are ineligible for or unable to tolerate intrathecal administration, risdiplam will be the only available disease modifying therapy option.

As an oral therapy, risdiplam provides an easy and sustainable route of administration at home to best support a life-long chronic disease. Not only will this provide benefits to people with SMA and their caregivers, home care therapy will alleviate the burden on health care systems, resources and budgets, while expanding the population able to receive treatment with a disease modifying therapy. Moreover, homecare provision will also provide a welcome alternative option for vulnerable patients who are currently unable to attend health care facilities due to the COVID-19 pandemic.

Despite the robust clinical evidence available to support a broad indication for risdiplam, there are inherent uncertainties and limitations within the evidence base, consistent with other currently available treatments and published data. For instance, further evidence is required on the long-term efficacy and safety of risdiplam along with gaining evidence to support appropriate treatment sequencing and individual treatment decisions in the rapidly evolving treatment landscape (70).

Considering the inevitable accumulation of disability that all people with SMA face, and the demonstrated remaining unmet need, Roche recognises the need to balance the urgency for all people with SMA in the UK to gain access to a sustainable oral treatment as soon as possible, while also addressing the uncertainties with the current available evidence. Roche therefore considers that funding through a MAA for risdiplam with additional data collection over an approximate 5 year period (similar to the TA588 MAA), or sooner depending on data availability, might be needed to enable the NICE appraisal committee to make a better informed and evidence-based decision for routine funding at the end of the MAA period based on the more robust and broader evidence base that will be available at NICE re-review.

B.2.13.1 End-of-life criteria

End-of-life criteria should apply to the SMA type 1 population as per what is outlined in this section, and as per the precedent from NICE TA588 (18). While we do not anticipate end-of life criteria will apply for the SMA type 2/3 population, we do believe that the NICE committee should take into account decision modifiers to recognise that SMA is a severe and rare condition, with a broad impact on patients, many of whom are children and people with disabilities, and their carers, These decision modifiers were taken into account in NICE TA588, and should also be recognised in this appraisal in order to ensure consistency in NICE decision making.

Table 9: End-of-life criteria

Criterion	Data available	Reference in submission
The treatment is indicated for people with a short life expectancy, normally less than 24 months	Survival will vary between severities of the disease. An extensive summary of natural history studies was summarised in TA588 (18), demonstrating that the mean or median age of death or permanent respiratory support is well below 24 months. End-of-life criteria were recognised for the SMA type 1 population in NICE TA588. Most recent natural history studies have focused upon a combined survival endpoint of age at death or a surrogate of survival free of permanent ventilation, on the assumption that the infant would have died without such support (103). Natural history of the infantile-onset (type 1 SMA) demonstrates that 50% of infants, who only have two copies of SMN2 gene, will die or require permanent daily non-invasive ventilation support by 10.5 months of age. This statistic reaches 92% for type 1 toddlers by 20 months of age (23). In other clinical trials and natural history studies in SMA type 1 patients, the median age for death or permanent respiratory support as reported is approximately 9–13 months (23, 104, 105). Results of our economic model for type 1 patients demonstrate that for patients in the BSC arm the median age of death or permanent respiratory support is 10 months.	B.1.3.1, page 13
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The proportion of type 1 infants alive at Month 12 of risdiplam treatment was 92.7% (38/41; 90% CI: 82.2%, 97.1%). This proportion is significantly higher than the pre-defined performance criterion of 60% based on natural history data ($p<0.0005$). The median time to death was not estimable in FIREFISH Part 2 as few patients had an event. Results of our economic model for type 1 patients demonstrate that patient on risdiplam achieve incremental 7.29 life years compared to BSC over the lifetime horizon of the economic model. In none of the sensitivity or scenario analyses considered do the incremental life years gained fall below 4.89 years.	B.2.6.1.2, page 46 B.3.7 – B.3.9, page 150–165

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted in August 2019 to identify economic evaluations for treatment options in SMA. Eligibility criteria were not limited by type of SMA, severity or age of onset.

A total of 3,276 articles were identified from the searches, of which 42 papers relevant to cost-effectiveness were identified for full text review. Ultimately, two full publications, four conference abstracts, and three previous HTA submissions met the eligibility criteria and were included in the review.

The results of the cost-effectiveness SLR for studies relevant to the UK setting are presented in Table 5; full details of the search strategy and the complete results are presented in Appendix G.

Table 47: Summary list of published cost-effectiveness studies in SMA

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	LYs	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Previous HTA submissions (N=3)							
CADTH, 2018 (106)	2018	• Model: Three Markov models for SMA type 1, 2 and 3 • Time horizon: o SMA type 1: 25 years o SMA type 2: 50 years o SMA type 3: 80 years • Perspective: Canadian public health care system • Cycle length: o SMA type 1: patients could transition between health states at 2-, 6-, 10-, 13- and 14-months o SMA type 2: 3 months conforming to CHERISH, subsequent cycles every 4 months o SMA type 3: 3 months (for the first 27 months,	Patients with SMA – stratified by SMA type (type 1, 2 and 3)	Total QALYs: • SMA type 1: o Nusinersen: 3.919 o RWC: -0.881 • SMA type 2: o Nusinersen: 23.278 o RWC: 19.602 • SMA type 3: o Nusinersen: 12.053 o RWC: 10.490	Total LYs: • SMA type 1: o Nusinersen: 8.373 o RWC: 3.583 • SMA type 2: o Nusinersen: 28.527 o RWC: 26.348 • SMA type 3: o Nusinersen: 44.155 o RWC: 44.155	Total costs (CAD, 2017): • SMA type 1: o Nusinersen: $3,534,854 o RWC: $339,683 • SMA type 2: o Nusinersen: $8,336.271 o RWC: $708,620 • SMA type 3: o Nusinersen: $5,554,707 o RWC: $1,091,307	ICER/QALY: • SMA type 1: o Nusinersen vs RWC: $665,570 • SMA type 2: o Nusinersen vs RWC: $2,075,435 • SMA type 3: o Nusinersen vs RWC: $2,855,818

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	LYs	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		subsequent cycles every 4 months) • Discount rate: 1.5% costs and benefits • Health benefits: LYs, QALYs					
ICER, 2019 (107)	2019	• Model: Three *de novo* Markov models: o Symptomatic infantile-onset model o Symptomatic later-onset model o Pre-symptomatic model • Time horizon: Lifetime (all models) • Perspective: USA health care sector perspective • Cycle length: 1 month • Discount rate: 3.0% costs and benefits • Health benefits: LYs, QALYs	SMA patients of all ages and types	Total QALYs: • Infantile-onset: o Nusinersen: 3.24 o BSC: 0.46 • Infantile-onset: o AVXS: 12.23 o BSC: 0.46 • Later-onset: o Nusinersen: 12.28 o BSC: 11.34 • Pre-symptomatic: o Nusinersen: 21.94 o BSC: 6.25	Total LYs: • Infantile-onset: o Nusinersen: 7.64 o BSC: 2.40 • Infantile-onset: o AVXS: 18.17 o BSC: 2.40 • Later-onset: o Nusinersen: 18.90 o BSC: 18.90 • Pre-symptomatic: o Nusinersen: 26.58 o BSC: 9.51	Total costs (USD, 2002), • Infantile-onset: o Nusinersen: $3,884,000 o BSC: $789,000 • Infantile-onset: o AVXS: $3,657,000 o BSC: $789,000 • Later-onset: o Nusinersen: $9,148,000 o BSC: $1,442,000 • Pre-symptomatic: o Nusinersen: $11,929,000 o BSC: $801,000	ICER/LYG: • Infantile-onset: o Nusinersen vs BSC: $590,000 o AVXS vs BSC: $182,000 • Later-onset: o Nusinersen vs BSC: Dominated • Pre-symptomatic: o Nusinersen vs BSC: $652,000 ICER/QALY: • Infantile-onset: o Nusinersen vs BSC: $1,112,000 • Infantile-onset: o AVXS vs BSC: $243,000

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	LYs	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
							• Later-onset: o Nusinersen vs BSC: $8,156,000 • Pre-symptomatic: o Nusinersen vs BSC: $709,000
NICE TA588, 2019 (18)	2019	• Model: Two Markov models: o Early-onset: o Later-onset • Time horizon: o Infantile-onset: 40 years (lifetime) o Later-onset: 80 years • Perspective: Payer (UK NHS and PSS) (including caregiver burden; societal perspective considered in scenario analysis) • Cycle length: o Early-onset: 2, 6, 10, 13 and 14, 18 and every 4 months after. o Later-onset: 3, 6, 9, 12, 15, 19,	Infantile (type 1) and later-onset (type 2/3) SMA patients	Total QALYs: • Early-onset (patient): o RWC: 2.49 o Nusinersen: 7.86 • Later-onset (patient): o Nusinersen: 14.52 o RWC: 16.88 • Early-onset (patient and caregiver): o RWC: 2.17 o Nusinersen: 7.61 • Later-onset (patient and caregiver): o Nusinersen: 12.36 o RWC: 15.66	Total LYG: • Early-onset (patient): o RWC: 3.39 o Nusinersen: 9.34 • Later-onset (patient) (list price): o Nusinersen: 19.61 o RWC: 20.99 • Early-onset (patient and carer): o RWC: 3.39 o Nusinersen: 9.33 • Later-onset (patient and carer: o RWC: 19.61 o Nusinersen: 20.99	Total costs (GBP, 2016): • Early-onset (patients): o RWC: £71,540 o Nusinersen: £2,258,852 • Later-onset (patients): o RWC: £184,312 o Nusinersen: £3,148,754 • Early-onset (patients and carer): o RWC: £71,540 o Nusinersen: £2,258,852 • Later-onset (patients and carer): o RWC: £184,312 o Nusinersen: £3,148,754	ICER/QALY: • Early-onset (patient): o Nusinersen vs RWC: £407,605 • Later-onset (patients) (list price): o Nusinersen vs RWC: £1,252,991 • Early-onset (patient and carer): o Nusinersen vs RWC: £402,361 • Later-onset (patient and carer) (list price): o Nusinersen vs RWC: £898,164

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	LYs	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		23 and every 4 months thereafter. • Discount rate: 3.5% costs and benefits • Health benefits: LYs, QALYs					
Published economic evaluations (N=6)							
Malone, 2019a (108) (study linked to Malone 2019b (109))	2019	• Model: Markov model • Time horizon: Lifetime • Perspective: USA commercial payer • Cycle length: six months for the first three years, and then 12 months for all cycles thereafter • Discount rate: 3.0% costs and benefits • Health benefits: Lys, QALYs	Paediatric patients with SMA type 1 and two copies of SMN2, diagnosed before the age of six months, and treated with either a therapeutic dose of AVXS or nusinersen	Total QALYs: • Discounted: o AVXS: 15.65 o Nusinersen: 5.29 • Undiscounted: o AVXS: 29.86 o Nusinersen: 7.21	Total LYs: • Undiscounted: o AVXS: 37.20 o Nusinersen: 9.68 • Discounted: o AVXS-10: 19.81 o Nusinersen: 7.11	Total average cost per year per patient (USD, reference year NR): • AVXS (reported by hypothetical cost): o $2.5M: $4,214,379 o $3M: $4,699,816 o $4M: $5,670,690 o $5M: $6,641,564 • Nusinersen: $6,316,711	ICER/QALY, AVXS vs nusinersen (reported by hypothetical costs): • $2.5M: AVXS dominates • $3M: AVXS dominates • $4M: AVXS dominates • $5M: $31,379
Malone, 2019b (109) (study linked to Malone 2019a (108))	2019	• Model: Markov model • Time horizon: Lifetime • Perspective: NR • Cycle length: NR • Discount rate: 3.0% costs and benefits • Health benefits: QALYs	Patients with SMA type 1	Total QALYs: • Undiscounted: o AVXS: 30.3 o Nusinersen: 7.2 • Discounted: o AVXS: 15.9 o Nusinersen: 5.3	NR	NR	ICER/QALY: • AVXS vs nusinersen: AVXS dominates

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	LYs	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Thokala, 2019 (110)	2019	• Model: *de novo* economic model • Time horizon: NR • Perspective: USA health care sector perspective • Cycle length: NR • Discount rate: 3.0% cost and benefits • Health benefits: QALYs	• Patients diagnosed with infantile-onset SMA in the USA	NR	NR	NR	ICER/QALY: • Nusinersen vs BSC: did not fall below $1 million (scenario/one-way sensitivity analyses) • AVXS vs BSC: $205,000-$412,000
Zuluaga-Sanchez, 2019a (111)	2019	• Model: Markov model: o Infantile-onset o Later-onset • Time horizon: o Infantile onset: 40 years o Later-onset: 80 years • Perspective: Societal perspective in Sweden • Cycle length: 4 months • Discount rate: 3% discount for both costs and benefits • Health benefits: LYs and QALYs	Infantile-onset and later-onset SMA patients	Total patient QALYs (discounted): • Infantile-onset: o Nusinersen + SOC: 3.65 o SOC: −0.20 • Later-onset: o Nusinersen + SOC: 9.25 o SOC: −0.29 Total caregiver QALYs (discounted): • Infantile-onset: o Nusinersen + SOC: −0.10 o SOC: −0.12 • Later-onset: o Nusinersen + SOC: −1.37 o SOC: −3.76	• Total LYs (discounted): • Infantile-onset: o Nusinersen + SOC: 7.23 o SOC: 1.01 • Later-onset: o Nusinersen + SOC: 23.13 o SOC: 21.28	Total infantile-onset costs (SEK, 2018): • Nusinersen + SOC: 23,920,567 • SOC: 2,066,516 • Incremental: 21,854,051 • Total later-onset costs (SEK, 2018): • Nusinersen + SOC: 66,053,350 • SOC: 28,029,941 • Incremental: 38,023,409	ICER/QALY, nusinersen + SOC vs SOC: • Infantile-onset: 5,635,978 SEK • Later-onset: 3,187,222 SEK

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	LYs	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Zuluaga-Sanchez, 2019b (112)	2019	• Model: Markov model • Time horizon: 80 years • Perspective: Third-party payer perspective • Cycle length: NR • Discount rate: NR • Health benefits: LYs and QALYs	Later-onset SMA	NR	Total LYs (discounted): • Nusinersen: 21.39 • SOC: 21.04 • Total QALYs (discounted): • Nusinersen: 13.89 • SOC: 12.71	NR	ICER/QALY, nusinersen vs SOC: Exceeded $500,000/QALY
Zuluaga-Sanchez, 2019c (113)	2019	• Model: Markov model • Time horizon: 60 years • Perspective: Third-party payer • Cycle length: NR • Discount rate: NR • Health benefits: LYs, QALYs	Patients with infantile-onset SMA (most likely to develop SMA type 1 or 2)	NR	• Total LYs (discounted): • Nusinersen: 4.37 • SOC: 2.15 • Total QALYs (discounted): • Nusinersen: 2.05 • SOC: 0.41	NR	ICER/QALY, nusinersen vs SOC: Exceeded $500,000/QALY

BSC, best supportive care; CAD, Canadian dollar; ICER, incremental cost-effectiveness ratio; ICER, Institute for Clinical and Economic Review; LY, life year; LYG, life year gained; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; NR, not reported; PSS, Personal Social Services; QALY, quality adjusted life year; RWC, real world care; SEK, Swedish krona; SMA, spinal muscular atrophy; SOC, standard of care; UK, United Kingdom; USA, United States of America; USD, United States Dollar.

B.3.2 Economic analysis

As described in Section B.3.1, no prior cost-effectiveness analyses that assess risdiplam in SMA patients were identified in the SLR of published economic evaluations. Two de novo economic models were therefore developed to determine the cost-effectiveness of risdiplam versus BSC in SMA type 1 and type 2/3. It was deemed necessary to model patients with type 1 and 2/3 SMA separately due to the differences in natural history, severity and prognosis between the individual types of SMA. The structure of the models was informed by previous SMA models, clinical guidelines and clinical expert opinion, as described below.

Within each subsection of Section B3, unless the same methodology applies for both models, the cost-effectiveness model for type 2/3 SMA is described first, followed by a description of the model for type 1 patients.

B.3.2.1 Patient population

Type 2/3 model: The patient population of this model mirrors that of the SUNFISH Phase 2/3 randomised clinical trial for risdiplam, which included both ambulant and non-ambulant patients aged 2–25 years at the time of enrolment with type 2 and 3 SMA. The patient population is in line with the anticipated marketing authorisation for risdiplam and final scope for this submission.

Type 1 model: The patient population of this model mirrors that of the FIREFISH Phase 2/3 clinical trial for risdiplam, which included infants with symptomatic type 1 SMA aged 1–7 months at the time of enrolment. The patient population is in line with the anticipated marketing authorisation for risdiplam and the final scope for this submission.

The detailed eligibility criteria for the FIREFISH and SUNFISH trials are described in Section B.2.3.3.

B.3.2.2 Model Structure

The design of the structure for both the type 2/3 and type 1 economic models was informed by a number of sources including reviews of the literature, clinical guidelines, prior HTA reports and consultations with expert clinicians and physiotherapists working with SMA patients on a regular basis. Two UK advisory boards with clinical experts were also conducted to further validate the model structures. A report summarising the results from the UK advisory board are available in Appendix N. At the UK advisory boards, 10 neurology/neuromuscular disorder experts (8 clinicians and 2 physiotherapists) with experience of treating a broad population of SMA patients in the UK were consulted. Focus was placed on understanding the natural history and survival of SMA patients in order to model this as accurately as possible.

The key finding from consultation of these sources was that SMA is highly driven by patients' achievement of developmental motor abilities. Within clinical practice, the achievement of motor milestones informs classification of SMA type, and also informs guidance on the monitoring and treatment of patients (15, 114). Achievement of motor milestones, in turn, is linked with healthcare resource use and corresponding treatment costs, patient and caregiver HRQoL and survival (16, 115). With this in mind, Markov models were developed for both type 2/3 and type 1 SMA with health states, informed by clinical expert opinion, reflecting the major motor milestone achievements deemed possible within the natural

history of patients living with each type of SMA. A Markov model was deemed an appropriate model structure to capture patients' current motor ability, whilst allowing for progression and regression to higher and lower motor milestone health states, respectively. Indeed, Markov models were also built for the NICE technology appraisal and ICER review of nusinersen in early- and late-onset SMA (TA588), with the former deemed suitable for decision-making by the NICE Committee (18, 107).

In addition to motor milestone health states, for the type 1 SMA model, a permanent ventilation (PV) health state was additionally included. This is reflective of the greater severity and inferior prognosis of SMA type 1 patients compared to type 2/3 patients, for whom a significant proportion of patients require PV during their lifetime in order to prolong life.

Whilst the experts consulted deemed the motor milestone model structure to align with the natural history of SMA, they noted that models have inherent limitations and cannot capture all aspects of SMA experienced patients and their carers. This is a well-documented limitation of most economic models, which are a simplification of reality and cannot fully capture all elements of a disease process. For example, the clinical experts noted that factors such as ability to feed and frequency of hospital visits may also affect patient and carer HRQoL. There may also be within-milestone improvements that positively affect patient and carer HRQoL, such as improvements in upper limb function for patients in wheelchairs (Appendix N). As a result, the full value of SMA treatments such as risdiplam may not be captured in their entirety in cost-effectiveness models. This was further acknowledged by NICE in the appraisal of nusinersen (TA588) (18), where it was noted that the broad and severe impact of SMA on patients and carers cannot fully be captured by the economic models or the NICE reference case. Therefore, in order to ensure consistency in NICE decision making, similar flexibility should be acknowledged in the appraisal of risdiplam to recognise that some benefits of new treatments in SMA cannot be fully captured by health economic modelling.

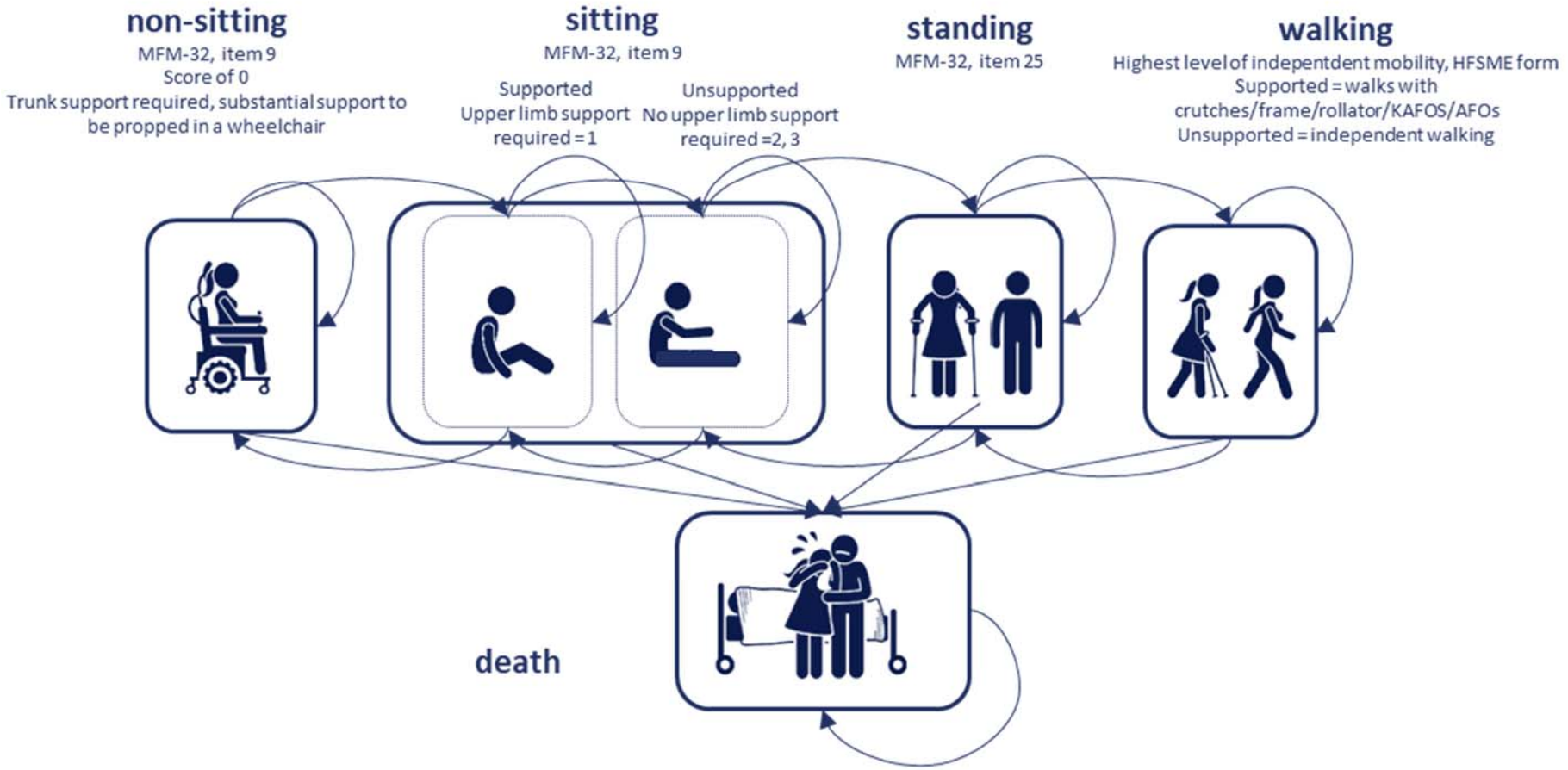
The structures of each economic model are described further below.

Type 2/3 SMA (SUNFISH) model

A Markov model was developed in Microsoft Excel with five health states representing key motor milestones that type 2/3 SMA patients may achieve during their lifetime, in addition to an absorbing 'death' health state. The motor milestone health states comprised 'not sitting', 'sitting with support', 'sitting unsupported', 'standing' (with or without support) and 'walking' (with or without support). This set of motor milestones was validated by UK and international clinical experts as being feasible for type 2/3 patients to achieve in their lifetime as well as clinically meaningful to patients and their caregivers (Appendix N) (116). The 'sitting' health state was split into sitting 'with' and 'without support', as it was deemed important to represent the clinical significance for patients with type 2/3 SMA of being able to progress from being dependent on a form of support to sitting independently. Furthermore, whilst type 2/3 patients are expected to reach relatively more advanced motor milestones compared to type 1 patients, it was deemed appropriate to include the 'not sitting' health state, as without disease-modifying therapy, patients are likely to lose the functional gains they have made over time (24).

A diagram of the type 2/3 SMA (SUNFISH) model is presented in Figure 10.

Figure 10: Diagram of the type 2/3 SMA (SUNFISH) model



AFO: ankle-foot orthosis; HFMSE: Hammersmith Functional Motor Scale Expanded; KAFOS: knee-ankle-foot-orthosis; MFM32: 32 Item Motor Function Measure.

The definition of the ‘not sitting’, ‘sitting with support’, ‘sitting unsupported’ and ‘standing’ health states is informed by items of the MFM-32 scale, a measure of motor ability described in detail in Table 4 and B.2.4.2. The health states of the model thus align with the primary endpoint from the SUNFISH trial. Clinical experts consulted during model development concurred that the MFM-32 is an appropriate measure to demonstrate achievement of motor function milestones for the broad population of type 2/3 SMA patients recruited in SUNFISH, and validated the questionnaire items used to represent the selected health states. Furthermore, feedback from UK clinical experts sought at the advisory boards was that the MFM-32 scale is able to capture a wider spectrum from the weakest to strongest patients than the Hammersmith Functional Motor Scale Expanded (HFMSE) scale, and is therefore appropriate for use in the broad SUNFISH patient population.

The MFM-32 items and scores underpinning these model health states are presented below.

Table 48: MFM-32 scores representing health states in the type 2/3 SMA (SUNFISH) model

Health state	MFM-32 item	Score
Not sitting	Item 9 (maintain seated position)	0
Sitting with support	Item 9 (maintain seated position)	1
Sitting without support	Item 9 (maintain seated position)	2, 3
Standing (with or without support)	Item 25 (maintain standing position)	1, 2, 3

MFM32, 32 item Motor Function Measure.

With regards to the definition of the walking health state, given that neither the MFM-32 nor the HFMSE scale contain items that can appropriately capture the ‘Walking’ health state, data regarding the motor milestone achieved by patients was informed by the HFMSE ‘level of independent mobility: highest current level of independent mobility’, as recorded on patients’ electronic Case Report Forms (eCRFs) in SUNFISH. Responses of ‘Walks with crutches/frame/rollator’, ‘Walks with knee-ankle-foot-orthosis/ankle-foot orthosis’ or ‘independent walking’ were deemed to meet the definition of the ‘walking’ health state.

In line with the baseline characteristics observed in the SUNFISH trial, patients start in one of the five motor milestone health states (see Section B.3.3.1) and are assigned to treatment with either risdiplam or BSC. From these health states, patients’ motor abilities may improve, decline, or stay the same in each model cycle. A cycle length of one month was considered sufficiently granular to capture changes in patient outcomes and costs. Within the cycle length of one month, patients may improve or deteriorate by no more than one health state, as informed by clinical opinion.

In accordance with the NICE reference case, the cost-effectiveness analysis is conducted from the perspective of the NHS and Personal Social Services in the base case, taking account of the costs directly related to the medical treatment of SMA patients, the quality of life of SMA patients and their carers. The approach to including cost and resource use in the model is described further in Section B.3.5.2. The approach to modelling health state utility values (HSUVs) for patients and carers is outlined in Section B.3.4.5. As noted above, the model cycle length is one month, and a half cycle correction is applied to account for mid-cycle transitions. Costs and benefits are discounted at 3.5% per year, as per the NICE reference case (117).

Table 49: Features of the economic analysis (type 2/3 model)

Factor	Previous appraisals	Current appraisal	
	TA588	Chosen values	Justification
Time horizon	Lifetime (80 years)	Lifetime (90 years)	The mean baseline age in the model is [redacted]. In line with the NICE reference case (117), a lifetime time horizon of 90 years was selected to capture all costs and benefits associated with risdiplam or treatment with BSC.
Long-term clinical outcomes	In the manufacturer's original base case later-onset SMA model, on-treatment transition probabilities during trial follow-up reflect motor milestone achievements from the CHERISH trial. After trial follow-up, patients on nusinersen could only improve in health state, whilst patients on BSC could only decline or remain constant. The Committee deemed that this approach substantially overestimated the proportion of patients receiving nusinersen who reached the best health states, as those who remained on treatment would continue to improve indefinitely. The company's final iteration of the model included an option for patients to plateau whilst remaining on treatment, resulting in a more plausible proportion of patients who could reach the best health states.	In the base case, after a period of 24 months, the majority of patients on risdiplam treatment either improve (in terms of health states achieved) or remain stable. Patients receiving BSC are assumed to remain stable or deteriorate.	This approach was informed by clinical expert opinion sought at UK advisory boards, which stated that the majority of patients receiving active treatment would remain stable or improve in the long-term (Appendix N). This is in line with data from Part 1 and Part 2 of the SUNFISH trial, where the majority of patients in the risdiplam arm demonstrated improvement or stabilisation of the disease. Furthermore, the proportion of patients improving and stabilising was greater with risdiplam than in the placebo arm. This was further confirmed by the 24-months follow-up data from Part 1 of the SUNFISH trial. Clinicians at the advisory boards also noted that it was clinically appropriate to assume that patients treated with BSC remain stable or deteriorate in the long term (Appendix N). Evidence from the literature further illustrates that type 2/3 patients treated with BSC deteriorate over time (24). For completeness, scenario analyses have been conducted to explore this

			assumption, whereby alternative values for backwards transitions for risdiplam are assumed, the transition probabilities sourced from the SUNFISH trial (described in Section B.3.3.1) are applied for the entirety of the time horizon for BSC and 'long-term' transition probabilities are implemented after 12 months.
Source of utilities	The manufacturer included both patient and carer utilities in their later-onset SMA model. In the original manufacturer's later-onset model, PedsQL collected from patients in the CHERISH trial were mapped to the EQ-5D, however, the revised base case (and ERG-preferred approach) was based on the Lloyd et al. 2019 EQ-5D vignette study (118). Estimates provided by the clinical advisors were additionally explored in scenario analyses, and whilst not preference-based, were deemed to show face validity. For caregiver utilities, the 'best' health state was assumed to be equal to general population utilities, and 'worst' health was assumed to be equal to mean caregiver utility scores from Bastida et al. 2017 (119). An equal difference in utility was assumed between adjacent health states.	**Patient HSUVs** Utility values from the Lloyd et al. 2019 EQ-5D vignette study were selected to inform the base case in accordance with the ERG and Committee's preference for final decision-making in TA588 (118).The utility values provided by the ERG's clinical advisors were explored in a scenario analyses. EQ-5D data collected from the SUNFISH study are additionally explored as a scenario analysis. **Carer HSUVs** In line with the approach taken in TA588, carer HSUVs in the model were informed by Bastida et al. 2017 (119). EQ-5D-5L utility values were additionally collected from caregivers of SMA patients in the Roche UK burden of illness study, and cross-walked to the EQ-5D-3L and valued using UK tariffs. These HSUVs are applied in a scenario analysis.	**Patient HSUVs** In the base case analysis, HSUVs from the Lloyd et al. 2019 vignette study (118) were selected on the basis that they were previously deemed acceptable by the ERG in the TA588 appraisal in SMA (18) and were also selected as more clinically plausible by UK clinical experts consulted by Roche (Appendix N). EQ-5D-5L utility values (cross-walked to the EQ-5D-3L and valued using UK tariffs) elicited from type 2/3 SMA patients in the SUNFISH RCT underwent assessment by UK clinical experts, who concluded that the utilities lacked clinical validity, as they were too low and did not reflect the broad range of HRQoL levels observed between motor milestones ([Appendix N). Accordingly, the EQ-5D values collected in SUNFISH were not applied in the base case, but explored in a scenario analysis for completeness. **Carer HSUVs** Assessment of possible carer HSUVs was conducted by UK clinical experts. HSUVs used in TA588 (based on

			Bastida et al (119) and general population utility (120) were explored. Additionally, a UK burden of illness study was conducted by Roche, further details of which are presented in Section B.3.5.2, and resulting carer HSUVs were assessed by the UK clinical experts. The clinical experts deemed that the utility values informed by Bastida et al. and general population utility in TA588 demonstrated greater face validity than those collected as part of the Roche UK burden of illness study. As such, the former set of values were applied in the base case, and the latter applied in a scenario analysis.
Source of costs	Health state resource use was initially sourced from Bastida et al. 2017 (121). Following critique from the ERG that the Bastida et al. study greatly underestimated costs associated with SMA treatment, cost inputs were subsequently based on a UK real-world study using HES data linked to motor milestones. The costs relating to 'Type 1 milestones' had to be adjusted upwards, as clinical experts felt that the UK real-world study was still underestimating resource use in these patients.	Cost and resource use are informed by the UK-based real-world study applied during TA588. Additionally, the Roche UK burden of illness study was conducted. Healthcare resource use results from this study are used to inform a scenario analysis.	Extensive discussion took place to achieve consensus on appropriate cost and resource use for SMA in TA588 (18). A consistent criticism was that this was underestimated in all available sources. For consistency in decision-making, and given that SMA-related costs were a significant driver of cost-effectiveness results in TA588, the same source that informed the final NICE decision in TA588 has been utilised to inform costs in the base case for the risdiplam model.

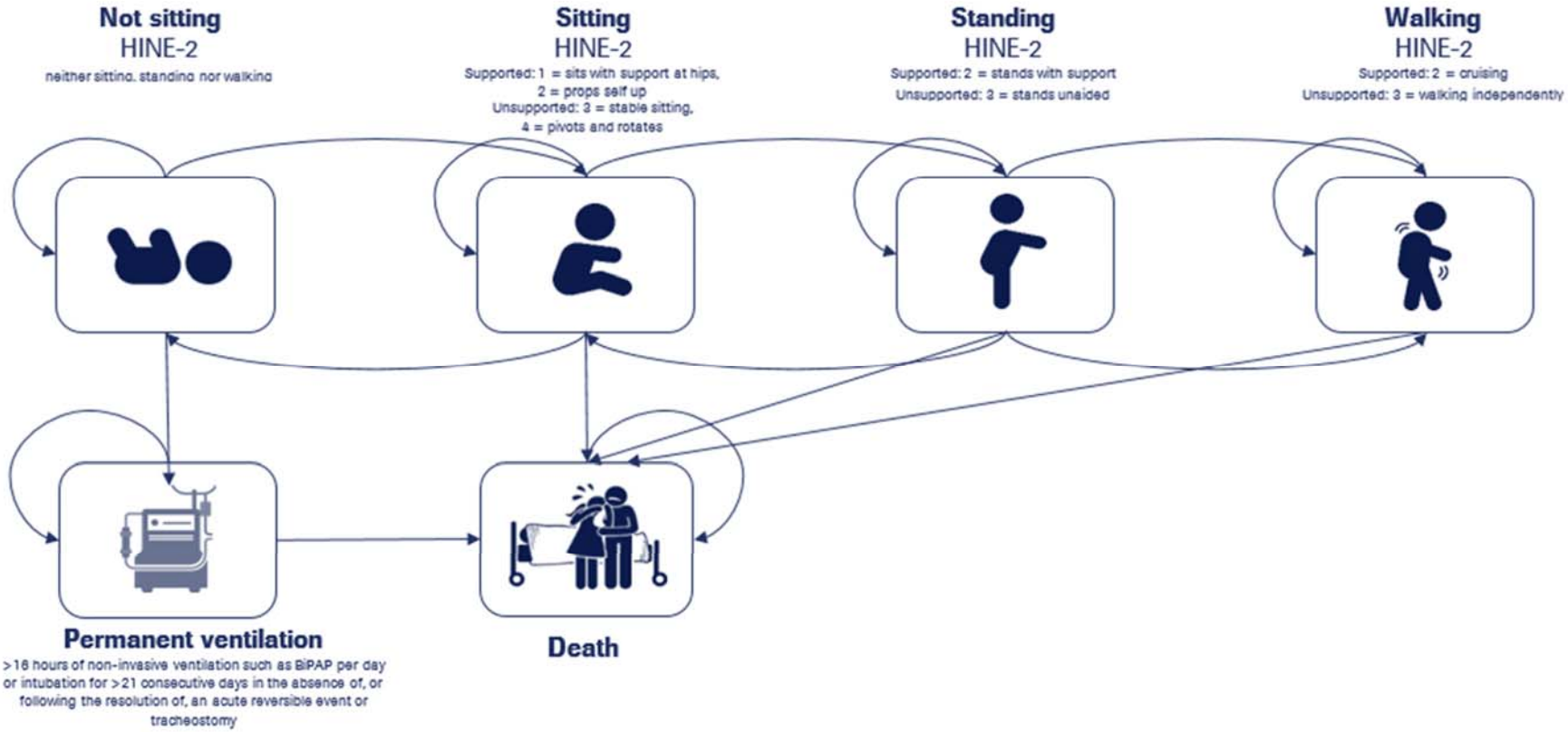
3L: 3-level; 5L: 5-level; BSC: best supportive care; EQ-5D: Euro-QoL 5 Dimensions; ERG: Evidence Review Group; HES: hospital episode statistics; HSUV: health-state utility value; NICE: National Institute for Health and Care Excellence; PedsQL: Paediatric Quality of Life Inventory; RCT: randomised controlled trial; SMA: spinal muscular atrophy

Type 1 SMA (FIREFISH) model

A Markov model was developed in Microsoft Excel with four health states representing key motor milestones that type 1 SMA patients may achieve during their lifetime when receiving disease-modifying therapy, in addition to a ‘permanent ventilation’ health state and an absorbing ‘death’ health state. The motor milestone health states comprised ‘not sitting’, ‘sitting’, ‘standing’ and ‘walking’. This set of motor milestones was validated by clinical experts as being feasible for type 1 patients to achieve in their lifetime when receiving disease-modifying therapy, as well as clinically meaningful to patients and their caregivers. Additionally, this model structure was similar to that considered for the economic models in TA588 and developed by ICER (18, 122).

A diagram of the type 1 SMA (FIREFISH) model is presented in Figure 11.

Figure 11: Diagram of the type 1 SMA (FIREFISH) model



HINE-2, Hammersmith Infant Neurological Examination.

The definition of the 'not sitting,' 'sitting' (with or without support), 'standing' (with or without support) and 'walking' (with or without support) health states is informed by items of the HINE-2 scale, a measure of motor ability included as a key secondary outcome of the FIREFISH trial.

The FIREFISH study captured several motor milestone-based outcome measures including the HINE-2, BSID-III and CHOP-INTEND. Based on internal clinical expertise and external clinical input from physiotherapists, the HINE-2 was determined to capture the broadest range of motor function during the early development of infants (116). Previous evidence has shown that without intervention, type 1 infants are not able to achieve many milestones within the HINE-2 during natural history (34). Hence, any achievements for type I patients within this scale would indicate an improvement from the natural history of the disease.

The HINE-2 measure is also the common endpoint to facilitate the indirect treatment comparison (ITC) to BSC (Section B.2.9). Clinical experts consulted during model development and during the UK advisory boards concurred that the HINE-2 is an appropriate measure to demonstrate achievement of motor function milestones for type 1 patients (Appendix N).

The HINE-2 scores representing these health states are presented in Table 50. The items of the HINE-2 selected to represent the motor milestones was validated within clinicians during model design.

Table 50: HINE-2 scores representing motor milestone health state in the type 1 SMA (FIREFISH) model

Health state	HINE-2 motor function group	Milestone progression score
Not sitting	NA	NA
Sitting (with or without support)	Sitting	1, 2, 3, 4
Standing (with or without support)	Standing	2, 3
Walking (with or without support)	Walking	2, 3

HINE-2: Hammersmith Infant Neurological Examination; NA: not applicable

Due to the inferior prognosis of type 1 patients compared to type 2/3 patients, and the corresponding greater likelihood of a need for permanent ventilation (123), an additional 'permanent ventilation' health state was included in the type 1 model. Feedback from expert clinicians practising in the UK was that due to advances in therapies for SMA in recent years, parents and physicians have become more willing to prolong patients' lives utilising permanent ventilation in the UK, despite the poor levels of quality of life associated with such treatment (124). Accordingly, it was deemed appropriate to include this health state within the model to reflect current clinical practice. Within the model, permanent ventilation is consistent with the definition in the FIREFISH trial: >16 hours of non-invasive ventilation such as Bilevel Positive Airway Pressure (BiPAP) per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy (68).

In line with the baseline characteristics observed in the FIREFISH trial, patients start in the 'not sitting' health state (see Section B.3.3.2) and are assigned to treatment with risdiplam or BSC. From this health state, patients' motor abilities may improve or the stay the same, or a

patient may deteriorate to the ‘permanent ventilation’ health state. Once patients have transitioned to the ‘permanent ventilation’ health state, they may not progress to any motor milestone gains; patients remain within this state until death. Within the cycle length of one month, patients may improve or deteriorate by no more than one health state, as informed by clinician input.

In line with the NICE reference case (117) and the type 2/3 model, the cost-effectiveness analysis is conducted from the perspective of the NHS and Personal Social Services in the base case, taking account of costs directly related to the medical treatment of SMA patients, the quality of life of SMA patients and their carers. The approach to including cost and resource use in the model is described further in Section B.3.5.2. The approach to modelling HSUVs for patients and carers is outlined in Section B.3.4.5. As noted above, the model cycle length is one month and a half cycle correction is applied to account for mid-cycle transitions. Costs and benefits are discounted at 3.5% per year, as per the NICE reference case (117).

Table 51: Features of the economic analysis (type 1 model)

Factor	Previous appraisals	Current appraisal	
	TA588	Chosen values	Justification
Time horizon	Lifetime (60 years)	Lifetime (90 years)	The mean baseline age in the model is 0.48 years (5.8 months). In line with the NICE reference case (117) a lifetime time horizon of 90 years was selected to capture all costs and benefits associated with risdiplam or treatment with BSC. A time horizon of 90 years was selected so that effectively all patients in both treatment arms of the model would be dead by the end of the time horizon, therefore allowing for all cost benefits to be captured.
Long-term clinical outcomes	In the manufacturer's original base case early-onset SMA model, on-treatment transition probabilities during trial follow-up reflect motor milestone achievements from the ENDEAR trial. After trial follow-up, patients on nusinersen could only improve in health state, whilst patients on BSC could only decline or remain constant. As the ENDEAR trial included a placebo arm, the placebo data could be used to inform transition probabilities to worse health states for BSC in TA588. The Committee deemed that this approach substantially overestimated the proportion of patients receiving nusinersen who reached the best health states, as those who remained on treatment would continue to improve indefinitely. The company's final iteration of the model included an option for patients to plateau whilst remaining on treatment, resulting in a more plausible proportion of patients who could reach the best health states.	In the base case, patients on risdiplam treatment are assumed to either improve (in terms of health states achieved) or remain stable in the long-term (after 24 months). Whilst no advances to walking were observed during the FIREFISH trial (up to the latest cut-off), in the base case, a transition to the 'walking' health state for risdiplam was considered, on the basis that some patients in the study acquired further developmental milestones towards developing the walking function (bouncing). UK clinical experts agreed with this assumption. This assumption was tested in scenario analyses. Patients receiving BSC are assumed to remain stable or	This approach was validated by UK clinical expert opinion sought at advisory boards, which stated that the majority of patients receiving active treatment would remain stable or improve in the long-term. Clinicians also noted that it was clinically plausible for type 1 patients treated with BSC to only deteriorate in the long term, and to not remain stable when considering motor milestones in the long term (Appendix N). Evidence from the literature further illustrates that type 1 patients treated with BSC deteriorate over time (34). For completeness, scenario analyses have been conducted to explore the base case long-term assumptions, including varying the timepoint of initiation of 'long-term transition probabilities, varying the values of the 'long-term' transition probabilities in both arms and varying the proportion of

		deteriorate in the long-term. However, it was not possible to generate comparative efficacy estimates for 'backwards' transitions in the ITC described in Section B.2.9. As such, in the base case, backwards transition probabilities for BSC are assumed to be the same as risdiplam. This is a conservative assumption because it is anticipated that the risdiplam backwards transition probabilities will capture delayed regression to worse health states compared to BSC. This assumption is explored in a scenario analysis.	patients in the risdiplam arm who may achieve the 'walking' health state.
Source of utilities	The manufacturer included both patients and carer utilities in their early-onset SMA model. No HRQoL measures were included in the ENDEAR trial due to difficulties of these measurements in children. Therefore, in the original manufacturer's early-onset model, PedsQL collected from patients in the CHERISH trial were mapped to the EQ-5D, however, the revised base case (and ERG-preferred approach) was based on the Lloyd et al. 2019 EQ-5D vignette study (118). Estimates provided by clinical advisors were explored in scenario analyses and expected to show greater face validity but were not preference based. For caregiver utilities, the 'best' health state was assumed to be equal to general population utilities, and 'worst' health was assumed to be equal to mean caregiver utility scores from Bastida et al. 2017 (119). An equal difference in utility was assumed between adjacent health states.	**Patient HSUVs** HSUVs provided by the ERG clinical advisors in TA588 were selected for the base case due to their greater face validity and clinical plausibility. The Lloyd et al. 2019 EQ-5D vignette study (also used in TA588) will be explored in a scenario analysis (118). **Carer HSUVs** In line with the approach taken in TA588, carer HSUVs in the model were informed by Bastida et al. 2017 and general population utility (119, 120). EQ-5D-5L utility values were additionally collected from caregivers of SMA patients in a	**Patient HSUVs** Assessment of available sources of patient HSUVs for type 1 patients was conducted by UK clinical experts, who deemed the values provided by the ERG clinical advisors in TA588 to possess the greatest face validity in type 1 patients (Appendix N). **Carer HSUVs** Assessment of possible carer HSUVs was conducted by UK clinical experts, who deemed that the utility values informed by Bastida et al. and Ara et al. in TA588 demonstrated greater face validity than those collected as part of the Roche UK burden of illness study (Appendix N).

		Roche UK burden of illness study, and cross-walked to the EQ-5D-3L and valued using UK tariffs. These HSUVs are applied in a scenario analysis.	
Source of costs	Health state resource use was initially sourced from Bastida et al. 2017 (119). Following critique from the ERG that the Bastida et al. study greatly underestimated costs associated with SMA treatment, cost inputs were subsequently based on a UK real-world study using HES data linked to motor milestones. The costs relating to 'Type 1 milestones' had to be adjusted upwards, as clinical experts felt that the UK real-world study was still underestimating resource use for these patients.	Cost and resource use in the base case analysis is informed by the UK-based real-world study and estimates that informed the final NICE decision-making in TA588 (18). Given that costs for the permanent ventilation state were not explicitly included in TA588, an informed assumption had to be made for this health state. Therefore in the base case, the cost of the permanent ventilation health state is assumed to be 175% times the 'not sitting' health state. Additionally, the Roche UK burden of illness study was conducted. These data are used to inform a scenario analysis.	Extensive discussion took place to achieve consensus on appropriate cost and resource use for SMA in TA588 (18). For consistency in decision-making, and given that SMA-related costs were a significant driver of cost-effectiveness results in TA588, the same source has been utilised to inform costs in the base case for the risdiplam model. The permanent ventilation state was assumed to be associated with increased cost compared to the not sitting health state, as confirmed by UK clinical experts. Data from the Roche UK burden of illness study conducted by Roche were included in a scenario analysis.

3L: 3-level; 5L: 5-level; BSC: best supportive care; EQ-5D: Euro-QoL 5 Dimensions; ERG: Evidence Review Group; HES: hospital episode statistics; HRQoL: health-related quality of life; HSUV: health state utility value; ITC: indirect treatment comparison; PedsQL: Paediatric Quality of Life Inventory; RCT: randomised controlled trial; SMA: spinal muscular atrophy

B.3.2.3 Intervention technology and comparators

In both the type 2/3 and type 1 cost-effectiveness models, risdiplam is compared to BSC, as per the final NICE scope for this appraisal. No other therapies for the treatment of SMA had been recommended by NICE for routine NHS funding at the point of the risdiplam NICE evidence submission, therefore no other therapies were considered as relevant comparators.

In line with the anticipated SmPC wording (1) risdiplam was implemented in the models to be taken orally once a day. The recommended once daily dose of risdiplam is determined by patients' age and body weight, as presented in Table 52.

Table 52: Risdiplam dosing regimen by age and weight

Age	Recommended daily dose
2 months to <2 years of age	0.20 mg/kg
≥2 years of age (< 20 kg)	0.25 mg/kg
≥2 years of age (≥ 20 kg)	5 mg

Source: Draft risdiplam SmPC (1)

In the type 2/3 model, efficacy and safety for both risdiplam and BSC is informed by the risdiplam and placebo arms of the SUNFISH RCT, respectively.

In the type 1 model, efficacy and safety for risdiplam is informed by the single arm FIREFISH trial. Corresponding efficacy and safety estimates for BSC were generated through an ITC, as described in Section B.2.9.

Calculation of acquisition costs for risdiplam based on the average patient weight from the SUNFISH and FIREFISH trials are presented in Section B.3.5.1. Baseline weight and a fixed risdiplam dose is applied for patients in the type 2/3 model. For the type 1 model, weight and risdiplam dosage increase with age until patients have reached a weight of 20 kg, at which point a fixed dose is applied. For both models, costs applied to each health state are informed by TA588 in the base case and by the Roche UK burden of illness study described in Section B.3.5.2 in a scenario analysis. Health state costs are considered to be the same regardless of treatment arm (risdiplam or BSC), as per TA588 (18).

B.3.3 Clinical parameters and variables

B.3.3.1 Type 2/3 SMA (SUNFISH) Model

Baseline characteristics

The baseline characteristics for patients included in the type 2/3 (SUNFISH) model are presented in Table 53.

Table 53: Baseline characteristics (type 2/3 model base case)

Baseline characteristic	Value
Age, years; mean (SE)	[redacted]
Female (SE)	[redacted]
Type 2	71.1%
Type 3	28.9%

Not sitting	[redacted]
Sitting (supported)	[redacted]
Sitting (unsupported)	[redacted]
Standing	[redacted]
Walking	[redacted]
Respiratory support	[redacted]
Severe scoliosis (>40 degrees curvature)	32%

SE, standard error

It may be noted the baseline characteristics presented for the cost-effectiveness analysis differ from those presented in Section B.2.3. This is due to the following reasons: 1. In the model, the health states are mutually exclusive. Although patients that are able to walk are also able to stand, these will not appear in the model baseline proportions in the 'standing' state, but will be assigned to the 'walking' state due to their ability to walk. This is different from Section B.2.3, where all patients with the ability to stand are counted (irrespective if they are also able to walk or not). 2. Walking was defined differently in Section B.2.3 as compared to the model. In Section B.2.3, 'walking' is defined as HFMSE item 20 score ≥2 at baseline. However, in the model, 'walking' is defined as the highest current level of independent mobility.

Motor milestone transition probabilities

Clinical data from Part 2 of the SUNFISH trial up to 52 weeks were utilised to develop transition probabilities for the risdiplam and BSC arms in the Type 2/3 cost-effectiveness model. For the base case, the transition probabilities were informed by a subgroup of patients from the SUNFISH trial that excluded patients from Asia (China and Japan) (n=31), and were thus based in the Americas and Europe (n=149). This exclusion was performed to take into account UK clinical expert opinion at the advisory boards that potential differences in standard of care, such as physiotherapy practices, could mean that baseline characteristics may vary between regions (Appendix N). Transition probabilities from the entire population of the SUNFISH study are used in a scenario analysis.

As described in Section B.3.2.2, the motor milestone health states of 'not sitting', 'sitting supported', 'sitting unsupported' and 'standing' were defined by MFM-32 score, whilst the 'walking' health state was defined by HFMSE highest current level of independent mobility. In order to estimate the probability of transitions between motor milestone health states, continuous time Markov multi-state models were fitted to the data from the trial using the R package msm 1.6.7 (125). A single covariate for treatment effect was applied in the generation of transition probabilities. No further covariates were applied to avoid risking 'over-fitting' to the data.

A set of assumptions were made during the calculation of transition probabilities. Firstly, imputation was conducted to account for missing inputs in the calculation of transition probabilities. Specifically, if the motor milestone achieved in the next assessment to take place was equal to or better than the previously conducted assessment, the imputation was based on the last observation carried forward (LOCF). If the motor milestone achieved in the next assessment to take place was worse than the previous assessment, the imputation was based on the next observation carried backwards (NOCB). No values were imputed after patients discontinued the study (n=[redacted] in Part 2 of SUNFISH) (74). Imputed transition probabilities are utilised in the base case, whilst non-imputed transition probabilities are explored in a scenario analysis (Section B.3.8.3).

Finally, the assumption was made that a patient's improvement or deterioration in motor milestone achievement was sequential. Accordingly, if the raw data indicated that a patient

was observed to be at a milestone such as 'not sitting' during one visit and a better, non-sequential motor milestone at the next visit (e.g. 'standing' [item 25]), it was assumed the patient was capable of the intermediate motor function (e.g. 'sitting' [item 9]). Accordingly, whilst the multi-state model automatically calculates non-sequential health state transitions, these were not incorporated into the cost-effectiveness model. This assumption was consistent with clinical opinion that improvement or deterioration by greater than one milestone within the period of one month would not be expected in type 2/3 patients (126).

UK clinical experts agreed that the majority of SMA Type 2 or 3 patients receiving active treatment would be likely to maintain their health states or improve in the long-term (Appendix N). Therefore, the risdiplam transition probabilities were adjusted such that after 24 months, transition probabilities to worse milestones were reduced by [redacted]. Similarly, feedback from the clinicians was that in the long term, patients receiving BSC would only remain stable or deteriorate (Appendix N). Accordingly, after 24 months, transition probabilities were adjusted such that transitions to improved motor milestones were set to 0%. A timepoint of 24 months in the base case for the point up to which trial-based transition probabilities were applied was considered conservative, given that trial data were available up to a cut off of just 1 year.

The transition probabilities utilised in the base case (prior to the 24-month timepoint) for risdiplam and BSC are presented in Table 54 and Table 55, respectively.

Table 54: Risdiplam motor milestone monthly transition probabilities (Type 2/3 model base case)

	Non-sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
Non-sitting	[redacted]	[redacted]			
Sitting (supported)	[redacted]	[redacted]	[redacted]		
Sitting (unsupported)		[redacted]	[redacted]	[redacted]	
Standing			[redacted]	[redacted]	[redacted]
Walking				[redacted]	[redacted]

Footnotes: Top row represents resulting health state; left column represents originating health state. A patient's improvement or deterioration in motor milestone achievement was sequential; grey boxes represent transitions that are not possible.

Table 55: BSC motor milestone monthly transition probabilities (Type 2/3 model base case)

	Non-sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
Non-sitting	[redacted]	[redacted]			
Sitting (supported)	[redacted]	[redacted]	[redacted]		
Sitting (unsupported)		[redacted]	[redacted]	[redacted]	
Standing			[redacted]	[redacted]	[redacted]
Walking				[redacted]	[redacted]

Footnotes: Top row represents resulting health state; left column represents originating health state. A patient's improvement or deterioration in motor milestone achievement was sequential; grey boxes represent transitions that are not possible.

Assumptions around transition probabilities were varied in scenario analyses. For the risdiplam arm, the probability of transitioning to worse milestones after a period of 24 months was varied from a [redacted] reduction to between a [redacted] to a [redacted] reduction. The timepoint of initiation of the 'long-term' transition probabilities was also varied in a scenario to 12 months. In addition, a scenario was conducted where transition probabilities calculated based on the SUNFISH trial for the BSC arm were applied for the duration of the time horizon.

Overall survival

Mortality is treated separately in the model for type 2 and type 3 SMA patients. In order to inform mortality for type 2 patients in a systematic and explicit manner, the SLR conducted to identify HSUV data, reported in Section B.3.4.3 and Appendix H, was expanded to explore the natural history and survival of type 2 SMA patients. Briefly, search terms for mortality and survival were included in the electronic database searches of this SLR. During screening based on title and abstract; and full publication review, studies reporting survival curves in patients with SMA type 2 were tagged for consideration in the generation of SMA type 2 survival estimates. Following title/abstract screening a total of 79 publications were tagged as potentially relevant. At full publication review, seven studies were identified reporting type 2 SMA survival curves: Belter et al. 2018 (127), Chung et al. 2004 (128), Farrar et al. 2013 (129), Ge et al. 2012 (130), Mannaa et al. 2009 (131), Petit et al. 2011(132) and Zerres et al. 1997 (133). Given the likely heterogeneity between the studies captured, further consideration was given to the most appropriate studies to utilise to inform final survival estimates. Upon inspection of the individual and pooled Kaplan-Meier curves, it was observed that the study by Belter et al. reported higher survival compared to the other studies. The Belter et al. study used data from the Cure SMA database, a patient-reported data repository on SMA patients (127). As noted by the authors, limitations of the study include enrolment bias (Cure SMA membership may represent a more engaged population) and that data was patient reported, which is prone to reporting inaccuracies, incomplete information and errors in memory. As such, the Belter et al. study was conservatively excluded from the data set.

Data from the selected six studies were reported in the form of Kaplan-Meier curves, which were digitised and subsequently used to apply an algorithm devised by Guyot 2012 (134) using statistical software in R, in order to recreate pseudo-individual patient data (IPD). Following recreation of the pseudo-IPD, the data for each study were pooled to create one data set for survival in type 2 patients, which is presented in Figure 12. The survival predictions based on the pooled dataset alongside predictions made by clinicians are presented in Table 56.

Table 56: Long-term survival in type 2 patients: clinical opinion and pooled analysis excluding Belter et al. 2018

Year	Clinical opinion	Pooling scenario excluding Belter 2018
15	[redacted]	84%
30	[redacted]	71%
50	[redacted]	31%

Figure 12. Pseudo-IPD generated from studies identified in type 2 overall survival SLR (excluding Belter et al. 2018)

Footnotes: Units of time are months

Survival analysis based on the NICE decision support unit (DSU) guidance provided in NICE TSD 14 (135) was subsequently conducted in order to fit the most appropriate parametric survival function to the pseudo-IPD data. Specifically, goodness-of-fit statistics were obtained to understand which parametric form had the best fit to the SLR data, assessment of visual fit was conducted, and clinical expert opinion was sought regarding the plausibility of the long-term extrapolations of each function.

The parametric survival functions are presented against the Kaplan-Meier data in Figure 13. The goodness-of-fit statistics are presented in Table 57, which suggest that the generalised gamma offers the best fit to the data, followed by the Gompertz and the Weibull curves.

On visual inspection, the curves mostly closely aligned to the Kaplan-Meier data between years 0 to 25 are the Gompertz, Weibull and generalised gamma. Following the 25-year timepoint visual fit becomes difficult to assess due to the lower frequency of events in the Kaplan-Meier data. Feedback from the UK clinical experts was that the Gompertz and Weibull offer the most plausible long-term extrapolations for type 2 survival. The Gompertz is therefore used in the base case, with the Weibull explored in a scenario analysis.

Figure 13: Type 2 SMA overall survival parametric functions versus SLR Kaplan-Meier data (excluding Belter et al. 2018)

Table 57: Goodness-of-fit statistics for type 2 overall survival

Parametric distribution	AIC (rank)	BIC (rank)
Exponential	3434.1 (6)	3438.2 (6)
Weibull	3338.0 (3)	3346.1 (3)
Log-normal	3376.9 (5)	3385.1 (5)
Generalised gamma	3314.2 (1)	3326.5 (1)
Log-logistic	3363.9 (4)	3372.1 (4)
Gompertz	3328.0 (2)	3336.1 (2)

AIC: Akaike information criterion; BIC: Bayesian information criterion

There is evidence from the literature that the overall survival of type 3 patients is similar to that of the general population (98). Accordingly, type 3 patients in the model followed mortality estimates generated by the Office for National Statistics (ONS) for England (2019) (136).

In addition, as informed by the approach taken by the manufacturer in TA588, and UK clinical expert opinion (Appendix N), who noted that patients who reach advanced motor milestones are likely to follow an improved survival trajectory, type 2 patients who reach the advanced motor milestone of standing or walking, switch to the overall survival estimates generated by the ONS 2019 data (136).

Finally, in line with the approach taken for nusinersen in TA588, a 0.75 hazard ratio (HR) is applied to the risdiplam arm for type 2 patients, to reflect the anticipated reduced likelihood of mortality associated with treatment with risdiplam compared to BSC.

Discontinuation

Within Part 2 of the SUNFISH trial, [redacted] discontinued treatment during the placebo-controlled period; [redacted] patients in the risdiplam and [redacted] patient in the placebo arm. All [redacted] patients discontinued in order to switch to another treatment, specified as nusinersen in [redacted] patients and not specified in [redacted] patient. As such, there were very few data to inform likely discontinuation from risdiplam in clinical practice. Accordingly, it was necessary to seek UK clinical expert opinion on the likely discontinuation rate of risdiplam in clinical practice. Most clinical experts at the UK advisory boards indicated that they would likely not discontinue treatment in response to a patient plateauing. Furthermore, even if a patient worsened on risdiplam treatment, clinical experts would base their decision on discontinuation on whether the patient is declining at a slower rate than expected with BSC and whether alternative treatments are available.

Based on the trial data and clinical expert feedback, it was concluded that discontinuation of risdiplam was likely to take place rarely in clinical practice, and therefore no discontinuation was assumed.

Respiratory support (scenario analysis)

As described above, impaired lung function is an important cause of morbidity in SMA. Evidence from the literature is that a correlation exists between the need for respiratory support and motor milestone achieved. In a study of 170 treatment-naïve patients with SMA type 1c–4, respiratory function was assessed through measurement of patients' Forced Expiratory Volume in 1 s (FEV1), Forced Vital Capacity (FVC), and Vital Capacity (VC). The results of the study illustrated a correlation between lung function and SMA type from 1–4, which was used as a proxy for motor milestone achieved. The authors noted the progressive pattern of lung function decline in patients with SMA aligns with the observed progressive pattern of muscle strength decline (137). In addition, feedback from UK clinical experts on this matter was that any child requiring respiratory support (irrespective of SMA type) is going to be at a higher risk of chest infections. It was also noted that respiratory weakness mirrors muscle weakness (Appendix N).

Accordingly, within the type 2/3 model, a scenario analysis is explored whereby each motor milestone is associated with a proportion of patients who require respiratory support (the proportions, presented in Appendix N, were informed by UK clinical experts). The need for respiratory support is associated with a disutility sourced from the analyses of EQ-5D-5L data conducted from the SUNFISH trial (Section B.3.4).

B.3.3.2 Type 1 SMA (FIREFISH) Model

Baseline characteristics

The baseline characteristics for patients included in the type 1 (FIREFISH) model are presented in Table 58.

Table 58: Baseline characteristics (type 1 model base case)

Baseline characteristic	Value
Age, years; mean (SE)	0.48
Female	57%
Body weight, kg; mean (SE)	[redacted]
Type 1	[redacted]
Permanent ventilation	[redacted]
Not sitting	[redacted]
Sitting	[redacted]
Standing	[redacted]
Walking	[redacted]
Non-permanent respiratory support	[redacted]
Severe scoliosis (>40 degrees curvature)	[redacted]

SE, standard error

Motor milestone transition probabilities

Clinical data from the population who received the final dose of risdiplam in the FIREFISH trial who had at least 52 weeks follow-up were utilised to develop transition probabilities between motor milestone health states for the risdiplam arm in the type 1 cost-effectiveness model. The decision was made to incorporate Part 1 patients (who achieved the final risdiplam dose) so that the transition probabilities would be informed by a greater number of patients, and results would have greater robustness and statistical power. A subgroup analysis excluding patients in some regions (similarly to the SUNFISH model) was not performed, as the lower number of patients in the FIREFISH study was not deemed sufficient to generate robust transition probabilities.

As described in Section B.3.2.2, the motor milestone health states of ‘not sitting’, ‘sitting’ and ‘standing’ were defined by HINE-2 scores. In order to estimate the probability of transitions between motor milestone health states, a continuous time Markov multi-state model was fitted to the data from the trial using the R package msm 1.6.7. Baseline HINE-2 total score centred around the mean was included as a covariate for the “not sitting” to “sitting” transition only, as this transition occurred more frequently in the clinical data compared to transitions between other motor health states. No transitions to ‘walking’ took place in the timeframe of the FIREFISH study (up to the latest data cut-off), however, within the model, transitions were enabled for patients treated with risdiplam from ‘standing’ to ‘walking’ from the age of 2 onwards. This transition was calculated to be one third (33%) of the transition probability for ‘sitting’ to ‘standing.’ This adjustment is supported by the fact that some patients during the one-year follow-up period of the FIREFISH study acquired further development milestones towards developing the walking function, such as bouncing. UK clinical experts agreed with this assumption (Appendix N) and similar discussion in TA588 concluded that there is evidence that a small proportion of type 1 patients reach the ‘walking’ milestone in their lifetime. Furthermore, after 24 months (as per the type 2/3 analysis, this timepoint was varied to 12 months in a scenario), patients treated with risdiplam remain stable or improve in the long-term, whilst patients in the BSC arm remain stable or deteriorate in the long term. This is similar to the approach taken for the type 2/3 model.

These long-term assumptions are informed by the precedent in TA588 and UK clinical expert opinion, and are further explored in scenario analyses.

Finally, the assumption was made that a patient's improvement or deterioration in motor milestone achievement was sequential. Accordingly, if the raw data indicated that a patient was observed to be at a milestone such as 'sitting' during one visit and a better, non-sequential motor milestone at the next visit (e.g. walking), it was assumed the patient was capable of the intermediate motor function (e.g. standing). Therefore, whilst the multi-state model automatically calculates non-sequential health state transitions, these were not incorporated into the cost-effectiveness model. It was clinically validated that improvement or deterioration by greater than one milestone within the period of one month would not be expected in type 1 patients (126).

Since FIREFISH was a single-arm study, transition probabilities for the BSC arm could not be directly estimated from the study. Therefore, an ITC was implemented, with a naïve comparison used in the base case of the economic model and a matching-adjusted indirect comparison (MAIC) in the scenario analysis, as described in Section B.2.9. The following approach was taken in order to subsequently generate transition probabilities for the BSC arm. Odds ratios were generated for risdiplam versus BSC from the naïve comparison or the MAIC. The transitions between 1) 'not sitting' and 'sitting' and 2) 'sitting' and 'standing' were informed by the HINE-2 outcomes of 'sitting with and without support' and 'standing with support and unaided' assessed in the ITC analysis, respectively.

The ITC presents results of the HINE-2 at the 12-month timepoint. The resulting odds ratio for the BSC comparator was applied to the annual odds ratio for risdiplam, which was transformed to generate monthly transition probabilities. The odds ratios for 'not sitting' to 'sitting' and 'sitting' to 'standing' were applied as forward transitions.

$$Pbsc_{annual} = \text{odds ratio risdiplam} * 1/\text{odds ratio BSC}$$

For the incorporation into the model, these had to be adjusted to the cycle length of 1 month. Therefore, the annual probability was converted to a monthly probability using the following formula:

$$P_{1m}=1-EXP(LN(1-P_{12m})/12)$$

Within the ITC it was not possible to generate comparative estimates for backwards transitions, i.e. 'sitting' to 'not sitting'. At the UK clinical advisory boards, HCPs validated that risdiplam was highly likely to delay deterioration to worse health states compared to BSC (Appendix N). In the base case, in lieu of data, backwards transitions for BSC were conservatively assumed to be the same as risdiplam. However, in a scenario analysis, the per-cycle transition probabilities for backwards transitions for BSC were assumed to be 2 times that of risdiplam backwards transitions.

Accordingly, the transition probabilities includes in the base case for risdiplam and BSC (prior to 24 months) are presented in Table 59 and Table 60.

Table 59: Risdiplam motor milestone transition probabilities (Type 1 model base case)

	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]		

Sitting	[redacted]	[redacted]	[redacted]	
Standing		[redacted]	[redacted]	[redacted]
Walking			[redacted]	[redacted]

Footnotes: Top row represents resulting health state; left column represents originating health state. A patient's improvement or deterioration in motor milestone achievement was sequential; grey boxes represent transitions that are not possible.

Table 60: BSC motor milestone transition probabilities (Type 1 model base case)

	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]		
Sitting	[redacted]	[redacted]	[redacted]	
Standing		[redacted]	[redacted]	[redacted]
Walking			[redacted]	[redacted]

Footnotes: Top row represents resulting health state; left column represents originating health state. A patient's improvement or deterioration in motor milestone achievement was sequential; grey boxes represent transitions that are not possible.

Transitions to permanent ventilation

Transitions to the 'permanent ventilation' can only be made from the 'not sitting' health state, and this transition was informed through parametric survival analysis of ventilation-free survival data for risdiplam from Part 1 and 2 patients from FIREFISH who had received the final risdiplam dose at the 1 year cut-off date. The definition of permanent ventilation in the trial is >16 hours of non-invasive ventilation, such as BiPAP, per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy. Ventilation-free survival is a composite endpoint of time to permanent ventilation or death, and is measured as time in months from the date of enrolment. Accordingly, in order to isolate transitions to the 'permanent ventilation' health state only, it was necessary to subtract the ventilation-free survival curves from the overall survival curves (please see below for overall survival).

As described in Section B.2.6.1.2, time to permanent ventilation data from the FIREFISH trial were immature, with median time to permanent ventilation not having been reached at the time of data cut-off. Given the few data available at this early cut-off and finite length of the FIREFISH trial, it was necessary to use techniques to extrapolate the trial data for the length of the model time horizon. Given that data are extrapolated into the long term, this process is associated with uncertainty, which has been mitigated as far as possible through informing parametric survival curve selection with clinical opinion, and varying curve selection in scenario analyses, as recommended by NICE TSD (135). Survival analysis was conducted to fit the most appropriate parametric survival functions to the Kaplan-Meier data for risdiplam from FIREFISH. Goodness-of-fit statistics were obtained to understand which parametric form had the best fit to the Kaplan-Meier data from the FIREFISH trial, UK clinical expert opinion was sought regarding the plausibility of the long-term extrapolations of each function. Due to current short follow-up of the FIREFISH trial, performing an assessment of visual fit of the curves to the short-term Kaplan-Meier data was not feasible.

Analysis of log-cumulative hazard plots (presented in Appendix N) for both the naïve comparison and MAIC for ventilation-free survival indicate that the proportional hazards assumption was held, with both treatment arms (risdiplam and BSC) remaining parallel.

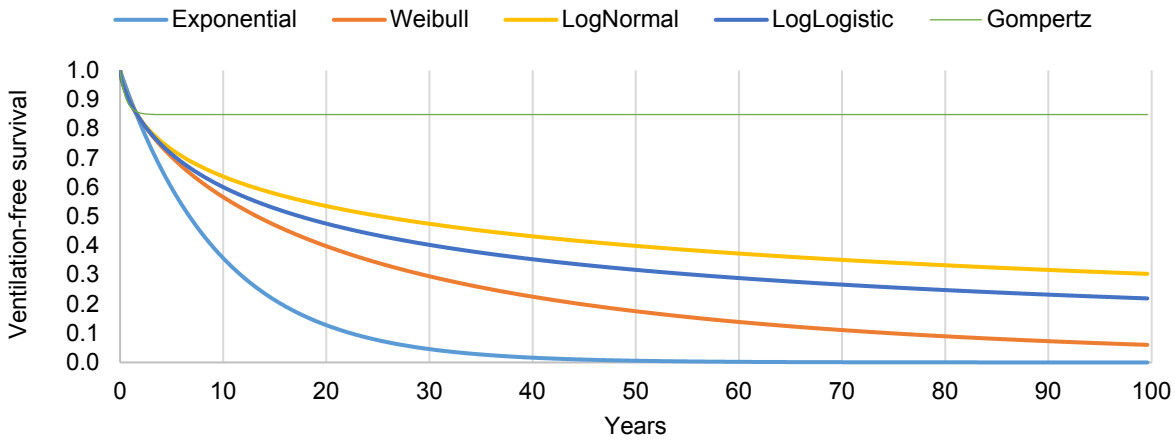
The parametric survival functions tested are presented in Figure 14. The goodness-of-fit statistics are presented in Table 61, which suggest that all curves offer a similar fit to ventilation-free survival data from FIREFISH, but that Gompertz offers the best fit to the data. However, due the current short follow-up duration of the FIREFISH trial, emphasis was placed on the long-term clinical plausibility of the survival curves. Two UK clinical experts was consulted to assess the curves, and it was deemed that the exponential curve offered the greatest clinical plausibility in terms of long-term predictions for ventilation-free survival in type 1 patients. As such, the exponential parametric form was selected for the model base case. Other parametric models were not explored in scenario analyses, as the clinicians did not deem them to have clinical validity.

Table 61: Goodness-of-fit statistics for type 1 ventilation-free survival

Parametric distribution	AIC (rank)	BIC (rank)
Exponential	94.10 (3)	96.20 (1)
Weibull	94.80 (5)	99.00 (5)
Log-normal	93.70 (2)	97.80 (3)
Generalised gamma	Did not converge	Did not converge
Log-logistic	94.60 (4)	98.70 (4)
Gompertz	92.30 (1)	96.40 (2)

AIC: Akaike information criterion; BIC: Bayesian information criterion

Figure 14: Type 1 ventilation-free survival parametric functions



Footnotes: Kaplan-Meier data are not shown due to the short follow-up for which survival data are available. The generalised gamma curve is not presented as it did not converge.

In order to generate ventilation-free survival estimates for BSC to inform the equivalent transition, the HR for event-free survival (EFS) generated within the ITC (see Section B.2.9) was applied to the risdiplam arm.

Overall survival

In order to estimate mortality for patients in the type 1 model, parametric survival analysis of OS data for risdiplam from Part 1 and 2 patients from FIREFISH who had received the final risdiplam dose at the 1-year cut-off date was conducted. Time to death was a secondary efficacy endpoint in the FIREFISH study and is defined as time in months from date of enrolment until the date of death from any cause. As described above for EFS, OS data from

the FIREFISH trial were immature, with median time to death not having been reached at the time of data cut-off (Section B.2.6.1.2). As per permanent ventilation, survival analysis was conducted in line with NICE TSD 14, with goodness-of-fit statistics obtained to understand which parametric form had the best fit to the Kaplan-Meier data from the FIREFISH trial and UK clinical expert opinion sought regarding the plausibility of the long-term extrapolations of each function.

Analysis of log-cumulative hazard plots (presented in Appendix O) for both the naïve comparison and MAIC for overall survival indicate that the proportional hazards assumption was held, with both treatment arms (risdiplam and BSC) remaining parallel.

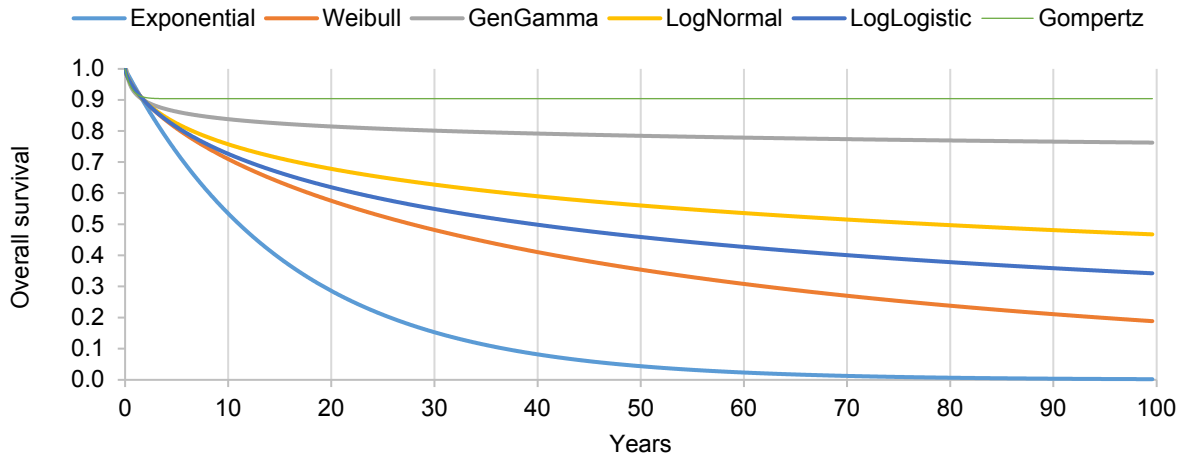
The parametric survival functions for overall survival are presented in Figure 15. The goodness-of-fit statistics are presented in Table 62, which suggest that the generalised gamma, Gompertz and exponential curves offer the best fit to the data. However, in line with ventilation-free survival, the timeframe over which overall survival data are available is currently short, and emphasis was placed on the long-term clinical plausibility of the curves over fit to trial data. Two UK clinical experts consulted deemed the exponential to be the most plausible extrapolation. The exponential parametric form was therefore selected for the model base case. Other parametric models were not explored in scenario analyses, as the clinicians did not deemed them to have clinical validity.

Table 62: Goodness-of-fit statistics for type 1 overall survival

Parametric distribution	AIC (rank)	BIC (rank)
Exponential	64.60 (3)	66.60 (1)
Weibull	65.70 (6)	69.80 (5)
Log-normal	65.10 (4)	69.20 (4)
Generalised gamma	62.50 (1)	68.70 (3)
Log-logistic	65.60 (5)	69.80 (5)
Gompertz	64.30 (2)	68.40 (2)

AIC: Akaike information criterion; BIC: Bayesian information criterion

Figure 15: Type 1 overall survival parametric functions



Footnotes: Kaplan-Meier data are not shown due to the short follow-up for which survival data are available.

The HR for OS generated within the ITC (see Section B.2.9) was applied to the risdiplam arm for patients in the 'not sitting' health state. Survival was assumed to be the same between the risdiplam and BSC arms for the remainder of the health states.

Similarly to the approach taken for mortality in the type 2/3 model, within the type 1 model, patients who achieved the advanced milestones of either 'standing' or 'walking' transitioned to type 2 mortality, details of which are described in the methodology for the type 2/3 model in Section B.3.3.1.

Discontinuation

Within the FIREFISH trial, [redacted] in Part 2 had discontinued treatment as of the latest data cut-off.
[redacted] Feedback from UK clinicians regarding conditions in which they would discontinue risdiplam treatment was sourced during the advisory board, which was reported in Section B.3.3.1 and in Appendix N. Based on the trial data and clinical expert feedback, it was concluded that discontinuation of risdiplam was unlikely to take place in clinical practice, and therefore no discontinuation was assumed.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Type 2/3 (SUNFISH) model

EQ-5D-5L data were collected from patients within the SUNFISH trial (74). As described in Section B.3.4.5, these data were cross-walked to the EQ-5D-3L and valued using the UK value set (138), and utilised in a scenario analysis for type 2/3 cost-effectiveness analysis. However, the health-related quality-of-life data from the SUNFISH trial lacked differentiation between health states and face validity compared to the values from TA588 according to UK clinical expert opinion (Appendix N).

Type 1 (FIREFISH model)

Within the FIREFISH study, the Infant Toddler Quality of Life (ITQOL) Questionnaire was used. However, utility data were not collected, as the EQ-5D is not validated in children and there are well-known limitations in conceptualising, collecting and measuring utility data in infants and young children (139). Proxy assessments of patient HRQoL may be possible by parents or carers, but may nevertheless fail to produce a balanced assessment of HRQoL in SMA.

B.3.4.2 Mapping

Due to the availability of the EQ-5D data to inform both the type 2/3 and type 1 models, sourced from the literature and previous NICE appraisals (18, 118), it was not deemed necessary to undertake any mapping from HRQoL scales to HSUVs for either cost-effectiveness model.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted in August 2019 to identify HSUV studies in patients with SMA. Eligibility criteria were not limited by type of SMA, severity or age of onset.

A total of 6,188 articles were identified from the searches, of which 443 papers relevant to cost-effectiveness were identified for full text review. Ultimately, four full publications and one conference abstract of HSUV studies were included in the review.

The results of the HSUV SLR are presented in Table 63; full details of the search strategy and the complete results are presented in Appendix H.

Table 63: Summary of identified studies reporting HSUVs associated with SMA (n=5)

Study, country	Population (sample size)	Interventions/ comparators	Method used to derive utilities	Health states	HSUV (95% CI) [SD]	Summary of reported study conclusions and limitations	Summary of quality and relevance to HTA assessment (including NICE reference case)
Lloyd, 2019 UK (118) (full publication; supplemented by health-state caregiver disutility values taken from Zuluaga-Sanchez et al [2019] (111-113)	UK clinical experts on behalf of patients with SMA type 1 and 2 (N=5)	• Nusinersen • SOC	Instrument: EQ-5D-Y Valuation method: UK tariff	Patients with SMA type 1, baseline	-0.120 [0.19]	Study conclusions • The utility scores obtained in this study highlight the substantial burden experienced by SMA patients Study limitations • Utilities derived from clinical experts for a set of vignettes health states on behalf of patients with SMA	• This study does not meet the requirements of the NICE reference case; clinical experts were used to provide a proxy assessment for patients with SMA. • This is a UK study which would likely be relevant for a UK setting • Absence of measures of uncertainty for caregiver utilities may restrict their usefulness for informing economic evaluation. However, the standard deviations around the mean scores reported for patients are quite low, despite the fact that the study included only a small number of experts (n=5) • Small sample size and absence of
				Patients with SMA type 1, worsened	-0.240 [0.14]		
				Patients with SMA type 1, improvement	-0.170 [0.17]		
				Patients with SMA type 1, sits without support [reclassified as type 2]	-0.040 [0.12]		
				Patients with SMA type 1, stands with assistance	0.040 [0.09]		
				Patients with SMA type 1, walks with assistance‡	0.520 [0.22]		
				Patients with SMA type 1, stand/walks unaided [reclassified as SMA type 3]	0.710 [0.14]		
				Patients with SMA type 1, after scoliosis surgery	-0.22 [0.22]		
				Patients with SMA type 1, gastric/nasogastric tube	-0.17 [0.17]		

Study, country	Population (sample size)	Interventions/ comparators	Method used to derive utilities	Health states	HSUV (95% CI) [SD]	Summary of reported study conclusions and limitations	Summary of quality and relevance to HTA assessment (including NICE reference case)
				Patients with SMA type 1, requires ventilation	-0.33 [0.27]		details regarding response rates and missing data
				Patients with SMA type 2, baseline	0.04 [0.10]		
				Patients with SMA type 2, worsened	-0.130 [0.06]		
				Patients with SMA type 2, mild improvement	0.040 [0.11]		
				Patients with SMA type 2, moderate improvement	0.100 [0.09]		
				Patients with SMA type 2, stands/walks with assistance‡	0.390 [0.29]		
				Patients with SMA type 2, stands/walks unaided‡	0.720 [0.12]		
				Patients with SMA type 2, loss of ambulation with/without assistance‡	-0.120 [0.16]		
				Caregiver SMA type 1/2, worsened	−0.160 (NR)		
				Caregiver SMA type 1/2, stabilisation of baseline function	−0.040 (NR)		

Study, country	Population (sample size)	Interventions/ comparators	Method used to derive utilities	Health states	HSUV (95% CI) [SD]	Summary of reported study conclusions and limitations	Summary of quality and relevance to HTA assessment (including NICE reference case)
				Caregiver SMA type 1/2, improvement	−0.090 (NR)		
				Caregiver SMA type 1/2, sits without support	0.000 (NR)		
				Caregiver SMA type 1/2, stands with assistance	0.000 (NR)		
				Caregiver SMA type 1/2, walks with assistance	0.000 (NR)		
				Caregiver SMA type 1/2, stands/walks unaided	0.000 (NR)		
				Caregiver SMA type 1/2, loss of later-onset SMA advanced motor function	−0.160 (NR)		
Lopez-Bastida, 2017 Spain (119) (full publication)	Caregivers on behalf of patients with SMA type 1 (N=8), 2 (N=60), and 3 (N=13)	NA	Instrument: EQ-5D-3L (caregivers as proxies for patients) EQ-5D-5L (for caregivers) Valuation method: NR	Caregivers on behalf of patients with SMA, all patients (N=81)	0.158 [0.44]	Study conclusion • Patients with SMA and their caregivers experience a significant deterioration in HRQoL compared with the general Spanish population Study limitations	• This study does not meet the requirements of the NICE reference case; caregivers were used as proxy respondents on behalf of patients • This study was based in Spain and utilised Spanish
				Caregivers on behalf of patients with SMA type 2 (N=60)	−0.012 [0.347]		

Study, country	Population (sample size)	Interventions/ comparators	Method used to derive utilities	Health states	HSUV (95% CI) [SD]	Summary of reported study conclusions and limitations	Summary of quality and relevance to HTA assessment (including NICE reference case)
				Caregivers of patients with SMA (N=81)	0.484 [0.448]	• Potential selection and recall bias • Potential misrepresentation when assigning a health status to children	data; it is unclear if the results are generalisable to the UK setting • Small sample size and absence of details regarding response rates and missing data
				Caregivers of patients with SMA type 2 (N=60)	0.472 [0.475]		
Malone, 2019 USA (108) (full publication)	Patients with SMA type 1 (sample size, NR)	• AVXS • Nusinersen	Instrument: PedsQL data (from CHERISH trial) mapped to EQ-5D-Y Valuation method: NA	Patients with SMA type 1, permanent ventilation	0.730	Study conclusions • AVXS has potential to restore normal motor and respiratory function in paediatric patients, and represents a step-change in the management of SMA type 1 Study limitations • The data reported is only generalisable to SMA type 1 patients with two copies of the SMN2 gene patients due	• This study does not meet the requirements of the NICE reference case; PedsQL data from the CHERISH trial was mapped to EQ-5D-Y utilities using a published algorithm • This study was based in the USA and utilised American data; it is unclear if the results are generalisable to the UK setting • Absence of measures of
				Patients with SMA type 1, aligns with SMA type 1	0.756		
				Patients with SMA type 1, aligns with SMA type 2	0.764		

Study, country	Population (sample size)	Interventions/ comparators	Method used to derive utilities	Health states	HSUV (95% CI) [SD]	Summary of reported study conclusions and limitations	Summary of quality and relevance to HTA assessment (including NICE reference case)
				Patients with SMA type 1, aligns with SMA type 3	0.878	to the clinical trial population	uncertainty for reported utilities may restrict their usefulness for informing economic evaluation • Absence of details regarding response rates, loss to follow up, and missing data
				Patients with SMA type 1, aligns with a broad spectrum of normal development	0.878		
Sampson, 2018 Europe (France, Germany, Spain, and the UK) (140, 141) (full publication; linked to BURQOL-RD study (142)†; used as a source of caregiver utilities in NICE TA588 (18)	Caregivers of patients with SMA (no further details provided) (sample size, NR)	NA	Instrument: EQ-5D-3L (parent-proxy) Valuation method: NR	Caregivers on behalf of patients with SMA	0.22	Study conclusion • The study highlighted potential strategies for improvement of the quantity and quality of data available to inform decision makers in the context for rare diseases Study limitations • None reported	• This study does not meet the requirements of the NICE reference case; caregivers were used as proxy respondents on behalf of patients • The study enrolled caregivers across France, Germany, Spain, and the UK; the results are therefore likely to be generalisable to the UK setting • Absence of details regarding response rates and missing data

Study, country	Population (sample size)	Interventions/ comparators	Method used to derive utilities	Health states	HSUV (95% CI) [SD]	Summary of reported study conclusions and limitations	Summary of quality and relevance to HTA assessment (including NICE reference case)
Thompson, 2017 (143) Europe (France, Germany, Spain, and the UK)	Parents of paediatric patients with SMA (N=167) and patients with SMA type 2 (sample size, NR)	NA	Instrument: EQ-5D-3L (parent-proxy) PedsQL mapped to EQ-5D-Y Valuation method: NR	Parents on behalf of patients with SMA, Spain (N=81)	0.158	Study conclusion • In general, parents rated HRQoL highly which is consistent with studies in other paediatric diseases Study limitations • None reported	• This study does not meet the requirements of the NICE reference case; parents were used as proxy respondents on behalf of patients • The study was based across France, Germany, Spain, and the UK; the results are therefore likely to be generalisable to the UK setting • Absence of measures of uncertainty for some reported utilities may restrict their usefulness for informing economic evaluation • Absence of details regarding response rates and missing data
				Parents on behalf of patients with SMA, UK (N=34)	0.167		
				Parents on behalf of patients with SMA, France (N=26)	0.116		
				Parents on behalf of patients with SMA, Germany (N=26)	0.532		
				Patients with SMA type II, worsened (N=131)	0.730 [SE 0.0132]		
				Patients with SMA type 2, stabilisation of baseline function (N=146)	0.756 [SE 0.0188]		
				Patients with SMA type 2, mild improvement (N=79)	0.716 [SE 0.0174]		
				Patients with SMA type 2, moderate improvement (N=154)	0.764 [SE 0.0142]		
				Patients with SMA type 2, stands/walks with	0.807 [SE 0.0182]		

Study, country	Population (sample size)	Interventions/ comparators	Method used to derive utilities	Health states	HSUV (95% CI) [SD]	Summary of reported study conclusions and limitations	Summary of quality and relevance to HTA assessment (including NICE reference case)
				assistance (N=53)			
				Patients with SMA type 2, stands unaided (N=28)	0.805 [SE 0.0256]		
				Patients with SMA type 2, walks unaided (N=10)	0.878 [SE 0.0297]		
				Patients with SMA type 2, loss of motor function (N=11)	0.774 [SE 0.0303]		

BURQOL-RD, Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe; CI, confidence interval; EQ-5D-Y, European Quality of Life-5 Dimensions – Youth version; EQ-5D-3L, European Quality of Life-5 Dimensions-3 levels; EQ-5D-5L, European Quality of Life-5 Dimensions-5 levels; HRQoL, health related quality of life; HSUV, Health state utility value; HTA, Health Technology Assessment; ISPOR, international society of pharmacoeconomics and outcomes research; NICE; National Institute for Health and Care Excellence; NA, not applicable; NR, not reported; PedsQL, Paediatric Quality of Life Inventory; SD, standard deviation; SE, standard error; SMA, spinal muscular atrophy; SMN, survival-motor-neuron; SOC, standard of care; UK, United Kingdom, USA, United States America.

†Data referenced from López-Bastida et al (2017) (142); however, utility data for SMA are not reported in this publication.

‡Denotes health states where two index scores were calculated by one of the participants. This clinician had some difficulties providing a rating for some domains of the EQ-5D-Y for some case studies. In order to reflect this uncertainty, for these health states two index scores were calculated for this clinician, one using the less severe response and one using the more severe response; both index scores were included in the calculation of the mean score and standard deviation for those health states.

B.3.4.4 Adverse reactions

Treatment related adverse events of Grade 3+ were planned to be included in the models if they occurred in >5% of patients in the risdiplam trials. However, as the incidence of adverse events experienced by patients that were considered to be related to treatment in both the SUNFISH and FIREFISH trials was very low (<5% overall), adverse events have not been included in either the type 2/3 or type 1 models (Section B.3.5.3). This is in line with the nusinersen NICE submission (TA588) (18) where adverse events were also excluded.

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

Type 2/3 (SUNFISH) model

Within the model base case, given the substantial amount of care that SMA patients require from family members or professional carers, and in line with the approach taken in TA588 (18) and the NICE reference case (117) HSUVs were included in the model for both patients and carers.

With regards to HSUVs for patients, as described in Section B.3.4.1, HSUVs were available from the RCT for risdiplam in type 2/3 patients (SUNFISH). In order to understand the effects of motor milestone achievement on utility values, a repeated measures model with fixed and random effects was applied to the EQ-5D-5L data from the ITT population of Part 2 of the SUNFISH study. Analyses by presence of scoliosis and respiratory support at baseline were also conducted, the results of which identified scoliosis and respiratory support to be drivers of additional disutility. Disutilities for these two morbidities were calculated accordingly. In addition to scoliosis and respiratory support, the model also showed improvements to utility when patients were old enough to self-report (12 years old and older), and an additional utility was applied upon patients reaching this age. This highlights again the difficulties of capturing utilities in young children Data were subsequently cross-walked to the EQ-5D-3L and valued using the UK tariffs using the algorithm by van Hout et al. 2012 (138).

In addition, a number of utility sources for type 2/3 patients explored in the NICE appraisal for nusinersen in SMA (TA588) were available (18). Within the appraisal for nusinersen, the two sets of utilities considered to have the greatest face validity by the ERG were those estimated in an EQ-5D vignette study of SMA patients by Lloyd et al (118) and values estimated by clinical advisors to the ERG (18). These two sets, in addition to those sourced from the SUNFISH trial, were presented to UK clinical experts at the advisory boards in order to receive their commentary on the clinical validity of the values. Feedback from the HCPs was that the utility values from TA588 were more realistic than the SUNFISH values, as they better reflect the broad range of HRQoL between milestones. Whilst the HSUVs elicited from the SUNFISH trial align with the requirements of the NICE reference case, the clinicians deemed the minimal difference between HSUVs of different health states to be unreflective of the independence and gains in quality of life with each motor milestone advance made by a patient. UK clinical experts advised that utilities would be expected to increase with higher motor milestones (Appendix N). The utility values sourced from the Lloyd et al (2019) vignette study were chosen as the base case to align with what was considered for final decision-making in the TA588 submission (18, 118), while the utility values derived from the TA588 ERG clinical advisers and SUNFISH were included as scenario analyses.

The health states used in the manufacturer's model in TA588 were based on motor milestones, but the structure differed slightly from the risdiplam model (18). Accordingly, HSUVs from the TA588 model were applied to the closest corresponding motor milestone health states in the risdiplam model. Where a health state in the risdiplam model was deemed to fall between two health states, the mid-point HSUV was calculated. The same principle applies for the carer utilities and type 1 utilities (patients and carers) described below. Further details of the translations in HSUVS are presented in Appendix Q.

The HSUVs utilised in the base case are presented in Table 64. The HSUVs elicited from the TA588 ERG clinical experts and those from SUNFISH were explored in scenario analyses and are presented in Table 65 and Table 66, respectively.

Table 64: Summary of patient utility values for cost-effectiveness analysis (type 2/3 base case model) (Lloyd et al. 2019)

State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	−0.170	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Lloyd et al. study possessed the greatest clinical validity for type 2/3 patients (Appendix N) (118).
Sitting (supported)	0.040	NA		
Sitting (unsupported)	0.040	NA		
Standing	0.555	NA		
Walking	0.555	NA		

HSUV, health state utility value; NA, not applicable

Table 65: Summary of patient utility values for cost-effectiveness analysis (type 2/3 scenario analysis) (utilities from TA588 ERG clinical experts)

State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	0.350	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Lloyd et al. study possessed the greatest clinical validity for type 2/3 patients (Appendix N) (118).
Sitting (supported)	0.600	NA		
Sitting (unsupported)	0.600	NA		
Standing	0.800	NA		
Walking	0.800	NA		

HSUV, health state utility value; NA, not applicable

Table 66: Summary of patient utility values for cost-effectiveness analysis (type 2/3 scenario analysis) (SUNFISH EQ-5D-3L utilities)

State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	[redacted]	[redacted]	Section B.3.4.5	HSUVs (EQ-5D-5L) were directly elicited from patients in the SUNFISH trial. However, feedback from UK clinical experts was that HSUVs sourced from the Lloyd et al. study possessed the greatest clinical validity for type 2/3 patients (Appendix N) (118).
Sitting (supported)	[redacted]	[redacted]		
Sitting (unsupported)	[redacted]	[redacted]		
Standing	[redacted]	[redacted]		
Walking	[redacted]	[redacted]		
Disutilities				
Severe scoliosis	[redacted]	[redacted]	Section B.3.4.5	As above, in addition, scoliosis and respiratory support were deemed to have a significant impact on utility. Disutilities were used as part of a scenario analysis exploring the impact of severe scoliosis and the need for respiratory support.
Respiratory support	[redacted]	[redacted]		
Additional utility				
Patient-reported utilities (over 12 years old)	[redacted]	[redacted]	Section B.3.4.5	Age over 12 was deemed to have a significant impact on utility

EQ-5D-3L, European Quality of Life-5 Dimensions-3 levels; HSUV, health state utility value

In line with the approach taken for patient utilities, alternative sources were considered for carer HSUVs. Firstly, values were available from the Roche UK burden of illness study conducted by Roche in caregivers of SMA patients in the UK [Appendix P]. Within this study, carers were administered the EQ-5D-5L questionnaire and scores were subsequently cross-walked to the EQ-5D-3L and valued using UK tariffs (138). The motor milestone level of the patient for whom the carer was associated with was recorded; carer utilities associated with the motor milestone health states for patients in the cost-effectiveness model were thereby obtained. Further details of the study methodology can be found in Appendix P. The results

of this study demonstrated that the overall mean EQ-5D-5L cross-walked value for carers was [redacted], with similar values recorded for carers of patients in all mobility groups.

Carer HSUVs were available from a study by Bastida et al. (119), which were also used to inform carer utilities in TA588 (18). As per the approach taken in TA588, the utility derived from Bastida et al. was assigned to the lowest health state ('not sitting'), whilst general population utility derived from a study by Ara et al. was assigned to the highest health state (120). HSUVs for intermediate health states were then calculated with an even distribution. Similarly to the patient HSUVs, the two sets of carer utility values were presented to UK clinical experts at two advisory boards to understand which would be most appropriate to include in the model base case. The consensus was that the value set based on Bastida et al. and general population utility was more plausible than the set sourced from the Roche UK burden of illness study, due to the distribution of values more accurately reflecting the levels of dependence of patients on their carers at the different health states. Furthermore, UK clinical experts thought that the carer utility values from the Roche UK burden of illness study were too high, particularly for the lower health states (Appendix N). As such, the HSUVs based on the Bastida et al. study, presented in Table 67, were included in the base case, to ensure consistency in NICE decision-making with TA588, whilst the carer utilities from the Roche UK burden of illness study were explored in a scenario analysis (Table 68)

Table 67: Summary of carer utility values for cost-effectiveness analysis (type 2/3 base case model) (Bastida et al. 2017 and Ara et al. 2010)

State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	0.484	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. study and general population utility possessed the greatest clinical validity for carers of SMA patients (Appendix N) (119, 120)
Sitting (supported)	0.610	NA		
Sitting (unsupported)	0.735	NA		
Standing	0.861	NA		
Walking	0.861	NA		

HSUV, health state utility value; NA, not applicable

Table 68: Summary of carer utility values for cost-effectiveness analysis (type 2/3 scenario model) (Roche UK burden of illness study)

State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	[redacted]	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. and Ara et al. studies possessed the greatest clinical validity for
Sitting (supported)	[redacted]	NA		
Sitting (unsupported)	[redacted]	NA		

Standing	[redacted]	NA		carers of SMA patients (Appendix N) (119, 120)
Walking	[redacted]	NA		

HSUV, health state utility value; NA, not applicable

The average number of caregivers per SMA patient applied in the model was 2.2, based on data obtained in the Roche UK burden of illness study.

Type 1 SMA (FIREFISH) model

As noted in Section B.3.4.1, utility data were not collected in the FIREFISH trial. As such, sources of patient HSUVs from the NICE nusinersen appraisal (TA588) were considered for the type 1 model; utility values sourced from the Lloyd et al. case vignette study (118), and the ERG clinical advisor values from TA588 (18). While these values were not directly presented to the UK clinical experts at the advisory boards, experts felt that utilities worse than death (i.e. negative values) were unlikely to be clinically plausible, and therefore preference was given to the TA588 ERG clinical advisor utilities, which did not contain negative values (Appendix N) The HSUVs utilised in the base case of the type 1 SMA model are presented in Table 69. Values from the vignette study are presented Table 70 and were explored in the scenario analysis.

Table 69: Summary of patient utility values for cost-effectiveness analysis (type 1 base case model) (TA588 ERG Clinical Advisors)

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Permanent ventilation	0.200	NA	Section B.3.4.5	Based on UK clinical expert preference for positive utility values (Appendix N)
Not sitting	0.250	NA		
Sitting	0.475	NA		
Standing	0.750	NA		
Walking	0.800	NA		

NA, not applicable

Table 70: Summary of patient utility values for cost-effectiveness analysis (type 1 scenario model) (Lloyd et al. 2019)

State	Utility value: mean (standard error)	Standard error	Reference in submission (section and page number)	Justification
Permanent ventilation	−0.240	0.02	Section B.3.4.5	Alternative patient utility values available from TA588 (18)
Not sitting	−0.120	0.01		
Sitting	−0.105	0.01		
Standing	0.375	0.04		
Walking	0.615	0.06		

As described above for the type 2/3 model, carer utility values based on Bastida et al. and general population utility were deemed more appropriate than the values from the Roche UK burden of illness study by the clinical experts during the advisory board (119, 120).The carer

utility values based on the Bastida et al. study and general population utility (Table 71) were applied in the Type 1 model base case, with the Roche UK burden of illness study values (derived as described above in the type 2/3 section, Table 72) explored in a scenario analysis, for consistency across the two models.

Table 71: Summary of carer utility values for cost-effectiveness analysis (type 1 base case model) (Bastida et al. 2017 and Ara et al. 2010)

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Permanent ventilation	0.484	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. study and general population utility (Ara et al.) possessed the greatest clinical validity for carers of SMA patients (Appendix N) (119, 120).
Not sitting	0.484	NA		
Sitting	0.628	NA		
Standing	0.771	NA		
Walking	0.915	NA		

HSUV, health state utility value; NA, not applicable; SMA, spinal muscular atrophy

Table 72: Summary of carer utility values for cost-effectiveness analysis (type 1 scenario model) (Roche UK burden of illness study)

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Permanent ventilation	[redacted]	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. and Ara et al. 2010 studies possessed the greatest clinical validity for carers of SMA patients (Appendix N) (119, 120).
Not sitting	[redacted]	NA		
Sitting	[redacted]	NA		
Standing	[redacted]	NA		
Walking	[redacted]	NA		

NA, not applicable; SMA, spinal muscular atrophy

Similarly to the type 2/3 model, the average number of caregivers per SMA patient applied in the type 1 model was 2.2, based on data obtained in the Roche UK burden of illness study.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted in August 2019 to identify cost/resource use studies in patients with SMA. Eligibility criteria were not limited by type of SMA, severity or age of onset.

A total of 2,447 articles were identified from the searches, of which 199 papers relevant to cost/resource use were identified for full text review. Ultimately, 16 full publications, 17 conference abstracts, and one slide deck were included in the review.

Of the 34 publications identified by the review, only three UK-based studies were found; two of these were conference abstracts and reported resource use only (no cost data). For one of these conference abstracts the SMA type was unclear, the other focussed on patients with type 1 SMA. The final study with UK relevance was a slide set presenting the unpublished findings of two surveys and reported data on direct non-medical costs, indirect costs and resource use. This slide deck covered patients with SMA type 1, 2 and 3. One additional study provided some UK-relevant data with regards to hours spent per caregiver; within this study data were collected in the UK, France, Germany and Spain.

Despite the substantial amount of care and support that SMA patients require outside of a medical setting, the SLR noted a paucity of robust evidence relating to the indirect costs associated with SMA (only eight studies identified in the SLR reported indirect cost data, only one of which was UK-based). Furthermore, cost and resource use data (both direct and indirect) associated with motor milestone achievement, which were required to support the model structures for type 1 and type 2/3 SMA, were not identified in the SLR.

The results of the cost/resource use SLR for studies relevant to the UK setting are presented below; full details of the search strategy and the complete results are presented in Appendix I.

Table 73: Summary list of published UK-based cost and resource use studies in SMA

Study, country, currency (year)	Study design and aim	Population (sample size)	Cost collection approach	Direct costs (medical/non-medical)	Indirect costs	Total costs and drivers	Resource use	Suitability for CEA and applicability to UK clinical practice
UK based-studies reporting both cost and resource use data (N=1)								
SMA UK 2019 (144) UK GBP (reference year, NR) *(slide deck)*	**Design:** Prospective surveys (survey A and B) **Aim:** To assess how SMA impacts patients' and caregivers' lives	• Survey A, n=125 (SMA type 2, 39%; type 3, 61%) • Survey B, n=188 (SMA type 1, 15%; type 2, 57%; type 3 28%)	NR	Mean out of pocket costs per SMA patient (survey B): £8,025	Mean annual cost for loss of productivity per unpaid caregiver (based on reducing their hours by 25 hours per week): £14,350	Total annual direct cost per patient (survey A): £49,723	HCRU for patients with SMA type 1, 2 and 3 reported in the slide deck for the following: • Average number of interventions and equipment per person with SMA • The percentage of Patients with SMA who visit HCPs each year • The average number of daily activities per patient with SMA and the support needed to perform ADLs • Total number of caregiver hours per SMA person per week by level of mobility • The number of unpaid caregivers providing support to one SMA patient • Unpaid caregivers who support Patients with SMA each week	• These findings should be used with caution; data from two un-published surveys that have not been peer-reviewed. • Study reports cost and resource use for SMA types 1, 2 and 3 which would be useful for informing economic evaluation • Study based in the UK; therefore, results are applicable to a UK setting. • Reports recent data which may also reflect current clinical practice in the UK.
UK based-studies reporting resource use data only (N=1)								
Ali 2019 (145) UK NA	**Design:** Retrospective analysis **Aim:** To establish the	Paediatric patients with SMA type 1 who received	NR	NR	NR	NR	Resource use per patients with SMA type 1 over a lifetime (assumed): • Median number of	• This study reports data relating to resource use associated with

Study, country, currency (year)	Study design and aim	Population (sample size)	Cost collection approach	Direct costs (medical/non-medical)	Indirect costs	Total costs and drivers	Resource use	Suitability for CEA and applicability to UK clinical practice
(conference abstract)	hospital utilisation and associated costs for paediatric patients treated with nusinersen	nusinersen (n=9)					nusinersen doses (range): 5 (4–6) • Children who received BiPAP: n=7 • Ventilated via tracheostomy: n=1 • Number of days in hospital since diagnosis (range): 665 (4–177) days • Median number of days in hospital since diagnosis: 64 days • Total number of days in HDU (range): 52 (4–116) days • Total number of days in PICU (range): 4 (0–103) days	nusinersen treatment in SMA type 1 patients which may be useful for informing economic evaluation. • This study is based in the UK, therefore the resource use reported would be applicable to a UK setting.
Pelton 2016 (146) UK NA *(conference abstract)*	**Design:** Retrospective analysis **Aim:** To determine the value and impact of physiotherapy in patients	Neuro-muscular patients able to walk (n=10); MD (n=7), DMD (n=1), SMA (n=1) and Congenital Dystrophy (n=1)	NR	NR	NR	NR	Mean number of physiotherapy sessions (August 2012-July 2015) (SD): 32 (15)	• Study reports resource use which may be useful for informing economic evaluation • Study based in the UK and recent data reported which may reflect current clinical practice in the UK setting
Sampson 2019 (140) UK NA	**Design:** ISPOR symposium briefing	Primary caregivers in France, Germany, the	NR	NR	NR	NR	• In all countries, the average time spent on caregiving per patient per	• Study reports resource use from Lopez-Bastida et al

Study, country, currency (year)	Study design and aim	Population (sample size)	Cost collection approach	Direct costs (medical/non-medical)	Indirect costs	Total costs and drivers	Resource use	Suitability for CEA and applicability to UK clinical practice
(full publication; data from BURQOL-RD registry)	**Aim:** To discuss the impact of SMA on quality of life	UK and Spain completed online the EQ-5D-3L, Barthel Index and Zarit caregiver interview					day exceeded eight hours • The average caregiving hours for a SMA type 1 patient was around 13 hours per day *Figure 2 and Figure 3 of the full publication report the estimated time spent by caregivers (per day) on BADLs and IADL by country and disease type*	(2016) (142) • Some study data reported in the UK, and recent data reported which may reflect current caregiving resource use; therefore, results applicable to a UK setting

ADLs: activities of daily living, BADLS: Basic activities of daily living; BiPAP: bilevel positive airway pressure support; DMD: Duchenne Muscular Dystrophy; EQ-5D-3L: European Quality of Life-5 Dimensions-3 levels; GBP: Great British pound; HCP: health care professional; HCRU: healthcare resource use; HDU: high dependency unit; IADL: Instrumental activities of daily living; ISPOR: The International Society for Pharmacoeconomics and Outcomes Research; MD: muscular dystrophy; NR: not reported; PICU: paediatric intensive care unit; SMA: spinal muscular atrophy.

B.3.5.1 Intervention and comparators' costs and resource use

The list price per one 60 mg/80 ml vial of risdiplam is £[redacted].

[redacted].

It is anticipated that the majority of patients will receive risdiplam via homecare, the cost for which will be covered by Roche. However, a small proportion of patients (assumption: 10%) may choose to have risdiplam administered through the hospital instead of home delivery, in which case pharmacist time is required for the preparation of risdiplam. It is assumed that 5 minutes of pharmacist time (cost: £44 per hour) (147) will be required to reconstitute one vial of risdiplam. For the purpose of economic modelling, patients with type 1 SMA were assumed to require a vial approximately every 44 days and 12 days, respectively, until they reach a bodyweight >20 kg. This assumption was based on risdiplam dosing and patient baseline characteristics in the risdiplam studies.

Type 2/3 (SUNFISH) model

The acquisition costs for risdiplam were applied in the model in line with the age- and weight-based dosing table described in the SmPC (Section B.3.2.3). Given that the baseline average age of patients in the SUNFISH trial exceeded 20 kg, it was assumed all patients would receive a daily dose of 5 mg. This was a conservative assumption, as it is expected that younger and lighter type 2/3 patients would receive risdiplam in UK clinical practice in line with the expected placement of risdiplam into the patient pathway.

Within Part 2 of the SUNFISH trial, a relative dose intensity of [redacted]% was observed for the risdiplam arm. It is anticipated that relative dose intensity will also not be 100% in clinical practice; therefore, this value has been applied to the acquisition costs for risdiplam accordingly.

There is no treatment acquisition cost associated with BSC. SMA-related costs for BSC are applied to each motor milestone health states in the economic models, and the derivation of resource use and costing for the model health states is described in Section B.3.5.2.

Type 1 (FIREFISH) model

The acquisition costs for risdiplam were applied in the model in line with the age- and weight-based dosing table described in the SmPC (Section B.3.2.3). As the baseline age of patients was less than 2 years, weight-based dosing was applied.

The model is able to estimate the potential weight of a patient to ensure that a suitable monthly price is calculated. Data for patient weight, height and age were pooled from the TRO19622 (148), OLEOS (149), SUNFISH (74), FIREFISH (68) and NatHis-SMA studies (150).

The results depicted in Figure 16 demonstrate that weight increases most rapidly in the early years, and then plateaus in early adulthood, with gender contributing to the changes. This resulted in two formulae to describe the weight estimation related to age and gender as follows:

[redacted]

[redacted]

These formulae were included in the model to calculate the relationship between patient age and weight.

Figure 16: Weight algorithm for SMA patients

[redacted]

Within Part 2 of the FIREFISH trial, a relative dose intensity of [redacted]% was observed for the risdiplam arm.

It is anticipated that relative dose intensity will also not be 100% in clinical practice; therefore, this value has been applied to the acquisition costs for risdiplam accordingly. There is no treatment acquisition cost associated with BSC.

B.3.5.2 Health-state unit costs and resource use

An SLR was conducted to identify studies providing data for cost and resource use in SMA to potentially inform the cost-effectiveness models for risdiplam. The review highlighted a number of data gaps in the current published literature, identifying only three UK-based studies. Robust evidence was sparse, particularly in relation to indirect (non-medical) costs associated with SMA, despite patients' requirement for a substantial amount of care and support.

In the nusinersen appraisal for SMA (TA588) (18), health state resource use was initially sourced from Bastida et al. 2017 (119) and later based on a real-world evidence study using Hospital Episode Statistics (HES) data (linked to motor milestones). The suitability of Bastida et al. 2017 was challenged by the ERG and the NICE committee in this appraisal. In particular, it was noted that the estimated costs for SMA type 1 and 2 milestones were likely to be underestimated. Given the high degree of dependency on carers and medical support associated with these patients and the healthcare resources required to manage their condition, there are substantial costs borne by patients and their families. The ERG preferred the use of data from a real-world evidence study conducted by the manufacturer. The real-world evidence study involved the circulation of a survey to a sample of leading paediatric neurological consultants representing nine UK centres, in order to determine healthcare resource use in the treatment of SMA type 1, 2 and 3 patients. The results from the survey indicated an expected trend, whereby costs were highest for type 1, followed by type 2, with type 3 accruing the lowest cost. However, the clinicians consulted by the company during the NICE appraisal process indicated that they expected the costs for type 1 to be higher than estimated, driven by more significant costs accrued in major clinical interventions (closer to a factor of 2). Table 74 presents the results of the real-world study with the cost adjustment factor of 2 applied to the type 1 estimates and the health states these costs would be applied to in the risdiplam models. The health state costs as they would be applied in the risdiplam type 2/3 and type 1 models per monthly cycle are presented in Table 75 and Table 76, respectively. For the type 1 model, in the absence of data available for the permanent ventilation health state in the TA588 real-world evidence study, an assumption needed to be made. UK clinical experts (Appendix N) confirmed that it is reasonable to assume that the 'permanent ventilation' health state will require increased healthcare resource use (i.e. costs) compared to the 'not sitting' health state. Therefore, in

the base case analysis an assumption was made that 'permanent ventilation' is associated with a cost increase of 175% times the 'not sitting' health state. This was informed by the review of submission papers for NICE ID1473 (not published online at time of submission) and the study by Noyes et al. (151) with details for the resource use and service costs for ventilator-dependent children and young people in the UK, both in a hospital and at-home setting. The cost of the 'permanent ventilation' health state was varied in scenario analyses.

Table 74: Real-world study (TA588) health states

	TA588 real-world evidence study motor milestone classification		
	Type 1 motor milestones	**Type 2 motor milestones**	**Type 3 motor milestones**
Application in type 2/3 SMA (SUNFISH) model	Not sitting, sitting with support	Sitting without support	Standing, walking
Application in type 1 SMA (FIREFISH) model	Not sitting	Sitting with/without support average (i.e. average of Type 1 and Type 2 from TA588)	Standing, walking
Weighted average of health state costs (annual)	£148,214	£68,322	£21,765

Table 75: Real-world study (TA588) applied to type 2/3 SMA (SUNFISH) model health states per monthly cycle

Health state	Total costs per cycle
Not sitting	£12,351
Sitting with support	£12,351
Sitting without support	£5,694
Standing	£1,814
Walking	£1,814

Table 76: Real-world study (TA588) applied to type 1 SMA (FIREFISH) model health states per monthly cycle

Health state	Total costs per cycle
Permanent ventilation[a]	£21,614
Not sitting	£12,351
Sitting	£9,023
Standing	£1,814
Walking	£1,814

Footnotes: [a]The permanent ventilation health state was calculated to be 175% of the 'not sitting' health state

A UK burden of illness study was conducted by Roche, in collaboration with patient groups, in UK-based SMA patients and their carers in order to generate resource use estimates for

patients with type 2/3 and 1 SMA. This study was also considered as a source of health state costs for the economic models. The aim of this study was to collect more data and to enrich the evidence base around resource use in SMA patients, given the paucity of data in this area as identified in the CRU SLR, and explore their use in the NICE evidence submission for risdiplam. The methodology for the Roche UK burden of illness study is described in detail in Appendix P. In brief, online surveys collected data from SMA patients and their carers. The online surveys were designed to capture direct medical, direct non-medical, indirect and carer-specific cost and resource use associated with SMA types 1, 2 and 3. A total of 122 patient surveys and 80 carer surveys were completed. The survey results showed that healthcare resource use was high in patients with SMA, with frequent planned and unplanned healthcare visits, tests or procedures in the previous 12 months. Unit costs were sourced from NHS reference costs (152) and applied to the proportion and frequencies (per cycle) of healthcare resource utilisation derived from the survey results. The resulting total costs for type 2/3 and type 1 SMA are shown in Table 77 and Table 78, respectively.

Table 77: Roche UK burden of illness study applied to type 2/3 SMA (SUNFISH) model health states

Health states	Total costs per cycle	
	Paediatric	Adult
Not sitting	[redacted]	[redacted]
Sitting with support	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]
Standing	[redacted]	[redacted]
Walking	[redacted]	[redacted]

Table 78: Roche UK burden of illness study: per-cycle total costs (type 1 SMA)

Health states	Total costs per cycle	
	Paediatric	Adult
Permanent ventilation	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]
Sitting	[redacted]	[redacted]
Standing	[redacted]	[redacted]
Walking	[redacted]	[redacted]

This study, in addition to the real-world evidence study conducted to inform the models in TA588, were both considered to potentially inform the type 2/3 and type 1 models for risdiplam. The real-world evidence study from the TA588 submission was chosen to inform the base case, with the Roche UK burden of illness study explored in a scenario analysis. The rationale for this choice was that health state costs calculated as part of the Roche UK burden of illness study were lower than those utilised in TA588. Given the significant critique within TA588 was that health state cost estimations were consistently too low, it was deemed appropriate to use the final costs from TA588. Using health state cost inputs

consistent with TA588 in the base case analysis also helps with ensuring consistency in NICE decision-making in SMA.

B.3.5.3 Adverse reaction unit costs and resource use

As described in Section B.3.3, adverse events have not been included in either the type 2/3 or type 1 models due to the very low incidence (<5%) of adverse events experienced by patients that were considered to be related to treatment in the SUNFISH and FIREFISH trials, respectively (Section B.2.10).

B.3.5.4 Miscellaneous unit costs and resource use

No further costs were included in the models in addition to those described in the sections above.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 79: Base case inputs: type 2/3 SMA (SUNFISH) model

Input	Value	Section
Patient characteristics		
Age, years	[redacted]	Section B.3.3.1
Female (SE)	[redacted]	
Type 2	71.1%	
Type 3	28.9%	
Not sitting	[redacted]	
Sitting (supported)	[redacted]	
Sitting (unsupported)	[redacted]	
Standing	[redacted]	
Walking	[redacted]	
Respiratory support	[redacted]	
Severe scoliosis	31.67%	
Transition probabilities	*Various*	Section B.3.3.1
Type 2 OS	Gompertz	Section B.3.3.1
Type 3 OS	General population mortality (ONS)	
HR – mortality with risdiplam	0.75	
Discontinuation, patients per cycle	0	Section B.3.3.1
Patient utilities		
Not sitting	−0.170	Section B.3.4.5
Sitting (supported)	0.040	
Sitting (unsupported)	0.040	
Standing	0.560	
Walking	0.560	

Carer utilities		
Not sitting	0.484	Section B.3.4.5
Sitting (supported)	0.610	
Sitting (unsupported)	0.735	
Standing	0.861	
Walking	0.861	
Risdiplam costs		
Cost per 60 mg/80 ml vial	[redacted] (list price) [redacted] (net price)	Section B.3.5.1
Pharmacy time (cost per reconstitution of one vial) for proportion of patients not receiving via homecare	£3.67	
Relative dose intensity	[redacted]	
Health state costs		
Not sitting	£12,351	Section B.3.5.2
Sitting with support	£12,351	
Sitting without support	£5,694	
Standing	£1,814	
Walking	£1,814	

HR, hazard ratio; ONS, Office for National Statistics; OS, overall survival; PAS, patient access scheme; SE, standard error

Table 80. Base case inputs: type 1 SMA (FIREFISH) model

Input	Value	Section
Patient characteristics		
Age, years	0.48	Section B.3.3.2
Female	57%	
Body weight, kg; mean	[redacted]	
Not sitting	[redacted]	
Sitting	[redacted]	
Standing	[redacted]	
Walking	[redacted]	
Non-permanent respiratory support	[redacted]	
Severe scoliosis	[redacted]	
Transition probabilities		
Motor milestone health states	*Various*	Section B.3.3.2
Permanent ventilation health state	Exponential	
Overall survival	Exponential	Section B.3.3.2
Discontinuation, patients per cycle	0	Section B.3.3.2
Patient utilities		

Permanent ventilation	0.200	Section B.3.4.5
Not sitting	0.250	
Sitting	0.475	
Standing	0.750	
Walking	0.800	
Carer utilities		
Permanent ventilation	0.484	Section B.3.4.5
Not sitting	0.484	
Sitting	0.628	
Standing	0.771	
Walking	0.915	
Risdiplam costs		
Cost per 60 mg/80 ml vial	[redacted] (list price) [redacted] (net price)	Section B.3.5.1
Pharmacy time (cost per reconstitution of one vial) for proportion of patients not receiving via homecare	£3.67	
Relative dose intensity	[redacted]	
Health state costs		
Permanent ventilation	£21,614	Section B.3.5.2
Not sitting	£12,351	
Sitting	£9,023	
Standing	£1,814	
Walking	£1,814	

PAS, patient access scheme

B.3.6.2 Assumptions

The key assumptions made in the type 2/3 and type 1 models are presented in Table 81.

Table 81: Key assumptions made in the type 2/3 and type 1 base case analyses

Model	Assumption	Justification	Section
Clinical efficacy			
Both	Patients' improvement or deterioration in motor milestone achievement was sequential.	It was clinically validated that improvement or deterioration by greater than one milestone within the period of one month would not be expected in SMA patients of all types (126).	B.3.3.1 B.3.3.2
Type 2/3	After 24 months, the majority of type 2/3 patients treated with risdiplam may only improve or remain stable in terms of motor milestones gained, whilst patients treated with BSC may only remain stable or deteriorate.	These assumptions were consistent with the assumptions considered in the final NICE decision for TA588 (18). Furthermore, these assumptions were also validated by clinical experts at UK advisory boards and supported by findings from the literature, as described in Section B3.10.	B.3.3.1
Type 1	After 24 months, patients treated with risdiplam may only improve or remain stable in terms of motor milestones gained, whilst patients treated with BSC may only remain stable or deteriorate.	These assumptions were consistent with the assumptions considered in the final NICE decision for TA588 (18). Furthermore, these assumptions were also validated by clinical experts at UK advisory boards and supported by findings from the literature, as described in Section B.3.10.	B.3.3.2
Type 1	No transitions to 'walking' took place in the timeframe of the FIREFISH study (up to the latest data cut-off), however, within the model, transitions were allowed for patients treated with risdiplam from 'standing' to 'walking' from the age of 2 onwards. This transition was calculated to be one third (33%) of the transition probability for 'sitting' to 'standing.'	This adjustment is supported by the fact that some patients in the FIREFISH study acquired further developmental milestones towards developing the walking function (bouncing). It is also supported by discussion in TA588 that there is evidence to suggest that a small proportion of type 1 patients reach the 'walking' milestone (18).	B.3.3.2
Type 1	Within the ITC it was not possible to generate comparative estimates for backwards transitions for BSC, i.e. 'sitting' to 'not sitting'. Backwards transitions were conservatively assumed to be the same as risdiplam.	This assumption was conservatively made in lieu of data; however, a scenario analysis was conducted whereby the per-cycle transition probabilities for backwards transitions for BSC were assumed to be 2 times that of risdiplam backwards transitions.	B.3.3.2
Both	Mortality for patients with SMA type 3 and patients with SMA type 2 that reach the standing or walking health states is equal to general population mortality (136). Mortality for patients with SMA type 1 that reach the standing or walking health states becomes equal to type 2 mortality, informed by an SLR of mortality in type 2 patients.	There is evidence from the literature that the overall survival of type 3 patients is similar to that of the general population (98) The approach for type 2 patients was informed by the approach taken in TA588, and UK clinical expert opinion (Appendix N; Section B.3.3.1). A similar approach was taken for type 1 patients reaching the highest health states, i.e. setting their mortality equal to type 2 patients, for consistency (B.3.3.2).	
Cost and resource use			

Both	10% of patients choose to have risdiplam administered through the hospital instead of home delivery, for which pharmacist costs are required.	As this comes down to patient choice, it was deemed appropriate to consider that not 100% of patients would wish to receive home delivery of risdiplam.	B.3.5.1
Type 1	In line with TA588 (18), healthcare costs calculated in the real-world evidence study for 'type 1' were doubled.	This approach was deemed to produce the most plausible cost input data by the ERG in TA588 (18).	B.3.5.2
Type 1	In the absence of cost and resource use data for the 'permanent ventilation' health state in the TA588 real-world study (18) costs for the 'permanent ventilation' state were increased by 175% compared to the 'not sitting' health state.	This was based on UK clinical expert opinion that costs for the 'permanent ventilation' health state were likely to be higher than the 'not sitting' health state, due to the amount of care and treatment patients in this health state are likely to require.	B.3.5.2
Utilities			
Both	Where HSUVs were based on sources utilised in the cost-effectiveness models developed by the manufacturer in TA588 (18), in order to apply the HSUVs appropriately it was necessary to make assumptions in deciding which health states in the risdiplam models were most aligned to the health states in TA588 models (Appendix Q).	This approach was necessary in order to be able to apply utility values deemed as being clinically valid by expert clinicians to the risdiplam cost-effectiveness models.	B.3.4.5
Both	For carer utilities, a HSUV was obtained from the study conducted by Bastida et al. 2017 (119) and assigned to the lowest health state in each model. General population utility was sourced for the highest health states, and intermediate values were calculated for the health states in between.	This approach aligns with that conducted by the manufacturer in TA588 (18).	B.3.4.5

BSC: best supportive care; ERG: evidence review group; HSUV: health-state utility values; ITC: indirect treatment comparison; NICE: National Institute for Health and Care Excellence; SMA: spinal muscular atrophy; SLR: systematic literature review.

B.3.7 Base-case results

Cost-effectiveness results for risdiplam at list price are presented in Sections B.3.7 and B.3.8.4. Cost-effectiveness results at the PAS price are presented in Section B.3.7 (base case results) and in Appendix S. Disaggregated model results are presented in Appendix J.

The base case results for the type 2/3 analysis are presented in Table 82 for the list price of risdiplam and Table 83 for the with-PAS price. At both list and PAS price, risdiplam is associated with substantially greater quality-adjusted life years (QALYs) compared to BSC (45.19 QALYs vs. 23.04 QALYs, respectively). This difference in QALYs reflects the improvements in HRQoL for both patients and carers associated with risdiplam treatment compared to BSC. Additionally, risdiplam extends patients' lives compared to BSC, as reflected in the QALYs, as well as

the life years gained (LYG) (23.12 vs. 20.31 years, respectively). The incremental cost-effectiveness ratio (ICERs) were £185,197 and [redacted] at the list and with-PAS prices, respectively.

The base case results for the type 1 model are presented in Table 84 for the list price and Table 85 for the with-PAS price of risdiplam. The ICER is reduced from £97,729 to [redacted] following application of the PAS. Risdiplam may therefore be considered cost-effective at PAS price, in the context of end-of-life therapies. Risdiplam results in greater improvements in HRQoL for both patients and carers in comparison to BSC, as reflected by the substantial gain in QALYs from 8.59 with BSC to 31.33 with risdiplam. Furthermore, risdiplam extends patients' lives compared to BSC, as shown by the increase in QALYs, as well as the increase in LYG of 6.70 years with BSC and 13.99 years with risdiplam.

Table 82: Base case results for the type 2/3 SMA (SUNFISH) model (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	20.31	23.04	-	-	-	-
Risdiplam	[redacted]	23.12	45.19	[redacted]	2.81	22.15	£185,197

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 83: Base case results for the type 2/3 SMA (SUNFISH) model (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	20.31	23.04	-	-	-	-
Risdiplam	[redacted]	23.12	45.19	[redacted]	2.81	22.15	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 84: Base case results for the type 1 SMA (FIREFISH) model (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	6.70	8.59	-	-	-	-
Risdiplam	[redacted]	13.99	31.33	[redacted]	7.29	22.74	£97,729

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 85: Base case results for the type 1 SMA (FIREFISH) model (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	6.70	8.59	-	-	-	-
Risdiplam	[redacted]	13.99	31.33	[redacted]	7.29	22.74	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life year

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 2,000 iterations, in order to calculate the uncertainty in costs and outcomes. A summary of the distributions chosen for the probabilistic parameters in the type 2/3 and type 1 models are provided in Table 86: Appendix R.

The results of the probabilistic base case results for the type 2/3 and type 1 analyses for risdiplam at list price are presented in Table 86 and Table 87, respectively. For the type 2/3 model, the cost-effectiveness plane (with a willingness-to-pay threshold of £30,000 per QALY) shows that all iterations of the list price are above the cost-effectiveness threshold (Figure 17). The PSA found that the probability of risdiplam being cost-effective at the willingness-to-pay threshold of £30,000 is [redacted] at list price for the type 2/3 model (Figure 18). Meanwhile, for the type 1 model the cost-effectiveness plane (with a willingness-to-pay threshold of £50,000 per QALY under end-of-life criteria) demonstrates that risdiplam is cost-effective at list price for a small number of iterations (Figure 19). The PSA found that the probability of risdiplam being cost-effective at the willingness-to-pay threshold of £50,000 is 2.55% at list price for the type 1 model (Figure 20). With-PAS PSA results are presented in Appendix S.

Table 86: Probabilistic base case results for the type 2/3 SMA (SUNFISH) model (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	17.40	-	-	-
Risdiplam	[redacted]	39.94	[redacted]	22.15	£183,281

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

Table 87: Probabilistic base case results for the type 1 SMA (FIREFISH) model (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	9.59	-	-	-
Risdiplam	[redacted]	33.58	[redacted]	22.74	£98,650

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

Figure 17. Incremental cost-effectiveness plane for the type 2/3 SMA (SUNFISH) model (list price)

Figure 18. Cost-effectiveness acceptability curve for the type 2/3 SMA (SUNFISH) model (list price)

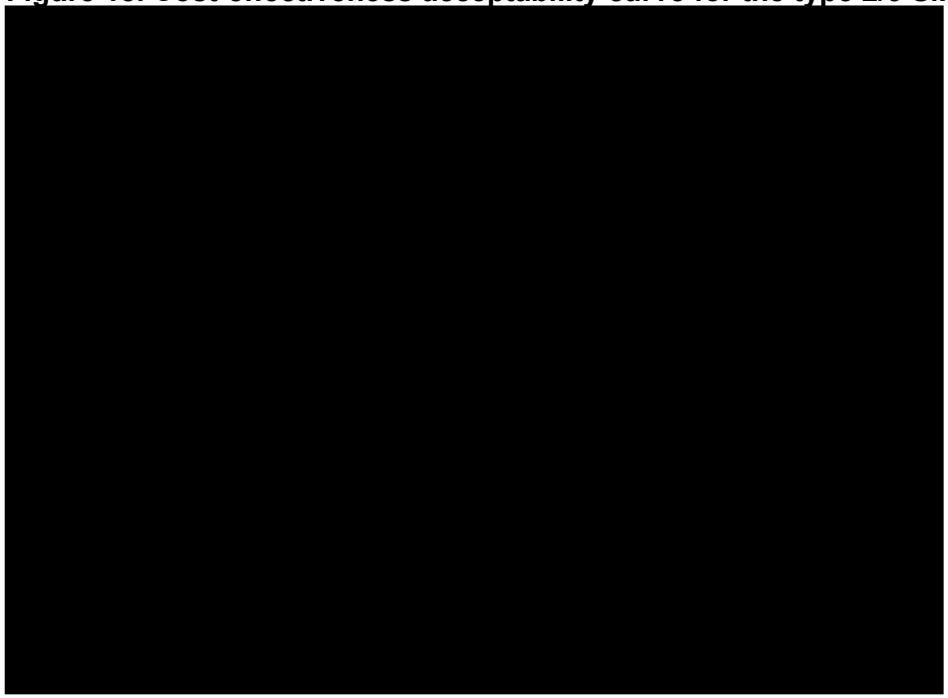
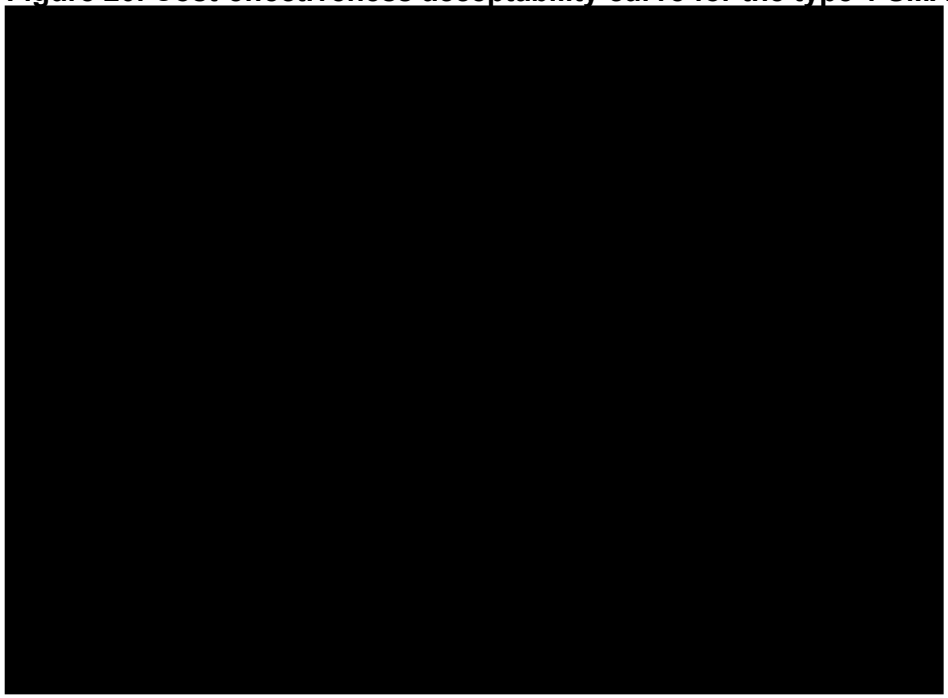


Figure 19. Incremental cost-effectiveness plane for the type 1 SMA (FIREFISH) model (list price)

Figure 20. Cost-effectiveness acceptability curve for the type 1 SMA (FIREFISH) model (list price)



B.3.8.2 Deterministic sensitivity analysis

For the type 2/3 model, the inputs with the greatest impact on incremental costs were the cost per risdiplam vial, the discount rate for costs, the adult patient costs of the 'not sitting' health state, the relative dose intensity of risdiplam and the HR for type 2 mortality with risdiplam treatment (Figure 21). The most influential parameters on the incremental QALYs were discount rate for benefits, the number of carers and annual HSUVs of caregivers for patients in the 'not sitting', 'sitting without support' and 'walking' health states (Figure 21). The inputs with the greatest effect on the ICER were the cost per risdiplam vial, the number of carers, the discount rate for benefits, the annual HSUVs of caregivers for patients in the not sitting health state and the discount rate for costs (Figure 21).

For the type 1 model, the inputs with the greatest impact on incremental costs were the cost per large bottle of risdiplam, the discount rate for costs, the OS HR (vs risdiplam) for the 'not sitting' health state, the costs for permanent ventilation and the EFS HR (vs risdiplam) (Figure 22). The most influential parameters on the incremental QALYs were the number of carers, the discount rate for benefits, the annual HSUVs of caregivers for patients in the standing health state, the OS HR (vs risdiplam) for patients in the 'not sitting' health state and the annual HSUV of caregivers for patients in the 'sitting' health state (Figure 22). The inputs with the greatest effect on the ICER were the cost per large bottle of risdiplam, the number of carers, the discount rate for benefits, the discount rate for costs and the costs for permanent ventilation (Figure 22).

The cost of risdiplam is therefore consistently an influential parameter, which is addressed by the confidential PAS that Roche have provided to NICE PASLU.

Figure 21: Deterministic sensitivity analysis results for the type 2/3 SMA (SUNFISH) model (list price)

[redacted]

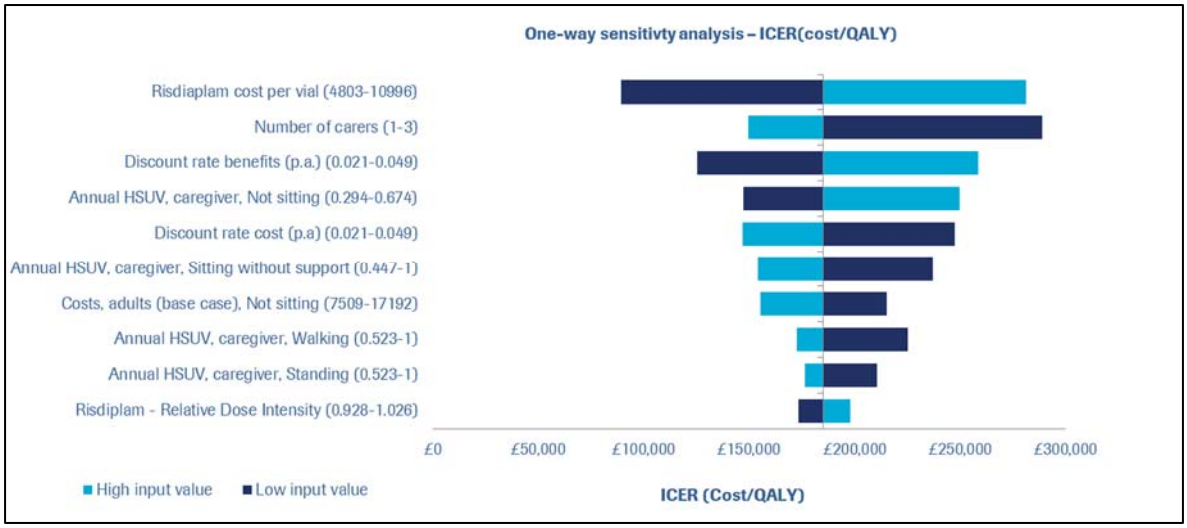
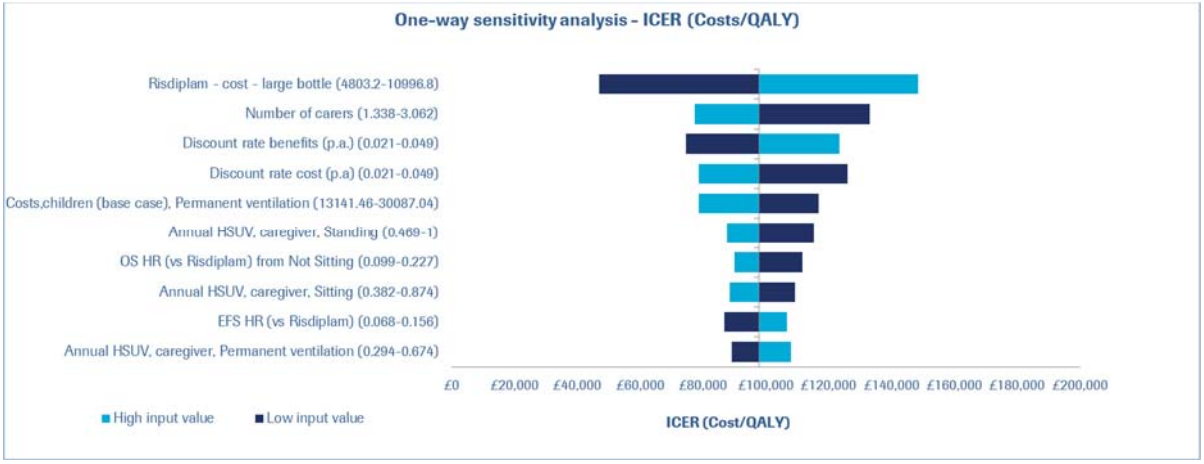


Figure 22: Deterministic sensitivity analysis results for the type 1 SMA (FIREFISH) model (list price)

[redacted]

[redacted]



B.3.8.3 Scenario analysis

The scenario analyses for the type 2/3 model are detailed in Table 88. The scenarios that have the greatest effect on the base case ICER are outlined below.

Reducing the probability of worsening in the risdiplam arm, as informed by trial-based transition probabilities, by [redacted] resulted in a change of +26.57% to the base case ICER. This scenario is not supported by UK clinical expert opinion, which indicated that the majority of patients on risdiplam would remain stable or improve in terms of motor milestones in the long-term (Section B.3.2.2, Appendix N).

The scenario where the BSC transition probabilities from the SUNFISH trials were used throughout the model time horizon changed the base case ICER by +71.07%. As the trial transition probabilities are based on the data from the 1-year follow-up it is not appropriate to extrapolate them to the 90-year time horizon of the model. Furthermore, clinical expert opinion confirmed that it was reasonable to assume that patients on BSC would remain stable or deteriorate in the long-term (Section B.3.2.2, Appendix N).

The use of the SUNFISH utilities as the source for patient utility values increased the base case ICER by +39.42%. UK clinical expert opinion confirmed that these utility values lacked face validity (Section B.3.4.5, Appendix N).

The scenario that uses the Roche UK Burden of Illness Study as the source of caregiver utility values changed the base case ICER by +88.36%. UK clinical experts indicated that the

carer utility values from the Roche UK Burden of Illness Study lacked face validity (Section B.3.4.5, Appendix N).

Furthermore, as an innovative, life-extending therapy, the scenario that explores a discount rate of 1.5% for benefits and 3.5% for costs lowers the ICER by -44.65% in comparison to the base case.

Table 88: Scenario analysis results for the type 2/3 SMA (SUNFISH) model (list price)

Scenario	Incremental costs	Incremental LYs	Incremental QALYs	ICER	% ICER change from the base case
Base case	[redacted]	2.81	22.15	£185,197	-
Efficacy scenarios					
BSC and risdiplam transition probabilities sources: SUNFISH (excl. Asia) no imputations	[redacted]	2.83	22.25	£184,516	-0.37%
BSC and risdiplam transition probabilities sources: SUNFISH (full population), imputations	[redacted]	2.41	18.90	£221,472	+19.59%
Risdiplam efficacy post follow-up: Probability of worsening, as informed by trial-based transition probabilities, is reduced by [redacted] ('less optimistic', i.e. reduced to [redacted] of its original value)	[redacted]	1.96	17.42	£234,410	+26.57%
Risdiplam efficacy post follow-up: Probability of worsening, as informed by trial-based transition probabilities, is reduced by [redacted] ('more optimistic', i.e. reduced to [redacted] of its original value)	[redacted]	3.71	26.84	£155,136	-16.23%
BSC post follow-up: extrapolation as per trial follow-up	[redacted]	2.81	14.87	£316,810	+71.07%
Survival scenarios					

Weibull used for Type 2 extrapolation	[redacted]	2.94	22.18	£184,904	-0.16%
HCRU scenarios					
UK Burden of Illness Study as source for HCRU	[redacted]	2.81	22.15	£213,579	+15.32%
Utility values scenarios					
Source for patient utility values: NICE TA588 (ERG Clinical Advisor)	[redacted]	2.81	21.48	£191,013	+3.14%
Source for patient utility values: EQ-5D-3L (SUNFISH utilities) including disutility for respiratory support and scoliosis	[redacted]	2.81	15.89	£258,197	+39.42%
Source for caregiver utility values: UK Burden of Illness Study	[redacted]	2.81	11.76	£348,830	+88.36%
Other Scenarios					
Number of carers lowered to 2	[redacted]	2.81	20.83	£196,991	+6.37%
Number of carers increased to 3	[redacted]	2.81	27.46	£149,416	-19.32%
Varied % patients in need of respiratory support (by motor milestone) in line with UK clinical input (Appendix N)	[redacted]	2.81	22.65	£181,116	-2.20%
'Long-term' transition probabilities start at 12 months	[redacted]	2.86	22.79	£178,735	-3.49%
Discount rate for both costs and benefits is lowered to 1.5%	[redacted]	6.34	40.02	£160,329	-13.43%
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%	[redacted]	6.34	40.02	£102,511	-44.65%

BSC: best supportive care; EQ-5D-3L: European Quality of Life-5 Dimensions-3 levels; ERG: Evidence Review Group; HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; LY: life year; NICE: National Institute for Health and Care Excellence; QALY: quality-adjusted life year

The scenario analyses for the type 1 model are detailed in Table 89Table 88. The scenarios that have the greatest effect on the base case ICER are outlined below.

Reducing the probability of worsening on risdiplam, as informed by trial-based transition probabilities, by [redacted] resulted in a change of +28.12% or +36.20%, respectively, in

comparison to the base case ICER. These scenarios are not supported by UK clinical expert opinion, which indicated that the effectively all patients on risdiplam are expected to remain stable or improve in terms of motor milestones in the long-term (Section B.3.2.2, Appendix N).

The scenario where the permanent ventilation health state costs were increased to 250% of the not sitting health state decreased the ICER by -26.10% in comparison to the base case. UK clinical expert opinion confirmed that the permanent ventilation health state was likely to have increased cost and resource use in comparison to the not sitting health state (Appendix N). This is further supported by the Noyes et al. study (151).

Furthermore, as an innovative, life-extending therapy, the scenario that explores a discount rate of 1.5% for benefits and 3.5% for costs, lowers the ICER by -33.43% in comparison to the base case.

Table 89: Scenario analysis results for the type 1 SMA (FIREFISH) model (list price)

Scenario	Incremental costs	Incremental LYs	Incremental QALYs	ICER	% ICER change from the base case
Base case	[redacted]	7.29	22.74	£97,729	-
Efficacy scenarios					
Comparative efficacy vs. BSC: Source for BSC set to MAIC	[redacted]	9.21	25.21	£106,671	+9.24%
Risdiplam efficacy post follow-up: Probability of worsening ('backward transitions'), as informed by trial-based transition probabilities, is reduced by [redacted]	[redacted]	5.89	17.71	£114,378	+17.04%
Risdiplam efficacy post follow-up: Probability of worsening ('backward transitions'), as informed by trial-based transition probabilities, is reduced by [redacted]	[redacted]	5.25	15.43	£125,211	+28.12%
Risdiplam efficacy post follow-up: Probability of worsening milestones ('backward transitions'), as informed by trial-based transition probabilities, is reduced by [redacted]	[redacted]	4.89	14.13	£133,106	+36.20%
Risdiplam long-term transition probability from standing → walking at 67% of the probability of sitting → standing	[redacted]	7.29	23.28	£95,442	-2.34%
Risdiplam post follow-up transition probability from standing → walking is 0	[redacted]	7.28	21.60	£102,854	+5.24%

BSC long-term extrapolations as per trial follow-up (instead of no continued improvement)	[redacted]	7.28	22.71	£97,878	+0.15%
BSC long-term probability of backward transitions twice as high as for risdiplam	[redacted]	7.30	22.77	£97,494	-0.24%
HCRU scenarios					
UK Burden of Illness Study as source for HCRU	[redacted]	7.29	22.74	£109,148	+11.68%
PV health state costs: More optimistic 250% increase from the “Not Sitting” health state	[redacted]	7.29	22.74	£72,222	-26.10%
PV health state costs: less optimistic 125% increase from the “Not Sitting” health state	[redacted]	7.29	22.74	£114,734	+17.40%
Utility values scenarios					
Source for patient utility values: EQ-5D-3L (NICE ERG TA588)	[redacted]	7.29	20.03	£110,951	+13.53%
Source for patient utility values: EQ-5D-Y (Lloyd et al, 2019)	[redacted]	7.29	20.78	£106,915	+9.40%
Source for caregiver utility values: UK Burden of Illness Study	[redacted]	7.29	20.29	£109,498	+12.04%
Other Scenarios					
Number of carers lowered to 2	[redacted]	7.29	21.34	£104,126	+6.55%
Number of carers increased to 3	[redacted]	7.29	28.32	£78,450	-19.73%
‘Long-term’ transition probabilities start at 12 months	[redacted]	7.57	23.76	£94,773	-3.02%
Discount rate for both costs and benefits is lowered to 1.5%	[redacted]	11.00	34.15	£95,505	-2.28%
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%	[redacted]	11.00	34.15	£65,061	-33.43%

BSC: best supportive care; EQ-5D-5L: EuroQoL 5 Dimensions 3 Levels; EQ-5D-Y: European Quality of Life-5 Dimensions – Youth version; ERG: Evidence Review Group; HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; LY: life year; MAIC: matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; PV: permanent ventilation; QALY: quality-adjusted life year

B.3.8.4 Summary of sensitivity analyses results

The results of the probabilistic base case in both analyses were closely reflective of the deterministic analysis, demonstrating that the models are robust to variation in input parameters. This was mirrored in the results of the deterministic sensitivity analyses, where

only a small number of inputs had a significant impact on the ICERs when varied to their limits.

The sensitivity analyses of the type 2/3 and type 1 models demonstrated that the cost of risdiplam is an influential parameter. This is addressed by the PAS that has been provided to NICE confidentially. Scenario analyses indicated that the probability of worsening in the long-term for patient treated with risdiplam influences the ICER for both the type 2/3 and type 1 model. Importantly though, worsening of patients on risdiplam in the long-term is not supported by UK clinical expert opinion, which indicated that the majority of patients on risdiplam would remain stable or improve in terms of motor milestones in the long-term (Section B.3.2.2, Appendix N). This is reflected in the base-case analysis inputs we have selected, both in the type 2/3 and type 1 model

B.3.9 Subgroup analysis

No subgroup analyses were performed.

B.3.10 Validation

B.3.10.1 Advisory boards and technical validation

As described in Section B.3.2.2, expert clinicians and specialist physiotherapists were consulted during model design and throughout model development. The experts consulted are from several geographies around the world and are considered leaders in their field. Additionally, in order to ensure that the models for type 1 and 2/3 SMA were as reflective of patients and clinical practice in the UK as possible, two advisory boards were conducted in order to clinically validate model inputs and assumptions and long-term model outcomes. Each advisory board was attended by four clinicians and one physiotherapist in order to gather feedback on SMA treatment from multiple perspectives. The advisory board report is presented in Appendix N.

The topics discussed included motor function measures informing motor milestones, patient and carer HSUVs, transition probabilities, respiratory support needs and mortality. Furthermore, given the paucity of data in the literature regarding long-term outcomes, particular emphasis was placed on validating the long-term assumptions and trajectories of patients treated with BSC or risdiplam to ensure this was modelled as accurately as possible. These discussions are summarised further below. Where possible (e.g. where multiple data sources/assumptions were available), clinicians were presented with a choice of options, such that they could choose the option most relevant to UK clinical practice.

Both cost-effectiveness models underwent a strategic review by an academic UK health economics expert. Additionally, both models underwent rigorous technical validation comprising error checking, validation of all formulae and Visual Basic coding and sense checking to ensure the model responded appropriately to extreme scenarios.

B.3.10.2 Comparison of model outcomes with clinical data

Type 2/3 (SUNFISH) model

The long-term clinical outcomes from the type 2/3 (SUNFISH) model for BSC and risdiplam for the base case analysis are presented in Table 90 and Table 91, respectively.

Table 90: Long-term clinical outcomes from type 2/3 (SUNFISH) model: BSC arm

Years	Not sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 91: Long-term clinical outcomes from type 2/3 (SUNFISH) model: risdiplam arm

Years	Not sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Motor milestone data up to 12 months are currently available from the SUNFISH trial. These data were compared to the model predictions for motor milestone achievement at 1 year. Within Part 2 of the SUNFISH trial, after 1 year, [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% had achieved the motor milestones of 'not sitting,' 'sitting with support,' 'sitting without support,' 'standing,' and 'walking,' respectively, in the BSC arm. In the risdiplam arm of SUNFISH, after 1 year, [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% had achieved the motor milestones of 'not sitting,' 'sitting with support,' 'sitting without support,' 'standing,' and 'walking,' respectively. The model predictions for risdiplam align very closely with trial data (Table 91). Model predictions for the BSC arm are slightly optimistic with regards to the proportions of patients reaching advanced motor milestones such as standing and walking at 1-year (it should also be noted that a proportion of patients in the 'dead' health state are also accounted for in the model predictions). This indicates the model results are conservative with regards to clinical outcome predictions between risdiplam and BSC.

Feedback from the clinical advisors at the advisory board was that in the long-term type 2/3 patients treated with BSC would be expected only to remain stable or deteriorate (Appendix N). The long-term outputs from the model reflect this feedback; following the 1-year mark, the proportions of patients in relatively more advanced health states ('sitting without support', 'standing' and 'walking') decreases over time for the remainder of the time horizon. The proportion of patients entering the 'not sitting' and 'death' health states increases with time. This deteriorating trajectory for type 2/3 patients treated with BSC further agrees with published literature. In a French study performed by Vuillerot and colleagues (24), MFM

scores were measured over time in patients with type 2/3 SMA who received no treatment other than physical therapy and nutritional or respiratory assistance. In patients with >6 months' follow up, a moderate inverse relationship between age and MFM total score was identified, reflecting patients' decline in muscle strength and motor function over time (24). A similar observation was made in two studies by Corrati et al. in which the natural history of patients with type 2 and type 3 SMA from centres around the world (including the UK) was recorded. Patients were followed-up over 0.46–13.34 years and 12 months, respectively. Within these studies, relative stability in motor function was observed until the ages of 5 and 7, after which patients' functional ability began to decline (12, 13). The model results for patients in the BSC arm declining in terms of motor function in the long term in the model is therefore in line with the published data.

UK clinical experts also fed back that it was reasonable to assume that the majority of type 2 or type 3 patients treated with risdiplam would remain stable or improve in the long term. This is reflected in Table 91, whereby [redacted] of patients maintain the ability to sit without support for at least 10 years, and the proportions of patients in the advanced health states of 'standing' and 'walking' initially increase over time up to the 30-year mark.

With regards to mortality in type 2/3 patients, type 3 patients have been shown to reach a normal life expectancy, although they remain disabled (26). Life expectancy in type 2 patients is lower, with one German/Polish observational study published by Zerres et al. in 1997 reporting a survival rate of 68.5% at 25 years (133). The predicted mortality rate for 25 years in type 2/3 patients in the model was [redacted]. A direct comparison to the type 2 and 3 life expectancy values in the literature is not possible due to both SMA types being included in the model together, however, it is supportive of the external validity of the model results that the model 25-year predication reflects an intermediate estimate between normal life expectancy and the mortality rate observed by Zerres et al (133).

Type 1 (FIREFISH) model

The long-term clinical outcomes from the type 1 (FIREFISH) model for BSC and risdiplam for the base case analysis are presented in Table 92 and Table 93, respectively.

Table 92: Long-term clinical outcomes from type 1 (FIREFISH) model: BSC arm

Years	Permanent ventilation	Not sitting	Sitting	Standing	Walking	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 93: Long-term clinical outcomes from type 1 (FIREFISH) model: risdiplam arm

Years	Permanent ventilation	Not sitting	Sitting	Standing	Walking	Dead
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Motor milestone data up to 12 months are currently available from the FIREFISH trial. These data were compared to the model predictions for motor milestone achievements at 1 year. Within Part 1 and 2 the FIREFISH trial, after 1 year, [redacted]%, [redacted]% and [redacted]% had achieved the motor milestones of 'not sitting,' 'sitting,' and 'standing with support,' respectively, with risdiplam treatment. These data compare well with the year 1 data presented in Table 93 (it should be noted that a proportion of patients in the 'dead' health state are also accounted for in the model predictions), demonstrating the clinical validity of the type 1 model in the short term.

Feedback from the clinical advisors at the advisory board was that in the long-term, type 1 patients treated with BSC would be expected only to remain stable or deteriorate. The long-term outputs from the model reflect this feedback; no patients in the BSC arm ever achieve 'standing' or 'walking', and a very small proportion of patients achieve 'sitting' in the first 5 years of the time horizon. The proportion of patients deteriorating to the permanent ventilation health state increases up to year 5, after which this proportion decreases as more patients enter the 'death' health state.

This poor prognosis for type 1 patients treated with BSC further aligns with published literature. De Sanctis and colleagues performed a retrospective study in which motor milestone achievements of type 1 SMA patients included in patient databases in Italy and the United States 2010–2014 were recorded over time using the HINE measure (34). Infants who had two or more assessments over 2 years were assessed in the study. It was identified that none of the infants achieved independent sitting, nor more advanced milestones such as standing. Indeed, it was found that even stronger patients identified at baseline failed to make any further motor milestone gains following their first visit (34). The risdiplam model therefore conservatively predicts slightly optimistic clinical outcomes for the BSC arm, with a small number of patients reaching the 'sitting' health state in the first 5 years of the time horizon.

With regards to mortality of type 1 patients, as described in Section B.1.3.1, an observational study showed that without active treatment, 50% of infants with type 1 SMA are expected die or require permanent ventilation by the age of 10.5 months, and 92% are expected to die or require permanent ventilation by 20 months of age (23). By the 1-year (12-month) timepoint in the model, [redacted]% of patients were predicted to be in the 'permanent ventilation' or 'death' health state, whilst [redacted]% were in one of these two health states at 2 years (24 months). This suggests the model BSC predictions for mortality and permanent ventilation are in reasonable agreement with published literature.

The clinical experts also fed back that it was reasonable to assume that type 1 patients treated with risdiplam would remain stable or improve in the long term. The model predicted outcomes show that approximately 50% of patients maintain the ability sit for up to 5 years, and approximately 34% and 22% of patients will achieve the motor milestones of 'standing' and 'walking' in their lifetime.

B.3.10.3 Comparison of health economic outcomes with TA588

A comparison of the economic results for BSC between the nusinersen (TA588) and risdiplam (ID1631) base case models for type 2/3 and type 1 SMA are presented in Appendix T. These results are based on the final manufacturer's base case in TA588, following implementation of initial critique from the ERG and Committee. However, it should be noted that comparisons between the two models should be made with caution due to differences in model structure, inputs, assumptions and inclusion of carer impact.

B.3.11 Interpretation and conclusions of economic evidence

Comparison with published economic literature

This is the first economic evaluation focussed on assessing the cost-effectiveness of risdiplam for the treatment of SMA. No studies assessing the cost-effectiveness of risdiplam in SMA were identified in the SLR and it was therefore not possible to compare the risdiplam results produced by the economic model developed in this submission with any available publications. Nevertheless, extensive validation of the BSC results of the economic models was performed against the clinical studies results, published literature and clinical expert opinion (see Section B.3.10) and confirmed the internal and external validity of the model results.

Cost-effectiveness of risdiplam in type 1 and type 2/3 SMA patients

The results of the cost-effectiveness analyses for risdiplam versus BSC in both type 2/3 and type 1 SMA illustrate that risdiplam is associated with substantially greater QALYs and LYGs compared to BSC. These results illustrate the benefits that risdiplam may bring to SMA patients over and above current BSC in the UK, in terms of gains in both HRQoL and survival for patients and HRQoL for carers of patients with SMA.

In the type 2/3 SMA base case analysis, risdiplam was associated with an ICER of £[redacted] per QALY (with PAS). In the type 1 SMA base case analysis, risdiplam was associated with an ICER of £[redacted] per QALY (with PAS), which may be considered cost-effective for an end-of-life therapy.

Importantly, as a disease-modifying therapy, risdiplam is anticipated to contribute to patient outcomes that are well beyond the natural history of patients with SMA. The incremental benefit that risdiplam brings is explicitly reflected in the motor milestones that patients may achieve. In the type 2/3 model [redacted] of patients are predicted to maintain the ability to sit without support for at least 10 years, and the proportions of patients reaching the advanced health states of 'standing' and 'walking' are predicted to [redacted]. In the type 1 model, predicted outcomes show that approximately [redacted] of patients will maintain the ability sit for up to 5 years, and approximately [redacted] of patients will achieve the motor milestones of 'standing' and 'walking' in their lifetime.

Strengths and limitations of the evaluation

The cost-effectiveness models developed for type 2/3 and type 1 SMA are associated with a number of strengths.

- Firstly, thorough research was undertaken during the conceptualisation and development stage of the economic models to ensure that they were as reflective as possible of the natural history of SMA patients, without becoming overly complex. Literature searches on the natural history of SMA and treatment guidelines were conducted, and these were supplemented by consultations with UK-based and international clinical experts working routinely with SMA patients. The aim of these activities was to ensure that the health states are reflective of abilities SMA patients may feasibly achieve in their lifetimes and represent meaningful changes in patients' and carers' lives in terms of HRQoL. Furthermore, during model design, previous models developed for the treatment of SMA were carefully reviewed, including the cost-effectiveness models built for the NICE appraisal for nusinersen in early- and later-onset SMA (TA588), from which substantial learnings were taken into account based on the ERG and Committee's critique, as well as the model developed by ICER in the US for the same disease area (18, 107).
- A comprehensive approach was taken for sourcing inputs for the cost-effectiveness model. Evidence was generated *de novo* where possible and this was supplemented by systematically searching for and considering existing data. Following collection of all potential data sources for inputs, precedent with prior NICE appraisals in SMA and ensuring clinical plausibility through consultation with UK clinical experts was prioritised. As described above, two advisory boards were conducted with UK clinical experts in order to validate model inputs and assumptions and predicted long-term model outcomes, to ensure that they closely mirror clinical practice and the natural history of SMA patients in the UK (Appendix N). Importantly, Roche also acknowledged the limitations and gaps of the evidence base in SMA and the challenges in reaching consensus for many important model inputs in TA588, and made all possible efforts to ensure our company base case is an appropriate basis for NICE decision making. Where areas of uncertainty exist these were thoroughly explored through extensive scenario and sensitivity analyses.
- Even though UK trial sites were not included in FIREFISH or SUNFISH, UK clinical advisors confirmed that the clinical development programme of risdiplam is generally reflective of the prevalent SMA population seen in UK clinical practice (95). Of note, for the SUNFISH study, there were no exclusion criteria for SMA complications such as severe scoliosis and joint contractures as in other clinical studies of active treatments for SMA (57), and UK clinical experts confirmed that the recruited population resembled the global spectrum of the disease, supporting the external validity of the trial results.
- A particular strength of the type 2/3 model was the underlying data source; SUNFISH was a well-designed randomised controlled trial between the risdiplam and the relevant comparator to the submission, BSC, conducted in a broad SMA population that resembles the global spectrum of disease. A direct comparison to the comparator of interest negated the need to conduct an indirect comparison and data could be used directly to inform transition probabilities. The sample size of the SUNFISH trial was

sufficiently large that a patient subgroup more closely reflecting UK SMA patients could be utilised to inform the base case analysis.

- Importantly, as described in Section B.3.3, appropriate outcome measures were used to inform the motor milestone health states. In the type 2/3 model, the MFM-32 was used to define motor milestones, which, as noted by experts at the UK advisory boards (Appendix N) is a measure that can capture a wide spectrum of motor ability, from the weakest to strongest patients. The HINE-2 outcome measure was used to inform health state definitions in the type 1 model, which was deemed appropriate to use by UK clinical experts but also allowed for an ITC to be conducted against BSC.
- Both models are fully aligned to the NICE final scope for this appraisal, with model populations and the comparator accurately reflecting the submission decision problem. Evidence sources and model settings were also aligned with the NICE reference case, with risdiplam and BSC evaluated from the NHS/PSS perspective, over a lifetime horizon, with costs and utilities discounted at 3.5% (117).

Nevertheless, the economic analysis is also associated with limitations:

- A key limitation is the lack of long-term trial data available to appropriately validate the natural history for patients treated with BSC in the long-term, and the benefits that patients may experience with long-term treatment with risdiplam. Additional data cut cuts for both trials are expected, as presented in Section B.2.11, which to some extent will increase certainty for long-term outcomes. Long-term uncertainty, however, is a limitation currently inherent to the evidence base in SMA, as was discussed in detail during the NICE appraisal for nusinersen in SMA (TA588). Acknowledging this limitation of the evidence base for risdiplam and SMA more broadly, Roche made extensive efforts to seek validation from UK clinical experts on the likely long-term assumptions and trajectories for patients treated with either BSC or risdiplam, such that long-term model predictions were as reflective of UK clinical opinion as possible (see more details in Section B.3.10). The validation of model results was also supplemented through comparison of model outputs to available natural history studies published in the literature. The results of these validation efforts support the long-term outcomes predicted by type 2/3 and type 1 models (Section B.3.10).
- The single-arm nature of the FIREFISH trial can potentially be considered a limitation of the evidence base, as it necessitated an ITC to be conducted to generate comparative efficacy estimates and transition probabilities for the BSC arm. The FIREFISH study was single arm in design, due to both the small prevalent and incident patient population in rare conditions such as SMA and the fact that it was not considered appropriate (unethical) to treat infants with SMA with placebo when it was thought there could be a clinical benefit of risdiplam treatment. Nevertheless, it was possible to conduct an ITC versus BSC (using both naïve and population-adjusted methods) using data from the BSC arm of the ENDEAR trial; this trial was to be a good match for FIREFISH, as patient baseline characteristics were closely aligned between the two trials. Both the naïve and population-adjusted analysis were explored in the cost-effectiveness analysis. Therefore, the limitation of having single-arm evidence from FIREFISH was addressed as comprehensively as possible.
- As highlighted by the expert clinicians as part of the UK advisory boards, and discussed as part of TA588, health economics cost-effectiveness models may not fully

reflect the patient and carer experience of SMA, with some clinical manifestations of SMA and the impact on the carer community not being fully captured. This is a well-documented limitation of most economic models, which are a simplification of reality and cannot fully capture all elements of a disease process. From this perspective, however, the economic analysis in this evidence submission should be considered conservative, as it is likely that the full benefits that risdiplam may bring to patients and carers are not fully captured and reflected. This could include benefits such as improvements to respiratory and bulbar function, and in particular to upper limb function, which can bring substantial independence in patients' lives. A further likely benefit not necessarily captured is reduced hospitalisation, which will benefit the HRQoL of patients and carers alike. It is important that recognition of the fact that the broad and severe impact of SMA cannot be fully captured by the economic models or the NICE reference case, is taken into account in the NICE decision-making process. Additional considerations and NICE decision modifiers should be recognised for this appraisal, similarly to NICE's decision-making for nusinersen in TA588.

- Although the clinical development programme of risdiplam is generally reflective of the prevalent SMA population seen in UK clinical practice (95), in the risdiplam trials (as with most trials) there were month long delays between diagnosis and the start of the trials, as patients had no option for a disease modifying therapy before the start of clinical trials in this disease area. UK clinical experts confirmed to Roche that patients would be expected to be treated almost immediately in clinical practice, leading to a better prognosis and clinical outcomes (95). With time, patients may be treated earlier than the starting age in SUNFISH, as current treatments were not available when the studies were conducted. This implies that clinical efficacy outcomes from the risdiplam studies could potentially be considered conservative compared to outcomes that could be achieved in clinical practice. This would also translate to the economic analyses results, which are also likely to be conservative and not capture the full magnitude of treatment benefit that could be seen with earlier treatment initiation in UK clinical practice.
- Within the type 2/3 model, the mean baseline age was [redacted] It is anticipated that in clinical practice, risdiplam would be initiated at a much younger age than this, such that patients start receiving the benefits of therapy as early as possible. Due to the mean starting age in the SUNFISH trial, it is anticipated that patients had a worse prognosis than UK patients that would be treated in clinical practice. This means that the clinical results informing the model are likely to be conservative.
- A final limitation of the economic analysis is the combination of type 2 and type 3 patients, which is a heterogeneous group, in one economic model. It should be noted that even with type 3 patients there are considerable differences in characteristics between ambulant and non-ambulant patients. Additionally, subgroups such as type 3a and type 3b patients could not be explored. Results of the type 2/3 economic model should be interpreted in light of the heterogeneous population of the SUNFISH trial. Despite limitations inpatient numbers in the study, Roche plan to further explore the feasibility of exploring subgroups in the future where risdiplam may demonstrate increased cost effectiveness.

Cost-effectiveness analysis conclusions

Overall, since the majority of the key approaches and assumptions in the base-case analysis of the economic evaluation are either conservative in nature, or in line with UK clinical expert opinion, or based on precedent from TA588, we believe that the base-case cost-effectiveness results presented in our submission are appropriate as a basis for NICE decision-making. The Type 1 model results support the conclusion that risdiplam is a cost-effective treatment option versus BSC for Type 1 SMA patients, at PAS price and within the context of innovative end-of-life therapies. In type 2/3 SMA, results of the economic model demonstrate that risdiplam is associated with substantial improvements to patient and carer HRQoL, in addition to an extension to patients' lives, compared to BSC.

As demonstrated in our evidence submission, risdiplam is therefore a therapy with statistically significant and clinically meaningful efficacy outcomes across patients with both type 1 and type 2/3 SMA. Based on the comprehensive economic analysis presented, it should also be considered a cost-effective treatment option compared to BSC for type 1 patients. Importantly, results of the economic analysis should also be seen in light of the fact that SMA is a severe and rare condition, with a broad impact on patients, many of whom are children and people with disabilities, and their carers. NICE decision modifiers to account for the rarity, severity and broad impact of SMA should therefore explicitly be applied in this appraisal, similarly to what was recognised in TA588 (18).

There is currently no routinely funded therapy for SMA - nusinersen is reimbursed through a MAA for a period of up to 5 years - and there is a high remaining unmet need for patients who are either not eligible to receive nusinersen or for whom nusinersen is not reimbursed. Risdiplam offers a valuable, efficacious and clinically relevant additional therapeutic option for all patients across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status), and, importantly, the only available treatment option for a proportion of patients who may not be eligible for treatment with nusinersen through the existing MAA.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Clarification questions

November 2020

File name	Version	Contains confidential information	Date
ID1631_Risdiplam_Clarification_Response_14.12.2020	1	Yes/no	14/12/2020

Section A: Clarification on effectiveness data

Literature searching and systematic literature review

A1. CS Appendix D, page 11. The ERG notes that the same strategy was used to search MEDLINE and Embase simultaneously. Given that the two sources use different controlled vocabularies (MeSH and Emtree respectively), please explain how subject headings were selected and any other steps taken to optimise retrieval across both databases?

The SLR used Embase.com platform to search for articles from Embase and Medline concurrently. Embase.com indexes all Medline articles and maps the relevant MeSH terms and Emtree terms before indexing to ensure robust coverage for both databases concurrently. Therefore, searching Medline using MeSH terms (via PubMed or any other platform) was not required.

A2. CS Appendix D, page 11. Why was the MeSH Heading "Muscular Atrophy, Spinal/" not included in the search strategy? If the intent was for terms to be retrieved by "spinal muscular atrophy"/de, shouldn't this be exploded to also pick up the narrower heading "spinal muscular atrophies of childhood"?

As the search protocol for both Embase and Medline was developed in the Embase.com platform, MeSH headings were not considered. In Embase, the term "spinal muscular atrophy" includes the sub-node for motor neuron disease, which further covered acute motor axonal neuropathy, amyotrophic lateral sclerosis, primary lateral sclerosis and progressive muscular atrophy. None of the indications in the sub-node of "spinal muscular atrophy" were of interest for the SLR. In the event of exploding "spinal muscular atrophy", the search hits for all the indications mentioned above were also retrieved and therefore we de-exploded "spinal muscular atrophy" to keep the focus on articles indexed with the specific term. In order to ensure that all synonymous search terms for SMA were captured, we included multiple title/abstract search terms and also conducted extensive supplementary searches.

A3. CS Appendix D, page 11. Intervention terms were only searched in descriptor (de) and title/abstract fields. There are a number of other fields in MEDLINE and Embase where drugs may be mentioned (e.g. "drug name" in Embase, "name of substance word" in MEDLINE) – why were none of these searched?

As the search protocol for both Embase and Medline was developed in Embase.com platform, the index terms and ti/ab terms for interventions were considered. Using "Drug name" in Embase did not result in any further additional articles and therefore was not

considered. In order to ensure comprehensiveness of searches, the structured searches in Embase were supplemented with extensive bibliography and pragmatic searches.

A4. CS Appendix D, Section D.1, page 14. Please explain why the JEWELFISH study was excluded from the SLR based on this study being conducted in treatment-experienced patients, given that treatment-naive patients are not specifically mentioned in the inclusion criteria for the SLR, or in the scope, and risdiplam is positioned both as a first-line and second-line treatment in the proposed patient pathway provided in the CS (Figure 1, Section B.1.3.6, page 22).

The JEWELFISH study was not excluded from the SLR (see Table 7 in Appendix D for list of included studies). The text in Appendix D describes that this study was excluded from the indirect treatment comparison as this was conducted for studies with treatment-naïve patient populations only.

A5. Priority question. CS Appendix D, Section D.1, Figure 2, page 16. Please explain why the flow diagram shows 222 records included after full text screening, but only 64 studies reported on in the following box. Please address the discrepancy in numbers and explain what happened to the other 158 records.

A total of 222 publications were included after full text screening. For data extraction, multiple publications of the same trial were linked together resulting in 64 primary studies. The remaining 158 publications are linked to these 64 primary studies.

A6. Priority question. CS Appendix D, Section D.1, Figure 2, page 16. Please explain why the flow diagram shows five primary studies included in the ITC, but only two studies have actually been included in the ITC. Please explain what happened to the remaining three studies, and, if necessary, why they were excluded from the ITC.

As stated in the CS in section B.2.9.1, the scope of the SLR was broader than the ITC, with the two primary populations of interest for the SLR being patients with Type 1 (infantile-onset) SMA and patients with Type 2/3 (late-onset) SMA. However, a head-to head trial is available to compare risdiplam to BSC in patients with type 2 or 3 SMA (SUNFISH), therefore an ITC is not needed for this patient population. Only an ITC in Type 1 SMA patients was conducted within the CS. The SLR identified five primary studies that met the eligibility criteria: 3 in Type 1 SMA and 2 in Type 2/3 SMA. However, as the scope of the ITC in the CS was to compare risdiplam to BSC in Type 1 patients, only 2 of the Type 1 SMA studies were relevant to inform this comparison. This is outlined in more detail in section B.2.9 of the CS.

A7. CS, Appendix D, Section D.1, page 13. Please clarify which fields were extracted in the process of data extraction.

Table 1: Data extraction fields

Parameters	Sub-parameters
Study characteristics	
Eligibility criteria (inclusion/exclusion)	
Details of study-treatment	
Patient characteristics	Age at symptom onset
	Age at study entry/first dose
	Time since SMA diagnosis
	Gender distribution
	Race/ethnicity
	Region
	SMA Type
	SMN2 copy number
	% scoliosis at baseline
	% contractures at baseline
	% scoliosis/hip surgery at baseline
Efficacy outcomes	Overall survival
	Ventilation free survival/Event-free survival
	Time to permanent ventilation
	Time of treatment
	Motor milestones (sitting, standing and walking)
	Hammersmith Functional Motor Scale (HFMS)
	Hammersmith Functional Motor Scale Expanded (HFMSE)
	Motor Function Measure (MFM) and MFM-32/MFM-20
	Children's Hospital of Philadelphia Infant Neuromuscular Disorders (CHOP INTEND)
	Hammersmith Infant Neurological Examination (HINE) and HINE-2
	Bayley Scales of Infant and Toddler development (BSID-III)
	6-Minute Walk Test (6MWT)
	Revised Upper Limb Module (RULM)
	Scoliosis, contractures, hip surgery/orthopaedic surgery
	Respiratory function
	Forced Vital Capacity (FVC)
	Forced Expiratory Volume in 1 Second (FEV1)
	Sniff nasal inspiratory pressure (SNIP)

	Maximal inspiratory pressure (MIP)
	Maximal expiratory pressure (MEP)
	Peak cough flow (PCF)
	Clinical Global Impression – Change (CGI-C)
	HrQoL (including SF 36, EQ-5D, HUI)
Safety and tolerability outcomes	Any adverse events (AEs) and serious AEs
	Overall discontinuations and discontinuations due to AEs
	Number of deaths
	Hospitalizations

A8. Priority question. CS, Appendix D, Section D.1, Table 8, pages 19 to 21. Please provide full texts for the following papers listed in Table 8: Bharucha-Goebel 2017; Calder 2016; Ridler 2018; Zanetta 2014; Finkel 2019 (S. No. 15); Finkel 2019 (S. No. 16).

Please see the accompanying reference pack for the full texts of these papers.

Clinical effectiveness evidence and statistical analysis - Type 2/3 SMA

A9. Priority question. CS, Section B.1.3.6, Figure 1, page 22. Please explain the position on the treatment pathway for SMA as a second-line treatment (following nusinersen) in Type 2/3 SMA when the SUNFISH trial excluded patients who had previous treatment, and thus there is no evidence of the efficacy of risdiplam in patients with Type 2/3 SMA who have received nusinersen to support this position in the pathway.

It is important to clarify that risdiplam is not positioned as a first- or second-line treatment. While the company acknowledges there is currently an absence of evidence to determine the optimum sequence or combination of therapy, clinical experts confirmed to Roche that treatment decisions should be based on multiple factors including an overall benefit risk analysis, unmet need and clinician and patient choice. The latter of these considerations is of critical importance; given the heterogeneity in disease severity among the patient population, each patient and family affected by SMA will have different perceptions of what is considered to be a clinically meaningful outcome with respect to desired benefits or avoided risks from a regimen, therefore patient preference is important to consider when making treatment decisions.

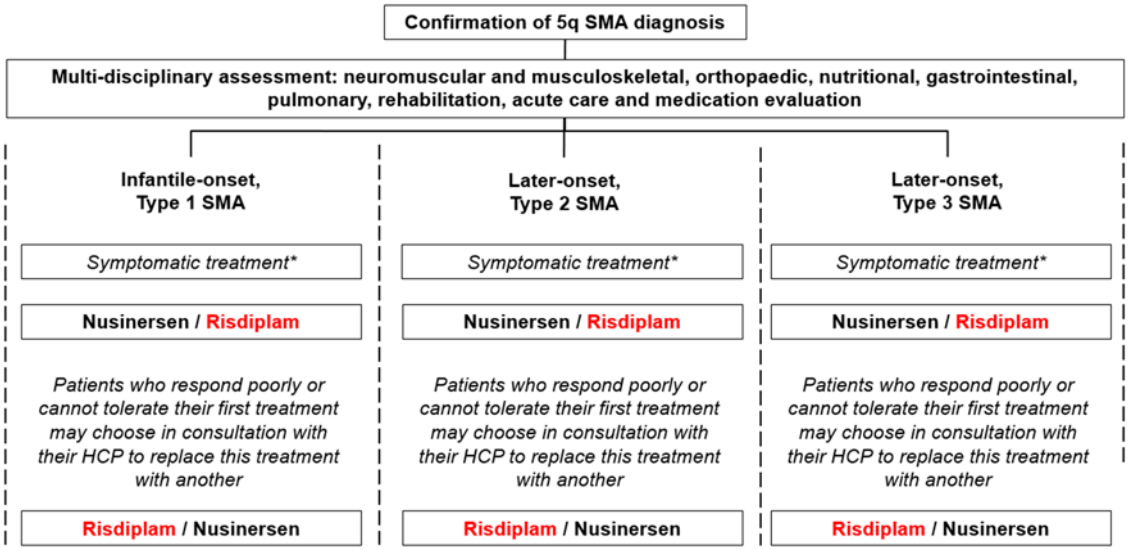
A consideration in deciding the position of risdiplam is that, due to the progressive nature of SMA, there is still a large unmet need in patients who have previously received nusinersen but who have had to discontinue treatment. This is supported by a recent consensus survey conducted by the paediatric SMA Reach clinical network on proposed patient criteria for the risdiplam EAMS, in which there was a high consensus (22/23 respondents) that a

nusinersen-treated patient who meets the stopping criteria for the Managed Access Agreement should subsequently be offered risdiplam under the EAMS and the same consensus (22/23) who felt that a patient who is already receiving nusinersen under the MAA deteriorates to the point of meeting the stopping criteria for nusinersen in the MAA should be offered risdiplam (1).

As such, we propose that risdiplam will provide an additional therapeutic option for all patients across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status). This will include treatment-naïve patients, (i.e. those who choose not to receive or are unsuitable for nusinersen due to severe complications and those who are ineligible for the nusinersen MAA), as well as those patients who have previously received nusinersen but cannot tolerate it and/or respond poorly.

The original positioning pathway figure in the company submission has been amended below to clarify that risdiplam is not seen specifically as either a first- or second-line treatment.

Figure 1: Proposed position of risdiplam in the pharmacologic treatment pathway for SMA (UPDATED)



*Symptomatic treatment will be based on individual clinical need and symptom severity following multi-disciplinary assessment

A10. CS, Section B.2.3.5, Table 8, page 34. The range for median age of symptoms for the risdiplam arm of the SUNFISH trial is 0-57 months. Please verify that none of these were Type 1 SMA patients, and explain how some Type 2/3 SMA patients had a symptom onset of 0 months?

The Type 2 and Type 3 SMA patients were enrolled in study BP39055 based on a confirmed diagnosis of 5q-autosomal recessive SMA, including genetic confirmation of homozygous

deletion or heterozygosity predictive of loss of function of the SMN1 gene and clinical symptoms attributable to Type 2 or Type 3 SMA.

Due to personal data protection regulations in some EU countries, some of our clinical sites are not able to report full dates of birth (DOB) or other personal identifiers for their patients. When partial dates are reported, the following programming rule is applied for the missing data to enable derivations that refer to the partial dates reported: 15 for the Day and June for the Month.

There are 2 patients in SUNFISH Part 2 data set with an apparent onset of symptoms of 0 months. The cases are presented below.

- **Pt 2501:** This case (patient #2501) refers to a female patient from France whose DOB was reported as unknown (UNK) for the day in Jul 1995 (i.e. UNK, Jul, 1995). The date of symptoms onset was reported as UNK, Jul, 1995. Thus, the derived age of symptoms onset is 0. The initial symptom reported was hypotonia, SMA was diagnosed at age 1 year 5 months. SMA was genetically confirmed on 28 Oct 2014. The patient had head control at age 4 months (function still maintained), sat supported at 7 months (function still maintained), sat unsupported at 9 months (ability lost at age 6 years), and stood with support at 12 months (ability lost at age 6 years). The patient did not have any type of respiratory support at the time of inclusion in the study. This patient was reported as Type 2 SMA.
- **Pt 2601:** This case (patient #2601) refers to a male patient from France whose DOB was reported as UNK for the day in Jul 1999 (i.e. UNK, Jul 1999). The reported date of initial symptoms was UNK, UNK, 1999. Thus, the derived age of symptoms onset is 0. Initial SMA symptom was developmental motor delay. SMA was diagnosed at 12 years and 9 months of age. SMA was genetically confirmed on 30 Apr 2012. The child had head control at age 1 month (function still maintained), he rolled completely at 1 month (function still maintained), sat supported and unsupported at 4 months (function still maintained), stood with support at 5 months (ability lost at 16 years), stood without support at age 1 year (ability lost at 8 years), walked with support and independently at age 1 year 2 months (abilities lost at age 16 years 5 months). The patient did not have any type of respiratory support at the time of inclusion in the study. This patient was reported as Type 3 SMA.

In conclusion, these patients had the clinical history of the Type 2 and 3 SMA as required by the SUNFISH inclusion criteria.

A11. CS, Section B.2.2, Table 5, page 26. Please explain why an upper age limit of 25 years is used in the SUNFISH inclusion criteria.

An upper age limit of 25 years is used in the SUNFISH inclusion criteria due to the following reasons:

- In Part 1 (first in patient evaluation of risdiplam), the objective was to study safety and tolerability across the Type 2 and Type 3 SMA patient population, which was also expected to be associated with various co-morbidities. Beside safety and tolerability, part of the primary objective of this dose-finding part was to study the multiple-dose PK and PD effects of risdiplam in terms of increase in full-length SMN2 mRNA and SMN protein in order to select a dose for the confirmatory Part 2 of this study. Accordingly, Part 1 of the study included Type 2 and 3 (ambulant and non-ambulant) SMA patients aged 2-25 years.
- Part 2 included Type 2 and non-ambulant Type 3 SMA patients aged 2-25 years. The objective was to investigate the clinical efficacy and safety of risdiplam in a broad sample of patients with Type 2 and 3 SMA, representative both in age and disability status of those seen in clinical practice.

A more narrow study population focusing on young patients only would have allowed a more homogeneous and easier assessment of efficacy (as size and type of treatment effects may vary by age) and could lead to a higher chance for the study to be successful. However, on the other hand, disease progression in non-ambulant patients has been reported to be slower after the age of 15 years (2). Therefore, extending recruitment beyond the age of 25 could have lowered the chance to detect a difference between risdiplam and placebo after 12 months of treatment.

Nonetheless the heterogeneity of patients enrolled in the SUNFISH trial allowed the characterization of the effects of treatment with risdiplam on the most prevalent SMA patient population: children, teenagers and adults living with Type 2 and 3 SMA, representative of the broad clinical spectrum of the disease. This supports the generalizability of study results to the wide range of people living with SMA.

The uniqueness of the SUNFISH study design has provided the first opportunity to assess the efficacy of a SMN protein increasing treatment in adults living with SMA, facilitating translation of the trial data to the real-world patient population living with an advanced disease who may not have access to other forms of approved therapies.

A12. CS, Section B.2.3.1, page 27. Please explain how the patients included in the SUNFISH trial were identified and recruited.

Patients were identified from the study centres own patient population or via referrals from other SMA treating physicians. Written informed consent for participation in the study was obtained before performing any study-specific screening tests or evaluations.

Screening/enrolment into the SUNFISH trial was competitive and managed via a study portal. The study portal was used to allow the sponsor to have control and oversight of the enrollment process. Study sites were granted access to the study portal following training provided by the Study Monitors. In addition, a user guide (SUNFISH Portal User Guide, dated 25 April 2019) was distributed to the sites. The portal's primary function during the screening/enrolment period was to:

1. Manage the per protocol required stratification of patients according to age groups in a controlled way and
2. Provide the sites with a tool to register potential patients for screening

Sites were able to add patients to the portal queue and book their screening slots up to 14 days before the planned screening date. In addition, the portal provided an overview of globally screened and enrolled patients as well as a cohort overview of free places, patients in queue, in screening and randomized. Towards the end of the screening phase, the CRO sent various e-mails to sites on behalf of the Sponsor to communicate the status of free slots and closure of cohorts.

A13. CS, Section B.2.3.3, Table 6, page 28. Given that neither the FIREFISH nor SUNFISH trials had an investigational site within the UK, and given that standards of healthcare can vary worldwide, please explain the relevance of the data from these trials to the UK context.

Although no patients from the UK were enrolled to either FIREFISH or SUNFISH, clinical experts have confirmed to Roche that these studies provide substantial evidence of effectiveness for risdiplam to a broad and heterogeneous population of people with SMA that is generally reflective of the prevalent SMA population seen in UK clinical practice. Moreover, the endpoints collected in each study are relevant to burden of disease for people with SMA in the UK and therefore the studies provide evidence that risdiplam addresses the unmet medical need for this patient population.

We acknowledge the standards of healthcare can vary worldwide. However, in 2007 a consensus statement for the standard of care of SMA was published and has been widely adopted by clinicians all over the world. To reflect updates in evidence related to the natural history of disease, a committee of international experts in SMA convened to provide an

update to these guidelines. Nine separate working groups, each led by a European and US clinician, were formed to focus on specific topics for this update, including diagnosis, pulmonary care, nutrition and medication. The subsequent updated guidelines (3, 4), which included UK authors were published in 2017 and serve to provide a consensus on the optimum standard of care for people with SMA, including those patients in the UK.

It should be noted that 61% and 81% of patients in FIREFISH and SUNFISH respectively were enrolled from Europe and North America, regions in which the standard of care for SMA is informed by these guidelines and not expected to deviate hugely from UK clinical practice. The company is therefore confident that there is no concern regarding the relevance of the data from these trials to the UK context.

A14. Priority question. CS Appendix D, Section D.2, page 24. Please explain why "All 4 patients discontinued in order to switch to other treatment, specified as nusinersen in 3 patients, and not further specified in 1 patient." Was this because of a lack of efficacy, adverse effects, and/or some other reason?

The reasons for early discontinuation were provided by patients as part of a free text field. The responses provided were as follows:

Risdiplam arm:

- "Change to other treatment" [redacted]
- "Move to nusinersen" [redacted]
- "Request discontinuation to initiate nusinersen" [redacted].

Placebo arm:

- "Access to nusinersen" [redacted]

A15. CS, Section B.2.6.2, Table 22, page 50. Change from baseline is a statistically inefficient outcome measure and it is better to use analysis of covariance using baseline response as a covariate. Please present an analysis of the primary endpoint in SUNFISH with baseline MFM-32 included as a covariate and recreate Table 22 and Figure 3 accordingly.

The MFM32 assessment results are collected repeatedly on the same patient across different visits throughout the study. Therefore, it would be more appropriate to perform the Mixed Model Repeated measure analysis (MMRM) than using the analysis of covariance analysis. MMRM analysis takes into account that repeated measurements are taken for the same subject, in addition to all available data from each patient visit up to week 52. In comparison, the focus of ANCOVA would be the

change in results from baseline to Week 52. In addition, the baseline MFM32 total scores have already been taken into account and included as a covariate in the model in the MMRM primary analysis. Therefore, the primary analysis result has been adjusted with patients' baseline total MFM32 scores.

A16. CS, Section B.2.7, pages 56 and 57, and Appendix E. Categorising continuous variables, including by using sample estimates of percentiles as done in the case of MFM-32, is problematic for various reasons (see https://discourse.datamethods.org/t/categorizing-continuous-variables/3402). In preference to separate subgroup analyses, please provide results for each outcome measure using a single model with continuous variables included as continuous variables (for example, using splines), and assess higher order terms and interactions between variables. Baseline response should be included in any change from baseline analyses.

SUNFISH and its sample size have been designed to evaluate a pre-specified analysis plan:

"Changes from baseline in the total MFM scores will be summarised descriptively at each time-point by treatment group for the ITT population and a Mixed Model Repeated Measures (MMRM) analysis will be performed to utilize all the data collected in Part 2 up to 12 months. The model will include the absolute change from baseline total MFM score as the dependent variable. The model will include as independent variables, the baseline total MFM score (continuous), treatment group, time, treatment-by-time interaction and the randomisation stratification variable of age (categorical: 2 to 5, 6 to 11, 12 to 17, 18 to 25 years at randomisation)" (5).

Given the sample size, additional covariates in a post-hoc analysis, including their corresponding interactions and high order terms, may result in overfitting the model.

An analysis using a single model with all subgroup variables, including higher-order and interaction terms, would result in a model with a very large number of independent variables and interaction terms. For example, fitting a single model for the primary endpoint of change from baseline in MFM32 total score at Month 12 using all subgroup variables (age, region, MFM baseline score, SMA type, SMN2 copy number), interactions of subgroup variables with visit and treatment, and quadratic terms for the continuous variables age and MFM baseline score would

result in a total of 25 terms. This does not include other possible two- and three-way interactions between subgroup variables and cubic terms of continuous variables. Assuming the rule of thumb of 10 events per term, this model would require at least 250 observations. However, as interaction terms would also be included, an even larger sample size would be required. Simulation studies have shown that in order to detect two-way and three-way interactions in a mixed effects model, the sample size is required to be fourfold that to detect a main effect for a two-way interaction and fourfold that to detect a two-way interaction for a three-way interaction (6-8).

The SUNFISH and FIREFISH studies were not powered for these analyses and there is a high risk of overfitting the data. Fitting such complex models to the available data may lead to unreliable and misleading results, as the sample sizes are not large enough to describe the (approximately) true relationship between the dependent variable and all of the included covariates.

In addition, due to country rules, not all patients could provide the full date of birth, and hence the age of some patients may not be very accurate. This has to be taken into consideration on whether it would be suitable to include age as a continuous variable, including the corresponding interactions and high order terms in the model, too. Age group (2-5, 6-11, 12-17 and 18-25 years) was a stratification factor in SUNFISH and in accordance with ICH-E9 age group (categorical) was included as a covariate in the main statistical model.

A17. CS Appendix F, Section F.3, Table 13, page 39. Please clarify whether this table includes adverse event data from just the RCT period, or from both the RCT period and open-label period combined.

These adverse event data are from the placebo-controlled, double-blind treatment period only.

Clinical effectiveness evidence and statistical analysis - Type 1 SMA

A18. CS, Section B.2.3.2, page 27: Please explain how the patients included in the FIREFISH trial were identified and recruited.

In the FIREFISH trial, local patients as well as cross-border patients were identified as potential patients.

Local patients were identified through the following means:

- Patients identified from the hospital's outpatient clinics
- Patients identified from the study centers own potential patient population
- Principal Investigator in contact with other paediatrician/emergency units making them aware of the SMA 1 enrolment open at their sites
- Patients identified via referrals from e.g. SMA associations
- Patient recruitment letters sent to paediatrics, obstetrics and gynaecologists

Cross-Border patients were identified differently, as explained below:

- Patient's family contacted Patient Association Group (PAG) in home country or abroad; PAG informed Roche Patient Support Partner (PSP) about family's interest in participating in the study and confirmed family's wish to be contacted by Roche PSP to learn more about trial and steps to participate
- Patient's family contacted the site directly and the Investigator contacted Roche/CRO to ask for support in bringing the potential patient to the site. Roche PSP then contacted the family
- Patient's family contacted Roche Affiliate (Medical Information Portal) in the patient's home country to enquire as to how the family should proceed to participate in FireFish (family left their contact details with their message). Roche Affiliate contacted Roche PSP, who then contacted the family

Patient recruitment:

- Prior to obtaining patient informed consent for participation into the study, the site completed a pre-screening notification form (SNF) and submitted it to the Sponsor (or CRO) for review
- Upon review of the SNF and based on the availability of screening/enrolment allocations in the study, Roche provided Screening Approval (or reason if not approved)
- Written informed consent for participation in the study was obtained (by the parents/guardians) before performing any study-specific screening tests or evaluations
- For cross border patients, the ICF was in the parents/guardians' own language. An interpreter was also required to sign the ICF, as an impartial witness
- An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria was completed by the Investigator and sent to Roche (or CRO) prior to randomising the patient.

A19. Priority question. CS, Section B.1.3.6, Figure 1, page 22. Please explain the position on the treatment pathway for SMA as a second-line treatment (following nusinersen) in Type 1 SMA, when the FIREFISH trial excluded patients who had

previous treatment, and thus there is no evidence of the efficacy of risdiplam in patients with Type 1 SMA who have received nusinersen to support this position on the pathway.

Please see response to A9.

A20. Priority question. CS, Section B.2.3.1, page 27. Please clarify why it was possible to design ENDEAR as a randomised control trial for nusinersen, but not possible to design FIREFISH as a randomised control trial for risdiplam.

The majority of untreated infants with Type 1 SMA will either die or require permanent ventilation before the age of 2 years. Given the severity of this subtype, it was decided that it would be unethical to place some infants on placebo; therefore, FIREFISH was designed as a single arm trial to ensure all infants with Type 1 SMA received active treatment.

The natural history data in Type 1 SMA is well established; by definition, a patient with Type 1 SMA will never be able to sit unsupported without treatment. Therefore, the ability to achieve this motor milestone would be an improvement that is never seen in untreated patients. For this reason, the primary endpoint used in FIREFISH Part 2 is robust and documents treatment benefit in a consistent way.

The results from FIREFISH Part 2 are compared with data describing the natural history of untreated infants with Type 1 SMA. These natural history data were used to define thresholds of achievement, i.e. objective performance criteria or performance goals, against which to assess the efficacy of risdiplam treatment. The predefined performance criterion for the primary endpoint was 5%. This threshold was chosen based on the well-defined natural history of Type 1 SMA in which untreated infants never achieve sitting without support.

A21. FIREFISH CSR, Section 3.2, page 44. Please explain who the independent readers for the evaluation of the BSID-II gross motor scale were and how they were recruited. Please clarify their independent role, including any conflicts of interest.

The Independent Central Readers (ICRs) for the evaluation of the BSID-III gross motor scale are expert Paediatric Physical Therapists with backgrounds in spinal muscular atrophy.

Signant Health were responsible for identifying, approaching and contracting the ICRs on behalf of Roche, as part of the scope of services provided for the BP39056/FIREFISH study.

The role of the ICRs was to review and score the BSID-III assessments conducted by the Clinical Evaluators at the site as per protocol.

The BSID-III gross motor scale videos are reviewed and scored in a blinded manner according to a robust and detailed Central Review process. The key features of the process that promoted independency during the review are as follows:

- The site-submitted video is first reviewed for quality assurance by the Signant Health Project Team ensuring that any patient-identifying information is identified and removed from the video that is then provided to the ICRs
- Each BSID-III assessment video is assigned a Unique Meeting ID. The Unique Meeting ID is used to link the scores that the ICRs provide following their central review, and the specific assessment video, in a blinded fashion
- Two ICRs review each patient visit. They have to both agree independently on the visit meeting the primary end-point criteria, for it to be recorded as such. If the ICRs score differently on the first scoring, then one re-score is permitted
- In addition, ICRs are unaware if a video is a first scoring or a second scoring (re-score)

Prior to contacting viable candidates to be external consultants, Signant Health screened and removed any candidates that had evident affiliations with a study site or related institution to remove any local conflicts of interest.

The consultancy agreements signed between the ICR representatives and Signant Health ensured that the ICRs would conduct the services for the study without conflicts of interest and in an independent manner.

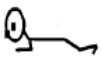
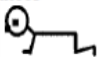
A22. Priority question. FIREFISH CSR, Section 5.3.1.2, Table 17, page 104. [redacted] patients are labelled as 'cannot test' for the HINE-2 walking milestone. Why was this?

The high incidence of "cannot test" for walking in the HINE-2 assessment can be explained by the lack of a no-achievement option for walking in the HINE-2 scale, as described below.

Study sites were provided a HINE-2 score sheet with a study-specific cover page including general instructions for administering the HINE-2 and data fields for if the assessment was performed, including date, time, name and signature of the evaluator. See Figure 3 for an image of the HINE-2 score sheet.

Each motor item of the HINE-2 (head control, Sitting, voluntary grasp, etc.), except for walking, has an option to indicate that the patient cannot achieve any attainment level. For example, for head control, the lowest option is "unable to maintain head upright". However, for walking, the lowest option is "bouncing" which is the first attainment level towards walking independently. For patients that cannot achieve any level of walking, there is no option on the HINE-2 assessment that corresponds to the patient's lack of ability.

Figure 2: HINE-2 score sheet

Head control	unable to maintain head upright	wobbles	all the time maintained upright			
Sitting	cannot sit	sits with support at hips 	props 	stable sit 	pivots (rotates) 	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) 	touches leg 	touches toes 	Observed: Reported (age):
Rolling	no rolling	rolling to side	prone to supine	supine to prone		Observed: Reported (age):
Crawling	does not lift head	on elbow 	on outstretched hand 	crawling flat on abdomen 	crawling on hands and knees 	Observed: Reported (age):
Standing	does not support weight	supports weight	stands with support	stands unaided		Observed: Reported (age):
Walking		bouncing	cruising (walks holding on)	walking independently		Observed: Reported (age):

In the study database (eCRF), HINE-2 data is entered for each component by selecting from a drop-down list of options. For walking, the options are:

1. Bouncing
2. Cruising (walks holding on)
3. Walking independently
4. Cannot Test
5. Not Done

There is no “0” option in the eCRF for patients unable to achieve any level of walking, which reflects the HINE-2 scoresheet. The eCRF completion guidelines for the HINE-2 indicate, “If the observation could not be tested then the ‘CNT’ [Cannot test] option should be selected.”

In the analysis of the HINE-2 data, the summary of the level of attainment is presented as they are answered in the eCRF. The Statistical Analysis Plan (SAP) states: ‘Cannot test (CNT)’ will be included as a separate response category for each milestone. In the analysis

of HINE-2 motor milestone responders, if an individual item is missing, or ‘Not Done’ or ‘Cannot Test (CNT)’ is recorded, the item score will be set to 0.

In summary, the scoring and data entry of the walking motor item on the HINE-2 is unique in the lack of an explicit option for no achievement, and this is reflected in the analysis.

A23. Priority question. FIREFISH CSR, Section 6.4, p.151. Treatment-related adverse events are reported as being those “considered by the investigator as related to medication”. What procedure was used to determine whether an adverse event was related to study medication?

Investigators were asked to use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event was considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance was taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study drug, or reintroduction of study drug
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

A24. CS, Section 2.9.3, page 62: Covariates included in a propensity-score type model for a MAIC should include all relevant prognostic factors and treatment effect modifiers irrespective of whether there is evidence statistically that they are predictive of outcome. If gender is thought to be predictive of outcome then it should be included in the model. Please discuss.

An SLR was conducted in order to identify potential treatment-effect modifiers and prognostic factors in individuals with SMA. In the SLR, four studies were identified that investigated the impact of gender on survival outcomes in Type 1 SMA (9-12). None of those studies found a statistically significant difference (p-value <0.05) in survival outcomes between males and females. Hence, we did not find evidence for gender being prognostic from the SLR.

In addition to the SLR, we asked Roche internal and external medical experts on which factors they thought to be potentially prognostic or predictive in Type 1 SMA. Gender was not flagged as a prognostic or predictive factor.

A25. CS, Section 2.9.3, Table 33, page 63. For event-free survival and overall survival, the expectation is that the MAIC generates an adjusted risdiplam Kaplan-Meier survival function in a population of patients matched to the population represented by the patients who received BSC in ENDEAR, as per Figure 8 of the CS. For the purpose of the economic evaluation there is no reason to assume proportional hazards. Please provide a justification for the assumed parametric survival functions used in the economic model.

Although the MAIC indeed generates an adjusted risdiplam Kaplan-Meier survival function in a population similar to ENDEAR, using this adjusted curve assumes that the population represented by ENDEAR is closer the target population. However, since FIREFISH also included patients with a more severe disease at baseline that were not included in ENDEAR, the population represented in FIREFISH was considered to be closer to the target population. Therefore, we considered it more appropriate to use the originally observed FIREFISH survival data for risdiplam and to derive the BSC curve by applying a hazard ratio to the risdiplam curve.

As described in section B.3.3.2, the choice of the parametric survival function for overall survival and ventilation-free survival was based on goodness-of-fit to the observed data (using AIC and BIC statistics) and, more importantly, on input from clinical experts and the long-term plausibility of the survival curves. For both overall and ventilation-free survival, the exponential distribution was considered the most plausible.

Evidence to support holding of the proportional hazards assumption for ventilation-free survival between the risdiplam and BSC arms is presented in Appendix O. Specifically, log-cumulative hazard plots are presented for the data generated for the naïve comparison and MAIC (which informed the base case and a scenario analysis, respectively). Both log-cumulative hazards plots demonstrate that the risdiplam and BSC arms remain parallel over time, supporting holding of the proportional hazards assumption.

A26. CS, Section B.2.9.4, page 64. The CS states that "A high number of patients received weights of zero or close to zero." Please provide details on the

characteristics of the patients from FIREFISH who are being excluded from the analysis.

None of the patients in FIREFISH received a weight of 0 and were completely excluded from the analysis.

Twenty-eight patients were assigned a rescaled weight of <0.5. These patients were characterised by a slightly more severe disease at baseline, as illustrated by an average lower CHOP-INTEND scores, lower HINE-2 scores, and lower ulnar CMAP negative peak amplitude at baseline compared to the total pooled FIREFISH data set. A higher proportion of these patients required ventilator support at baseline and were male compared to the total pooled FIREFISH data set.

Patient characteristics of these patients with a re-scaled weight of < 0.5 are presented in Table 2.

Table 2: Baseline characteristics of patients with a re-scaled weight of < 0.5

Baseline characteristic	**Risdiplam (FIREFISH) N=28**
Mean age at first dose in days (sd, [range])	160 days (47, [78-212])
Female gender	39%
Mean age at symptom onset in weeks (sd, [range])	6.5 weeks (2.6, [4.1-13.1])
Mean disease duration at screening in weeks (sd, [range])	13.0 weeks (6.5, [4.4-23.3])
Mean age at diagnosis in weeks (sd, [range])	11.5 weeks (6.2, [4-25.9])
Mean score on CHOP INTEND scale (sd, [range])	16.5 (3.49, [8-23])
Patients with nutritional support: Unable to swallow†/Gastrointestinal tube feeding	11%
Patients with ventilatory support	43%
Mean HINE-2 score (sd, [range])	0.68 (0.67, [0-2])
Mean CMAP negative peak amplitude (mV) - ulnar nerve (SD, [range])	0.164 (0.13, [0-0.44])

†Baseline data on gastrointestinal tube feeding was not available for most patients in Part 1, as the questionnaire was only introduced 6 months after start of the study. Ability to swallow was used as a proxy for tube feeding for these patients.

A27. CS, Section B.2.9.4, Table 34, page 64. Please add to the table the standard deviations for continuous variables and clarify either that the analysis matched for differences in standard deviations or the potential consequences of not doing so. In

addition, four of five variables that were not included in the adjustment model are not obviously well matched, although they may not be prognostic or treatment effect modifiers in practice. Nevertheless, the ERG would like to see an additional analysis in which matching also accounts for these variables - please present this analysis.

The standard deviations for continuous variables are listed below in Table 3.

Table 3: FIREFISH baseline characteristics post ENDEAR-matching (including SD)

Baseline characteristic	Pre-Matching: Risdiplam (Pooled FIREFISH)	Post-matching: Risdiplam (Pooled FIREFISH matching-adjusted to ENDEAR)	Nusinersen & BSC (ENDEAR)
Sample size (ESS)	58	[redacted]	121
Mean age at first dose in days	[redacted]	[redacted]	169 days (NR)
Female gender	57%	[redacted]	55%
Mean age at symptom onset in days	[redacted]	[redacted]	60 days (NR)
Mean disease duration at screening in days	[redacted]	[redacted]	94 days (NR)
Mean age at diagnosis in weeks	[redacted]	[redacted]	14.3 weeks (NR)
Mean score on CHOP-INTEND	[redacted]	[redacted]	27.24 (7.94)
Mean HINE-2 score	[redacted]	[redacted]	1.37 (1.15)
Patients with ventilatory support	[redacted]	[redacted]	22%

NR: Not reported

The analysis did not match for differences in standard deviations. A recent simulation study on unanchored Matching-Adjusted Indirect Comparison has shown that matching on first moments performed well in a number of scenarios, while this was not always the case for matching on higher moments (13). The authors found that matching on higher moments showed the potential for large errors, especially when data are not normally distributed, and that poor performance could be exacerbated by matching on higher moments. It was concluded that matching on higher moments did not provide a meaningful advantage over matching on first moments, while posing a clear potential for harm.

Selection of matching variables was based on the availability of patient characteristics reported in the comparator study, an SLR on prognostic and predictive factors and input from Roche internal and external medical experts.

Nevertheless, as requested by the ERG, we have conducted an analysis that also matched for the other baseline characteristics, including those without evidence on prognostic or predictive status. Matching was conducted on the following variables: age at first dose, sex, symptom duration, age at symptom onset, CHOP-INTEND score at baseline, HINE-2 score at baseline, ulnar nerve CMAP amplitude at baseline, proportion of patients with feeding tube / unable to swallow at baseline and the proportion of patients on ventilation at baseline. This analysis reduced the ESS to 20.1. Baseline characteristics after matching are presented in Table 4.

Table 4: FIREFISH baseline characteristics post ENDEAR-matching

Baseline characteristic	**Pre-Matching: Risdiplam (Pooled FIREFISH)**	**Post-matching: Risdiplam (Pooled FIREFISH matching-adjusted to ENDEAR)**	**Nusinersen & BSC (ENDEAR)**
Sample size (ESS)	[redacted]	[redacted]	[redacted]
Mean age at first dose in days	[redacted]	[redacted]	[redacted]
Female gender	[redacted]	[redacted]	[redacted]
Mean age at symptom onset in days	[redacted]	[redacted]	[redacted]
Mean disease duration at screening in days	[redacted]	[redacted]	[redacted]
Mean age at diagnosis in weeks	[redacted]	[redacted]	[redacted]
Mean score on CHOP-INTEND	[redacted]	[redacted]	[redacted]
Mean HINE-2 score	[redacted]	[redacted]	[redacted]
Patients with ventilatory support	[redacted]	[redacted]	[redacted]
Proportion of patients with feeding tube / unable to swallow at baseline	[redacted]	[redacted]	[redacted]
Ulnar nerve CMAP amplitude at baseline	[redacted]	[redacted]	[redacted]

Ventilation-free survival

The updated analysis results of ventilation-free survival are provided in Figure 3 and Table 5. The hazard ratio generated by the updated MAIC of risdiplam versus BSC is [redacted] (95%CI [redacted]), reduced from the original MAIC HR of [redacted].

Figure 3: Ventilation-free survival Kaplan-Meier curves

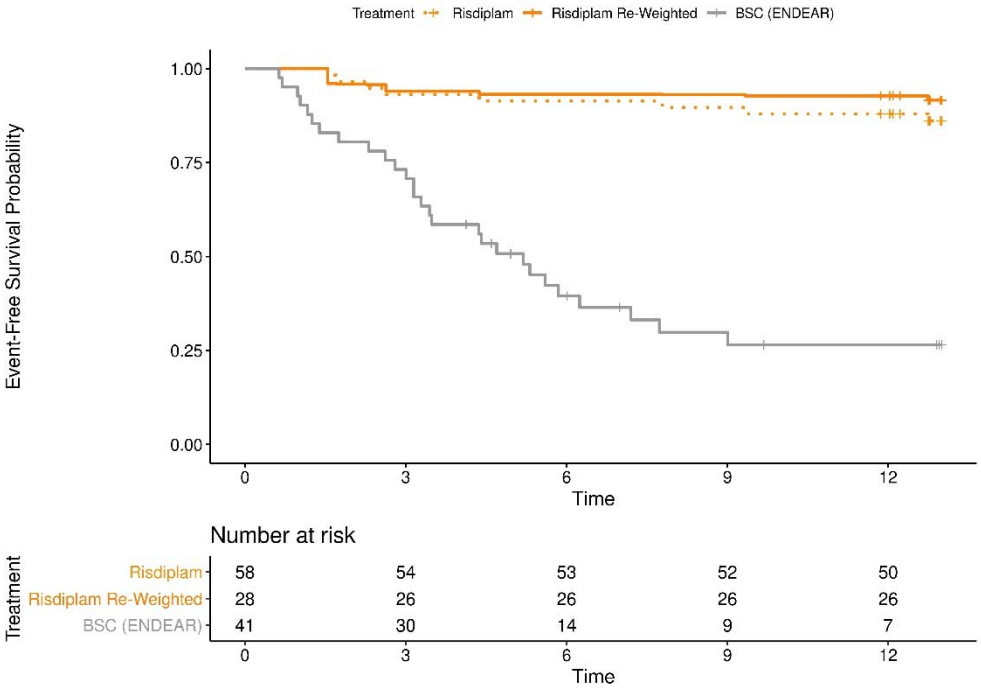


Table 5: Ventilation-free survival hazard ratios

Comparator (STUDY)	Naïve Comparison		MAIC	
	Pre-match Number of events / Sample Size	Hazard Ratio for Risdiplam against Comparator (95%CI)	Post-match Weighted number of events / Sum of weights	Hazard Ratio for Risdiplam against Comparator (95%CI)
Risdiplam (FIREFISH)	8/58	[redacted]	2.31/27.76	[redacted]
BSC (ENDEAR)	28/41	[redacted]	28/41	[redacted]

CI, Confidence Intervals (Bootstrap; N=1000 Bootstrap samples)

Overall survival

The updated analysis results of OS are provided in Figure 4 and Table 6. The hazard ratio generated by the updated MAIC of risdiplam versus BSC is [redacted] (95%CI [redacted]), reduced from the original MAIC HR of [redacted]).

Figure 4: Overall survival Kaplan-Meier curves

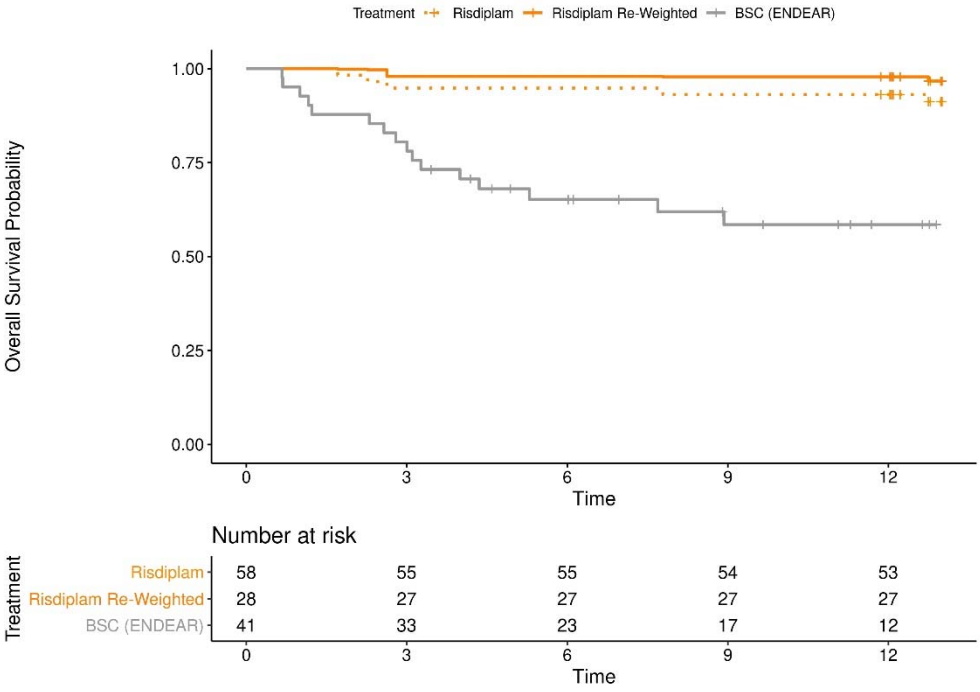


Table 6: Overall survival hazard ratios

Comparator (STUDY)	Naïve Comparison		MAIC	
	Pre-match Number of events / Sample Size	Hazard Ratio for Risdiplam against Comparator (95%CI)	Post-match Weighted number of events / Sum of weights	Hazard Ratio for Risdiplam against Comparator (95%CI)
Risdiplam (FIREFISH)	5/58	[redacted]	0.90/27.76	[redacted]
BSC (ENDEAR)	16/41	[redacted]	16/41	[redacted]

CI, Confidence Intervals (Bootstrap; N=1000 Bootstrap samples)

HINE-2 results (Table 7) were also in line with the original MAIC analysis, suggesting that risdiplam is more effective than BSC in terms of HINE-2 motor milestone response (OR: [redacted] The analyses also suggest superiority on achievement of full head control ([redacted], sitting without support ([redacted]) and sitting with and without support endpoints ([redacted] with estimates that favour risdiplam over BSC (OR <1). For the rolling and standing motor milestones, no relative efficacy estimates (ORs) were calculated due to 0 events for both risdiplam and BSC.

Table 7: HINE-2 motor milestones using FIREFISH data up until 6 months prior to data cut

Milestone	Comparator (STUDY)	Naïve Comparison		MAIC	
		Pre-match Number of responders / Sample size	Odds Ratio for Risdiplam against Comparator	Post-match Weighted number of responders / Sum of weights	Odds Ratio for Risdiplam against Comparator

		(% Responders [95%CI])	(95%CI)	(% Responders [95%CI])	(95%CI)
Motor milestone response	Risdiplam‡ (FIREFISH)				
	BSC§ (ENDEAR)				
Full head control	Risdiplam‡ (FIREFISH)				
	BSC§ (ENDEAR)				
Rolling (supine to prone rolling)	Risdiplam‡ (FIREFISH)				
	BSC§ (ENDEAR)				
Sitting without support (stable sits and pivots)	Risdiplam‡ (FIREFISH)				
	BSC§ (ENDEAR)				
Sitting with and without support (sits with support at hips, props, stable sit and pivots)	Risdiplam‡ (FIREFISH)				
	BSC§ (ENDEAR)				
Standing (with support and unaided)	Risdiplam‡ (FIREFISH)				
	BSC§ (ENDEAR)				

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

‡ HINE motor milestone achievement in infants at the later of Days 0, 119, 245 and 364

§ HINE motor milestone achievement in infants at the later of Days 183, 302 and 394

* ORs calculated using half-cell correction

° Clopper-Pearson CIs

† No ORs were calculated due to 0 events in both arms.

A28. CS, Section B.2.6, page 41 and Section B.2.9.4, Table 37, page 68. The pre-defined performance criterion for HINE-2 was 12% based on natural history data. Please provide an explanation as to why this is higher than observed in the FIREFISH study (i.e. there were 0 out of 37 patients with a motor milestone response giving an upper limit of the 95% confidence interval of 10%, which is lower than expected).

The results described in the question (0 out of 37 motor milestone responders) are taken from ENDEAR. The proportion of motor milestone responders in FIREFISH is 64% (90% CI: 52%-76%). The lower limit of the CI for FIREFISH is above 12%.

A29. CS, Section B.2.9.4, Table 39, page 71. Please provide an explanation for why a greater proportion of patients had an adverse event leading to discontinuation and a

serious adverse event when treated with BSC in ENDEAR compared to patients treated with risdiplam in FIREFISH

Adverse events reported in the FIREFISH study were reflective of the age and the underlying SMA disease of the patients. In general, the type of AEs reported in ENDEAR and FIREFISH are considered to be similar across the studies. No SAEs that were reported in the pooled FIREFISH cohort (patients from 'Cohort 2' in Part 1 and all patients from Part 2) were considered by the investigator to be related to study medication.

It must be noted that both SAEs and AEs leading to discontinuation include AEs with fatal outcomes. Hence, these estimates may partly reflect the differences in overall survival between risdiplam and BSC.

A30. CS, References. Please provide the CSR for Part 1 of FIREFISH

Please see the accompanying reference pack.

Section B: Clarification on cost-effectiveness data

Literature searching

B1. CS Appendix G, pages 43-45. Please comment on the reasons for expanding the population terms in the economic searches (and those for HRQoL and costs as reported in Appendices H and I) to cover a broader range of "SMA-related health states" including additional conditions like ALS and muscular dystrophy. Given the choice to do so, why was the common term "motor neuron* disease" not used as a common synonym for ALS?

Although additional terms were added to cover a broader range of health states, the intention was still to keep the search terms focused. The terms were restricted to ALS as this had been specifically mentioned in the ERG response in the previous nusinersen NICE submission (TA588) (14).

B2. CS Appendices G,H and I. The ERG would anticipate a considerable overlap between the result of the economic, HSUV and cost/resource use searches. Were these results screened together as a single review or as three separate reviews (as reported)?

The results were screened as three separate reviews as reported. Results were crosschecked to ensure that reported costs or utilities collected from the review of economic evaluations were also captured for the HSUV and cost & health resource SLRs.

B3. CS Appendices G,H and I. Please cite the source of the economic filters used in the Medline, Embase and EBM reviews searches (Tables 15-17); those to identify HSUV evidence (Tables 24-26) and cost and resource use data (Tables 34-36).

Economic evaluation filter: Based on the validated economic evaluation filter as detailed on the University of York Centre for Reviews and Dissemination website.

Reference: University of York Centre for Reviews and Dissemination (CRD) [online]. Available at: https://www.crd.york.ac.uk/CRDWeb/#nhseedmedline

Cost/resource use: Adapted from the Scottish Intercollegiate Guidelines Network (SIGN) filter for economic studies (an adaptation of the strategy designed by the NHS Centre for Reviews and Dissemination at the University of York).

Reference: Scottish Intercollegiate Guidelines Network (SIGN). Search filters [online]. Available at: https://www.sign.ac.uk/search-filters.html

HSUV filter: Based on the 'sensitivity maximising' filter as reported in Table 2 of Arber et al (2017).

Reference: Arber M. Performance of OVID Medline search filters to identify health state utility studies. Int J Technol Assess Health Care. 2017: 4; 472-480 (15).

Type 2/3 SMA model - Transition probabilities and treatment effects

B4. Priority question. CS, Section B.3.2.2, page 102. The CS states "This is in line with data from Part 1 and Part 2 of the SUNFISH trial, where the majority of patients in the risdiplam arm demonstrated improvement or stabilisation of the disease." What proportion of patients in the risdiplam group of SUNFISH improved/worsened/had no change from baseline at the final endpoint?

In SUNFISH, the proportion of people with a change from baseline in MFM32 of any threshold ≥0 (i.e., ≥0, ≥1, ≥2, ≥3, or ≥4), representing stabilisation or improvement in this measure, was greater in those receiving risdiplam than in those receiving placebo at all post-baseline scheduled assessment visits. The proportion of people with a change from baseline <0, representing decline in MFM32 total score, was greater in the placebo arm than in the risdiplam arm at all scheduled assessment visits.

Table 8: Proportion of patients with change from baseline in MFM32 total score at Month 12 (SUNFISH Part 2; ITT Population)

	Risdiplam n=115*	**Placebo n=59***
Change in MFM32 total score at month 12 ≥4		
Responders, n (%) (95% CI)	33 (28.7) (20.65, 37.88)	10 (16.9) (8.44, 28.97)

Change in MFM32 total score at month 12 ≥3		
Responders, n (%) (95% CI)	44 (38.3) (29.35, 47.49)	14 (23.7) (13.62, 36.59)
Change in MFM32 total score at month 12 ≥2		
Responders, n (%) (95% CI)	55 (47.8) (38.43, 57.34)	17 (28.8) (17.76, 42.08)
Change in MFM32 total score at month 12 ≥1		
Responders, n (%) (95% CI)	65 (56.5) (46.96, 65.74)	23 (39.0) (26.55, 52.56)
Change in MFM32 total score at month 12 ≥0		
Responders, n (%) (95% CI)	80 (69.6) (60.29, 77.8)	32 (54.2) (40.75, 67.28)
Change in MFM32 total score at month 12 <0		
Responders, n (%) (95% CI)	32 (27.8) (19.87, 36.95)	26 (44.1) (31.16, 57.60)

*112 and 58 valid results available for risdiplam and placebo, respectively
CI, confidence interval; MFM-32, Motor Function Measure, 32-item version

B5. CS, Section B.3.3.1, pages 113-114, Table 53 and Section B.2.3.5, pages 34-35, Table 8. According to Table 8, 10.5% of patients could stand/walk at baseline. According to Table 53, [redacted] of patients could stand/walk at baseline. Please clarify the reason underpinning this difference.

The differences in baseline characteristics between Sections B.2.3 and B.3.3.1 are due to the following reasons. Firstly, walking was defined differently in Section B.2.3 as compared to the model. In Section B.2.3, 'walking' is defined as HFMSE item 20 score ≥2 at baseline. However, in the model, 'walking' is defined as the highest current level of independent mobility. Secondly, the health states are mutually exclusive in the model. Although patients that are able to walk are also able to stand, these will not appear in the model baseline proportions in the 'standing' state. Instead, these patients will be assigned to the 'walking' state due to their ability to walk. This is different from Section B.2.3, where all patients with the ability to stand are counted (irrespective if they are also able to walk or not). Thirdly, the clinical section used patient characteristics from the overall patient population, while the model base case utilised patient characteristics from a subgroup of patients that excluded patients from Asia. In Table 53 of the submission the characteristics of the overall patient population were included in error. However, Table 9 shows that the patient characteristics from the subgroup in Asia (used for the base case) are very similar to the characteristics form the overall patient population.

Table 9: Baseline character tics in the type 2/3 model base case and overall patient population

Baseline characteristic	Overall population	Base case*
Age, years; mean (SE)	[redacted]	[redacted]
Female (SE)	[redacted]	[redacted]

Type 2	[redacted]	[redacted]
Type 3	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]
Sitting (supported)	[redacted]	[redacted]
Sitting (unsupported)	[redacted]	[redacted]
Standing	[redacted]	[redacted]
Walking	[redacted]	[redacted]
Respiratory support	[redacted]	[redacted]
Severe scoliosis (>40 degrees curvature)	[redacted]	[redacted]

Footnotes: *Base case values were derived from the subgroup of patients that excluded patients from Asia.
Abbreviations: SE, standard error

B6. Priority question. CS, Section B.3.3.3.1, page 115. In the risdiplam arm, all backward transitions are assumed to be reduced by [redacted] after 2 years whilst in the BSC arm, all forward (improved) transitions are set equal to [redacted] after 2 years.

a) Please clarify the precise source of these values and describe how they were derived. If formal elicitation was used, please describe this process.

These values were selected following two clinical ad-boards with UK clinical experts. A confidential appendix with a report from these ad-boards is provided as part of the CS. No formal elicitation method was used. Following discussions, UK clinical experts agreed that the majority of SMA Type 2 or 3 patients receiving active treatment would be likely to maintain their health states or improve in the long-term, and that patients receiving BSC would only remain stable or deteriorate in the long-term. Based on these discussions and conclusions from UK clinical experts, the values for adjusting transition probabilities after 24 months in the base-case were selected. The adjustment for risdiplam is varied in scenario analyses.

b) The cycle in which these multipliers are applied appear to be one cycle too early (when model time at the start of the cycle is 1.92 years, rather than 2 years, for example see Type 2/3 SMA model, worksheet "risdiplam", cell J32). Please clarify if this was intentional.

This was not intentional but due to a minor error in the part of the calculations comparing the current cycle against the 2-year duration of the SUNFISH trial, after which the multiplier is intended to be applied, i.e. using ">=" instead of ">".

c) **Please clarify the source of the 2-year timepoint for applying these assumed modifications to the transition probabilities.**

The time-point of 24 months for adjusting transition probabilities was conservatively selected for both economic models, to account for the period in which observed data were available and therefore observed transition probabilities should be applied. However, the actual observed period was shorter than 24 months in both studies; in SUNFISH it was 12 months and in FIREFISH was >12 months, as patients from Part 1 of the study were also included. Therefore, as noted, applying the long-term assumptions for transition probabilities at 24 months should be considered conservative in nature. This assumption was varied in scenario analyses.

B7. Priority question. CS, Section B.3.3.3.1, page 115.The company has used the msm package in R to derive transition probabilities using a time-homogenous approach. However, the full matrix derived from the msm package has been amended to only allow progressions/regressions to adjacent states in a given cycle.

a) **Please clarify why this assumption was considered necessary? Why was it not considered appropriate to use the msm outputs directly (including transitions to non-adjacent states)?**

After our analysis of the data using the MSM package in R, we noticed that several transitions were mathematically feasible (i.e. patients could progress to a non-adjacent health state) that violated our underlying clinical assumption and model structure (i.e. patients progress sequentially). Hence, any non-adjacent transitions in progression were assumed to be part of the next sequential health state.

b) **Please provide the actual transition probability matrices estimated by the msm package for each treatment group. Please also provide a simple spreadsheet which shows how the probabilities from the msm package have been transformed into the probabilities used in the model.**

These calculations are provided in the ‘Treatment Efficacy’ tab, cells H11 to L15. These cells call in the original values of the MSM model from the R package, which are also located in the same tab, cells P11 to T15.

c) Please provide additional information regarding the input data used in the multi-state model, specifically:

(i) How many observations were there?

591 observations

(ii) How frequent were the visits?

Every 4 months

(iii) How many events were directly observed?

588

(iv) How many events were imputed?

3

(v) is there evidence from SUNFISH that the transition rates are constant with respect to time (i.e. that a time-homogenous model is appropriate)?

Due to the small sample size and small number of transitions occurring during the study period, it was not possible to robustly assess changes in transition rates over time in SUNFISH.

(vi) Please provide evidence to demonstrate goodness of fit of the model, including the use of the prevalence function

Goodness of model fit was assessed using likelihood ratio tests and the prevalence function from the msm package.

MSM models without any covariates and with a covariate for treatment with risdiplam were compared via likelihood ratio tests. The model with risdiplam treatment as a covariate was found to have a significantly better fit compared to the base model without covariates ($p = 0.0022$).

In addition, observed state prevalences were compared to those predicted with the final MSM model using the prevalence function from the msm package. In general, the model predicted the state prevalences well for both risdiplam and placebo arms. Risdiplam results are available in Table 10 and Figure 5. Placebo results are available in Table 11 and Figure 6.

Table 10: Risdiplam prevalence table - Goodness of fit using prevalence function from msm package applied to model excl. Asia (with imputations)

	Observed prevalence (%)					Predicted prevalence (%)					Absolute difference predicted vs observed				
Timepoint	Not Sitting	Sitting with support	Sitting without support	Standing with or without support	Walking with or without support	Not Sitting	Sitting with support	Sitting without support	Standing with or without support	Walking with or without support	Not Sitting	Sitting with support	Sitting without support	Standing with or without support	Walking with or without support
0	0.00	16.16	71.72	5.05	7.07	0.00	14.09	73.15	6.04	6.71	0.00	-2.07	1.44	0.99	-0.36
120	2.02	13.13	71.72	6.06	7.07	2.49	11.43	73.07	7.13	5.88	0.47	-1.70	1.35	1.07	-1.19
240	4.12	10.31	70.10	9.28	6.19	3.50	10.58	72.83	7.78	5.31	-0.62	0.27	2.72	-1.50	-0.87
360	3.70	11.11	70.37	9.88	4.94	3.95	10.38	72.60	8.15	4.92	0.25	-0.73	2.23	-1.72	-0.02

Figure 5: Risdiplam prevalence plot

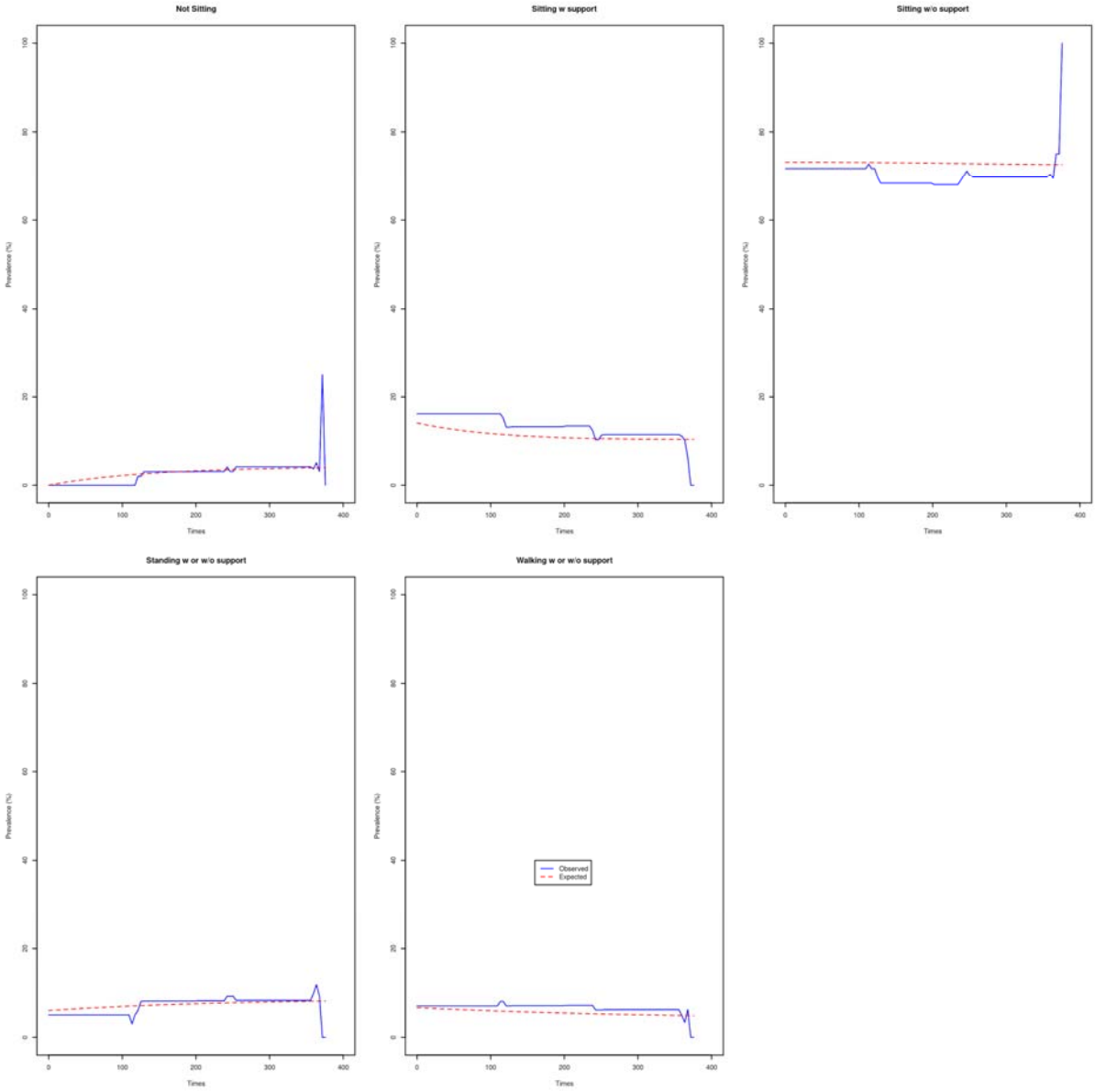
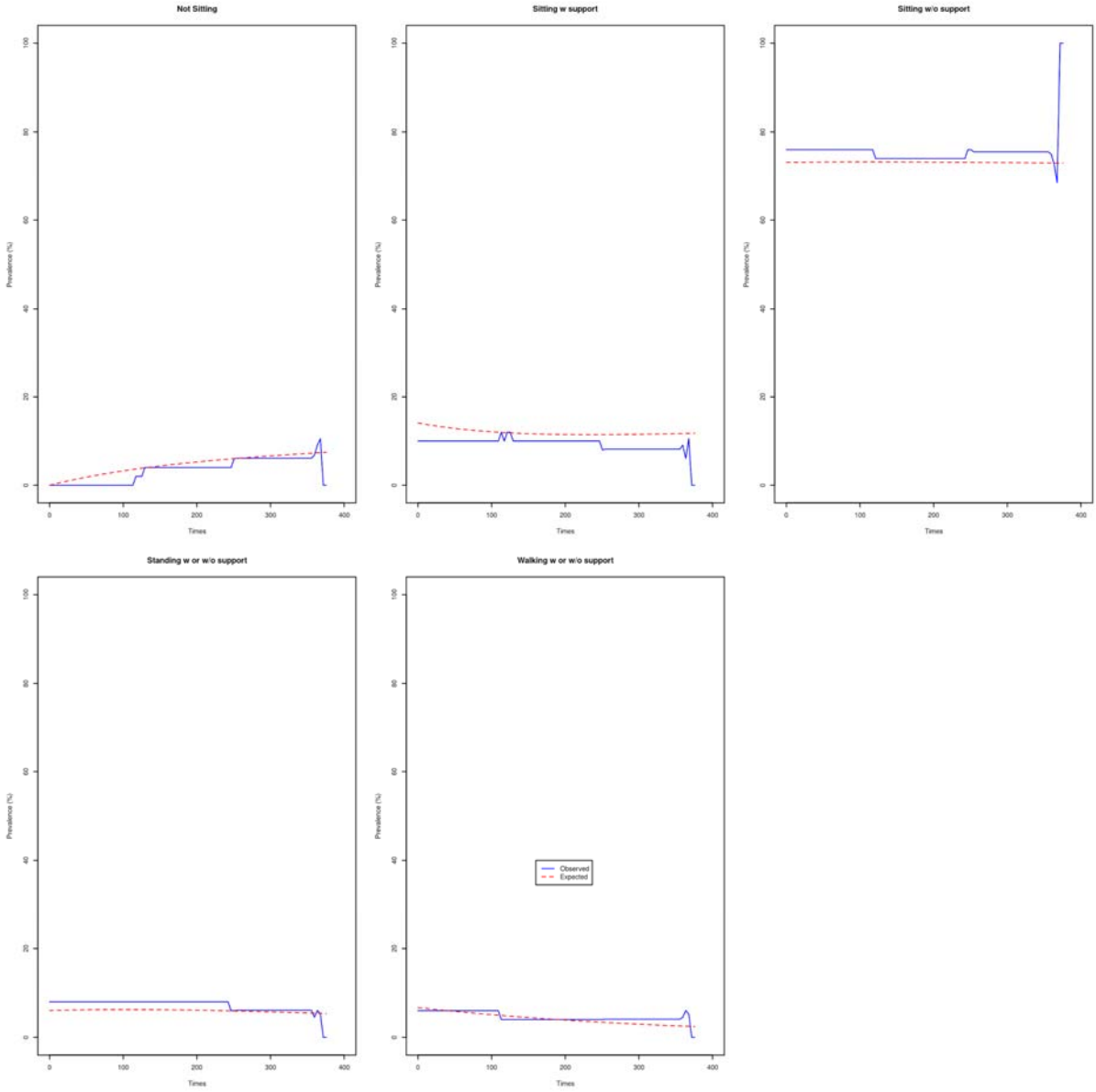


Table 11: Placebo prevalence table

	Observed prevalence (%)				Predicted prevalence (%)						Absolute difference predicted vs observed				
Timepoint	**Not Sitting**	**Sitting with support**	**Sitting without support**	**Standing with or without support**	**Walking with or without support**	**Not Sitting**	**Sitting with support**	**Sitting without support**	**Standing with or without support**	**Walking with or without support**	**Not Sitting**	**Sitting with support**	**Sitting without support**	**Standing with or without support**	**Walking with or without support**
0	0.00	10.00	76.00	8.00	6.00	0.00	14.09	73.15	6.04	6.71	0.00	4.09	-2.85	-1.96	0.71
120	2.00	12.00	74.00	8.00	4.00	3.73	11.90	73.25	6.27	4.85	1.73	-0.10	-0.75	-1.73	0.85
240	4.00	10.00	74.00	8.00	4.00	5.88	11.45	73.17	5.99	3.51	1.88	1.45	-0.83	-2.01	-0.49
360	6.82	9.09	75.00	4.55	4.55	7.31	11.72	72.98	5.45	2.54	0.49	2.63	-2.02	0.91	-2.01

Figure 6: Placebo prevalence plot



(vii) Please clarify how many patients in each group improved from baseline to reach the milestones of (a) standing/walking and (b) walking in SUNFISH.

A) On risdiplam, 5 patients gained the ability to stand or walk at Week 17 (1 did not maintain the standing ability in Weeks 35 and 52, 1 did not maintain the walking ability in Weeks 35 and 52, but was able to stand, and 1 patient gained the ability to stand or walk at Week 52. On placebo, 0 patients gained the ability to stand or walk.

B) On risdiplam, 1 patient gained the ability to walk at Week 17, however did not maintain the walking ability in Weeks 35 and 52. 1 patient gained the ability to walk at Week 52. On placebo, 0 patients gained the ability to walk.

B8. CS, Section B.3.3.1, page 114. The description of the imputation rules for the data used in the multistate model (LOCF and NOCF) are not entirely clear from the CS. Please provide an example of each of the rules applied and explain why they were necessary.

Since the health state membership was derived from multiple questionnaires (MFM-32 and the highest current level of independent mobility, as described in section B.3.2.2) and different items within these questionnaires (MFM-32 item 9 and item 25), there were occasions when information was missing from one of the items/questionnaires, but available for the others. Without imputation, if one of those answers were missing, it would not have been possible to determine the health state membership for that time point, and the other available information on motor function ability would have been lost. Hence, it was decided to impute those missing items in order to minimize the information loss.

Last observation carried forward (LOCF) was used as the imputation rule for a missing item at one visit, when the achievement for that item in the next visit was better than the achievement for that item in the previous visit. For example, if we assume the 'highest current level of independent mobility' question was not completed at Week 35, it would not be possible to determine if that patient was able to walk at that visit. If at the following visit (Week 52), the patient was able to walk according to the 'highest current level of independent mobility' question, but at the previous visit (Week 17), the patient was not able to walk according to the 'highest current level of independent mobility' question, the patient would have then be imputed to not being able to walk in Week 35.

On the other hand, next observation carried backwards (NOCB) was used as the imputation rule, when the achievement for that item in the next visit was worse than the achievement for that item in the previous visit. For example, if we again assume the 'highest current level of independent mobility' question was not completed at Week 35, therefore it was not possible to determine if that patient was able to walk at that visit. If at the following visit (Week 52), the patient was not able to walk according to the 'highest current level of independent mobility' question, but at the previous visit (Week 17), the patient was able to walk according to the 'highest current level of independent mobility' question, the patient would have then be imputed to being able to walk at Week 35.

Although these two imputation rules were defined, the data showed that for each of the occasions where an item was missing, the ability on that item was the same before and after the missing visit, and therefore there would be no difference between using LOCF or NOCB.

B9. Priority question. CS, Section B.3.4, page 118. The model assumes that patients receiving risdiplam can progress to worse health states, but the model assumes that all patients remain on treatment indefinitely.

a) **Given that some discontinuation was observed in SUNFISH, please comment on why discontinuation is excluded from the model and whether this would be expected in clinical practice.**

Discontinuation was excluded from the model for the following reasons: Firstly, as costs would continue to incur whilst patients remain on treatment, excluding discontinuation was deemed a conservative approach. Secondly, an effort was made to keep the model as simple as possible, as it is not clear what the outcomes of discontinuation would be. Due to the paucity of data from the trials, assumptions for outcomes would have to be made if the model allowed patients to discontinue treatment.

Only [redacted] patients discontinued treatment within Part 2 of the SUNFISH trial. As such, there were very few data to inform likely discontinuation from risdiplam and its outcome in clinical practice. UK clinical expert opinion was sought on the likely discontinuation rate of risdiplam in clinical practice (Appendix N), and most clinical experts at the UK advisory boards indicated that they would likely not discontinue treatment in response to a patient plateauing. Furthermore, even if a patient worsened on risdiplam treatment, clinical experts would base their decision on discontinuation on whether the patient is declining at a slower rate than expected with BSC and whether alternative treatments are available. Based on the trial data and clinical expert feedback, it was concluded that discontinuation of risdiplam was likely to take place rarely in clinical practice, further supporting the assumption of no discontinuation in the model.

Furthermore, clinical expert opinion was sought at the UK clinical advisory boards about the expected treatment effect of risdiplam after discontinuation. UK clinical experts stated that any treatment benefit following discontinuation of risdiplam would be expected to reflect the survival motor neuron (SMN) protein levels over several months following discontinuation (Appendix N).

b) **In clinical practice, if a patient did discontinue risdiplam, might they go on to receive nusinersen?**

Nusinersen could be an available treatment option in clinical practice for some patients, if they discontinue from risdiplam. However, as stated in our response to question A9, while we acknowledge there is currently an absence of evidence to determine the optimum sequence of therapy, clinical experts confirmed to Roche that treatment decisions should be based on multiple factors including an overall benefit risk analysis, unmet need and clinician

and patient choice. We anticipate that risdiplam will provide an additional therapeutic option for all patients across the continuum of SMA; this will include treatment-naïve patients, as well as those patients who have previously received nusinersen but cannot tolerate it and/or respond poorly.

Importantly though, nusinersen was not considered a relevant comparator in the NICE final scope for ID1631 and has not been considered as part of our economic analysis. Any comparison or inclusion of nusinersen was considered to be out of scope for the cost-effectiveness analysis of our CS.

c) **Please consider including discontinuation in the model, including adjustment of outcomes, if appropriate.**

Based on our response to part a, it was not considered appropriate to make further changes to patient discontinuation in the model. However, please note that functionality to discontinue is built into the model, but it only adjusts costs and not outcomes.

d) **Please comment on whether a formal stopping rule for risdiplam (e.g. for non-responders) was considered. Please also comment on the appropriateness of continuing treatment in patients who have lost or never achieved motor milestones.**

A formal stopping rule was not considered for risdiplam, as our key priority is to provide broad and unrestricted access to risdiplam for UK SMA patients. A stopping rule however might be a pragmatic option that might need to be considered in order to ensure that risdiplam is made available to as broad as possible SMA patient population in the UK. However a key challenge with establishing a stopping rule is that the SMA population is very heterogeneous (especially for Type 2/3 SMA) and the definition of treatment benefit or patient improvement significantly differs for SMA patients with different characteristics such as Type of disease, age, duration of disease etc. Therefore it would be difficult to establish a stopping rule, and any stopping rule would need to take into account input from the UK SMA clinical community as well.

The appropriateness of continuing treatment in patients who have plateaued or worsened on treatment was discussed at the ad-boards with UK clinical experts (Appendix N). If a patient plateaued on treatment, most clinical advisors would keep the patient on the same treatment, as this contrasts with the well-demonstrated progressive deterioration that untreated patients demonstrate. Informed discussion, the patient's/family's preference for palliative care, and factors like recurrent respiratory infections, would influence the decision. If a patient worsened on treatment, advisors would sometimes discontinue treatment. The availability of an alternative treatment and whether a patient is declining at a slower rate than

expected on BSC, would also be key considerations. The clinical expert opinion outlined above demonstrates how difficult it is to establish a treatment stopping rule in a disease with such a broad and severe impact in a very heterogeneous population.

B10. Priority question. CS, Section B.3.2.2, page 103, Table 49. In TA588, the final iteration of the model assumed that patients treated with nusinersen plateau (stay in the same state) after a fixed period of time (around 2 years). The risdiplam model assumes that, on average, risdiplam-treated patients have a better prognosis in the extrapolation phase compared with the first 2 years. Why does the risdiplam model not include a plateau?

Although a plateau health state is not explicitly included in our Type 2/3 economic model, our approach is not entirely different to NICE TA588. In the long-term, the majority of risdiplam-treated patients in our model remain in the same health state. The proportion of risdiplam-treated patients not improving after year 2 varies from 97-99% in the more improved health states (i.e. sitting unsupported, standing, walking); see economic model "Risdiplam worksheet, columns BP-CP. In addition, the long-term assumptions for both risdiplam and BSC were discussed and validated with UK clinical experts during ad-boards. Importantly, outcomes from the economic model both in the short-term (up to 1 year) as well as in the long-term seemed to compare very well with study results, results from the broader literature and expectations from clinical experts (CS, section B.3.10).

B11. Priority question. Type 2/3 SMA model, worksheet "risdiplam". The model predicts that in the long-term, up to [redacted] of the surviving cohort reach either the standing or walking health states.

a) **Given the available data on patients reaching these milestones in SUNFISH, please comment on the plausibility of this projection.**

The follow-up period for SUNFISH Part 2 was 12 months at the point of CS, therefore it would not be appropriate to compare long-term patient outcomes from the economic model with observed data after 1 year only. In the absence of long-term outcomes for risdiplam-treated patients, we validated our approach for the long-term trajectory of patients treated with risdiplam with UK clinical experts through ad-boards (Appendix N). UK clinical experts advised that it was reasonable to assume that the majority of type 2 or type 3 patients treated with risdiplam would remain stable or improve in the long term. This is reflected in the outcomes of the economic model, whereby greater than 50% of patients maintain the ability to sit without support for at least 10 years, and the proportions of patients in the advanced health states of 'standing' and 'walking' initially increase over time up to the 30-year mark (CS, section B.3.10). In the validation section of the CS (section B.3.10) we made our best effort to validate and compare the model outputs against all available evidence

(from our clinical studies, natural history studies and the broader literature), as well as how well they align with UK clinical expert opinion. This was to ensure that our base case is as robust as possible and an appropriate basis for decision-making.

b) Please provide a comparison of observed health state occupancy in SUNFISH at 12 months and model-predicted health state occupancy at 12 months.

A comparison of observed health state occupancy in SUNFISH at 12 months with the health state occupancy after 12 months predicted by the model is provided in section B.3.10.2 (page 165–166). Please note that the model data is labelled as 1 year, rather than 12 months, in Table 90 and Table 91. Table 12 provides a direct comparison between the trial data and model predictions, and shows that the model predictions at 12 months align very closely with the data from the SUNFISH trial for both risdiplam and BSC. Model predictions for the BSC arm are slightly optimistic with regards to proportions of patients reaching advanced motor milestones, such as standing and walking, after 12 months. This indicates that the model results are conservative with regards to clinical outcome predictions between risdiplam and BSC.

Table 12: Health state occupancy at 12 months in the SUNFISH trial and type 2/3 model

Treatment	Treatment	Not sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
BSC	Trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risdiplam	Trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Please note that the 12-month trial data demonstrating the distribution of patients across motor milestones did not include the proportion who had died by this time point, however, the proportion of patients falling into the death state over time in the type 2/3 model can be found in Table 90 and Table 91 of the company submission. Abbreviations: BSC: best supportive care.

Type 2/3 SMA model - Survival

B12. Priority question. CS, Section B.3.4, page 116. The model applies general population mortality rates to patients in the standing and walking states and a comparatively worse survival for patients in the non-standing states, with an additional relative treatment effect for risdiplam versus BSC applied in the non-standing states.

a) Please provide a rationale for assuming a constant hazard ratio over time of 0.75 for risdiplam versus BSC.

A mortality adjustment factor of 0.75 was applied to reflect the anticipated reduced likelihood of mortality associated with risdiplam treatment in comparison to BSC in the non-standing

states in type 2 patients (all type 3 patients were assumed to have general population mortality in the model). This assumption is in line with the approach taken in the later onset model in TA588, where a mortality adjustment factor of 0.75 to best supportive care was also assumed (14). It is noteworthy that the mortality adjustment factor was tapered over 120 months in the nusinersen arm of the infantile onset model in TA588, which was criticised by the ERG. This is because tapering mortality risk in one group was considered to be inconsistent with the proportional hazards assumption underlying the method adopted to model survival. It was therefore decided to keep the hazard ratio constant over time in the risdiplam submission.

b) The general population life tables assume a constant proportionate split of men and women at every age. Please clarify if this assumption was intentional.

We can confirm that the assumption of a constant proportionate split of men and women at every age was intentionally chosen as a simplification.

c) In the model, worksheet "Survival", columns E and D, the calculations divide the annual mortality probability ("qx") by 12 and then apply a rate to probability conversion. However, "qx" is a probability, not a rate. Please confirm that this is an error.

We can confirm that this is an error and the annual mortality probability should first be converted to a rate and then a probability, to calculate a per cycle probability of mortality.

d) Worksheet "Survival", columns AD. The treatment effect is described as a hazard ratio. Why is the Type 2 SMA monthly mortality probability for risdiplam-treated patients multiplied by this hazard ratio? Why is mortality risk not calculated using the cumulative survival probabilities from the Gompertz model raised to the power of the HR?

As explained in response to 12a, a mortality adjustment factor of 0.75 was applied for risdiplam, as was assumed for nusinersen in TA588 (14). Please note that it should not be interpreted as a hazard ratio, and the notation in the model is incorrect. As such, we believe that the approach taken to include the mortality adjustment factor, relative to BSC, is correct.

B13. CS, Section 3.3.1, page 116. Mortality for Type 2 SMA is modelled using a Gompertz distribution fitted to pseudo-IPD from six natural history studies.

a) The CS states "…limitations of the study include enrolment bias (Cure SMA membership may represent a more engaged population) and that data was patient reported, which is prone to reporting inaccuracies, incomplete

information and errors in memory". Given that the outcome of interest is death, are these issues likely to apply?

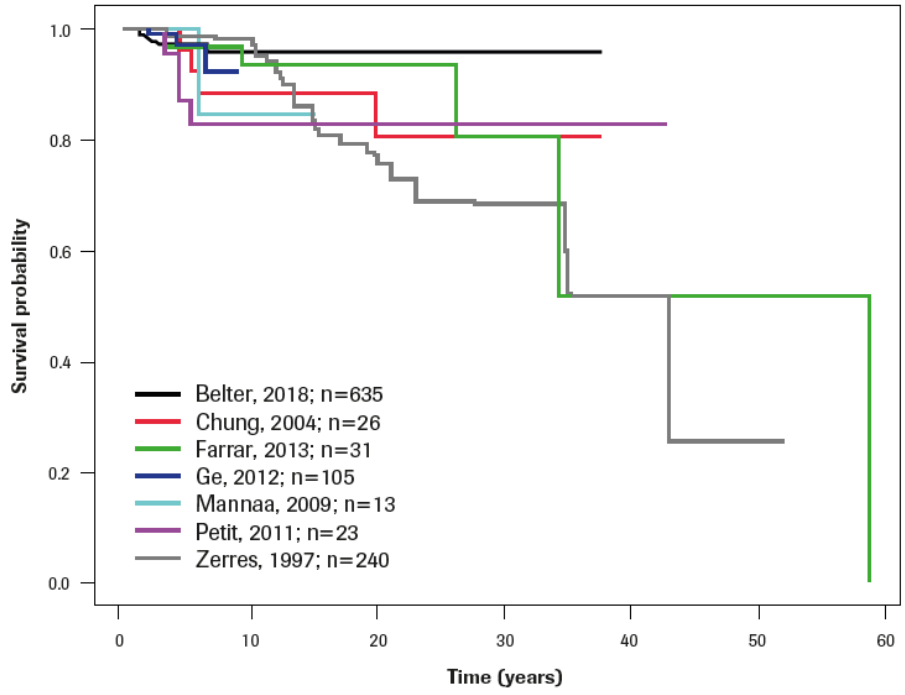
The Cure SMA database is based on data from self-identified individuals with SMA. As such, only individuals that had previously contacted Cure SMA are included in the data set. This may represent a more engaged population, who may be more likely to have the resources and knowledge to receive better supportive care associated with improved survival, such as nutritional and respiratory support. Further, as the mean (SD) time from diagnosis to contacting Cure SMA was 61.3 weeks (224.7) (16), patients with more severe Type II SMA that died early and therefore did not contact Cure SMA, will not have been captured in this data set.

Incomplete information in the form of missing birthdates was present for 12.3% of individuals with Type II SMA. These patients were excluded from the survival analysis.

b) **Please provide an explanation for the two large drops in the tail of the pooled Kaplan-Meier survival function presented in Figure 12.**

There is a paucity of data on longer-term follow up (>30 years), with only two studies (Farrar 2013 and Zerres 1997) reporting data >45 years follow up, being the main contributors to the long-term survival data. See Figure 7 below (17).

Figure 7: KM curves based on recreated IPD by study



Although the number of patients at risk over time have not been reported for any of the studies, Kaplan-Meier curves of the individual studies indicate that the majority of patients

were censored by 30 years of age. The two large drops in the tail of the pooled Kaplan-Meier curve are likely to be a result from the small number of patients at risk at longer follow-up.

c) **It is generally not a good idea to pool data across different studies without acknowledging heterogeneity between studies. For the base case survival model (i.e. the Gompertz distribution) and any other plausible distributions, please perform a random effects meta-analysis of the joint distribution of parameters and generate the survival function based on the predictive distribution of the joint distribution of parameters. The ERG recommends that parameters are estimated using Markov Chain Monte Carlo simulation in order to simplify the analysis, to allow the predictive distribution to be calculated exactly and to allow parameter constraints to be included to omit implausible parameter sets.**

As requested by the ERG, we conducted a random-effects meta-analysis of the joint distribution of parameters from the survival model. This was conducted for the base case Gompertz distribution and for the Weibull distribution, as these two distributions were deemed to be the most plausible by the UK clinical experts.

We applied a two-step approach similar to the one described by Cope et al. (18). First, we fitted the respective distribution (Gompertz/Weibull) to the reconstructed pseudo individual patient data of each of the individual studies. Second, for each distribution, we synthesized the survival model parameter estimates from all studies via a bivariate random-effects meta-analysis. The bivariate random-effects meta-analysis model was fit using code from TSD 20, Appendix A.1.2 (19), adapted to the purposes of this analysis.

Gompertz distribution

The summary outputs from the random-effect meta-analysis model are provided below. Rhat values are well below 1.05, indicating convergence.

The ‘d[1]’ and ‘d[2]’ values correspond to the population summary estimates of the Gompertz distribution. The ‘delta’ values give the study specific estimates. The ‘tau1’, ‘tau2’ and ‘rho’ correspond to the between study standard deviations and correlation (Figure 8)

Figure 8: Summary outputs from the random-effect meta-analysis model

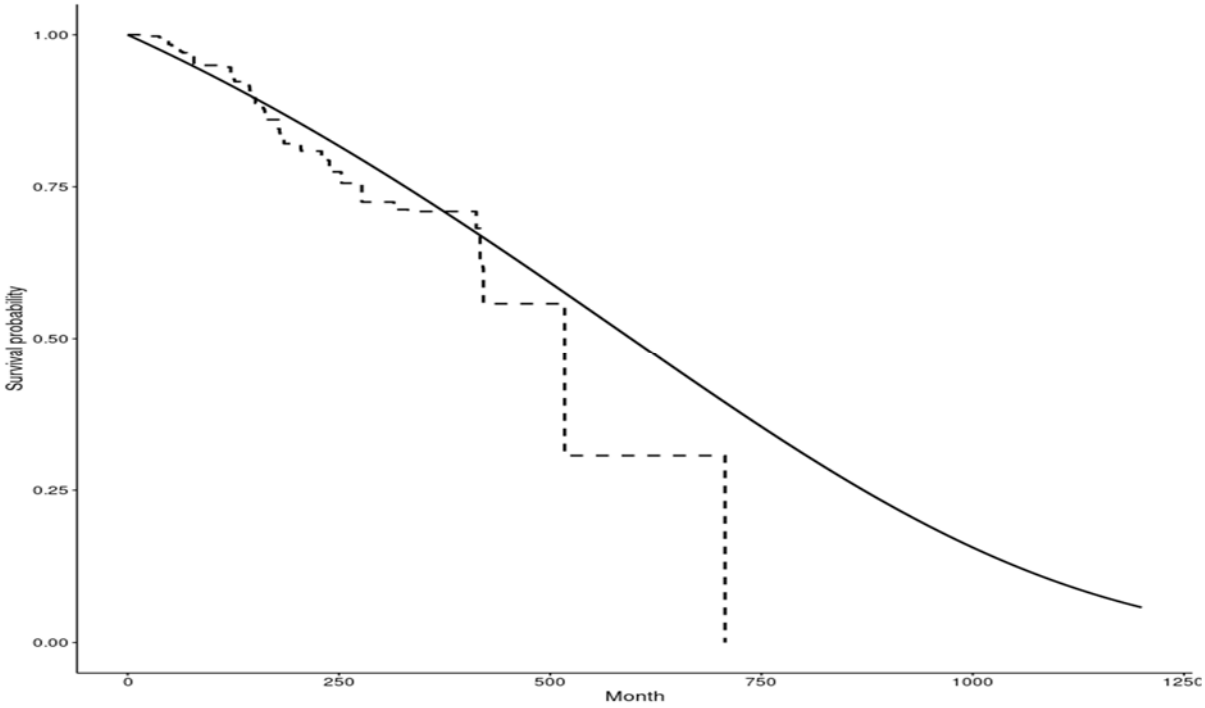
```
Inference for Bugs model at
"/home/bceuser/aponterv/BP39055_SUNFISH_HE/inst/BUGScode/bvma-re-TSD20-
adapted.txt", fit using jags,
 3 chains, each with 80000 iterations (first 5000 discarded)
 n.sims = 225000 iterations saved
           mu.vect sd.vect    2.5%     25%     50%     75%   97.5%  Rhat  n.eff
d[1]         0.001   0.004  -0.008  -0.001   0.002   0.004   0.008 1.002   3900
d[2]        -7.326   0.434  -8.142  -7.582  -7.364  -7.096  -6.359 1.001   5400
delta[1,1]  -0.002   0.004  -0.010  -0.005  -0.002   0.001   0.005 1.002   1500
delta[2,1]   0.005   0.001   0.003   0.004   0.005   0.005   0.007 1.001   8800
delta[3,1]   0.003   0.006  -0.008   0.000   0.003   0.006   0.016 1.001  18000
delta[4,1]   0.000   0.006  -0.015  -0.003   0.002   0.004   0.012 1.001   4900
delta[5,1]  -0.004   0.007  -0.021  -0.008  -0.002   0.002   0.006 1.002   1800
delta[6,1]   0.004   0.000   0.003   0.004   0.004   0.004   0.005 1.001 220000
delta[1,2]  -7.123   0.552  -8.110  -7.501  -7.184  -6.769  -5.934 1.002   2300
delta[2,2]  -8.025   0.561  -9.290  -8.387  -7.929  -7.590  -7.196 1.001  12000
delta[3,2]  -7.417   0.463  -8.389  -7.677  -7.421  -7.149  -6.474 1.001  35000
delta[4,2]  -7.168   0.654  -8.329  -7.574  -7.264  -6.810  -5.665 1.001   7000
delta[5,2]  -6.753   0.646  -7.739  -7.270  -6.828  -6.320  -5.354 1.002   2300
delta[6,2]  -7.489   0.166  -7.816  -7.601  -7.488  -7.377  -7.163 1.001 220000
rho         -0.518   0.470  -0.988  -0.881  -0.686  -0.293   0.734 1.002   3200
tau[1]       0.006   0.005   0.000   0.003   0.005   0.008   0.019 1.004   1200
tau[2]       0.719   0.462   0.035   0.355   0.662   1.016   1.763 1.001   5000
deviance   -44.285   5.535 -53.641 -48.562 -44.684 -40.249 -33.194 1.002   2100

For each parameter, n.eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor (at convergence, Rhat=1).

DIC info (using the rule, pD = var(deviance)/2)
pD = 15.3 and DIC = -29.0
DIC is an estimate of expected predictive error (lower deviance is better).
```

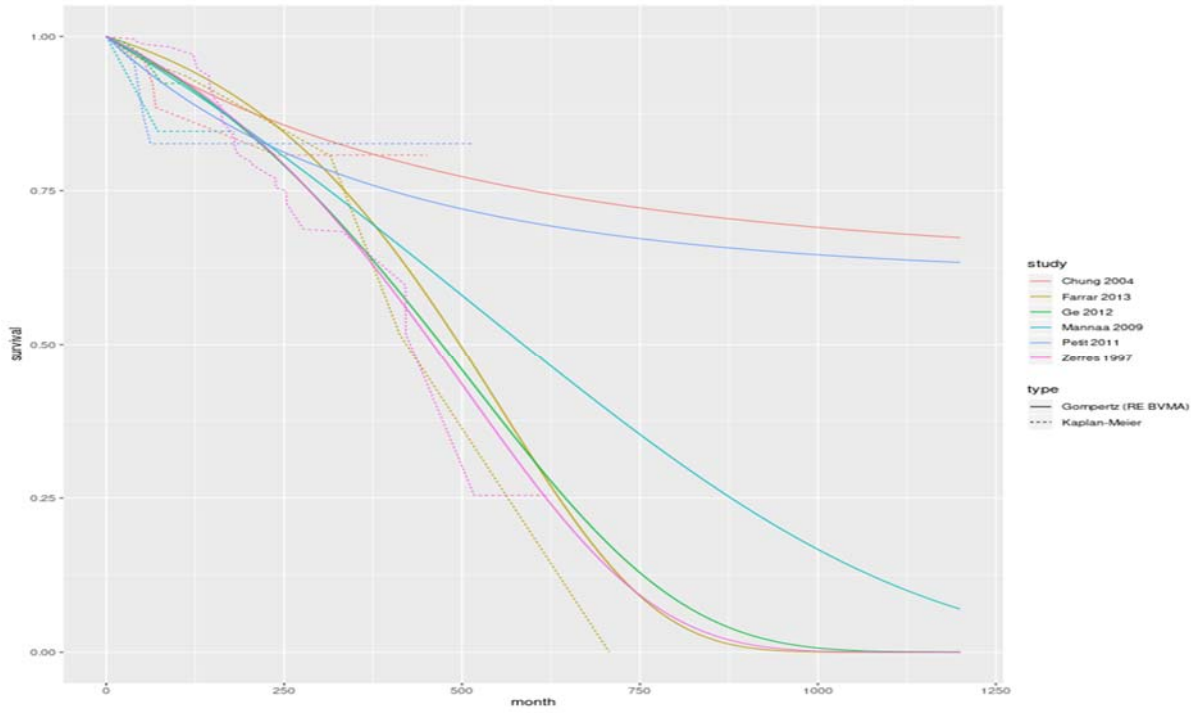
The resulting population survival curve using the posterior median parameter estimates plotted against the SLR pooled Kaplan-Meier data is presented in Figure 9. It must be noted that 5.8% of patients are predicted to be alive at 100 years of age using this model.

Figure 9: Population survival curve plotted against the SLR pooled Kaplan-Meier



The study-specific survivor function estimates from the random-effects meta-analysis (using the posterior median parameters) plotted against the observed Kaplan-Meier data of the individual studies are presented in Figure 10. The Gompertz fits for the data from Chung 2004 and Petit 2011 lack face validity as over 50% of patients are predicted to survive to the age of 100 years.

Figure 10: Study-specific survivor function estimates from the random-effects meta-analysis (using the posterior median parameters) plotted against the observed Kaplan-Meier data of the individual studies



Please see Table 13 and Table 14 for model results using the updated Gompertz parameters. Evidently, the application of a random-effects meta-analysis of the joint distribution of parameters from the survival model reduces the ICERs very slightly compared to the base case. This is due an increase in incremental QALYs between Risdiplam and BSC.

Table 13: Updated results for the type 2/3 SMA (SUNFISH) model (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	21.91	24.50	-	-	-	-
Risdiplam	[redacted]	24.10	47.06	[redacted]	2.19	22.56	£183,977

Table 14: Updated results for the type 2/3 SMA (SUNFISH) model (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)

BSC	[redacted]	21.91	24.50	-	-	-	-
Risdiplam	[redacted]	24.10	47.06	[redacted]	2.19	22.56	[redacted]

Weibull distribution

The summary outputs from the random-effect meta-analysis model are provided below. Rhat values are well below 1.05, indicating convergence.

The 'd[1]' and 'd[2]' values correspond to the population summary estimates of the Weibull distribution. The 'delta' values give the study specific estimates. The 'tau1', 'tau2' and 'rho' correspond to the between study standard deviations and correlation (Figure 11).

Figure 11: Summary outputs from the random-effect meta-analysis model

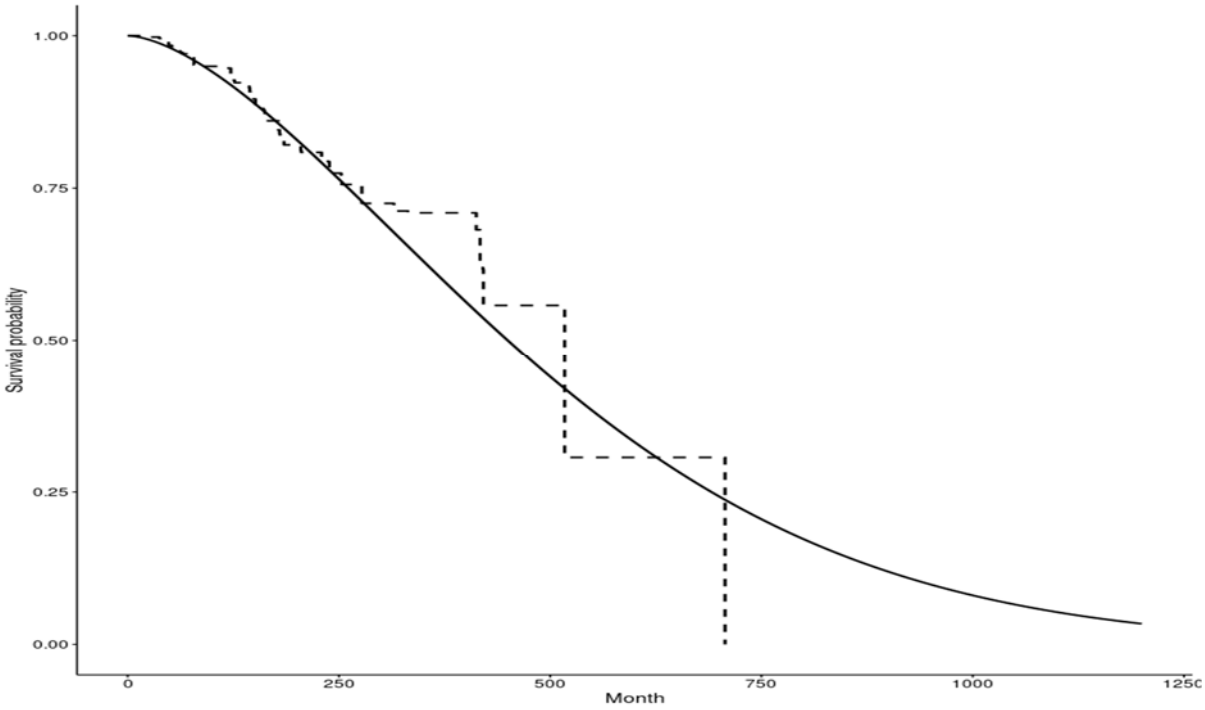
```
Inference for Bugs model at
"/home/bceuser/aponterv/BP39055_SUNFISH_HE/inst/BUGScode/bvma-re-TSD20-
adapted.txt", fit using jags,
 3 chains, each with 80000 iterations (first 5000 discarded)
 n.sims = 225000 iterations saved
           mu.vect sd.vect   2.5%    25%    50%   75%  97.5%  Rhat  n.eff
d[1]         0.462   0.273 -0.126  0.319  0.480 0.619  0.970 1.001  98000
d[2]         6.412   0.310  5.971  6.266  6.336 6.485  7.254 1.001  18000
delta[1,1]   0.279   0.283 -0.373  0.118  0.307 0.473  0.755 1.001  41000
delta[2,1]   0.966   0.160  0.656  0.857  0.965 1.074  1.280 1.001  65000
delta[3,1]   0.460   0.201  0.040  0.344  0.464 0.578  0.865 1.001  22000
delta[4,1]   0.369   0.338 -0.366  0.170  0.391 0.591  0.981 1.001 220000
delta[5,1]   0.023   0.296 -0.617 -0.161  0.039 0.228  0.552 1.001  99000
delta[6,1]   0.671   0.065  0.543  0.627  0.671 0.715  0.799 1.001 180000
delta[1,2]   6.555   0.534  5.924  6.267  6.368 6.680  8.091 1.001  51000
delta[2,2]   6.351   0.062  6.238  6.308  6.348 6.392  6.477 1.001  73000
delta[3,2]   6.315   0.278  5.703  6.205  6.307 6.426  6.939 1.001  12000
delta[4,2]   6.411   0.429  5.672  6.232  6.330 6.520  7.543 1.001  23000
delta[5,2]   6.567   0.653  5.740  6.244  6.362 6.710  8.421 1.001  32000
delta[6,2]   6.283   0.038  6.209  6.258  6.284 6.309  6.356 1.001  31000
rho         -0.151   0.602 -0.965 -0.697 -0.252 0.362  0.946 1.001  13000
tau[1]       0.532   0.286  0.158  0.336  0.469 0.655  1.293 1.001 150000
tau[2]       0.338   0.379  0.008  0.080  0.194 0.454  1.460 1.001   7700
deviance     3.461   4.458 -3.666  0.329  2.870 5.959 13.921 1.001  33000

For each parameter, n.eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor (at convergence, Rhat=1).

DIC info (using the rule, pD = var(deviance)/2)
pD = 9.9 and DIC = 13.4
DIC is an estimate of expected predictive error (lower deviance is better).
```

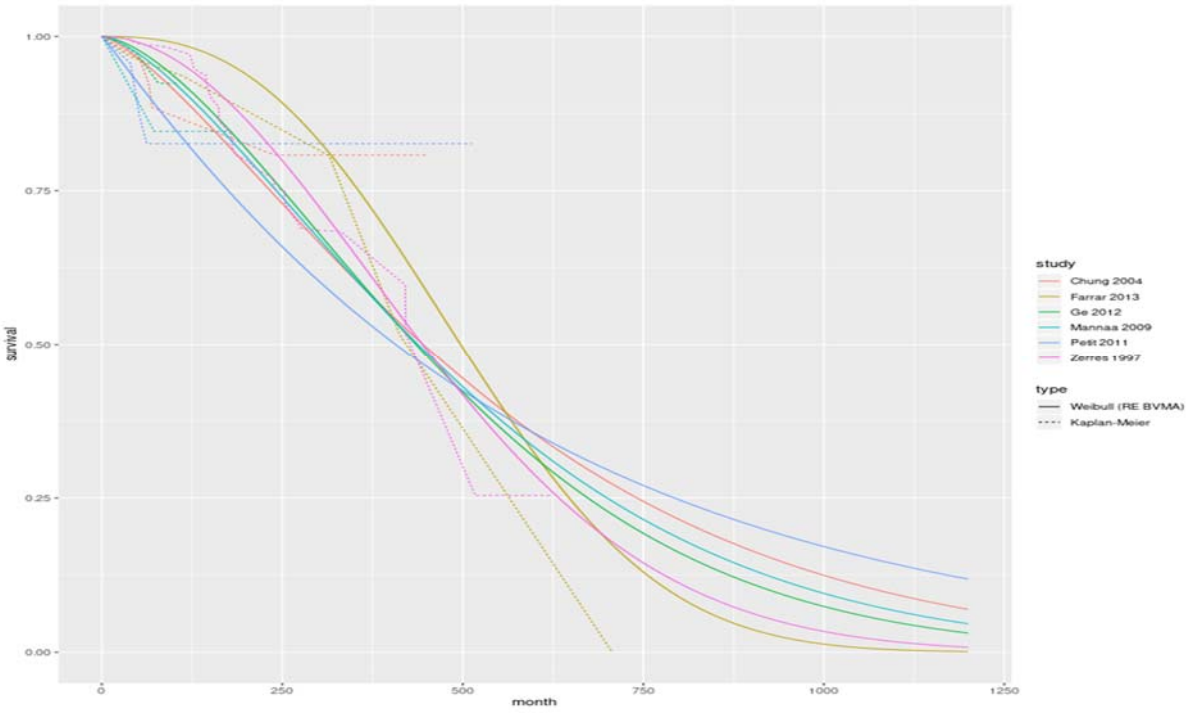
The resulting population survival curve using the posterior median parameter estimates plotted against the SLR pooled Kaplan-Meier data is presented below in Figure 12. 3.4% of patients are predicted to be alive at 100 years of age using this model.

Figure 12: population survival curve using the posterior median parameter estimates plotted against the SLR pooled Kaplan-Meier data



The study-specific survivor function estimates from the random-effects meta-analysis (using the posterior median parameters) plotted against the observed Kaplan-Meier data of the individual studies are presented below in Figure 13. The Weibull distribution appears to fit fairly well to most studies, although for studies Chung 2004 and Petit 2011 >5% of patients are predicted to survive beyond 100 years of age.

Figure 13: Study-specific survivor function estimates from the random-effects meta-analysis (using the posterior median parameters) plotted against the observed Kaplan-Meier data of the individual studies



d) Please comment on the appropriateness of the assumption that the time origin for the pooled dataset is the same as the initial patient age in the economic model.

From the Type II SLR that we conducted, the range of results of the included studies baseline characteristics (mean age of onset 8.7 to 22.1 months, female 31.9-65%) were considered broadly comparable to our SUNFISH population (mean age of onset 14 months, 50% female). However, as stated in the CS, given the likely heterogeneity between the studies captured, further consideration was given to the most appropriate studies to utilise to inform final survival estimates. Upon inspection of the individual and pooled Kaplan-Meier curves, it was observed that the study by Belter et al. reported higher survival compared to the other studies. The Belter et al. study used data from the Cure SMA database, a patient-reported data repository on SMA patients (127). As noted by the authors, limitations of the study include enrolment bias (Cure SMA membership may represent a more engaged population) and that data was patient reported, which is prone to reporting inaccuracies, incomplete information and errors in memory. As such, the Belter et al. study was conservatively excluded from the data set (see CS, Section B.3.3.1)

B14. Type 2/3 SMA model, worksheet "survival", column AA. The =ROUND() function applied in the formulae in this column means that the lookup value for the first cycle is equal to the start age plus 0.50 years. Was this intentional? Please clarify.

Yes, this was intentional. During the validation, it was noted that the formula was not recognizing non integer age inputs. Hence, this slight adjustment corrects this in MS Excel.

Type 2/3 SMA model - Health utilities

B15. CS, Section B.3.4, page 125. Please clarify why patient and caregiver utilities have not been adjusted for age.

Based on clinical expert feedback, and in order to ensure maximum possible face validity of model inputs, utilities for both patients and caregivers have been based on the company submission for TA588 (14). Within TA588 it was stated that "as there was no basis for varying utilities by the age of the patient […] utilities are assumed to be constant over time"; similarly, as part of the clarification questions, it was stated further that "that applying a fixed disutility over time would add less uncertainty by not assuming a specific behaviour of the disutility over time", with this not having been further challenged as part of the Evidence Review Group report. Consequently, in alignment with the applied NICE-specific precedence and in order to avoid introducing additional uncertainty, both sets of TA588-derived utilities have not been adjusted for age.

B16. CS, Section B.3.2.2, page 104, Table 49. The CS states that the EQ-5D estimates from SUNFISH "lacked clinical validity, as they were too low and did not reflect the broad range of HRQoL levels observed between motor milestones." Please clarify how observed data can lack clinical validity and suggest why such low estimates may have been obtained.

The observed utility data from the SUNFISH trial may be unrealistic as a response to utilising the EQ-5D method to evaluate quality of life. It has been previously reported that EQ-5D may lack sensitivity in mobility impaired populations, such as patients with SMA, as the EQ-5D does not accurately reflect HRQoL in methods of mobility other than walking (20). Limited choices for individuals with impaired mobility results in the choice of a level that does not reflect the actual state of mobility. Bray et al. provide the following illustrative example using the EQ-5D-3L scale (20). Under the 'mobility' dimension of the questionnaire, in lieu of more precise options, a patient might select 'I am confined to bed' as a substitute for 'I am confined to an electric wheelchair', 'Confined to bed', as the lowest possible mobility level of the EQ-5D-3L, is associated with a disutility of −0.664. Therefore, patients that are unable to walk, but are otherwise mobile and have no other HRQoL impacts, can only achieve a

maximum utility value of 0.336 (1 [perfect health]–0.664) using the EQ-5D-3L instrument. This is likely to explain why patients of differing abilities within the spectrum of SMA may demonstrate similar, as well as low levels of utility, when measured by the EQ-5D.

As described in Section B.3.4.1 of the CS, the EQ-5D-5L was utilised in the SUNFISH trial, with values subsequently cross-walked to the -3L format. Nevertheless, the five options available to select under the 'mobility' dimension of the EQ-5D-5L are similarly walking-focussed, and therefore insensitive to differences in HRQoL among patients who cannot walk.

Given that four out of the five motor milestone health states in the type 2/3 model informed by the SUNFISH trial represented motor abilities less advanced than walking, it is unsurprising that HSUVs were low and similar to each other. Furthermore, the majority of patients in the SUNFISH trial did not reach the walking health state, meaning there were few data to inform the utility value associated with this health state.

UK clinical experts consulted at the advisory boards confirmed that the SUNFISH trial utilities were much lower than would be realistically expected (Appendix N). Furthermore, UK clinical experts noted that the narrow range of utilities across motor milestones for patients treated with risdiplam as observed in the SUNFISH trial is not reflective of reality (Appendix N). Both these observations can be explained by the EQ-5D approach offering limited choices for individuals with impaired mobility.

B17. Priority question. CS, Section 3.4.5, page 134. The patient utility values for the health states in the Type 2/3 model are based on the Lloyd et al vignette study. The CS states that the Lloyd utilities were preferred over the estimates given by the ERG's clinical advisors and refers to Appendix N. However, Appendix N does not appear to provide any information to indicate this. Please elaborate on why the company's advisors preferred the Lloyd utilities over the ERG's clinical experts' estimates.

As detailed in the main submission, section 3.4.5 (page 133), feedback from the attendees at the UK clinical advisory board was that utility values from TA588 were more realistic than the utility values collected in the SUNFISH trial, as they better reflect the broad range of HRQoL levels observed between different motor milestones. This information is provided in Appendix N. The attendees of the UK clinical advisory board did not comment on whether the Lloyd et al. utility values were preferable to those given by the ERG's clinical advisors (21). Instead, the decision to choose the utility values from Lloyd et al. as the base case was made to align with what was considered for final decision-making in the TA588 submission, whilst the utility values derived from the TA588 ERG clinical advisers and SUNFISH were

included in scenario analyses, as explained on page 133 of the submission. We appreciate that the wording used in the justification column of Tables 64, 65 and 66 ("Feedback from UK clinical experts was that HSUVs sourced from the Lloyd et al. study possessed the greatest clinical validity for type 2/3 patients (Appendix N)") may therefore be misleading. We would suggest to replace this with the following text: "Feedback from UK clinical experts was that HSUVs from TA588 possessed greater clinical validity for type 2/3 patients than the SUNFISH utility values (Appendix N). The Lloyd et al. utility values were chosen as the base case, rather than the values from the ERG's clinical advisors, to align with the TA588 submission considered for final decision making."

B18. CS, Section 3.4.5, page 134. The caregiver utility for the worst state is assumed to be 0.484. However, this value appears to reflect a Spanish population. Please clarify why this value was selected for use in the model.

The caregiver utility value for the worst health state (0.484) was indeed derived from a study in a Spanish population (Lopez-Bastida et al.) (22). In the absence of any alternative suitable utility data for carers of SMA patients identified in the HRQoL SLR, this value was selected for use in the model to align with the approach taken in TA588.

B19. Priority question. Type 2/3 SMA model, worksheet "HSUV". The ERG understands how each of the patient utility values have been derived. However, the justification for selecting particular values for each state is not always clear from the CS. Please provide a brief justification for each patient utility value used in the model

The justifications for the utility values and how the health states from the risdiplam model were matched to the health states from the nusinersen appraisal are outlined in Table 15 and Table 16 for the base case and scenario utilities, respectively. The base case utility values for the risdiplam type 2/3 model were derived from the base case utility values used in the nusinersen appraisal (sourced from Lloyd et al.) and the scenario utility values were derived from the scenario analysis in the nusinersen appraisal (sourced from the ERG clinical advisors during the TA588 submission. Generally, health states were matched as closely as possible in terms of motor function achieved and averages of utilities from several nusinersen health states were taken where deemed appropriate. Furthermore, utility values from the SUNFISH trial were used to inform an additional scenario analysis. Particular values for each health state in this scenario analysis were directly elicited from patients in the SUNFISH trial, please see Table 66 in Section B.3.4.5 of the original submission.

Table 15: Justification of type 2/3 model base-case patient utilities per health state

Risdiplam type 2/3 health states	Risdiplam type 2/3 base case utility value: mean	Translation information from nusinersen models (mean utility value*)	Justification
Not sitting	−0.170	Moderate milestones (−0.170†)	The lowest health state in the later onset model for nusinersen was 'sits without support but does not roll'; there was no health state equivalent to 'not sitting'. However, the early onset model for nusinersen included health states below sitting. Therefore, the 'moderate milestones' health state, which was immediately below the 'sits without support' health state and represented losing the ability to sit, was considered most appropriate to inform the 'not sitting' utility value in the risdiplam model.
Sitting (supported)	0.040	Sits without support but does not roll (0.040); sits and rolls independently (0.040)	The 'sits without support but does not roll' and 'sits and rolls independently' health states from the later-onset nusinersen model were deemed the most appropriate health states to inform the 'sitting (supported)' and 'sitting (unsupported)' health states in the risdiplam model. The next higher utility value was from the 'sits and crawls with hands and knees' health state (0.100) from the nusinersen model. This was not taken into account as it was assumed that this motor function would not be captured by the 'sitting (unsupported)' health state.
Sitting (unsupported)	0.040	Sits without support but does not roll (0.040); sits and rolls independently (0.040)	
Standing	0.555‡	Average of stands/walks with assistance (0.390) and stands unaided/walks unaided (both 0.720)	As the health states from the nusinersen appraisal did not exactly match the risdiplam health states, it was decided to take the average of the utilities associated with the 'stands/walks with assistance' health state and 'stands unaided'/'walks unaided' health states (0.390 and 0.720, respectively) from the later-onset nusinersen model to inform the utilities associated with the 'standing' and 'walking' health states in the risdiplam model.
Walking	0.555‡		

*Sourced from Lloyd et al. 2019 (21). †This utility is taken from the type I nusinersen SMA model. ‡Please note that these are the correct utilities, rather than the utilities listed for standing and walking in Appendix Q of the submission.

Table 16: Justification of type 2/3 model scenario patient utilities per health state

Risdiplam type 2/3 health states	Risdiplam type 2/3 scenario utility value: mean	Translation information from nusinersen models (mean utility value*)	Justification
Not sitting	0.350	Moderate milestones (0.350†)	The lowest health state in the later onset model for nusinersen was 'sits without support but does not roll'; there was no health state equivalent to 'not sitting'. However, the early onset model for nusinersen included health states below sitting. Therefore, the 'moderate milestones' health state, which was immediately below the 'sits without support' health state and represented losing the ability to sit, was considered most appropriate to inform the 'not sitting' utility value in the risdiplam model.
Sitting (supported)	0.600	Sits without support but does not roll (0.600); sits and rolls independently (0.600); sits and crawls with hands and knees (0.600)	The 'sits without support but does not roll' and 'sits and rolls independently' health states from the nusinersen appraisal were deemed the most appropriate health states to inform the 'sitting (supported)' and 'sitting (unsupported)' health states in the risdiplam model. While it was assumed that the motor function in the 'sits and crawls with hands and knees' health state of the nusinersen model would not be captured by the 'sitting (unsupported)' health state, it is included here, as the utility value is identical to the other health states.
Sitting (unsupported)	0.600	Sits without support but does not roll (0.600); sits and rolls independently (0.600); sits and crawls with hands and knees (0.600)	
Standing	0.800‡	Average of stands/walks with assistance (0.750) and stands unaided/walks unaided (both 0.850)	As the health states from the nusinersen appraisal did not exactly match the risdiplam health states, it was decided to take the average of the utilities associated with the 'stands/walks with assistance' health state and 'stands unaided'/'walks unaided' health states of the nusinersen model (0.750 and 0.850, respectively) to inform the utilities associated with risdiplam's 'standing' and 'walking' health states.
Walking	0.800‡		

*Sourced from the ERG clinical advisors during the TA588 submission (14). †This utility is taken from the type I nusinersen SMA model. ‡Please note that these are the correct utilities, rather than the utilities listed for standing and walking in Appendix Q of the submission.

Type 2/3 SMA model - Costs

B20. CS, Section B.3.5.1, page 143. Why has wastage been excluded from the model?

Within the cost-effectiveness model, risdiplam dosage is estimated by weight, and hence the required dose for patients was explicitly calculated and wastage did not need to be considered in our base case. The respective efficacy – in line with the appropriate dose as per the SmPC - was also reflected in the model.

Type 2/3 SMA model - Other

B21. Type 2/3 SMA model, worksheets "risdiplam" and "BSC". [redacted] of BSC-treated patients are estimated to still be alive in the final model cycle (when patients are age 95 years), whilst 0% of risdiplam-treated patients are alive in the final model cycle (age 100 years). Why is the number of cycles included in the model less for BSC than risdiplam (1079 versus 1020 cycles)?

We can confirm that this is an error within the "BSC" worksheet, which could be corrected by amending the included traces to cover the same number of cycles as the "risdiplam" worksheet (by extending all includes tables and formulae until row 1089, and ensuring that the newly extended ranges are fully covered by the results calculation in rows 5/6).

Type 1 SMA model - Transition probabilities and treatment effects

B22. Priority question. CS, Section B.3.3.2, page 120. The CS states "Clinical data from the population who received the final dose of risdiplam in the FIREFISH trial who had at least 52 weeks follow-up were utilised to develop transition probabilities between motor milestone health states for the risdiplam arm in the type 1 cost-effectiveness model." The msm function does not require all patients to have the same duration of follow-up and excluding observations will lead to a loss of information. Please clarify why the full FIREFISH dataset with all observations was not used to derive transition probabilities. Please explain how much data has been excluded from the analysis.

The full FIREFISH dataset (Pooled High-dose Part 1 + Part 2) was used for the transition probabilities. No data was excluded.

B23. CS, Section B.3.3.2, page 120. The datasets used to inform transition probabilities and survival includes some patients from Part 1 of FIREFISH. Please provide more detail about these patients, including information about how many Part

1 patients were included and whether their baseline characteristics are similar to those for the Part 2 patients.

Patient baseline characteristics were very similar across Part 1 and Part 2. Please see Figure 14. Please refer to Appendix L from the company submission for further details on the patient characteristics from Part 1 of FIREFISH.

Figure 14: FIREFISH Parts 1 and 2: patient baseline characteristics (SMA).

	FIREFISH Part 1* n=17	FIREFISH Part 2 n=41	All infants N=58
Female/Male, n (%)	11 (65) / 6 (35)	22 (54) / 19 (46)	33 (57) / 25 (43)
Median age, months (range)			
At onset of symptoms	1.5 (0.9–3.0)	1.5 (1.0–3.0)	1.5 (0.9–3.0)
At diagnosis	3.0 (0.9–5.4)	2.8 (0.9–6.1)	2.8 (0.9–6.1)
At enrolment	6.3 (3.3–6.9)	5.3 (2.2–6.9)	5.5 (2.2–6.9)
Median disease duration, months (range)	4.0 (2.0–5.8)	3.4 (1.0–6.0)	3.4 (1.0–6.0)
≤3 months, n (%)	6 (35)	14 (34)	20 (34)
>3 months, n (%)	11 (65)	27 (66)	38 (66)
Median CHOP-INTEND score (range)	24.0 (16.0–34.0)	22.0 (8.0–37.0)	23.0 (8.0–37.0)
Median HINE-2 score (range)	1.0 (0.0–2.0)	1.0 (0.0–5.0)	1.0 (0.0–5.0)

*Only data from Cohort B (high-dose cohort, dose adjusted per protocol) in FIREFISH Part 1 is included in these pooled analyses. An additional four infants were in the low-dose cohort (Cohort A) in FIREFISH Part 1 and started on a lower dose which was adjusted per the protocol. One infant from Cohort A died on study Day 21
Source: (23)

B24. CS, Section B.3.3.2, page 120. The CS states "Baseline HINE-2 total score centred around the mean was included as a covariate for the "not sitting" to "sitting" transition only." Please clarify why this approach was deemed necessary and provide an analysis in which this approach was not used.

Baseline HINE-2 score was included as a covariate as it was thought to be predictive of later milestone achievement. A recent study in infants with Type 1 SMA treated with nusinersen found that a higher baseline motor function score was associated with a higher probability of acquiring the sitting milestone (24). As described in our answer to question B29, we conducted a likelihood ratio test to compare the models with and without baseline motor function score as a covariate, and the model including a covariate for baseline score had a significantly better fit ($p = 0.0004$).

Please see Table 17 for updated risdiplam transition probabilities excluding all covariates. The transition probabilities are very similar to the original values that include 'Baseline HINE-2 total score' as a covariate (Table 59, CS).

Table 17: Risdiplam motor milestone transition probabilities (excluding covariates)

	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]		
Sitting	[redacted]	[redacted]	[redacted]	
Standing	[redacted]	[redacted]	[redacted]	[redacted]
Walking			[redacted]	[redacted]

B25. Priority question. CS, Section B.3.3.2, page 121. The CS states that a naïve analysis was used in the base case for transition probabilities, ventilation-free survival and overall survival. Why was the matched analysis (i.e. the MAIC) not used instead?

As noted in the CS, two approaches were taken in indirectly comparing between risdiplam and BSC, in line with NICE DSU guidance: a naïve comparison and a comparison based on a population matching technique (unanchored MAIC) to adjust for observed differences between trial characteristics. Results from the both analyses were consistent, and suggested superior efficacy of risdiplam compared to BSC on several key endpoints, including ventilation-free survival, overall survival, HINE-2 motor milestone response and achievement of the sitting without support motor milestone. However, as stated by UK HE experts, differences between the study populations used for this indirect comparison were small and the studies were deemed as broadly comparable. Therefore, both the naïve analysis and the MAIC are potentially appropriate sources of relative efficacy estimates for risdiplam vs BSC in Type 1 SMA, with the naïve analysis providing more conservative estimates, as differences in baseline motor function are not considered. Based on this, the naive comparison was conservatively included in the base-case analysis, and the MAIC results were used in a scenario analysis.

B26. Priority question. CS, Section B.3.2.2, Table 51, page 110. The model assumes that, with the exception of patients on permanent ventilation, zero percent of patients in the risdiplam group can progress to a worse health state after 2 years. Please clarify the precise source of this value and explain how it was derived. Please also clarify the source of the timepoint of 2 years.

The assumption of no patients in the risdiplam group deteriorating after 2 years was selected following two ad-boards with UK clinical experts. A confidential appendix with a report from

these ad-boards is provided as part of the CS. No formal elicitation method was used. During the ad-boards, UK clinical experts agreed that it would be accurate to assume that in the long-term Type 1 patients treated with active treatment can only improve or remain constant. On the basis of these discussions with UK clinical experts, the adjustment of transition probabilities after 24 months in the base-case was selected. This adjustment was varied in scenario analyses. For the selection of the timepoint of applying this assumption at 2 years, please see response to question B6.

B27. Priority question. CS, Section 3.3.2, Table 59, page 121. The model assumes that patients in the risdiplam group who reach the walking state at any timepoint can never lose this milestone. Please clarify the basis for this assumption.

This is in line with the broader assumption no patients in the risdiplam group are anticipated to deteriorate in motor milestone achievement after 2 years, following UK clinical expert input. We made a conscious effort not to overcomplicate the model structure or the approaches to populate it, as this would increase the need for making additional assumptions. Meanwhile, the proportion of patients reaching the walking health state was varied in a scenario analysis and was found to not have significant impact on results. Therefore, we considered it would not be a priority to include an adjustment to allow backward transitions only for this health state and introduce additional complexity, especially as the impact on model results was tested in a scenario analysis.

B28. Priority question. CS, Section 3.2.2, Table 51, page 110. The CS comments that no patients in FIREFISH reached the milestone of walking within the follow-up period but this transition is included in the model with the transition probability "…calculated to be one third (33%) of the transition probability for 'sitting' to 'standing.'"

a) **Please clarify the source of the value of 33% and explain how this was derived**

UK clinical experts conceptually agreed that a proportion of patients treated with risdiplam would be anticipated to transition to walking within their lifetime (Appendix N). It was difficult for clinical experts to provide a numerical response for this transition probability and therefore in our base case analysis the transition probability from standing to walking was calculated to be one third (33%) of the transition probability for sitting to standing, as a starting point to evaluate the impact on results. This probability was tested in scenario analyses in the CS and was found to have a very small impact on model results.

b) **Please provide the evidence available to support the assumption that Type 1 SMA patients treated with risdiplam may achieve the milestone of (a) standing and (b) walking.**

As stated in the CS, whilst no advances to walking were observed during the FIREFISH trial (up to the latest cut-off), a transition to the 'walking' health state for risdiplam was considered, on the basis that some patients in the study acquired further developmental milestones towards developing the walking function (bouncing). UK clinical expert were asked and agreed with this assumption (Appendix N).

B29. Priority question. CS, Section B.3.3.2, page 120. The company has used the msm package in R to derive transition probabilities using a time-homogenous approach. However, the full matrix derived from the msm package has been amended to only allow progressions/regressions to adjacent states in a given cycle.

a) **Please clarify why this assumption was considered necessary? Why was it not considered appropriate to use the msm outputs directly (including transitions to non-adjacent states)?**

After our analysis of the data using the MSM package in R, we noticed that several transitions were mathematically feasibile (i.e. patients could progress to a non-adjacent health state) that violated our underlying clinical assumption and model structure (i.e. patients progress sequentially). Hence, any non-adjacent transitions in progression, were assumed to be part of the next sequential health state.

b) **Please provide the actual transition probability matrices estimated by the msm package for each treatment group. Please also provide a simple spreadsheet which shows how the probabilities from the msm package have been transformed into the probabilities used in the model.**

These calculations are provided in the 'Treatment Efficacy' tab, cells I11 to N16. These cells call in the original values of the MSM model from the R package, which are also located in this same sheet, cells S11 to U14.

c) **Please provide additional information regarding the input data used in the multi-state model. Specifically:**

(i) How many observations were there?

278 observations

(ii) How frequent were the visits?

Every 4 months

(iii) How many events were directly observed?

278

(iv) How many events were imputed?

No imputations

(v) Is there evidence from the FIREFISH data that the transition rates are constant with respect to time (i.e. that a time-homogenous model is appropriate)?

Due to the small sample size it was not possible to robustly assess changes in transition rates over time in FIREFISH

(vi) Please provide evidence to demonstrate goodness of fit of the model, including the use of the prevalence function

Goodness of fit was assessed using likelihood ratio tests and the prevalence function from the msm package.

MSM models without any covariates and with a covariate for baseline HINE-2 total score centred around the mean were compared via a likelihood ratio test. The model with baseline HINE-2 total score as a covariate was found to have a significantly better fit compared to the base model without covariates (p = 0.0004).

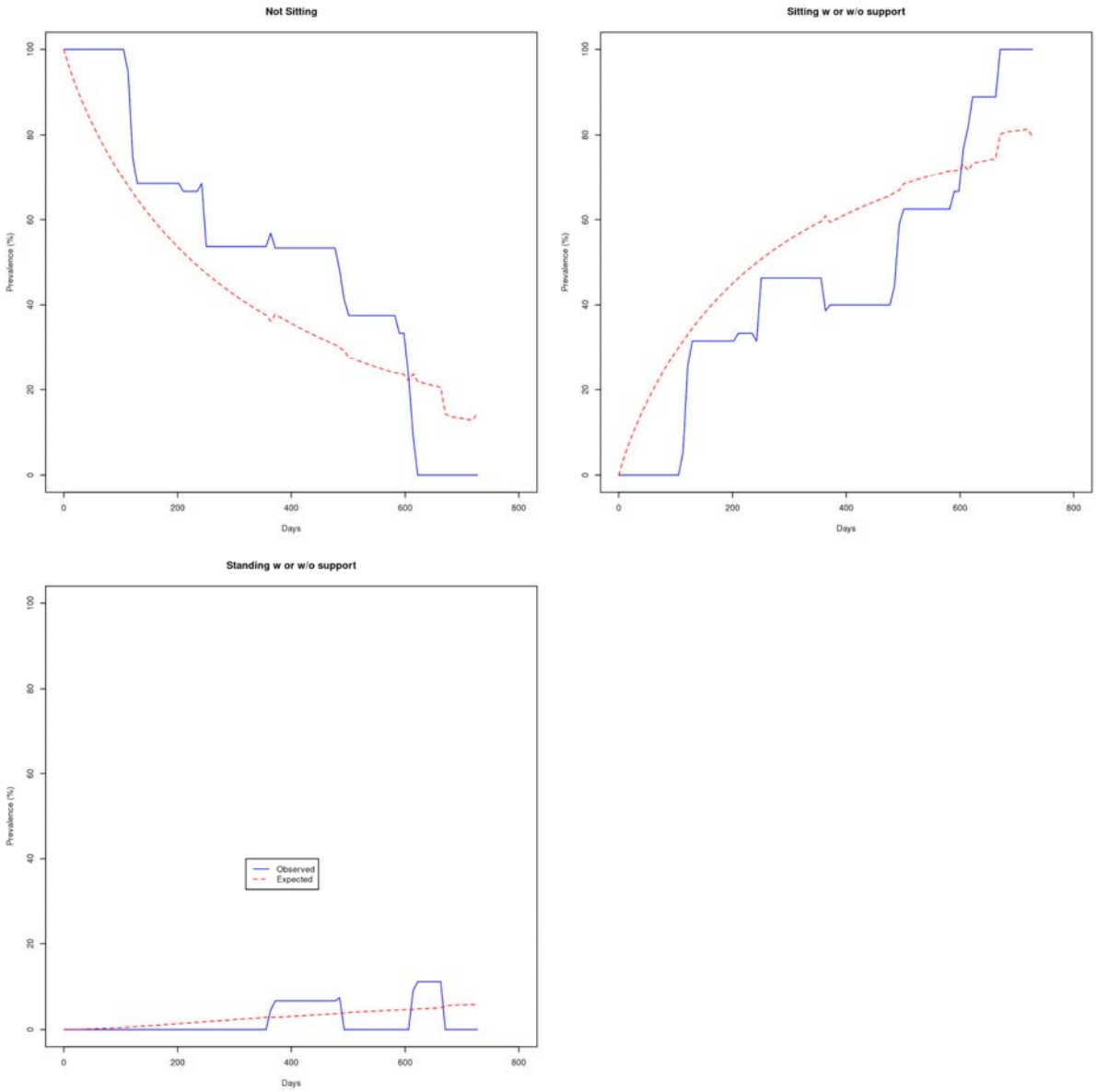
In addition, observed state prevalences were compared to those predicted with the final MSM model using the prevalence function from the msm package. Prevalences in the "Sitting" health state were slightly overestimated and prevalences in the "Not Sitting" health state underestimated. However, overall, the model was considered to fit the data reasonably well. Further, since transition probabilities for BSC were derived using ORs versus risdiplam, the overestimation of the "Sitting" health state would not have an effect on incremental outcomes. Results are available in Table 18 and Figure 15.

Table 18: Risdiplam prevalence table - Goodness of fit using prevalence function from msm package applied to base case model (incl. baseline HINE-2 score covariate)

	Observed prevalence (%)			Predicted prevalence (%)			Absolute difference predicted vs observed		
Timepoint	Not Sitting	Sitting with or without support	Standing with or without support	Not Sitting	Sitting with or without support	Standing with or without support	Not Sitting	Sitting with or without support	Standing with or without support
0	100.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00
119	81.82	18.18	0.00	66.77	32.61	0.62	-15.05	14.42	0.62
245	57.41	42.59	0.00	48.02	50.19	1.79	-9.39	7.59	1.79
364	54.55	40.91	4.55	36.14	60.92	2.93	-18.40	20.01	-1.61

490	39.13	56.52	4.35	28.36	67.75	3.89	-10.77	11.23	-0.46

Figure 15: Risdiplam prevalence plot



(vii) Please clarify how many patients in each group improved from baseline to reach the milestones of (a) standing/walking and (b) walking in FIREFISH.

3 infants achieved the 'Standing' milestone and maintained the ability in subsequent visits (if available); 2 at Day 364 and 1 at Day 609. No infant achieved the 'Walking' milestone.

B30. Priority question. CS, Section 3.3.2, page 121. Please provide the odds ratios used to estimate transition probabilities for the BSC group and clarify which transitions these are applied to and in which part of the CS these are reported.

The odds ratios used to inform the model transition probabilities for the BSC arm are based on the ITC analysis (naive comparison) of the HINE-2 outcomes 'sitting with and without support' and 'standing (with support and unaided)' at the 12-month timepoint. These odds ratios inform the transitions between the 'not sitting' and 'sitting' health states and 'sitting' to 'standing' health states, respectively. The 12-month HINE-2 ITC results are presented in Appendix M of the company submission and are repeated in Table 19 below for clarity.

Table 19: HINE-2 motor milestones using FIREFISH data at 12 months

Milestone	Comparator (STUDY)	Naïve Comparison		MAIC	
		Pre-match Number of responders / Sample size (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Post-match Weighted number of responders / Sum of weights (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)
Motor milestone response	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Full head control	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Rolling (supine to prone rolling)	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Sitting without support (stable sits and pivots)	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]
Sitting with and without support (sits with support at hips, props, stable sit and pivots)	Risdiplam‡ (FIREFISH)	[redacted]		[redacted]	
	BSC§ (ENDEAR)	[redacted]	[redacted]	[redacted]	[redacted]

Standing (with support and unaided)	Risdiplam‡ (FIREFISH)				
	BSC§ (ENDEAR)				

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

‡ HINE motor milestone achievement in infants at 12 months visit

§ HINE motor milestone achievement in infants at the later of Days 183, 302 and 394

* ORs calculated using half-cell correction

° Clopper-Pearson CIs

B31. Priority question. CS, Section B.3.2.2, page 110, Table 51. In TA588, the final iteration of the model assumed that patients treated with nusinersen plateau (stay in the same state) after a fixed period of time (around 5 years). In contrast, the risdiplam model assumes that after 2 years, with the exception of those on permanent ventilation, patients in the risdiplam group cannot move to a worse health state. Why does the risdiplam model not include a plateau?

Please see response to question B10. The proportion of risdiplam-treated patients remaining in the same health state after 2 years is extremely high and varies from 98.5% to almost 100% for the health states of sitting, standing, or walking; see economic model "Risdiplam" worksheet, columns CB-CP.

B32. Priority question. CS, Section B.3.3.2, page 124. The model assumes that patients remain on treatment indefinitely.

a) Given that some discontinuation was observed in FIREFISH, please comment on why discontinuation is excluded from the model and whether this would be expected in clinical practice.

Discontinuation was excluded from the model for the following reasons. Firstly, as costs would continue to incur whilst patients remain on treatment, excluding discontinuation was deemed a conservative approach. Secondly, an effort was made to keep the model as simple as possible, as it is not clear what the outcomes of discontinuation would be. Due to the paucity of data from the trials, assumptions for outcomes would have to be made if the model allowed patients to discontinue treatment.

Only [redacted] patients discontinued treatment within Part 2 of the FIREFISH trial. As such, there were very few data to inform likely discontinuation from risdiplam and its outcome in clinical practice. UK clinical expert opinion was sought on the likely discontinuation rate of risdiplam in clinical practice (Appendix N), and most clinical experts at the UK advisory boards indicated that they would likely not discontinue treatment in response to a patient plateauing. Furthermore, even if a patient worsened on risdiplam treatment, clinical experts would base

their decision on discontinuation on whether the patient is declining at a slower rate than expected with BSC and whether alternative treatments are available. Based on the trial data and clinical expert feedback, it was concluded that discontinuation of risdiplam was likely to take place rarely in clinical practice, further supporting the assumption of no discontinuation in the model.

Furthermore, expert opinion was sought at the UK clinical advisory boards about the expected treatment effect of risdiplam after discontinuation. UK clinical experts stated that any treatment benefit following discontinuation of risdiplam would be expected to reflect the survival motor neuron (SMN) protein levels over several months following discontinuation (Appendix N).

b) In clinical practice, if a patient did discontinue risdiplam, might they go on to receive nusinersen?

Nusinersen could be an available treatment option in clinical practice for some patients, if they discontinue from risdiplam. However, as stated in our response to question A9, while we acknowledge there is currently an absence of evidence to determine the optimum sequence of therapy, clinical experts confirmed to Roche that treatment decisions should be based on multiple factors including an overall benefit risk analysis, unmet need and clinician and patient choice. We anticipate that risdiplam will provide an additional therapeutic option for all patients across the continuum of SMA; this will include treatment-naïve patients, as well as those patients who have previously received nusinersen but cannot tolerate it and/or respond poorly.

Importantly though, nusinersen was not considered a relevant comparator in the NICE final scope for ID1631 and has not been considered as part of our economic analysis. Any comparison or inclusion of nusinersen was considered to be out of scope for the cost-effectiveness analysis of our CS.

c) Please consider including discontinuation in the model, including adjustment of outcomes, if appropriate.

Based on the response to part a, it was not considered appropriate to make further changes to patient discontinuation in the model. However, please note that functionality to discontinue is built into the model, but it only adjusts costs and not outcomes.

d) Please comment on whether a formal stopping rule for risdiplam (e.g. for non-responders) was considered. Please also comment on the appropriateness of

continuing treatment in patients who have lost or never achieved motor milestones.

A formal stopping rule was not considered for risdiplam, as our key priority is to provide broad and unrestricted access to risdiplam for UK SMA patients. A stopping rule however might be a pragmatic option that might need to be considered in order to ensure that risdiplam is made available to as broad as possible SMA patient population in the UK. However a key challenge with establishing a stopping rule is that the SMA population is very heterogeneous (especially for Type 2/3 SMA) and the definition of treatment benefit or patient improvement significantly differs for SMA patients with different characteristics such as Type of disease, age, duration of disease etc. Therefore it would be difficult to establish a stopping rule, and any stopping rule would need to take into account input from the UK SMA clinical community as well.

The appropriateness of continuing treatment in patients who have plateaued or worsened on treatment was discussed at the ad-boards with UK clinical experts (Appendix N). If a patient plateaued on treatment, most clinical advisors would keep the patient on the same treatment, as this contrasts with the well-demonstrated progressive deterioration that untreated patients demonstrate. Informed discussion, the patient's/family's preference for palliative care, and factors like recurrent respiratory infections, would influence the decision. If a patient worsened on treatment, advisors would sometimes discontinue treatment. The availability of an alternative treatment and whether a patient is declining at a slower rate than expected on BSC, would also be key considerations. The clinical expert opinion outlined above demonstrates how difficult it is to establish a treatment stopping rule in a disease with such a broad and severe impact in a very heterogeneous population.

B33. Priority question. Model, worksheet "risdiplam". The model predicts that in the long-term, the vast majority of surviving patients receiving risdiplam will reach the health states of standing and walking. Given the absence of data on patients reaching these milestones in FIREFISH, please comment on the plausibility of this projection.

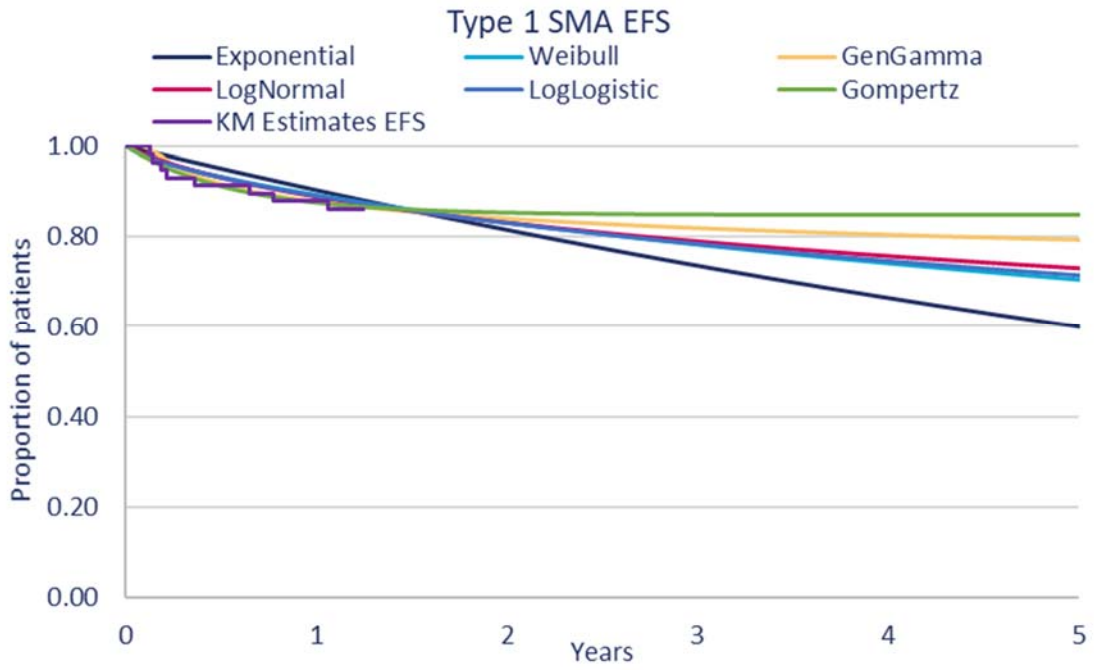
Please see response to question B11. An identical approach was taken for the Type 1 model, validating model long-term outcomes against all available evidence from natural history studies and from the literature, as well as from clinical expert opinion (CS section B3.10 and Appendix N)

Type 1 SMA model - Survival and ventilator-free survival

B34. CS, Section 3.3.2, Figure 14, page 123. Please provide a revised version of Figure 14 including the observed empirical Kaplan-Meier survivor function.

A revised version of Figure 14 from the submission is provided below in Figure 16, presenting the Kaplan-Meier data from the FIREFISH trial for event free survival against the six parametric survival functions explored. The Kaplan-Meier data were not provided in the original submission due to the current immaturity of the data. A time horizon of 5 years has therefore been chosen for the x axis to assist with comparison of the short-term Kaplan-Meier data with the parametric functions. However, as noted in the original submission, the exponential function was the only extrapolation deemed to have long-term face validity.

Figure 16: Event-free survival Kaplan-Meier data from FIREFISH

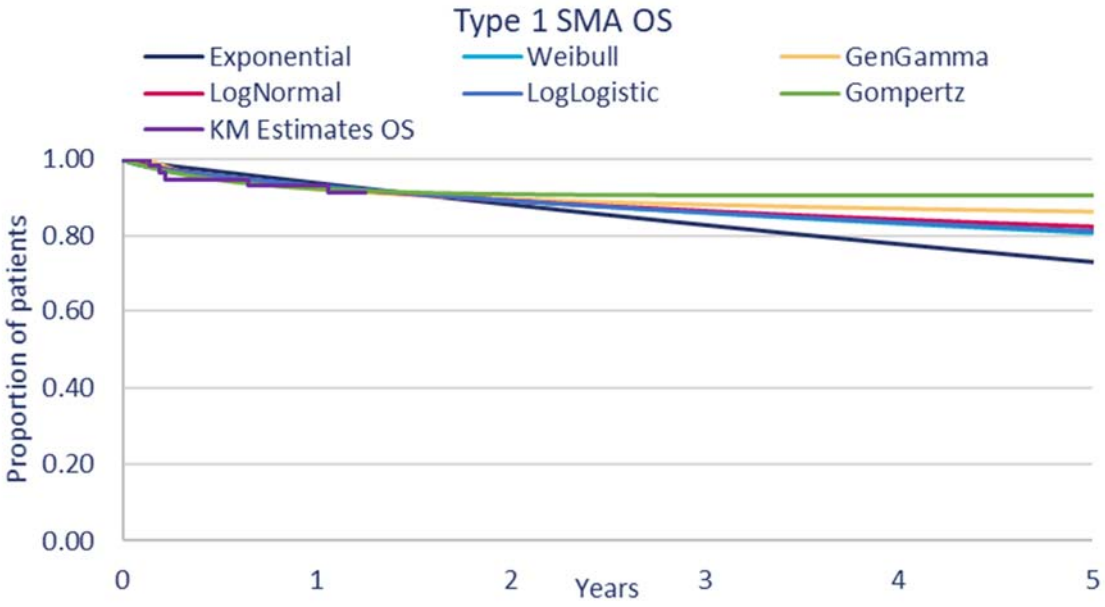


EFS: event-free survival; SMA: spinal muscular atrophy

B35. CS, Section B3.3.2, Figure 15, page 124. Please provide a revised version of Figure 15 including the observed empirical Kaplan-Meier survivor function.

A revised version of Figure 15 from the original submission is provided below in Figure 17, presenting the Kaplan-Meier data from the FIREFISH trial for overall survival against the six parametric survival functions explored. The Kaplan-Meier data were not provided in the original submission due to the current immaturity of the data. A time horizon of 5 years has therefore been chosen for the x axis to assist with comparison of the short-term Kaplan-Meier data with the parametric functions. However, as noted in the original submission, the exponential function was the only extrapolation deemed to have long-term face validity.

Figure 17: Overall survival Kaplan-Meier data from FIREFISH



B36. CS, Section B.3.3.2, page 122. Proportional hazards is a modelling assumption that may not hold in practice. Please provide results for ventilation-free survival without assuming proportional hazards.

Evidence to support holding of the proportional hazards assumption for ventilation-free survival between the risdiplam and BSC arms is presented in Appendix O. Specifically, log-cumulative hazard plots are presented for the data generated for the naïve comparison and MAIC (which informed the base case and a scenario analysis, respectively). Both log-cumulative hazards plots demonstrate that the risdiplam and BSC arms remain parallel over time, supporting holding of the proportional hazards assumption. Accordingly, no further analyses have been conducted which assumed violation of this assumption.

B37. CS, Section B.3.3.2, page 123. Please provide results for overall survival without assuming proportional hazards. Please also provide a justification for assuming that the hazards of death are constant over the lifetime of patients.

Evidence to support holding of the proportional hazards assumption for overall survival between the risdiplam and BSC arms is presented in Appendix O. Specifically, log-cumulative hazard plots are presented for the data generated for the naïve comparison and MAIC (which informed the base case and a scenario analysis, respectively). Both log-cumulative hazards plots demonstrate that the risdiplam and BSC arms remain parallel over time, supporting holding of the proportional hazards assumption. Accordingly, no further analyses have been conducted which assumed violation of this assumption

Type 1 SMA model - Health utilities

B38. Priority question. Type 1 SMA model, worksheet "HSUV". The ERG understands how each of the patient utility values have been derived. However, the justification for selecting particular values for each state is not always clear from the CS. Please provide a brief justification for each patient utility value used in the model.

The justifications for the patient utility values that were considered in the submission and how the health states from the risdiplam model were matched to the health states from the nusinersen appraisal are outlined in Table 20 and Table 21 for the base case and scenario utilities, respectively. The base case utility values were derived from the TA588 ERG clinical advisor utilities, as UK clinical experts consulted at the advisory boards felt that utilities worse than death (i.e. negative values) were unlikely to be clinically plausible (Appendix N). Therefore, utilities from Lloyd et al., which included some negative values, were explored in a scenario analysis. Generally, health states were matched as closely as possible in terms of motor function achieved and averages of utilities from several nusinersen health states were taken where deemed appropriate.

Table 20: Justification of type 1 model base case patient utilities per health state

Risdiplam type 1 health states	Risdiplam type 1 base case utility value: mean	Translation information from nusinersen models (mean utility value*)	Justification
Permanent ventilation	0.200	No milestones achieved (0.200)	The lowest health state from the nusinersen appraisal ('no milestones achieved') was used to inform the utility of the lowest risdiplam health state ('permanent ventilation').
Not sitting	0.250	Mild milestones (0.250)	The second lowest health state from the nusinersen appraisal ('mild milestones') was used to inform the utility of the second lowest risdiplam health state ('not sitting').
Sitting	0.475	Average of two health states: moderate milestones (0.350);	As the risdiplam 'sitting' health state covers sitting with and without support, it was considered

		sits without support (0.600)	appropriate to use the average utility of the 'sits without support' health state from the nusinersen model and the health state below it ('moderate milestones').
Standing	0.750	Average of two health states: stands with assistance (0.650) and stands/walks unaided (0.850)	As the risdiplam 'standing' health state covers walking with and without support, it was decided to take the average of the utilities associated with the 'stands with assistance' health state and 'stands/walks unaided' health state in the nusinersen model (0.650 and 0.850, respectively) to inform the utilities associated with risdiplam's 'standing' health states.
Walking	0.800†	Average of two health states: walks with assistance (0.750) and stands/walks unaided (0.850)	As the risdiplam 'walking' health state covers walking with and without support, it was decided to take the average of the utilities associated with the 'walks with assistance' health state and 'stands/walks unaided' health state in the nusinersen model (0.750 and 0.850, respectively) to inform the utilities associated with risdiplam's 'walking' health states.

*Sourced from the ERG clinical advisors during the TA588 submission (14). †Please note that this is the correct utility value for the walking health state, rather than the utility value listed for walking in Appendix Q of the submission.

Table 21: Justification of type 1 model scenario patient utilities per health state

Risdiplam type 1 health states	Risdiplam type 1 scenario utility value: mean	Translation information from nusinersen models (mean utility value*)	Justification
Permanent ventilation	−0.240	No milestones achieved (−0.240)	The lowest health state from the nusinersen appraisal ('no milestones achieved') was used to inform the utility of the lowest risdiplam health state ('permanent ventilation').
Not sitting	−0.120	Mild milestones (−0.120)	The second lowest health state from the nusinersen appraisal ('mild milestones') was used to inform the utility of the second lowest risdiplam health state ('not sitting').
Sitting	−0.105	Average of two health states: moderate milestones (−0.170); sits without support (−0.040)	As the risdiplam 'sitting' health state covers sitting with and without support, it was considered appropriate to use the average utility of the 'sits without support' health state in the nusinersen model and the health state below it ('moderate milestones').
Standing	0.375	Average of two health states: stands with assistance (0.040); stands/walks unaided (0.710)	As the risdiplam 'standing' health state covers standing with and without support, it was considered appropriate to use the average utility of the 'stands with assistance' health state and 'stands/walks unaided' health state in the nusinersen model.

Walking	0.615	Average of two health states: walks with assistance (0.520); stands/walks unaided (0.710)	As the risdiplam 'walking' health state covers walking with and without support, it was decided to take the average of the utilities associated with the 'walks with assistance' health state and 'stands/walks unaided' health state in the nusinersen model (0.520 and 0.710, respectively) to inform the utilities associated with risdiplam's 'walking' health states.

*Sourced from Lloyd et al. 2019 (21)

Type 1 SMA model - Costs

B39. Priority question. CS, Section 3.2.2, Table 51, page 112. The CS states "the cost of the permanent ventilation health state is assumed to be 175% times the 'not sitting' health state." Please clarify the source of this value and explain how it was derived.

As stated in the CS, the assumption that the 'permanent ventilation' health state is associated with increased cost compared to the 'not sitting' health state was confirmed with UK clinical experts (Appendix N). The cost of 175% versus the 'not sitting' health state was informed by the review of submission papers for NICE ID1473 (not published online at time of submission) and by the study by Noyes et al (25). with details for the resource use and service costs for ventilator-dependent children and young people in the UK, both in a hospital and at-home setting (CS section B.3.5.2). Importantly, the cost of the 'permanent ventilation' health state was also varied in scenario analyses.

B40. CS, Section B.3.5.1, page 143. Why has wastage been excluded from the model?

Within the cost-effectiveness model, risdiplam dosage is estimated by weight, and hence the required dose for patients was explicitly calculated and wastage did not need to be considered in our base case. The respective efficacy – in line with the appropriate dose as per the SmPC - was also reflected in the model.

B41. CS Appendix N. Please provide the full minutes of the advisory board meetings held with SMA experts.

The discussions and conclusions from all advisory board discussions relevant to the NICE submission for ID1631 are provided in the confidential report in Appendix N. UK clinical experts reviewed this report, agreed with its content and agreed to be named as part of the CS. The full minutes from the advisory boards were developed for internal use only; they cover the two advisory boards separately and they also include discussions not relevant to the NICE submission.

Section C: Textual clarification and additional points

None

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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. [Please note that declarations of interests relevant to this topic are compulsory].

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] **and** [redacted]
2. **Name of organisation**	Spinal Muscular Atrophy UK (SMA UK) and Muscular Dystrophy UK (MDUK)

3. **Job title or position**	[redacted] ([redacted]) [redacted] ([redacted])
4a	**Brief description of the organisation (including who funds it). How many members does it have?**
	SMA UK is a charity (previously known as the Jennifer Trust / SMA Support UK; merged in 2018 with The SMA Trust) that, since 1985, has provided free information and support to anyone affected by any form of SMA in the UK and has also funded research-related initiatives. We currently have contact with some 775 households of adults with SMA / parents living with a child with SMA. We estimate this to be over 60% of the total UK SMA population. We are also in touch with 364 households of parents bereaved by SMA. These figures exclude households of other relatives / friends. SMA UK is accredited to the Information Standard. Our SMA-related guides are signposted by the NHS website. Our Research Correspondents (a clinical and a research doctor) and Research Coordinator report to the SMA Community on the development of all drug treatments and clinical trials. We have regular contact with the SMA REACH UK paediatric and adult clinical networks. SMA UK's funding comes from donations, gifts, grants, trusts and merchandise sales. In 2019 / 20 we raised £925,870, comprising £795,531 donations and gifts, £124,302 Lotteries grant, £5,262 from merchandise sales and £775 from investment income. Founded in 1959, **Muscular Dystrophy UK** (previously known as the Muscular Dystrophy Campaign) brings together over 60 rare neuromuscular 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. MDUK's funding comes from donations, gifts, grants and trusts. In 2019 / 20, we raised £6.2m, comprising £5.9m in fundraised income, £200k in investments and £100k other income. We have also received a grant of £2m Changing Places grant to be distributed on behalf of the Department for Transport.
4b	**Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? If so, please state the name of manufacturer, amount, and purpose of funding.**
	SMA UK Since 1st November 2019, we have received the following funds from pharmaceutical companies:

Date	Manufacturer	Amount	Purpose of Funding
Jan 2020	Roche	£21,000	Towards two-year events programme – cancelled due to covid – agreed in view of Covid's impact on charity income that this could cover running costs
May 2020	AveXis	£40,000	Covid emergency grant to support core services
May 2020	Biogen	£39,124	Covid emergency grant to support core services
June 2020	Roche	£25,000	Covid emergency grant to support core services
June 2020	Roche	£8,200	Grant to support Community Connections project
	Total	**£133,324**	

This was 16.3% of our income during this period. Our applications for help to maintain services were driven by the huge impact of Covid-19 on income experienced across the economy and charity sector. In the financial year 2019 / 20, 6.8% of total income was from pharmaceutical grants.

MDUK

Manufacturer	Amount	Purpose of Funding
PTC Therapeutics International	£40,412	MDUK / NorthStar funding to support data collection for ataluren MAA (four x quarterly payments of £10,103)
PTC Therapeutics International	£15,000	Sponsorship of the Muscles Matter online seminar series; Living with a muscle-wasting condition in 2020 and beyond
BIOGEN IDEC LIMITED	£6,000	Sponsorship for 2017 Neuromuscular Translational Research Conference
Roche	£20,000	Grant to support MDUK services during Covid-19 pandemic

4c. **Do you have any direct or indirect links with, or funding from, the tobacco industry?**

SMA UK - No **MDUK** - No

5 **How did you gather information about the experiences of patients and carers to include in your submission?**

	Though the SMA Community has been inundated with surveys over the last 4 years and, as one respondent put it, "*I'm tired of filling out a million surveys explaining my view, my life, my experiences",* we decided that this was still one important way to obtain a cross section of views about risdiplam. Our survey was advertised via SMA UK and MDUK communication channels. It was open 25th Sept - 18th Oct 2020. We received **137 responses**: 71 adults / young adults who have SMA (52%); 32 parents of young people < 18 years old who have SMA (23%); 32 other relatives (23%); 2 parents bereaved by SMA (2%). The clinical classification given to the person with SMA who was subject of the survey was: Type 1 - 7%; Type 2 - 50%; Type 3 - 38%; Type 4 - 3%. (See Appendices 1 - 7). Rather than repeat the same questions, we have also drawn on results of the joint charities' (SMA UK, MDUK, TreatSMA) 2018 survey which were submitted to NICE as part of the nusinersen appraisal. These included 128 returns describing the health-related impacts of SMA (full survey results not included as appendices but available here: smauk.org.uk/our-surveys-about-the-impact-of-sma-and-views-about-access-to-nusinersen Our submission is also informed by the contact our Support & Outreach Service has with many adults and families and our community contact networks.
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?**
	Although 5q SMA is clinically classified into different 'Types' (see also Q.12) which reflect the potential severity of its impact, it is considered a spectrum. For children and adults, the severity of the condition varies from person to person, both within and between 'Types' - each child and adult is affected differently. Care and management as recommended in the 'International Standards of Care for SMA' should always be provided. The physical milestones describing people's ability to sit, stand and walk are increasingly important when it comes to care and management decisions. For simplicity, the summary words 'non-sitters', 'sitters' and 'walkers' are often used. The 128 respondents to our 2018 survey were either adults / teenagers with SMA or parents of children who have SMA, with the person with SMA ranging in age from < 2 years to 66+ years. They vividly described their day-to-day experiences in many pages of responses to the question, '***What are the biggest challenges of living with SMA?***' A few representative quotes: "*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*." **Father – child age 0-2 years** "*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*." **Grandparent – child age 3-4 years**

	In terms of mobility, 83% used powered wheelchairs, 68% used manual wheelchairs and 21% used 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*." **Aunt / Uncle – child age 5-12 years** "*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."* **Grandparent – child age 13-17 years** Full support - more than would be expected considering the age of the person - was needed for people to go to the toilet (78%), wash (74%), dress (81%), transfer (80%), eat and drink (31%) and, for those who required this, to prepare meals (75%). Between 10 – 42% of others required some support with these tasks. 66% required night care as they were unable to turn over at night or were, for example, needing night-time invasive ventilation (29%). For 64% of these, this care was 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*." **Young person - age 13-17 years** "*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."* **Mother - child age 13-17 years** Support was 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…"* **Adult age 46-55 years** 48% had no paid support, 25% had between 1 – 10 hours each 24-hour period and 27% had 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 had other caring responsibilities as well. 51% cared 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*." **Mother - child age 5-12 years** All those affected by and living with the condition and their carers described in their different ways the emotional impact of the condition – the 'chronic sorrow' associated with their ongoing living loss.
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, 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. In the 2020 survey responses, breathing ability was affected and interventions needed for 59% of children and 48% of adults. **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. In the 2020 survey response, 61% of adults and 68% of the children had had interventions due to scoliosis. **Physiotherapy** helps manage contractures (2020 survey: moderate / severe experienced by 50% of children and 46% of adults) and resultant pain, chest physiotherapy helps manage breathing difficulties. Few adults have access to the physio they need, and many children miss out. Interventions 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, also, is vigilance and time on the part of carers and with this comes the stress of being constantly 'on high alert'. To manage the impact of their condition, the children, young people and adults who responded to the 2018 survey were 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 required **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'*." **Father - child age 0-2 years** 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*." **Mother - child age 5-12 years** 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 were not, and still 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 was not funding 50% of their powered wheelchairs, 27% of hoists, 36% of toilet and bathroom adaptations, 52% of other home adaptations. The majority of children under the age of 3 years could not, and still cannot, access NHS funded powered chairs so 71% of families find funding for their 'Wizzybugs'.** As best supportive care is the comparator, we have not referenced views on nusinersen treatment here. We do though note that: as it is delivered by lumber puncture, spinal scoliosis / intervention can prevent safe administration; the current Managed Access Agreement combined with the very slow roll out of treatment, in particular for adults, means that its availability is limited.
8.	**Is there an unmet need for patients with this condition?**
	Yes – best supportive care does not prevent the progressive weakening of muscles. A number of adults in their 2020 responses clearly state this and their unmet need: *"It's a devastating disease no matter what type you are. It steals your abilities and in turn steals your life."* "*It would mean a lot to be able to continue to support my neck and head as this is so important for safe eating and swallowing. It is so important that my muscles maintain as much strength and stability possible to make breathing and fighting illness easier. I really want to be able to keep my independence and carry on using my hands to drive my wheelchair, hold my toothbrush, use my phone, write and use the computer for as long as I possibly can*."

	"*SMA is unpredictable and can progress at any speed, at any moment. Anything to delay that progression, or maintain existing strength, will do the world of good to people's physical and mental health. It's not fun thinking you've reached middle age at 15, and society has a lot to do to make the world more inclusive and accessible*." *"Tiny margins of increase or halting decrease would have a huge impact on all areas of my life."* In terms of access to any new drug treatment, we note the comparator is best supportive care, also that of the 2020 survey respondents, 38% of children and 93% of adults had not had access to any clinical trial / new drug treatment.
Advantages of the technology	
9.	**What do patients or carers think are the advantages of the technology?**

To accompany our 2020 survey, our Scientific Research Correspondent compiled summaries of the clinical trial evidence to date (Appendices 5-6). This was made available to all 137 respondents and was read by 91%. These were the views expressed:

Q. What in your view are the advantages / disadvantages of aspects of risdiplam treatment

	Strong Advantage		**Advantage**		**Neither Advantage nor Disadvantage**		**Disadvantage**		**Strong Disadvantage**		
	1		2		3		4		5		Total
	%	Nos	%	Nos	%	Nos	%	Nos	%	Nos	
How it is taken (syrup by mouth)	89	122	7	10	3	4	0	0	1	1	137
How often it has to be taken (daily)	51	70	24	33	23	32	1	1	1	1	137
How long it has to be taken for (as long as treatment continues)	48	66	23	32	27	37	1	2	0	0	137
Where it can be taken (at home)	93	128	4	6	1	2	0	0	1	1	137
Where it must be stored / kept (refrigerated)	48	66	23	32	25	34	4	5	0	0	137
See also Appendix 4 for additional comments									**Total answering**		**137**

Q. Views on aspects of what is known so far about risdiplam

	Very positive		Positive		Neither positive nor negative		Negative		Very negative		Don't know		Total
	%	Nos	%	Nos	%	Nos	%	Nos	%	Nos	%	Nos	
Its safety profile	52	71	36	49	7	9	1	1	0	0	4	6	136
Its recorded adverse events profile	25	34	36	49	29	40	3	4	1	1	6	8	136
Its impact on motor milestones	59	80	34	46	4	6	0	0	0	0	3	4	136
Its impact on swallowing	46	62	30	41	13	17	0	0	0	0	12	16	136
Its impact on ability to communicate	35	48	35	47	15	20	0	0	0	0	15	21	136
Its impact on breathing ability	46	63	33	45	9	12	1	1	0	0	11	15	136
Its impact on frequency and duration of hospital stays	46	63	29	39	10	13	1	1	0	0	15	20	136
Its impact on stamina and fatigue	53	73	35	48	3	4	0	0	0	0	9	12	137
Its impact on quality of life	66	91	25	34	2	3	0	0	0	0	7	9	137
Its impact on female menstruation	11	14	8	10	41	54	6	8	4	5	32	42	133
Its impact on female fertility	7	9	5	6	42	56	8	10	5	6	34	45	132
Its impact on male fertility	6	8	8	11	42	57	10	14	6	8	27	37	135
See also Appendix 4 for additional comments										**Total answering**			**137**

As one adult put it: "*It's non-invasive and can be self-administered at home without medical professionals. That's a milestone*."

A family member stated:
"The lack of requirement to have a surgical procedure with risk of infection is a plus. Loss of school days for visiting hospital 150 miles return in a day is of enormous benefit. At a time when hospital visits are only possible in emergency cases home treatment and administration is a definite positive to reduce risk of catching COVID 19 on journeys and in hospital. It releases clinicians to do other essential work."

100% of the 71 adults with SMA responding said they would want access to risdiplam. 97% (30) of the 31 parents of < 18-year olds with SMA responding said they would want their child to have access. We note that this includes 17 children under 18 years and one adult who are all currently receiving nusinersen treatment and live in England (see Appendix 7).

Disadvantages of the technology	
10.	**What do patients or carers think are the disadvantages of the technology?**
	Please see above tables.
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.**
	In general, both clinical trial and real-world evidence for all current drug development suggests that early treatment may be necessary to maximise the potential benefits. Though we acknowledge this, the importance of stabilisation or even the smallest benefit for people impacted by a progressive muscle wasting condition cannot be stressed enough. In 2019, **96.7% of 1,327 validated responses to SMA Europe's SMA Community survey** stated they would "*consider it to be progress if there was a drug to stabilize their current clinical state*." All who have 5q SMA should have the opportunity to have NHS funded access to this treatment with a decision to go ahead or not based on a grounded and realistic discussion with their clinician about the potential benefits and any risks to them individually.
Equality	
12	**Are there any potential <u>equality issues</u> that should be taken into account when considering this condition and the technology?**
	The clinical classifications and 'Typing' of SMA was introduced in 1990 by a committee of clinicians and geneticists to promote collaborative studies between different centres and to identify the genes of SMA. Their classification was based primarily on the age of onset and the age of death, with the ability to sit unaided and stand and walk unaided added on. The classifications were never meant as a way to make decisions about who should / should not have access to treatment (V Dubowitz writing in 'SMA Disease Mechanisms and Therapy' edited by Summer, Paushkin & Ko, 2016).

	As one respondent put it, "*The diagnosis needs to be as dynamic as the condition…The etymology of the disease dictates that wherever people start on the continuum of sma they are on an ever-decreasing scale. As such if you start as a type 3 or type 2 eventually those people have the same end point."* To tie access to this treatment to 'Type' would be discriminatory. This includes those who are labelled as 'Type 4' who have the same genetic cause for their condition. As one person put it: "*In the past all research has been focusing on type 1 and 2 and 3. Nothing on type 4. Is type 4 not as important? Is my life over with nothing to look forward to except caregivers and an old folks' home?"* We note that: young adults may 'deny' symptom onset or have symptoms dismissed; that the road to diagnosis can be very delayed; in some countries, where the clinical classification of Type 3b and Type 4 is sometimes viewed as less distinct, drug treatment may be possible for some individuals with SMA symptom onset over the age of 19 years of age; numbers with this clinical classification are very small; life expectancy is normal and a treatment that could stabilise or improve progressive muscle weakness would greatly improve its quality. We are very concerned about the potential for geographical inequalities in accessing treatment for SMA. We know some neuromuscular centres have not been able to provide nusinersen for adults with SMA who are eligible for treatment. In addition, there have been challenges in equitably rolling out the Early Access to Medicines Scheme for risdiplam across all sites (again for adults). Many adults and children with SMA are powerchair users who, with the support of personal assistants and / or parents / carers, manage a complex and challenging disability due to their progressive muscle weakness. Travel is always a logistical challenge and though this is a treatment that is taken at home, at least initial health assessments will need to be centre based. It is therefore vital that access to treatment is offered at a centre as close as possible to where people live.
Other issues	
13	**Are there any other issues that you would like the committee to consider?**
	We recommend **access for all** but recognise that when it comes to NICE making a recommendation and NHS England and clinicians rolling out an access programme, there will need to be prioritisation. To some extent this will be impacted by what access to other treatments is possible for different groups. We suggest priority needs to be given to **those who have no other treatment option**, in particular those who are prevented from accessing nusinersen due to the Managed Access Agreement's eligibility, starting and stopping criteria and, if funded, those infants who are, for clinical reasons, unable to access onasemnogene abeparvovec. It will be vital to have:

- accurate evidence-based, user-friendly summaries about each treatment and how they compare to each other that clinicians can use to discuss options with patients and their families
- comparable clinical outcomes recorded for all treatments on the SMA REACH UK paediatric and adult databases linked with appropriate databases / ways of recording patient reported outcomes
- publication of reliable accurate evidence-based, user-friendly updates and reviews that compare the performance of new treatments

14. **Please outline what carers and patients consider to be meaningful treatment outcomes for each SMA type**

The above comments (Q.11) on the value of 'stabilisation' needs to be borne in mind when considering the following responses to our 2020 survey question as to what outcomes would be valued by respondents. For '*improvements'* the vast majority of people would substitute '*stabilisation*' as a meaningful outcome. The value, meaning and measurement for each of these outcomes should not be determined by Type, but be based on how an individual's SMA is impacting on them at the time treatment starts.

Q16. How important would improvements in different aspects of the person with 5qSMA's health and daily living be if these could be affected by a drug treatment

	Very important		Important		Neither important or not		Not important		Not at all important		Total
	%	Nos	%	15	%	Nos	%	Nos	%	Nos	
Improved motor milestones - e.g. ability to sit, stand, walk	79	105	17	22	5	7	3	4	2	2	133
Improved breathing ability	66	87	16	21	11	14	5	7	2	2	132
Improved swallowing / ability to eat	64	85	14	19	12	16	5	7	2	3	132
Improved ability to communicate	44	57	18	24	24	31	9	12	9	12	131
Improved stamina and reduced fatigue	79	108	17	23	2	3	0	0	1	2	137
Improved fine motor skills (e.g. movement of fingers)	77	103	11	15	3	4	2	3	1	1	134
Increased independence	84	115	15	20	4	5	1	1	1	1	137
Reduced reliance on caregivers and personal assistants	73	99	2	3	7	10	4	6	1	1	136
See Appendix 4 for all additional comments										**Total answering**	**137**

	These adults and parents clearly illustrate what are meaningful outcomes for so many: "…*maintain the milestone of sitting up in my wheelchair and ensure I can maintain the ability to type, use my phone, and put on my make-up. I would love it if I could one day open a packet of crisps. I thrive off independence and I would be so much less reliant on people if I could open a pen to write, open a door, or open a bottle of water. I am terrified of losing my ability to swallow and communicate."* **Adult** *"Ability to move in bed, possibly go to the toilet or make a cup of tea would be amazing."* **Adult** *"Maintaining strength for independence and mental health is vital*." **Parent** *"Walking 5 independent steps is by far not the most valuable…Improvement in back and neck strength, the ability to transfer, cut up food is of far greater importance…"* **Parent** *"Self-confidence and mental health would improve dramatically with treatment as well as my daughter's general belief of self-worth, which she has very little of currently because of her SMA condition!"* **Parent** *"She is of an age where image and independence Is key as much as stamina to keep up with peers at secondary school where workload has quadrupled!"* **Parent**

15. Key messages

In up to 5 bullet points, please summarise the key messages of your submission:

- Best supportive care does not prevent the progressive weakening of muscles.
- The importance of stabilisation and even the smallest benefit of a treatment for people impacted by a progressive muscle wasting condition cannot be stressed enough.
- **All** who have 5q SMA should have the opportunity to have NHS funded access to risdiplam treatment, with a decision to go ahead or not based on a grounded and realistic discussion with their clinician about the potential benefits and any risks to them individually.
- The value, benefit and measurement for each meaningful outcome should not be determined by 'Type' but be based on how an individual's SMA is impacting on them at the time treatment starts. The classifications by 'Type' were never meant as a way to make decisions about who should / should not have access to treatment.
- We suggest priority needs to be given to those who have no other treatment option.

Thank you for your time. Please log in to your NICE Docs account to upload your completed submission.

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Appendix 4 – Comments from Surveys

Q. How important would improvements in different aspects of their health and daily living be / have been if these could be / have been affected by a drug treatment?

Adults with SMA responses

Very important to maintain my current abilities and not deteriorate.

For myself any improvement would be fantastic. I have weak neck muscles, and while I can support my head most of the time, I really want to be able to maintain this ability. It is so important for so many everyday functions. As important, is improving or maintain my breathing and swallowing.

Breathing, swallowing and communication for the SMA patient are high functioning at the moment, as such the questions above are not applicable

All of the above are extremely important. I have severely reduced lung capacity and anything to improve that or prevent it from deteriorating would save my life. It could extend my life expectancy and no words can convey how important that is to me. It would also ensure I can maintain the milestone of sitting up in my wheelchair and ensure I can maintain the ability to type, use my phone, and put on my make-up. I would love it if I could one day open a packet of crisps. I thrive off independence and I would be so much less reliant on people if I could open a pen to write, open a door, or open a bottle of water. I am terrified of losing my ability to swallow and communicate, treatment will stop that.

Improved mental health.

Walking with aids (Crutches) is not easy and there is always a danger of falling down and breaking a leg or arm. It will be impossible to do anything myself if that happens.

General mental wellness

It’s very important to maintain as much independence as possible, both for physical & mental health. It’s one thing using an electric wheelchair because you cannot walk, it’s totally different losing the ability to use your arms. Maintaining strength for independence and mental health is vital.

The SMA has a general negative effect on life, from mental health to work, leisure time and domestic abilities

Ability to move in bed, possibly go to the toilet or make a cup of tea would be amazing

To have my independence back. I live alone. And cannot even go to the toilet alone I need caregivers to help. To be in charge of my own life.

Every single bit of improvement matters.

Maintenance of ability to self-drive electric wheelchair, which is becoming increasingly difficult

Although breathing eating and communicating are not currently a problem, it's not abilities I wish to lose.

The ability to drive again.

Parents of young people age < 18 years responses

Breathing, swallowing and communication for the SMA patient are high functioning at the moment, as such the questions above are not applicable

Walking 5 independent steps is by far not the most valuable this and should not even be in the MAA criteria. Improvement in back and neck strength, the ability to transfer, cut up food is of far greater importance for a Type 3a.

Ease for me her mum as it is hard work looking after her everyday. Quite exhausting and also limits social interactions. It is important for her to lead a normal life and be able to interact, engage and participate in activities with other children of similar age.

Self-confidence and mental health would improve dramatically with treatment as well as my daughter's general belief of self-worth, which she has very little of currently because of her SMA condition!

To be more consistent and not having 1 illness of a simple cold - lose a function she has worked so hard to gain and maintain.

Ability to be more independent and stay healthy being able to fight off infections

To have a general overall increase in health and ability to be the same as their peers

Upper body strength to write, do hobbies, self-care with personal hygiene. Especially arm strength, brush hair, teeth, lift cutlery, cups, use computer

Other responses

I think her mental state would be very much improved.

Can now roll over independently in bed at night so carer does not have to administer assistance.

the prevention of loss of upper body strength would have been a huge improvement.

Improved use of arms cannot hold anything heavier than small cup of tea and knife and fork. Cannot cut food. Cannot sit herself up. Turn over move legs in bed.

As my sister gets older, she will lose the mobility that she has, and her independence will decline.

Q. Please rate whether you consider each aspect to be an advantage / disadvantage of this treatment.

Adults with SMA responses

I think the main advantage of this treatment is that it can be taken orally, as a liquid. This is fantastic for someone like myself, who has difficulty with swallowing, and may not be suitable for other treatments that are more invasive.

The non-invasive nature of this treatment (and accessibility for those with fused spines and contractures) gives it strong advantage in all categories, especially in Covid times. There are fewer complications with oral medicine, and it is easier and safer to use.

Could be different to store when on holiday

I would prefer tablet form as I can take this independently, and preferably something that does not require refrigeration.

Refrigeration could be a problem if you frequently travel, otherwise it's not really an issue

It doesn't need to be taken at home - people often buy small portable refrigerators. The biggest disadvantage is possible side effects of the drug, not necessarily any of the points mentioned above.

Infinitely better than a lumber puncture which may not even be possible.

the biggest disadvantage would be side effects and what other activities it would limit

The strong advantages are significant.

Parents of young people age < 18 years with SMA responses

Major advantage is that it is none invasive, so not side effects from the lumbar puncture. No theatre space required.

This is a small sacrifice for a potential gain in strength

For my daughter, having Spinraza every 4 months is quite a disturbing experience, as she doesn't feel very comfortable being around people she doesn't know very well and who does put a needle on her back. Also for me ,as a mother (even that I trust the doctors and all the people who treat my daughter), is a very hard time to see her crying and scared, so yes , a drug that can be given at home, it is a very important advantage.

Others' responses

in my opinion my sister would try even the most painful procedure if there is a hope that she can be more independent. However, Risdiplam seems like very easy and effectful so I am really hoping that she can be able to get it.

In our case, the syrup will be administered via feed tube. Hugely advantageous due to spinal curve which currently entails the involvement of a radiologist as well as the neurologist for administration of Spinraza.

This 1 to 5 scale does not really work for me. There are NO strong disadvantages in the list but there are things which make no difference e.g. refrigeration.

The lack of requirement to have a surgical procedure with risk of infection is a plus. Loss of school days for visiting hospital 150 miles return in a day is of enormous benefit. At a time when hospital visits are only possible in emergency cases home treatment and administration is a definite positive to reduce risk of catching COVID 19 on journeys and in hospital. It releases clinicians to do other essential work

The risks associated with regular lumbar puncture in my opinion are too great for my sister. She has reasonable mobility in her lower body and the risk of damage to the spinal cord is too high. Therefore, taking an oral medication would be much more suitable for my sister.

Q. NICE will assess what impact this drug has on aspects of 5q SMA. Considering what is known so far about risdiplam (see clinical trials summary), what are your views on this

Adults with SMA responses

It is looking extremely encouraging in trials so far, especially improvements with motor skills, breathing and swallowing.

I need to do further research into impact on fertility.

There doesn't seem to be enough data to confirm/deny any side effects caused by the drug.

If you choose to take this medicine, then you take any risk of side effects. That's why I've answered the way I have.

I'm not sure if there is definitive proof about impact on male and female fertility, I think it is currently not advised to have children whilst on this drug but I am unaware of a significant study done that would indicate whether this was more than "safety first" rather than something that is proven to be a definite risk.

It would be useful to know the side effects from all trials, especially those with older people rather than children.

If given a real choice between Risdiplam and Spinraza - I would choose Spinraza in a heartbeat. I am going to start Risdiplam on EAMS because I am exhausted but if side effects occur, I will stop taking it. I will have to stop taking it at some point to have my own children. I feel MY personal concerns are not a reason to delay this drug - EVERY SINGLE PERSON with SMA should have the option to take Risdiplam. It has been amazing and life- saving for the many. We need every option on the table for every single person with SMA and we needed it yesterday.

Until there are results from the Jewelfish group, it is difficult to tell what impact the treatment may have on me.

Parents of young people age < 18 years with SMA responses

SMA is degenerative as such all stablisation and improvements are extremely positive.

Although the fertility issues come with cons this is something, we would discuss but as a 6-year-old we would choose quality of life as there are other means of fertility available

At this stage in my daughter's deterioration (i.e. a constant, marked and gradual weakening), even a stopping of progression without a gain in strength would be vital to her. Every day that passes she loses a daily function that is vital to independence. I.e. unable to press a lift button, unable to stay warm at school (jumpers limit movement), unable to eat outside home for fear of choking, unable to cough anymore. Unable to manage school or working day due to poor stamina. A bright, clever child about to put back in society who within a year will not be able to do that and will require society to look after her.

Q. Consider the information about risdiplam treatment as a whole, please rate how acceptable it is in your view as a treatment option for 5q SMA.

Adults with SMA responses

I feel it would be a great treatment, the ease of taking it, is a real bonus.

It's non-invasive and can be self-administered at home without medical professionals. That's a milestone.

I would like more info about the side effects; however, the pros seem to outweigh the cons.

This is an opportunity for me to finally access a treatment after a lifetime of nothing! That's 64 years, a long time! It would be 100% acceptable for me!

Not only is it acceptable, it is vital.

I accept everything, I just want to stop the progression of my illness and give me more strength

I have to say I don't believe that repeated lumbar punctures are a safe method of administering a drug over a prolonged period. Oral medicine kept at home and able to be dispensed direct to the patient via postage/courier makes much more sense in terms of cost effectiveness as well as patient safety. In addition, I believe that a measured dose every day will be more likely to provide consistent results over a long period rather than the "peaks and troughs" experienced by those taking other medication spaced out over a longer period of time

If my doctors are recommending it for me, then I would be very keen.

I believe that, for the majority of the SMA population, the advantages will far outweigh the possible risks.

Parents of young people age < 18 years with SMA responses

Would like to see comparisons of different treatments, improvement and side effects.

It is easy to administer. As it will be taken orally at home. I don't have to wake baby up early to get her ready to travel to the hospital. She will be free from lumber puncture pain.

There is no other treatment for her as she is non ambulatory type 3.

Which of the following groups do you think should have access to risdiplam?

Adults with SMA responses

Ideally, I would like this treatment to be available to all with SMA. Everyone deserves the chance or to improve their condition, enabling them to be healthier and more independent. However, as type 0, 1 and 2 are life threatening, cause individuals to be so reliant on others, and have serious disability, I feel that they should definitely have access to the treatment.

all should receive the hope of more independence!

All those with SMA should be eligible.

We should all have this treatment

At all age groups. Very specific tests should be set up to make sure the drug is providing improvements.

I think everyone should have the option to access the medication and decide if this is the right option for them.

SMA affects us all very differently. It's a devastating disease no matter what type you are. It steals your abilities & in turn steals your life. Every person with SMA should be given treatment.

Everyone should have the opportunity

And SMARD too if it will also have a positive impact.

As someone with SMA, I believe everyone has the right to access treatment where available in order to get the highest quality of life possible. My primary concern will always be the wellbeing of someone with SMA rather than the value for money of any treatment.

Treatment for all

I know several people on trials of this drug, from many different "type groups", nearly all of them have experienced minor to major improvements (major in the case of children), I do not know anyone personally from any type that would not benefit from at least having the SMA stabilised so that they can get on with their life without SMA affecting it (obviously, other things may affect it but if this can be eradicated then that would be a massive advantage to everyone).he

I believe everyone affected shod have the option to the drug if they want. I understand that different types have differing deterioration rates/abilities to do things i.e. sitting up, walking etc. However, all types see deterioration of some sort that does affect the person and their families.

Are you getting the message yet NICE? EVERYONE.

I would like to choose more than 1 type, I believe all treatment should be available to all types, no discrimination please

Anybody who is eligible should be allowed to trial

I am type 3 but everybody deserves the chance for an improvement in their lives.

Anyone of any type whose clinician believes it would benefit

Really all should be given the opportunity to make their own decision

Q. Other comments

Adults with SMA responses

Having SMA myself, it affects my everyday life and I rely on carers for everything. I am confined to a power chair and am extremely weak, with very limited mobility. I am unable to do so many things like lift my arms to brush my hair, but I am still able to brush my teeth, which is so important for me. It impacts everything from getting out of bed, using the toilet, eating, going out, and even just getting comfortable in my chair or bed. Most important is the difficulty I have with my respiratory and swallowing functions which causes most frustration and worry. I hope that potentially the treatment would provide some improvement with my physical strength and movement, or even help to maintain my current level. It would mean a lot to be able to continue to support my neck and head as this is so important for safe eating and swallowing. It is so important that my muscles maintain as much strength and stability possible to make breathing and fighting illness easier. I really want to be able to keep my independence

and carry on using my hands to drive my wheelchair, hold my toothbrush, use my phone, write and use the computer for as long as I possibly can.

I have been depending upon my family the whole of my life! all I want is to be able to live more independently with my day to day activities! I really would like to have a hope!

To have a non-invasive treatment within reach but not quite accessible is tantalising. SMA is unpredictable and can progress at any speed, at any moment. Anything to delay that progression, or maintain existing strength, will do the world of good to people's physical and mental health. It's not fun thinking you've reached middle age at 15, and society has a lot to do to make the world more inclusive and accessible, but Risdiplam will also help with the barriers like progressive breathing and swallowing challenges and motor functions. Let's not make disabled people fight for a good quality of life anymore.

My condition has deteriorated considerably over the last ten years & I cannot overemphasise the effect this has had on me. Ten years ago, I was completely independent and an active member of the community but now have to have help everyday and my activities are becoming increasingly limited. I find my situation extremely distressing and I fear the discomfort and misery that old age currently offers. I have been excluded from accessing Nusinersen despite evidence showing it could prevent any further deterioration. Risdiplam is the only hope I have of maintaining my current level of mobility.

I've been on drug 10 months now and doing very well, I'm 59 and this is the first treatment for me, I've had no illnesses, no hospital stays and no pneumonia since starting the drug so amazing for me

Tiny margins of increase or halting decrease would have a huge impact on all areas of my life.

I would hope that when NICE are making their decision about the use of this drug, they will take into not only the possible cost savings of people living more independently, also the availability and cost of careers.

As long as the drug company aren't looking to rip the NHS off, considering the information provide, it seems a no brainer to supply Risdiplam now, why is any time being wasted if no further data is going to be considered. Put very specific tests in place to make sure improvements are real and then it can be stopped if needed.

I probably won't get Spinraza due to spinal deformities and fusion so Risdiplam is my best option to alleviate my condition or at least minimise further progression.

Any treatment that will improve my mobility will be absolutely wonderful and will immensely improve the quality of my life. I am living with this condition for over 20 years and would like to see some help from medication that would improve my mobility.

I believe Risdiplam should be considered as a suitable treatment for SMA as it would open the market to different medications and allow those with the condition to make informed choices as to which treatment is suitable for them.

I've had restrictive SMA since diagnosed at the Radcliffe Hospital when I was early 40's, I am now 73. I have seen a slow decline in my condition, from walking straight legged, through stages - walking with a stick, to two sticks, to walker frame, to frame and wheelchair. I have been told (specialist at Salisbury hospital) that the years of additional leg use knowing that some muscles in my upper leg don't work have put additional strain on my knees especially my left knee which now bends backward.. It would be great to walk again instead of the wheelchair, but at my age I believe the available treatments should go to the young.....

As an older adult with SMA I feel completely forgotten about. We have no feisty parents

fighting for our every need. I'm sick of struggling, every time we lose an ability it hits so hard, and this happens on a regular basis. It hits us physically, but also mentally, and it's very frightening. To receive a treatment like Risdiplam would be an absolute miracle, to have the hope of no further progression, or the hope that we could actually improve and maintain our strength, our health & independence would be beyond anything I could even wish for. Also, to receive treatment would mean so much to our families, those that live with us, that love us, that can see daily just how much living with SMA does to us, the ones that watch us struggle & cry. I know for them just what this medicine would mean.

Treatment for all

I have type 2. I am "lucky" enough to have been to uni and am still, aged 47, in full-time employment. This treatment gives me hope that I can continue to do my job, contribute to society and pay taxes like everybody else gets the chance to do

With the potential increase of mobility and breathing functionality, I think it will significantly improve the quality of life of myself and many others that are in the same or similar situation. This could possibly remove the need of ventilators and potentially increase the chances of us gaining employment. Not only that, it could reduce the reliance on the NHS equipment which should help make it more cost effective. Additionally, with it being administered at home, and how simple it is to take, I think that it will allow many of us to have the opportunity to increase our quality of life, as I know myself and many others are unable to participate in some of the other drug trials due to spinal rods / fusions etc..

I am 53 years old; I need access to this treatment to prolong my life and to also give me more ability hopefully…

It is extremely difficult for our mental health, to know there is a treatment available, but it is out of reach. Risdiplam is a medication we could only have dreamed of when I was growing up, especially due to the non-invasive administration. I personally would prefer tablet form but am more than happy to take a liquid medication if it means I do not have to take time off work for hospital administration of a drug (like nusinersen).

I am 27, and with Risdiplam, this is really the first time in my life where treatment seems like a possibility and there is some chance to maintain my current level of strength, and quality of life (which is very high), and perhaps even to gain some strength and motor milestones. The delivery method seems such a great advantage compared to nusinersen. I am in no position to be able to offer any view of value for money for this treatment compared to the current cost of care for people with SMA but I can certainly guarantee the hope it offers with Risdiplam becoming available, and the clear benefits it could bring to my life.

I think everyone with SMA should have access to this drug. This is life changing treatment for people, even a slight improvement for someone with SMA is life changing

SMA progress has accelerated in the last two years. I cannot keep straight position, I cannot raise my arms, I have a very weak cough, I am starting to have breathing problems. I would like to stop the progress of SMA I hope for some more strength, more energy I would like to use my right hand I want to breathe by myself

I am 52 years old, I never believed in my life there would be any kind of treatment for SMA and now that there is, it is coinciding with a rapid decline in my functional ability. I would like the opportunity to, at a minimum, arrest this decline to enable me to continue to be a functional member of society rather than dependent on the state and/or charity for my ongoing well-

being. I have lost major functionality in my hands, arms and fingers, it has happened very rapidly, and it is now affecting my ability to drive my chair and operate a computer. Any opportunity to alter this, even to arrest it, would deliver a significant impact to my life and that of my wife and children. I would also hope that any potential improvements could even lead to me resuming my extremely successful professional career that has had to be interrupted due to my physical deterioration over the last 2 years.

Risdiplam would be a life changing treatment for me and others like me. I have watched myself deteriorate slowly over my life, getting weaker, struggling to eat food I love and participate in the independent and active life I enjoy. Anything that can prolong my life would be the best thing to ever happen. Making Risdiplam available to as many people with SMA as possible is the only right course of action.

In the past all research has been focusing on type 1 and 2 and 3. Nothing on type 4. Is type 4 not as important? Is my life over with nothing to look forward to except caregivers and an old folks' home?

As a 45 year old female with SMA type 2, I would benefit greatly from risdiplam as in recent years my strength, stamina, breathing etc have deteriorated and in order to allow me to continue to work in the future (I'm a self-employed Counsellor) some medication may be a great benefit.

I'm tired of filling out a million surveys explaining my view, my life, my experiences, when NICE and the SMC never listen. Why don't you educate yourself NICE? Why don't you read up on disability politics and stories already out there on the internet, in books and media? Why don't you do the hard work for once in your life? There is so much information out there- the level of ignorance on disability is unacceptable. If we were talking about any other minority - women, LGBT+, BAME, etc - there would be zero tolerance on ignorance. We're not here to provoke pity or repeat the worst parts of our lives to evoke emotions from the people in charge of deciding this over their morning coffee. Having every single treatment option available to every single person with SMA is a human right. My life is valuable and as a human being I deserve to benefit from any advances in medicine that make my life easier and more independent. Get your act together NICE.

The thought of an oral liquid treatment makes me very happy, as lumbar puncture is very frightening and I also struggle to swallow pills.

Risdiplam seems safe and effective. It's vital that all SMA patients have access to this drug ASAP as we are all deteriorating.

I'm 34 years old and at this present time I've received no help at getting any of the drugs that are available. I'm hoping that sometime in the future I will be able to have access to a drug that would provide a great improvement on my life. Nobody knows what an individual goes through with my condition. Any help at all would be very much appreciated. I read up on everything that is happening and the advantages that are being given by the new drugs on the market would provide such an improvement in people's lives.

I am slowly losing any independence I have left. I will need a full-time carer and a hoist if I continue without a treatment. This had put more reliance on my ageing mother who has her own health problems. The current rules for Spinraza don't make sense. If I never walked, I can get Spinraza yet if I was walking now, I could get it. This is unfair and I don't want this to happen to Risdiplam. Risdiplam has very good efficacy and is easy to take. It's a no brainer to use it. There isn't a lag period either like Spinraza has when you are waiting between doses. I just hope that the NHS/NICE come to the right conclusion and provide Risdiplam for all that

need it. I will lose faith with the NHS if they continue to withhold a much-needed treatment for myself and others like me.

Every opportunity to test therapies should be offered to all individuals with SMA. I was able to continue working until 60 years but on reduced 3-day week for the last 15 due solely to fatigue and difficulties with walking.

Parents of young people age < 18 years with SMA responses

I hope that we will be able to take this medicine and that it will improve our condition

To stablilise and reverse the effects of a degenerative disease like SMA is amazing. Criteria should be based on facts and clinical guidance. The 5 independent steps in 12 months criteria placed in the Spinraza approval should be removed. There are many more abilities and skills far more important to everyday life, cutting up food, back, neck strength, ability to transfer. It's been written that SMA is a spectrum and the Typing system was implemented by a team of clinicians and geneticists to allow centers to compare finding when trying to identify the genes. This is now being used to discriminate.

My 11-year-old daughter has type 2 and is getting significantly weaker especially since her spinal surgery followed by lockdown and then to have her current anti fatigue medication discontinued (salbutamol) has had a devastating heartbreak effect of her. She is weaker all over especially in her arms now. She is of an age where image and independence Is key as much as stamina to keep up with peers at secondary school where workload has quadrupled! My daughter needs treatment urgently before she declines further. My daughter is vulnerable enough and no parent should have to watch their child fade away in the way she will if she does not receive risdiplam and SOON! she's already been through so much in her 11 years of life on this earth. She deserves treatment and fast DD

My son has started access to Spinraza however the treatment is difficult to access due to spinal fusion surgery. He wants to maintain his strength, health and independence so he can lead a full and happy life. He hopes to access a treatment that is effective, safe and easier to access.

5q SMA is surely one of the most devastating conditions for anyone to endure. It governs every aspect of their life as well as their family. Any potential treatment is good, but as risdiplam has already been proven to be effective, and can be easily administered, it is essential that it is made available for all types as soon as possible. This should be funded immediately by the NHS. Considering the amount of money that seems to have magically grown on trees to fight Covid19, then there is no excuse at all for funds not being made available to ensure that everyone with 5q SMA gets risdiplam straight away. Every day without treatment is a day that someone's health declines just that little bit further and living gets just that bit harder.

Risdiplam has made such a big difference so far in so many ways - more energy, more strength, better appetite, better sitting ability, better digestion - generally much healthier in every way - so so grateful he's accessing it.

It is a must asap

Even a small change made to improve the condition would make a massive improvement to the life and well-being of the sufferer.

I believe that anything that can help my daughter have greater strength in her muscles so that she can do things like raise her hand, pick heavier objects up, greater head control, can only be a good thing. It would give her greater independence both at home and school.

I have heard great things about risdiplam and as my son has no option for Spinraza this would be perfect being able to take orally and still show improvements.

Surely this treatment if rolled out on the NHS would be cheaper option than Spinraza for all types of SMA if oral and can be administer Ed at home

It is heartbreaking to watch your loved one failing to thrive and deteriorating before your eyes with this irreversible condition. This is compounded by knowing there are drug trials she cannot access and drugs funded in other countries that if she had had access to 3 years ago would have kept her walking and prevented scoliosis and back surgery. As a carer, I used to be a nurse working in the NHS, I had to give this up to care for her. The impact on the family is also great. Overwhelmingly, the psychological impact of being unable to access a drug (you could never fund yourself), that could stop your child fading away in front of your eyes, is the most tormenting part of this situation. I am actually in disbelief that this could happen in a country with state funded health care. Risdiplam could change the course of her life forever.

As we all know, to have SMA, or to have someone you love with SMA, is hard, very hard. I had times when I've cried seeing my daughter in distress, maybe in pain, and not being able to do nothing to help her. My daughter has so far 13 Spinraza. From her 3rd injection, I have been allowed to be with her in the room while she was having it. But I never find the courage to actually look at the needle going in her spine. So, a drug as Risdiplam, that can be taken orally in the comfort of our own home, is a dream come true.

It would be a lot less intrusive & reduce hospital trips. For 1 dose of Nusinersen for my son it involves: Transport to & from gosh, A room on a ward, Anaesthetist, Radiologist, Medical nurse, After care on ward, IV fluids & painkillers, Time off school, Time off work for myself & husband, All this could be avoided giving risdiplam at home

Others' responses

This could make a huge difference to my nephew's life. If it could reduce or slow the progress of his disease it would enable him to live as independent a life as possible.

my sister has SMA, she is 7 years older than me. When I was young all I remember was her struggle with everyday activities, the most important thing in my childhood her possibility of any possible treatments. My parents tried their best. For the last few years as my parents are getting older I am helping caring for my sister - she is very nice person, and is dreaming for "even to use the toilet alone without any help". We live all together and I married and have a 4 yr old boy. She loves him to bit, and is always saying that she will not have her own kid, so he is like a son she would never has! this is really heart-breaking. she barely cry and she is very positive person, however one day my son wanted to play hide and seek so, she said she wants to play as well - he then replied very innocent, but you CAN'T walk (he knows and usually don't comment or say anything or act weird etc) - this was the saddest moment in my life - she then cried - I think was the first time for some years she cried! I think everyone deserve the hope and the chance for a better-quality life! I think NHS should invest as this will minimise other costly treatments e.g. mental or physiotherapies etc

I am the grandmother of the 7-year-old patient in question who was able to start treatment with Spinraza in December 2019. There has been a remarkable change for the better in his strength and stamina. There was a worrying problem at his 4th treatment when the

neurologist's inability to find a space due to curvature of the spine resulted in abandonment on that occasion. Another attempt with the assistance of a radiologist went very smoothly and this is now the routine practice. A tube fed drug would be beneficial in eliminating future problems; would avoiding invasive procedures greatly reducing clinical expense.

She is my granddaughter, 20 years old with a good quality of life despite her disability. However, she has been warned that her supply of motor neurons will inevitable decline as she matures.....

Family friend 9/27 my wife's sister is with SMA – I've been married for 5 years and know my sister-in-law for 6 -she is very clever lady but not able to perform her day to day tasks such as using toilet, bath, etc my wife or her parents are taking care of her - she really need some independence since the parents are getting older. I am trying to help as well, but if she can have a drug to help her situation will be a life saver!

I can honestly say that my sister is very strong person, very well educated and Knowledgeable. She was till few years ago be able to eat herself, but not anymore, she can't use the toilet, can't get dress, brush her teeth, comp her hair - she need help with everything. She has been on a wheelchair and fully depended since toddlerhood - she needs some home; she deserves some independence and she is really hoping that she can get the risdiplam! Please, Please, Please NHS approve the funding and please let the Risdiplam be available to everyone not a person with specific type or age, give a chance to everyone!

The fact we have to go through this procedure is ridiculous. The drug should be made available to all those who need it now..... no exceptions... everyone.

Risdiplam is the only option left for continuing improvement to my grandson's improvement.

Every SMA patient fears each small deterioration in their remaining function whether it be walking or upper limb movement, swallowing or fine motor movement. The gradual progression to complete dependence is heart breaking..

I have read both the Information Summary and the Trial Outcomes documents and I understand the pros and cons of Risdiplam treatments. I played a big part in my granddaughter's in life from birth, the realisation of her problems and the eventual diagnosis of SMA type 3, up to the present day. Although Risdiplam will not be a miracle cure it will give her much more independence and freedom from worry that her present store of motor neurons will gradually deplete and her present quality of life will disappear.

As a family friend of a young adult (that I've known since birth) I've seen the struggles, frustration and impact that 5q SMA causes, on the individual and family. It is my understanding, that over time this condition could remain stable but there is a possibility that mobility in the upper limbs could dramatically deteriorate. This would have a huge impact on the individual's independence and the life they currently live.

Q. Are there any groups of people who have 5q SMA you think should have priority access to risdiplam?

Adults with SMA responses

I think the less strong types should get priority

I feel that people with types 1 and 2 should have priority as their condition is life threatening, and the quicker they receive treatment, the better.

everyone should get it depending upon their needs and not age or type of SMA

Type 1 and Type 2 as these are the sub groups with greater risk of life expectancy implications with breathing, swallowing etc. That being said, Type 3 can also face these challenges as SMA progresses, so it needs to be universal eligibility.

I think newborns should be given asap

Type 1

Infants with the most acute and life-threatening conditions should get priority..

Any group that includes me because I am biased. Trying to move away from my bias but still considering my situation. I was able to work with very little, if any, specific assistance, with not much more physical ability than I have now (I currently can't work but do actually live independently, cleaner every other week to do things I can't do and have to employ people to do all DIY and gardening etc.).

Anyone who cannot access Spinraza

Perhaps people who didn’t qualify for other treatments. Anyone single with no family ties

Many people have access to SPINRAZA, there is approximately 50% of the SMA population that cannot get access to it. Surely, it’s about time that those left with nothing should get the option now to be included.

Type II who cannot access Spinraza

children

1&2

Those who have lived with it the longest…

Those with more frequent hospital stays, those with rapid deterioration and those without access to Nusinersen.

This depends on the availability of risdiplam. If shortages to begin with, then I could understand priority being granted to type 1 patients. However, I still believe everyone has the right to access treatment.

type 1 SMA should have priority. However, everyone should have access to it, there should not be discrimination because of age.

The forgotten adult group, 50+

For one, it will be a drama that he cannot walk. For the other, the drama will be that he will never raise his hand again. Still others will cry because they can't breathe on their own.

Living with SMA is hard for everyone... For me, for my friends with SMA, for their parents. I'm unable to travel, I have no one who can travel with me to hospital. Risdiplam at home will be the best solution

everyone should get it, no one should be left out.

Type 4 should be given a chance. Up till now they have been forgotten about.

Although people the drug will help most significantly should have access, I do think that all people affected should, in time, have the opportunity.

I am sure everyone feels they are a priority. I feel it's important not to forget about middle and older age groups who have had to manage this condition for many years and who would still be greatly from treatment to reduce further deterioration.

Type 1 and weak Type 2 [those struggling most with health and breathing]. But there's no need to delay others getting treatment, it's not really a hospital dependent treatment.

Those who aren't eligible for or don't have access to Spinraza

As a young adult who is clinging onto any ounce of independence I may have, it's so important to maintain this before losing it

Those that can’t access Spinraza due to medical or practical reasons, those currently not receiving treatment.

Type 2 and 3

Everyone should have access to the drug if it can be given to them.

Anyone who cannot access other treatments (e.g. lumber puncture issues)

The more severe types should have priority access

Type 1 and 2 (who are more severely affected by SMA) who have not already been able to access treatment

Type 3 who are unable to walk are unable to get treatment at the moment. Also, people who can't be injected with Spinraza.

Type 1

People who are not eligible for Spinraza or Zolgensma (with spinal fusion, scoliosis, etc)

Parents of young people age < 18 years with SMA responses

Anyone who is suffering an impact on their quality of life should receive treatment. Definitely initial focus should be given to those not accessing Spinraza on the MAA or is has lost Spinraza as a treatment on the MAA. Including Type 3a who have lost Spinraza due to not meeting the 5 steps and those who could not access treatment due to when they lost ambulation.

Should be available to all

I think there are a finite amount of type 3s left now as all new SMA diagnosis should be in a category that will get treatment. I am unsure how type 3s can be refused treatment as this seems against united nations human rights. To leave children / adults to fade away while there's something that could at the least arrest progression seems unbelievable in a developed country. Type 3s are not lucky to have been born stronger than other types, they are unlucky to have been born weaker than the general population. They should not be side lined because their lives are not immediately under threat. They deserve equal treatment after inheriting this debilitating condition.

Those not currently receiving any other treatment

I think everyone should get it if they want it, it isn't like there are many people with SMA out there anyway! But if you have to do it in groups, then always type 0 and 1 first, then type 2 and 3, based on severity, I think!

Those who lose Spinraza after 1 year as they did not reach the 5 independent steps milestone within 12 months as per MAA Those who did not qualify for Spinraza.

Babies. Infants. Toddlers. Because of the ease of dosage.

Every living person with spinal muscular atrophy should have priority to improve their quality of life! You can’t put a price on that!!

Those who cannot gain or maintain access to Spinraza

Everybody

those that have more severe forms of SMA

People with SMA who have been excluded from Spinraza

SMA 3 AS MISSED OUT ON OTHER DRUGS AVAILABLE

Children/adults who have not been offered any other therapy or trial

I think that everyone with SMA, if they want, they should be allowed to have access to risdiplam.

Others’ responses

Type 1 to 4

I think everyone should have the same option - it should not be age determined - if it is a young person - has a whole life ahead to be more independent. If it is an older person – they had struggle long time, surely, they deserve to see and enjoy a future more independently

Those that are not currently receiving any other treatment

Yes. Types 1, 2 and 3 without restriction to be closely followed by Type 4.

Those in whom trial data shows any benefit. Every SMA patient fears each small deterioration in their remaining function whether it be walking or upper limb movement, swallowing or fine motor movement. The gradual progression to complete dependence is upsetting.

The group who have been refused Spinraza after being told they could have it in August 19

Groups of teenagers/ young adults with type 3 or 4 should have priority access as they are approaching an age where their mobility is potentially going to decline. If it's possible to maintain the mobility they currently have in their lower limbs in particular that should be taken advantage of.

Each case should be treated individually

Risdiplam Information Summary - September 2020

1. How does risdiplam work?

Risdiplam is a small molecule drug that specifically modulates how effectively the *survival motor neuron 2* (*SMN2*) gene is used to make SMN protein. Signals (called messenger RNAs) are generated from *SMN2,* and risdiplam selectively interacts with these, resulting in more SMN protein being made by cells throughout body. **Read more**.

2. How is risdiplam administered / taken?

Risdiplam is given daily in liquid form. It is taken at the prescribed dose, at approximately the same time each day. This is by mouth or feeding tube, using the syringe provided.

3. Where does risdiplam get to in the body?

Risdiplam distributes throughout the body to many different types of cell, tissue and organ, including the brain, spinal cord, muscles and blood.

4. Where do you have to be to take risdiplam and where is it stored between doses?

Risdiplam is imported as a powder, which has to be reconstituted with purified water by a pharmacy, usually within the hospital. The first treatment will normally be at the treating centre. Subsequent doses may then be taken at home, if this is a local possibility and agreed by the treating clinician.

Risdiplam must be kept between 2°C and 8°C, so can be stored in a regular, domestic fridge.

5. When did human clinical trials of risdiplam begin?

The first in-human trials of risdiplam, which were conducted in healthy volunteers (*i.e*. a Phase 1 clinical trial), were initiated in late 2015, with the first volunteers enrolled in early 2016 (clinicaltrials.gov trial identifier: NCT02633709). SMA patients were first enrolled in clinical trials of risdiplam in late 2016: the FIREFISH trial involving infants with Type 1 SMA and the SUNFISH trial involving participants with SMA Type 2 and 3 (see below). JEWELFISH and RAINBOWFISH trials followed later.

6. What clinical trials with SMA patients have been initiated/conducted so far?

Trial Name	Identifier	Type of SMA	Age of participants	Participants enrolled
FIREFISH	NCT02913482	Type 1	1 - 7 months	62
SUNFISH	NCT02908685	Types 2 and 3	2 - 25 years	231
JEWELFISH	NCT03032172	Type 1, 2 and 3, previously receiving SMA therapeutic	6 months - 60 years	174
RAINBOWFISH	NCT03779334	Genetically diagnosed with 5q SMA, but pre-symptomatic	Up to 6 weeks	25

7. What are the major results to date from the four key clinical trials of risdiplam?

Please also see the summary table

Treatment with risdiplam was associated with an increase in SMN protein that was maintained over at least a 12-month treatment period in FIREFISH, SUNFISH and JEWELFISH trials. Data is not yet available for RAINBOWFISH.

(You can find information about some physiotherapy-based measures used to monitor outcomes here

FIREFISH

➢ **Patients enrolled via Part 1 of the trial**

Patients involved in Part 1 continued to receive treatment at the dose selected from the 12-week dose-finding study.

Outcomes for infants with SMA Type 1 following 12 months of risdiplam treatment were:

- 7 out of 17 (41%) able to sit without support for at least five seconds, compared to 0% of untreated infants (natural history data).
- 11 (65%) able to sit (with or without support),
- 9 (53%) achieved upright head control (assessed by HINE-2)
- 1 (6%) achieved the milestone of standing (supporting own weight).

- 10 out of 17 (59%) achieved a CHOP-INTEND total score of 40 points or more.
    - Median change from baseline to month 12 in CHOP-INTEND was 17.5 points.
    - The maximum CHOP-INTEND score was 57 points after 12 months treatment, increasing from a maximum of 49 points after 8 months.
    - After 16 months of treatment, 82% (14/17) of high-dose patients had a CHOP-INTEND score ≥40.

- After 16 months of treatment, no infant required tracheostomy or reached permanent ventilation

- 86% (18/21) of all infants were event-free after receiving risdiplam for 16 months. An event is defined as the time when ventilation support for breathing is required for at least 16 hours a day for 14 consecutive days, or sadly when a patient dies.

➢ **Patients enrolled via Part 2 of the trial**

Outcomes for infants with SMA Type 1 receiving 12 months of risdiplam treatment:

- 29% of infants (12/41; $p<0.0001$) able to sit without support for at least five seconds, compared to 0% of untreated infants (natural history data).
- 18 (43.9%) able to hold their head upright.
- 13 (31.7%) able to roll to the side.
- 2 (4.9%) able to stand with support (measured with HINE-2).

- 90% (37/41) had a CHOP-INTEND score increase of at least 4 points.
- 56% (23/41) achieved a score above 40; the median increase was 20 points.

- 85% (35/41) were event-free

SUNFISH

Outcomes for those with SMA Type 2 or 3 aged 2 – 25 years

➢ **Patients enrolled via Part 1 of the trial**

Patients involved in Part 1 continued to receive treatment at the dose selected from the 12-week dose-finding study.

- risdiplam significantly improved motor function after 24 months of risdiplam treatment:
  - MFM-32 (Motor function measure which assesses 32 items) total change from baseline was greater in patients receiving risdiplam - 3.99 point difference (95% CI: 2.34, 5.65) $p< 0.0001$) compared with natural history data.

➢ **Patients enrolled via Part 2 of the trial**

- risdiplam significantly improved motor function after 12 months of treatment:
  - MFM-32 total change from baseline was greater in patients receiving risdiplam, compared to placebo (1.55 point mean difference; $p=0.0156$).
  - the RULM (Revised Upper Limb Module which assesses the functioning of the arm) also showed an improvement (1.59 point difference; $p=0.0028$).

JEWELFISH

➢ Key efficacy findings not yet reported: the first patients were enrolled in March 2017.

RAINBOWFISH

➢ Key results not yet reported: the first patients were enrolled in August 2019.

8. What is the safety profile of risdiplam?

To date, there have been no drug-related safety findings leading to withdrawal of patients from FIREFISH, SUNFISH or JEWELFISH. There are no data available for RAINBOWFISH.

All trials and testing to date indicate that risdiplam has a tolerable safety profile.

9. What adverse events were reported from the clinical trials?

Overall, reported adverse events were designated as "not risdiplam-related", because they are issues commonly observed in untreated SMA patients. Detailed reports were as follows:

FIREFISH

➢ **Patients enrolled via Part 1 of the trial**

- Most common adverse events were fever (pyrexia; 52%), upper respiratory tract infections (43%), diarrhoea (29%), vomiting (24%), cough (24%) pneumonia (19%) and constipation (19%).
- Most common serious adverse event was pneumonia (10/21).
- Three infants experienced fatal complications of their disease after approximately 1, 8, and 13 months of treatment.

➢ **Patients enrolled via Part 2 of the trial**

- Most common adverse events were upper respiratory tract infection (46%), pneumonia (39%), pyrexia (39%), constipation (20%) nasopharyngitis (12%), rhinitis (12%) and diarrhoea (10%).
- Most common serious adverse events were pneumonia (32%), bronchiolitis (5%), respiratory failure (5%) and hypotonia (5%).
- At 12 months, 93% (38/41) of infants were alive.

SUNFISH

➢ **Patients enrolled via Part 1 of the trial**

- Most common adverse events fever (pyrexia; 55%), cough (35%), vomiting (33%), upper respiratory tract infections (31%), cold (nasopharyngitis; 24%) and sore throat (oropharyngeal pain; 22%).
- Most common serious adverse event was pneumonia (3/51).

➢ **Patients enrolled via Part 1 of the trial**

- Most common adverse events were upper respiratory tract infection (32%), nasopharyngitis (26%), pyrexia (21%), headache (20%), diarrhoea (17%), vomiting (14%) and cough (14%).
- While the rate of lower respiratory tract infections overall was similar between risdiplam (19%) and placebo (20%), serious lower respiratory tract infections occurred in more patients in the risdiplam group (10% versus placebo 2%).

JEWELFISH

- Most common adverse events were upper respiratory tract infections (13%), headache (12%), fever (8%), diarrhoea (8%), nasopharyngitis (7%) and nausea (7%).
- No serious adverse events or risdiplam-related eye complications have been reported thus far.

Across clinical studies

➢ **Impact of risdiplam on menstruation**

Across clinical studies, approximately 20% of patients (90 in total) were of child-bearing potential. Adverse events related to the menstrual cycle were reported in some patients:

- Menstrual pain and cramps (dysmenorrhea) reported by 35/90
- Irregular menstrual bleeding (metrorrhagia) reported by 3/90
- Menstrual disorder reported by 1/90
- Absent menstruation (amenorrhea) reported by 1/90

Roche report that trial investigators stated that there was no indication that these events were related to any risdiplam-related safety issues on the menstrual cycle.

➢ **Pregnancy, contraception, breast-feeding and male fertility**

In risdiplam trials, no female participants were pregnant and no participants – male or female – were trying to conceive; it is ethically unacceptable for any clinical trials of new treatments to include participants from these groups.

The following information is part of the **patient information** for anyone receiving risdiplam treatment via the Early Access to Medicines Scheme (EAMS) in the UK as a pre-licensed treatment approved by the Medicines and Health Regulatory Products Agency (MHRA). It was published by the MHRA on 17th September 2020 following their assessment of all the trial evidence about risdiplam and preceding related studies.

➢ **Pregnancy**

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. This is because taking this medicine while you are pregnant could harm your unborn baby.
- Before you start treatment with risdiplam, your doctor should do a pregnancy test. This is because risdiplam may harm your unborn baby. Your doctor will consider the benefit of you taking risdiplam against the risk to your baby.
- If you do become pregnant during your treatment with risdiplam, tell your doctor straight away. You and your doctor will decide what is best for you and your unborn baby.

➢ **Contraception**

For women
Do not become pregnant:
- during your treatment with risdiplam and
- for at least one month after you stop taking risdiplam.

Talk to your doctor about highly effective methods of birth control that you and your partner should use during treatment and for one month after you stop treatment.

For men

If your female partner is of childbearing potential, you both need to avoid pregnancy. Remain abstinent or use condoms plus an additional contraceptive method that results in highly effective contraception during your treatment with risdiplam and continue to use them for at least 4 months after treatment has finished. You should not donate sperm for the same period.

Please be aware that no method of contraception is 100% effective.

- **Breast-feeding**

Do not breast-feed while taking this medicine. This is because risdiplam may pass into breast milk and may therefore harm your baby.

Discuss with your doctor if you should stop breast-feeding or if you should stop taking risdiplam.

- **Male fertility**

Risdiplam may affect male fertility. For your family planning, ask your doctor for advice.

Do not donate sperm during your treatment and for 4 months after your last dose of risdiplam.

We have sent a request to Roche for more information about the studies that led to these conclusions and will publish their reply here as soon as it is available.

25th September 2020

Risdiplam Trial outcomes / what is known so far in relation to the questions NICE will explore about the treatment

	FIREFISH	SUNFISH	JEWELFISH	RAINBOWFISH
Identifier	NCT02913482[1]	NCT02908685[2]	NCT03032172[3]	NCT03779334[4]
Phase and trial type	2/3, open-label, multi-centre study[1]	2/3, randomised, double-blind, placebo-controlled, multi-centre study[2]	2, exploratory, single-arm, open-label, multi-centre study[3]	2, single-arm, open-label, multi-centre study[4]
Main aims	Investigate safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy[1]	Investigate safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy[2]	Investigate safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy[3]	Investigate safety, pharmacokinetics, pharmacodynamics and efficacy[4]
Parts and timing	**Part 1**: exploratory dose-finding part for 12 weeks[1] **Part 2**: confirmatory part to investigate Risdiplam for 24-months at the dose selected in Part 1[1]	**Part 1**: exploratory dose-finding part for 12 weeks[2] **Part 2**: confirmatory part to investigate Risdiplam for 24-months at the dose selected in Part 1[2]	Parts not applicable. Participants will receive doses of risdiplam orally once daily for 24 months[3]	Parts not applicable. Participants will receive doses of risdiplam orally once daily for 24 months[4]
Type of SMA	Type 1[1]	Types 2 and 3[2]	Types 1, 2 and 3, who have previously having received SMA therapeutic[3] [d]	Genetically diagnosed with 5q SMA, but pre-symptomatic[4]
Age of participants	1 - 7 months[1]	2 - 25 years[2]	6 months - 60 years[3]	Up to six weeks[4]
Participants enrolled	62[1]: 21 (Part 1) and 41 (Part 2)[5]	231[2]: 51 (Part 1) and 180 (Part 2)[6]	174[3]	25[4]
Study start date[a]	December 24, 2016[1]	October 20, 2016[2]	March 3, 2017[3]	August 8, 2019[4]
Primary completion Date[b]	November 14, 2019[1]	September 6, 2019[2]	*(January 31, 2022)*[3]	*(June 21, 2021)*[4]
***(Estimated)* Study completion date**[c]	*(November 17, 2023)*[1]	*(September 2, 2023)*[2]	*(January 31, 2025)*[3]	*(March 4, 2026)*[4]
Safety	**Parts 1 & 2**: No treatment-related safety findings leading to withdrawal[5, 7]	**Parts 1 & 2**: No treatment-related safety findings leading to withdrawal[6-8]	No treatment-related safety findings leading to withdrawal[6]	Not yet reported
Adverse events	**Part 1**: most common were fever (pyrexia; 52%), upper respiratory tract infections (43%), diarrhoea (29%), vomiting (24%), cough (24%)	**Part 1**: most common were fever (pyrexia; 55%), cough (35%), vomiting (33%), upper respiratory tract infections (31%), cold (nasopharyngitis;	Most common were upper respiratory tract infections (13%), headache (12%), fever (8%), diarrhoea (8%),	Not yet reported

	pneumonia (19%) and constipation (19%)[7] **Part 2**: most common were upper respiratory tract infection (46%), pneumonia (39%), pyrexia (39%), constipation (20%) nasopharyngitis (12%), rhinitis (12%) and diarrhoea (10%)[5]	24%) and sore throat (oropharyngeal pain; 22%)[6] **Part 2**: most common were upper respiratory tract infection (32%), nasopharyngitis (26%), pyrexia (21%), headache (20%), diarrhoea (17%), vomiting (14%) and cough (14%)[8]	nasopharyngitis (7%) and nausea (7%)[6]	
Serious adverse events	**Part 1**: most common was pneumonia (10/21)[9] **Part 2**: most common were pneumonia (32%), bronchiolitis (5%), respiratory failure (5%) and hypotonia (5%)[5]	**Part 1**: most common was pneumonia (3/51)[6] **Part 2**: While the rate of lower respiratory tract infections overall was similar between risdiplam (19%) and placebo (20%), serious lower respiratory tract infections occurred in more patients in the risdiplam group (10% versus placebo 2%)[8]	No serious adverse events or risdiplam-related eye complications have been reported so far[10]	Not yet reported
Outcomes:				
Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking)	**Part 1:** after 12 months of treatment, among the infants who received the dose selected for the confirmatory Part 2 of the study (n=17), 7 (41%) were able to sit without support for at least five seconds (assessed by BSID-III[e]). 11 (65%) infants were able to sit (with or without support), 9 (53%) achieved upright head control (assessed by HINE-2[f]), and 1 infant (6%) achieved the	**Part 1:** treatment significantly improved motor function after 24 months; MFM-32[h] total change from baseline was greater in patients receiving risdiplam (3.99 point difference (95% CI: 2.34, 5.65) $p < 0.0001$) compared with natural history data[6] **Part 2:** treatment significantly improved motor function after 12 months; MFM-32[h] total change from baseline was	Not yet reported	Not yet reported

	milestone of standing (supports weight). 10 out of 17 infants (59%) in the therapeutically dosed group achieved a CHOP-INTEND[g] total score of 40 points or more. Median change from baseline to month 12 in CHOP-INTEND[g] was 17.5 points. The maximum CHOP-INTEND[g] score was 57 points after 12 months treatment, increasing from a maximum of 49 points after 8 months[7] After 16 months of treatment, 82% (14/17) of high-dose patients had a CHOP-INTEND[g] score ≥40[11] **Part 2:** at 12 months, 29% of infants (12/41; *p*<0.0001) sat without support for five seconds (assessed by BSID-III[e]), compared with natural history data indicating no untreated patients achieve this milestone. 18 (43.9%) infants were able to hold their head upright, 13 (31.7%) were able to roll to the side and 2 (4.9%) were able to stand with support (measured with HINE-2[f]). 90% (37/41) had a CHOP-INTEND[g] score increase of at least 4 points, with 56% (23/41) achieving a	greater in patients receiving risdiplam, compared to placebo (1.55 point mean difference; *p*=0.0156). The RULM[i] also showed an improvement (1.59 point difference; *p*=0.0028). The strongest responses in MFM-32[h] versus placebo were observed in the youngest age group (2-5 years) (78% vs 53% achieving ≥3 point increase). Disease stabilisation was observed in the 18-25 years age group (57% vs 38%, with stabilisation defined as a ≥0 point increase)[8]		

	score above 40; the median increase was 20 points[5]			
Bulbar function (including, for example, swallowing and ability to communicate)	**Part 1:** no infant lost the ability to swallow during the study[9] **Part 2:** 95% of infants who were alive at 12 months (36/38) maintained the ability to swallow and 89% (34/38) were able to feed orally[5]	Not identified	Not yet reported	Not yet reported
Respiratory function	**Part 1:** after 16 months of treatment, no infant has required tracheostomy or reached permanent ventilation[7, 11]	Not identified	Not yet reported	Not yet reported
Need for non-invasive or invasive ventilation	**Part 1:** 86% (18/21) of all infants were event-free after receiving risdiplam for 16 months[11] **Part 2:** at 12 months, 85% (35/41) were event-free[5]	Not identified	Not yet reported	Not yet reported
Mortality	**Part 1:** Three infants experienced fatal complications of their disease after ≈1, 8, and 13 months of treatment[7] **Part 2:** at 12 months, 93% (38/41) of infants were alive[5]	Not identified	Not yet reported	Not yet reported
Female menstruation	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]
Female fertility and pregnancy	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]
Male fertility	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]
Other	**Part 1:** median two-fold increase in blood SMN protein levels after four weeks, which was sustained at 12[9]	Part 1: median two-fold increase in blood SMN protein levels after four weeks, which was sustained at 12[11]	Median two-fold increase in blood SMN protein levels after four weeks, which was sustained at 12 months and 24 months (18 patients)[6]	

References

[1] https://clinicaltrials.gov/ct2/show/NCT02913482 (last accessed September 23, 2020)
[2] https://clinicaltrials.gov/ct2/show/NCT02908685 (last accessed September 23,2020)
[3] https://clinicaltrials.gov/ct2/show/NCT03032172 (last accessed September 23,2020)
[4] https://clinicaltrials.gov/ct2/show/NCT03779334 (last accessed September 23, 2020)
[5] Roche Press Release, April 28, 2020: https://www.roche.com/media/releases/med-cor-2020-04-28.htm (last accessed September 23, 2020)
[6] Roche Press Release, June 12, 2020: https://www.roche.com/media/releases/med-cor-2020-06-12.htm (last accessed September 23, 2020)
[7] Roche press release, May 7, 2019: https://www.roche.com/media/releases/med-cor-2019-05-07.htm (last accessed September 23, 2020)
[8] Roche press release, February 6, 2020: https://www.roche.com/investors/updates/inv-update-2020-02-06.htm (last accessed September 23, 2020)
[9] Baranello, G *et al.* Survival, ventilation and swallowing ability in infants with Type 1 SMA receiving risdiplam (RG7916) (1-year results). Presented at the CureSMA Congress, 28 June-1 July 2019, Anaheim, California.
[10] Chiriboga CA, *et al.* JEWELFISH: Risdiplam (RG7916) increased survival of motor neuron (SMN) protein levels in non-naïve patients with spinal muscular atrophy (SMA). Presented at the CureSMA Congress, 28 June-1 July 2019, Anaheim, California.
[11] Cision PR Newswire article, October 2, 2019: https://www.prnewswire.com/news-releases/risdiplam-spinal-muscular-atrophy-data-demonstrating-continued-benefit-presented-at-world-muscle-society-congress-300929363.html (last accessed September 23, 2020)

Footnotes

[a] **Study Start Date**: The actual date on which the first participant was enrolled in a clinical study.[1-4]
[b] **Primary Completion Date**: The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure.[1-4]
[c] ***(Estimated)*** **Study Completion Date**: The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events (that is, the last participant's last visit).[1-4]
[d] Patients previously enrolled in Study BP29420 ("Moonfish") with the splicing modifier RO6885247 or previously treated with nusinersen, olesoxime or onasemnogene abeparvovec[4]. Of the 174 patients enrolled, 76 were previously treated with nusinersen and 14 with onasemnogene abeparvovec. The remaining 83 patients had been treated with compounds then being developed by Roche.[6]
[e] **BSID-III**: Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (uses a series of play tasks to assess the development of babies/infants aged 1–42 months).
[f] **HINE-2**: Hammersmith Infant Neurological Examination Module 2 (a scale used to assess an infant's ability to move their head, kick, roll on their side, walk, crawl, sit up and grasp objects).
[g] **CHOP-INTEND**: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (a scale used for infants with Type 1 SMA)
[h] **MFM-32**: Motor Function Measure-32 (a scale designed to detect motor function changes in a broad range of SMA patients, from weak Type 2 to strong Type 3)
[i] **RULM**: Revised Upper Limb Module (a scale developed to assess arm movement and coordination in individuals with SMA).
[j] Roche letter to SMA UK about fertility and menstruation: https://smauk.org.uk/blog/treatments-research/effect-of-risdiplam-on-female-fertility-and-menstruation
[k] **See: Risdiplam Information Summary - September 2020 Page 5 'Across All Clinical Studies'**

25th September 2020

Appendix 5 Those currently receiving nusinersen treatment in England

18 of those replying who are currently receiving nusinersen treatment live in England. Two replies are form parents who can be identified as referring to the same child, so best est. is that 17 of the children / adults with SMA in England who replied to the survey are currently receiving nusinersen. All of them responded that they would want risdiplam treatment.

Clinical classification	
Type 1	4
Type 2	10
Type 3	3

Age in years	
0 - 4	5
5 - 11	9
12 -17	2
35 - 44	2

Comments

A port will be left for lumbar puncture but no guarantee how effective this will be.

In our case, the syrup will be administered via feed tube. Hugely advantageous due to spinal curve which currently entails the involvement of a radiologist as well as the neurologist for administration of Spinraza.

For my daughter, having Spiranza every 4 months is quite a disturbing experience, as she doesn't feel very comfortable being around people she doesn't know very well and who does put a needle on her back. Also for me ,as a mother (even that I trust the doctors and all the people who treat my daughter), is a very hard time to see her crying and scared, so yes , a drug that can be given at home, it is a very important advantage. The last two lumbar punctures have been very difficult……As we all know, to have SMA, or to have someone you love with SMA, is hard, very hard. I had times when I've cried seeing my daughter in distress, maybe in pain, and not being able to do nothing to help her. My daughter has so far 13 Spiranza. From her 3rd injection, have been allowed to be with her in the room while she was having it. But I never find the courage to actually look at the needle going in her spine. So, a drug as Risdiplam, that can be taken orally in the comfort of our own home, is a dream come true.

I am the grandmother of the 7 year old patient in question who was able to start treatment with Spinraza in December 2019. There has been a remarkable change for the better in his strength and stamina. There was a worrying problem at his 4th treatment when the neurologist's inability to find a space due to curvature of the spine resulted in abandonment on that occasion. Another attempt with the assistance of a radiologist went very smoothly and this is now the routine practice. A tube fed drug would be beneficial in eliminating

My son has started access to Spinraza however the treatment is difficult to access due to spinal fusion surgery. He wants to maintain his strength, health and independence so he can lead a full and happy life. He hopes to access a treatment that is effective, safe and easier to access.

It would be a lot less intrusive & reduce hospital trips. For 1 dose of Nusinersen for my son it involves • Transport to & from gosh • A room on a ward • Anaesthetist • Radiologist • Medical

nurse • After care on ward • IV fluids & painkillers • Time off school • Time off work for myself & husband All this could be avoided giving risdiplam at home

NICE National Institute for Health and Care Excellence

Patient organisation submission

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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. [Please note that declarations of interests relevant to this topic are compulsory].

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?	Is a charity dedicated to advocating for treatment of all with SMA as well as supporting the community and its well-being. Formally we have 6 trustees and no official members, but a community of 1500 people either with or affected by SMA.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No.

4c. 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?	All trustees are directly affected by condition: [redacted], [redacted] – have children with SMA Type 1 (both currently receiving Spinraza) [redacted] – Has child with SMA Type 2 (currently on Risdiplam) [redacted] and [redacted] – both adults with SMA Type 2 (no treatment) [redacted] – Had child with SMA Type 1 Non-trusties also have children with SMA type 3 and adults with SMA type 3 (no treatment) We have carried out extensive surveys within the SMA community inside the UK and globally (from those people who are receiving Risdiplam) to collect real world evidence (RWE). The three most important surveys are included in the appendices of this submission. The questions used are those which are important to patients rather than clinical assessments, thus giving patients a chance to voice what is important to them. We would strongly recommend that the panel reads through the survey results as well as our summary below.
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?	1. **What is it like to live with the condition:** From the observation of SMA families and personal experience: living with SMA is complex and challenging in many ways . Everyday tasks we take for granted are either difficult or impossible for those with SMA. From toileting to eating, to brushing teeth, to turning in bed, the ability to cope with respiratory infections, to being “independent” – these tasks are extremely

hard. It is the physical manifestation of the condition that causes the greatest harm both physically and mentally. Every task takes longer and exhausts stamina very fast.

NATURAL HISTORY for adults:

Whilst there is extensive knowledge of natural history of SMA in paediatric population, there are no systematic studies of natural history in adults with SMA Type 2 and 3 as consensus has always been that there is no need. It has been always assumed that adults remain in a steady state once they stop growing, with minor declines. This assumption is not validated. To the best of our knowledge, there is no validated study of natural history in SMA Adult patients and therefore there is no suitable base line. In the short time available to us and with limited resource we undertook such a study using accepted EK scale (developed for SMA and Duchene) and requested patients to evaluate themselves accordingly at intervals: today, year ago, 5 years ago and 10 years ago (we did ask that if the patient could not remember that far back, the should not answer. Many people however tend to remember when one day the lost ability to do something… so the **39** replies we analysed were robust). The score of 0 on EK scale represents the best functional ability and the maximum score of 51 presents the worst case.

We have split population into types (2 and 3) and each type was split into two age groups (18-45 years old and 45+ years old). Table 1 and 2 summarise the average results.

Type	Today	1 Year	5 Year	10 Year
Type 2 average score	24.5	23.8	19.3	14.4
Type 3 average socre	16.2	14	10.1	7.1

Table 1: Showing Average scores for people with SMA Type 2 and 3 in the 18-45 age bracket

Type	Today	1 Year	5 Year	10 Year
Type 2 average score	31.0	30.7	32.3	23.7
Type 3 average score	21.5	18.5	11.5	6.8

Table 2 Showing Average scores for people with SMA Type 2 and 3 in the 45+ age bracket

In both cases there is a **clear continuing decline**. Type 2 adults particularly showing functional loss of 50% over period of their life and on average. Interestingly to see that the progression between that age groups is consistent, and the older person becomes the more pronounced the loss is. Whilst not a validated study, this must be treated as real world evidence. Complete breakdown of data is submitted as appendix and available for review and analysis.

ADDITIONAL SURVEYS to gain general insight into life with SMA.

TreatSMA has reviewed responses from **141** people living with SMA Type 1 (14 responses), 2 (81 responses) and 3 (46 responses) from various age groups and backgrounds to offer meaningful insight into life with SMA, asking people to review their state of health and how it affects them physically, socially and mentally/emotionally. The conclusion is that SMA affects all aspects of health, but the most significant concerns are respiratory, swallowing functions, scoliosis, hip displacement, subluxation of shoulders, chronic pain , contractures and depression. Many people questioned said that their health has deteriorated over the last 12 months.

During our survey we have noted that swallowing, breathing and arm-strength were the most common abilities people feared losing. Some people admitted that they worried a lot about loss of ambulation, however after they lose ambulation they realised that arm strength, swallow and respiratory was by far the most important. This is a very important point, as during the appraisal we tend to focus a lot on loss of ambulation, but many other abilities are by far more important to people with SMA.

The impact of loss of swallow and respiratory functions (breathing and coughing) is mainly self explanatory as we all can relate to the fear of being unable to eat and breath. The loss of

	independent sitting and arm strength is not as obvious to people who are not directly affected by the condition on an everyday basis. These functions allow for easier and more independent lives – work, social interactions, ability to do self transfers (going to the toilet without other peoples help for example or getting from wheelchair into bed etc…) Many people we talked to are afraid that if they lose arm strength their career will be over. Children would not be able to participate in school activities (unable to write, type, draw, play with the sand). "*I have very weak cough, I'm suffering more and more. I am unable to use my hands, I waste a lot of energy to keep straight position(back muscles too weak)*"- quote from SMA patient. Patients with SMA continue live in fear that further abilities will be lost. The knowledge that they can wake up one day and lose something else damages their mental health. Children and adults are affected equally. A 13 years old Type 3 patient lost ambulation and had to undergo spinal surgery to correct scoliosis – after 6 months of recovery from surgery she lost ability to self-transfer and now is depressed to the point where her mother simply at "wits end" for her child. Adults tend to hide their emotions better, but the fact is that suicides are not that uncommon within SMA community. "*Living with a progressive condition like SMA means that fear of losing physical function is never far from your mind. I feel very anxious when I think about losing the use of my hands and arms as that would take away most of my remaining independence, my ability to work and engage in many essential daily activities*." – Quote from SMA patient. "*I have severe depression. It was the decision that triggered it due to losing 40 years of built up hope that one day there would be a treatment and that i may not completely lose my independence. Now i have, i have been unable to accept or cope with the new me. I am fearful of what's coming next. Its also been very hard to cope with seeing others with lesser ability than I, now thriving with more ability than I have now and that they now have a choice of 2 treatments where i have none*." – Extract from survey For more examples on how life without treatment looks for patients please read through the attached appendixes and these clearly show the complexity (including medical complexity) of SMA. **2. What do carers experience:**

	Let us clarify something here. SMA does not affect only the person who physically shows symptoms. The whole family is affected. Not just husbands, wives,parents and siblings. Extended family, grandparents, Uncles and aunties, cousins all are affected both physically and emotionally. Often Parents, spouses and grandparents are affected the most physically because the majority of care falls on their shoulders and impacts their physical health! The studies done and published in the literature do not reflect the reality and true cost of SMA. This has been clearly demonstrated during the appraisal of Nusinursen by NICE in 2019. There are several aspects that must be taken into account here, however this could be divided into mental and physical. The emotional journey through this is something that is very unique to the family. However, I do not know a single family who has said that SMA has enriched their lives. I do know a few who committed suicide because of SMA and because being a carer of someone with SMA places such a huge burden on them personally. You make numerous sacrifices which many people do not understand. For example, during the colder months staying away from public places to reduce chances of getting a respiratory infection – this leads to isolation and loneliness of both carers and individual . On-going worry about what to do next, how to get the next best equipment, how to make sure that the patient has a safe way to go to school, how to make sure that the person can attend work safely – something that constantly drives the carer/s crazy. As a carer we think how we can set up a life for the child for the years AFTER we are dead. For many people it is too much and they give up. Families, which otherwise would have been happy, fall apart and eventually isolation instigate suicides and in some cases physical abuse of each other and of children. Physical experience is highly relevant to this appraisal in particular. On-going exhaustion leads to increased health problems for the carers. Lifting children causes back problems. Lack of suitable sleep has been linked to the development of Alzheimer's disease later in life. Muscle strain injuries are also not uncommon for carers. All of this adds up to a large total bill for the NHS. "*My husbands work is affected as he is my primary carer. He has had to turn down jobs involving travel. He is suffering back and neck injury due to lifting me and needs to do more housekeeping that I can no longer do. He is a diabetic himself who is bitter over the financial and physical pressures i have put on him. …My depression also directly affect my husband and my daughters mood. So much so, we are on the cusp of divorce. My daughter (15) also has mental health issues*

and has to pick up some of the caring duties as well as general housekeeping that i can no longer do. This has had a knock on effect on her school work. Due to access I can no longer see my elderly parents who themselves are housebound."

"The pressure placed on the spouse of someone with SMA is immense. As the condition progresses the spouse becomes more like a professional carer which overtakes the marriage and believes both parties feeling bitter. I am in the process of going through a divorce at the moment caused almost entirely by these pressures, and will now be in a position where the government will have to provide the support that my spouse has been providing free of charge for many years."

Basically, being a carer for someone with SMA means you have to be switched on 24/7 365 days of the year for the rest of your life. You take on a number of roles, carer, nurse, doctor, social worker, occupational therapist and often counsellor.

"*I need someone all the time, I am avoiding eating if I am alone because I am worry about choking) I am unable to leave my home on my own(I can't move my hands, I can't keep straight position) I need someone who can support me, help me move my arms, hands or just push all me on the left side if I am too weak to keep me straight*" – another SMA Patient.

3. Adaptation to life with SMA:

physical health:

a) Most people with SMA have severe respiratory issues due to their inability to have an effective cough and weak breathing muscles. Often SMA people find themselves in ICU, PICU at least once a year to treat a common cold. In a number of cases this can be much more frequent. In order to prevent this, many families remain indoors for the duration of colder months and reduce their contact with the outside world to a minimum. The use of BiPAP and Cough Assist is a must for most people with SMA Type 1 and type 2 and is strongly recommended and used for type 3.

b) Gastrointestinal problems can also arise in many cases regardless of SMA type. Constipation is one of the most common problems - ongoing use of medicines and finding a suitable diet is needed.

	As there is little known about diet in SMA this can be tricky. Swallowing issues are often addressed through surgery. c) Lack of movement also affects bone density leading to fragile bones. Weak torso muscles allow for development of scoliosis in almost all cases – which exasperates other problems (including breathing) and almost always requires a surgical intervention. Lack of walking means that hip sockets do not develop and therefore another type of surgery is often required to correct the problem. Hoisting, wheelchairs, suitable physiotherapy equipment must be purchased and installed. Various households would accumulate massive bills for equipment: Powerchair (£25k) Wheelchair (£3k), manual handling equipment Innowalk (£15k), Stander (£3k) and smaller equipment (£3k). None is supported by NHS or social services. House adaptations are also a must as level access is needed everywhere as well as a suitable bathing room, toileting system and hoisting to enable transfers. Beds and cushions to prevent sores are also vital as well as suitable cars for driving and carrying equipment. The list is endless! emotional wellbeing: a) This is generally affected a lot within the SMA community. The use of anti-depressants is not uncommon. Seeing therapists and enhancing emotional wellbeing of the carer and patient through exercise can be done, however this requires dedicated time and often this may not be the case. In some severe cases communication with children can be limited as they do not develop the ability to talk and therefore expression of emotion is very hard. Some recent advances with IT enables this communication now, but it requires specialist set up and costs money. The devices for this cost around £10,000. everyday life including: a) ability to work – Many people with SMA hold steady jobs and have successful careers! Baroness Jane Campbell sits in the House of Lords! One of our Trustees manages a hospital trust. Our children from an early age are involved in child modelling. However this all depends on the access to buildings, and their strength. As the condition progresses without treatment the ability to do work becomes harder. Eventually people who work will lose their ability to drive their wheelchair or type and they will lose their job. Often buildings are not accessible and therefore people with SMA will miss out on such opportunities. Those skilled adults who manage to overcome daily “inclusion”

	obstacles to have successful careers in teaching, management, research, business are at the mercy of SMA progression. As weakness grows their ability to work continues to deteriorate. Eventually these brilliant people will lose their job as a result of depletion of physical strength and stamina rather than lack of skill. ”In my job as a senior manager I regularly have to attend meetings or events which may include lunches, drinks or meals. I now actively avoid these events which has a direct impact on my career, because of the embarrassment of not being able to feed myself. “ Quote from SMA patient “I manage to hold down a successful job despite having very limited physical capabilities. Outside of breathing and talking, the only physical use I have is of my right hand. Should I lose this function I would no longer be able to adequately do my job and would lose my livelihood, put my family’s financial future at jeopardy and to all intents and purposes lose my reason for being.” Carers must also adapt to different working environments. Parents and spouses have had to give up their work to care for their loved one . Those who do go to work have to be very careful how they deal with people outside the family to prevent bringing infections into the home and after work is done they can offer respite to their partner! These are the lucky one! Single parents are hit even harder! b) adaptations to your home – In many cases families are forced to move from a comfortable accommodation into council housing. Those who have their own houses still must make adjustments. For example rearranging the house to have the living room as a ground floor bedroom and installing an en-suite bathroom with required taps (often must be temperature and touch controlled because if you and me put our hand under a hot tap we can quickly pull it out, a person with SMA will simply burn their hand), adjustable sinks (to get wheelchairs under), bath/shower chairs and hoisting. Kitchens are often overlooked, but we do need to have accessible kitchens which also means rethinking how things are done. Basically, to make a house accessible requires lots of work and money. As a person with no physical disability we do not take these things into account, but they must be considered!

	c) financial impact – The loss of earnings is phenomenal. Overnight a happy mid-range income family is plunged into a single salary household whilst adding equipment and physiotherapy on top. Families on low income are hit even harder! Most SMA families will ask for financial support to buy equipment from one charity or the other. Often multiple charities will have to step up to help. d) relationships – There is massive strain on the relationship within families. People are tired, highly charged emotionally and thus a perfect storm for fall outs. Many families are broken apart by the condition. Even when strong relationships come across SMA it grinds these down. e) social life – Some people are still trying to see friends and family and have a bit of social interaction, but this becomes harder and very often the people who we interact with are other SMA families. f) carers social life - It's not uncommon for the carer to be isolated from their family or friends due to the constant need to care for someone and the complications of taking that individual with you g) Adults who perhaps once enjoyed a social life going out with friends or to the pub no longer can because of their progression or they are too embarrassed to ask for help with simple things such as picking up a drink Adults going to work As we have seen recently with large numbers of people being compelled to work from home, the benefits of work on people's emotional well-being is huge. The ability to interact with others and engage in activities is not just beneficial to the person with SMA, but also those around them. Many with SMA have higher than average IQ scores and are intelligent and provide exceptional leadership and intellectual input into working environments. There are programs to support those with disabilities to work, such as the Access to Work programme. There is also a legal requirement for employers to make "reasonable adjustments" for those employees who are disabled. However, none of this takes into account the emotional toll of not being able to take part in group activities without constantly seeking help from colleagues, which is demeaning and embarrassing in many cases. Very few have the emotional strength to be able to cope with being in such a position and therefore withdraw themselves. Also, often the nature of the job cannot simply be solved by the Access to Work scheme, complex roles may not be something you can either do with adaptive

	equipment or having physical assistance. In many cases work has contributed to ensuring the physical and mental well-being to those individuals, but the sudden realisation that they cannot, or soon won't be able to, continue to work has a massive impact. The child's ability to go to school: Children with SMA have exceptional levels of intellect. Repeat studies show that they have higher than average IQ and have brilliant minds. Any intellectual and cognitive developments are only hampered by the environment we live in. This simply reflects everyday life. However, in order to be able to access mainstream education an EHCP and similar provisions must be introduced to help people with SMA to carry out physical tasks. For example adaptations within school to allow accessibility, one-to-one help with simple physical tasks like writing. Many stronger SMAers are capable of using modern IT to do their homework and as long as there is suitable physical support and provisions made the child is capable of attending the school. During the winter seasons the school attendance is significantly reduced due to illnesses and if the school does not provide a suitable remote teaching platform, the child's education is damaged. So whilst SMA does not preclude the child's education, it does make things difficult and how well the child is included in the school environment really depends on the school. The child's development emotionally: SMA children could have normal emotional development. However, due to stress experienced by the parents and caregivers, children with SMA can develop certain anxieties and issues. Saying that, it is reflective of the environment the child lives in. There are many SMA children who are loved far more than non-SMA children and they develop into kind and caring adults. One trait is obvious though, is that SMA children can influence the emotional state of parents more so than non-SMA children. Participation in school and social life: The level of participation in school and social life would reflect that of the parents and varies from family to family. However if the aspect of a social life is not adapted to be physically accessible then it automatically excludes the children and adults with SMA. SMA itself does not stop people with this condition from participation, but lack of adaptation does. However… as the condition progresses and weakness grows the participation becomes harder. Any activity requires stamina

	and at some point this will be depleted far too much. Again, if you have a loving family around they will work out what to do, if you do not, loneliness will eventually take over. Adults face similar consequences and outcomes. Even simple tasks like venturing out to go shopping can become challenging due to progression as the patient loses the ability to drive their power wheelchair or requires too much assistive technology for simple journeys. Simple tasks like going to the pub becomes physically and emotionally impossible, going to the cinema with someone when you need someone to feed you the popcorn? That alone rules out many dating possibilities for those with SMA. Even the ability to have the strength in a finger to press the lift button, all of these things that many take for granted on a day-to-day basis, if lost or given back to someone with SMA, are life changing.
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 palliative care is unacceptable in a world where new treatments are becoming more widespread. The palliative approach does not do anything well as this condition is progressive and symptom management now can be viewed as throwing good money after bad. It does not address the patient's needs . It excludes innovation. It prevents a happy life. Genomic medicine is a significant part of the government's health strategy, why if every time an advancement in treatment is discovered, we do not provide access to those who the research was for. Current costs of care: There have been a few attempts to estimate the financial impact of SMA on the NHS and the general agreement is that it varies. Models used do not quite reflect the real costs. Respiratory events, stays in ICU (ICPU), surgeries, orthotics, equipment etc all add up to various figures from several thousands per year to several hundreds of thousands. On top the costs associated with caregivers must be taken into account, as well as the cost of mental health. Whilst these costs will not disappear over-night, it is expected that they will be reduced. There is Nusinersen MAA treatment which is currently undergoing evaluations. The treatment is effective, however whilst it is beyond the scope of this appraisal, it is important to note that a significant majority of

	SMA patients have various spinal issues which precludes them from being able to access the required lumbar puncture. For those receiving treatment the procedure is extremely resource intensive on the NHS, often requiring interventional radiology, CT and MRI scans.
8. Is there an unmet need for patients with this condition?	Absolutely. Even Assuming a full and unconditional approval of Nusinursen and Gene Therapy there is a significant prevalent population of SMA people that will not be able to access those treatments due to their medical health. For example, many adults with SMA have undergone spinal fusions which makes accessing the spinal canal impossible. Those where it is not impossible, there is a significant drain on NHS resources such as CT scans, interventional radiology and MRIs, all at a time when the NHS is struggling to meet its existing diagnostic targets due to Covid-19.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The treatment has many advantages. In clinical trials and in the real world the treatment has shown significant impact on the health and well-being of the patients compared to the natural history of the condition. TreatSMA has conducted a detailed “before” and “after” survey of the patients who currently receive Risdiplam. We have asked about swallow, respiratory functions, fine motor skills etc. Please see attached survey results in the appendix. As the patients are not assessed within a stringent clinical study environment and their access to contributing modifiers such as physiotherapy is not equal we expect variation in the responses. We have asked the community if stopping progression of SMA would be a satisfactory outcome and 124 out of 141 (88%) strongly agree that it would be. The survey of people being treated with Risdi plam clearly shows that the condition does not deteriorate further! Thus, clearly highlighting that for the majority of the people with SMA this treatment means a world! It’s vital to remember that stability is just as important as improvement in a large number of people’s lives, particularly when livelihoods are at stake. Every single patient regardless of type and age has shown multiple improvements since starting the treatment. Increased stamina, improved finer motor skills, better body control, improved respiratory

	functions, improved swallow. It is true that different people show different level of improvement in different areas, but this is to be expected as motor neurons are affected differently in different patients. The most important point here is that the life of the patient can be saved. Without treatment life expectancy for the SMA Type 1 patient is 2 years; type 2 teenage years though with modern interventions like BiPAP, Cough Assists, surgeries this could be into adulthood. With the treatment people with SMA are fully expected to have much longer life expectancy. In all cases the data clearly shows that progression of the condition is halted and very often reversed. Since the physical weakness is reduced, the quality of life for both patient and carer is improved. After all, if you do not have to fight for every breath of air you can write a book (for example). Higher levels of mobility are expecting to reduce many other problems and stronger bodies should be able to prevent scoliosis and other complications due to the nature of the condition in children. It is possible and plausible to expect that all aspects of life will be improved by having access to the treatment. In the prevalent adult population, the access to the treatment will reduce the risk and complications generally associated with SMA. A win-win for everybody! We also noted mental health improvement associated with families of patients who receive the treatment as well as reduction of caregiver burdens. As the treatment has not been around for long and not widely used yet, the full impact of it is hard to estimate at this point, however it is expected to continue on a positive trajectory. Often some of the emotional trauma that caregivers suffer from is related to the feeling of hopelessness, they cannot do anything to help their loved one. Being able to provide treatment, while being realistic in its outcomes, has a significant positive emotional impact on both the patient and the carer. There is a clear advantage of the treatment being available as an oral suspension which can be delivered to the patient door directly by the pharmaceutical company, thus avoiding complicated administration procedures and associated costs! We know that post Covid-19 the NHS is struggling to get back to levels seen before the pandemic, especially in diagnostics. The other available treatment has a significant impact on diagnostic requirements, and must be delivered on schedule. These two factors alone make an oral solution much more palatable to the NHS. We must understand that SMA is a rare condition and clinical trials are limited thus the amount of data will always be small whereas the levels of uncertainty will always be high. Without offering the treatment to

broad population there will never be enough data!

Below is comprehensive summary from parent whose child has been receiving Risdiplam:

1.Swallow

A. Before starting Risdiplam Patient A was starting to aspirate. After having a videofluoroscopy due to recurrent chest infections we were told Patient A would require thickening fluids to stop the aspirating. The weak swallow caused constant time off of school and he was often admitted into hospital due to being so poorly with chest infections.

B. Not only did the aspirating stop once Patient A started on Risdiplam so then did the recurring Chest Infections. Patient A has not had one hospital admission since being on treatment.

This has enhanced Patient A's quality of life by miles. Less hospital stays means less time away from work for one of his parents, less additional care for his sibling and time away from her.
The stronger swallow means he can finish his meals, eat what he pleases and it also means he is now the right weight for his age and height when before he was extremely under weight.

The stronger swallow also means he is at less risk of choking on food and also vomit when he is poorly which was a risk to his life.

2.Recovery

A. Patient A recovers much quicker from illness. Previously it took about a month to recover fully from a chest infection. The time spent ill and in bed contributed to physical deterioration with muscles getting weaker and contractures getting tighter with regular physio and appointments not attended. Time was taken off of work by extended family to help and assist with shopping etc and school runs for Patient A's sibling. Education was missed as well as social interaction with his peers.

	B. Patient A requires little intervention at all, if any now. As mentioned in number one he has had no hospital admissions since starting treatment. His attendance at school has improved, less hours of help is required from people outside of the home, appointments and physio resume within two weeks at least after a chest infection and Patient A's weight does not plummet when poorly. Mentally and emotionally the anxiety and fear of Patient A getting ill is less knowing he can handle infections better than before. Also, the concern about managing his care whilst he is ill day and night is of less concern as a parent. 3.Fine motor skills A. Before Risdiplam Patient A's fine motor skills were very weak. He struggled to do the simplest of tasks and got tired when trying. This meant he needed constant assistance and it got increasingly frustrating for him not being independent. It also caused a little anxiety at the thought of me not being around should he need me. The fine motor skills affected play, writing, eating and more. B. Since being on Risdiplam the list is endless as to what Patient A can now achieve so I will list a few. Opening crisp packets, writing longer and clearer, yogurt pot lids, taps, door handles, tearing, pushing lego together, picking up small objects, squeezing out tooth paste and using a knife to cut up his own dinner. This gives Patient A independence. He is very proud to accomplish these things and obviously it takes away the care and help needed from myself. 3. Arm strength A. Prior to starting Risdiplam Patient A was starting to lose the strength in his arms. Using a manual chair was harder, raising his arms was nearly becoming impossible, strength to pull open a cupboard or door which he once had was no longer. He was losing the strength in his arms to put himself into a sitting position and at the age of two he lost the ability to get on all fours and crawl. Reaching up for books, toys and playing computer games etc was becoming a mammoth task.

	This led to frustration, upset on Patient A's behalf and as a parent it was harder work as more support was needed for him and it was agonising watching him deteriorate in front of me and effected my mental health greatly. I was fearful of what he would loose next, anxious and scared for his future. B. Patient A can now reach cupboards, open doors, open lifts and is now even working on self-transferring from his chair to his bed. He gained the ability of getting on all fours which was lost six years ago and is working hard on learning to crawl. He can open a fridge door, wash up, stack the dishwasher, comb his hair, put on his coat and shoes to name only a few. Much of what he has gained was lost over six years ago. This has given Patient A massive amounts of confidence; he likes to help with housework in the home simply because he can and be as independent possible. He is very proud of his new gains in strength as are we all. New strength simply means more independence and less care from me, and my time I feel is more equally spread with his sibling and it means visits from family members are visits not to care but to enjoy and play as it should be with memories made. 4. Neck Control A. Patient As head and neck control was getting weaker prior to Risdiplam. He needed a lot of additional support in all of his equipment and wheelchairs. With the head being the heaviest part of his body, it became the weakest part during the course of the day. From writing to eating, both tasks were often cut short because the head became too hard to hold up. Standing in an orthotic suit and frame was also being questioned as there was no head support on the equipment to assist this and it was becoming harder to do. Sometimes Patient A would flop forward and need help to sit back up and I think the poor head and neck strength contributed in starting to lose the ability to sit. B. After starting treatment Patient A's head started to really get stronger after three months in. Neck and head strength played a big part in increased stamina and now he has had most of his head rest supports removed on the equipment. Patient A has complete control over his neck and head and can do controlled stretching exercises alone. The fact he has so much control helps to eliminate a possibility of choking. Eating and writing, getting on all fours and sitting has all improved because of the new strength here.

	5.Sitting A. I would say Patient A was just starting to lose the ability to get into a sitting position before the trial and maintain that sitting position. It was one of the things I was most fearful of going for him. Floor time is great as he is out of his chair so to be reliant on a seat or a piece of equipment would mean using his upper body muscles to stretch, reach etc would have become more limited. I think this would have been one of the saddest things to lose, to be able to sit up for him personally. B. Patient A has kept the skill of being able to get into a sitting position and remain seated. This is with lots of growth and added weight. He can bum shuffle into different rooms, he can get on a peanut ball himself to exercise, play games on the floor, roll and get back up into a seated position and also lay down onto his tummy and get back to a seated position. This is a massive amount taken of the carer physically and time wise, not to mention all the muscles Patient A is now using giving him a workout by simply doing this movements. He is maintaining his strength, gaining it and making his heart race. 6. Stamina A. Stamina plays a big part in Patient A's quality of life. From whether it is full days at school, days out, hospital trips, playing with friends and eating. Days were always carefully thought out taking inti consideration Patient A's tiredness. Even his school calendar had half days every other day or a day off mid-week to recuperate. Tiredness often led to illness and Patient A often picked up something if he was run dun. Being aware of how tired he got limited time with friends and family, especially in the winter months when there are more bugs to catch. B. Patient A school calendar changed six months after starting treatment. His attendance (even with trips to attend the trial site) went up 22%. Patient A along with the better swallow and head control gained more weight and actually enjoyed his food, he became more interested in food rather then seeing food as a battle to win every evening because he was so tired. He has play dates after school, our trips are not cut short and again like points 1 & 2 does not pick up illness as easily. Massive impact on the family

overall. Our lives mirror his. If he can handle a day trip so can we, if he has a full day off of school it means chores/work can be accomplished.

7. Assisted Standing
A. Standing with orthotics and a frame is something Patient A did from the age of one. However, as time went on his head became more and more of a problem and it was discussed that Patient A may had to discontinue standing with orthotics which is something he did daily.

C. Patient A continues to stand two and half years after starting treatment, with weight gain and length thrown in to. Standing has maintained good bone density, it allows his internal organs to expand, it improves his circulation and helps with his posture and hips. I am in no doubt that Patient A's time standing would have come to an end now without treatment unless a specific frame with head support was given to him have but would have to be approved by local authority, but often children with SMA stop standing around the age of six and seven. This is because SMA without treatment is a progressive condition and unfortunately many professionals feel the money is wasted in delaying something if it will happen anyway.

I believe standing plays an important part in maintaining good health with all the things I listed previously and helps to regulate his bowels with little to no constipation issues whatsoever.
It is also good for his self-esteem. Patient A is proud to stand.

8.Mental Health
A. Patient A's has always luckily been a very happy little boy by nature. He is fiercely independent and this has served him well. Sight cracks started to appear as he declined. Worrying about me hearing him, mention of a fire and how he would open a door or use a phone. To be completely reliant on someone in a crisis situation must be extremely scary. He most definitely became aware of not being able to play with lego anymore without assistance, this did upset him. He would insist on doing it alone until frustration got the better of him and tears began to roll down his cheeks. Lego may seem small but this was I think a feeling he had for most things even though he did not show it.

The family's mental health deteriorated. Myself and Patient As dad split up. The pressure and immense responsibility was too much for Anthony (Patient As dad) and he self destructed and had to leave the

	family home. I was left with not only the diagnosis to come to terms with but suddenly lots of professionals entering into the family which I found intrusive and overwhelming and the breakdown of the family unit which hurt us all. It took a few years to adjust. Sibling, who is very much loved became a little carer. Sibling picked up things Patient A had dropped, assisted him in combing his hair and getting the toothpaste out, opening crisps, taking pen lids off, so so much. It was a new world for us all. Overnight I became a physio, OT, Specialist and carer and our wowork had changed forever. It fell apart mainly because there was no hope. The progressiveness of the condition was what broke our hearts. That it would only get worse for Patient A. If you have no hope, what do you have? B. Hope. Risdiplam gave us hope. It stopped the progressiveness of the condition and on top of that gave Patient A back some of the strength he has lost and continues to do so. Now there is a spark in his eyes “look at me" “look what I can do now "mummy quick look at this". The lost feeling has gone. The pain has eased for sure; the heavy heart is not so heavy. Patient As upper body strength is getting better and better and this not only gives him independence, especially if he can learn to self-transfer, but it gives him better respiratory meaning his life is not at risk like it was before. To put it simply, SMA wasn’t the SMA it once was for our family after Risdiplam.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	At the moment there are no obvious disadvantages to the technology.

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.	Define benefit. Different patients have different ideas of benefit. For some walking is a benefit, for others being able to swallow or speak or breath is a benefit? How do you define what is more important? Our survey clearly demonstrates that ALL patients will benefit simply by stopping SMA from getting worse. From a clinical point of view and based on understanding of how the treatment works at cellular level and understanding of how condition progresses it is easy to expect the greatest gains in younger patients and newly diagnosed as their motor neurons and muscles are still intact or very close to it. This must not be seen as the group to focus upon those. For this particular treatment ALL patients, ALL types, ALL ages must be seen as a single group that will benefit as recently agreed by the FDA and MHRA scientific opinions.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Yes.** During the last couple of appraisals SMA Adults and Type 3 patients got overlooked. No patient should be excluded because they are older or less impacted. The very nature of delivery of the currently approved treatment for SMA precludes a large number of patients. We also need to ensure that we do not discriminate against the starting position of a patient, for example, the ability to maintain walking to one person is essential, yet another it may simply be being able to lift a cup. It should not be anybody's decision about equality issues other than those affected by the condition.

Other issues	
13. Are there any other issues that you would like the committee to consider?	Due to the nature of the condition there will not be enough data to address the uncertainties, but a working solution for ALL patients must be found. Looking at the current research landscape for SMA, there will not be another treatment in the pipeline for some time, thus the committee should take into consideration that for many people access to Risdiplam will be their only shot at living a longer and healthier life.
14. Please outline what carers and patients consider to be meaningful treatment outcomes for each SMA type	For each group stopping progression of SMA is considered a meaningful outcome. Everything else is viewed as a bonus. Type 1: preservation of life and improvement with regards to respiratory condition is a meaningful outcome Type 2: improvement/stability of respiratory, swallow and arm strength are meaningful outcomes Type 3: preservation of torso and arm strength is a meaningful outcome However ANY improvements is meaningful for patients with SMA and would vary from person to person.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Life with SMA is complex and challenging for patients, carers and clinicians
- Arresting progression of SMA is the most important aspect to most SMA patients
- Risdiplam is an effective treatment for Type 1, 2 and 3 regardless of the patient age or initial ability
- ALL patients with SMA must be able to have access to Risdiplam to treat their condition
- Most patients with SMA lead active and productive lives both in terms of family and work. However, at all levels of age and types, all have a metaphorical sword of Damocles hanging over their heads, not knowing what function they are likely to lose next week, next

month or next year. We cannot continue to put life sciences at the front of the country's post Brexit strategy and yet not allow patients access to the fruits of these labours.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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.

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- 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] **and** [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? **x** other (please specify): A Neurologist with a specialist interest in peripheral neuropathy
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is an organisation representing adult neurologists in the UK. It is funded by its membership.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. 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.)	The main aim of treatment of this condition is to stop or slow progression
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	The ability to maintain independence of activities of daily living e.g. independence to transfer to and from a wheelchair, to wash or toilet independently.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Treatment for SMA in adult patient includes Nusinersen for ambulant patients with type 3 SMA and patients with type 2 SMA with preserved upper limb function. The mainstay of treatment is centred on supportive care which may include non-invasive ventilation for patients with respiratory muscle involvement.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are NICE guidelines for the use of Nusinersen in adult patients with SMA
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	A pathway of care for adult patients with SMA is lacking and there is widespread geographical variation in the services available for adult patients with SMA

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	This would be the first oral therapy for SMA. Nusinersen is delivered by intrathecal injection with considerable delivery related costs.
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 between the technology and current care?	Current medical therapy for SMA (Nusinersen) requires repeated intrathecal injections undertaken in hospital by an interventional radiologist.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The decision to start treatment should be undertaken by specialist tertiary neuromuscular clinics with experience in SMA the drug oral and it needs little/no monitoring so would be entirely reasonable to have shared care with GP taking over prescribing.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This is an oral medication with no additional technological requirements for administration

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?	I do not have access to the trial data and am unable to comment
• Do you expect the technology to increase health-related quality of life more than current care?	As above
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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 treatment will be easier to administer than current medical care (Nusinersen).
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Unable to comment
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?	
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?	This is the first oral medication for SMA that increases the translation of SMN2. It is an easily administered oral medication with little in the way of infrastructure costs for its introduction.
• 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 are no easily administered oral medications for SMA

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?	The clinical trials are unpublished and it is therefore not possible to comment
• 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?	
• 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?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I/ we are aware of.

21b. Consider whether these issues are different from issues with current care and why.	
22. Please describe the heterogeneity of SMA, including by SMA type. Please describe any known prognostic factors.	SMA is a degenerative disease of motor neurons most commonly due to recessive deletions in the SMN1 gene. The severity of the disease and age of onset is directly related to the number of copies of the pseudogene, SMN2. SMA is defined by the age of onset into types 1 to 4, with type 4 being adult onset. SMN2 is identical to SMN1 other than the presence of a single nucleotide substitution resulting in a cryptic splice site and non-sense mediated decay of the SMN2 transcript.
23. Please outline the key clinically relevant motor outcome measures for the motor skills of sitting, standing, and walking.	Unable to comment
24. Please describe any difficulties in translating short-term outcomes in the clinical	

trials to longer-term outcomes. Are there any information sources which may reduce this uncertainty?	
25. Please describe what considerations would be undertaken in the use of the technology for those with previously treated SMA.	

Key messages

26. In up to 5 bullet points, please summarise the key messages of your submission.

- First oral treatment for SMA
-
-
-
-

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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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.

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- 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] **and** [redacted]**, Dubowitz Neuromuscular Centre, UCL Great Ormond street Institute of Child Health and Great Ormond Street Hospital for children, London**
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).	In the UK, our group obtained since 2005 funding to link all the paediatric centres involved in the care of children with SMA. The network, originally called SMART-NET, and, since 2012, re-named SMA REACH UK (www.smareachuk.org, clinical trial Gov: NCT03520179), was originally supported by the advocacy group Jennifer Trust for SMA, and after that, and until 2019, by the charity SMA Trust. Currently the SMA REACH UK receives funding from Biogen, via an investigator initiated clinical study to UCL (Muntoni PI). This natural history study is sponsored by UCL. The network links more than 20 centres in the UK involved in the delivery of the care of SMA patients.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No, this organisation (SMA REACH UK) has not received any funding from Roche. In the UK, a few centres/ hospitals, have been involved in clinical trials in SMA (and in Duchenne muscular dystrophy) funded by Roche. These trials include the ongoing Jewelfish (Risdiplam) and previously completed Olesoxime trials in SMA which were performed in a few of the hospital sites affiliated to the SMA REACH UK network.

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No I do not
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.)	The biochemical aim of the treatment is to increase production of the SMN protein produced from the SMN2 gene in patients affected by SMA. From a clinical perspective, the efficacy of this (as for other SMA drugs that increase SMN protein levels) is partly related to the disease duration, the severity of the disease and the interval between first symptoms and initiation of therapy. There is an ongoing study in PRESYMPTOMATIC SMA children but there are no as yet available data for this patient population. It is anticipated that this will be the group of patients in whom the effect of treatment might induce the largest separation from the natural history, but this is speculative at this point in time In symptomatic children with SMA I – who met the inclusion criteria for the ongoing clinical trial for which data were presented at various international meetings, arrest of progression, and unequivocal and clinically meaningful stability and improvement in respiratory and bulbar function and improvement in mobility is achieved in a high proportion of patients. In the more chronic form of SMA such as II and III with longer disease duration, more modest improvement are observed, which however might be similar to what we see in patients with similar disease severity treated with Nusinersen; these improvements are clinically meaningful and it is expected that would lead to improved long term outcomes (for example upper limb and respiratory functions) although chronicity of the condition and various co-morbidities (for example contractures and scoliosis) do affect the extent of the potential clinical improvement. On the

	longer term, even stability (with no improvement) could be considered clinically meaningful, in view of the progressive nature of the weakness that affects the axial and limb muscles, and the progressive respiratory deterioration invariably seen in the natural history of SMA I, II and III.
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.)	Symptomatic SMA type I. Improvement in respiratory outcomes, with reduction of respiratory ventilator requirements; reduction of hospitalisation and partly preserved bulbar function with ability to feed orally are important milestones achieved by the majority of patients treated with Risdiplam. From a motor perspective, sitting unsupported is also a feature achievable in a proportion (between 30 and 40%) of patients treated with Risdiplam; a few patients acquire the ability to stand and could potentially acquire even higher level of function if treatment is initiated close to disease onset or at a pre-symptomatic stage. Symptomatic SMA II: improvement in upper limb strength Symptomatic SMA III (ambulant or having lost ability to walk). Most of the data presented at meetings come from the population of more severely affected SMA III with markedly reduced or no residual ambulation abilities. Upper limb strength and function are meaningful and achievable endpoints for these patients
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Until a few years ago there was no therapeutic option for SMA patients. Recently, Nusinersen was adopted for SMA I, II and ambulant SMA III. Nusinersen currently provides an important therapeutic option for SMA patients. However, a number of patients are currently excluded from the MAA. In addition complications of SMA either precludes or complicates the intrathecal administration of Nusinersen in a proportion of SMA II and III both in the paediatric and adult age. This patient population would immediately benefit from Risdiplam. Finally the oral administration route of Risdiplam is clearly advantageous compared to the intrathecal route for Nusinersen, which is invasive and requires logistical investment at the hospital sites. If on the longer term the safety and the efficacy of Risdiplam will demonstrate a similar profile to Nusinersen, it is likely that patients choice will favour a medicinal product which could be administered orally, with much less demands on the hospital settings.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	SMA is typically diagnosed and managed in tertiary care centres in collaboration with local secondary centres. The severity of SMA varies from severe type I; to intermediate type II, to milder type III, and the intensity of medical care is proportionate to the clinical severity of the condition. At the severe end of the spectrum, a complex MDT including neurologists, physiotherapists; respiratory physicians and therapists; occupational therapists; orthotists; wheelchair services, palliative care physicians; dietician and speech and language therapists, family therapists, all regularly contribute to the clinical care of these children. A complex home care arrangement for respite is also common. In SMA II there is a similar but less intense MDT team work, with the important addition of orthopedic surgeons as scoliosis is essentially inevitable. The milder condition in SMA III requires less intense MDT involvement
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Qian Y, Sejersen T; SMA Care group. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord*. 2018 Mar;28(3):197-207. doi: 10.1016/j.nmd.2017.11.004. Epub 2017 Nov 23. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Qian Y, Sejersen T; SMA Care Group. 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. Do
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	On the whole there is broad consensus on the management of SMA, although inevitably some differences in the ability to deliver care in different regions and CRGs affects specific aspects related to the care delivery. A typical example is the provision of cough assistance. Strongly recommended by the international SOC, and adopted in many hospitals/ regions, but with enormous difficulties to be provided in other regions. Provision of specialist physiotherapists and orthotics can also be variable in different parts of the country.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It is hoped that in the near future the Newborn Screening committee will revise previous negative decision related to NBS for SMA, as treatment in presymptomatic patients is likely to have the most dramatic effect on outcome. We anticipate that a therapy like this could be made available to all patients once adopted by NHSE, and a mechanism to manage both practicalities and ways to compare efficacy with Nusinersen will need to be considered, to allow a coherent and nationally agreed plan of when to offer one vs the other, at least in the broad context
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	We anticipate this technology could be made available in all centres currently involved in the care of SMA children and adults, affiliated to SMA REACH UK.
• How does healthcare resource use differ between the technology and current care?	We will need additional pharmacy resources and additional monitoring visits until the product is considered sufficiently safe that only outpatient prescriptions with no additional monitoring will be acceptable
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary neuromuscular services

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Pharmacy resources; we already have a training programme for therapists in the UK and we do not envisage to introduce new outcome measures. Investment in the functional and medical data acquisition in national registries would be desirable also considering there are other competing therapies and comparators in the real world will inform long term outcomes. Remote digital data capturing from patients through telemedicine implementation could be considered as well to reduce burden related to on-site clinic appointments for patients and caregivers
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes especially for all patients currently unable to obtain nusinersen. Based on the different biodistribution (central vs systemic) and the data so far presented at conferences, we expect that Risdiplam might have higher benefits than Nusinersen on bulbar and respiratory functions. In-human biodistribution studies of nusinersen in SMA I children who succumbed due to illness demonstrate an overall good biodistribution with higher levels in the thoracic and spinal cord compared to the cervical spinal cord. In-human data of the biodistribution of risdiplam (or of SMN protein expression) in the entire neuraxis are at the moment not available.
• Do you expect the technology to increase length of life more than current care?	If Nusinersen is not considered current care (as under MAA), Risdiplam will dramatically improve length of life for SMA I.
• Do you expect the technology to increase health-related quality of life more than current care?	As above, if nusinersen is not considered, this drug will increased significantly health-related quality of life, and reduce hospitalisation of affected patients, especially the severe SMA I.
12. Are there any groups of people for whom the technology would be more or	As for all drugs in SMA, there might be a point in the progression of the disease in which any therapeutic intervention is futile. There is little information on where that line should be at the moment

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less effective (or appropriate) than the general population?	
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.)	Children and adults recruited for this drug will require a baseline assessment and some additional safety assessment currently not part of the standards of care. It is envisaged that the additional safety assessment could with time be reduced, with the increasing confidence on the safety of the drug. However, as mentioned above, the way of administration (daily oral administration at home instead of regular intrathecal administrations in hospital) will represent a much easier and more desirable way of use for patients and healthcare professionals.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	It appears sensible to monitor safety of patients at regular but not necessarily very frequent intervals, as for any new medication introduced for a rare disease, in which the number of treated patients in trials is limited. Based on the data available so far, patients treated in clinical trials show either a stabilization or an

Do these include any additional testing?	improvement of the condition, so we do not currently envisage any specific rule to stop the treatment, provided that the safety profile is confirmed.
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?	Improvement in energy and stamina is a constant remark of patients treated with these medications, which is not captured well by QALY
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?	The use of an oral drug to modify gene splicing is highly innovative. The increase in production of SMN is increasingly recognised to be a key therapeutic target for SMA, and this drug clearly achieves this aim.

• Is the technology a 'step-change' in the management of the condition?	It is a step change from no-treatment in SMA III non ambulant, and in patients not eligible to receive Nusinersen.
• Does the use of the technology address any particular unmet need of the patient population?	Yes for all the population of SMA currently unable to obtain Nusinersen, or those in whom the administration of Nusinersen is particularly complex. Additionally, some aspects of the disease, including deterioration of bulbar, might potentially be better addressed by Risdiplam than Nusinersen, based on the data presented at international meetings, but awaiting peer review publication, available so far.
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 safety basis for this drug appears to be good although it is appreciate that only a few hundreds of individual have been exposed to this drug. None of the adverse events reported so far are severe or negatively affecting quality of life of treated patients.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Broadly speaking yes, although there have not been as yet trials in the adult non ambulant population. However extrapolation from younger patients suggest that a therapeutic benefit should be expected

• 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?	SMA1: survival free from permanent ventilator support; lack of deterioration of bulbar function and maintenance of swallowing abilities; achievement of significant motor milestones and improvement in gross-motor capacities; reduction in the number of hospital admissions. SMAII and III: improvement in gross-motor function, upper limb function and in daily independence compared to the placebo group All the above were measured in the trials
• 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?	Not that we are aware of.
19. Are you aware of any relevant evidence that might	Trial data not published yet

not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	No real-world data are available so far.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Risdiplam, if adopted across the entire spectrum of SMA, addresses one limitation of the current MAA for Nusinersen that excludes the SMA III patients who have lost the ability to walk.
21b. Consider whether these issues are different from issues with current care and why.	
22. Please describe the heterogeneity of SMA, including by SMA type. Please	5 q SMA includes a wide range of phenotypes that are classified into clinical groups on the basis of age of onset and maximum motor function achieved:

describe any known prognostic factors.	very weak infants unable to sit unsupported (type 1), non-ambulant patients able to sit independently (type 2), up to ambulant patients with childhood (type 3) and adult onset SMA (type 4). The severity of muscle weakness, bulbar dysfunction, respiratory impairment and other comorbidities varies across the spectrum of the different subtypes, with weakest forms having the most severe degrees of impairment. Lower age at treatment and disease duration have been shown to be associated with the higher rate of response to treatment.
23. Please outline the key clinically relevant motor outcome measures for the motor skills of sitting, standing, and walking.	Disease-specific motor outcome measures have been developed and validated for the different subtypes: SMA I: CHOP_INTEND scale; WHO motor milestones; HINE-2 SMA II and III: HFMSE; RHS; RULM SMA III: 6 minute walk test
24. Please describe any difficulties in translating short-term outcomes in the clinical trials to longer-term outcomes. Are there any information sources which may reduce this uncertainty?	SMA is a slowly progressively degenerative disease, especially in its more chronic later-onset forms. Long-terms real world studies may be required to appreciate additional benefits on motor and respiratory function, as well as on stamina and independence, compared to what already reported in clinical trials.

25. Please describe what considerations would be undertaken in the use of the technology for those with previously treated SMA.	A consensus within the SMA-REACH network will be developed in collaboration with NICE/NHSE to propose criteria to switch a patient from the ongoing treatment (Nusinersen) to the new treatment (Risdiplam). Some of the criteria could be ease of administration with Risdiplam and apparently similar efficacy with Nusinersen; presence of side effects for patients already on Nusinersen (mainly related to the intrathecal administration); potential additional benefits on bulbar function with Risdiplam

Key messages

26. In up to 5 bullet points, please summarise the key messages of your submission.

- The use of an oral drug to modify gene splicing is highly innovative.
- Treatment with Risdiplam has shown to meet the primary efficacy endpoints in clinical trials for SMA I, II and III.
- Risdiplam can address the unmet need of the population of SMA currently unable to obtain Nusinersen, or of those in whom the administration of Nusinersen is particularly complex
- The way of administration (daily oral administration at home instead of regular intrathecal administrations in hospital) may represent a much easier and more desirable way of use for patients and healthcare professionals
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NHS ENGLAND

3. Job title or position	[redacted], Highly Specialised Services
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **X** ☐ 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):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national NHSE clinical commissioning policies for spinal muscular atrophy
7. 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.)	NHS England commissions adult specialist neurosciences services (which includes both medical and surgical neurology as well as diagnostics) and specialist neurosciences services for children (multi-disciplinary diagnosis and management).
8. What impact would the technology have on the current pathway of care?	The technology would provide an additional treatment option for patients but would not alter the current pathway of care.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	This medication is currently available through an Early Access to Medicine Scheme (EAMS) at specialised paediatric and adult centres using eligibility criteria.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is anticipated that the technology would be administered through the existing arrangements according to any eligibility criteria determined by NICE.
• How does healthcare resource use differ between the technology and current care?	This drug is administered orally
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It is anticipated that patients/carers will be trained to administer the drug at home; some caution is required because of the drug's teratogenicity
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	No additional testing

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No additional equality issues
12b. Consider whether these issues are different from issues with current care and why.	

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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. Your response should not be longer than 10 pages.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**DR AYESHA ALI**
2. Name of organisation	**NHS ENGLAND**

3. Job title or position	**MEDICAL ADVISOR, HIGHLY SPECIALISED SERVICES**
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **X**☐ 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?	There are no national NHSE clinical commissioning policies for spinal muscular atrophy (SMA)
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	The pathway of care is well defined for this patient group and there are no significant differences of opinion between the professionals.

experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	This technology will provide an additional treatment option for patients with SMA
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 not routinely commissioned and is currently only accessible via an EAMS scheme
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be administered through existing commissioning arrangements
• How does healthcare resource use differ between the technology and current care?	The technology would provide an important alternative treatment option for this cohort due to mechanism of administration.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology would be delivered within the existing neuroscience centres and where clinically appropriate via homecare
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	
10. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England
Equality	

11a. Are there any potential equality issues that should be taken into account when considering this treatment?	No additional health inequality issues.
11b. Consider whether these issues are different from issues with current care and why.	

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.

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Risdiplam for treating spinal muscular atrophy: A Single Technology Appraisal

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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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 Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mark Clowes critiqued the company's search strategy. Emma Hock summarised and critiqued the clinical effectiveness evidence reported within the company's submission. John Stevens critiqued the statistical aspects of the submission. Paul Tappenden, Aline Navega Biz and Andrew Rawdin critiqued the company's health economic analyses and undertook the exploratory analyses. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse event
AFO	Ankle-foot orthosis
AIC	Akaike Information Criterion
ALS	Amyotrophic lateral sclerosis
ASA	Additional sensitivity analysis
AVXS-101	Onasemnogene abeparvovec
BIC	Bayesian Information Criterion
BiPAP	Bilevel Positive Airway Pressure
BSC	Best supportive care
BSID-III	Bayley Scales of Infant and Toddler Development - Third Edition
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Controlled Register of Trials
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CS	Company's submission
CSR	Clinical Study Report
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis
EC	European Commission
ECG	Electrocardiogram
EFS	Event-free survival
EMA	European Medicines Agency
Embase	Excerpta Medica Database
EoL	End of Life
EQ-5D-3L	Euroqol 5-Dimensions (3-level)
EQ-5D-5L	Euroqol 5-Dimensions (5-level)
EQ-5D-Y	Euroqol 5-Dimensions - youth
ERG	Evidence Review Group
ESS	Effective sample size
EU	European Union
FAD	Final Appraisal Determination
GOSH	Great Ormond Street Hospital
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE-2	Hammersmith Infant Neurological Examination Module 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HST	Highly Specialised Technology
ICER	Institute for Clinical and Economic Review
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITQOL-SF47	Infant and Toddler Quality of Life Questionnaire (47 item short form)
ITT	Intention-to-treat
KAFO	Knee-ankle-foot-orthosis
Kg	Kilogram
LYG	Life year gained
MAA	Managed Access Agreement

MAIC	Matching-adjusted indirect comparison
MCMC	Markov Chain Monte Carlo
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical subject heading
MFM32	Motor Function Measure - 32 items
Mg	Milligram
MSM	Multistate model
N/a	Not applicable
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
OR	Odds ratio
OS	Overall survival
PAG	Patient Association Group
PAS	Patient Access Scheme
PedsQL-NMM	Paediatric Quality of Life Inventory Neuromuscular Module
pre-mRNA	Precursor messenger ribonucleic acid
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PV	Permanent ventilation
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RULM	Revised Upper Limb Module
RWE	Real world evidence
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMAIS	SMA independence scale
SMN	Survival motor neuron
SMN1	Survival motor neuron 1
SMN2	Survival motor neuron 2
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TA	Technology Appraisal
TP	Transition probability
TSD	Technical Support Document
TTO	Time-trade-off
UK	United Kingdom
US	United States
WHO	World Health Organization
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision-making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. The results of the ERG's exploratory analyses are presented in Section 1.7. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

The company's submission (CS) includes two economic models of risdiplam for the treatment of spinal muscular atrophy (SMA):

- Type 2/3 SMA model (later onset). This model compares risdiplam versus best supportive care (BSC) for a combined population of patients with Type 2 and Type 3 SMA, and is informed by the SUNFISH randomised controlled trial (RCT), external data and assumptions.
- Type 1 SMA model (early onset). This model compares risdiplam versus BSC for patients with Type 1 SMA and is informed by the single-arm FIREFISH study of risdiplam, the placebo (sham) arm of the ENDEAR trial, other external data and assumptions.

The key issues identified by the ERG are summarised in Table 1.

Table 1: Overview of the ERG's key issues

ID1631	Summary of issue	Report sections
Issue 1	No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients	3.1
Issue 2	Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA	4.4
Issue 3	Uncertainty surrounding long-term benefits of risdiplam.	4.2.1.5
Issue 4	Caregiver QALY gain calculations implicitly assume that caregivers die or survive with utility equal to zero after the SMA patient dies	5.3.4
Issue 5	The company's models do not include any discontinuation from risdiplam	5.3.4
Issue 6	The company's models assume that in the subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely	5.3.4
Issue 7	The company's models predict that a large proportion of patients will reach the milestones of standing or walking, which appears to be optimistic.	5.3.4
Issue 8	None of the patient utility values for SMA are ideal; caregiver utility values by motor milestone are not available	5.3.4
Issue 9	The company's modelling assumptions are inconsistent with those used to inform decision-making in TA588 (nusinersen for SMA)	5.3.4
Issue 10	The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills	5.3.4
Issue 11	It is unclear whether NICE's End of Life criteria apply in Type 1 SMA	6

The key differences between the company's preferred assumptions and the ERG's preferred assumptions relate to:

(i) The long-term benefits of risdiplam – the company's models assume indefinite treatment benefits whereas the ERG assumes a plateau after which risdiplam-treated patients cannot achieve additional motor milestones.

(ii) The approach used to estimate relative treatment effects for risdiplam versus BSC in Type 1 SMA – the company's base case model uses naïve unadjusted comparisons whereas the ERG uses the company's matching-adjusted indirect comparison (MAIC).

(iii) The source of patient utility values – the ERG prefers the non-preference-based utility estimates used in the final models which informed NICE Technology Appraisal 588 (TA588; nusinersen for SMA), whilst the company uses a published EQ-5D vignette study in Type 2/3 SMA and other non-preference based estimates from TA588 in Type 1 SMA.

(iv) The approach used to estimate caregiver QALYs – the company's models assume that caregivers only gain health whilst the SMA patient is alive, whereas the ERG believes it is more appropriate to assume that the caregivers only lose health whilst the SMA patient is alive.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

In both models, risdiplam is assumed to affect QALYs by:

- Increasing the proportion of patients who achieve and maintain better motor milestones (standing and walking) relative to BSC. Backward transition probabilities to worse states for risdiplam are assumed to decrease (by [redacted] in Type 2/3 SMA and by 100% in Type 1 SMA) after 2 years and these assumed treatment effects apply indefinitely.
- Avoiding the need for permanent ventilation (PV; Type 1 SMA model only).
- Increasing overall survival (OS), relative to BSC, as lower mortality risks are applied in the better motor milestone health states (both models) and because an additional mortality risk reduction is applied to risdiplam-treated patients with Type 2 SMA who cannot stand or walk (Type 2/3 model SMA only).
- Generating additional caregiver QALYs, as caregiver utility is assumed to be higher for patients with more advanced motor milestones and because the company's model assumes that caregivers only gain health whilst the SMA patient is alive (see Issue 4).

Overall, risdiplam is assumed to affect costs by:

- Increasing total costs as a consequence of the acquisition cost of risdiplam
- Reducing health state costs, by reducing the amount of time that patients spend in the more expensive health states associated with limited motor milestone achievement.

Within both populations, the modelling assumptions that have the greatest effect on the ICER are:

- The assumed reductions in the probability of losing motor milestones for risdiplam-treated patients (applied after 2 years), together with the assumption that these treatment effects apply indefinitely.
- The company's erroneous assumption that caregivers accrue QALYs only whilst the SMA patient is still alive.
- It is likely that the inclusion of treatment discontinuation criteria would improve the cost-effectiveness of risdiplam; however, this has not been included in the company's models.
- The inclusion of potential additional health-related quality of life (HRQoL) benefits associated with gaining/maintaining upper limb function whilst on risdiplam could improve the ICERs for risdiplam; however, there is only evidence for Type 2/3 SMA and the magnitude of any potential benefits are unknown.

1.3 The decision problem: Summary of the ERG's key issues

The ERG considers the company's description of the underlying health problem and its impact on SMA patients and their caregivers to be appropriate. The decision problem addressed in the CS is generally in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). The target population in the CS is people with Type 1 or Type 2/3 SMA; this is narrower than the population defined in the NICE scope. The populations for whom no efficacy evidence is presented are summarised below. Whilst nusinersen is available through a Managed Access Agreement (MAA), this treatment option was not included as a comparator in the final NICE scope or in the CS.

Issue 1: No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients

Report section	3.1
Description of issue and why the ERG has identified it as important	The anticipated marketing authorisation states that risdiplam is [redacted] However, the CS presents evidence of clinical efficacy only for patients with Type 2/3 or Type 1 SMA. No evidence is presented for people with pre-symptomatic, Type 0 or Type 4 SMA. In addition, the company's intended positioning of risdiplam is as "*an additional therapeutic option for all patients across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status). This will include treatment-naïve patients, (i.e. those who choose not to receive or are unsuitable for nusinersen due to severe complications and those who are ineligible for the nusinersen MAA), as well as those patients who have previously received nusinersen but cannot tolerate it and/or respond poorly"* (company's clarification response, question A9). However, the CS does not present any evidence on the clinical efficacy of risdiplam in patients who are treatment-experienced.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	The clinical effectiveness and cost-effectiveness of risdiplam in these patient populations is unknown.
What additional evidence or analyses might help to resolve this key issue?	Ongoing studies will provide some evidence for the efficacy of risdiplam in patients with pre-symptomatic SMA (RAINBOWFISH) and previously-treated SMA (JEWELFISH); however, both of these are single-arm studies. There are no ongoing studies in people with Type 0 or Type 4 SMA.

1.4 The clinical effectiveness evidence: Summary of the ERG's key issues

The clinical evidence relating to risdiplam for treating SMA is based on two studies – SUNFISH (Part 2), a double-blind Phase II/III RCT, which examined the efficacy of risdiplam for treating Type 2 and non-ambulant Type 3 SMA, and FIREFISH (Part 2), a Phase II/III open-label single-arm study, which examined the efficacy of risdiplam for the treatment of Type 1 SMA.

The primary outcome of SUNFISH was motor function, assessed as the change from baseline to Month 12 in Motor Function Measure – 32 items (MFM32) total score. There was a greater improvement in MFM32 total score at Month 12 in the risdiplam arm (least squares mean change 1.36; SE 0.38) than in the placebo arm (least squares mean change -0.19; standard error [SE] 0.52), which showed a slight decline in function. The least squares mean difference between arms was 1.55 (95% confidence interval [CI]: 0.30, 2.81, unadjusted p=0.0156, adjusted p=0.0156). There were small, clinically meaningful improvements from baseline to Month 12 for risdiplam relative to placebo in motor function as assessed by the total Hammersmith Functional Motor Scale Expanded (HMFSE) score, upper limb function, as assessed by the Revised Upper Limb Module (RULM) total score and MFM32 distal motor function (D3) score, and independence, as assessed by the SMA Independence Scale (SMAIS) total score. In the risdiplam arm, four patients at Week 35 and five patients at Weeks 17 and 53 reached standing and walking motor milestones, compared with no patients in the placebo arm. In terms of adverse events (AEs), risdiplam appears to be generally well tolerated among patients with Type 2/3 SMA.

The primary outcome of FIREFISH was the proportion of infants sitting without support for five seconds after 12 months of treatment, as assessed by Independent Central Readers using the Bayley Scales of Infant and Toddler Development - Third Edition (BSID-III). Twelve of 41 patients (29.3%; 90% CI: 17.8, 43.1%) were sitting without support for five seconds, as assessed by the BSID-III, at Month 12, which is statistically significantly greater than the performance criterion of 5% (p<0.0001), and is clinically meaningful. Nine patients (22.0%; 90% CI: 12.0, 35.2%) were able to support weight or stand with support, as assessed by the Hammersmith Infant Neurological Examination Module 2 (HINE-2) at Month 12, and one patient (2.4%; 90% CI: 0.1, 11.1%) was able to bounce (the highest milestone on the 'walking' subscale of the HINE-2), at Month 12. Thirty-five patients (85.4%; 90% CI: 73.4, 92.2%) were alive without permanent ventilation at Month 12, and 38 patients (92.7%%; 90% CI: 82.2, 97.1%) were alive at Month 12. In terms of AEs, risdiplam appears to be generally well tolerated among patients with Type 1 SMA.

In order to assess the relative effectiveness of risdiplam in Type 1 SMA, the company performed a matching-adjusted indirect comparison (MAIC) using data from FIREFISH and the placebo arm of the ENDEAR RCT. This MAIC suggests that risdiplam is more effective than placebo in terms of OS (hazard ratio [HR] from company's updated analyses] = [redacted]; 95% CI: [redacted]), ventilation/event-free survival ([EFS] HR from updated analyses = [redacted]; 95% CI: [redacted]) and motor milestone achievement (odds ratio [OR] sitting with/without support = [redacted], 95% CI: [redacted]; OR standing with support/unaided = [redacted], 95% CI [redacted]). Given the unanchored nature of these comparisons, these estimates of relative treatment effects should be considered highly uncertain. It should also be noted that the company's base case Type 1 SMA model uses treatment effect estimates from unadjusted arm-based comparisons rather than those obtained from the MAIC.

The ERG is confident that no additional published or unpublished studies of risdiplam for treating SMA are likely to have been missed from the CS. The ERG's clinical advisor confirmed that the eligibility criteria for both SUNFISH and FIREFISH are representative of the Type 2/3 SMA and Type 1 SMA patients seen in routine clinical practice in England, except for the exclusion of ambulant Type 3 patients in SUNFISH Part 2 (although these only account for a small proportion of SMA patients). Key uncertainties in the clinical effectiveness evidence include issues surrounding the relative efficacy of risdiplam in Type 1 SMA, uncertainty surrounding the long-term benefits of risdiplam, and uncertainty concerning the validity of the SMAIS measure used to assess function-related independence in SUNFISH. These first two of these issues are discussed further below; the SMAIS is not discussed further as this measure is not used in the company's models.

Issue 2: Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA

Report section	4.4 and 5.3
Description of issue and why the ERG has identified it as important	There are no trials comparing risdiplam with BSC in patients with Type 1 SMA. The only study examining the efficacy of risdiplam in this population is FIREFISH, a single-arm open-label study. This raises several issues. First, the single-arm study design increases the possibility of potential biases such as attrition bias, natural recovery and regression to the mean, and the open-label nature of assessment may have impacted on the reporting of outcomes. The lack of any studies directly comparing risdiplam with BSC has necessitated the use of an indirect comparison. Whilst the CS reports the results of an unanchored MAIC of risdiplam using the placebo arm of the ENDEAR trial, the company's Type 1 SMA model uses unadjusted treatment effect estimates from a naïve comparison of these studies. Unanchored MAICs rely on strong assumptions, i.e. that all effect modifiers and prognostic variables are known and accounted for in the adjustment model. However, the ERG believes that this approach is preferable to ignoring the potential confounding effects of baseline imbalances in covariates between the study populations.
What alternative approach has the ERG suggested?	The ERG's preferred analysis for the Type 1 SMA population includes relative treatment effect estimates obtained from the company's MAICs for ventilation-free survival, OS and motor milestone transitions.
What is the expected effect on the cost-effectiveness estimates?	The inclusion of the treatment effects from the company's MAICs increases the ERG's corrected ICER for risdiplam versus BSC from [redacted] to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Evidence from an RCT would be preferable; however, such studies are not available. Whilst the company's indirect comparisons indicate that risdiplam is more effective than BSC, the results of this comparison are subject to considerable uncertainty.

Issue 3: Uncertainty surrounding long-term benefits of risdiplam

Report section	4.2.1.5
Description of issue and why the ERG has identified it as important	The SUNFISH and FIREFISH studies are ongoing. At the time of writing, 12-month data are available from both studies. In the SUNFISH trial, the placebo-controlled period ended at Month 12, thus even if further data were available from the 24-month treatment period, there would be no additional comparative data on the efficacy of risdiplam. Therefore, although both the SUNFISH and FIREFISH studies demonstrated a benefit of risdiplam in Type 2/3 and Type 1 SMA from baseline to Month 12, whether and to what extent this benefit persists beyond 12 months (and whether there are further improvements) is unknown. Very few patients achieved the milestone of walking in SUNFISH and no patients achieved walking in FIREFISH, yet as a consequence of numerous assumptions, both of the company's models predict that a substantial proportion of patients will reach the milestones of standing and walking within their lifetime (see Issue 6 and Issue 7). This is highly uncertain and the company's model predictions should be approached with caution.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Applying less optimistic assumptions regarding long-term treatment benefits has a marked impact on the cost-effectiveness of risdiplam (see Issue 6).
What additional evidence or analyses might help to resolve this key issue?	Longer-term data from the Month 24 analyses of the FIREFISH and SUNFISH studies will provide some additional information on the extent to which risdiplam-treated patients can achieve and maintain the ability to stand and/or walk. However, much longer-term evidence is required to corroborate the assumptions employed in the company's models.

1.5 The cost-effectiveness evidence: Summary of the ERG's key issues

The company submitted two separate health economic models of risdiplam versus BSC for Type 2/3 and Type 1 SMA. Both models adopt a state transition approach, with health states defined according to motor milestone health states (sitting, standing and walking), survival status and the requirement for PV (Type 1 SMA model only). Mortality risk is assumed to be conditional on the patients' current motor milestone health state, with an additional survival benefit assumed for risdiplam-treated Type 2 SMA patients in the non-standing states in the Type 2/3 model. Both analyses estimate the incremental cost-effectiveness of risdiplam from the perspective of the NHS, including health gains accrued by SMA patients and their caregivers (2.2. caregivers per SMA patient). The company has proposed a Patient Access Scheme (PAS) which takes the form of a simple price discount of [redacted]; the discounted cost per bottle of risdiplam is [redacted]. All results presented within the main ERG report include the PAS; key results using the list price for risdiplam are presented in Appendix 2.

Within the Type 2/3 SMA model, monthly transition probabilities applied during the initial period (up to 2 years) are informed by transition probabilities derived from a multistate model fitted to clinical

data from SUNFISH (Part 2). Patient survival, patient utility and caregiver utility are assumed to be higher in patients who achieve better motor milestones (e.g. standing and walking). During the subsequent period (after 2 years), the probability that risdiplam-treated patients lose milestones is assumed to be reduced by [redacted]. This assumption is applied indefinitely. The model predicts that up to [redacted] of risdiplam-treated patients will be able to stand or walk; as a consequence of this improved motor milestone trajectory, the model predicts that risdiplam is associated with an incremental OS gain of 12.76 years compared with BSC. The deterministic version of the company's Type 2/3 SMA model suggests that the ICER for risdiplam versus BSC is [redacted] per QALY gained.

Within the Type 1 SMA model, monthly transition probabilities for risdiplam-treated patients applied during the initial period (up to 2 years) are informed by clinical data from FIREFISH (all Part 2 patients and those Part 1 patients who received the final dose of risdiplam), together with an assumption that after 18 months (when patients are aged 2 years), a proportion of patients who can stand will achieve walking. Transition probabilities for the BSC group are based on an unadjusted arm-based indirect comparison of data from FIREFISH and the placebo arm of ENDEAR. Patient survival, patient utility and caregiver utility are assumed to be higher in patients who achieve better motor milestones (e.g. standing and walking). During the subsequent period (after 2 years), the model assumes that risdiplam-treated patients cannot lose motor milestones. This assumption is applied indefinitely. The model predicts that up to [redacted] of risdiplam-treated patients will be able to stand or walk; as a consequence of this improved motor milestone trajectory, the model predicts that risdiplam is associated with an incremental OS gain of 16.00 years compared with BSC. The deterministic version of the company's Type 1 SMA model suggests that the ICER for risdiplam versus BSC is [redacted] per QALY gained.

The ERG's key issues regarding the company's economic analyses are described in detail below.

Issue 4: Caregiver QALY gain calculations implicitly assume that caregivers die or survive with utility equal to zero after the SMA patient dies

Report section	5.3.4
Description of issue and why the ERG has identified it as important	The company's models predict that risdiplam generates substantial QALY gains for caregivers of SMA patients which lead to ICERs which are markedly lower than those which account only for QALYs accrued by SMA patients. The ERG believes that both of the company's models are subject to an unintended and erroneous assumption – that caregivers die (or survive with utility equal to zero) when the SMA patient dies. This is incorrect as caregivers will continue to accrue health gains after the SMA patient has died. This error leads to artificially low ICERs for risdiplam in both populations.
What alternative approach has the ERG suggested?	The ERG believes that the company's models should instead estimate caregiver QALY losses avoided, whereby caregiver QALY losses (calculated as a decrement from general population utility) apply only whilst the patient with SMA is alive. This approach was used in TA588.
What is the	The company's Type 2/3 SMA model suggests that the ICER for risdiplam

expected effect on the cost-effectiveness estimates?	versus BSC is [redacted] per QALY gained. The ERG's error-corrected Type 2/3 SMA model suggests a higher ICER of [redacted] per QALY gained. The company's Type 1 SMA model suggests that the ICER for risdiplam versus BSC is [redacted] per QALY gained. The ERG's error-corrected Type 1 SMA model suggests a higher ICER of [redacted] per QALY gained. It should be noted that the ERG's corrected models include other amendments; however, the other corrections have a comparatively smaller impact on the model results.
What additional evidence or analyses might help to resolve this key issue?	The ERG's exploratory analyses resolve this issue.

Issue 5: The company's models do not include any discontinuation from risdiplam

Report section	5.3.4
Description of issue and why the ERG has identified it as important	The models assume that patients remain on risdiplam treatment until death, irrespective of whether they lose or ever gain motor milestones. There are several problems with the company's approach: • Given that some discontinuation was observed in SUNFISH and FIREFISH, it is inappropriate to assume zero discontinuation within the models. • Treatment stopping criteria are useful for clinicians, as in their absence, it can be very difficult for clinicians to obtain agreement from patients and families to discontinue treatment if the patient is not obtaining benefit from it and it is clinically appropriate to do so. • Continuing to administer an expensive treatment to patients who are not benefitting from it does not represent an efficient use of health care resources. Determining clinically appropriate discontinuation criteria may improve the cost-effectiveness of risdiplam. However, the ERG notes the following additional factors: • The limitations of the company's model structures mean that certain discontinuation criteria (e.g. repeated worsening) cannot be appropriately modelled. • Determining clinically appropriate discontinuation criteria is likely to be difficult. • The Type 1 SMA model assumes that no patient worsens after 2 years which may suggest that discontinuation is not appropriate.
What alternative approach has the ERG suggested?	The ERG believes that the company should consider whether clinically appropriate discontinuation criteria can be determined. The ERG's clinical advisor commented that consideration might be given to factors such as: progression to PV; the incidence of AEs, and the repeated loss of motor function despite continued treatment.
What is the expected effect on the cost-effectiveness estimates?	It is likely that the application of clinically appropriate discontinuation criteria would improve the cost-effectiveness of risdiplam; however, the magnitude of their impact on the ICERs in Type 2/3 and Type 1 SMA is unknown.
What additional evidence or analyses might help to resolve this key issue?	The ERG believes that this is a matter for the company to consider. Clinical input from the SMA community, practising clinicians and NHS England will be essential in ensuring that discontinuation criteria are clinically appropriate, acceptable to patients and operationally feasible.

Issue 6: The company's models assume that in the subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely

Report section	5.3.4
Description of issue and why the ERG has identified it as important	During the subsequent period (after 2 years), the Type 2/3 SMA model assumes that the probability that risdiplam-treated patients lose motor milestones is reduced by [redacted] relative to the initial 2-year period, whilst the Type 1 SMA model assumes that risdiplam-treated patients cannot lose motor milestones after this timepoint. Within the Type 2/3 SMA model, a mortality adjustment factor of 0.75 (relative to mortality risk for BSC-treated patients) is assumed for risdiplam-treated patients with Type 2 SMA in the non-standing states. These assumptions override the probabilities obtained from the company's statistical analyses of transitions and survival. Overall, both models assume that risdiplam-treated patients are on a general trajectory of improvement towards the best motor milestone health states (standing and walking). The ERG has several concerns regarding these assumptions: • The assumptions were not obtained using formal elicitation • The models treat these assumptions as fixed parameter values without any consideration of uncertainty • The summary of the company's advisory board meetings (CS Appendix N) indicates that [redacted] • [redacted]. The ERG requested the minutes of the meetings; however, the company did not supply these. • It is unclear whether the company's clinical experts suggested the assumptions, or whether they were suggested by the company and ratified by their clinical advisors. • It is unclear whether the company's clinical advisors were asked to comment on the plausibility of the modelled milestone trajectories and OS projections resulting from the use of these assumptions. • The assumption of lifetime treatment effects is inconsistent with the final iterations of the models used to inform NICE TA588 (nusinersen for SMA), in which a treatment benefit plateau was applied (after Month 26 in later onset SMA and after Month 66 in early onset SMA). The company's assumptions lead to highly optimistic predictions of motor milestone achievement for risdiplam (see Issue 7).
What alternative approach has the ERG suggested?	The ERG does not consider it reasonable to assume that treatment effects apply indefinitely and believes that there is little justification for applying more optimistic assumptions than those used in TA588. The inclusion of a plateau in treatment benefit reduces the proportion of risdiplam-treated patients predicted to reach the milestones of standing and walking, which, in turn, reduces incremental OS gains for risdiplam.
What is the expected effect on the cost-effectiveness estimates?	Within the Type 2/3 SMA model, including a treatment benefit plateau after Month 26 increases the ERG's corrected ICER from [redacted] to [redacted] per QALY gained. Within the Type 1 SMA model, including a treatment benefit plateau after Month 66 increases the ERG's corrected ICER from [redacted] to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Given the available evidence, the ERG believes that it is reasonable to apply similar assumptions to those accepted in TA588. Longer-term evidence from SUNFISH and FIREFISH could help to clarify whether the company's assumptions are reasonable, although this would require very long periods of follow-up. Formal elicitation of expert beliefs regarding the long-term effects of risdiplam may have been valuable.

Issue 7: The company's models predict that a large proportion of patients will reach the milestones of standing or walking, which appears to be optimistic

Report section	5.3.4
Description of issue and why the ERG has identified it as important	The ERG believes that the company's modelled trajectories of motor milestone achievement and OS are highly optimistic. *Type 2/3 SMA model* The company's Type 2/3 SMA model predicts that by age 35 years, [redacted] of risdiplam-treated patients will be able to stand or walk and by a similar age, [redacted] of patients will be able to walk. The model also predicts that risdiplam generates an incremental OS gain of 12.76 years versus BSC. The ERG highlights the following key concerns: • The company's assumptions for BSC are generally appropriate. However, some Type 3 patients who receive BSC will be able to stand and walk at older ages. • The ERG's clinical advisor commented that: a) There is no reason to believe that the treatment effect of risdiplam on motor function would be better in the long-term than in the period for which observed data exist. b) There is uncertainty regarding whether short-term benefits of risdiplam would be sustained into the longer-term. c) It is unreasonable to expect that patients who have not previously been able to stand or walk will achieve these milestones at later ages, and many patients will develop contractures which would preclude standing and/or walking. • The final iterations of the later onset model in TA588 included an assumed plateau in treatment benefit which resulted in a smaller proportion of patients reaching the standing and walking health states and lower survival gains (for nusinersen). *Type 1 SMA model* The company's model indicates that by age 16 years, around [redacted] of risdiplam-treated patients will be able to stand or walk and by age 29 years, [redacted] of patients will be able to walk. The model predicts that risdiplam generate an incremental OS gain of 16.00 years versus BSC. The ERG highlights the following key concerns: • The company's estimated OS for BSC of 10.11 years is not clinically realistic. It is unlikely that Type 1 patients receiving BSC alone would survive to the age of 50 years or older. • The ERG's clinical advisor commented that: a) The assumption that no risdiplam-treated patients will ever lose milestones is not reasonable. Whilst patients might become stable on treatment, the company's assumption of continued improvement is not reasonable. b) Given that no patients achieved the milestone of walking in FIREFISH, the company's prediction that more than [redacted] of patients will achieve walking in the long-term is highly optimistic. c) The company's modelled OS projection for risdiplam appears to be optimistic. • The final iterations of the early onset model in TA588 included an assumed plateau in treatment benefit which resulted in a smaller proportion of patients reaching the standing and walking health states and lower survival gains (for nusinersen).

What alternative approach has the ERG suggested?	The ERG believes that two model amendments are appropriate: (i) In the Type 1 SMA model, the HRs obtained from the company's updated MAICs should be used in preference to the unadjusted comparisons (ii) In line with TA588, it may be reasonable to apply similar assumptions of a treatment benefit plateau for risdiplam.
What is the expected effect on the cost-effectiveness estimates?	The impact of including an assumed treatment benefit plateau for risdiplam is detailed above (see Issue 6). Within the Type 1 SMA model, the inclusion of the relative treatment effect estimates on EFS, OS and motor milestones from the company's MAICs increase the ERG's error-corrected ICER from [redacted] to [redacted] per QALY gained. This higher ICER is largely explained through the lower survival and lower health state costs for the BSC group.
What additional evidence or analyses might help to resolve this key issue?	The ERG believes that the ERG's preferred analyses may adequately address this issue.

Issue 8: None of the patient utility values for SMA are ideal; caregiver utility values by motor milestone are not available

Report section	5.3.4
Description of issue and why the ERG has identified it as important	Within the Type 2/3 SMA model, patient utility values are based on an EQ-5D vignette study (Lloyd *et al.*). Within the Type 1 SMA model, patient utility values are based on non-preference-based estimates obtained from the ERG's clinical advisors in TA588. Caregiver utility values were based on time-trade-off (TTO) estimates from Spanish caregivers (Lopez-Bastida *et al.*), general population utility (Ara and Brazier) and assumptions. As discussed in TA588, measuring and valuing health in children is very difficult and none of the available patient utility estimates for SMA are ideal. The final iterations of the TA588 models used non-preference-based patient utility estimates obtained from Biogen's clinical advisors. During that appraisal, the ERG agreed that this was likely to be the most appropriate approach, but noted several caveats. Given the company's intention to align with TA588, it is unclear why different sources of patient utility values have been used in the risdiplam models. The ERG notes that caregiver utility values associated with SMA patients achieving specific motor milestones are not available, and this aspect of the model is largely informed by assumptions. As such, any estimates of caregiver QALY gains should be interpreted with caution. In addition, the ERG notes that both risdiplam models assume that each SMA patient has 2.2 caregivers, whereas the final iteration of the later onset model in TA588 assumed that patients who cannot sit require 3 caregivers.
What alternative approach has the ERG suggested?	In the absence of more appropriate values, the ERG believes that it is reasonable to use the non-preference-based patient utility estimates obtained from Biogen's clinical advisors in TA588, together with the increased number of caregivers for non-sitters (Type 2/3 model only).
What is the expected effect on the cost-effectiveness estimates?	Within the Type 2/3 SMA model, the inclusion of Biogen's clinical advisors' patient utility estimates and the inclusion of 3 caregivers for patients who are unable to sit increases the ERG's corrected ICER from [redacted] to [redacted] per QALY gained. Within the Type 1 SMA model, the inclusion of Biogen's clinical advisors' patient utility estimates increases the ERG's corrected ICER from [redacted] to [redacted] per QALY gained.

What additional evidence or analyses might help to resolve this key issue?	The ERG believes that the ERG exploratory analyses adequately address this issue. Further preference-based health valuation studies in people with SMA and their caregivers would be valuable.

Issue 9: The company's modelling assumptions are inconsistent with those used to inform decision-making in TA588 (nusinersen for SMA)

Report section	5.3.4
Description of issue and why the ERG has identified it as important	Several aspects of the risdiplam models are inconsistent with the final models used to inform TA588. The assumptions applied in the risdiplam models lead to highly optimistic estimates of motor milestone trajectories and OS gains. The ERG believes that the most important inconsistencies relate to: • The company's approach used to value caregiver QALY gains (see Issue 4) • The presence/absence of an assumption of a plateau in motor milestone achievement (see Issue 6 and Issue 7) • The absence of discontinuation criteria for risdiplam (see Issue 5) • Unrealistically optimistic estimates of OS for patients receiving BSC in the Type 1 SMA risdiplam model (see Issue 7) • Inconsistent sources of patient utility values (see Issue 8).
What alternative approach has the ERG suggested?	The ERG believes that the risdiplam models should be generally aligned with the assumptions which were accepted by the Appraisal Committee in TA588.
What is the expected effect on the cost-effectiveness estimates?	The ERG's preferred analyses attempt to align the risdiplam models with the final models used in TA588. Within the Type 2/3 SMA model, the ERG's preferred analysis results in an ICER of [redacted] per QALY gained. This is considerably higher than the company's base case ICER of [redacted] per QALY gained. Within the Type 1 SMA model, the ERG's preferred analysis results in an ICER of [redacted] per QALY gained. This is considerably higher than the company's base case ICER of [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The ERG believes that the key uncertainties relate to uncertainty regarding the long-term benefits of risdiplam in terms of motor milestone achievement and survival, and uncertainties regarding HRQoL impacts on patients with SMA and their caregivers. In the absence of further evidence through which to corroborate the company's optimistic assumptions, the ERG's preferred analyses, which are intended to be consistent with the final models used in TA588, represent a more reasonable starting point for discussions on the cost-effectiveness of risdiplam.

Issue 10: The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills

Report section	5.3.4
Description of issue and why the ERG has identified it as important	The company's models assume that patient utility values are dependent on gross motor milestone health states but are independent of treatment group. The ERG notes that other factors besides gross motor milestone achievement may impact on patients HRQoL. In particular, for patients who lose ambulation, maintaining upper limb function may become increasingly important as it means that they can still perform certain basic tasks and

	retain some level of independence. In SUNFISH, a clinically meaningful improvement in RULM total score was reported for risdiplam over placebo. The ERG does not believe that these potential differences in HRQoL are reflected in the company's models. The inclusion of additional HRQoL benefits for risdiplam-treated patients will result in lower ICERs; however, empirical estimates of the magnitude of such HRQoL effects are absent.
What alternative approach has the ERG suggested?	The ERG's additional sensitivity analyses include additional utility gains of 0.05 and 0.10 for risdiplam-treated patients in the non-sitting and sitting states, respectively, based on a previous economic analysis reported by Thokala *et al.* However, these values are assumptions and are not evidence-based.
What is the expected effect on the cost-effectiveness estimates?	Within the Type 2/3 SMA model, the inclusion of these additional utility gains reduces the ERG's preferred ICER from [redacted] to [redacted] per QALY gained. Within the Type 1 SMA model, the inclusion of these additional utility gains reduces the ERG's preferred ICER from [redacted] to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Evidence regarding the HRQoL impact associated with improvements in fine motor skills is required to quantify the actual impact on the ICER for risdiplam.

1.6 Other key issues: Summary of the ERG's view

The CS argues that NICE's End of Life (EoL) criteria should apply to the Type 1 SMA population. Whilst the company acknowledges that the criteria are unlikely to apply for Type 2/3 SMA patients, the company argues that decision modifiers should be taken into account due to the rarity of the condition and its impact on SMA patients and caregivers. This issue is discussed below.

Issue 11: It is unclear whether NICE's End of Life criteria apply in Type 1 SMA

Report section	6
Description of issue and why the ERG has identified it as important	The CS highlights that NICE's EoL criteria were recognised in TA588. Evidence suggests that the median time to death or permanent respiratory support is less than 2 years. The CS also highlights that OS in FIREFISH was significantly higher than the pre-specified performance criterion based on natural history studies. The company's model predicts an incremental OS gain of 7.29 years in Type 1 SMA. The ERG notes that the company's model suggests that the mean OS for BSC-treated patients is 10.11 years and the company's modelled OS predictions for risdiplam are likely to be optimistic. As such, the ERG is unclear whether risdiplam meets NICE's EoL criteria.
What alternative approach has the ERG suggested?	The ERG believes that OS in the company's Type 1 SMA model should be informed by the MAIC, alongside other model amendments included within the ERG's preferred analysis. This results in a lower mean OS of 4.88 years for the BSC group, which may still be implausibly high. This estimate is still considerably higher than the 24-month duration specified as part of the EoL criteria.
What is the expected effect on	Not applicable

the cost-effectiveness estimates?	
What additional evidence or analyses might help to resolve this key issue?	Long-term RCTs comparing risdiplam versus BSC in Type 1 OS would provide useful evidence to resolve this issue; however, such studies are unlikely to be performed.

1.7 Summary of ERG's preferred assumptions and resulting ICER

Type 2/3 SMA model

The results of the ERG's exploratory analyses for the Type 2/3 SMA population are summarised in Table 2. Each analysis reflects individual model amendments relative to the ERG-corrected version of the model (EA1). The ERG's preferred analysis suggests that the ICER for risdiplam versus BSC is [redacted] per QALY gained. This is considerable higher than the company's base case ICER of [redacted] per QALY gained.

Table 2: Summary of ERG preferred assumptions and ICER – Type 2/3 SMA model

Scenario	Incremental QALYs (patients + caregivers)	Incremental cost	ICER (change from company base case)
Company's base case model	22.15	[redacted]	[redacted]
EA1: Correction of errors	16.48		
EA3: TA588 patient utility values and number of caregivers =3 for non-sitters	15.72		
EA4: Assumption of treatment plateau after 26 months	11.70	[redacted]	[redacted]
EA5: Inclusion of drug wastage (0.50 bottles)	16.48	[redacted]	
EA6: ERG-preferred analysis	11.89	[redacted]	
ASA1: Additional utility gains for non-sitters and sitters	13.69	[redacted]	
ASA2a: Risdiplam worsening probability =1%	3.18	[redacted]	
ASA2b: Risdiplam worsening probability =2%	0.48	[redacted]	
ASA3a: Assumption of treatment plateau after 38 months	12.68	[redacted]	
ASA3b: Assumption of treatment plateau after 14 months	11.84	[redacted]	
ASA4: Initial period transition probabilities applied without adjustments until plateau timepoint	11.68	[redacted]	

EA - exploratory analysis; ASA - additional sensitivity analysis; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

Type 1 SMA model

The results of the ERG's exploratory analyses for the Type 1 SMA population are summarised in Table 3. Each analysis reflects individual model amendments relative to the ERG-corrected version of the model (EA1). The ERG's preferred analysis suggests that the ICER for risdiplam versus BSC is [redacted] per QALY gained. This is considerable higher than the company's base case ICER of [redacted] per QALY gained.

Table 3: Summary of ERG preferred assumptions and ICER – Type 1 SMA model

Scenario	Incremental QALYs (patients + caregivers)	Incremental cost	ICER (change from company base case)
Company's base case model	22.74	[redacted]	[redacted]
EA1: Correction of errors	8.03		
EA2: Inclusion of treatment effects estimated from MAIC	5.57		
EA3: TA588 patient utility values and number of caregivers =3 for non-sitters	7.88	[redacted]	[redacted]
EA4: Assumption of treatment plateau after 66 months	5.20	[redacted]	
EA5: Inclusion of drug wastage (0.50 bottles)	8.03	[redacted]	
EA6: ERG-preferred analysis	1.21	[redacted]	
ASA1: Additional utility gains for non-sitters and sitters	1.91	[redacted]	
ASA2a: Risdiplam worsening probability =1%	-2.12	[redacted]	
ASA2b: Risdiplam worsening probability =2%	-3.09	[redacted]	
ASA3a: Assumption of treatment plateau after 78 months	1.72	[redacted]	
ASA3b: Assumption of treatment plateau after 54 months	0.60	[redacted]	
ASA4: Initial period transition probabilities applied without adjustments until plateau timepoint	-1.44	[redacted]	

EA - exploratory analysis; ASA - additional sensitivity analysis; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; MAIC - matching-adjusted indirect comparison; N/a - not applicable

The ERG's full critique of the company's economic analyses and the ERG's exploratory analyses can be found in the main ERG report (Sections 5.3 and 5.4, respectively).

2 BACKGROUND

This chapter presents a brief summary and critique of the company's description of the disease and the current treatment pathway for spinal muscular atrophy (SMA) in England.

2.1 Critique of the company's description of the underlying health problem

The company's submission (CS)[1] contains a reasonable description of SMA and its impact on patients and their caregivers; this is briefly described below, together with additional information provided by the Evidence Review Group (ERG).

SMA is a progressive neuromuscular disease which results from mutations in the SMN1 gene on chromosome 5q. The disease causes muscle weakness which is progressive and results in loss of movement and physical disability. In addition to musculoskeletal impacts, SMA also has severe effects on the respiratory and gastrointestinal systems. SMA is rare and has been recognised as an orphan disease by the European Medicines Agency (EMA).[2] The disease is recognised as the most common genetic cause of death in infants.[3]

SMA affects the motor neurons (the nerves from the brainstem 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. The SMN protein is essential for the normal functioning and survival of motor neurons and in its absence, the motor neurons deteriorate and eventually die, subsequently leading to muscle weakness and atrophy.[2]

It has been estimated that one in 6,000 to 10,000 babies worldwide are born with a type of SMA.[4, 5] According to Spinal Muscular Atrophy UK, approximately 100 children with SMA are born in the UK each year and there are between 1,200 and 2,500 children and adults living with SMA in the UK.[6] The disease presents across a spectrum of severity and is classified into subtypes (Types 0-4) related to the age of onset and maximum motor achievement (see Table 4). Younger age of onset is generally associated with greater severity of disease and poorer prognosis. 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] Type 1 (infantile onset) and Types 2/3 (later onset) SMA represent approximately 99% of all cases. Other types of SMA (Type 0 and Type 4) are extremely rare. The diagnosis of Type 1 SMA usually occurs during the first year of life. Most patients with Type 2 SMA are diagnosed in their second year of life, whilst Type 3 SMA is typically diagnosed between the ages 2 and 3 years, but diagnosis may occur later. The CS[1] notes that classifying a spectrum disorder such as SMA into discrete subtypes is problematic due to overlap in diagnostic criteria between infantile onset and later onset patients.

Table 4: Classification and subtypes of SMA (adapted from CS, Table 3)

SMA type	Age at onset	Highest motor function achieved	Typical symptoms	Lifespan if untreated
0	Prenatal/foetal	Nil	Severe hypotonia	<6 months
1	<6 months	Sit with support only*	Respiratory failure	<2 years
2	≥6 to <18 months	Sit independently	Respiratory complications and wheelchair bound	>2 years
3	≥18 months to <18 years†	Stand and walk	Muscle weakness	Normal
4	Adult (2nd or 3rd decade)	Walk during adulthood	Very slow progressive muscle weakness	Normal

SMA - spinal muscular atrophy
**Patients with subtype 1c (onset 3-6 months) may develop some motor skills such as head control or rolling*
†Age of onset is 18 to 36 months for subtype 3a and 36 months to 18 years for subtype 3b

The evidence presented in the CS[1] is restricted to people with Types 1, 2 or 3 SMA; the characteristics of these disease types are described briefly below.

Type 1 SMA (early onset)

Type 1 SMA has been reported to be the most common and severe form of the disease, accounting for approximately 60% of all cases.[4, 5] Type 1 SMA is associated with a particularly poor prognosis and very low survival, with the majority of patients dying before their second birthday unless they receive ventilator support.[8] Symptoms appear early, typically before six months of age, and include severe hypotonia (decreased muscle tone), the inability to lift the head or poor head control, and poor feeding.[7] Maximal motor function achievement is very limited; by definition, patients with Type I SMA will never develop the ability to sit independently. Patients experience a range of severe problems including pulmonary, nutritional and gastrointestinal complications. Patients progressively experience loss of independent swallowing and respiratory function, leading to the requirement for ventilation support and feeding tubes. Despite the severity of symptoms and limited motor function achievement, cognitive ability in patients with Type 1 SMA is normal.

Type 2/3 SMA (later onset)

Type 2 and Type 3 SMA together account for around 40% of all cases. Compared with Type 1 disease, Type 2 and 3 SMA are less severe forms of the disease. Age of onset is usually between 6 and 18 months for Type 2 SMA, and between 18 months and adulthood for Type 3 SMA. Both Type 2 and Type 3 SMA are associated with a loss of motor function over time, together with a number of secondary complications. The severity of motor function impairment varies considerably between patients, with some patients with Type 3 SMA maintaining the ability to walk without assistance and others with Type 2 SMA becoming unable to sit without support.[9, 10] Scoliosis is universally present in patients with Type 2 disease. The lifetime risk of undergoing scoliosis surgery is around 80% in Type 2a SMA (with a similar risk in Type 1c SMA) and around 40% in Type 3 SMA.[11] Spinal bracing is used to assist with

seating and support the spine prior to surgery, but does not prevent progression of scoliosis.[12] Patients have an increased risk of respiratory disease, and weaknesses of the intercostal muscles in the chest lead to difficulties breathing and coughing, thereby resulting in ineffective secretion clearance, an increased risk of chest infections and respiratory failure. Survival of patients with Type 2 SMA is typically greater than 25 years, and many patients survive considerably longer as a consequence of more aggressive supportive care, particularly nutritional support and respiratory care with assisted coughing and ventilatory support.[7] Survival of patients with Type 3 SMA is believed to be similar to that for people without SMA. As with more severe types of SMA, cognitive ability in patients with Types 2 and 3 SMA is normal.

The CS[1] highlights the substantial impact of the disease on patients' health-related quality of life (HRQoL), particularly with respect to the impact of severe disability and impaired motor and respiratory function, pain, infections, the need for frequent hospital visits and ventilator support, lack or loss of independence, and the inability to perform basic personal tasks. The CS also highlights the considerable economic and emotional burden that the disease places on caregivers of people with SMA. In addition, the CS asserts that small improvements can make a significant difference to the ability of people with SMA and their families to function and thrive. The CS also highlights the value placed on the stabilisation of the disease and the avoidance of further deterioration.

2.2 Critique of the company's overview of current service provision

In 2019, NICE issued a positive recommendation on the use of nusinersen (Spinraza®) for the treatment of pre-symptomatic SMA, or Types 1, 2 or 3 SMA.[13] Nusinersen is available through a Managed Access Agreement (MAA); the entry criteria for the MAA are summarised in Box 1. As nusinersen is not currently funded through routine NHS commissioning, it is not included in the scope of this appraisal (see Section 3.3).

Box 1: Entry criteria for the Managed Access Agreement for nusinersen (reproduced from NICE website)

All patients entering the MAA must fulfil the following entry criteria (this aligns to Type I, II, III, and pre-symptomatic):

- No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline;
- Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated;
- Must not have received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration of nusinersen;
- Must not have severe contractures which, in the opinion of the treating clinician, prohibit measurement of motor milestones;
- If gained independent ambulation prior to initiation of therapy must still be independently ambulant, with the exception paediatric patients who have lost independent ambulation in the previous 12 months. Independent ambulation is defined as per the WHO definition: patient takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object;
- Must not be type IV SMA patient i.e. must not have symptom onset at or after 19 years of age.
- Must not be type 0 SMA patient.

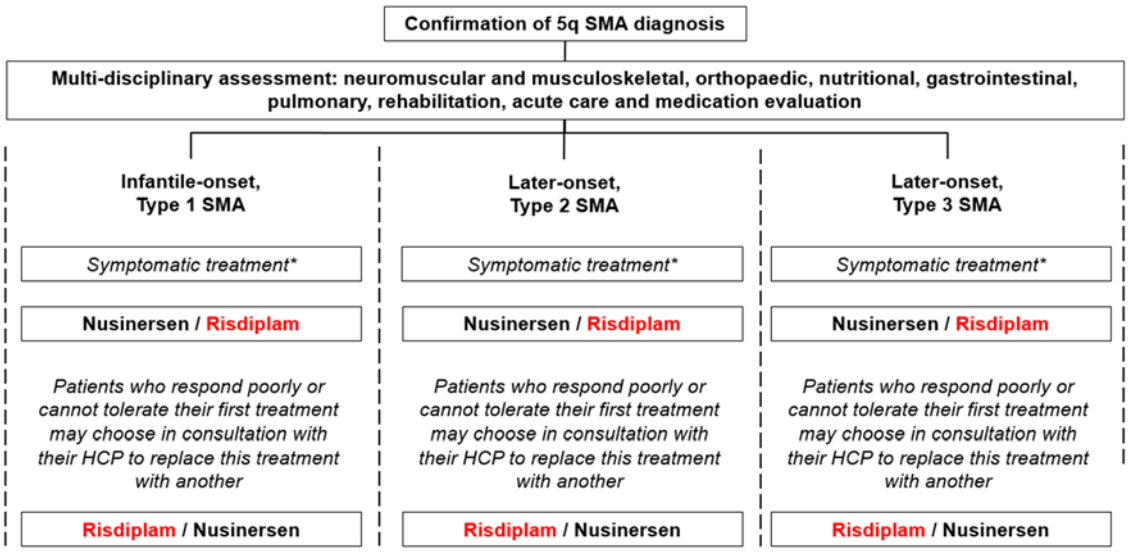
Providing a patient meets the entry criteria as specified above, due to equity considerations there is no upper limit of age on treatment initiation.

Onasemnogene abeparvovec (AVXS-101, Zolgensma®), a gene therapy medicine, is currently being appraised for the treatment of Type 1 SMA under the NICE Highly Specialised Technologies (HST) programme.[14] The NICE Final Appraisal Determination (FAD) is expected to be published in March 2021. This treatment is not currently available through routine NHS commissioning.

For patients who are not eligible for treatment with nusinersen under the MAA in England, best supportive care (BSC) remains the only treatment option. BSC is a multifaceted and holistic treatment approach, involving multidisciplinary care which is tailored to the needs of individual patients.[1] As described in the CS,[1] BSC includes: regular monitoring and support; postural management including the prevention and management of scoliosis and thoracic deformity and contractures; optimisation of nutrition; respiratory management including secretion clearance, immunisation, early treatment of infections and ventilatory support, and promotion of function with assistive technology and adaptive equipment.[15, 16]

The company's proposed positioning of risdiplam is shown in Figure 1. The company's clarification response[17] (question A9) describes the positioning of risdiplam as "*an additional therapeutic option for all patients across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status). This will include treatment-naïve patients, (i.e. those who choose not to receive or are unsuitable for nusinersen due to severe complications and those who are ineligible for the nusinersen MAA), as well as those patients who have previously received nusinersen but cannot tolerate it and/or respond poorly.*"

Figure 1: Company's proposed positioning of risdiplam in the pharmacologic treatment pathway for SMA (reproduced from company's clarification response, Figure 1)



SMA - spinal muscular atrophy; HCP - health care professional
**Symptomatic treatment will be based on individual clinical need and symptom severity following multi-disciplinary assessment*

The company's clarification response[17] (question A9) also states that *"It is important to clarify that risdiplam is not positioned as a first- or second-line treatment."* However, the ERG believes that the proposed positioning of risdiplam directly implies that risdiplam may be used as a second-line treatment following first-line nusinersen and that nusinersen might be used in the second-line setting after risdiplam. This is an important consideration as the CS[1] does not present any evidence to support the clinical effectiveness of risdiplam after nusinersen, or *vice versa*, and in line with the final NICE scope,[18] nusinersen is not included as a comparator in the company's clinical review or economic analyses. In addition, the company's economic models do not include nusinersen as a downstream treatment as patients are assumed to receive risdiplam indefinitely (see Section 5.2).

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 scope issued by the National Institute for Health and Care Excellence (NICE)[18] and addressed in the CS is presented in Table 5.

Table 5: 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 spinal muscular atrophy	As per NICE final scope and in line with NICE Reference Case	N/a
Intervention	Risdiplam	As per NICE final scope and in line with NICE Reference Case	N/a
Comparator(s)	Best supportive care	As per NICE final scope and in line with NICE Reference Case	N/a
Outcomes	• Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • 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 broadly aligns with the final scope issued by NICE. Not all outcomes listed in the final scope are however explicitly used in the economic models. • Type 1 SMA: Health state occupancy in the economic model was based on motor milestone achievement using HINE-2, similarly to TA588. A separate health state for patients on permanent ventilation was included, as permanent ventilation is associated with additional costs and a more severe prognosis for patients with SMA type 1. Additional clinical outcomes from the FIREFISH study will also be used to inform the economic model, such as event-free survival and respiratory outcomes. • Type 2/3 SMA: Health state occupancy in the economic model was based on motor milestone achievement using MFM, the primary endpoint of the SUNFISH study. The MFM was selected as a primary endpoint on the basis that it can offer sufficient gradation in the assessment of functional abilities, to fully enable assessment of treatment efficacy in a broad population of Type 2 or 3 SMA patients, like the one included in SUNFISH. Additional clinical outcomes from the SUNFISH study will also be used to inform the economic model.	Effort to simplify the model structure – based on previous economic models and clinical expert opinion - and avoid the use of additional assumptions where possible.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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 PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per NICE final scope and in line with NICE Reference Case	N/a

NICE - National Institute for Health and Care Excellence; SMA - spinal muscular atrophy; TA - technology appraisal; MFM - motor function measure; HINE-2 - Hammersmith Infant Neurological Examination Module 2; N/a - not applicable

3.1 Population

The patient population in the CS[1] relates to people with SMA and is limited to people with Type 1 (early onset) and Type 2/3 (later onset) disease. This is narrower than the population defined in the final NICE scope[18] and the wording of the anticipated marketing authorisation for risdiplam.[19] The final NICE scope defines the relevant population as *"people with spinal muscular atrophy"*, whilst the draft Summary of Product Characteristics (SmPC) states the following indication for risdiplam: [redacted] The CS does not present any clinical effectiveness evidence for the use of risdiplam in people with pre-symptomatic, Type 0, or Type 4 (adult onset) SMA. It is anticipated that ongoing studies (RAINBOWFISH[20] and JEWELFISH[21]) will provide further evidence for the use of risdiplam in Type 1-3 (JEWELFISH) and pre-symptomatic (RAINBOWFISH) SMA populations; however, both studies are ongoing and no clinical results are presented in the CS. There are no ongoing studies examining the efficacy and safety of risdiplam in patients with Type 0 or Type 4 SMA.

The clinical effectiveness evidence presented in the CS[1] includes the SUNFISH randomised controlled trial[22] (RCT; Type 2 and non-ambulatory Type 3 SMA) and the FIREFISH single-arm study[23] (Type 1 SMA). SUNFISH and FIREFISH were conducted across sites including Europe, the United States (US), and Asia. Neither study included sites in the UK. Despite this, the ERG's clinical advisor was satisfied that the populations recruited into these studies broadly reflect the SMA patient population who would be considered eligible for treatment with risdiplam in England.

Both FIREFISH[23] and SUNFISH[22] relate to patients with Type 1 and Type 2/3 SMA who are treatment-naïve. The CS[1] (Section B.1.3.6) states that the anticipated positioning of risdiplam within the SMA treatment pathway includes treatment-naïve patients as well as patients who have previously received nusinersen. The JEWELFISH single-arm study[21] includes people who have previously received treatment with nusinersen, olesoxime or AVXS-101. However, clinical outcomes from this study are not available and the CS does not contain any clinical evidence or cost-effectiveness estimates for risdiplam in patients who are treatment-experienced.

As risdiplam has not yet received a UK marketing authorisation, it is not clear whether certain medical conditions or patient groups may be contraindicated for treatment. [redacted]

3.2 Intervention

The intervention considered in the CS[1] is risdiplam (Evrysdi®, RG7916) taken orally in liquid form once daily, according to the following dosing regimen:

- Age 2 months to <2 years of age – 0.20mg/kg
- Age ≥2 years (weight <20kg) – 0.25mg/kg
- Age ≥2 years (weight ≥20kg) – 5mg (fixed dose).

Risdiplam is a survival of motor neuron 2 (SMN2) precursor messenger ribonucleic acid (pre-mRNA) splicing modifier designed to treat SMA caused by mutations in the SMN1 gene on chromosome 5q that lead to SMN protein deficiency.[19] Risdiplam is manufactured by Roche Ltd. Risdiplam was granted an orphan designation for the treatment of SMA by the European Commission (EC) in February 2019 (EU/3/19/2145). According to the CS,[1] the company anticipates that a decision on the full marketing authorisation will be made in [redacted].

The list price for risdiplam is [redacted] per 60mg bottle: this corresponds to an annual acquisition cost of approximately £240,456 per year for patients aged ≥2 years and/or those with a body weight ≥20kg. The company has proposed a Patient Access Scheme (PAS) which takes the form of a simple price discount of [redacted]; the discounted cost per bottle of risdiplam is [redacted].

[redacted]

3.3 Comparators

The final NICE scope[18] includes a single comparator: BSC. BSC is multi-faceted and holistic and involves multidisciplinary assessment and pro-active management tailored to the individual's needs. A consensus statement on standards of care in SMA was first published by a committee of experts in SMA in 2007[24] and revised recommendations were published in 2018/19.[15, 16] These include: the use of orthoses for postural management and prevention/limitation of contractures and spinal deformity; spinal surgery for scoliosis; assessment of swallowing; nutritional optimisation using tube feeds if required; management of gastro-oesophageal reflux and constipation; respiratory assessment and support including monitoring of respiratory function and cough effectiveness; immunisation; assisted secretion clearance; management of acute exacerbations and ventilatory support. The use of these measures has increased life expectancy in the condition.

Within the Type 2/3 SMA population, the pivotal trial (SUNFISH[22]) compared risdiplam versus placebo. Therefore, head-to-head evidence for risdiplam versus BSC is available in this population.

Head-to-head evidence is not available for the Type 1 SMA population, as the available clinical evidence for risdiplam is drawn from the FIREFISH single-arm study.[23] As such, the company undertook an indirect treatment comparison of motor milestone achievement, event-free survival (EFS – also referred to as ventilation-free survival) and overall survival (OS) for risdiplam versus BSC using the FIREFISH study and the sham (placebo) arm of the ENDEAR trial.[25] The company's indirect comparison is detailed and critiqued in Sections 4.3 and 4.4.

As discussed in the CS,[1] nusinersen was excluded from the final NICE scope[18] as it only available through an MAA and it is not funded via routine NHS commissioning. The ERG notes that whilst the approach taken in the CS is consistent with the final NICE scope, a substantial proportion of paediatric Type 1 and Type 2 SMA patients in England are receiving nusinersen rather than BSC alone. The ERG notes that restricting the comparator for this appraisal to BSC means that the comparative clinical and cost-effectiveness of risdiplam versus nusinersen is unknown.

3.4 Outcomes

Outcomes listed in the final NICE scope[18] include:

- Motor function (including, for example, swallowing and ability to communicate)
- Frequency and duration of hospitalisation
- 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 (adverse events, AEs)
- Health-related quality of life (HRQoL).

The clinical evidence reported in the CS[1] addresses the majority of these outcomes; however, evidence on these outcomes is not consistently available for both the Type 1 and Type 2/3 SMA populations. In particular:

- No evidence is presented for outcomes relating to stamina and fatigue or scoliosis or muscle contractures
- SUNFISH[22] does not include data on OS benefits, ventilation outcomes or hospitalisation outcomes for Type 2/3 SMA patients
- JEWELFISH[21] reports on AEs in previously-treated SMA; no clinical outcomes are presented in the CS.[1]

The company's economic models for the Type 1 and Type 2/3 SMA populations each include data relating to motor function from SUNFISH,[22] FIREFISH[23] (and ENDEAR,[25] via an indirect comparison). The Type 1 SMA model includes data on EFS and OS from FIREFISH[23] and ENDEAR.[25] Whilst SUNFISH included the measurement of HRQoL using the Euroqol 5-Dimensions 5-level (EQ-5D-5L), these data are not used in the company's base case Type 2/3 SMA model. Neither model includes data from the risdiplam studies on AEs, complications, or hospitalisations (see Section 5.2).

3.5 Other relevant factors

The CS[1] states that whilst risdiplam is being appraised under the Single Technology Appraisal (STA) Programme, it has several features which are commonly seen in HST appraisals, noting in particular the rarity of the disease, the value placed on the benefits of treatments by patients and their caregivers, and that the eligible population for risdiplam includes children and young people and people with disabilities. In line with the previous appraisal of nusinersen for SMA (NICE Technology Appraisal 588 [TA588]),[13] the CS argues that decision modifiers and flexibility in NICE's decision-making should be taken into account in the appraisal of risdiplam. The CS also indicates that NICE's End of Life (EoL) criteria[26] should be applied within the Type 1 SMA population (see Chapter 6).

4 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS[1] for risdiplam for the treatment of SMA. Section 4.1 provides a critique of the company's systematic review of clinical and safety evidence. Section 4.2 provides a summary of the clinical effectiveness and safety results, together with a critique of the included studies. Sections 4.3 to 4.5 present a summary and critique of the indirect comparisons performed by the company and details of additional work undertaken by the ERG. Section 4.6 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review

The company undertook a systematic literature review (SLR) to identify all clinical evidence regarding the efficacy and safety of risdiplam versus other interventions for the treatment of Type 1-3 SMA. The methods for the company's SLR of clinical evidence are detailed in CS Appendix D.[27]

4.1.1 Searches

The searches to identify evidence for the SLR of clinical effectiveness are reported in CS Appendix D.[27] Searches were originally conducted in January 2018 (updated in January 2020) and included Embase (incorporating MEDLINE) and CENTRAL (via Cochrane). The searches combined terms for the condition of interest (SMA Types 1-3) with risdiplam or any of its comparators. Intervention terms were only searched in descriptor (de) and title/abstract fields. There are a number of other database fields where drugs may be mentioned (e.g. "drug name" in Embase, "name of substance word" in MEDLINE) but the company chose not to search these, stating a belief that their title/abstract terms and supplementary searches would have been sufficient to avoid missing any relevant studies (see clarification response,[17] question A3).

A suitable range of synonyms for the interventions of interest were used, including the drug name RG7916. The ERG would have recommended including RG-7916 as well, as this hyphenated version retrieves additional results, although on this occasion the ERG's own searches suggest that none would be eligible for inclusion in the review.

Whilst the ERG broadly agrees with the way that the company's search has been designed and conceptualised, the decision to search MEDLINE and Embase simultaneously in a multi-file search on Embase.com (CS Appendices, Table 3) is questionable.

Multi-file searching is generally not advised for systematic searches; most of the benefits of searching two databases are lost if no steps are taken to optimise the search strategy for each. Although the

company argues that searching MEDLINE independently of Embase was not necessary (clarification response,[17] question A1), the ERG considers that relying exclusively on Emtree (Embase) headings without also exploring those offered by MEDLINE's own scheme (MeSH) significantly increases the risk of missing relevant studies.

The ERG understands that as MEDLINE records are imported to Embase.com, some reclassification (automatic, then manual) occurs; however, this comes at the cost of the original MeSH indexing and not all headings have a direct equivalent in Emtree, meaning that some of the specificity is lost in translation. Additional information on the benefits of searching both indexing schemes is available from https://www.clinfo.eu/databases-literature-searches/.

Unfortunately, the ERG does not have access to the Embase.com platform; hence, it has not been able to replicate the search strategies exactly as executed to measure the impact of these weaknesses on retrieval. Furthermore, the timelines for the STA process preclude the ERG from running its own parallel searching and screening exercise to allow comparison against the company's SLR. However, in the course of reviewing the CS, neither the ERG nor their clinical advisor identified any relevant studies that had been missed by the company.

4.1.2 Inclusion criteria

The inclusion criteria are generally consistent with the final NICE scope,[18] with two main inconsistencies: (1) the company's systematic review inclusion criteria are broader in terms of interventions, listing risdiplam, nusinersen, onasemnogene abeparvovec (AVXS-101), CK-107, branaplam and olesoxime, whereas the final NICE scope only refers to risdiplam; (2) the final NICE scope specifies BSC as the comparator of interest, whereas the company's systematic review inclusion criteria list BSC, placebo and interventions compared with one another as the comparator, in addition to no comparator (for single-arm studies). The company specified that the review was intentionally broad to inform future reimbursement activities in other countries and to allow for updates of the network of evidence in the future (CS,[1] Section B.2.9.1, pages 57-58). Whilst this is inconsistent with the decision problem set out in the final NICE scope, the ERG does not consider these differences to be problematic, as they would broaden rather than narrow the scope of the review, meaning that the relevant papers would still have been identified. Eligibility is restricted to English language publications, which introduces the risk that relevant data published in other languages may have been missed by the review. It is difficult to estimate the impact of this; however, the ERG does not anticipate that any relevant studies on SMA would have been published in another language and therefore missed.

4.1.3 Critique of study selection

CS Appendix D[27] states that two reviewers independently screened titles and abstracts of each record and then full texts, with any discrepancies adjudicated by a third reviewer. The ERG considers this to be an appropriate and high-quality reviewing method. The ERG screened the titles of the full texts excluded by the company (CS Appendix D,[27] Table 3, page 51) and examined the full texts of any potentially relevant studies, and agrees with the company's exclusion decisions. Neither the ERG nor their clinical advisor are aware of any additional relevant studies within the scope of this appraisal.

The PRISMA flow diagram (CS, Appendix D,[27] Section D.1, Figure 2, page 16) states that five trials were included in the company's indirect treatment comparison. The company's clarification response[17] (question A6) states that these five studies met the broader eligibility criteria for the systematic literature review and that only two of these studies were relevant to the indirect comparison. The ERG assumes that these are the FIREFISH[23] and ENDEAR[25] studies. The PRISMA flow diagram also reports that 222 records were included after full text screening; however, in the subsequent box in the flow diagram, 64 primary studies were reported as being included, leaving 158 records unaccounted for. The company's clarification response[17] (question A5) states that the 222 publications were all related to the 64 primary studies identified, which means that there is no discrepancy.

4.1.4 Critique of data extraction

CS Appendix D[27] states that two reviewers independently extracted data, with a third reviewer adjudicating any disagreements. The company's clarification response[17] (question A7) outlines the fields extracted, and the ERG is satisfied that these are comprehensive.

4.1.5 Critique of quality assessment

The quality of the SUNFISH trial[22] was assessed using the checklist recommended by NICE for assessing the methodological quality of RCTs; this checklist bears a close resemblance to the Cochrane Risk of Bias tool,[28] which is widely regarded as the most robust tool for assessing bias in RCTs. Two reviewers independently assessed the risk of bias and any disagreements were resolved through discussion or by consulting a third reviewer. The ERG considers this to be a robust reviewing method.

No judgement on the overall risk of bias for the SUNFISH trial is reported in the CS,[1] and no attempt has been made to integrate the quality assessment into the findings, or to consider the overall impact of the quality of the included study on the results.[29]

Quality assessment of the SUNFISH trial,[22] as undertaken by the company and the ERG, is presented in Section 4.2.3. A quality assessment of the FIREFISH study[23] is also presented in Section 4.2.3. The CS does not contain a quality assessment of FIREFISH;[23] the ERG has undertaken this using the

Newcastle-Ottawa Scale,[30] which is an appropriate and validated quality assessment tool for non-randomised studies. The ERG has also undertaken a quality assessment of the placebo arm of the ENDEAR trial,[25] which is included in the company's indirect comparison, using the Newcastle-Ottawa scale (see Section 4.3.1).

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The CS[1] includes two studies that examined the efficacy of risdiplam for treating SMA – the SUNFISH trial,[22] which examined the efficacy of risdiplam for treating Type 2/3 SMA, and the FIREFISH study,[23] which examined the efficacy of risdiplam for the treatment of Type 1 SMA (see Table 6). Each of these studies were conducted in two parts; Part 1 was an exploratory dose-finding part, whilst Part 2 was used to examine the efficacy and safety of the selected dose of risdiplam in each study. Different patients were recruited to Part 1 and Part 2 for each study.

Table 6: Characteristics of the SUNFISH (Part 2) and FIREFISH (Part 2) studies

Study	Design	Population	Interventions	Comparator	Primary outcome
SUNFISH	RCT	Children and young adults with Type 2/3 SMA not previously treated, non-ambulatory, age 2-25 years.	Risdiplam (n=120)	Placebo (n=60)	Change from baseline in MFM32 total score at Month 12
FIREFISH	Single-arm	Infants with Type 1 SMA with two copies of SMN2, not previously treated, not receiving chronic ventilation, age 1-7 months.	Risdiplam (n=41)	N/a (single-arm)	Proportion of infants sitting without support at Month 12, as assessed in the BSID-III

BSID-III - Bayley Scales of Infant and Toddler Development - Third Edition; MFM32 - Motor Function Measure - 32 items; N - number; RCT - randomised controlled trial; SMA - spinal muscular atrophy

The CS[1] focuses on evidence from Part 2 of SUNFISH, which aimed to assess the efficacy and safety of risdiplam in people with Type 2/3 SMA. The ERG agrees that this is appropriate, since Part 1 was an open-label dose-finding part. SUNFISH[22] (Part 2) is a pivotal multicentre, randomised, double-blind, placebo-controlled Phase II/III clinical trial. The CS and the Clinical Study Report (CSR)[22] state that Part 2 of the SUNFISH trial was conducted across 42 investigational sites in 14 countries: Belgium (3 sites), Brazil (1 site), China (2 sites) Canada (3 sites), Croatia (1 site), France (5 sites), Italy (5 sites), Japan (10 sites), Poland (3 sites), Russian Federation (1 site), Serbia (1 site), Spain (4 sites), Turkey (1 site) and the USA (2 sites).[1] There were no investigational sites in the UK. These sites differed from the countries where Part 1 of the trial was conducted (Belgium, France, Germany and Italy). Additional

information on the characteristics of the SUNFISH trial is presented in the CS[1] (Table 6, pages 28 to 31).

The CS[1] focuses on evidence from Part 2 of the FIREFISH study, which aimed to assess the efficacy and safety of risdiplam in people with Type 1 SMA. The ERG agrees that this is appropriate, since Part 1 was a dose-finding part. FIREFISH[23] (Part 2) is a pivotal prospective, open-label, single-arm, multicentre Phase II/III clinical study.[1] The CS[1] and CSR[23] state that Part 2 of FIREFISH was conducted across 14 investigational sites in 10 countries: Brazil (1 site), China (2 sites), Croatia (1 site), France (1 site), Italy (4 sites), Japan (1 site), Poland (1 site), Russia (1 site), Turkey (1 site) and the USA (1 site).[1] There were no investigational sites in the UK. These sites differed from the countries where Part 1 of the trial was conducted (Belgium, France, Italy, Switzerland and the USA). Additional information on the characteristics of the FIREFISH study is presented in the CS[1] (Table 6, pages 28 to 31).

During the clarification round, the ERG questioned the relevance of the data from these studies to clinical practice in the UK, given that no patients were recruited from the UK. The company's clarification response[17] (question A13) states that "*these studies provide substantial evidence of effectiveness for risdiplam to a broad and heterogeneous population of people with SMA that is generally reflective of the prevalent SMA population seen in UK clinical practice.*" The company presents the rationale for this statement on the basis that: (1) the endpoints are UK-relevant; (2) there is an international consensus on the standards of care for people with SMA, which were developed in 2007 and later updated in 2018/19, and (3) 81% and 61% of patients in the SUNFISH[22] and FIREFISH[23] studies, respectively, were enrolled in Europe and North America, where clinical practice is similar to the UK in terms of SMA care. In addition, the ERG's clinical advisor was satisfied that the patients enrolled in the SUNFISH and FIREFISH studies are representative of patients with SMA in England.

Two additional studies provide evidence for this appraisal: JEWELFISH[21] and ENDEAR.[25] JEWELFISH is an open-label, non-comparative study, which aims to assess the safety of risdiplam in patients aged 6 months to 60 years with Type 1, 2 and 3 SMA, who were previously enrolled in the MOONFISH trial (of RO6885247, which has been discontinued), or who have previously been treated with nusinersen, AVXS-101 or olesoxime.[1] Efficacy data from JEWELFISH are exploratory, and are not yet available (see Section 4.2.1.6). Safety data from the clinical cut-off date of the 31st of January 2020, where the median treatment duration with risdiplam was 3.0 months, are included in the pooled safety analysis (CS, Section B.2.10).[1] ENDEAR is a randomised, double-blind, sham-procedure controlled Phase III trial to assess the safety and efficacy of nusinersen versus BSC in infants with Type 1 SMA. Data from the placebo (sham control) arm of the ENDEAR trial has been used in the CS[1, 27] to inform an indirect comparison of risdiplam and BSC (see Sections 4.3 and 4.4).

The SUNFISH trial[22] is used in the model for the key comparison of risdiplam versus BSC in patients with Type 2/3 SMA, whilst an indirect comparison using data from FIREFISH[23] and ENDEAR[25] was used to compare risdiplam against BSC in the model for patients with Type 1 SMA.

4.2.1.1 Patients

Eligibility criteria for SUNFISH[22] and FIREFISH[23] are presented in Table 7. The ERG's clinical advisor confirmed that the eligibility criteria for both SUNFISH and FIREFISH are reasonable and representative of the patients seen in routine UK clinical practice (apart from exclusion of ambulant Type 3 patients in SUNFISH Part 2, although these only account for a small proportion of SMA patients). The company's clarification response[17] (question A11) justifies the upper age limit of 25 years for the SUNFISH trial as a means of ensuring that the study was representative of the patient population who would receive risdiplam in practice, and to allow an effect to be detected, whilst extending the age limit beyond childhood.

Table 7: Key inclusion criteria of the SUNFISH and FIREFISH studies (adapted from CS, Table 6)

Criteria	SUNFISH (Part 2)	FIREFISH (Part 2)
Inclusion criteria	• Males and females aged between 2 and 25 years (inclusive) at enrolment • Confirmed diagnosis of 5q-autosomal recessive SMA For Part 2: 1) RULM entry item ≥2; 2) ability to sit independently as assessed by item 9 of the MFM • Negative blood pregnancy test at screening and agreement to comply with measures to prevent pregnancy and restrictions on sperm donation	• Males and females aged between 28 days (1 month) of life and 210 days (7 months) (inclusive) at enrolment • Gestational age of 37 to 42 weeks • Confirmed diagnosis of 5q-autosomal recessive SMA, including: - Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene - Clinical history, signs or symptoms attributable to Type 1 SMA with onset after 28 days but prior to the age of 3 months • Two survival motor neuron 2 (SMN2) gene copies, as confirmed by central testing • Body weight ≥third percentile for age, using appropriate country-specific guidelines • Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the Investigator • Adequately recovered from any acute illness at the time of screening and considered well-enough to participate in the opinion of the Investigator
Exclusion criteria	• Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening or 5 half-lives, whichever is longer • Concomitant or previous administration of SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy study, either in a clinical study or as part of medical care • Any history of cell therapy • Hospitalisation for pulmonary event within the last 2 months, or planned at the time of screening • Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 months • Presence of clinically relevant ECG abnormalities before study drug administration • Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases • Participants requiring invasive ventilation or tracheostomy	• Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening or 5 half-lives, whichever is longer • Concomitant or previous administration of SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy study • Any history of cell therapy • Hospitalisation for pulmonary event within the last 2 months, or planned at the time of screening • Presence of clinically relevant ECG abnormalities before study drug administration • Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases • Participants requiring invasive ventilation or tracheostomy • Participants requiring awake non-invasive ventilation or with awake hypoxemia (arterial oxygen saturation < 95 percent %) with or without ventilator support • Participants with a history of respiratory failure or severe pneumonia, and have not fully recovered their pulmonary function at the time of screening • Multiple or fixed contractures and/or hip subluxation or dislocation at birth • Presence of non-SMA related concurrent syndromes or diseases

ECG - electrocardiogram; MFM - Motor Function Measure; RULM - Revised Upper Limb Module; SMA - spinal muscular atrophy; SMN1 - survival motor neuron 1; SMN2 - survival motor neuron 2

One key difference between the eligibility criteria for both the SUNFISH and FIREFISH studies, and the final NICE scope,[18] is that patients were excluded from the studies if they had been previously treated for SMA, including: "*Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening or 5 half-lives, whichever is longer*"; "*Concomitant or previous administration of SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy study*"; or "*Any history of cell therapy*" (CS,[1] Table 6, page 29). In contrast, the final NICE scope[18] presents the population broadly as "*People with spinal muscular atrophy*" (page 2). In addition to narrowing the potential population of people with SMA for which there is evidence of the efficacy of risdiplam (Type 1 and Type 2/3 SMA; see Section 2.2), these exclusion criteria are also inconsistent with the proposed positioning of risdiplam in the patient pathway, as indicated in Figure 1, whereby risdiplam is proposed for as a first-line and second-line treatment (following nusinersen) in people with Types 1, 2 and 3 SMA. The company's clarification response[17] (question A9), suggests that since there is currently no evidence to determine the optimal therapeutic sequence, risdiplam be positioned as "*an additional therapeutic option for all patients across the continuum of SMA*", including treatment-naïve patients and those who have previously received nusinersen, with a focus on patient preference and need, rather than as a definitive first-line and/or second-line treatment for SMA. Nevertheless, the ERG notes that there is currently no evidence available for the efficacy of risdiplam in a nusinersen-treated population, and limited safety data due to data only being available from a preliminary clinical cut-off date (31 January 2020) in the JEWELFISH study, where the median treatment duration was 3.0 months.

The company's clarification response[17] (question A12), includes details of how patients included in Part 2 of SUNFISH[22] were identified and recruited. Patients were recruited via referral from clinicians who treat SMA and directly by virtue of attending a study centre for SMA management. The screening and enrolment process was managed using a digital study portal, overseen by the sponsor, to which the study sites were granted access. The purpose of this portal was to manage the age stratification and to allow patients to be registered for screening into the trial.

A diagram illustrating patient flow in Part 2 of SUNFISH is presented in Figure 5 of CS Appendix D,[27] which was correct at the time of the clinical cut-off date (6th September 2019; CSR,[22] page 29). Initially, 211 patients were screened and of these, 180 were randomised (n=120 to the risdiplam arm and n=60 to the placebo arm) and received their designated treatment (risdiplam or placebo).[1] Of these, 176 patients (97.8%) completed the 12-month placebo-controlled period and were still receiving ongoing treatment at the clinical cut-off date (117 [97.5%] patients in the risdiplam arm and 59 [98.3%] patients in the placebo arm). After the first 12-month placebo controlled period of Part 2 of SUNFISH, all patients switched to risdiplam in a blinded manner (CSR,[22] page 42). At the time of the clinical cut-off date, [redacted] had discontinued treatment during the placebo-controlled period. For all [redacted] patients, the reason for

discontinuation was to switch to other treatment (nusinersen in [redacted]; not further specified in [redacted]). The CS[1] does not provide further detail regarding the reasons that these patients switched to another treatment, and the company's clarification response[17] (question A14) does not provide any further clarity. Thus, the ERG cannot rule out the possibility that the switch to other treatments was due to a lack or loss of the efficacy of risdiplam, in the case of three patients. Nevertheless, this number constitutes only a small proportion of the patients who received risdiplam in the trial. No patients withdrew due to adverse events. All enrolled patients (n=180) were included in the intention-to-treat (ITT) and safety populations.[22]

The company's clarification response[17] (question A18), provides details of how patients included in Part 2 of FIREFISH[23] were identified and recruited. Local patients were recruited via hospital outpatient clinics, the patient population of the study centres, the patient populations of other paediatric/emergency units whom the Principal Investigator had contacted, referrals (e.g. from SMA associations), and recruitment letters sent to paediatricians, obstetricians and gynaecologists. Cross-border patients were recruited when the patient's family made contact with the Patient Association Group (PAG), the PAG-informed Roche Patient Support Partner, the study site, or the Roche Affiliate (Medical Information Portal). The screening process was conducted using a pre-screening notification form, which the Sponsor reviewed and approved (or not). Written informed consent was obtained by parents/guardians and then an eligibility screening form was completed following the investigator's assessment of each screened patient in relation to the inclusion and exclusion criteria, which Roche reviewed.

A diagram illustrating patient flow in FIREFISH is presented in Figure 4 of CS Appendix D,[27] which was correct at the time of the clinical cut-off date (14th November 2019; CS Appendix D,[27] page 22). Initially, 41 patients were enrolled and received treatment with risdiplam.[27] Of these, 38 patients were still receiving ongoing treatment at the clinical cut-off date. Of the 41 patients enrolled in the study, three (7.3%) withdrew; two of whom died and one had progressive disease. No patients withdrew due to AEs, poor compliance with the protocol, patient choice, or any other reason. At the clinical cut-off date, the 38 patients remaining in the study had completed 12 months of treatment and 12-month follow-up assessments; however, no patients had completed the 24-month treatment period and moved into the open-label extension.

In the SUNFISH trial, demographic and clinical characteristics were comparable between the risdiplam and placebo arms at baseline (in the ITT population), with the following exceptions: patients in the risdiplam arm had a slightly longer median time between onset of initial symptoms to first treatment (106.3 months, range 17-275 months) than those in the placebo arm (96.6 months, range 1-271 months); a smaller proportion of patients in the risdiplam arm (78.3%) compared with the placebo arm (88.3%) had no fractures, and a greater proportion had 1-2 fractures (16.74% and 11.7% in the risdiplam and

placebo arms, respectively) and 3-5 fractures (4.2% and 0% in the risdiplam and placebo arms, respectively), and a smaller proportion of patients in the risdiplam arm (63.3%) than the placebo arm (73.3%) had scoliosis at baseline, with a smaller proportion having a degree of curvature of the spine due to scoliosis >40 (28.3% and 38.3% in the risdiplam and placebo arms, respectively), as acknowledged in the CSR (page 91).[22] The range for the median age of onset of initial symptoms in the risdiplam arm is 0-57 months; clinical advice received by the ERG confirmed that patients with Type 2/3 SMA do not typically develop symptoms at 0 months. The company's clarification response[17] (question A10) states that this is due to a rule for the imputation of missing data for date of birth, which was not reported from some sites in the EU due to data protection regulations, and that no patients with Type 2 SMA had a median onset of symptoms of 0 months. The company also provided case descriptions for the two patients with a recorded symptom onset of 0 months in response to clarification question A10, and the ERG is satisfied that age of symptom onset in not likely to have been 0 months in these patients. Clinical advice received by the ERG confirmed that the baseline demographic and clinical characteristics of the patients enrolled in this study were comparable with patients usually seen in clinical practice in England. In summary, the company claims that the characteristics are well balanced between the trial arms, however the ERG notes some differences, some of which work in favour of risdiplam (a higher prevalence of scoliosis and greater degree of curvature among those with scoliosis in the placebo arm), and some of which operate in favour of placebo (more delayed treatment and a higher prevalence of fractures in the risdiplam arm).

FIREFISH[23] used a single-arm design; however, clinical advice received by the ERG confirmed that baseline demographic and clinical characteristics of the patients enrolled in this study (CS, Table 7, pages 32 to 33) were comparable with patients usually seen in clinical practice in England.

Eligibility criteria for the JEWELFISH study are presented in the CSR (pages 26 to 31).[21] Patients were eligible for inclusion if they had previously participated in the MOONFISH study (which evaluated the splicing modifier RO6885247) or had previously received nusinersen, olesoxime or AVXS-101, [redacted]

4.2.1.2 Intervention

The doses of risdiplam administered in both the SUNFISH[22] and FIREFISH[23] studies are outlined in the CS[1] (Table 6, page 30). In Part 2 of SUNFISH, risdiplam was administered orally (or via a nasogastric or gastrostomy tube), once daily in the morning, at the following dose levels: 5mg for people with a body weight ≥20kg; and 0.25mg/kg for those with a body weight of <20kg. In Part 2 of FIREFISH, patients were administered risdiplam orally (or via a nasogastric or gastrostomy tube), once

per day, at the following starting dose levels: 0.04mg/kg for infants >1 month old and <3 months old at enrolment; 0.08mg/kg for infants ≥3 months old and <5 months old at enrolment; and 0.20mg/kg for infants aged ≥5 months old at enrolment. The administered dose was adjusted to 0.20mg/kg for all patients, following review of pharmacokinetic data from Parts 1 and 2 of the study. [redacted] The ERG believes this may have led to the efficacy of risdiplam being potentially underestimated in a small number of cases.

There were [redacted] protocol deviations that were considered to be "major" in Part 2 of SUNFISH;[22] [redacted] in the risdiplam arm and [redacted] in the placebo arm (CSR,[22] page 85), and [redacted] protocol deviations in Part 2 of FIREFISH (CSR,[23] page 84). Further details are provided in Section 4.2.3.3.

The dose administered in the JEWELFISH study is presented in the CSR,[21] and patients were continued on treatment indefinitely.[21] Patients aged 2-60 years were administered risdiplam orally once daily, at a fixed dose of 5mg if their body weight was >20kg, and 0.25mg/kg for those with a body weight of <20kg, adjusted from a dose of 3mg per day (among patients aged 12-60 years), following data on optimal dosing from Part 1 of the SUNFISH trial.[21] Patients aged 6 months to <2 years were administered a dose of 0.20mg/kg.[21] As of the clinical cut-off date (31 January 2020), there were 72 major protocol deviations recorded for 59 patients.[21]

4.2.1.3 Comparator

The comparator in Part 2 of the SUNFISH trial[22] was placebo. Placebo was administered orally, once daily. The placebo was prepared with riboflavin to match the colour of the risdiplam, and contained the same excipients (except for ascorbic acid and disodium edetate), but with no active substance (CSR,[22] page 52). This differs from the comparator in the final NICE scope,[18] which is BSC. However, the ERG's clinical advisor confirmed that BSC would have been provided to the patients in SUNFISH alongside risdiplam or placebo, so for this purpose, the ERG considers evidence from SUNFISH to be consistent with the NICE scope.[18] The ERG's clinical advisor confirmed that standards of BSC are likely to vary slightly internationally, more so in less developed countries than across the developed world.

Part 2 of FIREFISH adopted a single-arm design; hence, no comparator was included. Data from FIREFISH were indirectly compared with data from the placebo arm of the ENDEAR trial[25] (see Sections 4.3 and 4.4), to ensure consistency with the final NICE scope.[18] Guidance on performing clinical trials in Type 1 SMA recommends that trials of SMA treatments are placebo-controlled and adequately powered.[31] Therefore, the design of Part 2 of FIREFISH[23] is not consistent with these recommendations. JEWELFISH[21] also adopted a single-arm design and thus had no comparator.

4.2.1.4 Outcomes

The key outcomes listed in the CS[1] for the SUNFISH (Type 2/3 SMA) and FIREFISH (Type 1 SMA) studies are summarised in Table 8 and Table 9, respectively. All outcomes presented in the CS[1] were included in the final NICE scope.[1]

All efficacy and HRQoL outcome data in SUNFISH were analysed using the ITT population, defined as all randomised patients in Part 2 of the study, reported according to the treatment to which they were randomised.[1, 22] All efficacy and HRQoL outcome data in FIREFISH (with the exception of growth measures, which used the safety population) were analysed using the ITT population, consisting of all patients enrolled in Part 2 of the study, regardless of whether they were treated or not.[1, 23]

Table 8: Summary of SUNFISH key outcomes listed in the CS and their relationship to the final NICE scope and the company's economic model for Type 2/3 SMA

Outcome	In NICE scope?	Used in economic model?	Defined *a priori*?
Primary outcome			
Motor function, assessed by change from baseline in MFM32 total score at Month 12	Yes	Yes*	Yes
Secondary outcomes			
Proportion of patients who achieved a change from baseline ≥3 points in the MFM32 total score at Month 12	Yes	No	Yes
Proportion of patients who achieved stabilisation or improvement (change from baseline ≥0 points) in the MFM32 total score at Month 12	Yes	No	Yes
Change from baseline in RULM total score at Month 12	Yes	No	Yes
Change from baseline in HFMSE total score at Month 12	Yes	Yes*	Yes
Change from baseline in the patient- and caregiver-reported SMAIS total score at Month 12	Yes	No	Yes

HFMSE - Hammersmith Functional Motor Scale Expanded; MFM32 - Motor Function Measure - 32 items; RULM - Revised Upper Limb Module; SMAIS - SMA independence scale

** The company's economic model uses data on transitions between motor function states based on MFM32 and HFMSE over time rather than changes from baseline*

Table 9: Summary of FIREFISH key outcomes listed in the CS and their relationship to the final NICE scope and the company's economic model for Type 1 SMA

Outcome	In NICE scope?	Used in economic model?	Defined *a priori*?
Primary outcome			
Proportion of infants sitting without support after 12 months of treatment, as assessed in the BSID-III (defined as sitting without support for 5 seconds)	Yes (under motor function)	Yes*	Yes
Secondary outcomes			
Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline to Month 12	Yes	No	Yes
Proportion of motor milestone responders as assessed by the HINE-2 (showed improvement in more milestones than worsening) at Month 12	Yes	No	Yes
Proportion of patients able to support weight or stand with support as assessed by the HINE-2 at Month 12	Yes	Yes	Yes
Proportion of patients able to bounce while assessing the walking item of the HINE-2 at Month 12	Yes	Yes	Yes
Proportion of patients alive without permanent ventilation (≥16 hours of non-invasive ventilation such as BiPAP per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy) at Month 12	Yes	Yes	Yes
Overall survival (proportion of patients alive) at Month 12	Yes	Yes	Yes
Proportion of people with the ability to feed orally at Month 12	Yes	No	Yes
Proportion of people with the ability to swallow at Month 12	Yes	No	Yes
Number of hospitalisations per patient-year	Yes	No	Yes
Proportion of people with no hospitalisations	Yes	No	Yes
Change from baseline to Month 12 in the ITQOL-SF47 questionnaire domains and single item scores	Yes	No	Yes

BiPAP - Bilevel Positive Airway Pressure; BSID-III - Bayley Scales of Infant and Toddler Development - Third Edition; CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2 - Hammersmith Infant Neurological Examination Module 2; ITQOL-SF47 - Infant and Toddler Quality of Life Questionnaire (47 item short form)

** The company's model uses data on transitions between HINE-2 over time, rather than changes from baseline*

Primary outcome

The primary outcome of Part 2 of the SUNFISH trial[22] (Type 2/3 SMA) was motor function, assessed by change from baseline in Motor Function Measure - 32 items (MFM32)[32] total score at 12 months (see Appendix 1, Figure 22). This scale consists of three domains of motor function: standing and transfers (D1); axial and proximal motor function (D2); and distal motor function (D3).[1] Total scores on the MFM32 range from 0 to 100, whereby higher scores indicate greater functioning. Total score is expressed as a percentage of the maximum possible score; each of 32 items (across the three domains

of motor function) is scored from 0-3, then scores are summed and transformed to the 0-100 scale.[1] The MFM32 has been demonstrated to be a valid and reliable measure for assessing motor function in children and young adults with Type 2/3 SMA.[33, 34] The MFM32 scale was chosen over the Hammersmith Functional Motor Scale Expanded (HFMSE) as it is more sensitive to change in people with a low HFMSE score (<10) and also because it includes items relating to distal motor function,[1] which includes those assessing fine motor skills.[32] The CS[1] reports that improvement in fine motor skills constitutes a clinically meaningful change,[1] and clinical advice received by the ERG corroborates this view. The MFM32 has also been found to be responsive to change in the progression of SMA, in observational research.[35] This outcome was assessed at 12 months, with the last patient assessed at the time of the clinical cut-off date (6th September 2019). Change from baseline on MFM32 total score was compared between the risdiplam and placebo arms. The study was double-blinded and outcome assessors were blinded to treatment allocation.[22]

The primary outcome of Part 2 of the FIREFISH study[23] (Type 1 SMA) was the proportion of infants sitting without support (for five seconds) after 12 months of treatment, as assessed in item 22 the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) Gross Motor Scale.[1] Infants who did not achieve sitting, did not maintain sitting achieved previously, were withdrawn, died, or had a missing assessment at the 12-month follow-up timepoint, were classified as non-sitters.[1] The ERG agrees with the company's view that this is a conservative approach to classifying the achievement of this outcome. This outcome was selected as infants with Type 1 SMA never gain this motor milestone, by definition of their diagnosis,[1, 25, 36] thus the attainment of sitting would be clinically meaningful in this population.[1] Clinical advice received by the ERG concurs with this assertion. This outcome was assessed at the clinical cut-off date (14th November 2019). In Part 2 of FIREFISH, the purpose was to estimate the proportion of infants who were sitting without support at 12 months of treatment, and to assess this against a pre-defined performance criterion of 5%, which was conservative, given the natural history of Type 1 SMA.[1] The ERG's clinical advisor agreed that this performance criterion is reasonable, given that no infants with Type 1 SMA would be expected to sit without support. Although Part 2 of FIREFISH was open-label, the BSID-III Gross Motor Scale was evaluated by Independent Central Readers, who reviewed videos of the infants completing the BSID-III and scored them in a blinded manner, thus outcome assessors for the primary outcome were not aware of treatment allocation at the time of making assessments. The company's clarification response[17] (question A21) states that the Independent Central Readers were "*expert Paediatric Physical Therapists with backgrounds in spinal muscular atrophy.*"

Secondary outcomes

Outcomes listed in the final NICE scope[18] and reported in Table 10 of the CS[1] as key secondary outcomes for Part 2 of SUNFISH (Type 2/3 SMA) include:

- Proportion of patients who achieved a change from baseline ≥3 points in the MFM32 total score at Month 12
- Proportion of patients who achieved stabilisation or improvement (change from baseline ≥0 points) in the MFM32 total score at Month 12
- Change from baseline in Revised Upper Limb Module (RULM) total score
- Change from baseline in HFMSE total score at Month 12
- Change from baseline in the patient- and caregiver-reported SMA Independence Scale (SMAIS) total score at Month 12.

Of these outcomes, only one was similar to an outcome included in the company's health economic model for Type 2/3 SMA; the 'walking' state in the Type 2/3 SMA model is derived from the HFMSE (see Section 5.2.2.1). The company's Type 2/3 SMA model is based on rates of transition between motor milestones estimated from a re-analysis of underlying MFM32 (non-walking states) and HFMSE (walking, based on case notes). The ERG report focusses on the following outcomes: change from baseline in MFM32 total score at 12 months; change from baseline in HFMSE total score; AEs and changes in fine motor skills from baseline to 12 months (from the RULM, MFM32 and SMAIS). Data on all other outcomes, including the other key outcomes listed above and in Table 8, are presented in the CS.[1]

The HFMSE is a validated and reliable measure for assessing motor function in patients with Type 2/3 SMA.[37, 38] Total scores on the HFMSE can range from 0-66,[38] calculated from 33 items each assessed on a 0-2 scale by a clinical evaluator.[1] A qualitative study of perceptions of meaningful change in Type 2/3 SMA has highlighted that although the HFMSE covers important items, patients, carers and clinicians were concerned that this measure was not sufficiently sensitive to capture small changes which could improve quality of life.[39] Thus, the ERG believes that the inclusion of the MFM32 as well as the HFMSE is justified. The finding from qualitative research that small changes can be clinically meaningful to patients, carers and clinicians[39] also implies that any small improvement in motor function (including on the HFMSE scale) may signify important gains for patients and their families.

Patient representatives have highlighted the importance and clinical meaningfulness of fine motor function in people with Type 2/3 SMA, as even small improvements in motor function can improve independence.[40] Clinical advice received by the ERG has highlighted the importance of fine motor function and upper limb abilities (e.g. opening doors, opening food packets, adjusting clothing, adjusting position), particularly among people without ambulation, and loss of these functions can affect independence more than loss of ambulation. The ERG notes the company's economic model for Type 2/3 SMA does not explicitly include changes in fine motor function. Some data from the clinical

effectiveness analysis of the SUNFISH trial,[22] however, has examined fine motor function. This includes data from the RULM, MFM32 D3 and SMAIS. The RULM is a clinical motor function measure specifically designed to assess upper limb function in non-ambulatory patients with SMA (particularly children), and has demonstrated reliability and validity.[41] Total scores range from 0 to 37 (with higher scores indicating greater functioning), consisting of 18 items scored on a 0-2 scale and one item scored on a 0-1 scale.[1] The MFM32 D3 assesses distal motor function, which includes fine motor skills such as picking up coins from a table and drawing loops with a pencil.[32] For each domain, including D3, scores are expressed as a percentage of the maximum possible score.[1] The SMAIS was developed specifically for assessing function-related independence in SMA, and focuses on upper limb related activities of independence, such as writing, using a touchscreen, dressing and washing.[1] The total score for the SMAIS ranges from 0 to 44 (with higher scores indicating greater independence), and is summed from 22 of 29 items focused on upper limb ability (each item being scored on a 0-2 scale).[1] Content validity of the SMAIS has been established;[42] however, as a new scale, no information is currently available on its validity, reliability or ability to detect change.[42, 43] Therefore, the ERG cannot verify that the SMAIS is reliable or valid, or that is has the ability to detect change. In addition, the TREAT-NMD Core SMA Dataset: Outcome Measure Library[44] states that the SMAIS is "*not yet ready for use*". The ERG has only identified one other trial (NCT02628743[45]) which has used the SMAIS. In SUNFISH, patients aged ≥12 years and caregivers of patients aged 2-25 years completed the SMAIS.[1]

Outcomes listed in the final NICE scope[18] and reported in Table 9 of the CS[1] as key secondary outcomes for Part 2 of FIREFISH (Type 1 SMA) include:

- Proportion of patients who achieve an increase of at least 4 points in their Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score from baseline to Month 12
- Proportion of motor milestone responders as assessed by the Hammersmith Infant Neurological Examination Module 2 (HINE-2) (showed improvement in more milestones than worsening) at Month 12
- Proportion of patients able to support weight or stand with support as assessed by the HINE-2 at Month 12
- Proportion of patients able to bounce while assessing the walking item of the HINE-2 at Month 12
- Proportion of patients alive without permanent ventilation (≥16 hours of non-invasive ventilation such as BiPAP per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy) at Month 12
- OS (proportion of patients alive) at Month 12

- Proportion of people with the ability to feed orally at Month 12
- Proportion of people with the ability to swallow at Month 12
- Number of hospitalisations per patient-year
- Proportion of people with no hospitalisations
- Change from baseline to Month 12 in the Infant and Toddler Quality of Life Questionnaire 47 item short form (ITQOL-SF47) questionnaire domains and single item scores.

The company's health economic model for Type 1 SMA is based on rates of transition between motor milestones estimated from a re-analysis of the underlying HINE-2 data. Therefore, the ERG report focuses on the following key outcomes:

- Proportion of infants sitting without support after 12 months of treatment, as assessed in the BSID-III
- Proportion of patients able to support weight or stand with support as assessed by the HINE-2
- Proportion of patients able to bounce while assessing the walking item of the HINE-2
- Proportion of patients alive without permanent ventilation (≥16 hours of non-invasive ventilation such as BiPAP per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy)
- OS
- AEs.

Data on all other outcomes, including the other key outcomes listed above and in Table 9, are presented in the CS.[1]

Secondary efficacy endpoints for Part 2 of FIREFISH[23] were derived using data from real world data sources and natural history studies of untreated infants with Type 1 SMA, with similar baseline characteristics to the target population of FIREFISH, based on the associated upper limit of the 90% confidence interval (CI) from the historical data.[1] Guidance on performing clinical trials in Type 1 SMA cautions against using natural history data as a comparator in clinical studies due to evolving standards of care, and instead recommends the use of a placebo control arm.[31] The HINE-2 evaluates eight developmental motor milestones (each on a 3-5 point scale), including standing and walking (see Appendix 1, Figure 23), and has been previously used to assess motor function in infants with SMA.[1] Performance of each milestone is assessed incrementally, as a series of discrete states, which allows progression to be captured.[46, 47] Standing is assessed in terms of whether an infant does not support their own weight, supports their own weight, stands with support, or stands unaided, and walking is assessed in terms of whether an infant does not walk at all, bounces, cruises or walks independently.[47] The HINE-2 has been assessed alongside the CHOP-INTEND in infants with Type 1 SMA in the ENDEAR trial

of nusinersen,[25] and was found to be well tolerated and sufficiently sensitive to detect changes in motor milestones.[46] No performance criterion was available for the proportion of patients able to support weight or stand with support, nor for the proportion of patients able to bounce, as assessed by the HINE-2.[1] The ERG's clinical advisor confirmed that infants with Type 1 SMA would not normally be expected to reach these milestones.

OS and ventilation-free survival were assessed in terms of the number/proportion of patients alive (in total, and without permanent ventilation) at Month 12 of the FIREFISH study.[23] OS is considered to be an important outcome due to the natural history of the illness.[31] The performance criterion for this outcome was set at 60% for Part 2 of FIREFISH (CS,[1] Table 12, page 42). The ERG's clinical advisor confirmed that this performance criterion conservatively reflects the proportion of patients with Type 1 SMA who could be expected to survive to 12 months. This criterion is consistent with prior data on OS among infants with Type 1 SMA. For instance, in the ENDEAR trial,[25] 61% of patients in the placebo control arm were alive at data-cut-off (compared with 84% infants in the nusinersen arm),[25] and retrospective and observational data from patients with Type 1 SMA supports this.[10, 36, 48, 49] Permanent and non-invasive ventilation can considerably improve OS in infants with Type 1 SMA, meaning that many patients are alive but on permanent or chronic non-invasive ventilation for a number of years;[50] therefore, ventilation-free survival should also be assessed.

Ventilation-free survival is defined as the proportion of patients alive and without permanent ventilation, which was defined as "*≥16 hours of non-invasive ventilation such as BiPAP per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy*" (CS,[1] Table 9, page 36). Guidance on performing clinical trials in Type 1 SMA suggests that chronic non-invasive ventilation for >16 hours per day, for 2-4 weeks, can be considered a proxy outcome for death in clinical trials,[31] which supports the definition of ventilation-free survival used in Part 2 of FIREFISH.[23] The performance criterion for this outcome was set at 42% for Part 2 of FIREFISH (CS,[1] Table 12, page 42). The ERG's clinical advisor confirmed that this performance criterion conservatively reflects the proportion of patients with Type 1 SMA who could be expected to be alive and without permanent ventilation or chronic non-invasive ventilation at 12 months. This criterion is consistent with prior data on ventilation-free survival among infants with Type 1 SMA. For instance, in ENDEAR,[25] 32% of patients in the placebo control arm were alive and without permanent ventilation or chronic non-invasive ventilation (compared with 61% infants in the nusinersen arm) at data cut-off.[25] This is also corroborated by retrospective and prospective observational data from patients with Type 1 SMA.[10, 48, 49]

4.2.1.5 Study design

The SUNFISH trial (Part 2) is a pivotal multicentre, double-blind, placebo-controlled Phase II/III RCT, where eligible patients (n=180) were randomised to risdiplam or placebo. No patients from Part 1 were included in Part 2 of the trial.[22] Patients were randomised at a 2:1 ratio using an Interactive (voice/web) Response System, and randomisation was stratified by age group (2-5 years, 6-11 years, 12-17 years, and 18-25 years at randomisation, with ≤30 patients to be randomised into the 18-25 age group and ≥45 patients to be randomised into the other three groups).[22] Part 2 of SUNFISH is split into three periods: a 12-month randomised placebo-controlled treatment period; followed by a 24-month treatment period during which patients in the placebo arm were switched to risdiplam in a blinded manner; then an open-label extension phase, which could continue for an additional three years and included regular monitoring of safety, tolerability and efficacy.[22] Treatment will then continue until the drug is commercially available in the patient's country.[22] Patients and investigators are blinded to the treatment assigned at randomisation until the last patient has completed the assessments at the end of the 24-month treatment period.[22] Once the last patients completed the 12-month assessments at the end of the placebo-controlled part of the treatment period, the database was locked for the primary and secondary analyses; no patient in the trial had completed the 24-month treatment period and undertaken the 24-months assessment at this point. The sponsor was also unblinded at this point.[22] As a double-blind, placebo-controlled Phase II/III RCT, the ERG considers the study design to be rigorous.

The FIREFISH study[23] (Part 2) is a pivotal prospective, open-label, single-arm, multicentre Phase II/III clinical study of patients (n=41) who were treated with risdiplam. No infants from Part 1 were enrolled in Part 2 of the study.[23] Part 2 of FIREFISH is split into an open-label 24-month treatment period, followed by an open-label extension phase, which will continue until risdiplam is commercially available in the patient's country.[1] During the open-label extension phase, assessments are made less frequently than in the treatment period.[1] The primary endpoint was analysed at the 12-month assessment.[23] The ERG considers the design of FIREFISH (Part 2) to be open to potential biases such as attrition bias, natural recovery and regression to the mean,[51] due to being open-label and single-arm. A double-blinded placebo-controlled RCT would have been more rigorous in examining the efficacy and safety of risdiplam in infants with Type 1 SMA. The company's clarification response[17] (question A20), states that the decision was taken for FIREFISH to adopt a single-arm design as it would have been unethical to administer a placebo to some infants, due to the severity of Type 1 SMA. Another key factor in this decision was the natural history data in Type 1 SMA, which indicate that an infant with Type 1 SMA will never attain the milestone of sitting without support, and thus an attainment of this milestone would indicate a robust treatment effect.[36]

4.2.1.6 Ongoing studies

Both the SUNFISH and FIREFISH studies[22, 23] are currently ongoing with data still outstanding from the 24-month assessment, which is due to take place at the end of the 24-month treatment period (which is uncontrolled from Month 12 (where all patients in the placebo arm switch to risdiplam in a blinded fashion) in the case of SUNFISH; therefore there will not be any further placebo-controlled data on risdiplam in Type 2/3 SMA available from further timepoints in future). The 2-year analyses of Part 2 of SUNFISH and FIREFISH are expected in [redacted] and [redacted], respectively, and the final analyses of Part 2 of SUNFISH and FIREFISH are expected in [redacted] and [redacted], respectively.

The JEWELFISH study[21] is currently ongoing, with the interim analysis expected in [redacted] and the final analysis expected in [redacted].

An additional study – RAINBOWFISH (NCT03779334) – is reported in the CS[1] (page 81) as being currently ongoing. This is an open-label Phase II study examining the effectiveness of risdiplam among infants with pre-symptomatic and genetically diagnosed SMA. The ERG considers this study to be relevant to the current decision problem set out in the final NICE scope; however, the study is currently recruiting [redacted].[1]

The company anticipates that data from the entire treatment programme, consisting of these four trials, would inform future appraisal decisions on the efficacy and safety of risdiplam in SMA.[1]

4.2.2 Details of relevant studies not included in the submission

Despite the shortcomings associated with the company's searches described in Section 4.1.1, the ERG is confident that SUNFISH and FIREFISH (Part 2)[22, 23] are the only relevant studies in this patient population, that the ENDEAR trial[25] is potentially the only relevant comparator study to enable a comparison between risdiplam and BSC in infants with Type 1 SMA (see Section 4.3), and that no relevant studies have been omitted from the CS.[1] The methods employed by the company for this indirect comparison are detailed and critiqued in Section 4.4.

4.2.3 Summary and critique of the company's quality assessment

4.2.3.1 Critical appraisal of study quality of SUNFISH

The company provided a critical appraisal of the validity of Part 2 of the SUNFISH trial[22] using the checklist recommended by NICE (see Section 4.1.5). No explanation for the rating on each item was provided in the CS[1] or in CS Appendix D.[27] Table 10 presents a summary of the risk of bias in Part 2 of SUNFISH undertaken by the company alongside the ERG's independent quality assessment. The ERG has also specified its perceived level of risk of bias for each criterion.

The results of the company's and the ERG's quality assessments of SUNFISH[22] were similar. The ERG concludes that Part 2 of SUNFISH has a low risk of bias; the company did not provide a summary appraisal of risk of bias. The main difference between the company's and the ERG's ratings is that the company judged the concealment of treatment allocation to be accurate, whereas the ERG judged this to be unclear, due to a lack of information reported on who undertook randomisation, or who was overseeing the interactive response system.

Table 10: Company and ERG quality assessment of Part 2 of the SUNFISH trial (adapted from CS Table 11)

Quality assessment criterion question	Company quality assessment (yes/no/not clear/NA)		ERG quality assessment (yes/no/not clear/NA)	
	Grade	Explanation	Grade	Explanation
Was randomisation carried out appropriately?	Yes	Not given	Yes	Randomisation was carried out using an interactive response system.
Was the concealment of treatment allocation adequate?	Yes	Not given	Not clear	It is unclear who undertook randomisation.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Not given	Yes	Groups were similar on most characteristics, and where there were differences, the risdiplam arm might be expected to do worse.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Not given	Yes	Patients and investigators were blinded to treatment allocation; an identical placebo control was used.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Not given	No	There was only a difference of 0.8% in dropout rate between the arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Not given	No	The protocol is available online and all outcomes measured were reported on.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Not given	Yes	An ITT analysis was reported. Missing data were classed as non-response.

ITT - intention to treat; NA - not applicable

4.2.3.2 Critical appraisal of study quality of FIREFISH

Table 11 presents the ERG's quality assessment of Part 2 of the FIREFISH study[23] based on the Newcastle-Ottawa scale.[30] No quality assessment of FIREFISH was presented in the CS.[1]

Table 11: ERG quality assessment for Part 2 of the FIRFISH trial using the Newcastle-Ottawa Scale

Quality assessment question	ERG's quality assessment
Representativeness of the exposed cohort	Clinical advice received by the ERG has confirmed that the population of this trial are representative of Type 1 SMA patients seen in clinic.
Selection of the non-exposed cohort	N/a (single-arm study)
Ascertainment of exposure	Patients were administered risdiplam as a study treatment intervention. Administration was monitored.
Demonstration that outcome of interest was not present at start of study	The primary outcome was the proportion of infants sitting without support at 12 months. According to CS, Table 7, no patient had achieved sitting at baseline.[1]
Comparability of cohorts on the basis of the design or analysis	N/a
Assessment of outcome	The primary outcome was scored by independent readers. It is unclear who has assessed the other outcomes, although the design is specified as open-label.
Was follow-up long enough for outcomes to occur?	Patients were assessed for up to 12 months, which is long enough for outcomes to occur (although the outcomes examined are not expected in this population).
Adequacy of follow up of cohorts	38 of the 41 patients (93%) remained on treatment at the clinical cut-off date. Withdrawals were accounted for.
Stars total (out of a possible 6)	**5**

SMA - spinal muscular atrophy; ERG - Evidence Review Group; N/a - not applicable

The ERG has rated Part 2 of FIREFISH[23] as moderate in terms of study quality. The main source of bias is the unblinded nature of the outcome assessment for all but the primary outcome. Despite the company's justification for the use of a single-arm design, the ERG considers that this remains an important source of potential bias for any inference of relative treatment effects.

4.2.3.3 Protocol deviations

In Part 2 of the SUNFISH trial, [redacted] major protocol deviations were reported for [redacted] patients as of the clinical cut-off date (CSR,[22] page 85). A greater number of major protocol deviations were reported for the risdiplam arm than the placebo arm ([redacted] vs. [redacted] protocol deviations), in a greater number of patients ([redacted] vs. [redacted] in the risdiplam and placebo arms, respectively), although the proportion of patients in each arm with one or more protocol deviations was similar ([redacted] vs. [redacted] in the risdiplam and placebo arms, respectively). For the risdiplam arm, these included: clinically significant abnormal laboratory tests ([redacted]); drugs of abuse or alcohol use not confirmed ([redacted]); no re-screening ([redacted]); ophthalmology report not received at time of enrolment ([redacted]); no signed written informed consent ([redacted]); ambulant patient ([redacted]); patient received incorrect dose of study medication for ≥1 week ([redacted]). For the placebo arm, these included: clinically significant abnormal laboratory tests ([redacted]); drugs of abuse or alcohol use not confirmed ([redacted]); ophthalmology report not received at time of enrolment ([redacted]); no signed written informed consent ([redacted]); consistent non-compliance with daily use of study medication

([redacted]); medication – other ([redacted]); patient received incorrect dose of study medication for ≥1 week ([redacted]).[22]

In Part 2 of the FIREFISH study, [redacted] major protocol deviations were reported for [redacted] patients as of the clinical cut-off date (CSR,[23] page 84). These included: not receiving the ophthalmology report at the time of enrolment ([redacted]); failure to obtain informed consent ([redacted]); patient received prohibited concomitant medication ([redacted]); patient received a significant overdose or underdose for ≥1 week ([redacted]); failure to report a serious adverse event (SAE) per protocol ([redacted]); not undertaking a safety assessment within the scheduled time window ([redacted]); no subsequent re-consent ([redacted]); optical coherence tomography exam nor performed or repeated ([redacted]); optical coherence tomography obtained by non-certified person by Annesley Eye Brain Center ([redacted]).[23]

4.2.4 Summary and critique of results

The clinical cut-off date for the 12-month analyses in Part 2 of the SUNFISH trial[22] was the 6th September 2019, and the clinical cut-off date for the 12-month analyses for Part 2 of the FIREFISH study[23] was the 14th November 2019.

4.2.4.1 SUNFISH

The ITT population was used in all efficacy analyses. Table 12 summarises the efficacy results for Part 2 of the SUNFISH trial for the outcomes that are considered in this report. Other outcomes, including patients with a change in MFM32 ≥3 from baseline to Month 12 and patients with a change in MFM32 ≥0 from baseline to Month 12 are reported in Table 21, pages 49 to 50 of the CS.[1] *P*-values were adjusted to account for multiple testing using a hierarchical approach.[22]

Table 12: Clinical efficacy summary of outcomes focused on in the ERG report, SUNFISH (Part 2) (adapted from CS, Table 21)

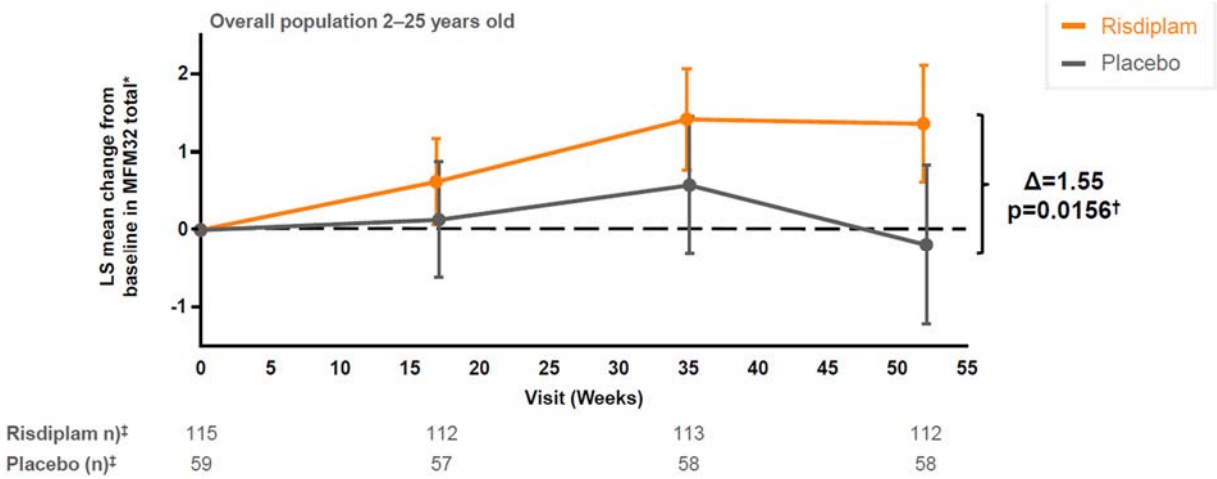
Outcome	Risdiplam n=120	Placebo n=60	Difference, risdiplam minus placebo (95% CI)	*p*-value
Primary endpoint				
Least squares mean change (SE) in MFM-32 Total Score from Baseline to Month 12	1.36 (0.38)	–0.19 (0.52)	1.55 (0.30, 2.81)	Unadjusted: 0.0156 Adjusted: 0.0156
Secondary endpoints				
Least squares mean change (SE) in HFMSE Total Score from Baseline to Month 12	0.95 (0.33)	0.37 (0.46)	0.58 (–0.53, 1.69)	Unadjusted: 0.3015 Adjusted: 0.3902
Least squares mean change (SE) in RULM Total Score from Baseline to Month 12	1.61 (0.31)	0.02 (0.43)	1.59 (0.55, 2.62)	Unadjusted: 0.0028 Adjusted: 0.0469
Least squares mean change (SE) in MFM32 D3 score from Baseline to Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean change (SE) in caregiver-reported SMAIS score from Baseline to Month 12	1.65 (0.50)	–0.91 (0.67)	2.55 (0.93, 4.17)	Unadjusted: 0.0022 Adjusted: 0.3902
Least squares mean change (SE) in patient-reported SMAIS Total score from Baseline to Month 12	1.04 (0.65)	–0.40 (0.86)	1.45 (–0.68, 3.57)	0.1778

CI - confidence interval; HFMSE - Hammersmith Functional Motor Scale Expanded; MFM32 - Motor Function Measure - 32 items; RULM - Revised Upper Limb Module; SE - standard error; SMAIS - SMA independence scale

Change from baseline in MFM32 (primary outcome)

The least squares mean (SE) change from baseline to Month 12 in MFM32 total score was 1.36 (0.38) in the risdiplam arm and -0.19 (0.52) in the placebo arm, which indicates a small overall improvement in function among patients in the risdiplam arm and a slight decline in function among patients in the placebo arm (see Table 12 and Figure 2). The CS[1] states that the improvement in MFM32 total score in the risdiplam arm is clinically meaningful, which was corroborated by clinical advice received by the ERG and qualitative research with SMA patients, carers and clinicians.[39] The least squares mean difference between arms was 1.55 (95% CI: 0.32, 2.81), which was statistically significant (unadjusted p=0.0156, adjusted p=0.0156).

Figure 2: **Least-squares mean change from baseline and 95% confidence interval in MFM32 total score at each timepoint up to Month 12 (SUNFISH Part 2; ITT Population) (reproduced from CS Figure 3)**



LS - least squares; MFM32 - Motor Function Measure – 32 items
**+/-95% confidence interval. †Mixed Model Repeated Measure, unadjusted p-value at 5% significance level. ‡Number of people with valid results = number of people with an available total score (result) at respective time points.*
Intent to treat patients. Data cut-off: 6th September 2019

Change from baseline in HMFSE total score

The least squares mean (SE) change from baseline to Month 12 in HFMSE total score was 0.95 (0.33) in the risdiplam arm and 0.37 (0.46) in the placebo arm, which indicates a slight overall improvement in function among patients in both arms (see Table 12). The least squares mean difference between arms was 0.58 (95% CI: -0.53, 1.69), which was not statistically significant (unadjusted *p*=0.3015 adjusted *p*=0.3902). This lack of effect of risdiplam on total HMFSE total score is explained in the CS as a function of a lack of sensitivity of the scale to detect a change in those with a low baseline score,[1] and qualitative evidence SMA patients, carers and clinicians[39] corroborates this explanation.

Change from baseline in fine motor skills

The least squares mean (SE) change from baseline to Month 12 in RULM total score was 1.61 (0.31) in the risdiplam arm and 0.02 (0.43) in the placebo arm, which indicates a small overall improvement in upper limb function among patients in the risdiplam arm and little difference in upper limb function among patients in the placebo arm (see Table 12 and CS,[1] Figure 4). The CS states that the improvement in RULM total score in the risdiplam arm is clinically meaningful. This was corroborated by clinical advice received by the ERG and qualitative research with SMA patients, carers and clinicians,[39] which suggests that small improvements in upper limb function can be valuable to people with SMA. The least squares mean difference between arms was 1.59 (95% CI: 0.55, 2.62), which was statistically significant (unadjusted *p*=0.0028, adjusted *p*=0.0469).

The least squares mean (SE) change from baseline at week 52 in MFM32 D3 score was [redacted] in the risdiplam arm and [redacted] in the placebo arm, which indicates [redacted] (see Table 12). The least squares mean difference between arms was [redacted], which was statistically significant ([redacted]).

The least squares mean (SE) change from baseline to Month 12 in SMAIS total score (as reported by caregivers, n=176, and patients aged ≥12 years, n=66) are reported in Table 12, and in Figure 5 of the CS.[1] Small gains in independence with risdiplam but small losses in independence with placebo were reported by both caregivers and patients. For the caregiver-reported assessment, the least squares mean difference between risdiplam and placebo was 2.55 (95% CI: 0.93, 4.17), which is statistically significant when unadjusted, although when accounting for multiplicity of testing, the *p*-value is no longer significant (unadjusted *p*=0.0022, adjusted *p*=0.3902).[1] For the patient-reported assessment, the least squares mean difference between risdiplam and placebo was 1.45 (95% CI: -0.68, 3.57), which was not statistically significant (unadjusted *p*=0.1778). Given that the SMAIS has not been validated and has only been used in one other trial (with the same sponsor as for the current appraisal; see Section 4.2.1.4), the ERG cannot assume that the SMAIS data from the SUNFISH trial is a reliable and valid indicator of upper-limb related independence among patients with SMA.

In addition to these outcomes, the company's clarification response[17] (question B7c) provides data on the number of patients reaching standing and walking milestones in Part 2 of SUNFISH[22] (see Table 13). Overall, more patients in the risdiplam arm attained these milestones than in the placebo arm, where no patients attained the ability to stand or walk; nevertheless, the proportion of patients is small.

Table 13: Number of patients attaining standing/walking and walking milestones in SUNFISH (Part 2)

Outcome	Follow-up timepoint	Risdiplam arm	Placebo arm
Ability to stand or walk	Week 17	5	0
	Week 35	4	0
	Week 53	5	0
Ability to walk	Week 17	1	0
	Week 35	0	0
	Week 53	1	0

Source: Company's clarification response,[17] question B7

4.2.4.2 FIREFISH

The ITT population was used in all efficacy analyses. Table 14 summarises the efficacy results for Part 2 of FIREFISH for outcomes that are considered in this report. Other outcomes, including number/proportion of patients who achieve a score of 40 or higher in the CHOP-INTEND at Month 12, number/proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND

score from baseline at Month 12, number/proportion of motor milestone responders as assessed by the HINE-2 at Month 12, number/proportion of patients with the ability to feed orally at Month 12, number of hospitalisations per patient-year at Month 12 and number/proportion (90% CI) of people with no hospitalisations at Month 12 are reported in the CS[1] (Table 12, pages 41 to 42).

Table 14: Clinical efficacy summary of outcomes focused on in the ERG report (FIREFISH Part 2, adapted from CS, Table 12)

Endpoint	Risdiplam n=41	Performance criterion	*p*-value[a]
Primary efficacy endpoint			
Number and proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 12	12/41 29.3% (17.8–43.1%)	5%	<0.0001
Secondary efficacy endpoints			
Number and proportion (90% CI) of patients able to support weight or stand with support[b] as assessed by the HINE-2 at Month 12	9/41 22.0% (12.0–35.2%)	N/a	–
Number and proportion (90% CI) of patients able to bounce while assessing the walking item of the HINE-2 at Month 12	1/41 2.4% (0.1–11.1%)	N/a	–
Number and proportion (90% CI) of patients alive without permanent ventilation at Month 12 (90% CI)	35/41 85.4% (73.4–92.2%)	42%	<0.0001
Number and proportion (90% CI) of patients alive at Month 12	38/41 92.7% (82.2–97.1%)	60%	0.0005

BSID-III - Bayley Scales of Infant and Toddler Development, third edition; CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI - confidence interval; HINE-2 - Hammersmith Infant Neurological Examination Module 2; N/a - not available.

[a] *p-values for survival and ventilation-free survival are based on a Z-test; p-values for all other endpoints (BSID-III, CHOP-INTEND, HINE-2) are based on an exact binomial test.*

[b] *Includes 7 patients (17.1%) who could support weight and 2 patients (4.9%) who could stand without support.*

Proportion of infants sitting without support (primary outcome)

Twelve (of 41) patients in Part 2 of FIREFISH[23] (29.3%; 90% CI: 17.8, 43.1%) were sitting without support for five seconds, as assessed by the BSID-III, at Month 12 (see Table 14). The CS[1] states that this is a clinically meaningful effect, and clinical advice received by the ERG concurs with this assertion. Correspondingly, the proportion of patients sitting without support for five seconds in Part 2 of FIREFISH was statistically significantly greater than the performance criterion of 5% ($p<0.0001$).

Proportion of patients able to support weight or stand with support

Nine (of 41) patients in Part 2 of FIREFISH[23] (22.0%; 90% CI: 12.0, 35.2%) were able to support weight or stand with support, as assessed by the HINE-2, at Month 12 (see Table 14). This includes seven (17.1%) patients who were able to support weight, and 2 (4.9%) patients who were able to stand without support. The CS[1] states that this is a clinically meaningful effect, and clinical advice received by the ERG concurs with this view, as Type 1 patients would not normally be expected to reach this milestone (see Section 4.2.1.4).

Proportion of patients able to bounce

One (of 41) patient in Part 2 of FIREFISH[23] (2.4%; 90% CI: 0.1, 11.1%) was able to bounce, as assessed by the HINE-2, at Month 12 (see Table 14). The CS[1] states that this is a clinically meaningful effect, and clinical advice received by the ERG agrees with this view, as Type 1 patients would not normally be expected to reach this milestone (see Section 4.2.1.4). The ERG notes that this is the highest milestone on the 'walking' subscale of the HINE-2 that any patient in the FIREFISH study attained at Month 12, with no patients progressing to cruising or walking independently by the clinical cut-off date. In Table 17 of the CS, 34 patients (82.9%) were categorised as 'cannot test' for the HINE-2 walking milestone at Month 12. The company's clarification response[17] (question A22) states that this was a proxy response option for no achievement of the milestone, for which there is no option on the scale.

Ventilation-free survival

Thirty-five (of 41) patients in Part 2 of FIREFISH[23] (85.4%; 90% CI: 73.4, 92.2%) were alive without permanent or chronic non-invasive ventilation at Month 12 (see Table 14). The CS[1] states that this is a clinically meaningful effect, and clinical advice received by the ERG agrees with this assertion (see Section 4.2.1.4). The proportion of patients alive without permanent or chronic non-invasive ventilation at Month 12 in Part 2 of FIREFISH was statistically significantly greater than the performance criterion of 42% ($p<0.0001$).

Overall survival

Thirty-eight (of 41) patients in Part 2 of FIREFISH[23] (92.7%; 90% CI: 82.2, 97.1%) were alive at Month 12 (see Table 14). The CS[1] states that this is a clinically meaningful effect, and clinical advice received by the ERG agrees with this assertion (see Section 4.2.1.4). The proportion of patients alive at Month 12 in Part 2 of FIREFISH was statistically significantly greater than the performance criterion of 60% ($p=0.0005$).

4.2.4.3 Safety and tolerability

Risdiplam appears to be generally well tolerated among patients with Type 2/3 SMA (see Table 15). In Part 2 of SUNFISH,[22] a greater proportion of patients in the risdiplam arm than the placebo arm experienced AEs leading to dose modification or interruption (6.7% vs 3.3%, respectively), treatment-related AEs (13.3% vs 10.0%, respectively) and grade 3-5 AEs (17.5% vs 13.3%, respectively). However, as of the clinical cut-off date, at the 12-month follow-up, no patients in either arm had experienced an AE with a fatal outcome, an SAE leading to withdrawal from treatment, or a treatment-related SAE, and the proportion of patients experiencing a SAE and SAE leading to dose modification or interruption was similar across arms (see Table 15). For further details, see Section F.3, in CS Appendix F.[27] The company's clarification response[17] (question A17) states that the AE data provided

for the SUNFISH trial in CS Appendix F, Section F.3, Table 13 refer to the placebo-controlled, double-blind period only.[17]

Table 15: Overview of adverse events from SUNFISH, FIREFISH and JEWELFISH (safety-evaluable population) (adapted from CS Appendix F, Tables 12, 13 and 14)

n (%)	SUNFISH (Part 2)		FIREFISH (Part 2) (n=41)	JEWELFISH (n=173)
	Risdiplam (n=120)	Placebo (n=60)		
Total number of patients with at least one AE	111 (92.5)	55 (91.7)	41 (100)	125 (72.3)
Total number of AEs, n	789	354	254	468
Total number of deaths	0	0	3 (7.3)	0
Total number of patients withdrawn from study due to an AE	0	0	0	0
Total number of patients with at least one AE with a fatal outcome	0	0	3 (7.3)	0
Total number of patients with at least one SAE	24 (20.0)	11 (18.3)	24 (58.5)	14 (8.1)
Total number of patients with at least one SAE leading to withdrawal from treatment	0	0	0	0
Total number of patients with at least one SAE leading to dose modification/interruption	4 (3.3)	2 (3.3)	1 (2.4)	3 (1.7)
Total number of patients with at least one treatment-related SAE	0	0	0	1 (0.6)
Total number of patients with at least one AE leading to withdrawal from treatment	0	0	0	0
Total number of patients with at least one AE leading to dose modification/interruption	8 (6.7)	2 (3.3)	2 (4.9)	10 (5.8)
Total number of patients with at least one treatment-related AE	16 (13.3)	6 (10.0)	7 (17.1)	23 (13.3)
Total number of patients with at least one treatment-related AE leading to withdrawal from treatment	0	0	0	0
Total number of patients with at least one treatment-related AE leading to dose modification/interruption		0	0	1 (0.6)
Total number of patients with at least one Grade 3–5 AE	21 (17.5)	8 (13.3)	22 (53.7)	14 (8.1)

AE - adverse event

Risdiplam also appears to be generally well tolerated among patients with Type 1 SMA (see Table 15). In Part 2 of FIREFISH,[23] 3 (7.3%) patients experienced an AE with a fatal outcome, 1 (2.4%) experienced an SAE leading to dose modification/interruption, 2 (4.8%) experienced an AE leading to dose modification/interruption, 7 (17.1%) experienced a treatment-related AE, and 22 (53.7%) experienced a grade 3-5 AE. However, no patients experienced an AE that resulted in withdrawal from

the study or from treatment, a treatment-related SAE, or a treatment-related AE leading to withdrawal from treatment or dose modification/interruption (see Table 15). For further details, see Section F.2, CS Appendix F.[27] Treatment-related AEs were those considered by the investigator to be related to the study medication.[23] The company's clarification response[17] (question A23), states that investigators were asked to consider "*Their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes*", including the timing of the onset of the AE in relation to study drug initiation, the effects of reducing, discontinuing and/or reintroducing the study drug, a known association between the event and the study drug or similar drugs, a known association of the event with the condition, risk factors that may be present in the patient, use of concomitant medications with a known relation to the event, and whether any treatment-related factors known to be associated with the occurrence of the event are present.[17] The ERG notes that a greater proportion of patients had an AE leading to discontinuation and an SAE when treated with BSC in the ENDEAR trial than patients treated with risdiplam in the FIREFISH trial. The company's clarification response[17] (question A29), states that no treatment-related AEs (considered by the investigator to be related to study medication) were reported in the pooled FIREFISH cohort (consisting of patients from 'Cohort 2' in Part 1 and all patients from Part 2), that AEs and SAEs leading to discontinuation include fatal AEs and so differences in OS might be contributing to these figures, and that the AEs reported were reflective of the age and disease of the Type 1 SMA patients enrolled.

Data from JEWELFISH[21] up to the clinical cut-off date of the 31st of January 2020 (at which point the treatment range for risdiplam was 0 to 32.8 months, with 24.9% of the 173 enrolled patients having a treatment duration of ≥6 months) suggest that risdiplam is well-tolerated among treatment-experienced patients with Type 1, Type 2 and Type 3 SMA (see Table 15). There were no deaths (or AEs with a fatal outcome), withdrawals (from treatment or the study) due to an AE or SAE. At the clinical cut-off date, 14 (8.1%) patients experienced SAEs, 3 (1.7%) experienced SAEs leading to dose modification or interruption, 1 (0.6%) experienced a treatment-related SAE, 10 (5.8%) experienced AEs leading to dose modification or interruption, 23 (13.3%) experienced treatment-related AEs, 1 (0.6%) experienced an AE leading to dose modification or interruption, and 14 (8.1%) experienced grade 3-5 AEs (see Table 15). For further details, see Section F.4, CS Appendix F.[27] The ERG notes that a greater proportion of patients with prior nusinersen had SAEs (11.8%) and AEs leading to treatment modification or interruption (9.2%) than for RO6885247 (7.7% and 7.7%, respectively), olesoxime (4.3% and 2.9%, respectively) and AVXS-101 (7.1% and 0%), and a relatively high proportion of patients with prior nusinersen experienced treatment-related AEs (19.7%), although this was exceeded slightly in patients with prior RO6885247 (23.1%) (see CS Appendix F,[27] Section F.4, Table 14). The ERG also notes that the proportion of patients with prior nusinersen who experienced AEs leading to dose modification or interruption and treatment-related AEs was higher at the generally earlier clinical cut-off date of JEWELFISH (median treatment duration of 3.0 months) than in both the SUNFISH trial

and FIREFISH studies after 12 months of risdiplam. This may have implications for the positioning of risdiplam in the treatment pathway. A comparative trial of treatment-naïve and nusinersen-treated patients would be required to corroborate this observation.

An additional pooled safety analysis of data from the SUNFISH, FIREFISH and JEWELFISH studies[21-23] is also presented in the CS (see CS Appendix F,[27] Section F.1). Table 10 (CS Appendix F, Section F.1) reports the AE rate adjusted for patient-years at risk by NCI CTCAE grade over time. The ERG notes that AE rates decreased over time, for all NCI CTCAE grades.

4.2.4.4 Subgroups

SUNFISH

In Part 2 of SUNFISH,[22] the primary efficacy endpoint and key efficacy endpoints were examined in terms of the following subgroups: (1) age group (2-5, 6-11, 12-17, 18-25 years at randomisation); (2) disease severity ($\leq 25^{th}$ percentile, $>25^{th}$ and $\leq 75^{th}$ percentile, and $>75^{th}$ percentile on MFM32 total score at baseline); (3) SMA type (Type 2 or Type 3); and (4) SMN2 copy number (<2, 2, 3, ≥4 copies, or unknown). The study was not powered to demonstrate efficacy among these subgroups. For the primary outcome, MFM32 total score was most improved relative to placebo among the younger age group patients (aged 2-5 years), [redacted] (see CS Appendix E,[27] Section E.2, Figure 9). The subgroup analyses for HMFSE total score change from baseline to 12 months were similar to the results of the whole sample analysis of this outcome, except that [redacted] (see CS Appendix E,[27] Section E.2, Figure 12). Change from baseline in RULM total score at 12 months for risdiplam relative to placebo was greatest among [redacted] (see CS Appendix E,[27] Section E.2, Figure 9). [redacted] The SUNFISH CSR reports [redacted] in total caregiver-reported SMAIS scores [redacted] Patient-reported total SMAIS scores [redacted]

The ERG notes that categorising continuous variables, such as age, is statistically inefficient, assumes that the relationship between response and the predictor is constant within each interval, and assumes that there is a discontinuity in response at the interval boundaries. In addition, it is unclear from the CS[1] whether there is a clinical justification for defining these age categories and whether these are universally agreed. Furthermore, the ERG notes that performing separate subgroup analyses to assess heterogeneity of treatment effects can be misleading. Heterogeneity of treatment effects should be assessed using model-based estimates on the whole sample and should demonstrate evidence for an interaction adjusted for all main effects.

FIREFISH

In Part 2 of FIREFISH,[23] the primary efficacy endpoint (the proportion of infants sitting without support at 12 months) and two secondary efficacy endpoints (proportion of patients who achieve a CHOP-INTEND score of ≥40 at Month 12, and time to death and permanent ventilation) were examined in terms of the following subgroups: (1) age at enrolment; (2) sex; (3) race; (4) region; (5) disease duration (time from symptom onset to first treatment); and (6) baseline CHOP-INTEND score. The study was not powered to demonstrate efficacy among these subgroups, and patient numbers in each subgroup were small. For the primary outcome, [redacted] The proportion of patients who achieve a CHOP-INTEND score of ≥40 at Month 12 and the proportion of patients alive without permanent ventilation [redacted] There were no subgroup analyses reporting other outcomes focused on by the ERG: the proportion of patients able to support weight or stand with support as assessed by the HINE-2; the proportion of patients able to bounce while assessing the walking item of the HINE-2; and OS.

The ERG notes that these are not subgroup analyses to assess heterogeneity of treatment effect with respect to different subgroups; rather, they are analyses which simply assess the difference in absolute response according to subgroup. It is perfectly possible for different subgroups to have different responses but for the relative treatment effect on an appropriate additive scale to be constant by subgroup. Hence, the ERG advises caution to avoid the misinterpretation of the results of the subgroup analyses as evidence for or against differential treatment effects.

Age and duration of disease were both dichotomised into two groups for the purpose of subgroup analyses. The problems regarding categorising continuous variables and justification of the selected categories described for SUNFISH also apply to the FIREFISH subgroup analyses. In addition, baseline CHOP-INTEND score was dichotomised according to the sample estimate of the median which is subject to sampling variation, is not the same as the median in the population, and is difficult to interpret.

As described previously, performing separate subgroup analyses can be misleading and heterogeneity, whether of treatment effects or response, should be assessed using model-based estimates on the whole sample and should demonstrate evidence for differential treatment effects after adjusting for all relevant predictor variables (i.e. main effects). Furthermore, in the FIREFISH subgroup analyses, it is unclear whether heterogeneity was assessed on an additive scale and how to interpret the results given that these are reported as proportions. In their clarification response[17] (question A16), the company stated that, "*not all patients could provide the full date of birth, and hence the age of some patients may not be very accurate*". Consequently, the company considered it inappropriate to include age as a continuous variable. In addition, the company deemed it inappropriate to assess the relevance of predictors in a single model because of the possibility of over-fitting and stated that "*the sample sizes are not large enough to describe the (approximately) true relationship between the dependent variable and all of the included covariates*".

4.3 Critique of trials identified and included in the indirect comparison

The CS[1] presents the results of a matching-adjusted indirect comparison (MAIC) of risdiplam versus BSC in Type 1 SMA using individual patient data (IPD) from FIREFISH[23] and aggregate data from the placebo (sham) arm of the ENDEAR trial.[25] Inclusion criteria were similar between FIREFISH and ENDEAR, except that: SMA Type 1 (and the corresponding signs and symptoms) were not specified for ENDEAR; ENDEAR excluded infants who would not be suitable for a lumbar puncture procedure, whereas FIREFISH did not; and FIREFISH excluded patients that required invasive ventilation or tracheostomy, whereas ENDEAR did not.[25, 27] However, in the ENDEAR trial publication (Finkel *et al.,*[25] page 1726), the authors note that "*At baseline, all the infants were symptomatic, hypotonic, and weak; these features are consistent with a phenotype that is most likely to be classified as spinal muscular atrophy type 1*" and the survival curves indicate that no patient required invasive ventilation at baseline. It is, however, possible that infants who would have been eligible for FIREFISH may have been ineligible for ENDEAR due to being unsuitable for lumbar puncture. The study duration also differs between FIREFISH and ENDEAR. FIREFISH has a 24-month treatment period and data are available for 12-months follow-up, whereas ENDEAR was terminated early, after the interim data cut-off, when patients had been enrolled for a minimum of six months, with a median time on study of 280 days (range 6-442 days) for patients in the placebo control group.[25] The treatment schedule and baseline characteristics are reported in the Finkel *et al*. publication,[25] and the baseline characteristics of the

FIREFISH and ENDEAR studies are shown in Table 16. The baseline characteristics shown in bold were included as covariates in the company's original adjustment model presented in the CS;[1] a broader set of covariates were included in updated analyses presented in question A27 of the company's clarification response.[17] This included: age at first dose; sex; symptom duration; age at symptom onset; CHOP-INTEND score at baseline; HINE-2 score at baseline; ulnar nerve CMAP amplitude at baseline; proportion of patients with feeding tube / unable to swallow at baseline and the proportion of patients on ventilation at baseline.

Table 16: Comparison of baseline characteristics of FIREFISH and ENDEAR post-matching (reproduced from CS Table 34)

Baseline characteristic	**Pre-Matching: Risdiplam (Pooled FIREFISH)**	**Post-matching: Risdiplam (Pooled FIREFISH matching-adjusted to ENDEAR)**	**Nusinersen & BSC (ENDEAR)**
Sample size / ESS	58	[redacted]	121
Mean age at first dose in days	[redacted]	[redacted]	**169 days**
Female gender	57%	[redacted]	55%
Mean age at symptom onset in days	[redacted]	[redacted]	60 days
Mean disease duration at screening in days	[redacted]	[redacted]	**94 days**
Mean age at diagnosis in weeks	[redacted]	[redacted]	14.3 weeks
Mean score on CHOP-INTEND	[redacted]	[redacted]	**27.24**
Mean HINE-2 score	[redacted]	[redacted]	1.37
Patients with ventilatory support	[redacted]	[redacted]	22%

CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2 - Hammersmith Infant Neurological Examination Module 2; ESS - effective sample size
Indirect comparison matched on variables in bold – see Section 4.4.2

4.3.1 Critical appraisal of study quality of ENDEAR (placebo arm)

Table 17 presents a quality assessment of the placebo arm of the ENDEAR trial[25] undertaken by the ERG, based on the Newcastle-Ottawa scale.[30] No quality assessment of the placebo arm of the ENDEAR trial was presented in the CS.

Table 17: ERG quality assessment for the placebo arm of the ENDEAR trial using the Newcastle-Ottawa Scale

Quality assessment question	ERG's quality assessment
Representativeness of the exposed cohort	Unclear. Representativeness (in terms of patients eligible for risdiplam) may be compromised by requirement of suitability for lumbar puncture.
Selection of the non-exposed cohort	N/a (placebo arm treated as single-arm study in analysis)
Ascertainment of exposure	All elements of patient care comprising BSC should have been documented in medical records. Standards of care guidelines were issued.
Demonstration that outcome of interest was not present at start of study	The two primary outcomes were HINE-2 motor response, which could not have been present at baseline, and ventilation-free survival as of one of five follow-up timepoints.
Comparability of cohorts on the basis of the design or analysis	N/a (placebo arm treated as single-arm study in analysis)
Assessment of outcome	Standard clinician-assessed outcome measurements were used, open-label to BSC (but BSC was not expected to vary as the exposure of interest in this trial was nusinersen [vs placebo])
Was follow-up long enough for outcomes to occur?	Patients were assessed for at least six months, which is sufficient for outcomes to occur.
Adequacy of follow up of cohorts	Twenty-four of the 41 enrolled patients (59%) completed the study. Discontinuations and withdrawals were accounted for; however, attrition was high.
Stars total (from a possible 6)	**4**

ERG - Evidence Review Group; BSC - best supportive care; N/a - not applicable

The ERG has rated the placebo arm of the ENDEAR trial[25] moderate in terms of study quality. The main source of bias is the high discontinuation rate.

4.4 Critique of the indirect comparison

4.4.1 Summary of key results from the company's indirect comparison

Table 18 summarises the key results of the company's MAIC for ventilation-free survival, OS and key motor milestone attainment. It should be noted that the unadjusted treatment effects for these endpoints are used in the company's Type 1 SMA model; the ERG believes this is likely to be more biased than estimates which include adjustment for differences in covariates (see Section 5.3.4). Section B.2.9 of the CS[1] and the company's clarification response[17] (question A27) include additional outcomes which are not reproduced here as they are not used in the company's Type 1 SMA model. As described in Section 4.3, the company's clarification response includes updated analyses which include additional covariates compared with the MAIC presented in the CS.

The company's unadjusted comparison suggests that risdiplam improves ventilation-free survival and OS and increases the odds of achieving important motor milestones in Type 1 SMA. The company's original and updated MAICs generate hazard ratios (HRs) for ventilation-free survival and OS which are lower (more favourable) than those generated from the unadjusted comparisons. The MAIC also

suggests increased odds for risdiplam versus placebo in terms of achieving the milestone of sitting, but slightly lower odds of achieving standing relative to the unadjusted comparison.

Table 18: Summary of key results of company's indirect comparison of risdiplam versus placebo

Outcome	Treatment effect - risdiplam versus placebo (as proxy for BSC)		
	Unadjusted (naïve) arm-based comparison (CS)	MAIC (CS)	MAIC (clarification response)
Ventilation-free survival - HR (95% CI))	[redacted]	[redacted]	[redacted]
Overall survival – HR (95% CI)	[redacted]	[redacted]	[redacted]
Sitting with and without support - sits with support at hips, props, stable sit and pivots - OR (95% CI)	[redacted]	[redacted]	Equivalent analysis not updated in clarification response
Standing with support and unaided – OR (95% CI)	[redacted]	[redacted]	Equivalent analysis not updated in clarification response

CS - company's submission; MAIC - matching adjusted indirect comparison; CI - confidence interval
** ORs calculated using half-cell correction*

4.4.2 Critique of company's indirect comparison

The selection of baseline characteristics as prognostic factors and treatment effect modifiers in the unanchored indirect comparison was based on the availability of baseline characteristics in the FIREFISH and ENDEAR studies,[23, 25] variables identified in the literature review and internal and external clinical expertise:

- The literature review found that age at onset of treatment was considered to be a treatment effect modifier based on the literature.
- Clinical experts noted that duration of symptoms/disease was associated with differences in the effect of nusinersen in subgroup analyses of the ENDEAR study.
- The literature review found that baseline total CHOP-INTEND score was considered to be predictive of later achievement of motor milestones.

Other baseline characteristics were considered by the company but were not deemed to be prognostic factors or treatment effect modifiers for various reasons. Notably, the literature review did not find gender to be a statistically significant predictor of outcomes; however, the ERG notes that absence of evidence is not evidence of absence and that other criteria such as the magnitude of the coefficient in a multivariable regression and expert opinion should have been used. In their clarification response[17] (question A24), the company reiterated that of the four studies that were identified that investigated the impact of gender on survival outcomes in Type 1 SMA, none found a statistically significant difference

in survival outcomes between males and females, and clinical experts did not suggest gender as being potentially prognostic or predictive. The ERG notes that the matching procedure created an imbalance in the proportion of female patients between FIREFISH[23] and ENDEAR[25] (i.e. proportion female 69% post-matching and 57% pre-matching in FIREFISH compared to 55% in ENDEAR; see Table 16). The ERG notes that in response to clarification question A26, the company stated that a higher proportion of the 28 patients who were assigned a rescaled weight of less than 0.5 were patients who required ventilator support at baseline and were male compared to the total pooled FIREFISH dataset. While this may simply reflect random variation, it may also indicate that these variables are relevant covariates.

Strictly, a propensity score model should also include all relevant higher order terms such as squared covariate values to balance variances (in order to balance covariate distributions) and interaction terms, else the result will generate a biased estimate. The company did not match treatment arms according to variances because of the limited number of patients included in FIREFISH (CS Appendix M[27]). There was some suggestion of a difference in variability with respect to CHOP-INTEND score between the risdiplam arm post-matching and the baseline in ENDEAR (clarification response,[17] question A27, Table 3 – CHOP-INTEND standard deviations [SDs] [redacted] and 7.94 for risdiplam post-matching and the baseline in ENDEAR, respectively). SDs were not available for the following variables in ENDEAR: age at first dose, age at symptom onset, duration of disease and age at diagnosis.

Treatment effects for ventilation-free survival and OS are presented as HRs. An HR is interpreted as an average treatment effect over the duration of follow-up (in this case, 1-year) but not necessarily as a measure of the time-specific treatment effect over the lifetime of patients. To do so would assume that there is no treatment-by-time interaction over the lifetime of patients. Such an assumption would need justification, else allowance for structural uncertainty as well as parameter uncertainty is required.

In their clarification response[17] (question A27), the company matched on additional variables, although the results were similar to the original adjusted results (see Table 18).

As the company acknowledges (CS,[1] Section B2.9.1), it is not clear whether other variables that were not available in the studies might also be relevant covariates.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence relating to risdiplam for treating SMA is based on two studies – the SUNFISH trial (Part 2),[22] a double-blind Phase II/III RCT, which examined the efficacy of risdiplam for treating Type 2/3 SMA, and the FIREFISH study (Part 2),[23] a Phase II/III open-label single-arm study, which examined the efficacy of risdiplam for the treatment of Type 1 SMA. The ERG is confident that no additional studies (published or unpublished) of risdiplam for treating SMA are likely to have been missed.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The ERG is confident that the relevant population, intervention and comparators have been included in the CS.[1] The primary outcome of the SUNFISH trial[22] was motor function, as assessed by change from baseline in MFM32 total score at Month 12, which is a valid and reliable measure of motor function in SMA, and has sufficient sensitivity to detect a treatment effect. There was a greater improvement in MFM32 total score at Month 12 in the risdiplam arm (1.36 [SE 0.38]) than in the placebo arm (least squares mean change -0.19 [SE 0.52]), which showed a slight decline in function. There were small, clinically meaningful (but not statistically significant) improvements in the risdiplam arm relative to the placebo arm in total HMFSE score from baseline to Month 12, and small, but clinically meaningful (and statistically significant), improvements in RULM total score, MFM32 D3 score and SMAIS total score, all of which indicate that risdiplam was effective in making small but clinically meaningful improvements in upper limb function and fine motor skills, which patients, carers and clinicians have indicated are important to patients with SMA. In addition, a small number of patients in the risdiplam arm reached standing and walking motor milestones, compared with no patients in the placebo arm. In terms of AEs, risdiplam appears to be generally well tolerated among patients with Type 2/3 SMA.

The primary outcome of the FIREFISH study[23] was the proportion of infants sitting without support for five seconds after 12 months of treatment, as assessed by Independent Central Readers using the BSID-III, which is a valid and reliable measure of motor function in SMA. Twelve (of 41) patients (29.3%; 90% CI: 17.8, 43.1%) were sitting without support for five seconds, as assessed by the BSID-III, at Month 12, which is a clinically meaningful effect, and statistically significantly greater than the performance criterion of 5% (p<0.0001). Nine patients (22.0%; 90% CI: 12.0, 35.2%) were able to support weight or stand with support, as assessed by the HINE-2, at Month 12, and one patient (2.4%; 90% CI: 0.1, 11.1%) was able to bounce, as assessed by the HINE-2, at Month 12, both of which are clinically meaningful effects. Bouncing was the highest milestone on the 'walking' subscale of the HINE-2 attained by any patient in FIREFISH at Month 12. Thirty-five patients (85.4%; 90% CI: 73.4,

92.2%) were alive without permanent or chronic non-invasive ventilation at Month 12, which is a clinically meaningful effect, and was statistically significantly greater than the performance criterion of 42% (p<0.0001). Correspondingly, 38 patients (92.7%%; 90% CI: 82.2, 97.1%) were alive at Month 12, which is a clinically meaningful effect, and was statistically significantly greater than the performance criterion of 60% (p=0.0005). In terms of AEs, risdiplam appears to be generally well tolerated among patients with Type 1 SMA.

Owing to the absence of head-to-head studies comparison risdiplam versus BSC, the company performed a MAIC using data from FIREFISH and ENDEAR. The MAIC suggests that risdiplam is more effective than placebo in terms of OS (HR [from company's updated analyses] = [redacted]; 95% CI [redacted]), ventilation-free survival (HR from updated analyses = [redacted]; 95% CI [redacted]) and motor milestone achievement (OR sitting with/ without support = [redacted], 95% CI [redacted]; OR standing with support/unaided = [redacted], 95% CI [redacted]). Given the unanchored nature of the MAIC, these estimates of relative treatment effects should be considered highly uncertain.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The first key uncertainty relates to the lack of evidence for the efficacy of risdiplam in a treatment-experienced population (particularly among patients treated with nusinersen), because patients in the SUNFISH and FIREFISH studies[22, 23] were treatment-naïve. This is inconsistent with the treatment pathway proposed by the company, which suggests that risdiplam could be offered to patients who have previously received nusinersen.

A second key uncertainty relates to the populations considered relative to the final NICE scope,[18] which defines the relevant population as *"people with spinal muscular atrophy"*. No clinical evidence has been presented for the use of risdiplam in people with pre-symptomatic, Type 0 or Type 4 (adult onset) SMA. It is anticipated that ongoing studies (RAINBOWFISH and JEWELFISH) will provide evidence for Type 1-3 (JEWELFISH) and pre-symptomatic (RAINBOWFISH) populations; however, both studies are ongoing and no clinical data are presented in the CS.[1] There are no ongoing studies examining the efficacy and safety of risdiplam in Type 0 or Type 4 SMA patients.

A third key uncertainty relates to the single-arm open-label design of FIREFISH,[23] which is the only study providing evidence for the efficacy of risdiplam in patients with Type 1 SMA. There is a possibility of potential biases such as attrition bias, natural recovery and regression to the mean; a double-blind RCT would have been a more rigorous study design. This would have allowed a direct comparison between risdiplam and BSC in patients with Type 1 SMA. Whilst the company's MAIC suggests that risdiplam is more effective than placebo (as a proxy for BSC) in terms of OS, EFS and motor milestone achievement, the results of these analyses should be considered uncertain owing to

limitations in the available clinical data and the strong assumptions upon which unanchored MAICs rely, in particular, that all treatment effect modifiers and prognostic variables are known and accounted for in the adjustment model.

Neither the SUNFISH nor FIREFISH studies[22, 23] included a study site in the UK. However, international standards of care for patients with SMA have been developed, and the majority of patients in both trials were recruited from countries with similar SMA care in clinical practice to the UK. The ERG's clinical advisor was satisfied that the patients enrolled in SUNFISH and FIREFISH are representative of patients with SMA in England.

The use of the SMAIS for assessing function-related independence in people with SMA provides a further source of uncertainty. The validity, reliability or ability to detect change of the SMAIS has not yet been established, and the scale only appears to have been used in one other study. Therefore, the results of the effects of risdiplam on total SMAIS scores (reported by carers and patients) should be interpreted with caution.

The duration of the SUNFISH and FIREFISH studies also introduces uncertainty. Although the treatment period for both studies is 24 months, results are only available from the 12-month follow-up, and the placebo-controlled part of the SUNFISH trial treatment period is only 12 months long. Therefore, there are no data on the longer-term efficacy of risdiplam in patients with Type 1 and Type 2/3 SMA, including data on whether patients maintain gains made, continue to improve, or worsen (including whether infants with Type 1 SMA will eventually progress to walking). This is particularly important given the long-term predictions of motor milestone gains and OS in the company's economic models (see Section 5.3.4).

In addition, in FIREFISH (Part 2), some patients received a lower dose than the recommended dose of 0.20mg/kg, which may have led to the efficacy of risdiplam being potentially underestimated in a small number of cases, although the overall impact is likely to be small.

5 COST EFFECTIVENESS

This chapter provides a summary and critique of the company's economic analyses of risdiplam for the treatment of SMA, together with additional exploratory analyses undertaken by the ERG. Section 5.1 summarises the company's SLR of existing economic analyses in SMA. Section 5.2 presents a detailed description of the methods and results of the company's economic models of risdiplam. Sections 5.3 presents the ERG's critical appraisal of the company's models. Section 5.4 presents the methods and results of additional exploratory analyses undertaken by the ERG. Section 5.5 presents a discussion of the available economic evidence for risdiplam for the treatment of SMA.

All results presented in the main ERG report include the PAS for risdiplam. Results of key analyses using the list price for risdiplam are presented in Appendix 2.

5.1 ERG's comment on company's review of cost-effectiveness evidence

5.1.1 *Summary and critique of the company's search strategy*

The company undertook an SLR to identify existing economic evaluations, health utility studies and cost and resource use studies in SMA. The searches used to identify evidence for these SLRs are reproduced in CS Appendices G, H and I, respectively.[27] Each search combined disease terms with an appropriate study type filter, for which the company subsequently provided citations (see clarification response,[17] question B3). Though these searches follow a similar structure and the ERG would anticipate a substantial overlap between their results, the company's clarification response (question B2) states that they were conducted as three separate reviews.

The searches were conducted on the Ovid platform on the 29th August 2019 and covered MEDLINE, Embase, EBM Reviews and EconLit. Care was taken to translate the search strategy to use appropriate subject headings for each database. Supplementary searches of conference proceedings and other grey literature sources were also conducted. For these searches, the condition of interest was defined more broadly to include "SMA-related health states" such as muscular dystrophy and amyotrophic lateral sclerosis (ALS) which were excluded from the clinical SLR. However, though ALS was included, the common synonym "motor neuron* disease" was omitted. The company stated this was because ALS was the term used in the previous NICE submission for nusinersen (TA588)[52] and they wanted to keep the searches *"focused"* (clarification response,[17] question B1).

Despite the minor issues identified above, the ERG is satisfied that the searches for all three reviews are unlikely to have failed to retrieve any relevant studies.

5.1.2 Summary of company's review findings

The company's review of existing economic evaluations included a total of nine separate publications which include economic analyses of treatments for SMA. Of these, three were HTA reports or company submissions,[52-54] two were full papers of economic analyses,[55, 56] and four were published conference abstracts.[57-60] The ERG notes that since the company's SLR was undertaken, the US analysis of nusinersen and AVXS-101 for SMA undertaken on behalf of the Institute for Clinical and Economic Review (ICER) has been published as a full paper (Thokala *et al.*[61]). All of the identified studies relate to the cost-effectiveness of nusinersen and/or AVXS-101 versus each other or against BSC; none of the included studies assess the cost-effectiveness of risdiplam. The included economic analyses are summarised briefly in Table 19. CS Appendix G[27] indicates that all of the included analyses except for Thokala *et al.* adopted a state transition approach, with variable time horizons dependent on the SMA type(s) under evaluation. CS Appendix G also highlights key issues identified across the available analyses, including: the lack of robust methods for measuring and valuing health in young patients; small sample sizes in clinical studies; the absence of long-term evidence of the clinical effectiveness of treatments for SMA, and cost-effectiveness estimates which exceed commonly cited thresholds. Table 47 of the CS[1] summarises the headline results from each model; however, none of these are directly relevant to the current appraisal, hence they are not reproduced here. Section B.3.2.2 of the CS also includes some justification of the approach taken within the risdiplam models and their accompanying assumptions through reference to the SMA models developed to inform NICE TA588;[52, 62] these assumptions are discussed in further detail in Section 5.3.4.

Table 19: Summary of existing economic analyses in SMA

Author (year)	Publication type	Intervention and comparator	Population(s)	Country	Model type
HTA reports / company's submissions					
CADTH (2018)[53]	HTA report	Nusinersen versus BSC	Separate models for SMA Types 1, 2 and 3	Canada	State transition model
ICER (2019)[54]	HTA report	Nusinersen versus BSC (all SMA population); AVXS-101 versus BSC (infantile onset only)	Separate models for infantile onset, later onset and pre-symptomatic SMA	US	State-based model
NICE TA588[52]	Company's submission	Nusinersen versus BSC	Separate models for early onset and later onset SMA	England	State transition model
Published papers / abstracts					
Malone *et al.* (2019)[57]	Abstract	Nusinersen versus AVXS-101	Type 1 SMA	US	State transition model
Malone *et al.* (2019)[55]	Full paper	Nusinersen versus AVXS-101	Type 1 SMA	US	State transition model
Thokala *et al.* (2019)[58]	Abstract	Nusinersen versus BSC (all SMA population); AVXS-101 versus BSC (infantile onset only)	Infantile onset SMA	US	State-based model
Zuluaga-Sanchez *et al.* (2019)[56]	Full paper	Nusinersen versus BSC	Separate models for infantile onset and later onset SMA	Sweden	State transition model
Zuluaga-Sanchez *et al.* (2019)[59]	Abstract	Nusinersen versus BSC	Infantile onset SMA	US	State transition model
Zuluaga-Sanchez *et al.* (2019)[60]	Abstract	Nusinersen versus BSC	Later onset SMA	US	State transition model

SMA - spinal muscular atrophy; AVXS-101 - onasemnogene abeparvovec; HTA - health technology assessment; ICER - Institute for Clinical and Economic Review; NICE - National Institute for Health and Care Excellence; BSC - best supportive care

5.2 Summary of the company's submitted economic evaluations

5.2.1 Scope of the company's economic analyses

As part of their submission to NICE,[1] the company submitted two model-based economic analyses of risdiplam. Both models were programmed in Microsoft Excel®.

- **Type 2/3 SMA model (later onset)**. This model compares risdiplam versus BSC for a combined population of both ambulant and non-ambulant patients with Type 2 and Type 3 SMA. The structure of this model is based on health states defined in terms of motor milestones as described by the MFM32 (for non-walking states) and the HFMSE (for the walking state) and survival status. The achievement of motor milestones within this model is informed by analyses of clinical data from the SUNFISH trial,[22] external data and assumptions.[1] This model is described in Section 5.2.2.
- **Type 1 SMA model (early onset)**. This model compares risdiplam versus BSC for patients with Type 1 SMA. The structure of this model is based on health states defined in terms of motor milestones as described by the HINE-2, the requirement for permanent ventilation (PV) and survival status. The achievement of motor milestones within this model is informed by arm-based unadjusted (naïve) indirect comparisons of data on motor function, ventilation-free survival (also referred to as EFS) and OS data from the single-arm FIREFISH study[23] (risdiplam) and the placebo arm of the ENDEAR RCT[25] (BSC), other external data and assumptions.[1] This model is described in Section 5.2.3.

The scope of the company's economic analyses is summarised in Table 20.

Table 20: Scope of the company's economic analyses

Population	**Type 1 SMA and Type 2/3 SMA models**
Time horizon	90 years
Intervention	Risdiplam
Comparator	BSC
Economic analysis approach	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS, including both patient and caregiver health gains
Discount rate	3.5% for health outcomes and costs
Price year	Variable – ranges from 2017 to current prices

SMA - spinal muscular atrophy; BSC - best supportive care; QALY - quality-adjusted life year; NHS - National Health Service

Both of the company's economic analyses assess the cost-effectiveness of risdiplam versus BSC in terms of the incremental cost per quality-adjusted life year (QALY) gained from the perspective of the NHS over a 90-year (lifetime) horizon. It is unclear whether Personal Social Services (PSS) costs are included. Both models include QALYs gained by SMA patients and their caregivers. For both analyses, costs are valued using 2017 to current prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

Populations

The company's economic analyses are intended to reflect two discrete populations: (i) patients with Type 2/3 SMA, based on the characteristics of non-Asian patients enrolled into Part 2 of the SUNFISH RCT,[22] and (ii) patients with Type 1 SMA, based on the characteristics of patients in the single-arm FIREFISH study (all Part 2 patients and those Part 1 patients who received the final dose of risdiplam).[23] In the Type 2/3 SMA model, patients are assumed to have a mean age of [redacted] years at model entry, [redacted] of patients are assumed to be female, and 71% of patients are assumed to have Type 2 SMA, with the remainder having Type 3 SMA. Separate analyses for Type 2 and Type 3 SMA patients were not undertaken. In the Type 1 SMA model, patients are assumed to have a mean age of 0.48 years (5.81 months) at model entry, 57% of patients are assumed to be female, and [redacted].

Intervention

The intervention evaluated within the company's economic analyses is risdiplam administered orally once daily. It is assumed that risdiplam is administered by the patient or by a caregiver in the home setting, with 90% of patients receiving the drug via homecare, the costs of which will be covered by the company, with the remaining 10% of patients receiving the drug via hospitals, thereby requiring pharmacy preparation (see CS,[1] page 143). In the Type 2/3 SMA model, a fixed dose of 5mg per day is assumed for all patients at all ages. In the Type 1 SMA model, risdiplam dosing is assumed to be determined according to the patient's age and weight:

- 2 months to < 2 years of age: daily dose = 0.20 mg/kg
- ≥2 years of age (<20 kg): daily dose = 0.25 mg/kg
- ≥2 years of age (≥20 kg): daily dose = 5 mg.

[redacted] the model does not include a formal stopping rule for risdiplam: patients are assumed to continue treatment indefinitely until death, irrespective of whether they have achieved, maintained or lost motor milestones or whether they require PV (note - this health state is applicable only to the Type 1 SMA model).

Comparators

In line with the final NICE scope,[18] both of the company's economic analyses include BSC as the sole comparator. The costs of BSC are assumed to include scheduled/unscheduled hospital visits, major clinical interventions, medical tests, and drugs.[62]

As detailed in Section 3.3, nusinersen is available through an MAA but is not funded through routine NHS commissioning;[13] hence, this treatment option was not included in the NICE scope.[18] The

company's models do not include nusinersen either as a comparator, or as a downstream treatment following risdiplam. In addition, AVXS-101 is not listed as a comparator in the final NICE scope and is not included in the company's analyses.

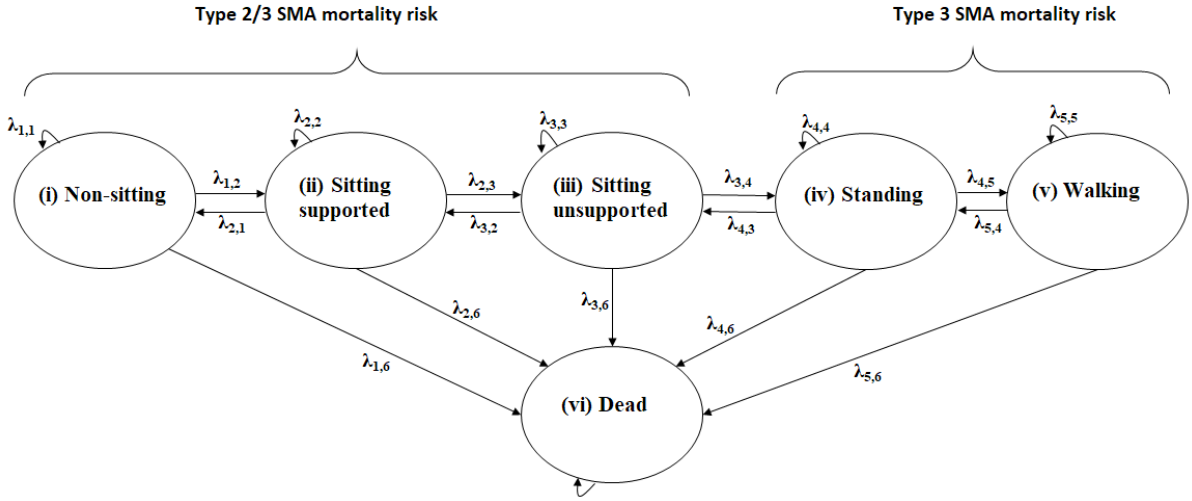
Whilst the comparator included in the company's models is consistent with the NICE scope, the ERG's clinical advisor commented that the majority of paediatric patients with Type 1 or 2 SMA who meet the entry criteria of the MAA are currently receiving nusinersen.

5.2.2 Type 2/3 SMA model: Risdiplam versus BSC

5.2.2.1 Model structure and logic – Type 2/3 SMA model

The general structure of the company's Type 2/3 (later onset) SMA model is presented in Figure 3. The model adopts a state transition approach, and is comprised of six health states: (i) non-sitting; (ii) sitting supported; (iii) sitting unsupported; (iv) standing; (v) walking; and (vi) dead.

Figure 3: Company's model structure, Type 2/3 SMA model (re-drawn by the ERG)



Where, transitions $\lambda_{1,6}$, $\lambda_{2,6}$ and $\lambda_{3,6}$ are governed by OS data pooled from six natural history studies (Type 2 OS) and general population mortality risks (Type 3 OS); whilst transitions $\lambda_{4,6}$ and $\lambda_{5,6}$ are governed by general population mortality risks (Type 3 OS). Transition probabilities between different alive health states are informed by SUNFISH and assumptions (see Section 5.2.2.3)

The model health states are defined according to the MFM32,[32] with the exception of the 'walking' state, which is based on criteria from the HFMSE.[63] The MFM32 and HFMSE state definitions used in the Type 2/3 SMA model are summarised in Table 21.

Table 21: Type 2/3 SMA model health state definitions based on milestones defined by MFM32 and HFMSE (adapted from CS, Figure 10 and Table 48)

Model health state	Instrument	Criteria for model health state
(i) Non-sitting	MFM32	Patients have a score of 0 in item 9 of the MFM32 (maintain seated position). Trunk support required, substantial support to be propped in a wheelchair.
(ii) Sitting supported	MFM32	Patients have a score of 1 in item 9 of the MFM32 (maintain seated position). Upper limb support required.
(iii) Sitting unsupported	MFM32	Patients have a score of 2 or 3 in item 9 of the MFM32 (maintain seated position). No upper limb support required.
(iv) Standing	MFM32	Patients have a score of 1, 2 or 3 in item 25 of the MFM32 (maintain standing position).
(v) Walking	HFMSE	HFSME form, highest level of independent mobility. Supported = 'walks with crutches/frame/rollator/KAFOs/AFOs' or unsupported = 'independent walking'.

AFO - ankle-foot orthosis; HFMSE - Hammersmith Functional Motor Scale Expanded; KAFOS - knee-ankle-foot-orthosis; MFM32 - Motor Function Measure - 32 Items

The logic of the company's Type 2/3 SMA model operates as follows. Patients enter the model in one of the five motor milestone health states according to the observed baseline distribution for non-Asian patients in SUNFISH,[22] and receive treatment with risdiplam or BSC. During each cycle in the "initial period" (up to 2 years), transitions between the motor milestone health states are governed by probabilities derived from a time-homogeneous multistate model fitted to data for non-Asian patients in Part 2 of SUNFISH (n=149), including a single covariate for treatment group. The estimated transition probabilities from the multistate model were subsequently adjusted to only allow patients to remain in their current state or to transition to an adjacent health state (the next best or next worst state). Patients receiving BSC who have reached the milestones of sitting unsupported (state [iii]) and standing (state [iv]) are assumed to only remain stable or worsen. During each cycle in the "subsequent period" (after 2 years), the probabilities that risdiplam-treated patients transition to worse health states are assumed to be reduced by [redacted] (compared with the initial period), whilst all BSC-treated patients are assumed to remain stable or worsen (no patients improve).

Mortality risk is assumed to be dependent on the patient's current motor milestone health state. For BSC-treated patients who are unable to stand or walk (states [i] to [iii]), mortality risk is based on a weighted survival model. Within this weighted survival model, patients with Type 3 SMA are assumed to have the same mortality risk as the general population,[64] whilst Type 2 SMA patients are assumed to have a comparatively worse survival prognosis, based on a Gompertz survival model fitted to replicated IPD for Type 2 SMA patients from six natural history studies.[9, 10, 48, 65-67] The mortality risk for risdiplam-treated patients who are unable to stand (states [i] to [iii]) is assumed to be the same as that for BSC, except that the risk for the Type 2 component of the weighted survival model is multiplied by a factor of 0.75, based on the final iteration of the later onset model used to inform TA588 (implicitly assuming

that risdiplam has the same effect as nusinersen).[62] Within the standing and walking health states (states [iv] and [v]), the model assumes general population mortality risk in both treatment groups.

The model assumes that treatment with risdiplam is continued indefinitely and that treatment effects on motor milestones and mortality reductions persist over the remaining lifetime of the Type 2/3 SMA population.

The model includes health outcomes for SMA patients and their caregivers, assuming that each SMA patient has an average of 2.2 caregivers. HRQoL for patients and caregivers is assumed to be dependent on the patient's motor milestone health state, with higher utilities applied to better motor milestones. Patient utilities are based on estimates reported by Lloyd *et al.*,[68] whilst caregiver utilities are based on estimates reported by Lopez-Bastida *et al.*,[69] Ara and Brazier[70] (general population utility) and assumptions. Utilities are not age-adjusted and the model does not include QALY losses associated with AEs or caregiver impacts associated with bereavement.

The Type 2/3 SMA model includes costs associated with drug acquisition and administration for risdiplam based on a fixed dosing regimen, and health state costs for both treatment groups based on estimates used in the final iteration of the later onset model in TA588.[62]

The incremental health gains, costs and cost-effectiveness of risdiplam versus BSC are modelled over a time horizon of 90 years using monthly cycles. Half-cycle correction is applied to account for the timing of events. Incremental cost-effectiveness is calculated based on the difference in costs divided by the difference in patient plus caregiver QALYs for risdiplam and BSC.

5.2.2.2 Key assumptions employed in the company's Type 2/3 SMA model

The company's Type 2/3 SMA model employs the following key assumptions:

- Patients enter the model according to the baseline distribution in SUNFISH (non-Asian subgroup).[22] [redacted].
- During the initial 2-year period, risdiplam-treated patients can remain in their current state, improve by one milestone or worsen by one milestone. BSC-treated patients can also remain in their current state, improve by one milestone or worsen by one milestone; however, transitions to standing and walking (states [iv] and [v]) are not permitted.
- During the subsequent period (after 2 years), backward transition probabilities, which reflect transitions to worse health states, for risdiplam-treated patients are reduced by [redacted]. During this period, BSC-treated patients can only remain in their current state or transition to the next worst state during each cycle; improvements are not permitted.

- Mortality risk is dependent on the patient's current motor milestone health state, based on a weighted survival model for patients who are unable to stand (states [i] to [iii]) and general population mortality rates for patients who are able to stand or walk (states [iv] and [v]). A survival advantage is also assumed for risdiplam-treated patients who cannot stand (states [i] to [iii]).
- HRQoL is dependent on the patient's motor milestone health state. Utilities are included both for patients and caregivers (n=2.2) and are the same for both treatment groups. Utilities are not age-adjusted.
- All patients are eligible for treatment with risdiplam, irrespective of their initial motor milestone. Risdiplam is given indefinitely over the patient's remaining lifetime.
- Transition probabilities applied in the subsequent period and the additional survival advantage applied to risdiplam-treated patients in the non-standing states persist indefinitely, thereby assuming lifetime treatment effects.
- Risdiplam is assumed to be administered orally at home; a small pharmacy cost is included for patients who do not receive the drug via homecare.
- BSC costs are dependent on the patient's motor milestone health state. The same costs are applied to the health states in both the risdiplam and BSC groups.
- The model does not include HRQoL or cost impacts resulting from AEs.
- Costs associated with wastage are not included for risdiplam.
- Relative dose intensity (RDI) is based on the median dose intensity in SUNFISH.[22]

5.2.2.3 Evidence used to inform the company's Type 2/3 SMA model parameters

Table 22 summarises the evidence sources used to inform the parameters in the company's base case model for the Type 2/3 SMA population. These are discussed in detail in the subsequent sections.

Table 22: Evidence used to inform the company's Type 2/3 SMA model parameters

Parameter group	Evidence source
Patient characteristics	Age, sex, baseline health state distribution, and proportion of patients with Type 2 SMA taken from SUNFISH[22]
Transition probabilities – initial period (up to 2 years), risdiplam group	Multistate model fitted to 52-week data on MFM32 and HFMSE for non-Asian patients in risdiplam arm of SUNFISH,[22] adjusted to allow only transitions to adjacent motor milestone health states.
Transition probabilities – subsequent period (after 2 years), risdiplam group	Same as risdiplam matrix for initial period, but including assumption that backward transitions to worse health states are reduced by [redacted], based on expert opinion.[1]
Transition probabilities – initial period (up to 2 years), BSC group	Multistate model fitted to 52-week data on MFM32 and HFMSE for non-Asian patients in placebo arm of SUNFISH,[22] adjusted to allow only transitions to adjacent motor milestone health states.
Transition probabilities – subsequent period (after 2 years), BSC group	Same as BSC matrix for initial period, but including an assumption that forward transitions to improved health states are no longer possible, based on expert opinion.[1]
Overall survival – standing/walking (states [iv] and [v]), both treatment groups	Age- and sex-matched general population mortality risk[64]
Overall survival – not sitting/sitting (states [i] to [iii]), BSC group	Based on weighted survival model including pooled dataset from six natural history studies in SMA[9, 10, 48, 65-67] and general population mortality risk[64]
Overall survival – not sitting/sitting (states [i] to [iii]), risdiplam group	Same as OS for non-standing states in BSC group, except that Type 2 SMA mortality risk is multiplied by a factor of 0.75, based on TA588.[62]
Patient HRQoL	EQ-5D vignette study reported by Lloyd *et al.*[68]
Caregiver HRQoL	Lopez-Bastida *et al.*,[69] Ara and Brazier[70] and assumptions[1]
Number of caregivers	Roche burden of illness study[1]
Risdiplam acquisition costs	CS[1]
Pharmacy costs	Curtis and Burns (PSSRU)[71]
Relative dose intensity	SUNFISH[22]
Health state costs	Biogen RWE resource use study presented in TA588 (GOSH and Newcastle only)[62]

SMA - spinal muscular atrophy; BSC - best supportive care; MFM32 - Motor Function Measure - 32 items; HFMSE - Hammersmith Functional Motor Scale Expanded; OS - overall survival; EQ-5D - Euroqol 5-Dimensions; HRQoL - health-related quality of life; CS - company's submission; TA - technology appraisal; GOSH - Great Ormond Street Hospital; RWE - real world evidence

Patient characteristics

Patient characteristics were based on those of the non-Asian subgroup in Part 2 of SUNFISH.[22] The model assumes that Type 2/3 SMA patients eligible for treatment with risdiplam have a mean age of [redacted] years at model entry, [redacted] of patients are female, and 71.1% of patients have Type 2 SMA, whilst the remainder have Type 3 SMA. The initial distribution of patients across the model health states is shown in Table 23.

Table 23: Initial distribution used in Type SMA 2/3 model (SUNFISH non-Asian subgroup)

Health state	Proportion of patients (both treatment groups)
(i) Not sitting	[redacted]
(ii) Sitting (supported)	
(iii) Sitting (unsupported)	
(iv) Standing	
(v) Walking	

Note - further details regarding how this distribution was estimated are provided in the CS[1] (page 114) and the company's clarification response[17] (question B5)

Motor milestone transition probabilities

Transition probabilities between the motor milestone health states for the risdiplam and BSC groups of the company's Type 2/3 SMA model are summarised in Table 24 and Table 25, respectively. Separate transition matrices are applied in each cycle during the first 2 years (the "initial period") and in all subsequent cycles (the "subsequent period").

Transition probabilities – initial period (first 2 years)

The company fitted a time-homogeneous multistate model including a single treatment-indicating covariate to clinical data from the SUNFISH trial.[22] The dataset was restricted to the subgroup of non-Asian patients enrolled in Part 2 of the trial (149 patients, 591 observations, 4-monthly visits[17]). According the CS[1] (page 114), Asian patients were excluded from the analysis due to concerns raised by the company's clinical advisors that BSC may have been different compared with that received by non-Asian patients. The company's base case analysis includes some imputation of missing data, although this affects only three events and is not discussed further here (see clarification response,[17] question B8). The multistate model was fitted using the *msm* package in R. Goodness-of-fit was assessed using likelihood ratio tests and the *prevalence* function; further details are provided in the company's clarification response[17] (question B7). The derived transition matrices were then adjusted to allow only for transitions to adjacent health states, reflecting the assumption that patients cannot gain or lose more than one milestone during each monthly cycle. The CS[1] states that this adjustment was informed by clinical opinion. The resulting monthly transition matrices for the initial period, excluding adjustments to account for the risk of death, are shown in the upper half of Table 24 and Table 25 for the risdiplam and BSC groups, respectively.

Transition probabilities – subsequent period (after 2 years)

The long-term transition probabilities in each group are based on the matrices for the initial period together with the following additional modifications: (a) in the risdiplam group, backward transitions (reflecting worsening) are assumed to be reduced by [redacted], and (b) in the BSC group, forward transitions (reflecting improvements) are not permitted. According to the CS,[1] these assumptions were informed

by clinical opinion. The resulting monthly transition matrices for the subsequent period, excluding adjustments to account for the risk of death, are shown in the lower half of Table 24 and Table 25 for risdiplam and BSC, respectively.

Table 24: Monthly transition probabilities (excluding mortality adjustments), Type 2/3 SMA model, risdiplam group

Transition probabilities applied during cycles in initial period (first 2 years)					
From\To state	(i) Not sitting	(ii) Sitting (supported)	(iii) Sitting (unsupported)	(iv) Standing	(v) Walking
(i) Not sitting	[redacted]	[redacted]	0	0	0
(ii) Sitting (supported)	[redacted]	[redacted]	[redacted]	0	0
(iii) Sitting (unsupported)	0	[redacted]	[redacted]	[redacted]	0
(iv) Standing	0	0	[redacted]	[redacted]	[redacted]
(v) Walking	0	0	0	[redacted]	[redacted]
Transition probabilities applied during cycles in subsequent period (after 2 years)					
From\To state	(i) Not sitting	(ii) Sitting (supported)	(iii) Sitting (unsupported)	(iv) Standing	(v) Walking
(i) Not sitting	[redacted]	[redacted]	0	0	0
(ii) Sitting (supported)	[redacted]	[redacted]	[redacted]	0	0
(iii) Sitting (unsupported)	0	[redacted]	[redacted]	[redacted]	0
(iv) Standing	0	0	[redacted]	[redacted]	[redacted]
(v) Walking	0	0	0	[redacted]	[redacted]

The company's model assumes that patients who improve/worsen can only transition to an adjacent health state. Cells with grey shading represent non-permitted transitions

** Backward transitions (worsening) assumed to be reduced by [redacted] relative to the first 2 years, leading to an increased probability of remaining in the current health state*

Table 25: Monthly transition probabilities (excluding mortality adjustments), Type 2/3 SMA model, BSC group

Transition probabilities applied during cycles in initial period (first 2 years)					
From\To state	(i) Not sitting	(ii) Sitting (supported)	(iii) Sitting (unsupported)	(iv) Standing	(v) Walking
(i) Not sitting	[redacted]	[redacted]	0	0	0
(ii) Sitting (supported)	[redacted]	[redacted]	[redacted]	0	0
(iii) Sitting (unsupported)	0	[redacted]	[redacted]	0	0
(iv) Standing	0	0	[redacted]	[redacted]	0
(v) Walking	0	0	0	[redacted]	[redacted]
Transition probabilities applied during cycles in subsequent period (after 2 years)					
From\To state	(i) Not sitting	(ii) Sitting (supported)	(iii) Sitting (unsupported)	(iv) Standing	(v) Walking
(i) Not sitting	[redacted]	0*	0	0	0
(ii) Sitting (supported)	[redacted]	[redacted]	0*	0	0
(iii) Sitting (unsupported)	0	[redacted]	[redacted]	0*	0
(iv) Standing	0	0	[redacted]	[redacted]	0*
(v) Walking	0	0	0	[redacted]	[redacted]

The company's model assumes that patients who improve/worsen can only transition to an adjacent health state. Cells with grey shading represent non-permitted transitions

** Forward transitions (improving) assumed to be equal to 0% after the first 2 years, leading to an increased probability of remaining in the current health state*

Survival

Mortality risk is assumed to be dependent on the patient's current motor milestone health state. Survival is assumed to be improved for Type 2 patients who are able to stand or walk (states [iv] and [v]) compared with those who cannot (states [i] to [iii]). In addition, the model assumes that risdiplam is associated with a relative survival advantage over BSC in patients who are unable to stand (states [i] to [iii]). The company's survival assumptions are summarised in Table 26; these are described in further detail in the subsequent text.

Table 26: Summary of per cycle mortality risks applied in Type 2/3 SMA model health states

Health state	Per cycle mortality risk applied whilst in health state	
	BSC group	**Risdiplam group**
(i) Not sitting	Estimated using a weighted survival model, whereby 28.9% of patients have general population mortality risk,[64] whilst 71.1% of patients have Type 2 SMA mortality risk, based on a Gompertz model fitted to replicated IPD from 6 natural history studies.[9, 10, 48, 65-67]	Same as BSC group, except that Type 2 SMA mortality risk is multiplied by a factor of 0.75.[62]
(ii) Sitting (support)		
(iii) Sitting (unsupported)		
(iv) Standing	Age-specific general population mortality risk[64]	Age-specific general population mortality risk[64]
(v) Walking		

Within both treatment groups, mortality risk for patients who are able to stand or walk (states [iv] and [v]) is assumed to reflect age- and sex-matched general population mortality, based on life tables for England from the Office for National Statistics (ONS).[64]

Mortality risk for BSC-treated patients who are unable to stand or walk (states [i] to [iii]) is based on a weighted survival model whereby 28.9% of the population are assumed to have Type 3 SMA whilst the remaining 71.1% of patients have Type 2 SMA. Type 3 SMA patients are assumed to have general population mortality risk.[64] Mortality risk for Type 2 SMA patients is modelled using a parametric survival function fitted to pooled OS data for patients with Type 2 SMA reported within six natural history studies which were identified as part of the company's SLR.[9, 10, 48, 65-67] A seventh study by Belter *et al.*,[72] which reports on outcomes for patients included in the Cure SMA database, was excluded from the analysis due to concerns regarding generalisability (see clarification response,[17] question B13). The company replicated the underlying IPD from each study using the algorithm reported by Guyot *et al.*[73] and pooled the data into a combined dataset (see Figure 4). The company then fitted six standard parametric survival models to the pooled IPD; these included the exponential, Weibull, log-normal, log-logistic, generalised gamma and Gompertz distributions. The 2-parameter gamma distribution was not fitted to the dataset. According to the CS,[1] model selection based on the approach described in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14,[74] including consideration of relative goodness-of-fit statistics (the Akaike Information Criterion [AIC] and the Bayesian Information

Criterion [BIC]), visual fit and clinical plausibility of the long-term extrapolation. The company selected the Gompertz model for inclusion in the base case model based on clinical advice.[1] The CS does not present plots of the empirical hazard for the combined dataset. A comparison of modelled OS and the Kaplan-Meier survival function from the pooled OS dataset is presented in Figure 5. AIC and BIC statistics for the fitted OS models are presented in Table 27.

Figure 4: Kaplan-Meier survival functions for Type 2 SMA from natural history studies, including Belter *et al.* (reproduced from clarification response, question B13)

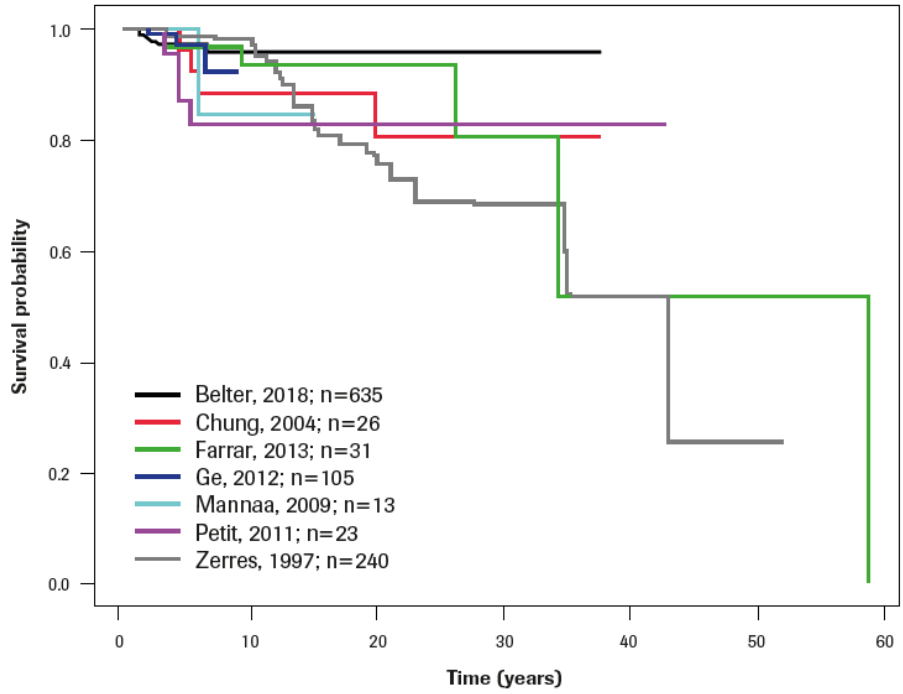


Figure 5: Modelled OS for Type 2 SMA based on pooled IPD from natural history studies (reproduced from CS Figure 13)

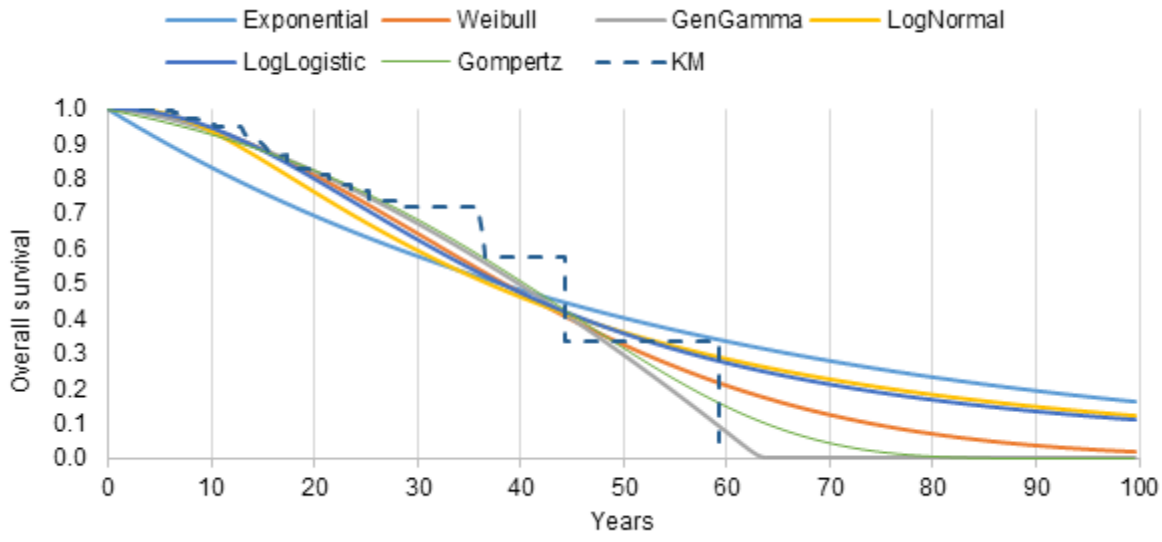


Table 27: AIC and BIC statistics, pooled OS for Type 2 SMA based on pooled IPD from natural history studies

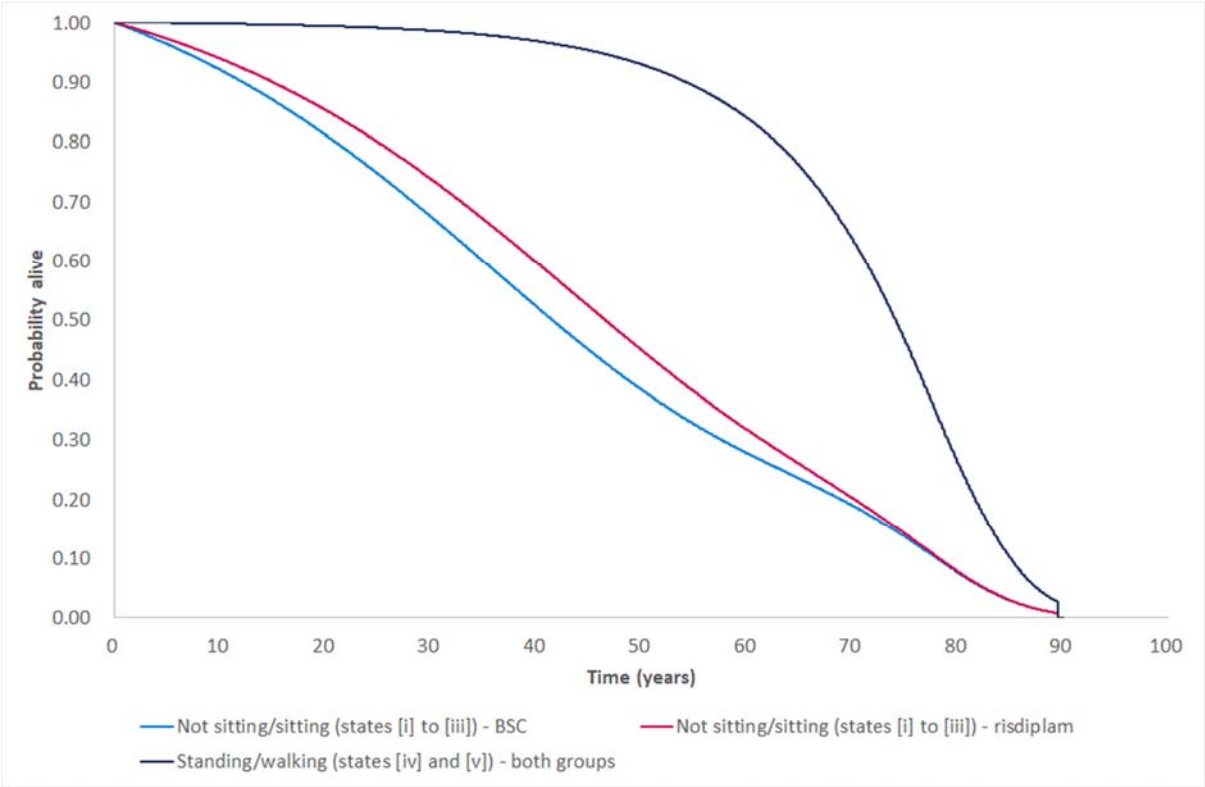
Model	AIC	BIC
Exponential	3434.1	3438.2
Weibull	3338.0	3346.1
Gompertz	3328.0	3336.1
Log-normal	3376.9	3385.1
Log-logistic	3363.9	3372.1
Generalised gamma	**3314.2**	**3326.5**

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best fitting model indicated in bold

Within the risdiplam group, the monthly mortality risk derived from the Gompertz model for Type 2 SMA is multiplied by a factor of 0.75 to reflect the anticipated reduced likelihood of mortality associated with treatment with risdiplam compared to BSC. This multiplication factor was based on an assumption applied in the final iteration of the later onset model in NICE TA588.[62]

The OS functions applied in the company's model, excluding the impact of health state switching over time, are summarised in Figure 6.

Figure 6: Survival functions applied in Type 2/3 SMA model health states, figure excludes impact of switching of health states over time



Patient and caregiver utilities

The SUNFISH trial[22] included the measurement of patient HRQoL using the EQ-5D-5L (mapped to the 3L tariff). However, the company's clinical advisors did not consider the utility estimates derived from SUNFISH to be clinical plausible; hence, these were not included in the company's base case model. Instead, the Type 2/3 SMA model uses patient utility values reported by Lloyd *et al*.[68] This is a vignette study in which clinical experts (n=5) rated SMA health states using the child-friendly EQ-5D-Y (scored using the EQ-5D-3L tariff) and the Paediatric Quality of Life Inventory Neuromuscular Module (PedsQL-NMM). Separate utility estimates were elicited for vignettes describing health states associated Type 1 and Type 2 SMA. The company qualitatively mapped the EQ-5D-3L estimates from Lloyd *et al.* to the health states used in the Type 2/3 SMA model. According to the CS[1] (page 133), the Lloyd et al. study was chosen for inclusion in the company's model *"to align with what was considered for final decision-making in the TA588 submission"*;[62] however, the ERG notes that this is not accurate and a different source was used in the final iterations of the models used to inform TA588[13] (further discussion of these issues is provided in Section 5.3.4).

The company conducted a burden of illness study among caregivers of patients with Type 1, 2 and 3 SMA using the EQ-5D-5L (mapped to the 3L tariff).[27] However, the company's clinical advisors deemed the resulting utility values to be inappropriate; hence, these data were not used in the base case model. Instead, the company applied similar assumptions to those used in the final iteration of the later onset SMA model in TA588.[62] The model assumes that the worst health state (not sitting) is associated with a caregiver utility value of 0.484 based on a time-trade-off (TTO) study conducted amongst SMA caregivers by Lopez-Bastida *et al.*,[69] the best health states (standing and walking) are associated with general population utility based on Ara and Brazier,[70] and that caregiver utility increases linearly with each successive milestone achieved, up to the milestone of standing (state [iv]). The number of caregivers for each SMA patient (n=2.2) was based on the company's burden of illness study.[27]

The patient and caregiver utility values applied in the company's Type 2/3 SMA model are summarised in Table 28.

Table 28: Type 2/3 SMA model – patient and caregiver utility values

Model health state	Mean utility	Source and derivation
Patient utility		
(i) Not sitting	-0.17	Lloyd *et al.*[68] - Type 1 SMA state "Improvement" state
(ii) Sitting (supported)	0.04	Lloyd *et al.*[68] - Type 2 SMA state "Mild improvement" state
(iii) Sitting (unsupported)	0.04	Lloyd *et al.*[68] - Type 2 SMA state "Mild improvement" state
(iv) Standing	0.56	Lloyd *et al.*[68] - mid-point between Type 2 SMA states "Stands/walks with assistance" and "Stands/walks unaided"
(v) Walking	0.56	
Caregiver utility		
(i) Not sitting	0.48	Lopez-Bastida *et al.*[69] - Spanish caregivers mean TTO score (all SMA types)
(ii) Sitting (supported)	0.61	Utility assumed to increase linearly between not sitting and standing/walking
(iii) Sitting (unsupported)	0.74	
(iv) Standing	0.86	Ara and Brazier[70] - general population utility
(v) Walking	0.86	
Number of caregivers =2.2 per SMA patient		

SMA - spinal muscular atrophy; TTO - time-trade-off
Further justification of the assumptions made in mapping the utility values reported in Lloyd et al.[68] to the health states used in the Type 2/3 SMA model are provided in the company's clarification response[17] (question B19, Table 17)

Resource costs

Drug acquisition and administration costs

The list price for risdiplam is [redacted] per bottle. The company has proposed a PAS which takes the form of a simple price discount of [redacted]; including this discount results in a cost per bottle of [redacted] risdiplam is assumed to be given at a fixed dose of 5mg per day within the Type 2/3 SMA population.

The CS[1] assumes that 90% of patients will receive risdiplam via homecare for administration in the home setting by the SMA patient or their caregiver. The remaining 10% of patients are assumed to have risdiplam administered through the hospital. The model includes costs relating to pharmacists' time, based on a cost of £44 per hour and a requirement of 5 minutes of pharmacy time to reconstitute one bottle of risdiplam.[71] The resulting preparation cost per bottle is estimated to be £3.67.

Health state costs

Health state costs are based on estimates used in the final iteration of the TA588 models, derived from a real world evidence (RWE) study conducted by Biogen in 2017.[62] This study included leading neurological consultants at nine centres in the UK, with costs estimated according to SMA type (1, 2 or 3). In line with the final iterations of the models used in TA588,[13] the company used the subset of resource use estimates from the Great Ormond Street Hospital (GOSH) and Newcastle only. As with TA588, the estimated cost for Type 1 SMA was assumed to be twice as high as the estimated value. The monthly costs for each health state are summarised in Table 29.

Table 29: Type 2/3 SMA model – health state costs

Model health state	Mean cost per month	Source
(i) Not sitting	£12,351.17	Biogen RWE resource use study in TA588 (GOSH and Newcastle only)[62] – Type 1 SMA costs
(ii) Sitting (supported)		
(iii) Sitting (unsupported)	£5,693.50	Biogen RWE resource use study in TA588 (GOSH and Newcastle only)[62] – Type 2 SMA costs
(iv) Standing	£1,813.75	Biogen RWE resource use study in TA588 (GOSH and Newcastle only)[62] – Type 3 SMA costs
(v) Walking		

SMA - spinal muscular atrophy; RWE - real world evidence; TA - technology appraisal; GOSH - Great Ormond Street Hospital

5.2.2.4 Model evaluation methods, Type 2/3 SMA model

The CS[1] presents base case incremental cost-effectiveness ratios (ICERs) for risdiplam versus BSC in the Type 2/3 SMA population based on total QALYs gained by SMA patients and their caregivers and costs borne by the NHS (and possibly PSS). Results are presented using both the deterministic and probabilistic versions of the model; the probabilistic ICERs are based on 2,000 Monte Carlo simulations. The results of the probabilistic sensitivity analysis (PSA) are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). The results of the deterministic sensitivity analyses (DSAs) are presented in the form of tornado plots. The CS also reports on a number of scenario analyses which explore the impact of alternative assumptions regarding: transition probabilities in the initial and subsequent periods; mortality risk for Type 2 SMA; patient and caregiver utilities; the number of caregivers; resource use and discount rates.

5.2.2.5 Company's model results, Type 2/3 SMA

This section presents the results of the company's Type 2/3 SMA model. Whilst double-programming the company's model, the ERG identified an important error relating to the estimation of caregiver health gains (see Section 5.3.4). As such, the ERG believes that the company's ICERs which include caregiver QALY gains are misleading and should be disregarded.

Central estimates of cost-effectiveness – Type 2/3 SMA population

Table 30 presents the central estimates of cost-effectiveness generated using the company's Type 2/3 SMA model. When only patient health gains are included, the probabilistic version of the company's model suggests that risdiplam is expected to generate an additional 9.52 QALYs at an additional cost of [redacted]; the corresponding ICER is expected to be [redacted] per QALY gained. The model also predicts that risdiplam will lead to an increase of 12.88 QALYs for caregivers of each SMA patient treated; when both patient and caregiver health gains are included in the analysis, the ICER for risdiplam versus BSC is expected to be [redacted] per QALY gained. The deterministic version of the model leads to noticeably higher ICERs compared with its probabilistic counterpart, particularly when only patient

QALYs are included in the analysis. These differences are a consequence of problems in the characterisation of uncertainty within the company's PSA; this issue is discussed in Section 5.3.4.

Table 30: Central estimates of cost-effectiveness, Type 2/3 SMA, risdiplam versus BSC

Option	LYGs*	QALYs (patients)	QALYs (carers)	QALYs (patients + carers)	Costs	ICER (patient QALYs)	ICER (patient + carers QALYs)
Probabilistic model							
Risdiplam	59.87	7.49	32.12	39.60	[redacted]	-	-
BSC	44.03	-2.03†	19.23	17.20	[redacted]	-	-
Incremental	15.84	9.52	12.88	22.40	[redacted]	[redacted]	[redacted]
Deterministic model							
Risdiplam	56.33	5.58	39.61	45.19	[redacted]	-	-
BSC	43.57	-1.98†	25.02	23.04	[redacted]	-	-
Incremental	12.76	7.56	14.59	22.15	[redacted]	[redacted]	[redacted]

* *Undiscounted; † negative QALYs predicted as patients tend toward the non-sitting state which is assumed to be associated with a utility value which is worse than dead (see Table 28)*
LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care

Company's PSA results – Type 2/3 SMA population

Figure 7 presents CEACs for risdiplam versus BSC within the Type 2/3 SMA population, including both patient and caregiver QALYs. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the company's model estimates that the probability that risdiplam generates more net benefit than BSC is [redacted] and [redacted], respectively.

Figure 7: Cost-effectiveness acceptability curves, Type 2/3 SMA, risdiplam versus BSC (patient and caregiver QALYs, generated by the ERG using the company's model)

[redacted]

Company's DSA results

Figure 8 presents the results of the company's DSAs for the Type 2/3 SMA population in the form of a tornado plot. As shown in the figure, the ICER for risdiplam is particularly sensitive to the acquisition cost of risdiplam, the costs associated with the not-sitting state, assumptions regarding the number of caregivers per SMA patient, caregiver utility values and discount rates for health outcomes and costs. The ERG notes that the cost per bottle of risdiplam and discount rates are not uncertain parameters and should not typically be included in DSAs.

Figure 8: Tornado plot, risdiplam versus BSC (patient and caregiver QALYs), Type 2/3 SMA (generated by the ERG using the company's model)

Company's scenario analysis results – Type 2/3 SMA population

Table 31 presents the results of the company's scenario analyses for the Type 2/3 SMA population. As shown in the table, when only patient health gains are included in the model, the ICER is estimated to range from [redacted] per QALY gained (QALYs discounted at 1.5%) to [redacted] per QALY gained (SUNFISH utilities, including disutilities for respiratory support and scoliosis). When caregiver health gains are included in the analysis (without correction of the calculation error identified by the ERG), the ICER is estimated to range from [redacted] per QALY gained (QALYs discounted at 1.5%) to [redacted] per QALY gained (BSC transition probabilities from the multistate model extrapolated indefinitely).

Table 31: Scenario analysis results, risdiplam versus BSC, Type 2/3 SMA (generated by the ERG using the company's model)

Scenario description	Inc. QALYs (patients)	Inc. QALYs (patients + carers)	Inc. costs	ICER (patient QALYs)	ICER (patient+carer QALYs)
Base case - deterministic	7.56	22.15	[redacted]	[redacted]	[redacted]
Scenario 1 – TPs estimated without imputation (non-Asian)	7.61	22.25			
Scenario 2 – TPs estimated with imputation (ITT)	6.30	18.90			
Scenario 3 – Risdiplam worsening reduction = [redacted]	5.53	17.42			
Scenario 4 – Risdiplam worsening reduction = [redacted]	9.62	26.84			
Scenario 5 – BSC TPs extrapolated indefinitely from MSM	5.33	14.87			
Scenario 6 – Type 2 SMA survival = Weibull	7.50	22.18			
Scenario 7 – Resource use = Roche burden of illness study	7.56	22.15			
Scenario 8 – Patient and carer utilities = TA588 ERG advisors' values	6.89	21.48			
Scenario 9 – SUNFISH utilities (including disutilities for respiratory support and scoliosis)	1.30	15.89			
Scenario 10 – Carer utilities = Roche burden of illness study	7.56	11.76			
Scenario 11 – No. carers = 2	7.56	20.83			
Scenario 12 – No. carers = 3	7.56	27.46			
Scenario 13 – No. patients requiring respiratory support based on UK clinical opinion*	8.06	22.65			
Scenario 14 – Apply long-term subsequent period assumptions from 1 year	7.82	22.79			
Scenario 15 – Discount rates for costs and QALYs = 1.5%	13.04	40.02			
Scenario 16 – Discount rates for QALYs = 1.5%, costs = 3.5%	13.04	40.02			

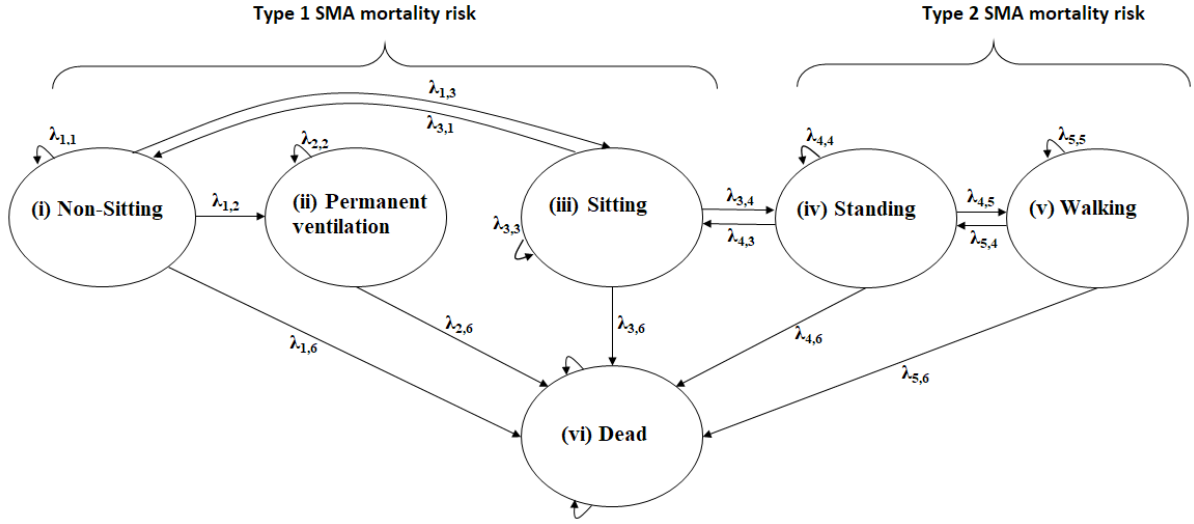
QALY - quality-adjusted life year; ITT - intention-to-treat; SMA - spinal muscular atrophy; MSM - multistate model; ICER - incremental cost-effectiveness ratio; Inc. - incremental
** Based on estimates provided by experts during company's advisory board meeting*

5.2.3 Type 1 SMA model: Risdiplam versus BSC

5.2.3.1 Model structure and logic – Type 1 SMA model

The general structure of the company's Type 1 SMA (early onset) model is presented in Figure 9. The company's model adopts a state transition approach, and is comprised of six health states: (i) non-sitting; (ii) permanent ventilation (PV); (iii) sitting; (iv) standing; (v) walking, and (vi) dead.

Figure 9: Company's model structure, Type 1 SMA model (re-drawn by the ERG)



Where transitions $\lambda_{1,6}$, $\lambda_{2,6}$ and $\lambda_{3,6}$ are governed by Type 1 OS risks and $\lambda_{4,6}$ and $\lambda_{5,6}$ are governed by Type 2 OS risks
Transition probabilities between different alive health states are informed by FIREFISH, ENDEAR and assumptions (see Section 5.2.3.3)

The motor function health states included in the model are defined according to HINE-2.[47] The HINE-2 and PV state definitions used in the Type 1 SMA model are summarised in Table 32.

Table 32: Type 1 SMA model health state definitions based on milestones defined according to HINE-2 scoring and permanent ventilation (adapted from CS, Figure 11 and Table 50)

Model health state	Criteria for model health state
(i) Non-sitting	Patients cannot sit, stand or walk.
(ii) Permanent ventilation	More than 16 hours of non-invasive ventilation such as BiPAP per day or intubation for more than 21 consecutive days in the absence of, or following the resolution of, an acute reversible event of tracheostomy.
(iii) Sitting	Patients have a score of 1, 2, 3 or 4 in sitting ability in HINE-2 motor function group. Supported corresponds to scores 1 (sits with support at hips) or 2 (props self up), whilst unsupported corresponds to scores 3 (stable sitting) or 4 (pivots and rotates).
(iv) Standing	Patients have a score of 2 or 3 in standing ability in HINE-2 motor function group. Supported corresponds to score 2 (stands with support), whilst unsupported corresponds to score 3 (stands unaided).
(v) Walking	Patients have a score of 2 or 3 in walking ability in HINE-2 motor function group. Supported corresponds to score 2 (cruising), whilst unsupported corresponds to scores 3 (walking independently).

BiPAP - Bilevel Positive Airway Pressure; HINE-2 - Hammersmith Infant Neurological Examination Module 2

The logic of the company's model for Type 1 SMA operates as follows. In line with FIREFISH,[23] [redacted] and receive treatment with risdiplam or BSC. During each cycle in the "initial period (up to 2 years), transitions between the motor milestone health states for the risdiplam group are governed by probabilities derived from a time-homogeneous multistate model fitted to data for patients with at least 52 weeks' follow-up in FIREFISH (all patients in Part 2 and those patients in Part 1 who received the final dose of risdiplam, n=58). The estimated transition probabilities were subsequently adjusted to only allow patients to remain in their current state or to transition to an adjacent health state (the next best or next worst state). The model also assumes that a proportion of patients in the non-sitting health state will require PV (state [ii]), with the risk of entering this state determined by the difference between the cumulative probabilities of OS and EFS in FIREFISH. For patients who require PV, the model assumes that the only remaining event is death.

During the initial period (up to 2 years), the relative effectiveness of risdiplam versus BSC on motor function is modelled via two mechanisms:

(a) Forward transitions (improvements) from non-sitting to sitting (state [i] to state [iii]) and from sitting to standing (state [iii] to [iv]) are estimated for BSC using odds ratios (ORs) derived from unadjusted arm-based indirect comparisons of motor milestone outcomes in FIREFISH[23] and the placebo arm of ENDEAR.[25]
(b) The probability of transitioning from non-sitting to PV (from state [i] to state [ii]) on BSC is estimated using HRs derived from unadjusted arm-based indirect comparison of EFS and OS from FIREFISH and the placebo arm of ENDEAR.

During each cycle in the subsequent period (after 2 years), risdiplam-treated patients are assumed to never transition to worse health states (including PV), whilst all BSC-treated patients are assumed to remain stable or worsen (patients never improve). The model also includes an additional assumption that after 18 months (patient age = 2 years), risdiplam-treated patients who have achieved the milestone of standing (state [iv]) have a probability of achieving walking (state [v]); this probability is assumed to be equal to one-third of the probability of moving from sitting to standing (state [iii] to [iv]). Risdiplam-treated patients who reach walking at any timepoint are assumed to never lose this milestone.

Mortality risk is assumed to be dependent on the patient's current motor milestone health state. For risdiplam-treated patients who are unable to stand or walk (states [i] to [iii]), mortality risk is based on an exponential survival model fitted to OS data for patients in FIREFISH (n=5 deaths).[23] In the BSC group, mortality risk for patients who require PV and those who are able to sit (states [ii] and [iii]) is assumed to be the same as that for the risdiplam group, whilst the mortality risk for patients who cannot sit (state [i]) is increased through the application of the inverse HR derived from the company's unadjusted indirect comparison of OS in FIREFISH[23] and ENDEAR.[25] Mortality risk for risdiplam-

treated and BSC-treated patients who are able to stand or walk (states [iv] and [v]) is based on the same Type 2 SMA Gompertz model applied in the Type 2/3 SMA model (see Section 5.2.2.3, Figure 5).

The model assumes that treatment with risdiplam is continued indefinitely and that treatment effects on motor milestones and mortality reductions persist over the remaining lifetime of the Type 1 SMA population.

The model includes health outcomes for SMA patients and their caregivers, assuming that each SMA patient has 2.2 caregivers. HRQoL for patients and caregivers is assumed to be dependent on the patient's motor milestone health state, with higher utilities associated applied to better motor milestones. Patient utilities are based on the ERG's clinical advisors' estimates in TA588,[75] whilst caregiver utilities are based on Lopez-Bastida *et al.*,[69] Ara and Brazier[70] (general population utility) and assumptions. Utilities are not age-adjusted, and the model does not include QALY losses associated with adverse events (AEs) or caregiver impacts associated with bereavement.

The Type 1 SMA model includes the costs of drug acquisition and administration costs for risdiplam, with dose levels conditional on patient age and weight (see Section 5.2.1). Health state costs for motor milestone health states for both treatment groups are based on estimates used in the final iteration of the early onset model in TA588.[62] Monthly costs for the PV state are assumed to be equal to the cost of the non-sitting state multiplied by 175%.

The incremental health gains, costs and cost-effectiveness of risdiplam versus BSC are modelled over a time horizon of 90 years using monthly cycles. Half-cycle correction is applied to account for the timing of events. Incremental cost-effectiveness is calculated based on the difference in costs divided by the difference in patient plus caregiver QALYs for risdiplam and BSC.

5.2.3.2 Key assumptions employed in the company's Type 1 SMA model

The company's Type 1 SMA employs the following key assumptions:

- [redacted].
- During the initial 2-year period, risdiplam-treated patients can remain in their current state, improve by one milestone or worsen by one milestone. Non-sitters (state [i]) may proceed to PV (state [ii]); these patients are assumed to never return to the other motor milestone health states. BSC-treated patients can also remain in their current state, improve by one milestone or worsen by one milestone; however, transitions to walking (state [v]) are not permitted in any cycle. Transitions from non-sitting to PV (state [i] to [ii]) are estimated to be higher for BSC than

risdiplam, whilst transitions from non-sitting to sitting (state [i] to [iii]), and from sitting to standing (state [iii] to [iv]) are assumed to be lower for BSC than risdiplam.

- A probability of transitioning from standing to walking (state [iv] to [v]) is assumed in the risdiplam group after 18 cycles. Patients who achieve this milestone are assumed to never lose it.
- During the subsequent period (after 2 years), backward transition probabilities, which reflect transitions to worse health states, for risdiplam-treated patients are not permitted (no patient ever worsens). During this period, BSC-treated patients can only remain in their current state or transition to the next worst state during each cycle; improvements are not permitted.
- Mortality risk is dependent on the patient's current motor milestone health state. The Gompertz model used to estimate outcomes for Type 2 SMA patients in the Type 2/3 SMA model is applied in the standing and walking states (states [iv] and [iv]), whilst an exponential model fitted to OS data from FIREFISH is applied for patients who cannot stand. Higher mortality risks are assumed for BSC-treated non-sitters (state [i]) compared with risdiplam non-sitters.
- HRQoL is dependent on the patient's motor milestone health state. Utilities are included both for patients and caregivers (n=2.2) and are the same for both treatment groups. Utilities are not age-adjusted.
- Risdiplam is assumed to be given indefinitely over the patient's remaining lifetime.
- Transition probabilities applied in the subsequent period and the additional survival advantage applied to risdiplam-treated non-sitters (state [i]) are assumed to persist indefinitely, thereby assuming lifetime treatment effects.
- Risdiplam is assumed to be administered orally at home; a small pharmacy cost is included for patients who do not receive the drug via homecare.
- Costs are dependent on the patient's motor milestone health state. The same costs are applied to the health states in both the risdiplam and BSC groups.
- The model does not include HRQoL or cost impacts resulting from AEs.
- Costs associated with wastage are not included for risdiplam.
- RDI is based on the mean dose intensity in FIREFISH.[23]

5.2.3.3 Evidence used to inform the company's Type 1 SMA model parameters

Table 33 summarises the evidence sources used to inform the parameters in the company's base case model for the Type 1 SMA population. These are discussed in detail in the subsequent sections.

Table 33: Evidence used to inform the company's Type 1 SMA model parameters

Parameter group	Evidence source
Patient characteristics	Age, sex, and baseline health state distribution taken from FIREFISH[23]
Transition probabilities – initial period (up to 2 years), risdiplam group	Multistate model fitted to 52-week data on HINE-2 for patients in risdiplam arm of FIREFISH (all Part 1 and those in Part 2 who received the final risdiplam dose),[23] adjusted to allow only transitions to adjacent motor milestone health states. The probability of transitioning to walking is based on an assumption. The probability of requiring PV is estimated based on the difference between cumulative probability of OS and EFS in FIREFISH.
Transition probabilities – subsequent period (after 2 years), risdiplam group	Same as risdiplam matrix for initial period, but including assumption that backward transitions to worse health states (including PV) are no longer possible, based on expert opinion.[1]
Transition probabilities – initial period (up to 2 years), BSC group	Based on initial matrix for risdiplam group, but with forward transitions to improved motor milestone states reduced using ORs and transition from non-sitting to PV (state [i] to [ii]) increased using inverse HRs from unadjusted arm-based indirect comparison of the risdiplam arm of FIREFISH[23] and the placebo arm of ENDEAR[25]
Transition probabilities – subsequent period (after 2 years), BSC group	Same as BSC matrix for initial period, but including assumption that forward transitions to improved health states are no longer possible, based on expert opinion.[1]
Overall survival – standing/walking (states [iv] and [v]), both treatment groups	Based on Type 2 SMA Gompertz survival model used in Type 2/3 SMA economic model[9, 10, 48, 65-67] (see Section 5.2.2.3)
Overall survival – not sitting, PV and sitting states (states [i] to [iii]), risdiplam group	Exponential model fitted to OS data from FIREFISH[23]
Overall survival – not sitting (state [i]), BSC group	Risdiplam group exponential model raised to power of inverse HR derived from unadjusted arm-based indirect comparison of FIREFISH[23] and ENDEAR[25]
Overall survival – PV and sitting (states [ii] and [iii]), BSC group	Same exponential model applied to not sitting, PV and sitting (states [i] to [iii]) in risdiplam group
Patient HRQoL	ERG's clinical expert's HRQoL estimates from TA588[75]
Caregiver HRQoL	Lopez-Bastida *et al.*,[69] Ara and Brazier[70] and assumptions[1]
Number of caregivers	Roche burden of illness study[1]
Risdiplam acquisition costs	CS.[1] Relationship between age and weight estimated using pooled data from TRO19622,[76] OLEOS,[45] SUNFISH,[22] FIREFISH[23] and NatHis-SMA[77]
Pharmacy costs	Curtis and Burns (PSSRU)[71]
Relative dose intensity	FIREFISH[23]
Health state costs	Biogen RWE resource use study presented in TA588 (GOSH and Newcastle only)[62]

SMA - spinal muscular atrophy; BSC - best supportive care; PV - permanent ventilation; HINE-2 - Hammersmith Infant Neurological Examination Module 2; OS - overall survival; EFS - event-free survival; HR - hazard ratio; HRQoL - health-related quality of life; ERG - Evidence Review Group; CS - company's submission; TA - technology appraisal; GOSH - Great Ormond Street Hospital; RWE - real world evidence

Patient characteristics

Patient characteristics were based on those of all patients in Part 2 and those patients who received the final risdiplam dose in Part 1 of FIREFISH.[23] The model assumes that Type 1 SMA patients eligible

for treatment with risdiplam have a mean age of 0.48 years (5.81 months) at model entry, 57% of patients are assumed to be female, and [redacted].

Motor milestone transition probabilities

Transition probabilities between the motor milestone health states for the risdiplam and BSC groups of the company's Type 1 SMA model are summarised in Table 34 and Table 35, respectively. As with the Type 2/3 SMA model, separate transition matrices are applied in the first 2 years (the "initial period") and in all subsequent cycles (the "subsequent period").

Transition probabilities – initial period (first 2 years)

For the initial period, the company fitted a time-homogeneous multistate model to clinical data from FIREFISH.[23] The dataset included patients in FIREFISH who had at least 52 weeks follow-up, including all patients from Part 2 and those in Part 1 who received the final risdiplam dose (58 patients, 278 observations, 4-monthly visits[17]). No imputation was required. The multistate model was fitted using the *msm* package in R; according to the CS,[1] a covariate was included for the transitions from "not sitting" to "sitting" (state [i] to [iii]), as this transition occurred more frequently compared with the transitions between other motor milestone health states and because baseline HINE-2 score was thought to be predictive of later milestone achievement.[17] Goodness-of-fit was assessed using likelihood ratio tests and the *prevalence* function; further details are provided in the company's clarification response[17] (question B29). As with the Type 2/3 SMA model, the matrix derived from the *msm* package was then adjusted to allow only for transitions to adjacent motor milestone health states, reflecting an *a priori* clinical assumption that patients cannot improve or worsen by more than one milestone per month.[1] In addition to transitions between the motor milestone health states, the Type 1 SMA model includes a further transition from non-sitting to PV (state [i] to [ii]). This probability was estimated as the difference between the probabilities of OS and EFS in the patients from Part 1 and 2 in FIREFISH.[23] The company fitted parametric survival models to the available data on EFS and OS; these included the exponential, Weibull, log-normal, log-logistic, generalised gamma and Gompertz, distributions. The 2-parameter gamma model was not fitted. Based on clinical plausibility, the company selected the exponential model for both EFS and OS, thereby assuming that both events follow a constant hazard. The resulting monthly transition matrix for the risdiplam group in the initial period, excluding adjustments to account for the risk of death, is shown in the upper half of Table 34.

The company estimated transition probabilities for BSC in the initial period using unadjusted arm-based indirect comparisons of data from FIREFISH[23] and the placebo arm of ENDEAR.[25] The model estimates the probability of transitioning from non-sitting to PV for BSC (state [i] to [ii]) by applying the inverse HRs from the indirect comparison to the probabilities of EFS and OS in the risdiplam group (OS - risdiplam versus BSC, HR = [redacted]; EFS - risdiplam versus BSC, HR = [redacted]

[redacted]; see Section 4.4). The model also applies ORs to the forward transitions from non-sitting to sitting (states [i] to [iii]) and from sitting to standing (states [iii] to [iv]) The probabilities of making these transitions in the BSC group were estimated by applying the inverse ORs from the company's indirect comparison of motor milestone outcomes at 12-months (see Table 18) to the probability of achieving these milestones in the risdiplam group, and then converting the estimated annual probabilities for BSC into monthly probabilities. The resulting monthly transition matrix for the BSC group, excluding adjustments to account for the risk of death, is shown in the upper half of Table 35.

Transition probabilities – subsequent period (after 2 years)

The long-term transition probabilities in each group are based on the matrices for the initial period together with the following additional modifications: (a) whilst no patient in FIREFISH reached the milestone of walking,[17] an assumption was made that a proportion of risdiplam-treated patients will achieve this milestone after reaching the age of 2 years (after 18 model cycles) - this probability is assumed to be equal to one-third of the probability of transitioning from sitting to standing (states [iii] to [iv]); (b) in the risdiplam group, backward transitions (reflecting worsening) including those to PV, are assumed to be zero after 2 years; (c) in the BSC group, forward transitions (reflecting improvements) are assumed to no longer be possible. According to the CS,[1] these assumptions were informed by clinical opinion. The resulting monthly transition matrices applied in the subsequent period, excluding adjustments to account for the risk of death, are shown in the lower half of Table 34 and Table 35 for risdiplam and BSC, respectively.

Table 34: Monthly transition probabilities (excluding mortality adjustments), Type 1 SMA model, risdiplam group

Transition probabilities applied during cycles in initial period (first 2 years)					
From\To state	(i) Not sitting	(ii) PV	(iii) Sitting	(iv) Standing	(v) Walking
(i) Not sitting	[redacted]	[redacted]	[redacted]	0	0
(ii) PV	0	1.0000	0	0	0
(iii) Sitting	[redacted]	0	[redacted]	[redacted]	0
(iv) Standing	0	0	[redacted]	[redacted]	0
(v) Walking	0	0	0	0	1.0000
Transition probabilities applied during cycles in subsequent period (after 2 years)					
From\To state	(i) Not sitting	(ii) PV	(iii) Sitting	(iv) Standing	(v) Walking
(i) Not sitting	[redacted]	0‡	[redacted]	0	0
(ii) PV	0	1.0000	0	0	0
(iii) Sitting	0‡	0	[redacted]	[redacted]	0.0000
(iv) Standing	0	0	0‡	[redacted]	[redacted]
(v) Walking	0	0	0	0‡	1.0000

Excluding PV, the company's model assumes that patients who improve/worsen can only transition to an adjacent health state. Cells with grey shading represent non-permitted transitions

** Estimated as difference between cumulative probabilities of OS and EFS in FIREFISH*

† Probability of reaching walking is assumed to be 33% of the probability for moving from sitting to standing (state [iii] to [iv]). This is applied after 18 months in the model (when patients are aged 2 years and older).

‡ Backward transitions (worsening), including moving to PV, assumed to be zero after 2 years

Table 35: Monthly transition probabilities (excluding mortality adjustments), Type 1 SMA model, BSC group

Transition probabilities applied during cycles in initial period (first 2 years)					
From/To state	(i) Not sitting	(ii) PV	(iii) Sitting	(iv) Standing	(v) Walking
(i) Not sitting	[redacted]	[redacted]	[redacted]	0	0
(ii) PV	0	1.0000	0	0	0
(iii) Sitting	[redacted]	0	[redacted]	[redacted]	0
(iv) Standing	0	0	[redacted]	[redacted]	0
(v) Walking	0	0	0	0	1.0000
Transition probabilities applied during cycles in subsequent period (after 2 years)					
From/To state	(i) Not sitting	(ii) PV	(iii) Sitting	(iv) Standing	(v) Walking
(i) Not sitting	[redacted]	[redacted]	0‡	0	0
(ii) PV	0	1.0000	0	0	0
(iii) Sitting	[redacted]	0	[redacted]	0‡	0
(iv) Standing	0	0	[redacted]	[redacted]	0‡
(v) Walking	0	0	0	0	1.0000

Excluding PV, the company's model assumes that patients who improve/worsen can only transition to an adjacent health state. Cells with grey shading represent non-permitted transitions

** Transition from not sitting to PV (state [i] to [ii]) calculated using inverse of HR derived from arm-based unadjusted indirect comparison of FIREFISH (risdiplam) and ENDEAR (placebo)*

†Transitions to improved motor function states estimated by applying inverse ORs from indirect comparison of FIREFISH (risdiplam) and ENDEAR (placebo)

‡ Forward transitions (improving) assumed to be equal to 0% after the first 2 years, leading to an increased probability of remaining in the current health state

Survival

As with the Type 2/3 SMA model, mortality risk is assumed to be dependent on the patient's current motor milestone health state. Survival is assumed to be improved for patients who are able to stand or walk (states [iv] and [v]) compared with those who cannot stand (states [i] to [iii]). In addition, risdiplam is assumed to be associated with a survival benefit over BSC in non-sitters (state [i]). The reasons for applying this assumption only in the not sitting health state, as opposed to all non-standing states (states [i], [ii] and [iii]) are not entirely clear from the CS.[1] The company's survival assumptions are summarised in Table 36; these are described in further detail in the subsequent text.

Table 36: Description of per cycle mortality risks applied in 1 SMA model health states

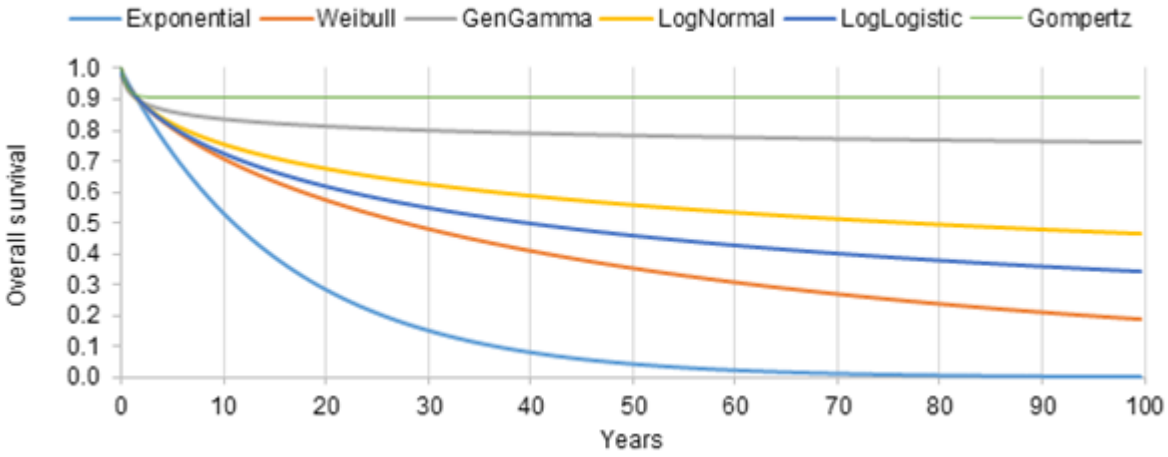
Health state	**Per cycle mortality risk applied whilst in health state**	
	BSC group	**Risdiplam group**
(i) Not sitting	Risdiplam group risk (from exponential model) raised to power of inverse HR derived from arm-based unadjusted indirect comparison of FIREFISH[23] and ENDEAR[25]	Exponential model fitted to OS data from FIREFISH[23]
(ii) PV	Same as risdiplam group	
(iii) Sitting	Same as risdiplam group	
(iv) Standing	Based on Type 2 SMA Gompertz distribution based on synthesis of natural history studies[9, 10, 48, 65-67]	Same as BSC group
(v) Walking		

BSC - best supportive care; PV - permanent ventilation; HR - hazard ratio; SMA - spinal muscular atrophy; OS - overall survival

Within both treatment groups, mortality risk for patients who are able to stand or walk (states [iv] and [v]) is assumed to follow the same Gompertz distribution for patients with Type 2 SMA used in the Type 2/3 model (see Section 5.2.2.3).

Mortality risk for risdiplam-treated patients who are unable to stand or walk, including those requiring PV (states [i] to [iii]), is based on a parametric survival model fitted to OS data from FIREFISH.[23] The company fitted six standard parametric survival models to the available data (as described above). According to the CS,[17] model selection was based on the approach described in NICE DSU TSD 14.[74] The company selected the exponential distribution for inclusion in the base case model based on clinical advice.[1] A comparison of modelled OS and the Kaplan-Meier survival function from FIREFISH is presented in Figure 10. AIC and BIC statistics for the fitted OS models are presented Table 37.

Figure 10: Modelled OS for Type 1 SMA (FIREFISH; reproduced from CS Figure 15)



Note - plots of cumulative EFS and OS including the Kaplan-Meier functions are provided in Figures 16 and 17 of the company's clarification response[17] (questions B34 and B35). These are not reproduced here as the time horizon shown is heavily truncated to allow the observed data to be visible (based on 5 deaths)

Table 37: AIC and BIC statistics, Type 1 SMA, OS from FIREFISH

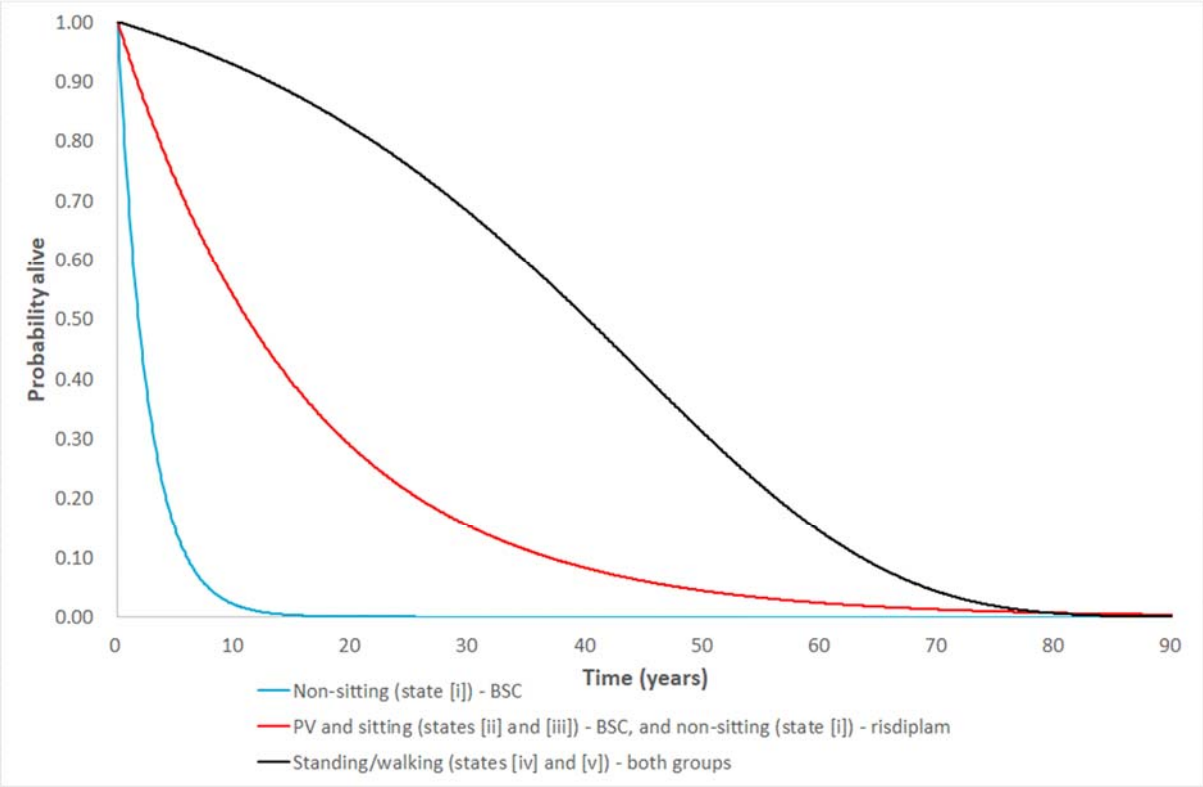
Model	AIC	BIC
Exponential	64.60	**66.60**
Weibull	65.70	69.80
Gompertz	64.30	68.40
Log-normal	65.10	69.20
Log-logistic	65.60	69.80
Generalised gamma	**62.50**	68.70

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best fitting model indicated in bold

Within the BSC group, mortality risk for non-sitters (state [i]) is assumed to be lower than that for risdiplam. The company's model applies the inverse of the HR estimated from the indirect comparison of OS data from FIREFISH[23] and the placebo arm of ENDEAR[25] (HR for OS risdiplam versus

BSC=[redacted]). The OS functions applied in the company's model, excluding the impact of health state switching over time, are summarised in Figure 11.

Figure 11: Survival functions applied in Type 1 SMA model health states, figure excludes impact of switching of health states over time



Patient and caregiver utilities

FIREFISH[23] did not include the measurement of patient HRQoL using a preference-based instrument. Whilst the Lloyd *et al.* vignette study[68] included the valuation of Type 1 SMA health states, the company's clinical advisors did not consider the reported utility estimates to be clinically appropriate. Instead, the company elected to use non-preference-based estimates of patient utility for early onset SMA states obtained from the ERG's clinical advisors in TA588.[75]

The company's approach for valuing caregiver utility was similar to that used in the Type 2/3 SMA model, with two exceptions: (i) the utility from Lopez-Bastida *et al.*[69] is applied to both the non-sitting and PV states, and (ii) a higher general population utility value is applied in the best health state (walking). As with the Type 2/3 SMA model, 2.2 caregivers are assumed for each SMA patient, based on the company's burden of illness study.[1]

The patient and caregiver utility values applied in the company's model are summarised in Table 38.

Table 38: Type 1 SMA model – patient and caregiver utility values

Model health state	Mean utility	Source and derivation
Patient utility		
(i) Not sitting	0.25	NICE TA588 ERG's clinical advisors[75] – Type 1 SMA, HINE-2 "Mild milestones" state
(ii) PV	0.20	NICE TA588 ERG's clinical advisors[75] – Type 1 SMA, HINE-2 "No milestones achieved" state
(iii) Sitting	0.48	NICE TA588 ERG's clinical advisors[75] – Type 1 SMA, mid-point of HINE-2 "Moderate milestones" and "Sits without support" states
(iv) Standing	0.75	NICE TA588 ERG's clinical advisors[75] – Type 1 SMA, mid-point of HINE-2 "Stands with assistance" and "Stands/walks unaided" states
(v) Walking	0.80	NICE TA588 ERG's clinical advisors[75] – Type 1 SMA, mid-point of HINE-2 "Walks with assistance" and "Stands/walks unaided" states
Caregiver utility		
(i) Not sitting	0.48	Lopez-Bastida *et al.*[69] – Spanish caregivers mean TTO score (all SMA types)
(ii) PV	0.48	
(iii) Sitting	0.63	Utility assumed to increase linearly between not-sitting/PV and walking
(iv) Standing	0.77	
(v) Walking	0.92	Ara and Brazier[70] - general population utility
Number of caregivers =2.2 per SMA patient		

SMA - spinal muscular atrophy; TA - technology appraisal; HINE-2 - Hammersmith Infant Neurological Examination Module 2; TTO - time-trade-off; PV - permanent ventilation
Further justification of the assumptions made in mapping the ERG's clinical advisors' estimates of patient utility in TA588 to health states used in the Type 1 SMA model are provided in the company's clarification response[17] (question 38, Table 22)

Resource costs

Drug acquisition and administration costs

The acquisition cost and PAS for risdiplam are detailed in Section 5.2.2.3. As with the Type 2/3 SMA model, the Type 1 SMA model assumes that 90% of patients will receive risdiplam through homecare, with the remaining 10% of patients having risdiplam administered through the hospital. The model assumes that the dose of risdiplam for Type 1 SMA patients is dependent on patient age and weight, based on a regression equation estimated using pooled data from TRO19622,[76] OLEOS,[45] SUNFISH,[22] FIREFISH[23] and NatHis-SMA.[77] The regression equation used to estimate patient weight is presented on pages 143 and 144 of the CS.[1] No information is provided in the CS regarding how the data were pooled. The modelled estimates of patient weight and risdiplam dose by age is shown in Figure 12.

Figure 12: Modelled risdiplam dose by age (constructed by the ERG)

Note – fixed dose of 5mg/day applied to all patients from age 5.4 years

Health state costs

As with the Type 2/3 SMA model, health state costs were taken from the GOSH and Newcastle subset of RWE estimates obtained by Biogen in TA588.[62] The cost associated with not sitting was based on the Type 1 SMA cost; in line with TA588, this estimate was doubled. PV was not included in the TA588 model; the cost of this state was assumed to be equal to the cost of the not sitting state multiplied by 175%. The sitting state was based on the mid-point between the Type 1 and 2 SMA costs. The costs of standing and walking were based on the Type 3 SMA costs. The monthly costs for each health state are summarised in Table 39.

Table 39: Type 1 SMA model – health state costs

Model health state	Mean cost per month	Source
(i) Not sitting	£12,351.00	Biogen RWE resource use study in TA588 (GOSH and Newcastle only)[62] – Type 1 SMA costs doubled
(ii) PV	£21,614.25	Assumed to be equal to costs of non-sitting state multiplied by 175%
(iii) Sitting	£9,022.50	Biogen RWE resource use study in TA588 (GOSH and Newcastle only)[62] – mid-point between Type 1 and Type 2 SMA costs
(iv) Standing	£1,814.00	Biogen RWE resource use study in TA588 (GOSH and Newcastle only)[62] – Type 3 SMA costs
(v) Walking		

SMA - spinal muscular atrophy; RWE - real world evidence; TA - technology appraisal; GOSH - Great Ormond Street Hospital

5.2.3.4 Model evaluation methods, Type 1 SMA model

The CS[1] presents base case ICERs for risdiplam versus BSC in the Type 1 SMA population, based on total QALYs gained by SMA patients and their caregivers and costs borne by the NHS (and possibly PSS). Results are presented using both the deterministic and probabilistic versions of the model; the probabilistic ICERs are based on 2,000 Monte Carlo simulations. The results of the PSA are presented as cost-effectiveness planes and CEACs, whilst the results of DSAs are presented using tornado plots. The CS also reports the results of scenario analyses which explore the impact of alternative assumptions regarding: the use of relative treatment effect estimates obtained from the company's MAIC; transition probabilities; patient and caregiver utilities; the number of caregivers; resource use and discount rates.

5.2.3.5 Company's model results, Type 1 SMA

This section presents the results of the company's Type 1 SMA model. Whilst double-programming the company's model, the ERG identified an important error relating to the estimation of caregiver health gains (see Section 5.3.4). As such, the ERG believes that the company's ICERs which include caregiver QALY gains are misleading and should be disregarded.

Central estimates of cost-effectiveness – Type 1 SMA population

Table 40 presents the central estimates of cost-effectiveness generated using the company's Type 1 SMA model. When only patient health gains are included, the probabilistic version of the company's model suggests that risdiplam is expected to generate an additional 7.83 QALYs at an additional cost of [redacted]; the corresponding ICER is [redacted] per QALY gained. The model also predicts that risdiplam will lead to an increase of 16.23 QALYs for caregivers of each SMA patient treated; when both patient and caregiver health gains are included in the analysis, the ICER for risdiplam versus BSC is expected to be [redacted] per QALY gained. The deterministic version of the model generates very similar ICERs compared with the probabilistic version of the model. However, there are differences between the deterministic and probabilistic estimates of mean costs and health outcomes in both treatment groups; as with the Type 2/3 SMA model, these reflect problems in the way that parameter uncertainty has been characterised (see Section 5.3.4).

Table 40: Central estimates of cost-effectiveness, risdiplam versus BSC, Type 1 SMA

Option	LYGs*	QALYs (patients)	QALYs (carers)	QALYs (patients + carers)	Costs	ICER (patient QALYs)	ICER (patient + carers QALYs)
Probabilistic model							
Risdiplam	27.65	9.53	24.05	33.58	[redacted]	-	-
BSC	11.63	1.69	7.83	9.52	[redacted]	-	-
Incremental	16.02	7.83	16.23	24.06	[redacted]	[redacted]	[redacted]
Deterministic model							
Risdiplam	26.11	8.79	22.53	31.33	[redacted]	-	-
BSC	10.11	1.42	7.17	8.59	[redacted]	-	-
Incremental	16.00	7.37	15.37	22.74	[redacted]	[redacted]	[redacted]

* *Undiscounted*

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care

Company's PSA results – Type 1 SMA population

Figure 13 presents CEACs for risdiplam versus BSC within the Type 1 SMA population, including both patient and caregiver QALYs. Assuming WTP thresholds of £20,000 and £30,000 per QALY gained, the company's model estimates that the probability that risdiplam generates more net benefit than BSC is [redacted] and [redacted], respectively.

Figure 13: Cost-effectiveness acceptability curves, risdiplam versus BSC (patient and caregiver QALYs), Type 1 SMA (generated by the ERG using the company's model)

[redacted]

Company's DSA results – Type 1 SMA population

Figure 14 presents the results of the company's DSAs for the Type 1 SMA population in the form of a tornado plot. As shown in the figure, the ICER for risdiplam is particularly sensitive to the acquisition cost of risdiplam, the costs associated with PV, the HRs for OS and EFS derived from the company's indirect comparison, assumptions regarding the number of caregivers and discount rates for health outcomes and costs. As noted previously, the cost per bottle of risdiplam and discount rates are not uncertain parameters and should not typically be included in DSAs.

Figure 14: Tornado plot, risdiplam versus BSC (patient and caregiver QALYs), Type 1 SMA (generated by the ERG using the company's model)

Company's scenario analysis results – Type 1 SMA population

Table 41 presents the results of the company's scenario analyses for the Type 1 SMA population. As shown in the table, when only patient health gains are included in the model, the ICER is estimated to range from [redacted] per QALY gained (PV costs = cost of not sitting x 250%) to [redacted] per QALY gained (patient utilities based on Lloyd *et al.*[68]). When caregiver health gains are included in the analysis (without correction of the calculation error identified by the ERG), the ICER is estimated to range from [redacted] per QALY gained (PV costs = cost of not sitting x 250%) to [redacted] per QALY gained (risdiplam probability of worsening in subsequent period = initial period probability x 0.30).

Table 41: Scenario analysis results, risdiplam versus BSC, Type 1 SMA (generated by the ERG using the company's model)

Scenario description	Inc. QALYs (patients)	Inc. QALYs (patients + carers)	Inc. costs	ICER (patient QALYs)	ICER (patient+carer QALYs)
Base case - deterministic	7.37	22.74	[redacted]	[redacted]	[redacted]
Scenario 1 – BSC effectiveness based on MAIC	7.78	25.21	[redacted]	[redacted]	[redacted]
Scenario 2 – Risdiplam probability of worsening in subsequent period = initial period probability x [redacted]	5.72	17.71	[redacted]	[redacted]	[redacted]
Scenario 2 – Risdiplam probability of worsening in subsequent period = initial period probability x [redacted]	4.98	15.43	[redacted]	[redacted]	[redacted]
Scenario 2 – Risdiplam probability of worsening in subsequent period = initial period probability x [redacted]	4.55	14.13	[redacted]	[redacted]	[redacted]
Scenario 5 – Risdiplam TP to walking equal to 67% of TP for sitting to standing	7.45	23.34	[redacted]	[redacted]	[redacted]
Scenario 6 – Risdiplam TP to walking = 0	7.22	21.60	[redacted]	[redacted]	[redacted]
Scenario 7 – BSC TPs extrapolated indefinitely from MSM	7.36	22.71	[redacted]	[redacted]	[redacted]
Scenario 8 – BSC backward TPs = twice backward TPs for risdiplam	7.38	22.77	[redacted]	[redacted]	[redacted]
Scenario 9 – Patient utilities = Roche burden of illness study	7.37	22.74	[redacted]	[redacted]	[redacted]
Scenario 10 – PV costs = cost of not sitting x 250%	7.37	22.74	[redacted]	[redacted]	[redacted]
Scenario 11 – PV costs = cost of not sitting x 125%	7.37	22.74	[redacted]	[redacted]	[redacted]
Scenario 12 – Patient utilities = Lloyd *et al.* EQ-5D-Y (mapping 1)	4.66	20.03	[redacted]	[redacted]	[redacted]
Scenario 13 – Patient utilities = Lloyd *et al.* EQ-5D-Y (mapping 2)	5.42	20.78	[redacted]	[redacted]	[redacted]
Scenario 14 – Carer utilities = Roche burden of illness study	7.37	20.29	[redacted]	[redacted]	[redacted]
Scenario 15 – No. carers = 2	7.37	21.34	[redacted]	[redacted]	[redacted]
Scenario 16 – No. carers = 3	7.37	28.32	[redacted]	[redacted]	[redacted]
Scenario 17 – Apply long-term TP assumptions from 1 year	7.71	23.76	[redacted]	[redacted]	[redacted]
Scenario 18 – Discount rates for costs and QALYs = 1.5%	10.94	34.15	[redacted]	[redacted]	[redacted]
Scenario 19 – Discount rates for QALYs = 1.5%, costs = 3.5%	10.94	34.15	[redacted]	[redacted]	[redacted]

QALY - quality-adjusted life year; MAIC - matching-adjusted indirect comparison; TP - transition probability; PV - permanent ventilation; ERG - Evidence Review Group; MSM - multistate model; ICER - incremental cost-effectiveness ratio; Inc. - incremental

5.3 Critical appraisal of the company's economic analyses

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's economic analyses and the underlying health economic models upon which these are based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[78, 79]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming the deterministic version of the company's models to fully assess the logic of the model structures, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the company's executable models and their description in the CS.[80]
- Replication of the results of the company's base case, PSA, DSAs and scenario analyses reported in the CS.
- Where possible, checking key 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 economic analyses and the assumptions underpinning the models.

5.3.1 Model verification by the ERG, Type 2/3 and Type 1 SMA models

Table 42 presents a comparison of the results of the deterministic versions of the company's models and the ERG's double-programmed models for the Type 2/3 SMA and Type 1 SMA populations. As shown in the table, the ERG's results are very similar to those generated using the company's models. However, the ERG's double-programming exercise revealed some implementation errors and conceptual flaws in both models. These issues are discussed in detail in Section 5.3.4 (critical appraisal point [1]) and are addressed as part of the ERG's exploratory analyses in Section 5.4.

Table 42: Comparison of results generated using the company's models and the ERG's double-programmed models, excludes correction of errors

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs total	Costs	ICER (patient QALYs)	ICER (patient+carer QALYs)
Type 2/3 SMA – Company's model							
Risdiplam	56.33	5.58	39.61	45.19	[redacted]	-	-
BSC	43.57	-1.98	25.02	23.04	[redacted]	-	-
Incremental	12.76	7.56	14.59	22.15	[redacted]	[redacted]	[redacted]
Type 2/3 SMA – ERG's double-programmed model							
Risdiplam	56.47	5.58	39.62	45.21	[redacted]	-	-
BSC	43.65	-1.98	25.02	23.04	[redacted]	-	-
Incremental	12.82	7.57	14.60	22.17	[redacted]	[redacted]	[redacted]
Type 1 SMA – Company's model							
Risdiplam	26.11	8.79	22.53	31.33	[redacted]	-	-
BSC	10.11	1.42	7.17	8.59	[redacted]	-	-
Incremental	16.00	7.37	15.37	22.74	[redacted]	[redacted]	[redacted]
Type 1 SMA – ERG's double-programmed model							
Risdiplam	26.11	8.79	22.53	31.33	[redacted]	-	-
BSC	10.11	1.42	7.17	8.59	[redacted]	-	-
Incremental	16.00	7.37	15.37	22.74	[redacted]	[redacted]	[redacted]

SMA - spinal muscular atrophy; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group
** Undiscounted*

5.3.2 Correspondence of the model inputs and the original sources of parameter values

The ERG identified two potential inconsistencies between the model parameter values and their original sources: (i) the ERG was unable to locate the cost of pharmacists' time in Curtis and Burns,[71] and (ii) the general population mortality risks included in the Type 2/3 SMA model do not match the ONS life tables for England 2016-2018 for individuals aged 90 years and older.[64] Both of these issues are minor and have a negligible impact on the model results.

Health state costs and utility estimates included in the company's models are consistent with their original sources.[62, 68, 75] The ERG was unable to verify the accuracy of the transition probabilities or the parametric survival model parameters as the IPD and source code for the multistate models and parametric survival models were not provided as part of the CS.[1]

5.3.3 Adherence of the company's model to the NICE Reference Case

The extent to which the company's economic analyses adhere to the NICE Reference Case[26] is summarised in Table 43. The company's analyses are generally in line with the NICE Reference Case. The key deviations relate to the measurement and valuation of patient and caregiver utility; this issue is described in Section 5.3.4 (critical appraisal points [10] and [11]).

Table 43: Adherence of the company's economic models to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's economic analyses are in line with the final NICE scope.[18] Separate economic analyses are presented for Type 1 and Type 2/3 SMA.
Comparator(s)	As listed in the scope developed by NICE	In line with the final NICE scope,[18] BSC is included as the sole comparator. Whilst nusinersen is available through an MAA, this treatment option is not routinely commissioned on the NHS.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The analysis adopts a direct NHS (and possibly PSS) perspective, including health effects on patients with SMA and their caregivers.
Perspective on costs	NHS and PSS	Costs include those borne by the NHS. It is unclear whether PSS costs are included in the motor milestone health state costs.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's models adopt a cost-utility approach. Results are presented in terms of the incremental cost per QALY gained, including both patient and caregiver health gains.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Both economic analyses adopt a 90-year (lifetime) horizon
Synthesis of evidence on health effects	Based on systematic review	Clinical outcomes for the initial 2-year period are based on studies identified from the company's systematic review.[27] Long-term outcomes for the subsequent period are based on assumptions.[1]
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	*Patient utility* • Type 2/3 SMA model: Patient utility is measured using the EQ-5D-Y (completed by clinical experts as proxy) and valued using the UK adult EQ-5D-3L tariff.[81] • Type 1 SMA model: Patient utility values reflect non-preference-based estimates provided by the ERG's clinical advisors in TA588.[75] *Caregiver utility* In both models, caregiver utility for the worst health states (not sitting [and PV in Type 1]) are based on a TTO study undertaken in caregivers of SMA patients (Spanish population, all SMA types).[69] Caregiver utility for the best health state is based on EQ-5D-3L estimates for the general population.[70] Caregiver utility values for other states are based on assumptions. Caregiver QALYs are only counted for surviving patients (see critical appraisal point [1c])
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	

Element	Reference case	ERG comments
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.
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	The acquisition cost of risdiplam is based on its expected list price and a confidential simple price discount.[1] Unit costs for pharmacists' time are reported to be based on 2019 values.[71] Health state costs are based on 2017 prices.[62]
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.

ERG - Evidence Review Group; NICE - National Institute for Health and Care Excellence; SMA - spinal muscular atrophy; BSC - best supportive care; MAA - Managed Access Agreement; PSS - Personal Social Services; QALY - quality-adjusted life year; EQ-5D - Euroqol 5-Dimensions; EQ-5D-Y - Euroqol 5-Dimensions (Youth); PV - permanent ventilation; TTO - time-trade-off

5.3.4 Key issues identified from the ERG's critical appraisal - Type 1 and Type 2/3 SMA models

This section presents a discussion of the main issues identified from the ERG's critical appraisal of the company's economic analyses for the Type 2/3 and Type 1 SMA models. The critical appraisal of these two models is presented together, as although they relate to different patient populations, the key issues are similar across both models. The main issues identified in the ERG's critical appraisal are summarised in Box 2, with a detailed discussion presented in the subsequent sections.

Box 2: Main issues identified from ERG's critical appraisal – Type 1 and Type 2/3 SMA models

1. Presence of model errors
2. Issues relating to comparators and positioning of risdiplam
3. Model structure issues
4. Absence of formal discontinuation criteria for risdiplam
5. Use of unadjusted (naïve) arm-based indirect comparison in Type 1 SMA
6. Issues related to time-to-event analyses
7. Concerns regarding methods used to elicit beliefs about uncertain quantities
8. Highly optimistic assumptions of long-term treatment effects
9. Highly favourable modelled predictions of motor milestone attainment and survival
10. Issues related to patient utility values
11. Issues relating to caregiver utility values
12. Issues relating to costs
13. Weak characterisation of parameter uncertainty
14. Inconsistent assumptions compared with the final models used to inform NICE TA588

(1) Presence of model errors

Type 2/3 SMA model errors

(a) "Subsequent period" motor milestone assumptions applied one cycle too early

According to the CS,[1] long-term assumptions for the "subsequent period" (the [redacted] reduction in probability of worsening on risdiplam, no improvement on BSC) were intended to be applied after 2 years. However, in the company's executable model, these alternative transition probabilities are applied after 23 months. This inconsistency favours risdiplam over BSC. The company's clarification response[17] (question B6b) confirms that this reflects an unintentional error. Moving the timepoint from which the subsequent period transition matrices are applied to 24 months leads to a small increase in the ICER for risdiplam versus BSC.

(b) Errors in mortality risk calculations

The company's Type 2/3 model applies general population mortality risks from ONS life tables[64] to all patients who are able to stand or walk (states [iv] and [v]) and to 28.9% of patients who cannot stand (patients with Type 3 SMA, states [i] to [iii]). The model uses column *"qx"* from the life tables and divides this annual risk by 12 to obtain the monthly risk for each given age. Monthly risks are then weighted according to a constant proportionate split of men and women in each cycle, based on the ratio of women to men at baseline in SUNFISH,[22] and converts the weighted rate onto the probability scale. The company's mortality risk estimates are subject to several problems:

(i) The *"qx"* values reported in life tables are probabilities, not rates. The ONS defines this measure as "*the probability that a person aged x exact will die before reaching age (x +1)"*.[64] The company's clarification response[17] (question B12c) confirms that their approach is incorrect.

(ii) The life tables indicate that men and women have different mortality risks by age. The company's assumption that the ratio of women to men is constant across all ages is therefore inappropriate. In their company's clarification response[17] (question B12b), the company states that this approach *"was intentionally chosen as a simplification"*. However, the ERG believes that this reflects a minor error and that it would be more appropriate to calculate monthly mortality risks based on a survival function weighted by the proportion of females and males at model entry, thereby allowing for different sex-specific mortality risks by age.

(iii) The =LOOKUP() functions used to determine mortality risk at each patient age *x* correspond to *x*+0.5 years. The company's clarification response[17] (question B14) states that this adjustment allows the model formulae to correctly recognise non-integer values. However, the formulae return the incorrect mortality risks.

(iv) As noted in Section 5.3.2, the annual mortality risks (*"qx"*) for individuals aged 90 years and over do not correspond to the ONS life tables for England for 2016-2018.[64] The reason underpinning this discrepancy is unclear.

(v) The CS[1] describes the Type 2 SMA mortality multiplication factor of 0.75 as an HR. The company's clarification response[17] (question B12a) confirms that this reflects inaccurate terminology in the CS rather than an error in the model.

The ERG notes that these issues are minor and do not have a marked impact on the ICER for risdiplam.

(c) Incorrect calculation of incremental caregiver QALYs

The company's model estimates absolute caregiver QALYs per month in each treatment group as the product of four factors: (i) the distribution of SMA patients across the motor milestone health states in a given cycle; (ii) the caregiver utility values, which are assumed to correspond to the SMA patient's motor milestone health state; (iii) the number of caregivers per SMA patient (n=2.2) and (iv) the cycle

duration (1 cycle = 0.083 years). For example, if all patients spend one month in the non-sitting state (caregiver utility = 0.48), the contribution to total caregiver QALYs is calculated as 1.0 x 0.48 x 2.2 x 0.083 = 0.088 QALYs. The ERG believes that this approach is subject to an unintended erroneous assumption – that caregiver QALYs are only counted when the SMA patient is alive. In simple terms, the company's approach implicitly assumes that the caregivers die (or survive with utility equal to zero) when the SMA patient dies. This is conceptually flawed as caregivers will continue to accrue health gains after the patient has died. The ERG believes that it would be more appropriate to instead estimate the incremental QALY losses avoided for risdiplam versus BSC as a function of carer disutilities relative to the general population; this alternative approach necessarily assumes that caregiver QALYs are only lost whilst the SMA patient remains alive, and is consistent with the assumptions employed in TA588.[52] This is an important issue which has a substantial impact on the ICER for risdiplam versus BSC (see Section 5.4).

(d) Inconsistent number of model cycles between the risdiplam and BSC groups

The model includes 1,080 monthly cycles in the risdiplam group and 1,020 cycles in the BSC group. The company's clarification response[17] (question B21) confirms that this is a minor error.

(e) Discrepancies between probabilistic and deterministic results

The ERG notes that there are noticeable differences between the cost-effectiveness results generated using the deterministic and probabilistic versions of the Type 2/3 SMA model. As shown in Table 30, the probabilistic estimates of absolute and incremental life years gained (LYGs), patient QALYs, and caregiver QALYs are markedly different from those estimated using the deterministic version of the model. When only patient QALYs are considered, the deterministic ICER for risdiplam versus BSC is estimated to be more than £50,000 higher than the corresponding ICER generated using the probabilistic model. The ERG's scrutiny of the company's PSA identified three factors which lead to this discrepancy:

(i) In the BSC group, the deterministic model assumes that the probability of transitioning from sitting without support to standing (state [iii] to [iv]) is zero. However, the probabilistic version of the model assumes that competing transitions follow a Dirichlet distribution which include a non-zero prior (n=1.0); hence, whilst this route is blocked in the deterministic model, it is permitted in the probabilistic model. The ERG believes that this probably reflects an unintended assumption. Setting this prior equal to zero leads to probabilistic outcomes for BSC which are similar to those generated using the deterministic version of the model.

(ii) In the risdiplam group, the deterministic version of the model features very low probabilities of leaving the sitting without support state (state [iii]; see Table 24). Again, uncertainty around these transitions is characterised by a Dirichlet distribution, which arbitrarily assumes that the sample data reflects 100 patients who will leave or stay in this state, with a prior of 1.0 for each

transition. This does not properly reflect the uncertainty in the parameters of the multistate model and leads to arbitrary skewness in the sampled transition probabilities, which in turn, leads to differences between the results of the deterministic and probabilistic models which are not meaningful. Removing the arbitrary characterisation of uncertainty for this transition leads to probabilistic outcomes for the risdiplam group which are similar to the deterministic version of the model. The company's model does not allow for an appropriate characterisation of genuine uncertainty around these parameters (e.g. bootstrapped matrices).

(iii) The number of caregivers per SMA patient is sampled from a gamma distribution, which is then unnecessarily forced to take an integer value (using the =ROUNDDOWN() function). The equivalent constraint is not applied in the deterministic version of the model. Removing this constraint leads to probabilistic estimates of caregiver QALY gains which are closer to those generated using the deterministic version of the model.

ERG believes that the apparent discrepancies between the results of the deterministic and probabilistic versions of the company's Type 2/3 SMA model reflect errors rather than non-linearity and, as such, the company's PSA results should not be used to inform decision-making.

Type 1 SMA model errors

(f) "Subsequent period" motor milestone assumptions applied one cycle too early

As with the Type 2/3 SMA model, the subsequent period assumptions are also applied after 23 months. This inconsistency slightly favours risdiplam over BSC.

(g) Incorrect calculation of incremental caregiver QALYs

The company's approach used to value incremental caregiver QALY gains in the Type 1 SMA model is subject to the same conceptual error as that described for the Type 2/3 SMA model. Correcting this error substantially increases the ICER for risdiplam in this population (see Section 5.4).

(h) Discrepancies between probabilistic and deterministic results

As with the Type 2/3 SMA model, the characterisation of uncertainty within the Type 1 model is also subject to several problems which produce some discrepancies in the model results:

(i) Within the BSC group, the model includes a prior of 1.0 for the transition from standing to walking (state [iv] to [v]). Whilst this route is blocked in the deterministic model, it is permitted in the probabilistic model. The ERG believes that this probably reflects an unintended assumption.

(ii) Uncertainty around transition probabilities is characterised as Dirichlet distributions assuming that each row in the transition matrix is informed by 100 observations with each transition being assigned a prior of 1.0. This is arbitrary and does not reflect the sample data from FIREFISH.

(iii) The SEs around the treatment effect parameters (HRs and ORs) from the company's indirect comparison are arbitrarily defined as being 20% of the mean.

(iv) The exponential model used to estimate mortality risks for patients who cannot stand (states [i] to [iii]) is highly uncertain and does not include any constraints. When combined with the inverse HR from the company's indirect comparison, draws from this distribution frequently lead to OS projections for BSC-treated Type 1 SMA patients which are better than those for the general population and/or for people with Type 2 SMA at some timepoints. In some probabilistic samples, a substantial proportion of patients are predicted to remain alive after 100 years. An example draw from the company's PSA which illustrates these issues is shown in Figure 15.

Figure 15: Example of an implausible sample of OS obtained from company's PSA routine, Type 1 SMA model

The ERG was unable to fully resolve these issues and, as such, the ERG believes the company's PSA results for the Type 1 SMA population should not be used to inform decision-making.

(2) Issues relating to comparators and positioning of risdiplam

The company's models compare risdiplam against a single comparator – BSC. Nusinersen was excluded from the final NICE scope[18] because this treatment is only available through an MAA. Whilst the comparisons included in the company's models are in line with scope, in reality, a proportion of paediatric SMA patients in England are currently being treated with nusinersen. Whilst the CS cannot

be criticised for adhering to the NICE scope, there remains uncertainty regarding whether risdiplam is more or less clinically effective and cost-effective than nusinersen.

The ERG also notes that the company's intended positioning of risdiplam in the treatment pathway includes the use of the drug as an alternative to or subsequent treatment following nusinersen (see Section 2.2, Figure 1). However, the CS does not provide any evidence of the clinical or cost-effectiveness effectiveness of risdiplam in patients who have previously received nusinersen.

(3) Issues relating to the company's model structure

The structures of both the Type 2/3 and Type 1 SMA models are focussed on the achievement, maintenance or loss of motor milestones (sitting, standing and walking) and survival (see Figure 3 and Figure 9). The Type 1 SMA model also includes a further health state to account for patients who require PV. The Type 2/3 SMA model health states are defined according to motor milestones described by the MFM32 and the HFMSE,[32, 63] whilst in the Type 1 SMA model, health states are defined according to motor milestones described by the HINE-2.[47] The model structures are broadly similar, albeit less granular, than the early and later onset SMA models used to inform TA588.[52]

The ERG's clinical advisor commented that achieving and maintaining motor milestones is important for people with SMA and that it is reasonable to characterise the disease in terms of gross motor milestones. The clinical advisor also commented that the MFM32 and the HFMSE are appropriate instruments through which to classify motor milestones in later onset SMA and that HINE-2 is appropriate in early onset SMA. The advisor also agreed with the company's structural assumption that survival is improved for patients who achieve the milestones of standing and walking compared with that for patients who do not achieve ambulation. The clinical advisor further commented that respiratory function is also an important aspect of SMA, particularly with respect to its relationship with expected survival. This may already be broadly captured in the models, as respiratory function typically mirrors motor function, although the correlation between the two is not perfect. The advisor noted that the requirement for respiratory support, including PV, is an important consideration particularly for patients with Type 1 SMA. Overall, the ERG considers that in terms of their characterisation of key SMA-related events and their impact on survival, the structure of the company's models is reasonable.

The ERG's clinical advisor also commented that, like many other neurodegenerative diseases, other aspects of SMA that are not captured in gross motor function milestones may also have important impacts on patients' HRQoL. In particular, whilst gaining the ability to walk is a very important milestone for people with SMA, for those patients who lose or never achieve ambulation, maintaining upper limb function becomes increasingly important as it means that they can still perform certain basic tasks and maintain some level of independence (for example, opening doors, using a tablet, opening

food packets, adjusting clothing or adjusting seating position). Losing or gaining upper limb function can therefore have a substantial impact on a patient's overall level of functioning, participation and independence, thereby leading to meaningful impacts on HRQoL. The ERG notes that these factors are not explicitly captured in the company's model health states, and it is unclear whether they are reflected in the patient utility estimates defined by motor milestone health states, in particular, the non-preference-based estimates provided by clinicians. In addition, whilst the company's models are defined according to gross motor skills, additional benefits in obtaining fine motor skills might apply within these broad motor milestone categories. For example, SUNFISH reported clinically meaningful improvements in fine motor function in the 12-month RULM total score, the MFM32 D3 and the SMAIS (see Section 4.2.4.1). As the company's model structures assume that health utility is dependent on gross motor milestone but independent of the treatment received, these additional health effects are not included in the company's models and the ICERs for risdiplam may be overestimated to an unknown degree.

The ERG also notes that the company's models are subject to some restrictive structural assumptions. As described in Section 5.2, the models are implemented as time-homogeneous Markov models which do not allow for event risks to be conditional on the time since entry into the model health states. This restrictive assumption has two main implications:

(1) Within the Type 1 SMA model, the company has estimated the monthly probability of requiring PV (an intermediate model health state) and dying in PV based on the assumption that the hazards of EFS and OS are constant (i.e. using exponential distributions for both endpoints). However, the company fitted other parametric survival distributions to the EFS and OS data which assume time-varying hazards (the Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions). If the company had selected any of these other models for EFS and/or OS, these could not have been included in the economic model as it cannot track patient history.
(2) Neither the Type 2/3 nor the Type SMA 1 models includes a discontinuation rule (see critical appraisal point [4]). If the company had wished to explore the impact of stopping treatment in patients with repeated loss of motor function, they could not have done so within the existing model structure. Again, this is because the model cannot track patient history.

Both of these limitations could have been avoided by including tunnel states; however, this would have increased the complexity of the models.

The model further assumes that only transitions to adjacent health states are possible. The predicted transition probabilities derived from the company's multistate models for both populations indicate that some patients transitioned by more than one state within a monthly cycle. [redacted]

[redacted]. In their clarification response[17] (questions B7 and B29), the company stated that these transitions to non-adjacent states *"violated our underlying clinical assumption and model structure."* Given that non-sequential transitions were observed in SUNFISH[22] and FIREFISH,[23] this indicates that the company's *a priori* assumption is incorrect and should be updated in light of the sample data. However, the ERG accepts that the numbers of transitions to non-adjacent states appear to be small and the impact on the ICER is likely to be minimal.

(4) Absence of formal discontinuation criteria for risdiplam

The company's models do not include any discontinuation from risdiplam, either in terms of natural discontinuation or a formal treatment stopping rule; instead, patients are assumed to remain on risdiplam until death, irrespective of whether they lose or ever gain motor milestones. In SUNFISH,[22] [redacted] patients discontinued treatment, whilst in FIREFISH,[23] [redacted] patients discontinued treatment. In their clarification response[17] (questions B9a and B32a), the company stated that discontinuation was excluded in *"an effort to keep the model[s] as simple as possible"* and based on clinical advice which suggested that the discontinuation rate for risdiplam in clinical practice was likely to be low. In addition, the company's clarification response highlights that outcomes following discontinuation of risdiplam are unknown. The summary of the company's clinical advisory board meetings[27] states that the attending clinical experts indicated [redacted] This indicates that some patients are likely to discontinue treatment.

The ERG's clinical advisor commented that treatment stopping criteria are useful for clinicians, as in their absence, it can be very difficult for clinicians to obtain agreement from patients and families to discontinue treatment if the patient is not obtaining benefit from it and it is clinically appropriate to do so. The ERG also comments more generally that continuing to administer an expensive treatment to patients who are not benefitting from it does not represent an efficient use of health care resources, and determining clinically appropriate discontinuation rules may improve the cost-effectiveness of treatment. The ERG believes that determining whether formal discontinuation criteria for risdiplam are appropriate is a matter for the company and NHS England. The ERG's clinical advisor commented that determining these criteria for risdiplam would be difficult, but considerations might include factors such as progression to PV, the incidence of AEs, and the repeated loss of motor function despite continued treatment. The clinical advisor also commented that non-sitters may still derive benefit from treatment if it helped to preserve upper limb function. [redacted]

[redacted]

As discussed in critical appraisal point [3], if such criteria were deemed appropriate, the company's existing model structures may require substantial revision in order to incorporate these.

(5) Use of unadjusted (naïve) arm-based indirect comparison in Type 1 SMA

The company's base case Type 1 SMA model applies relative treatment effects (HRs for time-to-event outcomes and ORs for motor milestone attainment) from unadjusted (naïve) indirect comparisons of FIREFISH[23] and ENDEAR.[25] Unadjusted arm-based indirect comparisons are likely to be biased because they do not have the protection that would otherwise be attained from randomisation i.e. that observed and unobserved variables that affect response are, on average, balanced between treatments. In Section 2.9.1 of the CS,[1] the company suggests that naïve indirect comparisons *"are expected to be less of a limitation"* because the FIREFISH and ENDEAR study populations "*were fairly similar*". However, in their clarification response[17] (question A25), the company stated, "*However, since FIREFISH also included patients with a more severe disease at baseline that were not included in ENDEAR, the population represented in FIREFISH was considered to be closer to the target population*." The ERG believes that whilst their unanchored MAICs are associated with a number of problems and potential biases, this approach should be preferred over naïve arm-based comparisons. In addition, the NICE Methods Guide[26] states that naïve indirect comparisons are not appropriate.

(6) Issues relating to time-to-event analysis

The ERG has a number of concerns regarding the company's modelling of time-to-event data and its incorporation within the economic models for Type 2/3 and Type 1 SMA.

(a) Overall survival and ventilation-free survival (Type 1 SMA model - applied in non-standing health states)

In general, MAICs of time-to-event data are used to estimate an adjusted HR or adjusted Kaplan-Meier survival functions in a population represented by the comparator treatment. An HR is interpreted as an average treatment effect over the duration of follow-up (i.e. in this case, 1-year) but not necessarily as a measure of the time-specific treatment effect over the lifetime of patients. Using an HR assumes that there is no treatment-by-time interaction over the lifetime of patients. Such an assumption would need justification, else allowance for structural uncertainty as well as parameter uncertainty is required. Nevertheless, the company's Type 1 SMA model makes the assumption of proportional hazards for EFS and OS over a time horizon of 90 years extrapolated from 12 months of sample data, albeit using unadjusted naïve comparisons. Nonetheless, the same concern regarding proportional hazards applies in both the base case and scenario analyses.

Section 2.9.1 of the CS[1] states that making inferences according to a population represented by the comparator treatment (ENDEAR) is "*expected to be less of a limitation in the comparison in Type 1 SMA, where study populations were fairly similar*". However, in their clarification response[17] (question A25), the company stated that the population represented in FIREFISH was expected to be closer to the target population. If it is believed that the treatment effect that is estimated relative to the comparator treatment is not consistent with the treatment effect in the target population, then the company could have referred to the methodology suggested in NICE TSD 18[82] for transposing indirect comparisons to other target populations. However, the ERG notes that this would not address the issue of whether it is reasonable to assume proportional hazards over the lifetime of patients.

The company assumed that the sample data on EFS (eight events) and OS (five events) from FIREFISH[23] were sufficient to estimate the underlying data generating process for risdiplam (i.e. the choice of probability distribution and the estimates of parameters associated with them). The company based its choice of parametric distribution on "*input from clinical experts and the long-term plausibility of the survival curves*" (clarification question,[17] question A25), goodness-of-fit statistics and log cumulative hazard plots. The ERG believes that the process that has been used is inappropriate and that it conflates the issue of structural uncertainty (i.e. what is known about the underlying hazard of an event) and parameter uncertainty (i.e. the ability to generate plausible parameter sets using sample data with or without experts' beliefs about uncertain quantities). A better approach would have been to elicit beliefs about the proportion of patients expected to survive as probability distributions at two distinct times. Strictly, if the elicitation was done with knowledge of the sample data from FIREFISH then the elicited quantities would represent current beliefs, else if it was done without knowledge of the sample data then the sample evidence could be used to update the prior beliefs. An important step in this process used to estimate parameter sets in survival models is to exclude implausible parameter sets i.e. those that imply that an implausible proportion of patients survive beyond unreasonable life years or that are associated with an implausible mean lifetime survival. Ultimately, the ERG does not accept that there is sufficient sample evidence alone with which to choose between models and to estimate their parameters. Hence, the ERG does not consider that the company's OS model estimated using the FIREFISH data is meaningful.

The company generated the BSC survival function by applying the inverse of the unadjusted HR to the fitted risdiplam survival function. This was done in an attempt to reflect the survival function for patients treated with BSC in a population represented by FIREFISH.[23] The ERG considers this to be inappropriate because: (a) it assumes that the risdiplam survival function has been estimated appropriately, and (b) it assumes proportional hazards. The ERG believes that a simpler and more direct approach would have been to quantify the BSC survival function based on an elicitation of experts' beliefs.

(b) Choice of base case Gompertz model to represent OS in Type 2 SMA OS (Type 2/3 SMA model - applied in non-standing health states, and Type 1 SMA model - applied in standing and walking states)
As described in Section 4.2.4.3, no patients died in SUNFISH.[22] The natural history mortality of Type 2 SMA patients was characterised using published evidence from six natural history studies.[9, 10, 48, 65-67] The company selected the Gompertz distribution fitted to the pooled dataset of pseudo-IPD from these studies based on goodness-of-fit statistics (AIC and BIC), visual comparison of the fitted parametric survival functions and the Kaplan-Meier survival function over the first 25 years and expert opinion on which survival function was associated with the most plausible long-term extrapolations (see Section 5.2.2.2).

The ERG notes that there did not appear to be any feedback from experts regarding the likely shape of the hazard function over time and the company did not present empirical hazard functions of the observed data within the CS[1] to support the model choice. Strictly, for a meaningful Gompertz survival function, the hazard is increasing over time. It is not clear why the company did not select the generalised gamma distribution given that there was strong evidence according to BIC that this distribution provided a better representation of the observed data. However, the ERG notes that applying the generalised gamma distribution in the Type 1 SMA model produces #DIV/0! errors which prevent the ICER from being calculated. The ERG also notes that whilst visual comparison of fitted parametric and Kaplan-Meier survival functions provides some information, it is not necessary that they coincide, and focusing on the central estimates ignores uncertainty in the estimates.

(c) Heterogeneity between studies in Type 2 OS model not adequately addressed (Type 2/3 and Type 1 SMA models)
The ERG believes that the two issues of structural uncertainty (i.e. the choice of parametric survival function) and parameter uncertainty are conflated. A particular probability distribution might be consistent with what is believed to be the true underlying hazard function and should not be dismissed because the fitted model generates implausible long-term predictions. Implausible long-term predictions might simply reflect uncertainty as a consequence of an insufficient number of events over the long-term. If so, this could be managed by introducing constraints at the analysis stage that omit implausible parameter sets.

The ERG considers it inappropriate to pool data from different studies without considering heterogeneity between them. Instead, the ERG believes that an appropriate use of the evidence from the natural history studies is to generate a meta-analytic predictive joint distribution of parameters with which to generate the required survival function and uncertainty about it.

In response to clarification question B13c,[17] the company performed Bayesian random effects meta-analyses of the study-specific joint distribution of the shape and scale parameters in Gompertz and Weibull distributions. Results were presented using summary statistics of the following uncertain parameters: study-specific population estimates of the shape and scale parameters; the mean shape and scale parameters of the random effects distribution; the between-study standard deviations of the shape and scale parameters and their correlation. Draws from the joint distribution of the mean shape and scale parameters of the random effects distribution were also provided to allow a PSA to be performed.

A Gompertz distribution is appropriate when the hazard increases over time so that $S(t) \to 0$ as $t \to \infty$; a negative value of the shape parameter, θ, implies that a proportion of people are immortal; a negative value of the scale parameter, λ, implies that the hazard of an event is negative until $\lambda > e^{\theta}$. In practice, values of λ and θ are generally restricted to a limited sample space and are highly correlated; the smaller the value of θ, the larger is the value of λ. The mode of a Gompertz distribution is:

$$\text{Mode}[X] = \frac{1}{\theta}\log\left(\frac{\theta}{\lambda}\right)$$

Hence, the mode is negative when $\theta < \lambda$ and is zero when $\theta = \lambda$, which implies that θ must be greater than λ for a plausible survival model.

The company's clarification response provided the CODA samples obtained from the model. Nearly 32% of the 10,000 parameter sets of the mean shape and scale parameters of the random effects distribution of the fitted Gompertz distribution included negative shape parameters and should have been excluded. It is clear from Figure 10 of the clarification response[17] (question B13) that this is a consequence of the study-specific parameters estimated for the Chung *et al.*[10] and Petit *et al.*[67] studies; this is acknowledged in the company's response. A benefit of using Markov Chain Monte Carlo (MCMC) simulation is the ability to include parameter constraints to exclude implausible values such as negative shape parameters. Similarly, a parameter constraint could have been imposed to exclude parameter sets that generate implausible values for mean survival. This would have avoided the suggestion based on the Mannaa *et al.* study[66] that a reasonably large proportion of patients will survive beyond 83 years. In their clarification response,[17] the company noted that 5.8% of patients are predicted to be alive at 100 years of age using their central estimates from the Gompertz random effects model without introducing plausible parameter constraints. The company did not generate the predictive joint distribution of the shape and scale parameters, which should also be constrained to allow only plausible parameter sets.

In the case of a Weibull distribution, the company stated that, "*3.4% of patients are predicted to be alive at 100 years of age using this model*". It would have been straightforward to incorporate constraints to exclude implausible parameter sets at the study level.

The ERG also notes that the central estimates of the survival functions are not computed correctly. The central estimate of a survival function is:

$$S(t) = E[\psi_t(\lambda, \theta)]$$

where $\psi_t(\lambda, \theta)$ represents the proportion of patients who survive at time t.

Whilst the company have attempted to address the ERG's concerns, the ERG does not believe that the resulting models are sufficiently robust for inclusion in the economic analysis. In particular, the joint distribution of parameters clearly includes implausible parameter sets that need to be omitted before considering whether it is a good model on which to make decisions.

(d) Assumed survival advantage for risdiplam in non-standing health states (Type 2/3 model)

The Type 2/3 model includes a survival advantage for risdiplam-treated patients in the non-standing health states, based on a fixed multiplication factor of 0.75 (relative to the mortality risk for BSC-treated patients), taken from the final later onset model used in TA588.[62] A more formal approach would have been to elicit beliefs about the proportion of patients expected to survival at two different times as probability distributions (or more precisely the difference between the proportion of patients expected to survive relative to the expected survival for patients treated with BSC and one time to induce correlation between parameters). This would make no assumption about the underlying hazard function and would allow uncertainty about parameters in survival models to be quantified. The ERG is unable to verify the extent to which the company's assumption represents reasonable plausibility.

(7) Concerns regarding methods used to elicit beliefs about uncertain quantities

A number of key assumptions included in the company's model are reported to be based on clinical input obtained from clinical experts at two UK advisory board meetings (see CS Appendix N[27]). [redacted] During these advisory board meetings, experts were asked their beliefs about uncertain quantities, but responses to questions were generally provided qualitatively rather than quantitatively, as would be the case in a formal elicitation of experts' beliefs. For example, in answer to the question whether [redacted] If a formal elicitation of experts' beliefs about uncertain quantities had instead been performed, it would have been clear to the experts that the expectation is not to provide exact quantities but to express genuine

uncertainty. In addition, whilst the experts stated that [redacted] Assuming no discontinuation when there is uncertainty about the true rate of uncertainty is inappropriate, although it is unclear what impact this has on the results. The ERG believes that, in addition to these examples, there are several other uncertain quantities that would have benefitted from performing a formal elicitation of experts' beliefs and/or a better representation of uncertainty.

(8) Highly optimistic assumptions of long-term treatment effects

The company's clarification response[17] (questions B7, B11 and B29) indicates that the multistate models fitted to data from SUNFISH[22] and FIREFISH[23] provide a reasonable fit to the observed data. However, the transition probabilities estimated using these models are overridden by assumptions in the subsequent period (after 2 years). Within the Type 2/3 SMA population, the company's model assumes that in the subsequent period, the probability of worsening is reduced by [redacted] for risdiplam-treated patients (relative to the initial period). Within the Type 1 SMA population, the model assumes that in the subsequent period, no risdiplam-treated patient can ever lose milestones; this model also assumes a probability of achieving walking which was not observed in FIREFISH. In both populations, patients are assumed to continue to gain additional motor milestones in the long-term. Both models are underpinned by two key assumptions: (1) that risdiplam will become more effective in the long-term compared with the period for which observed data are available, and; (2) the assumed increase in benefit will persist indefinitely over the patient's remaining lifetime.

The ERG has several concerns regarding these assumptions:

- According to the CS,[1] these assumptions were based on the views of clinical experts who attended two advisory board meetings. During the clarification round, the ERG requested the minutes of these meetings; however, these were not provided (see clarification response,[17] question B41). The only information provided to support these assumptions is the summary of the meetings provided in CS Appendix N.[27]
- The company's clarification response[17] (question B6) states that *"Following discussions, UK clinical experts agreed that the majority of SMA Type 2 or 3 patients receiving active treatment would be likely to maintain their health states or improve in the long-term, and that patients receiving BSC would only remain stable or deteriorate in the long-term."* However, CS Appendix N[27] reports that the company's advisors stated that [redacted] Individual responses from the company's advisors are not provided in the summary of the meetings provided in CS

Appendix N and the experts' estimates of the proportion of Type 2/3 and Type 1 SMA patients who might deteriorate despite treatment with risdiplam are not provided.

- It is unclear whether the [redacted] reduction in the probability of losing milestones in the Type 2/3 SMA model and the assumed probability of achieving walking in the Type 1 SMA model (the multiplier of 33% applied to the probability of transitioning from sitting to standing) are estimates which reflect the advice of the company's clinical advisors, or whether they were suggested by the company to the clinical advisors. Neither of these values is reported in CS Appendix N.[27]
- The company's clarification response[17] (question B6c) suggests that the 2-year timepoint at which the subsequent period assumptions are applied *"should be considered conservative in nature"* and highlights that this assumption is tested in the scenario analyses. However, the ERG considers that the selected timepoint is arbitrary and the only scenario tested uses a 1-year timepoint which is more optimistic than the base case scenario (see Table 31 and Table 41).
- All of the treatment effect assumptions applied in the subsequent period are assumed to be known with certainty and are held as fixed values in the PSA (see critical appraisal point [13]).
- Whilst it is clear from CS Appendix N[27] that the model assumptions were discussed with clinical experts in detail, it is not clear whether the experts were asked to comment on the plausibility of the resulting model traces given those assumptions.
- The ERG's clinical advisor considered the assumptions applied in the subsequent period in both models to be *"big assumptions"* and commented that there is considerable uncertainty around whether the treatment effects for risdiplam would persist in the long-term.
- The ERG also notes that the assumptions employed in the subsequent period are inconsistent with the final iterations of the models used in TA588[62] (see critical appraisal point [14]). The company's clarification response[17] (questions B10 and B31) argues that these long-term assumptions are *"not entirely different"* from those used in TA588 and comments that the proportion of patients remaining in the same health state after 2 years is *"extremely high"* through reference to the transition probabilities applied in the models. The ERG believes that this is misleading, as both of the risdiplam models predict that a substantial proportion of risdiplam-treated patients will reach and maintain the milestones of standing and walking within their lifetime, as shown in critical appraisal point [9], Figure 17 and Figure 20. Owing to these concerns, the ERG believes that the results of the company's economic analyses should be approached with considerable caution.

(9) Highly optimistic modelled predictions of motor milestone attainment and survival

As discussed in Section 4.2.4, there is considerably uncertainty surrounding the expected long-term motor function and survival gains for patients treated with risdiplam. Based on the latest data-cuts of SUNFISH[22] and FIREFISH,[23] the highest level of motor milestone attainment is as follows:

- In SUNFISH,[22] five patients in the risdiplam group gained the ability to stand or walk at Week 17 (one did not maintain the standing ability in Weeks 35 and 52, one did not maintain the walking ability in Weeks 35 and 52, but was able to stand, and one patient gained the ability to stand or walk at Week 52. No patients in the placebo group gained the ability to stand or walk. One patient in the risdiplam group gained the ability to walk at Week 17, but did not maintain walking ability in Weeks 35 and 52, and one patient gained the ability to walk at Week 52. No patients in the placebo group gained the ability to walk (clarification response,[17] question B7).
- In FIREFISH,[23] three infants achieved the milestone of standing and maintained this ability in subsequent visits (if available); two at Day 364 and 1 at Day 609. No infant achieved the milestone of walking (clarification response,[17] question B29).

Whilst the current evidence for the maximal motor milestone attainment and survival benefit on risdiplam is limited, the company's model suggests that a substantial proportion of risdiplam-treated patients will reach the milestones of standing and walking and that this will lead to considerable OS gains. This is a consequence of the assumptions described in critical appraisal point [8]. The ERG has a number of concerns regarding the plausibility of the company's modelled predictions of motor function and OS gains in both populations; these concerns are described for each model in turn below.

(a) Concerns regarding company's Type 2/3 SMA model predictions

The model-predicted proportions of Type 2/3 SMA patients who achieve the milestones of standing or walking for the BSC and risdiplam groups are shown in Figure 16 and Figure 17, respectively. Figure 18 presents a plot of model-predicted OS for risdiplam versus BSC.

Figure 16: Health state occupancy – standing/walking versus not standing/walking, Type 2/3 SMA – BSC group

Note – the dashed grey line (walking) is a subset of the solid grey line (standing or walking)

Figure 17: Health state occupancy – standing/walking versus not standing/walking, Type 2/3 SMA – risdiplam group

Note – the dashed grey line (walking) is a subset of the solid grey line (standing or walking)

Figure 18: Model-predicted survival, Type 2/3 SMA – risdiplam versus BSC

Note – the OS projection for the BSC group is slightly truncated due to the insufficient number of cycles included (see critical appraisal point [1d])

With respect to the company's modelled predictions of motor milestone trajectories and OS for BSC-treated Type 2/3 SMA patients, the ERG notes the following:

- The model indicates that a small proportion of patients are able to stand or walk at baseline, but that all surviving patients lose these milestones by around age 15 years (Figure 16, solid grey line).
- The ERG's clinical advisor commented that the company's assumption that BSC-treated patients will lose motor milestones over time is generally reasonable. However, it is not reasonable to assume that no patient over the age of 12 years (the age at which the subsequent period assumptions are applied) will ever achieve the milestones of standing or walking. In particular, some patients with Type 3 SMA may not yet have presented or developed symptoms by this age. The ERG's clinical advisor also noted that natural history studies show that with BSC alone, some Type 3 patients will retain the ability to stand and walk much longer than is suggested by the company's model. For example, Zerres *et al.*[9] report that 22% of Type 3a patients and 58.7% of Type 3b patients with a disease duration of 40 years remain ambulatory, whilst Chung *et al.*[10] report that 38% of Type 3a patients and 68% of Type 3b patients remain ambulatory at age 40 years. This indicates that the solid and dashed grey lines in Figure 16 should feature a longer tail. However, it would be unusual for Type 2 SMA patients, who

represent the majority of the target population, to reach the milestone of standing independently.

- The full model trace (not shown) suggests that over time, the vast majority of BSC-treated patients lose the ability to sit independently. The ERG's clinical advisor commented Type 3 patients who are ambulant at age 40 are unlikely to ever lose the ability to sit independently.
- The ERG's clinical advisor considered that the company's modelled estimates of OS for BSC (Figure 18, solid grey line) appear reasonable and noted that Type 3 patients who are ambulant at later ages will probably have an approximately normal life expectancy, although as noted above, this will represent only a small proportion of the broader Type 2/3 SMA patient population.

The ERG has more substantial concerns regarding the modelled predictions of motor milestone trajectories and OS for risdiplam-treated Type 2/3 SMA patients:

- The company's model indicates a substantially better motor milestone trajectory and marked improvements in OS for risdiplam compared with BSC (Figure 16, Figure 17 and Figure 18). This is largely a consequence of the assumption that the long-term probability of losing milestones is reduced by [redacted] in the subsequent period. This improved trajectory then leads to OS gains because patients spend longer in the standing/walking states.
- The company's model indicates that by age 35 years, [redacted] of risdiplam-treated patients will achieve standing or walking and by a similar age, [redacted] of patients will achieve walking (Figure 17, solid and dashed grey lines).
- The ERG's clinical advisor commented that there is no reason to believe that the treatment effect of risdiplam on motor function would be better in the long-term compared to the period for which observed data exist. They also noted that there is uncertainty around whether short-term benefits would be sustained. The clinical advisor further stated that it is unreasonable to expect that patients who have not previously been able to stand or walk will achieve these milestones at later ages, and many patients will develop contractures which would preclude standing and/or walking. As a consequence of these issues, the ERG considers that the predicted proportions of patients reaching the standing and walking states are likely to be very optimistic.
- Given that life expectancy for patients with Type 3 SMA is believed to be approximately the same as that for people without SMA, risdiplam would not be expected to extend survival in these patients and health gains would only relate to improved HRQoL due to better motor function. It is therefore likely that the cost-effectiveness of risdiplam would differ considerably between Type 2 and Type 3 SMA; however, the company's model does not allow for this aspect of heterogeneity to be assessed.

- In contrast to the optimistic assumptions regarding long-term motor function gains in the risdiplam models, the key assumption made in the final iteration of the models used to inform TA588[62] was that the treatment effect on gaining motor milestones plateaus after a maximum of 26 months. The Appraisal Committee considered this notion of a plateau in benefit to be clinically plausible. The ERG believes that given the available evidence for risdiplam, there is little justification for deviating from this previously accepted assumption. The ERG's clinical advisor agreed with this view. Applying an assumption of a plateau in motor function gains would substantially reduce the proportion of patients who reach the standing and walking states, thereby also reducing predicted modelled OS gains.

(b) Concerns regarding company's Type 1 SMA model predictions

The model-predicted proportions of Type 1 SMA patients who achieve the milestones of standing or walking for the BSC and risdiplam groups are shown in Figure 19 and Figure 20, respectively. Figure 21 presents a plot of model-predicted OS for risdiplam versus BSC in this population.

Figure 19: Health state occupancy – standing/walking versus not standing/walking, Type 1 SMA – BSC group

Note – the dashed grey line (walking) is a subset of the solid grey line (standing or walking). The proportions of patients standing or walking are approximately zero at all timepoints

Figure 20: Health state occupancy – standing/walking versus not standing/walking, Type 1 SMA – risdiplam group

Note – the dashed grey line (walking) is a subset of the solid grey line (standing or walking).

Figure 21: Model-predicted survival, Type 1 SMA – risdiplam versus BSC

With respect to the company's modelled predictions of motor milestone trajectories and OS for BSC-treated Type 1 SMA patients, the ERG notes the following:

- The model predicts that no patient will gain the ability to stand or walk (Figure 19). Model-predicted mean survival for BSC-treated patients is 10.11 years (Figure 21, solid grey line).
- The ERG's clinical advisor commented that the assumption that Type 1 SMA patients will worsen over time is appropriate and that no patients will reach the milestone of standing (Figure 19, solid black line declining, grey line not visible). The company's model predictions are in line with the clinical advisor's expectations in this respect.
- In terms of OS, the ERG's clinical advisor commented that the company's modelled OS for BSC (Figure 21, solid grey line) is not clinically realistic. Natural history studies[10, 48, 65, 67] indicate that around 70-80% of Type 1 patients will die by the age of 2 years, although survival in these patients has since improved as a consequence of a more aggressive treatment approach, including the increased use of respiratory support and PV. They also commented that whilst some Type 1 patients may have comparatively longer survival, it is hard to imagine that any Type 1 patients would survive to the ages of 50 or 60 years. Overall, the ERG considers the modelled OS estimates for BSC to be unrealistically high. This is likely to be a consequence of: (a) the use of the inverse HR from the company's unadjusted arm-based indirect comparison, and (b) the immaturity of the FIREFISH OS data used as the baseline model (based on 5 death events).[23]

The ERG has more substantial concerns regarding the modelled predictions of motor milestone trajectories and survival for risdiplam-treated Type 1 SMA patients:

- The company's model indicates a substantially improved motor milestone trajectory and marked improvements in OS for risdiplam compared with BSC (Figure 19, Figure 20 and Figure 21). This is a consequence of the assumption that no risdiplam-treated patient will lose motor milestones and no BSC-treated patient will gain motor milestones in the subsequent period (after 2 years). As such, all risdiplam-treated patients are assumed to be on a general trajectory of improvement towards the walking state. For example, by age 40 years, all surviving patients are predicted to be able to stand or walk. This, in turn, leads to large OS gains because risdiplam-treated patients spend longer in the standing/walking states.
- The company's model indicates that by age 16, around [redacted] of risdiplam-treated patients will achieve standing or walking and by age 29, [redacted] of patients will achieve walking (Figure 20, solid and dashed grey lines).
- The ERG's clinical advisor did not consider the company's model assumption of no worsening to be reasonable and commented that whilst patients might potentially become stable on

risdiplam, the assumption that patients would continue to gain milestones in the long-term was not reasonable.

- The ERG's clinical advisor commented that it was difficult to see how the short-term gains in patients achieving standing in FIREFISH[23] could translate to more than 20% of patients achieving walking in the long-term. The clinical advisor considered that in the absence of neonatal screening to detect people with pre-symptomatic SMA, it is likely that few risdiplam-treated patients would achieve this milestone, especially at later ages. [redacted].
- The ERG's clinical advisor commented that the company's modelled OS (Figure 21) appears somewhat optimistic given that these patients have Type 1 disease and because improving motor function in a Type 1 patient (e.g. with nusinersen) to that equivalent of someone who can sit (a Type 2 milestone) does not necessarily lead to the same survival outcome as that for a natural Type 2 patient.
- In contrast to the optimistic assumptions regarding long-term gains in motor function made in the risdiplam models, the key assumption made in the final iteration of the models used to inform TA588[62] was that the treatment effect on gaining motor milestones plateaus after a maximum of 66 months. The Appraisal Committee considered this notion of a plateau in benefit to be clinically plausible. Again, the ERG believes that there is little justification for deviating from this previously accepted assumption. Applying an assumption of a plateau in motor function gains would substantially reduce the proportion of patients who reach the standing and walking states, thereby also reducing predicted modelled OS gains.

(10) Issues relating to estimated patient utility values

Within the Type 2/3 SMA model, the company elected to use patient utility values from the EQ-5D vignette study reported by Lloyd *et al*.[68] According to the CS,[1] this source was selected *"to align with what was considered for final decision-making in the TA588 submission"* (CS, page 133). Whilst SUNFISH[22] included the measurement of HRQoL using the EQ-5D-5L, the clinicians consulted by the company did not consider the mapped EQ-5D-3L utility values to be reflective of the independence and gains in HRQoL associated with advances in each motor milestone. The CS includes scenario analyses using the Type 2/3 SMA model whereby patient utility values reflect the ERG's clinical advisors' non-preference-based estimates for the later onset model in TA588[75] and from SUNFISH[22] (see Table 31, Scenarios 8 and 9, respectively). Within the Type 1 SMA model, the company used the non-preference-based estimates for the early onset SMA population obtained from the ERG's clinical advisors in TA588.[75] The CS states that the company's clinical advisors preferred this source because the values reported by Lloyd *et al*, which included negative utility values (states valued worse than death), were

unlikely to be clinically plausible. The CS includes scenario analyses in which patient utility values for the Type 1 SMA model are taken from Lloyd *et al.*[68] (see Table 41, scenarios 12 and 13). In line with the approach used in TA588 and to avoid introducing additional uncertainty, utilities were not adjusted for age (see clarification response,[17] question B15).

The ERG notes that measuring and valuing health in infants and young children is very difficult and that gaining or losing motor milestones may have a differential impact on HRQoL as patients get older. In addition, other factors besides the achievement of gross motor milestones may impact on patients' HRQoL, as previously discussed in critical appraisal point [3].

The ERG agrees with the company's view that the mapped EQ-5D-3L estimates obtained from SUNFISH[22] lack face validity, as there are limited differences in utility between the motor milestone states and the mean values for all health states appear low (range [redacted] to [redacted]; CS[1] Table 66). The company's clarification response[17] (question B16) includes some discussion which postulates why the EQ-5D may be insensitive in mobility-impaired populations. The ERG does not believe that there is an ideal source of utilities which robustly reflects differences in HRQoL between motor milestones in people with SMA. Generally speaking, the choice regarding the most appropriate source of patient utility values in patients with SMA involves either selecting preference-based utility estimates which lack face validity (Lloyd *et al.*[68] or SUNFISH[22]), or using experts' non-preference-based estimates which lack scientific rigour. The ERG believes that the company's decision to use preference-based estimates for the Type 1 population and non-preference-based estimates for the Type 2 population is somewhat inconsistent – if it is appropriate to select the source of utility values on the basis of face validity in one SMA population, it appears inconsistent to apply different selection criteria in the other population.

The ERG also notes that whilst the CS[1] suggests that Lloyd *et al.*[68] was used in the Type 2/3 SMA model for consistency with TA588, the patient utility values used in the final iterations of both the early and later onset models were based on non-preference-based estimates obtained from Biogen's clinical advisors[62] (see TA588 guidance,[13] page 16). In TA588, the ERG concluded that given the problems associated with the existing preference-based utility estimates, this was the most appropriate approach. With the exception of the EQ-5D-3L estimates from SUNFISH,[22] the CS[1] does not present any new preference-based utility studies by motor milestone health state which were not previously considered in TA588. Therefore, the ERG believes that the estimates used in TA588 remain the most appropriate source for this appraisal. However, as discussed in TA588,[83] some caution is required when using clinicians' values as: (i) these are based on opinion rather than a formal elicitation of preferences for competing health states; (ii) the health states are defined only by the patient's level of gross motor milestone; (iii) different clinical advisors may suggest different valuations for the same health states,

and (iv) there is a possibility that the values obtained from the experts may not reflect the views of people with SMA or their carers.

(11) Issues relating to caregiver utility values

In TA588, the Appraisal Committee concluded that carer utilities are important and should be included in decision-making, but noted that quantifying these impacts is very difficult.[13] The ERG agrees with the company that caregiver impacts are also relevant to risdiplam.

The ERG believes that the company's estimate of 2.2 caregivers per patient, derived from their burden of illness study, may be reasonable, although the reporting of this analysis in CS Appendix P[27] is limited. For example, it is unclear whether the available data indicate that caregiver HRQoL impacts are the same or different between SMA types and/or the level of motor function achieved. The ERG's clinical advisor commented that losing or never achieving motor function milestones may lead to greater caregiver demands. In TA588,[62] the company's final models assumed 3 caregivers for each patient with early onset SMA, and 2 caregivers for each patient with later onset SMA (except in the worst health state where 3 caregivers was assumed).

The ERG's main concern relates to the dearth of evidence through which to estimate utility values for caregivers. Both the Type 2/3 and the Type 1 SMA models use a single value of caregiver HRQoL for SMA patients from a population of Spanish caregivers.[69] In line with the approach used in TA588,[62] this value is assumed to reflect caregiver utility for the worst health state in each model (not sitting [and PV in Type 1 SMA]). Caregiver utilities for the other health states are based on an assumption that HRQoL increases uniformly for patients in each adjacent improved health state up to a maximum value based on the level of HRQoL in the general population. This assumes that the relationship between a patient gaining/losing a milestone and caregiver HRQoL has interval properties whereby the gain or loss of any single milestone leads to an equal gain or loss in caregiver utility. It is unclear whether this assumption is reasonable.

Overall, the ERG considers that any estimate of caregiver QALY gains estimated from the company's model should be interpreted with caution as the caregiver utility values are largely driven by assumptions rather than evidence.

(12) Issues relating to costs

The company's clarification response[17] (questions B20 and B40) state that because risdiplam dosage is estimated by patient weight, costs resulting from drug wastage do not need to be included in the models.[1, 17] However, as risdiplam is an oral medication which is assumed to be given on a continuous lifetime basis, patients will incur wastage if they die part-way through a treatment cycle. The ERG

believes that it would be reasonable to assume that, on average, patients will waste half a bottle of risdiplam.

The ERG believes that the use of cost estimates from the Biogen RWE study[62] is appropriate and notes that this source was used in the final models in TA588.

The precise source of the assumption that health state costs in PV are equal to the costs for non-sitters multiplied by 175% is not clear from the CS.[1] The company's clarification response[17] (question B39) states that this assumption was informed by unpublished submission papers for the ongoing HST of AVXS-101 and a UK study of resource use and service costs of ventilator-dependent children and young people (Noyes *et al.*[84]). However, the ERG is unclear how this cost multiplier was estimated and whether it should be considered appropriate.

(13) Weak characterisation of parameter uncertainty

The ERG believes that the characterisation of uncertainty within both models is weak. In addition to the errors described in critical appraisal points [1e] and [1h], the ERG highlights the following problems in the company's PSA:

- No uncertainty is included around the key treatment effect assumptions/parameters employed in the company's models:
  - In the Type 2/3 SMA model, the [redacted] reduction in backward transition probabilities and the multiplication factor of 0.75 applied to Type 2 OS are not characterised as uncertain parameters.
  - In the Type 1 SMA model, the 0% probability of worsening for risdiplam, the assumed probability of reaching walking (33% of the probability of moving from siting to standing) and the 175% multiplication factor applied to estimate PV costs in both treatments groups are not characterised as uncertain parameters.
- The company has fitted multistate models to estimate transition probabilities. The uncertainty around these probabilities could have been estimated by bootstrapping the sampled parameter sets using the *boot.msm* function. Instead, the company's model samples the transition probabilities using Dirichlet distributions assuming that the observed data includes 100 patients in each row of the matrix and a prior of 1.0 for each permitted transition. This characterisation of uncertainty is arbitrary and does not reflect genuine uncertainty in the sample data.
- Standard errors (SEs) around the HRs from the indirect comparisons, health utility values and health state costs are arbitrarily defined as 20% of the mean, despite in some instances, SEs or 95% CIs being available from the original sources.

(14) Inconsistent assumptions compared with the final models used to inform NICE TA588

As discussed throughout this section, several aspects of the risdiplam models are inconsistent with the Appraisal Committee's final accepted assumptions within NICE TA588.[13] Table 44 presents a broad comparison of the key features of the final iteration of the models used to inform TA588 and the risdiplam models. Table 45 presents a comparison of model-predicted health outcomes in each SMA population represented by the TA588 models and the risdiplam models; as shown in the table, the predicted health gains differ substantially between the TA588 models and the risdiplam models. These differences are mostly driven by the following inconsistencies:

(1) The presence/absence of an assumption of a plateau in motor milestone attainment
(2) The absence of discontinuation criteria for risdiplam
(3) Unrealistically optimistic estimates of OS for patients receiving BSC in the Type 1 SMA risdiplam model (which in this case reduces the ICER for risdiplam due to high disease management costs and low mean utility in the BSC group)
(4) Inconsistent sources of patient utility values
(5) The error relating to approach used to estimate caregiver QALY impacts (see critical appraisal point [1]).

Whilst the ERG acknowledges that the TA588 models and the risdiplam models reflect different treatments which have not been formally compared, given the evidence available for risdiplam, the ERG does not consider it justifiable to deviate substantially from the Appraisal Committee's previously accepted assumptions in TA588. As shown in Table 45, these comparatively more favourable assumptions lead to substantially larger predicted QALY gains for risdiplam versus BSC.

Table 44: Comparison of key model features – risdiplam models versus final iteration of nusinersen models in TA588

Model features	Final iteration of models used to inform TA588 - early and later onset SMA[62, 83]	Risdiplam models - Type 1 and Type 2/3 SMA[1]	ERG comments
Structure	Early and later onset SMA models: Based on gross motor milestones (including not sitting, sitting, standing, walking). PV not explicitly included in either model. Includes sub-models of "improvers", "plateauers" and "worseners" and history of scoliosis surgery.	Type 1 and Type 2/3 SMA models: Based on gross motor milestones (including not sitting, sitting, standing, walking). PV included as additional state in Type 1 SMA model. Scoliosis excluded.	Broadly similar
Mortality risk	Early onset SMA model: Conditional on patient's current motor milestone. Separate Weibull models fitted to data from ENDEAR[25] (both groups) and SHINE (nusinersen group only). HR from trial applied and tapered over 120 months after end of observed period. Mortality adjustment factor of 0.75 applied to nusinersen group in states consistent with Type 2/3 SMA (sits without support to walks unaided). Later onset SMA model: Conditional on patient's current motor milestone. Flexible spline model (2-knots) based on Zerres *et al.*[9] and general population life tables.[85] Mortality adjustment factor of 0.75 applied to nusinersen group in states consistent with Type 3 SMA (stands unaided to walks unaided)	Type 1 SMA model: Conditional on patient's current motor milestone. Better survival assumed for standing and walking states (Type 2 SMA Gompertz model) versus not standing (exponential model fitted to FIREFISH data, with inverse HR applied to estimate BSC OS in non-sitters). Type 2/3 SMA model: Conditional on patient's current motor milestone. Better survival for standing and walking states (general population mortality[64]). Survival advantage assumed for risdiplam-treated Type 2 patients in non-standing states (Type 2 SMA Gompertz mortality risk applied in BSC group multiplied by 0.75).	Broad assumptions are similar. Nusinersen early onset model includes tapering of treatment effects on OS in worse states
Key assumptions regarding long-term trajectory through health states	Early onset SMA model: (a) Between Month 27 and Month 66, nusinersen-treated improvers can lose motor milestones (whilst remaining on treatment); (b) after Month 66, all nusinersen-treated improvers are subsequently assumed to plateau and cannot gain additional motor milestones. BSC patients cannot gain milestones in the extrapolation phase. Later onset SMA model: Between Months 15 and 27, nusinersen-treated improvers can lose motor milestones (whilst remaining on treatment); (b) after Month 27, no patient receiving nusinersen is assumed to gain additional motor milestones. BSC patients cannot gain milestones in the extrapolation phase.	Type 1 SMA model: After 2 years, risdiplam-treated patients cannot lose milestones (backward transitions to worse states are not possible in any model cycle). BSC patients cannot gain milestones after 2 years. Type 2/3 SMA model: After 2 years, risdiplam-treated patients have reduced probability of worsening (backward transitions to worse states reduced by [redacted] in all model cycles). BSC patients cannot gain milestones after 2 years.	Inconsistent approach in intervention groups BSC assumptions generally consistent

Stopping rules	Early onset: Patients discontinue if: (a) no milestones are achieved by end of Month 13, (b) patient cannot receive nusinersen treatment following scoliosis surgery, or (c) patient becomes a "worsener" Later onset: Patients discontinue if: (a) no milestones are achieved by end of Month 15, (b) patient cannot receive nusinersen treatment following scoliosis surgery, or (c) patient becomes a "worsener"	None	Inconsistent
Patient utilities	Both models: Company's experts' non-preference-based values[62]	Type 1 SMA - utilities based on ERG's advisors' non-preference based values[75] Type 2/3 SMA – utilities based on EQ-5D vignette study reported by Lloyd *et al*.[68]	Inconsistent
Caregiver utilities	Both models: Utility for worst motor function state based on TTO estimate for Spanish caregivers reported by Lopez-Bastida *et al.*[69] Utility for best motor function state assumed equal to general population utility.[70] Equal utility increments between states. Incremental QALY losses compared plus bereavement	Both models: Utility for worst motor function state based on TTO estimate for Spanish caregivers reported by Lopez-Bastida *et al.*[69] Utility for best motor function state assumed equal to general population utility.[70] Equal utility increments between states. Incremental QALY gains compared, no bereavement	Source consistent, caregiver QALY calculations inconsistent
Number of caregivers	Early onset SMA – 3 carers per SMA patient Later onset SMA – 3 carers per SMA patient in worst state, 2 carers in all other states	Both models: 2.2 caregivers per SMA patient	Inconsistent
Health state costs	Both models: Based on Biogen RWE study (Newcastle and GOSH only).[62] Type 1 non-sitter cost doubled.	Both models: Based on Biogen RWE study (Newcastle and GOSH only).[62] Type 1 non-sitter cost doubled. PV cost assumed equal to Type 1 SMA cost multiplied by 175%.	Generally consistent

SMA - spinal muscular atrophy; PV - permanent ventilation; HR - hazard ratio; OS - overall survival; BSC - best supportive care; EQ-5D - Euroqol 5-Dimensions; QALY - quality-adjusted life year; RWE - real world evidence; GOSH - Great Ormond Street Hospital; TTO – time-trade-off

Table 45: Comparison of model-predicted health outcomes – risdiplam models versus final iteration of nusinersen models in TA588

Early onset / Type 1 SMA						
Model-predicted outcome	**Final iteration of models used to inform TA588[83]**			**Risdiplam model[1]**		
	Nusinersen	**BSC**	**Incremental – nusinersen vs BSC**	**Risdiplam**	**BSC**	**Incremental – risdiplam vs BSC**
LYGs*	8.50	2.14	6.36	26.11	10.11	16.00
Patient QALYs	2.64	0.00	2.64	8.79	1.42	7.37
Caregiver QALYs†	-4.48	-2.60	-1.88	22.53	7.17	15.37
Later onset / Type 2/3 SMA						
Model-predicted outcome	**Final iteration of models used to inform TA588[83]**			**Risdiplam model[1]**		
	Nusinersen	**BSC**	**Incremental – nusinersen vs BSC**	**Risdiplam**	**BSC**	**Incremental – risdiplam vs BSC**
LYGs*	38.48	36.67	1.81	56.33	43.57	12.76
Patient QALYs	8.75	6.19	2.56	5.58	-1.98	7.56
Caregiver QALYs†	-9.02	-12.40	3.38	39.61	25.02	14.59

SMA - spinal muscular atrophy; TA - technology appraisal; BSC - best supportive care; LYG - life year gained; QALY - quality-adjusted life year
** Undiscounted*
† Note: Absolute caregiver QALYs should not be compared between the nusinersen and risdiplam models as the TA588 models estimated caregiver QALY losses, whereas the risdiplam models estimate absolute caregiver QALY gains. However, it is reasonable to compare incremental caregiver QALY gains

5.4 Exploratory analyses undertaken by the ERG

5.4.1 ERG exploratory analysis – methods

The ERG undertook exploratory analyses using both the Type 2/3 and Type 1 SMA models. These exploratory analyses differ slightly between the two models. The ERG's analyses include: correcting model errors (including the approach used to incremental caregiver QALY gains); applying relative treatment effects from the MAIC (Type 1 SMA model only); applying alternative patient utility values from TA588;[62] applying a higher caregiver burden for non-sitters (Type 2/3 model only); including costs of wastage, and assuming a plateau in motor milestone attainment for risdiplam. The ERG's preferred analyses include all of these amendments.

Additional sensitivity analyses were undertaken using the ERG's preferred models to explore the impact of: including additional patient utility gains associated with gains in fine motor skills for risdiplam and alternative assumptions regarding long-term motor milestone trajectories for risdiplam, including the possibility of worsening. It should be noted that there are some issues which could not be resolved within the ERG's exploratory analyses, in particular: the inclusion of clinically appropriate discontinuation criteria, a more appropriate representation of uncertainty around model parameters and

separate subgroup analyses of the cost-effectiveness of risdiplam in patients with Type 2 and Type 3 SMA.

All analyses were undertaken using the deterministic versions of the company's original models; the ERG believes that substantial revisions would be required in order for the company's PSA to generate meaningful results.

The exploratory analyses were implemented by two modellers to ensure that they are free from errors.

ERG Exploratory Analysis 1: Correction of model errors

As detailed in Section 5.3.4, critical appraisal point [1], the ERG identified several errors in the company's Type 2/3 and Type 1 SMA models; the following corrections were made to the company's models:

1(a) Subsequent period assumptions employed after 24 months (both models)

The model was amended such that the subsequent period transition matrices are applied one month later than the timepoint used in the company's base case models (i.e. after 24 months rather than 23 months).

1(b) Corrected general population mortality model (Type 2/3 SMA model only)

General population mortality risk was re-estimated based on the proportion of males and females in SUNFISH[22] at baseline, using the 2017-2019 life tables for England.[86] This revised mortality model treats the annual life table mortality risks (*"qx"*) as probabilities and estimates the relevant probabilities for the patient's current age in each cycle.

1(c) BSC extended to include 1,080 cycles (Type 2/3 SMA model only)

The BSC group of the Type 2/3 SMA model was extended to include 1,080 monthly cycles.

1(d) Valuation of incremental caregiver QALY losses avoided (both models)

The models were amended to estimate incremental caregiver QALY losses avoided for risdiplam versus BSC. Caregiver QALY losses in each cycle were estimated as the caregiver disutility for each motor milestone health state (relative to general population utility[70]) multiplied by the number of caregivers multiplied by the cycle duration. This approach avoids the company's implicit assumption that caregivers accrue no further QALYs after the patient dies. In line with TA588,[62] general population utility is not adjusted for increasing age.

All other exploratory analyses undertaken by the ERG include these model corrections.

ERG Exploratory Analysis 2: Use of relative treatment effects obtained from company's MAIC (Type 1 SMA model only)

Within this analysis, the company's Type 1 SMA model was amended to use HRs from the company's updated MAIC (risdiplam versus BSC: HR for OS=1/[redacted]; HR for EFS=1/[redacted]; see Table 18) and ORs for motor milestones derived from the company's original MAIC[1] (see Section 4.4).

ERG Exploratory Analysis 3: Use of utility estimates from company's clinical advisors in TA588

Within this exploratory analysis, the company's Type 2/3 and Type 1 SMA models were amended to reflect the patient utility estimates obtained from Biogen's clinical advisors in NICE TA588.[62] The ERG qualitatively mapped these values to the risdiplam model health states with input from the ERG's clinical advisor (see Table 46).

Table 46: Patient utility values applied in ERG's exploratory analyses

Type 2/3 SMA model			
Model health state	**Company's model (Lloyd *et al.*[68])**	**ERG exploratory analysis (TA588,[62] Biogen's clinical advisors)**	**ERG's assumptions applied in exploratory analysis**
(i) Not sitting	-0.17	0.20	Assumed equal to moderate milestones in early onset model in TA588[62]
(ii) Sitting (supported)	0.04	0.40	Assumed equal to sits but does not roll in TA588[62]
(iii) Sitting (unsupported)	0.04	0.50	Assumed equal to sits and crawls on hands and knees in TA588[62]
(iv) Standing	0.56	0.70	Assumed equal to stands/walks with assistance in TA588[62]
(v) Walking	0.56	0.85	Assumed equivalent to stands and walks unaided in TA588[62]
Type 1 SMA model			
Model health state	**Company's model (TA588,[68] ERG's clinical advisors)**	**ERG exploratory analysis (TA588,[62] Biogen's clinical advisors)**	**ERG's assumptions on utility estimates applied in exploratory analysis**
(i) Not sitting	0.25	0.10	Assumed equal to mild milestones achieved in TA588[62]
(ii) PV	0.20	-0.02	Assumed equal to no milestones achieved in TA588[62]
(iii) Sitting	0.48	0.20	Assumed equal to moderate milestones achieved in TA588[62]
(iv) Standing	0.75	0.70	Assumed equal to midpoint of stands with assistance and walks with assistance in TA588[62]
(v) Walking	0.80	0.85	Assumed equal to walks unaided in TA588[62]

ERG - Evidence Review Group; TA - technology appraisal; PV - permanent ventilation

In addition, two further amendments were applied within the Type 2/3 model for consistency with the final model used in TA588:[62]

(a) The number of caregivers was increased to 3 for patients who are unable to sit.
(b) Caregiver utility for the standing and walking states was set equal to general population utility (utility=0.915; disutility=0). The caregiver utility value applied in the worst health state (not sitting) was assumed to be 0.70 (disutility=0.215). Caregiver utility values for intermediate states were re-estimated assuming an equal utility gain for each successive milestone achieved.

ERG Exploratory Analysis 4: Inclusion of treatment benefit plateau for risdiplam

In order to be broadly consistent with the final iterations of the models in TA588,[62] a plateau in treatment benefit was applied after Month 26 in the Type 2/3 SMA model and after Month 66 in the Type 1 SMA model. Following this timepoint, no risdiplam-treated patient is assumed to subsequently gain or lose milestones.

ERG Exploratory Analysis 5: Inclusion of risdiplam drug wastage costs (0.5 bottles per patient)

Within this analysis, the cost of drug wastage was included for all patients who initiate treatment with risdiplam. This was applied as the undiscounted cost of 0.5 bottles per patient.

ERG Exploratory Analysis 6: ERG-preferred analysis

The ERG's preferred analysis includes ERG Exploratory Analyses 1-5.

Four sets of additional sensitivity analyses were conducted using the ERG's preferred versions of the company's models.

ERG Additional Sensitivity Analysis 1: Inclusion of additional HRQoL benefits

Within the risdiplam group, additional patient utility gains of 0.05 and 0.10 were applied to the non-sitting and sitting states, respectively. These values were taken from Thokala *et al.*[61] and are intended to reflect potential benefits in risdiplam-treated patients gaining fine motor skills. It should be noted that these values reflect assumptions made by the study investigators rather than preference-based utility estimates; as such, the results of this analyses should be interpreted with caution.

ERG Additional Sensitivity 2: Alternative assumptions regarding the probability of risdiplam-treated patients worsening

Two additional scenarios were explored whereby following the assumed treatment benefit plateau: (a) 1% of risdiplam-treated patients lose a milestone in each monthly cycle; (b) 2% of risdiplam-treated patients lose a milestone in each monthly cycle. It should be noted that these values are somewhat arbitrary and the true proportion of risdiplam-treated patients who worsen in the long-term is unknown.

ERG Additional Sensitivity 3: Alternative timepoints for assumed treatment benefit plateau

Additional scenarios were explored whereby the timepoint at which the assumed treatment benefit plateau is applied was amended to be: (a) 1-year later, and (b) 1-year earlier.

ERG Additional Sensitivity 4: Initial period transition matrices applied without adjustments until assumed plateau point

A further analysis was undertaken whereby the assumed reduction in the probability of worsening on risdiplam ([redacted] in Type 2/3 SMA and 100% in Type 1 SMA) was removed prior to the assumed timepoint of plateau.

5.4.2 Exploratory analysis results

This section presents the results of the ERG's exploratory analyses. All results include the PAS for risdiplam.

5.4.3.1 ERG exploratory analysis results: Type 2/3 SMA model

Table 47 presents the results of the ERG's exploratory analyses for the Type 2/3 SMA population. As shown in the table, the correction of errors (EA1) increases the company's original base case ICER (including caregiver QALYs) from [redacted] to [redacted] per QALY gained; this is largely a consequence of the inclusion of incremental caregiver QALY losses which apply only whilst the SMA patient is alive. The inclusion of an assumed treatment benefit plateau after 26 months (EA4) leads to a markedly higher ICER of [redacted] per QALY gained. The use of health utility assumptions which are consistent with TA588 and the inclusion of drug wastage (EA3 and EA5) do not substantially increase the ICER for risdiplam. The ERG's preferred analysis (EA6), which includes all of the ERG's individual exploratory analyses, results in an ICER for risdiplam versus BSC of [redacted] per QALY gained. When incremental caregiver health impacts are excluded from the analysis, the ICER for risdiplam versus BSC is estimated to be [redacted] per QALY gained.

Compared with the company's base case Type 2/3 SMA model, the ERG's preferred analysis leads to a considerably higher ICER for risdiplam versus BSC because: (a) patients are no longer assumed to gain milestones indefinitely; (b) lesser motor milestone gains reduce the expected OS and QALY gains for risdiplam; (c) incremental caregiver QALYs gains are reduced because caregivers are assumed to only lose QALYs whilst the SMA patient is alive, and (d) whilst risdiplam acquisition costs are lower due to a comparatively lower expected survival duration, total disease management costs are increased.

Table 47: Results of ERG exploratory analyses and preferred analysis, Type 2/3 SMA model

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs total	Costs	ICER (patients)	ICER (patients +carers)
Company's base case model							
Risdiplam	56.33	5.58	39.61	45.19	[redacted]	-	-
BSC	43.57	-1.98	25.02	23.04	[redacted]	-	-
Incremental	12.76	7.56	14.59	22.15	[redacted]	[redacted]	[redacted]
EA1: Correction of errors							
Risdiplam	56.61	5.58	-6.95	-1.38	[redacted]	-	-
BSC	43.77	-1.98	-15.87	-17.85	[redacted]	-	-
Incremental	12.83	7.56	8.92	16.48	[redacted]	[redacted]	[redacted]
EA3: TA588 patient utility values and number of caregivers =3 for non-sitters							
Risdiplam	56.61	14.07	-2.42	11.64	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	12.83	8.09	7.63	15.72	[redacted]	[redacted]	[redacted]
EA4: Assumption of treatment plateau after 26 months							
Risdiplam	50.20	2.55	-8.71	-6.16	[redacted]	-	-
BSC	43.77	-1.98	-15.87	-17.85	[redacted]	-	-
Incremental	6.42	4.53	7.16	11.70	[redacted]	[redacted]	[redacted]
EA5: Inclusion of drug wastage (0.50 bottles)							
Risdiplam	56.61	5.58	-6.95	-1.38	[redacted]	-	-
BSC	43.77	-1.98	-15.87	-17.85	[redacted]	-	-
Incremental	12.83	7.56	8.92	16.48	[redacted]	[redacted]	[redacted]
EA6: ERG-preferred analysis							
Risdiplam	50.20	11.42	-3.60	7.82	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.42	5.44	6.45	11.89	[redacted]	[redacted]	[redacted]

EA – exploratory analysis; LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; TA – technology appraisal; ERG – Evidence Review Group
** Undiscounted*

Table 48 presents the results of the ERG's additional sensitivity analyses using the ERG's preferred Type 2/3 model. These analyses indicate that the ICER may be markedly higher if patients lose motor milestones in the long-term (ASA2). The inclusion of additional treatment-specific utility gains for risdiplam-treated patients could lead to some improvement in the ICER for risdiplam (ASA1). The timepoint at which the treatment benefit plateau is applied and the assumption of a reduced probability of worsening prior to that plateau timepoint do not appear to be key drivers of the ICER (ASA3 and ASA4).

Table 48: Results of ERG additional sensitivity analyses, Type 2/3 SMA model

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs total	Costs	ICER (patients)	ICER (patients +carers)
EA6: ERG-preferred analysis							
Risdiplam	50.20	11.42	-3.60	7.82	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.42	5.44	6.45	11.89	[redacted]	[redacted]	[redacted]
ASA1: Additional utility gains for non-sitters and sitters							
Risdiplam	50.20	13.22	-3.60	9.62	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.42	7.24	6.45	13.69	[redacted]	[redacted]	[redacted]
ASA2a: Risdiplam worsening probability =1% per month							
Risdiplam	47.37	7.69	-8.59	-0.90	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	3.59	1.71	1.47	3.18	[redacted]	[redacted]	[redacted]
ASA2b: Risdiplam worsening probability =2% per month							
Risdiplam	47.11	6.60	-10.19	-3.60	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	3.33	0.62	-0.14	0.48	[redacted]	[redacted]	[redacted]
ASA3a: Assumption of treatment plateau after 38 months							
Risdiplam	50.97	11.87	-3.26	8.61	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	7.20	5.89	6.80	12.68	[redacted]	[redacted]	[redacted]
ASA3b: Assumption of treatment plateau after 14 months							
Risdiplam	50.15	11.40	-3.63	7.77	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.38	5.42	6.42	11.84	[redacted]	[redacted]	[redacted]
ASA4: Initial period transition probabilities applied without adjustments until plateau timepoint							
Risdiplam	50.04	11.31	-3.71	7.60	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.27	5.33	6.35	11.68	[redacted]	[redacted]	[redacted]

ASA - additional sensitivity analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

5.4.3.2 ERG exploratory analysis results: Type 1 SMA model

Table 49 presents the results of the ERG's exploratory analyses for the Type 1 SMA population. As shown in the table, the correction of errors (EA1) increases the company's original base case ICER (including caregiver QALYs) from [redacted] to [redacted] per QALY gained; again, this is largely a consequence of the inclusion of incremental caregiver QALY losses which apply only whilst the SMA patient is alive. The inclusion of treatment effects from the company's MAIC (EA2) substantially increases the ICER to [redacted] per QALY gained. The inclusion of an assumed treatment benefit plateau after 66 months (EA4) increases the ICER for risdiplam to [redacted] per QALY gained. The use of health utility assumptions which are consistent with TA588[62] and the inclusion of drug wastage (EA3 and EA5) have a minor impact on the ICER. The ERG's preferred analysis (EA6), which includes all of the ERG's individual exploratory analyses, results in an ICER for risdiplam versus BSC of [redacted]

per QALY gained. When incremental caregiver health impacts are excluded from the analysis, the ICER for risdiplam versus BSC is estimated to be [redacted] per QALY gained; this is lower than the ICER for the analysis including caregiver QALYs because the incremental caregiver QALY gains are negative.

Compared with the company's base case Type 1 SMA model, the ERG's preferred analysis leads to a considerably higher ICER for risdiplam versus BSC because: (a) patients are no longer assumed to gain milestones indefinitely; (b) lesser motor milestone gains reduce the expected OS and QALY gains for risdiplam; (c) caregivers are assumed to only lose QALYs whilst the SMA patient is alive and BSC-treated patients have a low expected survival duration; (d) whilst risdiplam acquisition costs are lower due to a comparatively lower expected survival duration, total disease management costs are increased, and (e) disease management costs for BSC are lower because mean survival in this group is lower.

Table 49: Results of ERG exploratory analyses and preferred analysis, Type 1 SMA model

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs total	Costs	ICER (patients)	ICER (patients +carers)
Company's base case model							
Risdiplam	26.11	8.79	22.53	31.33	[redacted]	-	-
BSC	10.11	1.42	7.17	8.59	[redacted]	-	-
Incremental	16.00	7.37	15.37	22.74	[redacted]	[redacted]	[redacted]
EA1: Correction of errors							
Risdiplam	26.05	8.76	-5.63	3.13	[redacted]	-	-
BSC	10.11	1.42	-6.32	-4.90	[redacted]	-	-
Incremental	15.94	7.34	0.69	8.03	[redacted]	[redacted]	[redacted]
EA2: Inclusion of treatment effects estimated from MAIC							
Risdiplam	26.05	8.76	-5.63	3.13	[redacted]	-	-
BSC	4.88	0.71	-3.14	-2.43	[redacted]	-	-
Incremental	21.17	8.05	-2.49	5.57	[redacted]	[redacted]	[redacted]
EA3: TA588 patient utility values							
Risdiplam	26.05	7.21	-5.63	1.58	[redacted]	-	-
BSC	10.11	0.02	-6.32	-6.31	[redacted]	-	-
Incremental	15.94	7.19	0.69	7.88	[redacted]	[redacted]	[redacted]
EA4: Assumption of treatment plateau after 66 months							
Risdiplam	21.68	6.98	-6.68	0.30	[redacted]	-	-
BSC	10.11	1.42	-6.32	-4.90	[redacted]	-	-
Incremental	11.57	5.56	-0.36	5.20	[redacted]	[redacted]	[redacted]
EA5: Inclusion of drug wastage (0.50 bottles)							
Risdiplam	26.05	8.76	-5.63	3.13	[redacted]	-	-
BSC	10.11	1.42	-6.32	-4.90	[redacted]	-	-
Incremental	15.94	7.34	0.69	8.03	[redacted]	[redacted]	[redacted]
EA6: ERG-preferred analysis							
Risdiplam	21.68	4.77	-6.68	-1.91	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	16.80	4.75	-3.54	1.21	[redacted]	[redacted]	[redacted]

EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; MAIC - matching-adjusted indirect comparison; TA - technology appraisal; ERG - Evidence Review Group
** Undiscounted*

Table 50 presents the results of the ERG's additional sensitivity analyses using the ERG's preferred Type 1 model. These additional sensitivity analyses indicate that the ICER for risdiplam in Type 1 SMA is highly sensitive to assumptions regarding treatment-specific utility gains, loss of motor milestones on risdiplam, the timepoint at which the assumed plateau in benefit is applied and the assumption of no worsening prior to that point (ASA1, ASA2, ASA3 and ASA4). Under pessimistic assumptions, risdiplam is [redacted]

Table 50: Results of ERG additional sensitivity analyses, Type 1 SMA model

Option	LYGs*	QALYs -patients	QALYs - carers	QALYs total	Costs	ICER (patients)	ICER (patients +carers)
EA6: ERG-preferred analysis							
Risdiplam	21.68	4.77	-6.68	-1.91	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	16.80	4.75	-3.54	1.21	[redacted]	[redacted]	[redacted]
ASA1: Additional utility gains for non-sitters and sitters							
Risdiplam	21.68	5.47	-6.68	-1.21	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	16.80	5.45	-3.54	1.91	[redacted]	[redacted]	[redacted]
ASA2a: Risdiplam worsening probability =1% per month							
Risdiplam	18.24	2.63	-7.88	-5.25	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	13.36	2.61	-4.73	-2.12	[redacted]	[redacted]	[redacted]
ASA2b: Risdiplam worsening probability =2% per month							
Risdiplam	17.45	2.01	-8.22	-6.22	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	12.57	1.99	-5.08	-3.09	[redacted]	[redacted]	[redacted]
ASA3a: Assumption of treatment plateau after 78 months							
Risdiplam	22.54	5.20	-6.61	-1.41	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	17.66	5.18	-3.47	1.72	[redacted]	[redacted]	[redacted]
ASA3b: Assumption of treatment plateau after 54 months							
Risdiplam	20.62	4.24	-6.76	-2.52	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	15.74	4.22	-3.62	0.60	[redacted]	[redacted]	[redacted]
ASA4: Initial period transition probabilities applied without adjustments until plateau timepoint							
Risdiplam	17.24	2.50	-7.06	-4.56	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	12.36	2.48	-3.92	-1.44	[redacted]	[redacted]	[redacted]

ASA - additional sensitivity analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

5.5 Discussion

The company's SLR did not identify any existing economic analyses of risdiplam for the treatment of SMA.

The CS[1] presents the methods and results of two separate economic models of risdiplam versus BSC for Type 2/3 and Type 1 SMA. Both models adopt a state transition approach, with health states defined according to motor milestone health states (sitting, standing and walking), survival status and the requirement for PV (Type 1 SMA model only). Survival is assumed to be conditional on the patient's current motor milestone health state, with an additional survival benefit assumed for risdiplam in the non-standing states for risdiplam in the Type 2/3 model. Both analyses estimate the incremental cost-effectiveness of risdiplam versus BSC from the perspective of the NHS, including absolute health gains accrued by SMA patients and their caregivers. The company has proposed a PAS which takes the form of a simple price discount of [redacted]. Both models assume that patients remain on treatment with risdiplam indefinitely, irrespective of whether they gain, maintain or lose motor milestones.

Within the Type 2/3 SMA model, monthly transition probabilities applied during the initial period (up to 2 years) are informed by transition probabilities derived from a multistate model fitted to clinical data from the SUNFISH trial.[22] Survival is assumed to be improved in patients who are able to stand or walk; mortality risks are based on external data[9, 10, 48, 65-67] and assumptions. During the subsequent period (after 2 years), the probability of risdiplam-treated patients worsening estimated from the multistate model is assumed to be reduced by [redacted]. This assumption is applied indefinitely. This model predicts that by age 35 years, around [redacted] of risdiplam-treated patients will be able to stand or walk and [redacted] of patients will be able to walk. As a consequence of this improved motor milestone trajectory, the model predicts that risdiplam is associated with an incremental OS gain of 12.76 years relative to BSC.

Within the Type 1 SMA model, monthly transition probabilities for risdiplam-treated patients applied during the initial period (up to 2 years) are informed by clinical data from FIREFISH,[23] together with an assumption that a proportion of patients who can stand will achieve walking after 18 months. Transition probabilities for BSC-treated patients are based on an unadjusted arm-based indirect comparison of data from FIREFISH[23] and the placebo arm of ENDEAR.[56] Survival is assumed to be improved in patients who are able to stand or walk; mortality risks are based on FIREFISH,[56] the company's indirect comparison[1] and other external data.[9, 10, 48, 65-67] During the subsequent period (after 2 years), the probability that risdiplam-treated patients worsen is assumed to be zero. This assumption is applied indefinitely. This model predicts that by age 16, around [redacted] of risdiplam-treated patients will be able to stand or walk and by age 29 years, [redacted] of patients will be able to walk. As a consequence of this improved motor milestone trajectory, the model predicts that risdiplam is associated with an incremental OS gain of 16.00 years relative to BSC.

The deterministic versions of the company's models suggest that the ICER for risdiplam versus BSC is [redacted] per QALY gained in the Type 2/3 SMA population and [redacted] per QALY gained in the Type 1 SMA population.

The ERG critically appraised the company's health economic analyses and double-programmed the deterministic versions of the company's original models for each SMA population. The ERG's critical appraisal identified several issues relating to the company's models and the evidence used to inform their parameters. These include: (i) the presence of model errors, in particular the implicit assumption that caregivers accrue no further health gains after the SMA patient dies; (ii) the use of unadjusted (naïve) arm-based comparisons (Type 1 SMA model only); (iii) the use of highly optimistic assumptions regarding treatment benefits; (iv) highly optimistic predictions of the proportions of risdiplam-treated patients who become able to stand and walk; (v) the absence of formal discontinuation criteria for risdiplam, and (vi) the use of patient utility values which are inconsistent with the final models used in TA588.

The ERG undertook exploratory analyses using both the Type 2/3 and Type 1 SMA models. These included: correcting model errors; applying relative treatment effects from the MAIC (Type 1 SMA model only); applying alternative patient utility values from TA588;[62] applying a higher caregiver burden for non-sitters (Type 2/3 model only); including costs of wastage, and assuming a plateau in motor milestone attainment for risdiplam which is consistent with the final models used to inform TA588. The ERG's preferred analyses include all of these amendments. Within the Type 2/3 SMA population, the ERG's preferred analysis suggests that the deterministic ICER for risdiplam versus BSC is [redacted] per QALY gained. Within the Type 1 SMA population, the ERG's preferred analysis suggests that the deterministic ICER for risdiplam versus BSC is [redacted] per QALY gained. The key drivers of these higher ICERs are: the correction of the error relating to valuing caregiver health gains; the use of the company's MAIC (Type 1 SMA only), and the inclusion of the assumption of a treatment benefit plateau in both SMA populations.

The ERG considers that the development of clinically appropriate discontinuation criteria could improve the cost-effectiveness of risdiplam. In addition, the ERG notes that the cost-effectiveness of risdiplam in patients with Type 3 SMA, whereby the propensity to extend survival is limited, is unknown.

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] argues that NICE's EoL criteria should apply to the Type 1 SMA population. Whilst the company acknowledges that the criteria are unlikely to apply for Type 2/3 SMA patients, the company argues that decision modifiers should be taken into account *"to recognise that SMA is a severe and rare condition, with a broad impact on patients, many of whom are children and people with disabilities, and their carers" (CS,*[1] page 90).

The company's arguments for applying the criteria within the Type 1 SMA population are summarised below.

Life expectancy criterion (<24 months)

- The EoL criteria were recognised in TA588.[13]
- An extensive review of natural history studies in Type 1 SMA undertaken in TA588 demonstrated that the mean or median age of death or permanent respiratory support is less than 24 months.
- Natural history studies in infantile-onset SMA demonstrate that 50% of infants, who only have two copies of SMN2 gene will die or require permanent daily non-invasive ventilation support by 10.5 months of age, increasing to 92% for Type 1 toddlers by 20 months of age.[49] In other clinical trials and natural history studies in Type 1 SMA patients, the median age to death or permanent respiratory support is reported to be approximately 9 to 13 months.[49, 87, 88]
- The predicted median age of death or PV in the company's Type 1 SMA model is 10 months.

Life extension criterion (≥3 months)

- In FIREFISH,[23] 92.7% of patients (90% CI: 82.2%, 97.1%) were still alive at 12 months. This is significantly higher than the pre-specified performance criterion of 60%, based on natural history studies.
- The company's Type 1 SMA model predicts a mean survival gain of 7.29 years.

With respect to these arguments, the ERG makes the following observations:

- Advances in BSC, including the more aggressive use of respiratory support has increased expected survival in patients with Type 1 SMA. Given the greater use of respiratory support, mean survival in Type 1 SMA is likely to be greater than 2 years. However, natural history studies indicate that in the absence of ventilation support, mean survival is likely to be less than 2 years.
- In TA588,[13] the Appraisal Committee considered it reasonable to accept that nusinersen could meet the short life-expectancy criterion for early-onset SMA.
- The availability of nusinersen through the MAA[13] is expected to increase mean survival duration in people with Type 1 SMA; however, nusinersen is not included as a comparator for risdiplam in this appraisal.
- The company's Type 1 SMA model predicts a mean survival duration of 10.11 years for BSC (see Table 40). However, the ERG does not consider the company's modelled OS estimates for BSC to be plausible.
- The model-based estimate of incremental OS for risdiplam cited by the company refers to discounted LYGs. The company's Type 1 model predicts a higher undiscounted incremental OS gain of 16.00 years (see Table 40). Whilst the ERG considers this estimate to be highly optimistic, it is likely that risdiplam will extend mean OS by more than 3 months.

On the basis of these issues, the ERG is unclear whether NICE's EoL criteria should be applied in Type 1 SMA. The ERG does not believe that the criteria apply to patients with Type 2/3 SMA.

7 OVERALL CONCLUSIONS

Clinical effectiveness conclusions

The clinical evidence relating to risdiplam for treating SMA is based on the SUNFISH RCT (Part 2) in Type 2/3 SMA, and the FIREFISH single-arm study (Part 2) in Type 1 SMA. The ERG's clinical advisor confirmed that the eligibility criteria for both SUNFISH and FIREFISH are representative of the Type 2/3 and Type 1 SMA patients seen in routine clinical practice in England. In the SUNFISH trial, there was a greater improvement in motor function, as assessed by MFM32 total score, from baseline to Month 12 in the risdiplam arm (least squares mean change 1.36 [SE 0.38]) than in the placebo arm (least squares mean change -0.19 [SE 0.52]), which showed a slight decline in function. There were small, clinically meaningful improvements from baseline to Month 12 in the risdiplam arm relative to the placebo arm in motor function as assessed by the total HMFSE score, upper limb function, as assessed by the RULM total score and MFM32 D3 score, and independence, as assessed by the SMAIS total score. A small number of patients in the risdiplam arm reached standing and walking motor milestones (compared with no patients in the placebo arm). In the FIREFISH study, 12 (of 41) patients (29.3%; 90% CI: 17.8, 43.1%) were sitting without support for five seconds, as assessed by the BSID-III, at Month 12, which was statistically significantly greater than the performance criterion of 5% (p<0.0001), and is clinically meaningful. Nine patients (22.0%; 90% CI: 12.0, 35.2%) were able to support weight or stand with support, as assessed by the HINE-2, at Month 12, and one patient (2.4%; 90% CI: 0.1, 11.1%) was able to bounce, as assessed by the HINE-2, at Month 12. Bouncing was the highest milestone on the 'walking' subscale of the HINE-2 attained by any patient in FIREFISH at Month 12. Thirty-five patients (85.4%; 90% CI: 73.4, 92.2%) were alive without permanent or chronic non-invasive ventilation at Month 12, and 38 patients (92.7%%; 90% CI: 82.2, 97.1%) were alive at Month 12. In terms of AEs, risdiplam appears to be generally well tolerated among patients with both Type 2/3 and Type 1 SMA.

The company's MAIC, which uses data from FIREFISH and the placebo arm of ENDEAR, suggests that risdiplam is more effective than placebo in terms of OS (HR [from company's updated analyses] = [redacted]; 95% CI [redacted]), ventilation-free survival (HR from updated analyses = [redacted]; 95% CI [redacted]) and motor milestone achievement (OR sitting with/ without support = [redacted], 95% CI [redacted]; OR standing with support/unaided = [redacted], 95% CI [redacted]). The ERG notes that given the unanchored nature of these comparisons, these estimates of relative treatment effects should be considered highly uncertain.

Key uncertainties concerning the clinical effectiveness evidence relating to the use of risdiplam to treat SMA include: the lack of evidence for the efficacy of risdiplam in a treatment-experienced population (particularly among patients treated with nusinersen); a lack of evidence for the efficacy of risdiplam

in pre-symptomatic, Type 0 and Type 4 SMA populations; a lack of evidence from SMA populations in the UK; and the single-arm open-label study design of FIREFISH, the only study providing evidence for the efficacy of risdiplam in patients with Type 1 SMA. In addition, the use of the SMAIS to assess function-related independence in the SUNFISH trial also introduced uncertainty as the validity, reliability or ability to detect change of this scale has not yet been established. The duration of the SUNFISH and FIREFISH studies is a further source of uncertainty, as the longer-term efficacy (i.e. beyond 12 months) of risdiplam is not known. Finally, some patients in the FIREFISH study received a risdiplam dose that was lower than the recommended dose.

Cost-effectiveness conclusions

Within the Type 2/3 SMA population, the ERG's preferred deterministic ICER for risdiplam versus BSC is [redacted] per QALY gained (including both patient and caregiver health gains). This is considerably higher than the company's base case ICER of [redacted] per QALY gained. The key factors which lead to a higher ICER within the ERG's preferred analysis are: (a) the ERG's alternative approach used to value caregiver QALY losses avoided, and (b) the inclusion of an assumed plateau in treatment benefit after 26 months.

Within the Type 1 SMA population, the ERG's preferred deterministic ICER for risdiplam versus BSC is [redacted] per QALY gained (including both patient and caregiver health gains). Again, this is considerably higher than the company's base case ICER of [redacted] per QALY gained. The key factors which lead to a higher ICER within the ERG's preferred analysis are: (a) the alternative approach used to value caregiver QALY losses avoided; (b) the inclusion of relative treatment effects from the company's MAIC, and (c) the inclusion of an assumed plateau in treatment benefit after 66 months.

The ERG's additional sensitivity analyses indicate that the inclusion of additional HRQoL benefits reflecting fine motor skills could, in principle, reduce the ICERs for risdiplam. However, evidence to inform the magnitude of these potential benefits is absent. The analyses also indicate that the inclusion of assumptions of long-term worsening on risdiplam leads to less favourable results in both populations.

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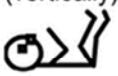
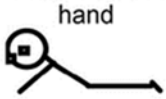
9 APPENDICES

Appendix 1: MFM-32 and HINE-2 motor function measures

Figure 22: Motor functions included in the MFM-32 (reproduced from Bérard *et al.*[32])

No.	Starting position	Exercise required and conditions for obtaining maximum score
1	Supine	Head in the axis: maintains the head in the axis and turns it completely to one side and then to the other
2		Raises the head and maintains the raised position
3		Flexes the hip and the knee more than 90 degrees by raising the foot from the mat
4		Lower limb supported by examiner: from the position in plantar flexion, raises the foot in dorsal flexion of 90 degrees in relation to the leg
5		Raises one hand from the mat and moves it to the opposite shoulder
6		Lower limbs half-flexed, patella facing up and feet resting on the mat: raises the pelvis, lumbar spine, pelvis and thighs aligned and feet slightly apart
7		Rolls to prone and frees the upper limbs
8		Without support of upper limbs, sits up on the mat
9	Seated on the mat	Without support of upper limbs, maintains the sitting position and is then capable of maintaining contact between the two hands
10		The tennis ball placed in front of the subject: without support of upper limbs, leans forward, touches the ball and sits up again
11		Without support of upper limbs, stands up
12	Standing	Without support of upper limbs, sits down on the chair, feet slightly apart
13	Seated on the chair	Without support of upper limbs or leaning against the back of the chair, maintains the sitting position, head and trunk in the axis
14	Seated on the chair or in their wheelchair	Head in flexion: from the fully flexed position, raises the head and maintains the raised position, head in the axis during the movement and when maintained
15		Forearms on the table but not elbows: raises both hands to the top of the head at the same time, head and trunk in the axis
16		The pencil on the table: reaches the pencil with one hand, elbow in complete extension at the end of the movement
17		10 coins placed on the table: successively picks up and holds 10 coins in one hand within 20 s
18		One finger placed in the center of the fixed CD: traces the complete border of the disk with one finger without support of the hand
19		The pencil on the table: picks up the pencil placed next to their hand and draws a continuous series of loops of 1 cm height in the 4-cm-long frame
20		Holding the sheet of paper: tears the paper folded in 4, beginning at the fold
21		The tennis ball on the table: picks up the ball, raises it off the table and turns over the hand holding onto the ball
22		A finger placed in the center of the fixed square: raises the finger and places it successively in the center of the 8 squares of the diagram without touching the lines
23		Upper limbs along the trunk: places the two forearms and/or hands on the table at the same time
24	Seated on the chair	Without support of upper limbs, stands up, feet slightly apart
25	Standing with support of upper limbs on equipment	Lets go of the support and maintains the standing position, feet slightly apart, head, trunk and limbs in the axis
26		Without support of upper limbs, raises one foot for 10 s
27	Standing	Without support, lowers theirself, touches the floor with one hand and stands up again
28	Standing without support	Walks forward 10 steps on both heels
29		Walks forward 10 steps on a straight line
30		Runs 10 m
31		On one foot: hops 10 times in place on one foot
32		Without support of upper limbs, attains the squatting position and gets up twice in a row

Figure 23: Motor milestones and categories included in the HINE-2 (reproduced from Haataja *et al.*[47])

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)	

Appendix 2: Cost-effectiveness results using risdiplam list price

This appendix presents the results of the analysis presented in the ERG report using the list price for risdiplam ([redacted] per large bottle).

1. Company's base case results

Type 2/3 SMA model

Table 51: Central estimates of cost-effectiveness (risdiplam list price), Type 2/3 SMA, risdiplam versus BSC (Table 27 of the ERG report)

Option	LYGs*	QALYs (patients)	QALYs (carers)	QALYs (patients + carers)	Costs	ICER (patient QALYs)	ICER (patient + carers QALYs)
Probabilistic model							
Risdiplam	60.16	7.59	31.92	39.51	[redacted]	-	-
BSC	44.17	-2.04	19.16	17.12	[redacted]	-	-
Incremental	15.99	9.63	12.76	22.39	[redacted]	**£427,391**	**£183,863**
Deterministic model							
Risdiplam	56.33	5.58	39.61	45.19	[redacted]	-	-
BSC	43.57	-1.98†	25.02	23.04	[redacted]	-	-
Incremental	12.76	7.56	14.59	22.15	[redacted]	**£542,381**	**£185,197**

***** *Undiscounted; † negative QALYs predicted as patients tend toward the non-sitting state which is assumed to result in a utility value which is worse than dead (see Table 28)*
LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care

Type 1 SMA model

Table 52: Central estimates of cost-effectiveness (risdiplam list price), risdiplam versus BSC, Type 1 SMA (Table 37 of the ERG report)

Option	LYGs*	QALYs (patients)	QALYs (carers)	QALYs (patients + carers)	Costs	ICER (patient QALYs)	ICER (patient + carers QALYs)
Probabilistic model							
Risdiplam	27.79	9.50	24.07	33.57	[redacted]	-	-
BSC	11.45	1.65	7.75	9.41	[redacted]	-	-
Incremental	16.34	7.85	16.32	24.17	[redacted]	**£304,764**	**£98,975**
Deterministic model							
Risdiplam	26.11	8.79	22.53	31.33	[redacted]	-	-
BSC	10.11	1.42	7.17	8.59	[redacted]	-	-
Incremental	16.00	7.37	15.37	22.74	[redacted]	**£301,447**	**£97,729**

***** *Undiscounted*
LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care

2. ERG's exploratory analysis results

Type 2/3 SMA model

Table 53: Results of ERG exploratory analyses and preferred analysis (risdiplam list price), Type 2/3 SMA model (Table 44 of the ERG report)

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs total	Costs	ICER (patients)	ICER (patients +carers)
Company's base case model							
Risdiplam	56.33	5.58	39.61	45.19	[redacted]	-	-
BSC	43.57	-1.98†	25.02	23.04	[redacted]	-	-
Incremental	12.76	7.56	14.59	22.15	[redacted]	**£542,381**	**£185,197**
EA1: Correction of errors							
Risdiplam	56.61	5.58	-6.95	-1.38	[redacted]	-	-
BSC	43.77	-1.98	-15.87	-17.85	[redacted]	-	-
Incremental	12.83	7.56	8.92	16.48	[redacted]	**£544,035**	**£249,534**
EA3: TA588 patient utility values and number of caregivers =3 for non-sitters							
Risdiplam	56.61	14.07	-2.42	11.64	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	12.83	8.09	7.63	15.72	[redacted]	**£508,452**	**£261,543**
EA4: Assumption of treatment plateau after 26 months							
Risdiplam	50.20	2.55	-8.71	-6.16	[redacted]	-	-
BSC	43.77	-1.98	-15.87	-17.85	[redacted]	-	-
Incremental	6.42	4.53	7.16	11.70	[redacted]	**£917,507**	**£355,534**
EA5: Inclusion of drug wastage (0.50 bottles)							
Risdiplam	56.61	5.58	-6.95	-1.38	[redacted]	-	-
BSC	43.77	-1.98	-15.87	-17.85	[redacted]	-	-
Incremental	12.83	7.56	8.92	16.48	[redacted]	**£544,558**	**£249,774**
EA6: ERG-preferred analysis							
Risdiplam	50.20	11.42	-3.60	7.82	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.42	5.44	6.45	11.89	[redacted]	**£765,223**	**£350,015**

** Undiscounted*

EA – exploratory analysis; LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; TA – technology appraisal; ERG – Evidence Review Group

Table 54: Results of ERG additional sensitivity analyses (risdiplam list price), Type 2/3 SMA model (Table 45 of the ERG report)

Option	LYGs *	QALYs - patients	QALYs - carers	QALYs total	Costs	ICER (patients)	ICER (patients +carers)
EA6: ERG-preferred analysis							
Risdiplam	50.20	11.42	-3.60	7.82	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.42	5.44	6.45	11.89	[redacted]	**£765,223**	**£350,015**
ASA1: Additional utility gains for non-sitters and sitters							
Risdiplam	50.20	13.22	-3.60	9.62	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.42	7.24	6.45	13.69	[redacted]	**£574,731**	**£303,937**
ASA2a: Risdiplam worsening probability =1% per month							
Risdiplam	47.37	7.69	-8.59	-0.90	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	3.59	1.71	1.47	3.18	[redacted]	**£2,921,541**	**£1,570,256**
ASA2b: Risdiplam worsening probability =2% per month							
Risdiplam	47.11	6.60	-10.19	-3.60	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	3.33	0.62	-0.14	0.48	[redacted]	**£8,383,468**	**£10,752,619**
ASA3a: Assumption of treatment plateau after 38 months							
Risdiplam	50.97	11.87	-3.26	8.61	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	7.20	5.89	6.80	12.68	[redacted]	**£698,167**	**£324,147**
ASA3b: Assumption of treatment plateau after 14 months							
Risdiplam	50.15	11.40	-3.63	7.77	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.38	5.42	6.42	11.84	[redacted]	**£767,626**	**£351,336**
ASA4: Initial period transition probabilities applied without adjustments until plateau timepoint							
Risdiplam	50.04	11.31	-3.71	7.60	[redacted]	-	-
BSC	43.77	5.98	-10.06	-4.08	[redacted]	-	-
Incremental	6.27	5.33	6.35	11.68	[redacted]	**£783,380**	**£357,424**

** Undiscounted*

ASA - additional sensitivity analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

Type 1 SMA model

Table 55: Results of ERG exploratory analyses and preferred analysis (risdiplam list price), Type 1 SMA model (Table 46 of the ERG report)

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs total	Costs	ICER (patients)	ICER (patients +carers)
Company's base case model							
Risdiplam	26.11	8.79	22.53	31.33	[redacted]	-	-
BSC	10.11	1.42	7.17	8.59	[redacted]	-	-
Incremental	16.00	7.37	15.37	22.74	[redacted]	**£301,447**	**£97,729**
EA1: Correction of errors							
Risdiplam	26.05	8.76	-5.63	3.13	[redacted]	-	-
BSC	10.11	1.42	-6.32	-4.90	[redacted]	-	-
Incremental	15.94	7.34	0.69	8.03	[redacted]	**£302,199**	**£276,221**
EA2: Inclusion of treatment effects estimated from MAIC							
Risdiplam	26.05	8.76	-5.63	3.13	[redacted]	-	-
BSC	4.88	0.71	-3.14	-2.43	[redacted]	-	-
Incremental	21.17	8.05	-2.49	5.57	[redacted]	**£377,325**	**£545,932**
EA3: TA588 patient utility values							
Risdiplam	26.05	7.21	-5.63	1.58	[redacted]	-	-
BSC	10.11	0.02	-6.32	-6.31	[redacted]	-	-
Incremental	15.94	7.19	0.69	7.88	[redacted]	**£308,364**	**£281,362**
EA4: Assumption of treatment plateau after 66 months							
Risdiplam	21.68	6.98	-6.68	0.30	[redacted]	-	-
BSC	10.11	1.42	-6.32	-4.90	[redacted]	-	-
Incremental	11.57	5.56	-0.36	5.20	[redacted]	**£362,955**	**£388,270**
EA5: Inclusion of drug wastage (0.50 bottles)							
Risdiplam	26.05	8.76	-5.63	3.13	[redacted]	-	-
BSC	10.11	1.42	-6.32	-4.90	[redacted]	-	-
Incremental	15.94	7.34	0.69	8.03	[redacted]	**£302,738**	**£276,713**
EA6: ERG-preferred analysis							
Risdiplam	21.68	4.77	-6.68	-1.91	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	16.80	4.75	-3.54	1.21	[redacted]	**£598,220**	**£2,347,587**

** Undiscounted*

EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; MAIC - matching-adjusted indirect comparison; TA - technology appraisal; ERG - Evidence Review Group

Table 56: Results of ERG additional sensitivity analyses (risdiplam list price), Type 1 SMA model (Table 47 of the ERG report)

Option	LYGs*	QALYs - patients	QALYs - carers	QALYs total	Costs	ICER (patients)	ICER (patients +carers)
EA6: ERG-preferred analysis							
Risdiplam	21.68	4.77	-6.68	-1.91	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	16.80	4.75	-3.54	1.21	[redacted]	**£598,220**	**£2,347,587**
ASA1: Additional utility gains for non-sitters and sitters							
Risdiplam	21.68	5.47	-6.68	-1.21	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	16.80	5.45	-3.54	1.91	[redacted]	**£521,449**	**£1,487,925**
ASA2a: Risdiplam worsening probability =1% per month							
Risdiplam	18.24	2.63	-7.88	-5.25	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	13.36	2.61	-4.73	-2.12	[redacted]	**£1,149,417**	**Dominated (-£1,413,252)**
ASA2b: Risdiplam worsening probability =2% per month							
Risdiplam	17.45	2.01	-8.22	-6.22	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	12.57	1.99	-5.08	-3.09	[redacted]	**£1,572,809**	**Dominated (-£1,010,824)**
ASA3a: Assumption of treatment plateau after 78 months							
Risdiplam	22.54	5.20	-6.61	-1.41	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	17.66	5.18	-3.47	1.72	[redacted]	**£557,543**	**£1,683,318**
ASA3b: Assumption of treatment plateau after 54 months							
Risdiplam	20.62	4.24	-6.76	-2.52	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	15.74	4.22	-3.62	0.60	[redacted]	**£659,277**	**£4,634,475**
ASA4: Initial period transition probabilities applied without adjustments until plateau timepoint							
Risdiplam	17.24	2.50	-7.06	-4.56	[redacted]	-	-
BSC	4.88	0.02	-3.14	-3.12	[redacted]	-	-
Incremental	12.36	2.48	-3.92	-1.44	[redacted]	**£1,052,369**	**Dominated (-£1,818,577)**

** Undiscounted*

ASA - additional sensitivity analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

Appendix 3: Technical appendix detailing implementation of ERG's exploratory analyses

This appendix details how to implement the ERG's exploratory analyses.

ERG Exploratory Analysis 1: Correction of model errors

1(a) Subsequent period assumptions employed after 24 months (both models)

In worksheet 'Treatment Efficacy', replace the value in cells H30 (Type 2/3 model) and I18 (Type 1 model) with value '24.001'.

1(b) Corrected general population mortality model (Type 2/3 SMA model only)

In Type 2/3 SMA model, copy the respective values in Table 57 to cells AA16:AA1096 in worksheet 'Survival'.

Table 57: Mortality risk based on national life tables for England, 2017-2019

Age	Mortality risk in cycle
10.00	0.00000566
10.08	0.00000566
10.17	0.00000566
10.25	0.00000566
10.33	0.00000566
10.42	0.00000566
10.50	0.00000566
10.58	0.00000566
10.67	0.00000566
10.75	0.00000566
10.83	0.00000566
10.92	0.00000566
11.00	0.00000595
11.08	0.00000595
11.17	0.00000595
11.25	0.00000595
11.33	0.00000595
11.42	0.00000595
11.50	0.00000595
11.58	0.00000595
11.67	0.00000595
11.75	0.00000595
11.83	0.00000595
11.92	0.00000595
12.00	0.00000673
12.08	0.00000673
12.17	0.00000673
12.25	0.00000673
12.33	0.00000673
12.42	0.00000673
12.50	0.00000673
12.58	0.00000673
12.67	0.00000673
12.75	0.00000673
12.83	0.00000673
12.92	0.00000673
13.00	0.00000848
13.08	0.00000848
13.17	0.00000848
13.25	0.00000848
13.33	0.00000848
13.42	0.00000848
13.50	0.00000848
13.58	0.00000848
13.67	0.00000848
13.75	0.00000848
13.83	0.00000848
13.92	0.00000848
14.00	0.00000866
14.08	0.00000866
14.17	0.00000866
14.25	0.00000866
14.33	0.00000866
14.42	0.00000866
14.50	0.00000866
14.58	0.00000866
14.67	0.00000866
14.75	0.00000866
14.83	0.00000866
14.92	0.00000866
15.00	0.00001109
15.08	0.00001109
15.17	0.00001109
15.25	0.00001109
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77.08	0.00268653
77.17	0.00268629
77.25	0.00268605
77.33	0.00268580
77.42	0.00268556
77.50	0.00268532
77.58	0.00268508
77.67	0.00268483
77.75	0.00268459
77.83	0.00268435
77.92	0.00268411
78.00	0.00268387
78.08	0.00302935
78.17	0.00302906
78.25	0.00302876
78.33	0.00302846
78.42	0.00302817
78.50	0.00302787
78.58	0.00302758
78.67	0.00302728
78.75	0.00302698
78.83	0.00302669
78.92	0.00302639
79.00	0.00302609
79.08	0.00336966
79.17	0.00336933
79.25	0.00336900
79.33	0.00336867
79.42	0.00336834
79.50	0.00336801
79.58	0.00336768
79.67	0.00336735
79.75	0.00336702
79.83	0.00336669
79.92	0.00336636
80.00	0.00336603
80.08	0.00379158
80.17	0.00379114
80.25	0.00379070
80.33	0.00379027
80.42	0.00378983
80.50	0.00378940
80.58	0.00378896
80.67	0.00378852
80.75	0.00378809
80.83	0.00378765
80.92	0.00378721
81.00	0.00378678
81.08	0.00424688
81.17	0.00424636
81.25	0.00424584
81.33	0.00424532
81.42	0.00424481
81.50	0.00424429
81.58	0.00424377
81.67	0.00424325
81.75	0.00424274
81.83	0.00424222
81.92	0.00424170
82.00	0.00424118
82.08	0.00475193
82.17	0.00475136
82.25	0.00475079
82.33	0.00475022
82.42	0.00474966
82.50	0.00474909
82.58	0.00474852
82.67	0.00474795
82.75	0.00474739
82.83	0.00474682
82.92	0.00474625
83.00	0.00474568
83.08	0.00543203
83.17	0.00543138
83.25	0.00543074

83.33	0.00543010
83.42	0.00542946
83.50	0.00542881
83.58	0.00542817
83.67	0.00542753
83.75	0.00542689
83.83	0.00542625
83.92	0.00542561
84.00	0.00542497
84.08	0.00617728
84.17	0.00617641
84.25	0.00617555
84.33	0.00617468
84.42	0.00617381
84.50	0.00617295
84.58	0.00617208
84.67	0.00617122
84.75	0.00617035
84.83	0.00616948
84.92	0.00616862
85.00	0.00616775
85.08	0.00699736
85.17	0.00699640
85.25	0.00699545
85.33	0.00699450
85.42	0.00699355
85.50	0.00699259
85.58	0.00699164
85.67	0.00699069
85.75	0.00698974
85.83	0.00698879
85.92	0.00698784
86.00	0.00698688
86.08	0.00798175
86.17	0.00798060
86.25	0.00797946
86.33	0.00797831
86.42	0.00797716
86.50	0.00797602
86.58	0.00797487
86.67	0.00797373
86.75	0.00797259
86.83	0.00797144
86.92	0.00797030
87.00	0.00796916
87.08	0.00898374
87.17	0.00898240
87.25	0.00898107
87.33	0.00897973
87.42	0.00897840
87.50	0.00897706
87.58	0.00897573
87.67	0.00897440
87.75	0.00897307
87.83	0.00897173
87.92	0.00897040
88.00	0.00896907
88.08	0.01023247
88.17	0.01023095
88.25	0.01022943
88.33	0.01022791
88.42	0.01022639
88.50	0.01022487
88.58	0.01022335
88.67	0.01022183
88.75	0.01022032
88.83	0.01021880
88.92	0.01021729
89.00	0.01021577
89.08	0.01151635
89.17	0.01151424
89.25	0.01151214
89.33	0.01151003
89.42	0.01150793
89.50	0.01150583
89.58	0.01150373
89.67	0.01150163
89.75	0.01149953
89.83	0.01149743
89.92	0.01149534
90.00	0.01149324
90.08	0.01274856
90.17	0.01274711
90.25	0.01274566
90.33	0.01274422
90.42	0.01274277
90.50	0.01274132
90.58	0.01273988
90.67	0.01273844
90.75	0.01273699
90.83	0.01273555
90.92	0.01273411
91.00	0.01273267
91.08	0.01440791
91.17	0.01440597
91.25	0.01440403
91.33	0.01440210
91.42	0.01440016
91.50	0.01439823
91.58	0.01439630
91.67	0.01439437
91.75	0.01439244
91.83	0.01439051
91.92	0.01438858
92.00	0.01438665
92.08	0.01608363
92.17	0.01608152
92.25	0.01607942
92.33	0.01607732
92.42	0.01607522
92.50	0.01607312
92.58	0.01607102
92.67	0.01606893
92.75	0.01606683
92.83	0.01606474
92.92	0.01606265
93.00	0.01606056
93.08	0.01785708
93.17	0.01785463
93.25	0.01785217
93.33	0.01784972
93.42	0.01784727
93.50	0.01784482
93.58	0.01784237
93.67	0.01783993
93.75	0.01783748
93.83	0.01783504
93.92	0.01783261
94.00	0.01783017
94.08	0.02000744
94.17	0.02000446
94.25	0.02000148
94.33	0.01999850
94.42	0.01999553
94.50	0.01999256
94.58	0.01998959
94.67	0.01998662
94.75	0.01998366
94.83	0.01998070
94.92	0.01997774
95.00	0.01997479
95.08	0.02242687
95.17	0.02242372
95.25	0.02242057
95.33	0.02241742
95.42	0.02241428
95.50	0.02241114
95.58	0.02240801
95.67	0.02240488
95.75	0.02240175
95.83	0.02239863
95.92	0.02239551
96.00	0.02239239
96.08	0.02508742
96.17	0.02508313
96.25	0.02507884

96.33	0.02507455
96.42	0.02507028
96.50	0.02506601
96.58	0.02506174
96.67	0.02505748
96.75	0.02505323
96.83	0.02504898
96.92	0.02504474
97.00	0.02504051
97.08	0.02675701
97.17	0.02675300
97.25	0.02674900
97.33	0.02674500
97.42	0.02674100
97.50	0.02673702
97.58	0.02673304
97.67	0.02672906
97.75	0.02672509
97.83	0.02672113
97.92	0.02671717
98.00	0.02671322
98.08	0.02932939
98.17	0.02932601
98.25	0.02932263
98.33	0.02931926
98.42	0.02931589
98.50	0.02931253
98.58	0.02930918
98.67	0.02930583
98.75	0.02930248
98.83	0.02929914
98.92	0.02929580
99.00	0.02929247
99.08	0.03255904
99.17	0.03254696
99.25	0.03253492
99.33	0.03252291
99.42	0.03251094
99.50	0.03249901
99.58	0.03248711
99.67	0.03247525
99.75	0.03246343
99.83	0.03245165
99.92	0.03243990
100.00	1.00000000

1(c) BSC extended to include 1,080 cycles (Type 2/3 SMA model only)

In worksheet 'BSC' of the Type 2/3 SMA model, edit the formula in cells J10: O10 such that all ranges in each formula end at row 1089. Drag each formula down until row 1089. Drag each formula in all remaining non-empty columns from C to CG down until row 1089. Update the column summary calculations in rows 5 and 6.

1(d) Valuation of incremental caregiver QALY losses avoided (both models)

Type 2/3 SMA model

In worksheet 'HSUV', replace the values in two contiguous empty cells (e.g. cell C23 and D23) with 'General population carer utility' and the value '0.915', respectively. Define the cell containing the value as a variable, naming it 'u_genpop_cg'.

In worksheet 'risdiplam', replace the formulae in cells BA8:BE8 with the following formulae:

- Cell BA8: '=$R8*u_no_cg*((u_genpop_cg-u_cg_notsitting)*-1)'
- Cell BB8: '=$S8*u_no_cg*((u_genpop_cg-u_cg_sittingwsupport)*-1)'
- Cell BC8: '=$T8*u_no_cg*((u_genpop_cg-u_cg_sittingwosupport)*-1)'
- Cell BD8: '=$U8 * u_no_cg *((u_genpop_cg-u_cg_standing)*-1)'
- Cell BE8: '=$V8 * u_no_cg *((u_genpop_cg-u_cg_walking)*-1)'

Drag each formula down until row 1088.

In worksheet 'BSC', replace the formulae in cells AR9:AR9 with the following formulae:

- Cell AR9: '=$R9*u_no_cg*((u_genpop_cg-u_cg_notsitting)*-1)'
- Cell AS9: '=$S9*u_no_cg*((u_genpop_cg-u_cg_sittingwsupport)*-1)'
- Cell AT9: '=$T9*u_no_cg*((u_genpop_cg-u_cg_sittingwosupport)*-1)'
- Cell AU9: '=$U9 * u_no_cg *((u_genpop_cg-u_cg_standing)*-1)'
- Cell AV9: '=$V9 * u_no_cg *((u_genpop_cg-u_cg_walking)*-1)'

Drag each formula down until row 1089.

Type 1 SMA model

In worksheet 'HSUV', repeat the procedure for Type 2/3 model to create a variable for the General population carer utility and assign it the value of '0.915'. Name the variable as 'u_genpop_cg'.

In worksheets 'risdiplam' and 'BSC', replace the formulae in cells BC10:BG10 with the following formulae:

- Cell BC10: '=$S10*u_no_cg*((u_genpop_cg-u_cg_notsitting)*-1)'
- Cell BD10: '=$T10*u_no_cg*((u_genpop_cg-u_cg_PV)*-1)'

- Cell BE10: '=$U10*u_no_cg*((u_genpop_cg-u_cg_sitting)*-1)'
- Cell BF10: '=$V10 * u_no_cg *((u_genpop_cg- u_cg_standing)*-1)'
- Cell BG10: '=$W10 * u_no_cg *((u_genpop_cg-u_cg_walking)*-1)'

Drag each formula down until row 1205.

All other exploratory analyses undertaken by the ERG include these corrections of errors. Apply all changes described above before running the following analyses.

ERG Exploratory Analysis 2: Use of relative treatment effects obtained from company's MAIC (Type 1 SMA model only)

In Type 1 SMA model, replace the cells S33 and S34 in worksheet 'Treatment Efficacy' with the values '[redacted]' and '[redacted]', respectively. In worksheet 'Summary', change the dropdown menu located near cells E34:E35 to 'MAIC - HINE'.

ERG Exploratory Analysis 3: Use of utility estimates from company's clinical advisors in TA588

Type 2/3 SMA model

In worksheet 'HSUV', replace the values in cells D9:D13 and D17:D21 with the values in Table 58 for patient and caregiver utilities, respectively.

In worksheet 'risdiplam' cell BA8 and 'BSC' cell AR9, replace the term 'u_no_cg' in the formula with the value '3'. Drag each formula down until rows 1088 and 1089, respectively.

Table 58: Patient and carergiver utility values applied in ERG's exploratory analyses

Model health state	Patient utility values	Caregiver utility values
Type 2/3 SMA model		
(i) Not sitting	0.20	0.700
(ii) Sitting (supported)	0.40	0.772*
(iii) Sitting (unsupported)	0.50	0.843*
(iv) Standing	0.70	0.915
(v) Walking	0.85	0.915
Type 1 SMA model†		
(i) Not sitting	0.10	0.484
(ii) PV	-0.02	0.484
(iii) Sitting	0.20	0.628
(iv) Standing	0.70	0.771
(v) Walking	0.85	0.915

TA - technology appraisal; PV - permanent ventilation

**Note that the values for 'sitting (supported)' and 'Sitting (unsupported)' were obtained by replacing the value in cells D18 and D19 by the formula '=$D$17+(($D$21-$D$17)*1/3)' and '=$D$17+(($D$21-$D$17)*2/3)', respectively.*

† Caregiver utility values used in the company's Type 1 SMA model have not been changed

Type 1 SMA model

In worksheet 'HSUV', replace the values in cells E8:E12 with the values in Table 58 for patient utility estimates. Note that the caregiver utility values and the number of caregivers for patients who are unable to sit were not amended in this model.

ERG Exploratory Analysis 4: Inclusion of treatment benefit plateau for risdiplam (both models)

Type 2/3 SMA model

In Worksheet 'risdiplam', replace the formula in cells BQ35, BU35, BW35, CA35, CC35, CG35, CI35 and CM35 with the value '0'. Drag the value in each column down until row 1088.

Type 1 SMA model

In Worksheet 'risdiplam', replace the formula in and BT77, CD77 and CJ77 with the value '0'. Drag the value in each column down until row 1205.

ERG Exploratory Analysis 5: Inclusion of risdiplam drug wastage costs (both models)

In Spreadsheet 'Results', include the term '+(c_risdi_large_disc*0.5)' at the end of the formulae in cells F7, F20, L7 and L20.

ERG Exploratory Analysis 6: ERG-preferred analysis

The ERG's preferred analysis includes ERG exploratory analysis 1 to 5 (with exception of Exploratory Analysis 2 for Type 2/3 SMA model); therefore, apply all the correspondent changes listed above.

All additional sensitivity analyses undertaken by the ERG were applied separately, using the ERG's preferred model as a starting point.

ERG Additional Sensitivity Analysis 1: Inclusion of additional HRQoL benefits (both models)

Type 2/3 SMA model

In Worksheet 'risdiplam', replace the formula:

(i) in cell AR8 with '=$R8 * (u_notsitting +0.05+ IF($E8 >= u_age_selfreported, u_patient12yrs))';

(ii) in cell AS8 with '=$S8 * (u_sittingwsupport + 0.1+ IF($E8 >= u_age_selfreported, u_patient12yrs))';

(iii) in cells AT8 with '=$T8 * (u_sittingwosupport +0.1+ IF($E8 >= u_age_selfreported, u_patient12yrs))';

Drag each formula down until row 1088.

Type 1 SMA model

In Worksheet 'risdiplam', replace the formula:

(i) in cell AT10 with =$S10 * (u_notsitting+0.05)';

(ii) in cell AV10 with =$U10 * (u_sitting+0.1)';

Drag each formula down until row 1205.

ERG Additional Sensitivity 2: Alternative assumptions regarding probability of risdiplam-treated patients worsening (both models)

Type 2/3 SMA model

In Worksheet 'risdiplam', replace the formula in cells BU35, CA35, CG35 and CM35 with: (a) the value '0.01' or (b) the value '0.02'. Drag the value in each column down until row 1088.

Type 1 SMA model

In Worksheet 'risdiplam', replace the formula in and BS77, CB77, CH77 and CN77 with: (a) the value '0.01' or (b) the value '0.02'. Drag the value in each column down until row 1205.

ERG Additional Sensitivity 3: Alternative timepoints for assumed treatment benefit plateau (both models)

Type 2/3 SMA model

In Worksheet 'risdiplam', apply the following amendments as follows:

(a) to change the plateau timepoint to 1-year later, drag the formula in cells BQ34, BU34, BW34, CA34, CC34, CG34, CI34 and CM34 down until row 46;

(b) to change the plateau timepoint to 1-year earlier, replace the formula in cells BQ23, BU23, BW23, CA23, CC23, CG23, CI23 and CM23 with the value '0'. Drag the value in each column down until row 1088.

Type 1 SMA model

In Worksheet 'risdiplam', apply the following amendments as follows:

(a) to change the plateau timepoint to 1-year later, drag the formula in cells BT76, CD76 and CJ76 until row 88;

(b) to change the plateau timepoint to 1-year earlier, replace the formula in cells BT65, CD65 and CJ65 with the value '0'. Drag the value in each column down until row 1205.

ERG Additional Sensitivity 4: Initial period transition matrices applied without adjustments until assumed plateau point (both models)

In Worksheet 'Control Panel', replace the value in cells F73 (Type 2/3 SMA model) and E119 (Type 1 SMA model) with the value '1'.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm** on **Thursday 28 January 2021** using the below 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 committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Typo in text

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14: The least squares mean difference between arms was 1.55 (95% confidence interval [CI]: 0.32 , 2.81	The least squares mean difference between arms was 1.55 (95% confidence interval [CI]: 0.30, 2.81	Incorrect lower CI	The ERG agrees. The text has been amended as suggested by the company.

Issue 2 Inaccurate interpretation of the company's approach to caregiver QALYs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17 (Section 1.5) and 121 (Section 5.3.4): "The ERG believes that both of the company's models are subject to an unintended and erroneous assumption – that caregivers die (or survive with utility equal to zero) when the SMA patient dies. This is incorrect as caregivers will continue to accrue health gains after the SMA patient has died." "The ERG believes that this approach is subject to an unintended erroneous assumption – that caregiver QALYs are only counted when the SMA patient is alive. In simple terms, the company's approach implicitly assumes that the caregivers die (or survive with utility equal to	The company would suggest that that this wording is altered to the following: "The company undertook an approach whereby caregiver QALY gains were not considered following patient death, deeming that caregiver QALYs should not be considered as part of the economic analysis upon the death of the patient they are caring for."	The company's rationale for not including caregiver QALY gains following patient death was not based on the assumption that the carer died, or that their utility fell to zero, rather that they deemed caregiver QALY gains should not be considered further in the analysis from this point onwards.	This is not a factual inaccuracy. The company's approach to only valuing caregiver QALYs whilst the patient is alive is equivalent to assuming that the caregivers die or survive with zero utility when the SMA patient dies. As shown in the extracted text in the left-hand column, this is described as *"an unintended and erroneous assumption"* arising from the approach rather than as a rationale. Irrespective of the company's rationale for the approach, these are the implicit assumptions which arise from it. The text has not been amended.

zero) when the SMA patient dies. This is conceptually flawed as caregivers will continue to accrue health gains after the patient has died."			

Issue 3 Incorrect ICER cited

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 19: the ERG report states "Within the Type 2/3 SMA model, including a treatment benefit plateau after Month 26 increases the ERG's corrected ICER from [redacted] to [redacted] per QALY gained"	As £[redacted] is the company's ICER, this value should be replaced with the ERG's corrected ICER on this occasion, which is [redacted] according to page 18 of the ERG report	This error will need correcting for consistency with the remainder of the document	The ERG agrees that this is an error. The first ICER mentioned in the extract of text has been amended to [redacted]

Issue 4 Incorrect ICER cited

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 21: the ERG report states "Within the Type 2/3 SMA model, the inclusion of Biogen's clinical advisors' patient utility estimates and the inclusion of 3 caregivers for patients who are unable to sit increases the ERG's corrected ICER from [redacted] to [redacted] per QALY gained"	Similarly to Issue 2, as [redacted] is the company's ICER, this value should be replaced with the ERG's corrected ICER on this occasion, which is [redacted] according to page 18 of the ERG report	This error will need correcting for consistency with the remainder of the document	The ERG agrees that this is an error. The first ICER mentioned in the extract of text has been amended to [redacted]

Issue 5 Typo in ICER

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 24: the company's base case ICER is described as [redacted]. Please note the correct value is [redacted]	Replace [redacted] with [redacted]	This error will need correcting for consistency with the remainder of the document	The ERG agrees that this is an error. The ICER has been amended to [redacted].

Issue 6 Typo in text

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 59 Table 11: Adequacy of follow up of cohorts: 28 of the 41 patients (93%) remained on treatment at the clinical cut-off date.	Adequacy of follow up of cohorts: 38 of the 41 patients (93%) remained on treatment at the clinical cut-off date.	Incorrect number	The ERG agrees. The text has been amended as suggested by the company.

Issue 7 Typo in text

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 62: Change from baseline in MFM32 (primary outcome) The least squares mean (SE) change from baseline to Month 12 in MFM32 total score was 1.36 (0.38) in the risdiplam arm and -0.19 (0.52) in the placebo arm, which indicates a small overall	The least squares mean (SE) change from baseline to Month 12 in MFM32 total score was 1.36 (0.38) in the risdiplam arm and -0.19 (0.52) in the placebo arm, which indicates a small overall (1.36 on average)	Not a percentage	The ERG agrees. The text has been amended as suggested by the company.

(1.36% on average)			

Issue 8 Typo in text

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 66 Table 15: Total number of patients with at least one treatment-related AE leading to dose modification/interruption – 21 (17.5)	Total number of patients with at least one treatment-related AE leading to dose modification/interruption – 0 Total number of patients with at least one Grade 3–5 AE - 21 (17.5)	Number needs to be moved to the row below	The ERG agrees. The text has been amended as suggested by the company.

Issue 9 Inaccurate description of patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 81 (Section 5.2.1): the ERG report states that the Type 2/3 SMA model "compares risdiplam versus BSC for a combined population of patients with Type 2 and *non-ambulatory* Type 3 SMA"	In line with the description of the Type 2/3 model as part of the CS (Section 3.2.1), the wording should be changed to "combined population of both ambulant and non-ambulant patients with Type 2 and Type 3 SMA"	The amended statement allows for a more accurate description of the Type 2/3 SMA model population – it is not expected that this would have any further impact on the content of the ERG report	This wording was used in line with the description of the SUNFISH population in Table 5 of the CS. However, the ERG has amended the text to reflect the company's preferred wording. This includes an additional amendment in the executive summary.

Issue 10 Incorrect use of mean when referring to median dose intensity

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 86 (Section 5.2.2.2): the	The statement should be changed to "Relative	The amended statement allows for	The ERG has amended the

ERG report states that the relative dose intensity for the Type 2/3 SMA model was based on the *mean* dose intensity in SUNFISH, whereas in this case it was actually the *median* dose intensity that had been used	dose intensity (RDI) is based on the *median* dose intensity in SUNFISH"	a more accurate description of the Type 2/3 SMA model – it is not expected that this would have any further impact on the content of the ERG report	text to reflect the use of the median rather than mean. The ERG does not believe this was clear from the CS and notes that the mean would have been more appropriate.

Issue 11 Inaccurate description of rationale underlying the choice of utility values in the company's submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 93 (*Patient and caregiver utilities*): the ERG report states that "),[…] the Lloyd et al. study was chosen for inclusion in the company's model to align with the final iteration of the later onset model in TA588 […]", which is not fully in line with the rationale and information presented in the CS	This statement should be further aligned with the wording used in the CS ("The utility values sourced from the Lloyd et al (2019) vignette study were chosen as the base case to align with what was *considered for final decision-making in the TA588* submission, while the utility values derived from the TA588 ERG clinical advisers and SUNFISH were included as scenario analyses."), and further information added that the ERG-preferred source of utility values was indeed provided as scenario analysis as part of the CS	The amended statement allows for a more accurate description of the rationale for choice of health-state utility values in the Type 2/3 SMA model – it is not expected that this would have any further impact on the content of the ERG report	The ERG agrees that the ERG report slightly misrepresents the CS with respect to this point. The text has been amended to read *"the Lloyd et al. study was chosen for inclusion in the company's model to align with what was considered for final decision-making in the TA588 submission"* The ERG notes that the ERG's clinical advisors' values were not used in the final iteration of the nusinersen models – these used estimates from Biogen's experts. In addition, the scenario analyses around utility values using estimates from SUNFISH and the ERG's clinical advisors in TA588 are

			discussed elsewhere in the report. As such, the other suggested amendments from the company have not been applied in the ERG report.

Issue 12 Inaccurate description of transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 121: the ERG report states that "the deterministic model assumes that the probability of transitioning from *sitting with support* to standing (state [iii] to [iv]) is zero"	This statement should be changed to correctly state that "the deterministic model assumes that the probability of transitioning from *sitting without support* to standing (state [iii] to [iv]) is zero"	The amended statement allows for a more accurate description of the Type 2/3 SMA model – it is not expected that this would have any further impact on the content of the ERG report	The ERG agrees this is a typographical error. The word "with" has been amended to "without"

Issue 13 Incomplete justification for the exclusion of discontinuation in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 126: the ERG report cites that the company stated that discontinuation was excluded in "*an effort to keep the model[s] as simple as possible*"	This statement should be amended to provide the full justification/rationale provided by the company ("an effort was made to keep the model as simple as possible, as it is not clear what the outcomes of discontinuation would be.", ERG clarification questions response; Issue 6)	The amended statement allows for a more accurate description of the rationale of the Type 2/3 SMA model – it is not expected that this would have any further impact on the content of the ERG report	This is not a factual inaccuracy; however, the ERG agrees that adding this further point provides a more complete justification for the exclusion of discontinuation from the model. The ERG has added a sentence which states *"In addition, the company's clarification response highlights that outcomes following discontinuation of risdiplam*

			are unknown."

Issue 14 Inaccurate description of the company's rationale for using naïve indirect comparison data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 127: the ERG report states that "company implies that naïve indirect comparisons might *not be problematic* […]"	For improved clarity, the original wording used by the company ("expected to be less of a limitation") should be used instead	The amended statement allows for a more accurate description of the company's rationale for use of the naïve indirect comparison data – it is not expected that this would have any further impact on the content of the ERG report	The ERG has amended the text as suggested by the company.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 10 March 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Summary of company's technical engagement response and revised cost-effectiveness results

The company thank the Evidence Review Group (ERG) and technical team for their feedback on the original submission. The company have taken the feedback on board, in particular the importance of alignment in assumptions with TA588.[1] The company have revised their cost-effectiveness analyses to align with the majority of outstanding assumptions noted by the ERG to be inconsistent with the final iterations of the TA588 cost-effectiveness models. The two exceptions to this are the approach to modelling caregiver quality adjusted life years (QALYs) (issue 4) and the assumption in the type 2/3 model that the 'not sitting' health state is associated with 3 caregivers (issue 8).

In a disease area such as spinal muscular atrophy (SMA) that is associated with high mortality levels (in particular in type 1 patients), introduction of a life-extending treatment brings substantial challenges to health economic modelling. The most predominant challenge in the case of risdiplam is the modelling of caregiver QALYs, where, depending on the approach taken, the extension to life granted by risdiplam results in reduced cost-effectiveness estimates for risdiplam (explored further in the response to issue 4). For example, in the case of the type 1 model, even at an acquisition cost of £0 for risdiplam, adopting the ERG-suggested approach to modelling caregiver QALYs does not produce a cost-effective incremental cost-effectiveness ratio (ICER), illustrating the issues with face validity with this approach.

A similar challenge is also observed with the comparative efficacy estimates between risdiplam and best supportive care (BSC), where utilising more favourable overall survival results from the matching adjusted indirect comparison (MAIC) for the type 1 model (instead of the naïve comparison results) results in reduced cost-effectiveness estimates for risdiplam (explored further in response to issue 2). Accordingly, a remaining limitation of the current models is that the value of the additional years of life that risdiplam may grant patients is extremely difficult to capture. This extension to life will nevertheless be extremely valued by patients' families, and it is the company's view that this benefit of risdiplam treatment should be recognised in the Committee's decision-making.

Finally, the company would like to highlight that both the type 1 and type 2/3 models do not adequately reflect a number of benefits of risdiplam that have a significant effect on patient quality of life, such as improved bulbar function and feeding/swallowing, reductions in hospitalisations[2] and improved upper limb function[3] (issue 10). It is important that recognition of the fact that the broad and severe impact of SMA cannot be fully captured by the economic models or the NICE reference case, is taken into account in

the NICE decision-making process. Additional considerations and NICE decision modifiers should be recognised for this appraisal, similarly to NICE's decision-making for nusinersen in TA588.

The results of the company's revised base case cost-effectiveness analyses for the type 2/3 and type 1 models are presented in xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxx

However, as discussed above, the company strongly believe that the models do not capture the full value and improvements to HRQoL that risdiplam will bring to patients and their carers, such as maintaining upper limb function, and that these benefits are consequently not captured in the base case ICERs.

Further, the long-term costs of risdiplam to the NHS may be overestimated in the base case ICERs, with a more realistic projection represented in scenario 2, in which the loss of exclusivity of risdiplam is accounted for. In addition to this, the base case does not capture both the challenges with current methods in assessing rare conditions highlighted in the NICE Methods Review, or the upcoming changes as part of this that may better capture long-term benefits resultant of risdiplam treatment, including discounting at a rate of 1.5%.

Finally, as discussed in the Final Appraisal Document for TA588,[1] the company believe it is important that the same set of decision-modifiers taken into account for the appraisal of nusinersen should also be applied in the case of risdiplam, due to the rarity and severe burden of disease experienced by SMA patients and their carers, and significant unmet need that remains for an effective treatment for patients in the UK that risdiplam can address.

With these considerations combined, the company believe their revised technical engagement cost-effectiveness results to provide sufficient evidence to the Committee of the value for money that risdiplam may offer to the NHS, and would be open and willing to engage and collaborate further with NICE and NHS England to ensure that patients gain access to risdiplam treatment as soon as possible.

Table 1: Revised base case results for the type 2/3 SMA model (revised PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	21.71	51.05	-	-	-	-
Risdiplam	[redacted]	20.33	39.23	[redacted]	1.38	11.82	[redacted]

Costs and benefits discounted at 3.5%. BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 2: Revised base case results for the type 1 SMA model (revised PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Risdiplam	[redacted]	12.51	23.55	-	-	-	-
BSC	[redacted]	3.33	3.58	[redacted]	9.19	19.97	[redacted]

Costs and benefits discounted at 3.5%. BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 3: Scenario analysis results for the type 2/3 SMA model (revised PAS price)

Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
1 (ERG caregiver QALYs)	[redacted]	1.38	9.04	[redacted]
2 (Long-term NHS costs)	[redacted]	1.38	11.82	[redacted]
3 (1.5% discount rate)	[redacted]	2.69	18.78	[redacted]

ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHS: National Health Service; QALYs: quality-adjusted life years

Table 4: Scenario analysis results for the type 1 SMA model (revised PAS price)

Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
1 (ERG caregiver QALYs)	[redacted]	9.19	1.48	[redacted]
2 (Long-term NHS costs)	[redacted]	9.19	19.97	[redacted]
3 (1.5% discount rate)	[redacted]	12.60	27.52	[redacted]

ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHS: National Health Service; QALYs: quality-adjusted life year and **Error! Reference source not found.**, respectively. In addition, for each model, three scenario analyses have been presented (Table 3 and Table 4, respectively), as follows:

1. ERG approach to modelling caregiver QALYs: As described further in the response to issue 4, guidance documentation available from NICE indicates that neither the ERG's approach nor the company's approach to modelling caregiver QALYs is more appropriate than the other. Accordingly, the company's approach to modelling caregiver QALYs has been retained in the base case, whilst the ERG's approach has been explored in scenario analysis 1.
2. Modelling the true long-term cost of risdiplam to the NHS: As described further in the response to issue 5, Roche have proposed discontinuation criteria for type 2/3 and type 1 SMA of maximum treatment durations of 30 and 50 years, respectively. Risdiplam is due to lose exclusivity in [redacted] when acquisition costs are expected to drop substantially. Accordingly, scenario 2 aims to more closely reflect the long-term cost of risdiplam to the NHS.
3. Costs and benefits discounted at 1.5%: As part of the ongoing methods review, NICE are considering a number of updates to their preferred methodology in order to reflect the evolving health technology landscape. One particular update of those under consideration is the potential revision to the preferred discount rate for costs and benefits from 3.5% to 1.5%.[4] This is a change that would enable the value of long-term treatment benefits to be better recognised.[4] Following completion of the review, NICE's revised methods will offer an improved framework for the assessment of new therapies for rare conditions, and the results of this particular scenario illustrate that such revisions are likely to be highly influential on cost-effectiveness results. The company believe it is in patients' interest that this and other potential upcoming changes are considered in the current decision-making. Given the remaining high unmet need for SMA patients and their carers in the UK despite other licensed treatments, which is demonstrated by the approval of the MHRA Early Access to Medicines Scheme for Risdiplam, the company strongly desires for access to risdiplam to be granted to patients as soon as possible, and do not wish to delay until the new methods are implemented. The incorporation of proposed changes to the discount rate in the revised methods, which would better reflect the value of medicines in rare conditions, has therefore been modelled to demonstrate indicative changes in ICER values (Scenario 3).

Furthermore, the company have updated the patient access scheme discount for risdiplam from [redacted] to [redacted], to offer further value for money to the NHS.

[redacted]

However, as discussed above, the company strongly believe that the models do not capture the full value and improvements to HRQoL that risdiplam will bring to patients and their carers, such as maintaining upper limb function, and that these benefits are consequently not captured in the base case ICERs.

Further, the long-term costs of risdiplam to the NHS may be overestimated in the base case ICERs, with a more realistic projection represented in scenario 2, in which the loss of exclusivity of risdiplam is accounted for. In addition to this, the base case does not capture both the challenges with current methods in assessing rare conditions highlighted in the NICE Methods Review, or the upcoming changes as part of this that may better capture long-term benefits resultant of risdiplam treatment, including discounting at a rate of 1.5%.

Finally, as discussed in the Final Appraisal Document for TA588,[1] the company believe it is important that the same set of decision-modifiers taken into account for the appraisal of nusinersen should also be applied in the case of risdiplam, due to the rarity and severe burden of disease experienced by SMA patients and their carers, and significant unmet need that remains for an effective treatment for patients in the UK that risdiplam can address.

With these considerations combined, the company believe their revised technical engagement cost-effectiveness results to provide sufficient evidence to the Committee of the value for money that risdiplam may offer to the NHS, and would be open and willing to engage and collaborate further with NICE and NHS England to ensure that patients gain access to risdiplam treatment as soon as possible.

Table 1: Revised base case results for the type 2/3 SMA model (revised PAS price)

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BSC	[redacted]	21.71	51.05	-	-	-	-
Risdiplam	[redacted]	20.33	39.23	[redacted]	1.38	11.82	[redacted]

Costs and benefits discounted at 3.5%. BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 2: Revised base case results for the type 1 SMA model (revised PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Risdiplam	[redacted]	12.51	23.55	-	-	-	-
BSC	[redacted]	3.33	3.58	[redacted]	9.19	19.97	[redacted]

Costs and benefits discounted at 3.5%. BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 3: Scenario analysis results for the type 2/3 SMA model (revised PAS price)

Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
1 (ERG caregiver QALYs)	[redacted]	1.38	9.04	[redacted]
2 (Long-term NHS costs)	[redacted]	1.38	11.82	[redacted]
3 (1.5% discount rate)	[redacted]	2.69	18.78	[redacted]

ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHS: National Health Service; QALYs: quality-adjusted life years

Table 4: Scenario analysis results for the type 1 SMA model (revised PAS price)

Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
1 (ERG caregiver QALYs)	[redacted]	9.19	1.48	[redacted]
2 (Long-term NHS costs)	[redacted]	9.19	19.97	[redacted]
3 (1.5% discount rate)	[redacted]	12.60	27.52	[redacted]

ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHS: National Health Service; QALYs: quality-adjusted life years

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients	**NO**	The company accept that no evidence is currently available for risdiplam in pre-symptomatic, type 0, or type 4 SMA. However, despite the sparsity of evidence in previously treated SMA patients, the company would like to reiterate that the eligible population for risdiplam includes those patients who cannot tolerate and/or respond poorly to nusinersen, and that a clear unmet need for another effective treatment exists in this population. This is highlighted by the baseline characteristics of patients included in the JEWELFISH trial. Of 74 patients previously treated with nusinersen, 35.1% (n=26) discontinued treatment with nusinersen owing to safety or tolerability concerns; 21.6% (n=16) owing to patient or caregiver preference or inconvenience; 17.6% (n=13) owing to lack of efficacy; 10.8% (n=8) owing to loss of efficacy; and 6.8% (n=5) owing to difficulties with accessing or obtaining intrathecal injections.[5] Therefore, there will be a proportion of patients previously-treated with nusinersen who require additional treatments.[6] This has been further illustrated by the uptake of risdiplam in the US, where risdiplam has been licenced since August 2020, of which 2/3 of >1000 patients treated with risdiplam had previously been treated with nusinersen.[7] Whilst data are not currently available to demonstrate the efficacy of risdiplam in this population, there is no plausible biological rationale to suggest prior treatment with nusinersen should alter the outcomes of risdiplam treatment observed in treatment-naïve SMA patients. Both molecules act on transient survival motor

		neuron 2 (SMN2) messenger RNA as splicing modifiers to promote production of functional SMN protein.[8] Accordingly, neither treatment makes any alteration to the underlying disease or patient's biology that would be expected to result in a differential treatment response. Pharmacodynamic data supports this position with the median increase in SMN protein levels in the in non-naïve patients treated with risdiplam in the JEWLEFISH trial being consistent with those in treatment naïve patients in the SUNFISH and FIREFISH studies.[9] As such, there remains a significant unmet need in this severe, progressive disorder, particularly for the proportion of patients who discontinue nusinersen treatment. Therefore, the company strongly believe that these patients should also have the option to receive risdiplam, in particular because the oral formulation provides an additional option for those patients who have difficulty obtaining and/or tolerating intrathecally administered treatments. Without access to risdiplam, these patients will have no other option than to receive BSC. Finally, while the company recognises the lack of evidence in pre-symptomatic patients, based on the progressive nature of the motor neuronal loss in SMA, the earlier patients are treated, the more effective, and therefore cost-effective, the treatment would be expected to be. In both the FIREFISH and SUNFISH trials, subgroups of patients treated earlier in their disease course showed improved outcomes.[2, 3] This is further corroborated by the results seen in SMA patients pre-symptomatically treated with other SMN modifying treatments with similar pharmacodynamics effects.[10, 11]
Key issue 2: Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA	**YES (see revised base case results)**	As FIREFISH was a single-arm trial, Roche conducted an indirect treatment comparison in order to estimate the relative efficacy of risdiplam vs BSC in type 1 SMA. Two options were presented in the submission; an unadjusted naïve comparison and a MAIC. A health economics expert confirmed that as the differences between the FIREFISH (risdiplam) and ENDEAR (BSC) study populations were small and the studies were deemed as relatively comparative, both the naïve analysis and the MAIC are potentially appropriate sources of relative efficacy estimates for risdiplam vs BSC in type 1 SMA.[12]

		It is important to note that compared to the naïve comparison, the MAIC is associated with a reduced hazard ratio (for risdiplam vs BSC) for overall survival. In other words, the MAIC suggests a greater survival benefit with risdiplam compared to BSC than the unadjusted comparison. Despite this, utilising the (updated) MAIC estimates in the model counterintuitively results in a less favourable cost-effectiveness estimate for risdiplam. This is a result of the greater difference in the hazard of death, which ultimately results in a higher risk of mortality, in the BSC arm. As a consequence, patients in the BSC arm die more quickly, and incur reduced health state costs. Accordingly, the potential greater survival benefit offered by risdiplam by the MAIC is penalised in cost-effectiveness terms. Roche accept that both methods have limitations and some residual bias as with any indirect treatment comparison. The company feel that neither method accurately reflects the clinical benefit of risdiplam in type 1 SMA patients. Nonetheless, we agree that the naïve comparison generates implausibly optimistic survival estimates of BSC, and therefore have agreed with the ERG that the MAIC should be used in the revised base case analysis for alignment with TA588 to assist committee decision-making. However, we would like to highlight that the counterintuitive effect of adopting this approach, specifically that the cost-effectiveness analysis penalises an innovative treatment that extends patients' lives.
Key issue 3: Uncertainty surrounding long-term benefits of risdiplam	**NO**	The company accept that uncertainty exists with regards to the long-term treatment benefit of risdiplam, given that follow-up data of up to 12 months for SUNFISH and FIREFISH trials were available at the point of submission. This is an inherent limitation of modelling chronic degenerative conditions, and NICE recently acknowledged that uncertainties about long-term benefits of treatments for rare diseases are common in relation to the approval of onasemnogene abeparvovec for type 1 SMA.[13] Given that SMA is a long-term disease, necessitating a lifetime horizon in the model, the company endeavoured to make informed assumptions regarding the long-term benefits of risdiplam in the models, informed through

		seeking clinical expert opinion and reviewing Committee meeting discussions from TA588. The company is committed to releasing longer follow-up data as it becomes available. Additional data releases are expected in 2021, and further data will continue to be collected through the open-label extension phase of the SUNFISH and FIREFISH trials, which is anticipated to run until risdiplam is commercially available in the country of the participating patients. These data will provide further insight into the duration of clinical benefits from risdiplam treatment and will contribute to addressing long-term uncertainty.
Key issue 4: Caregiver QALY gain calculations implicitly assume that caregivers die or survive with utility equal to zero after the SMA patient dies	**YES (see scenario 1 results)**	The company understand that for consistency with TA588, the ERG recommend that the same approach to modelling caregiver QALYs as was conducted in TA588 be adopted, whereby caregiver loss of quality of life is applied as a decrement to patient quality of life for each health state. This differs to the company's approach, whereby patient and caregiver QALYs are applied additively for each health state. The choice of approach for modelling caregiver QALYs is particularly impactful on cost-effectiveness results when a novel treatment results in an extension to patients' life compared to existing treatment. As patients' functional ability declines over time, their corresponding care needs increase, and both patient and carer quality of life decreases. When adopting the approach of modelling caregiver QALY losses, should the new treatment grant a sufficient extension to life, this may result in greater caregiver QALY losses for the life-extending treatment compared to the existing treatment. In cost-effectiveness terms, this means that the new treatment is penalised for extending life, rather than valued. The reason that this does not occur when using the additive QALYs approach is that for patients treated with the life-extending treatment, additional life years are gained by the carer whilst the patient is still alive, compared to the carer of a patient on the existing treatment. This is the case despite the fact that in reality, all else being equal, the carers would likely have a similar life span. To explore this issue further, the company reviewed a report published by the NICE Decision Support Unit in 2019 on the topic of "*Modelling Carer Health-*

		Related Quality of Life in NICE Technology Appraisals and Highly Specialised Technologies."[14] This report reviews 12 prior technology appraisals and 4 highly specialised technology appraisals that included caregiver QALYs in the economic evaluation. Within the evaluations, different approaches were adopted to model the inclusion of caregiver QALYs, however, in all cases, this resulted in a reduction to the ICER. The report goes on to discuss both the approach suggested by the ERG and the company's approach to modelling caregiver health-related quality of life. The report states that "*in reality, it is likely that neither of these are realistic*." It notes that including a utility value for the carer linked to patients' disease status assumes that the health-related quality of life (HRQoL) of the carer is equivalent to being dead when the patient dies (a limitation also noted by the ERG). However, modelling a carer disutility linked to patient health status whilst alive assumes there is no negative impact on carer HRQoL when the patient dies. The report concludes that "*the impact of patient death on carer HRQoL may be an area that requires further research to determine which modelling approach is most appropriate*", indicating that neither the ERG's approach nor the company's approach to modelling caregiver QALYs is more appropriate than the other. **Differential effect of caregiver QALY approach in type 1 vs type 2/3 model** The impact of the approach taken to modelling caregiver QALYs on cost-effectiveness results is greater in the analysis for type 1 patients compared to type 2/3 patients. In the type 2/3 model, total incremental QALYs are 22.15 in the company's original base case analysis and 16.48 when the ERG's preferred method is adopted (model version EA1). In the type 1 model, total incremental QALYs are 22.74 in the company's original base case analysis and 8.03 when the ERG's preferred method is adopted (model version EA1). Driving this differential impact on incremental QALYs is the differences in patient utility among health states in the type 2/3 and type 1 models. As described in the company submission, patients with type 1 SMA have particularly poor levels of HRQoL due to low levels of functional ability and motor milestone attainment, which considerably worsen upon deterioration of respiratory musculature and the consequent need for permanent ventilation.[15] In contrast, patients with type 2/3 SMA have less severe disease and are able to achieve

		higher levels of quality of life during their lifetimes, which is reflected in the health-state utility values in the model. Accordingly, in the type 1 model, due to the low values of the health state utilities, adding a subsequent caregiver decrement (as per the approach suggested by the ERG) results in a negative net utility value (i.e. the caregiver decrement exceeds the patient utility). As a result, upon death of the patient, the carer utility decrement is removed and the utility for that patient improves from a negative value to 0. Given that patients in the BSC arm die sooner, this decrement is removed more frequently and quickly, resulting in a lower incremental QALY difference between risdiplam and BSC overall. In other words, it is more favourable in the model to receive the intervention associated with poorer survival outcomes. Indeed, upon adopting the ERG's approach to modelling caregiver QALYs in the type 1 model, even when a 100% discount is applied, the ICER is [redacted] per QALY. This illustrates that the ERG approach lacks face validity, given that at zero cost, a life-extending treatment does not result in a cost-effective ICER. Accordingly, in the type 1 model, the implication of the caregiver QALY loss approach is that the advantage to BSC in cost-effectiveness terms, due to earlier patient death, is compounded. This phenomenon was similarly observed in the early-onset model in the TA588 appraisal,[1] with the patient expert consulted noting that it "*seemed perverse because it made a life-extending treatment appear to be less cost effective."* The extension to life as a result of risdiplam treatment will be extremely valued by patients' families, and it is the company's view that this benefit of risdiplam treatment should be recognised in the economic analysis. **Summary** Whilst the company understand the importance of precedent in NICE Committee decision-making, the company wish to highlight that neither the ERG's nor the company's approach to modelling caregiver QALYs is more appropriate than the other, as supported by the NICE Decision Support Unit report.[14] This methodological limitation becomes a particular issue in the case of type 1 SMA, where patients suffer from extremely low HRQoL, as it further limits the ability of

		the analysis to capture the value of a life-extending treatment. As such, the company would ask the Committee to consider that despite the methodological challenges associated with modelling caregiver QALYs, risdiplam is a life-extending treatment that enables caregivers, who, in the majority of cases are family members, to spend more time with the SMA patient they are caring for. Specifically, in the company's revised base case analysis of the type 2/3 model, the additional time for patients and families to spend together is predicted to be 4.79 life years (undiscounted), whilst in the type 1 model, it is predicted to be 17.03 life years (undiscounted). This additional time will be immensely valued by patients and their carers, and the company ask that the Committee take this key factor into account in their decision-making. To facilitate the Committee's decision-making, the company have provided alternative sets of cost-effectiveness results in their revised economic analyses for the technical engagement process. The original approach to modelling caregiver QALYs is adopted in the revised base case, and the ERG's preferred approach is taken in a scenario analysis.
Key issue 5: The company's models do not include any discontinuation from risdiplam	**YES (see revised base case results)**	In line with the recommendations from the ERG, the company have explored the introduction of discontinuation criteria for risdiplam. In considering potential discontinuation criteria, the company took into account the need for criteria that would ensure patients receive maximal benefit from risdiplam (i.e. patients would not be asked to stop treatment whilst they were still experiencing maintenance or gains in health from risdiplam), and be straightforward to understand and easily implemented in NHS clinical practice. Accordingly, to inform the development of potential stopping rules for risdiplam, the company consulted with two practising NHS clinicians to understand the types of discontinuation criteria they would deem acceptable in clinical practice. Within these discussions, it was noted that the milestone-based stopping rules and treatment discontinuation criteria for nusinersen (included in the managed access agreement with the NHS) have limitations, in particular that the criteria put patients and their families under immense pressure to achieve the outcomes specified in the managed access agreement in order to be permitted to continue treatment.[1]

		Therefore the company feel that a 'hard-stop', time-based discontinuation rule would be more appropriate for Risdiplam than an outcomes-based stopping rule. Accordingly, based on these discussions, the company have developed discontinuation criteria whereby patients may be treated with risdiplam for a maximum of: • Type 1: 50 years • Type 2/3: 30 years The company deem this stopping rule to be straightforward to implement in NHS clinical practice. These criteria are further supported by the assertion from one of the clinicians consulted that they would prefer that a broad population of patients have access to treatment for 30 years, to a narrow subgroup of patients having unlimited access indefinitely. To explore the impact on cost-effectiveness for risdiplam, the company have incorporated these discontinuation criteria into the type 1 and type 2/3 cost-effectiveness analyses. The following assumptions have been made for patients following discontinuation of risdiplam in the company's revised base case: • Treatment efficacy (in terms of motor milestone achievement) wanes from a plateau (as discussed in issue 6), to that of long-term BSC treatment over periods of 10 or 5 years for type 2/3 and type 1 patients, respectively • Patients continue their overall survival (and permanent ventilation) trajectories In lieu of available data, these assumptions were informed by the expectation that over an extensive treatment duration such as 30 or 50 years (for type 2/3 and type 1 patients, respectively), patients are likely to have built up both respiratory and skeletal musculature through years of restored SMN protein production. Additionally, research has shown that the disease progression of SMA patients, measured by walking function, has been shown to follow a steeper trajectory during puberty[16]. Clinical opinion suggested this to be due to musculoskeletal weakness during growth spurts exacerbating development of frame deformities such as scoliosis. Any patient with reduced neuronal loss due to treatment during this time would be expected to have a stronger frame which would change the

		trajectory of their disease later on in life, even when treatment was discontinued. It is therefore anticipated that the patients' rate of decline in functional ability would take place over an extended duration, and, given that mortality in SMA is largely driven by loss of respiratory ability, that their life expectancy would be minimally impacted. Further to the above, given that the revised cost-effectiveness analyses consider treatment durations of 50 and 30 years, it was deemed relevant to consider that risdiplam will lose exclusivity in [redacted]. Accordingly, a scenario analysis has been conducted that aims to more closely reflect the long-term cost to the NHS, in which the generic cost of risdiplam is assumed to be [redacted] of the current list price.[17] Finally, per cycle discontinuation has not been included in the revised base case models. This is due to the same rationale cited in the submission (a lack of data to support a per cycle discontinuation rate), combined with the added complexity this would introduce to the model through additional post-discontinuation assumptions for risdiplam.
Key issue 6: The company's models assume that in the subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely[redacted]	**YES (see revised base case results)**	Given the lifetime horizons of the models and the need to inform the analyses with long-term term assumptions regarding the efficacy of risdiplam, during model development the company consulted with clinicians on the assumptions made, who confirmed their clinical validity, and specifically that a proportion of patients would continue to improve in the long term. However, the company also understand the ERG's critique of these assumptions, and agree that the company's base case could be perceived as optimistic. The company wish to facilitate the Committee's decision-making as far as possible through alignment with assumptions made in TA588. As such, in their revised cost-effectiveness analyses for technical engagement, the company have adopted plateaus in efficacy for risdiplam at the timepoints of 66 months and 26 months for the type 1 and type 2/3 models, respectively.

Key issue 7: The company's models predict that a large proportion of patients will reach the milestones of standing or walking, which appears to be optimistic.	**YES (see revised base case results)**	As detailed in the response to issue 3, the company acknowledge that the data collected to date is limited for a long-term disease such as SMA, as at the point of submission only data from the first 12 months of the SUNFISH and FIREFISH trials were available. However, even within the short 12-month data collection period of the FIREFISH trial, one patient acquired the ability to bounce, a milestone that can be considered as development towards the walking milestone, a state that is not possible in the natural history of type 1 SMA patients.[2] The company agree that the assumption about reaching advanced milestones on risdiplam treatment could be perceived as optimistic, and that a plateau in motor milestone attainment is a reasonable assumption. The implementation of the plateau reduces the proportion of risdiplam patients reaching the standing or walking milestones in both models. It is noted that this is likely to be a conservative approach, as the opinion of some clinical experts consulted by the company was that [redacted] (Appendix N of the company's submission).[18] The company agree to take the conservative approach suggested by the ERG, implementing a treatment plateau in line with TA588 and using the MAIC in preference to the unadjusted comparison in the type 1 model base-case analysis. The company would, however, like to highlight that the models do not adequately reflect a number of benefits of risdiplam that have a significant effect on patient and caregiver quality of life, such as improved bulbar function and feeding/swallowing, reductions in hospitalisations[2] and improved upper limb function[3] (issue 10), and consequently the value of risdiplam is not fully captured by the ICER. It is important that the fact that the broad and severe impact of SMA cannot be fully captured by the economic models or the NICE reference case is recognised and taken into account in the NICE decision-making process. Furthermore, the fact that uncertainties about long-term benefits of treatments for rare diseases are common should be taken into account, as recently acknowledged by NICE.[13] Additional considerations and NICE decision modifiers

		should be recognised for this appraisal, similarly to NICE's decision-making for nusinersen in TA588.
Key issue 8: None of the patient utility values for SMA are ideal; caregiver utility values by motor milestone are not available	**YES (see revised base case results)**	The company would like to highlight that its general intention was to align the risdiplam models with the approach taken in TA588 wherever possible. The different potential sources of utilities for the type 2/3 model (utilities derived from the SUNFISH randomised controlled trial, utilities from the Lloyd et al. (2019)[19] vignette study and utilities estimated by the ERG clinical advisors in TA588) were discussed with clinical experts at the UK advisory boards. The clinical experts recommended the use of the Lloyd et al. (2019)[19] utilities or the TA588 ERG clinical expert values over the SUNFISH trial values, as they better reflect the broad range of HRQoL between milestones (please see Appendix N of the company's submission).[18] As noted in the company submission, and acknowledged by the ERG, it is particularly difficult to collect utility values in infants and young children. Additionally, HRQoL is difficult to measure in mobility diseases,[20] making SMA a very challenging disease to model. The utility values sourced from the Lloyd et al. 2019[19] vignette study were originally chosen as the base case in the type 2/3 model with the intention to align with what was considered for final decision-making in the TA588 submission. The company would like to apologise for missing that, in fact, the utility values for the later onset model in TA588 were based on non-preference-based estimates from Biogen's clinical advisors, as the ERG rightly pointed out. The company agree that, for alignment with TA588, the non-preference-based utility estimates obtained from Biogen's clinical advisors in TA588 should be used in both the type 2/3 and type 1 models instead. As a result, both the updated company's type 1 and type 2/3 models will consistently use patient utility values based on non-preference-based estimates from Biogen's clinical advisors, and therefore both models will align with the economic models in TA588. As indicated by the ERG, limited caregiver utility values by motor milestone are available. The company chose to take the same approach as TA588, making the assumption that the value of caregiver HRQoL for SMA patients from a population

		of Spanish caregivers (sourced from López-Bastida et al. 2017)[21] reflects the caregiver utility for the worst health state in the type 1 and type 2/3 models. The assumption was made that HRQoL increases uniformly for patients in each adjacent improved health state up to a maximum value based on the level of HRQoL in the general population. The company agree with the ERG that it is unclear whether this assumption is reasonable, however, due to the lack of evidence, it was deemed best to align with the approach taken in TA588, for consistency in modelling SMA. The final adaptation to the type 2/3 model suggested by the ERG to enable full alignment with TA588, was the inclusion of 3 caregivers for the 'not sitting' health state. The company have not incorporated this adaptation into their revised economic analysis. The rationale for this is that the number of caregivers for the 'not sitting' state is a spuriously influential input in the model. This is due to the fact that its impact is driven directly by the approach taken to model caregiver QALYs (discussed in issue 4). Evidence from the Roche UK burden of illness study showed that there was no trend in caregiver numbers by health state. Accordingly, given the additional uncertainty introduced into the analysis with this input, combined with the lack of supportive evidence, it was deemed appropriate to continue to assume 2.2 caregivers across all health states in the company's revised analyses.
Key issue 9: The company's modelling assumptions are inconsistent with those used to inform decision-making in TA588 (nusinersen for SMA)	**YES (see revised base case results)**	The company understand the ERG's comment but would like to highlight that the company made a conscious effort to align with the assumptions accepted by the Committee in TA588 where possible, with the purpose of facilitating NICE decision making. The TA588 Committee papers were reviewed in detail, learnings were taken forward from the ERG and the Committee's critique in TA588, and the assumptions of TA588 were tested with UK clinical experts. Deviations from the approach taken in TA588 were generally informed by clinical expert opinion, sought through advisory boards with UK clinical experts. The company would like to highlight that not all uncertainties were resolved in TA588, as SMA is a complex disease to model, and differences between risdiplam and nusinersen may warrant alternative assumptions. For example, the implementation of discontinuation will differ due to the different mode of administration between nusinersen and

		risdiplam. The above issues address the instances in which there was misalignment between the company's submission and the approach taken in TA588, and the company agree to accept the changes by the ERG in their revised base case. Accordingly, there now is alignment with TA588 on all issues, except the approach to modelling caregiver QALYs, and the number of caregivers modelled in type 2/3 model (please see the individual responses for further details).
Key issue 10: The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills	**YES (see revised base case results)**	The company accept the limitation that both models focus on gross motor milestones and accepts the ERG's critique that the model does not capture utility gains associated with fine motor skills, such as maintaining upper limb function. The company agree with the ERG that maintenance of upper limb function represents significant value to both patient and carers, in particular for patients who cannot stand or walk. A patient's loss of upper limb function results in reduced independence, social participation and quality of life.[22] The clinical advisors to the ERG confirmed that upper limb function grants patients the ability to perform a wide range of activities, such as opening doors, opening food packets, adjusting their position and their clothing, and that these capabilities are particularly important among people without ambulation. Therefore, the company agree that an additional utility gain should be incorporated into both the type 1 and type 2/3 models for non-sitting and sitting states. Accordingly, in the revised cost-effectiveness analyses for the technical engagement, upper limb function has been modelled through application of a treatment-specific utility for risdiplam. In line with the approach taken by Thokala et al. (2020)[23] and the sensitivity analyses conducted by the ERG, additional utility gains of 0.05 and 0.10 for risdiplam-treated patients in the non-sitting and sitting states, respectively, were included. However, as already noted by the ERG, these values are assumptions and are not evidence-based. Evidence in support of this approach may be derived from the SUNFISH trial, where a clinically meaningful improvement in upper limb function, as measured by the Revised Upper Limb Module total score (RULM), was observed after 12 months of treatment with risdiplam. This was also supported by improvements on

		the SMA independence scale (SMAIS), which focusses on upper limb-related activities of independence, such as writing, dressing and washing.[3] The company would like to note that fine motor skills were originally omitted from the model for simplicity, due to the difficulty of quantifying this benefit. The company also feel that the values included are conservative and do not fully capture the magnitude of impact on quality of life that upper limb function brings to SMA patients and carers.
Key issue 11: It is unclear whether NICE's End of Life criteria apply in Type 1 SMA	**NO**	Due to the single-arm nature of the FIREFISH trial, modelling overall survival for BSC in the type 1 population represents a significant challenge. The company acknowledge that both the naïve comparison and the MAIC have multiple limitations, one of which is the optimistic overall survival predictions in this population for BSC patients. When considering prior NICE appraisals, the end-of-life criteria were also applied to SMA type 1 in TA588, which argued that the median age of death/permanent ventilation in natural history studies for type 1 SMA is 9–13 months.[1] Notably, the mean survival estimate for BSC in the early onset model for nusinersen was longer than 2 years (2.14 years), as detailed in the final appraisal determination Committee papers.[1] Furthermore, feedback from patient organisations including Spinal Muscular Atrophy UK, Muscular Dystrophy UK, Genetic Alliance UK, in addition to the Royal College of Pathologists at the draft scope consultation for onasemnogene abeparvovec consistently emphasised the short life expectancy of type 1 SMA patients of 2 years or less.[24] Additionally, the recently published report of the onasemnogene abeparvovec evaluation also states that "*SMA type 1 typically causes death before 2 years of age*".[25] According to clinician expert opinion sought by Roche, respiratory care is more commonly used in recent years to artificially extend a patient's life.[26] The reason for using respiratory care may in part be due to parents holding on to hope that new therapies, such as risdiplam, would become available to treat their children. This indicates that the extension to life on BSC is not driven through improvements to BSC, but rather carer decisions to maintain patients on respiratory care.

		Accordingly, type 1 SMA patients who do not receive an active therapy or receive extended respiratory support have a life expectancy of approximately two years.[22] Given the precedent in prior NICE appraisals for SMA, and the fact that any extension to type 1 patients' lives may be considered artificial, and associated with extremely poor levels of patient HRQoL, the company consider that the end-of-life criteria also apply for type 1 patients in the risdiplam appraisal.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
NA	NA	NA	NA

NA: not applicable

Summary of changes to the company's cost-effectiveness estimate(s): SMA Type 2/3 (SUNFISH) Model

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement [a]
Issue 1: Presence of model errors	N/A	Corrections in line with those performed by the ERG were implemented in the model: - Formulae adjustments to correctly employ long-term assumptions after 24 months - Corrected general population mortality - BSC traces extended to include 1,080 cycles - The ERG-preferred calculation of caregiver QALYs was included as *optional* setting
Issue 10: Issues relating to patient utility values	Patient utilities had been aligned with previously published values by Lloyd et al.[19]	In line with the ERG-preferred analyses, patient utilities were aligned with the final values used in TA588 (as advised by Biogen's clinical advisors)
Issue 11: Issues relating to caregiver utility values	Caregiver utility values had been informed through relevant literature (López-Bastida et al. and Ara et al.),[27, 28] in line with considerations made during the development of TA588.	In line with the ERG-preferred analyses, caregiver utility values were aligned with the final model used in TA588 (i.e. applying a general population utility of 0.915 to the Standing/Walking states and a utility of 0.700 to Not Sitting, assuming equal utility gains for the intermediate states).
Issue 10: Issues relating to patient utility values	Health state utility values had been considered to be the same between risdiplam and BSC.	In line with the ERG additional sensitivity analyses, health state-specific incremental utility benefits for risdiplam have been included for the Not Sitting and Sitting states, to reflect potential benefits in risdiplam-treated patients gaining fine motor skills.

Issue 12: Issues relating to costs	Drug wastage for risdiplam had not been accounted for.	In line with the ERG-preferred analyses, drug wastage costs (assumed to be equal to 0.5 bottles) was included for all patients initiating treatment with risdiplam.
Issue 8: Highly optimistic assumptions of long-term treatment effects	A continuous treatment effect had been assumed for the entire period patients are treated with risdiplam.	In line with the ERG-preferred analyses, a plateauing of patients treated with risdiplam (taking effect after 26 months) has been implemented.
Issue 8: Highly optimistic assumptions of long-term treatment effects	Treatment duration had been assumed to be life-time (i.e. 90 years) and treatment discontinuation had not been accounted for.	A treatment duration of 30 years was assumed, after which patients gradually waned over 10 years to align with BSC-specific long-term efficacy (i.e. motor milestone development) while still retaining risdiplam-specific survival.
Issue 12: Issues relating to costs	The potential reduction in drug costs due to the future loss of exclusivity for risdiplam had not been accounted for.	An 85% reduction to the current list price of risdiplam after 15 years (i.e. the time risdiplam loses exclusivity and generics can be expected to enter the market) has been implemented. [*Please note, this change is only applied for scenario analysis 2*]

Company's preferred base case following technical engagement	The following changes (as described above) were considered for the revised base case: - Implementation of ERG error corrections - Update of patient and caregiver utility inputs in line with the ERG-preferred values - Inclusion of health state-specific incremental utility benefits for risdiplam - Addition of drug wastage costs for risdiplam - The company's preferred approach to modelling caregiver QALYs - Inclusion of the ERG-preferred change regarding the plateauing of RSD-treated patients after 26 months - 30 years treatment duration: - 10-year waning of efficacy (motor milestone achievement) to long-term BSC assumptions - Continued risdiplam survival	**Incremental QALYs: 11.82** **Incremental costs: £[redacted]** **ICER: £[redacted]** **(change from the company's original base-case ICER, incl. PAS: [redacted]**

[a] Please note, due to the comprehensive and interlinked nature for some of the performed changes to the model in response to the technical engagement it was not possible to calculate individual ICER estimates in relation to the original base-case ICER for single changes; a breakdown of the revised base case, including all changes informing this, was provided instead.

Summary of changes to the company's cost-effectiveness estimate(s): SMA Type 1 (FIREFISH) Model

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement [a]
Issue 1: Presence of model errors	N/A	Corrections in line with those performed by the ERG were implemented in the model: - Formulae adjustments to correctly employ long-term assumptions after 24 months - The ERG-preferred calculation of caregiver QALYs was included as an *optional* setting
Issue 5: Use of unadjusted arm-based indirect comparison	Results of naïve treatment comparisons had been applied.	In line with the ER-preferred analyses, results from an updated matching-adjusted indirect comparison (MAIC) presented in the company's response to the clarification questions have been used to inform comparative treatment efficacy.
Issue 10: Issues relating to patient utility values	Patient utilities had been aligned with values used in TA588 (ERG clinical advisor).	In line with the ERG-preferred analyses, patient utilities were aligned with the final values used in TA588 (as advised by Biogen's clinical advisors)
Issue 10: Issues relating to patient utility values	Health state utility values had been considered to be the same between risdiplam and BSC.	In line with the ERG additional sensitivity analyses, health state-specific incremental utility benefits for risdiplam have been included for the Not Sitting and Sitting states, to reflect potential benefits in risdiplam-treated patients gaining fine motor skills.
Issue 12: Issues relating to costs	Drug wastage for risdiplam had not been accounted for.	In line with the ERG-preferred analyses, drug wastage costs (assumed to be equal to 0.5 bottles) was included for all patients initiating treatment with risdiplam.

Issue 8: Highly optimistic assumptions of long-term treatment effects	A continuous treatment effect had been assumed for the entire period patients are treated with risdiplam.	In line with the ERG-preferred analyses, a plateauing of patients treated with risdiplam (taking effect after 66 months) has been implemented.
Issue 8: Highly optimistic assumptions of long-term treatment effects	Treatment duration had been assumed to be life-time (i.e. 90 years) and treatment discontinuation had not been accounted for.	A treatment duration of 50 years was assumed, after which patients gradually waned over 5 years to align with BSC-specific long-term efficacy (i.e. motor milestone development) while still retaining risdiplam-specific survival.
Issue 12: Issues relating to costs	The potential reduction in drug costs due to the future loss of exclusivity for risdiplam had not been accounted for.	An 85% reduction to the current list price of risdiplam after 15 years (i.e. the time risdiplam loses exclusivity and generics can be expected to enter the market) has been implemented. [*Please note, this change is only applied for scenario analysis 2*]
Company's preferred base case following technical engagement	The following changes (as described above) were considered for the revised base case: - Implementation of ERG error corrections - Application of MAIC results for relative treatment efficacy	**Incremental QALYs: 19.97** **Incremental costs: £**[redacted] **ICER: £**[redacted] **(change from the company's original base-case ICER, incl. PAS:** [redacted]

	- Update of patient utility inputs in line with the ERG-preferred values - Inclusion of health state-specific incremental utility benefits for risdiplam - Addition of drug wastage costs for risdiplam - The company's preferred approach to modelling caregiver QALYs - Inclusion of the ERG-preferred change regarding the plateauing of RSD-treated patients after 66 months - 50 years treatment duration: - 5-year waning of efficacy (motor milestone achievement) to long-term BSC assumptions - Continued risdiplam survival	

[a] Please note, due to the comprehensive and interlinked nature for some of the performed changes to the model in response to the technical engagement it was not possible to calculate individual ICER estimates in relation to the original base-case ICER for single changes; a breakdown of the revised base case, including all changes informing this, was provided instead.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with spinal muscular atrophy and current treatment options	
About you	
1. Your name	**Anne-Marie Childs**
2. Name of organisation	**Leeds Teaching Hospitals Trust**
3. Job title or position	**Consultant Paediatric Neurologist and Lead for Children's Regional Neuromuscular Service**
4. Are you (please tick all that apply):	**X** an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with spinal muscular atrophy? ☐ a specialist in the clinical evidence base for spinal muscular atrophy or technology? ☐ other (please specify):
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 **X** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation	☐ yes

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.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**I have no links to the tobacco industry**
The aim of treatment for spinal muscular atrophy	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to enhance quality of life by preventing progressive disability and loss of motor function that result in restricted mobility and loss of independence. The resulting respiratory, bulbar and axial weakness in untreated patients results in reduced life expectancy, the requirement for multiple medical and social interventions and frequent hospital admissions.
9. 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	Given the spectrum of disease severity and progressive nature of this condition, the clinically significant effects of treatment will be different at different ages In infants with type 1 SMA stabilisation of anterior horn cell function with resulting stabilisation in motor function, in particular maintaining effective respiratory and bulbar function improves overall survival considerably can allow an infant to develop new motor skills and acquire milestones over time that are not seen in untreated SMA1 cases. In the later onset forms of SMA and when the disease is more chronic, it is more likely to see stabilisation and more subtle improvements in motor skills - but maintaining upper limb strength to independently transfer, operate controls

by a certain amount.)	has a considerable impact on independence and in turn meaningful participation in society with less need for carer support and medical interventions I
10. In your view, is there an unmet need for patients and healthcare professionals in spinal muscular atrophy?	Yes, having access to Nusinersen via the MAA has transformed the lives of many affected patients. However the terms of the MAA mean that some affected individuals, who could benefit in particular those with type 3a SMA, those with complex spinal anatomy and others who are unable to tolerate repeated LP or indeed access a treatment centre with capacity are unable to receive treatment. In addition there are some 'non responders' to Nusinersen and the response is not always seen in respiratory and bulbar function
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Supportive MDT care remains a key part of SMA management across all disease types and states. This may include a range of interventions including mechanical secretion clearance, ventilator support, nutritional support including enteral feeding, postural management including orhopedic and/or spinal surgery, adaptations in home, education or workplace and additional support to maintain self care. In addition, those patients who meet criteria for the MAA for Nusinersen and wish to receive this, will be offered treatment depending on capacity of the treating sites. Some type 1 and 2 patients are also receiving Risdiplam via the EAMS
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is an international consensus on recommended standards of care in SMA (2007) updated in 2017, which provides a framework for management. The UK has a network of clinicians, specialist nurses and physiotherapists (SMA REACH) who work together to implement these standards, using standardised medical and therapy assessment tools to collect information on disease progression, function, complications and treatments. The data is stored, with patients consent, on a protected database as part of a national audit.
• Is the pathway of care well defined? Does it vary or are	The pathway is relatively well defined but there are points of clinical decision making that are not always 'clear cut' for example when to initiate ventilation is dependent on a number of variables. In addition the

there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	resources across different regions vary and so there is some variability for example in wheelchair provision, access to therapy, access to mechanical secretion clearance There are other barriers that particular groups may have in accessing treatment in particular among the socially deprived and in those from varying ethnic backgrounds who may have different cultural and ethical values in relation to health care choices and whose voice is often unrepresented (see treat SMA and SMA Uk surveys, which do not reflect the diverse ethnicity among the 40 young people with SMA under my care)
• What impact would the technology have on the current pathway of care?	The delivery of the drug is clearly more straightforward than intrathecal injection and so is feasible in a wider patient cohort than Nusinersen. Given the results form Firefish and non clinical trial use on both motor, respiratory and bulbar function in type 1 infants there may be greater benefits to respiratory and bulbar function from systemic administration, which have a significant benefit on overall well being, given that most hospitalisations in type 1 and 2 patients relate to decompensation in relation to chest infections
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	At present access is only via an EAMS for type 1 and 2 patients who cannot access Nusinersen, and there is likely to be a much broader use particular in adult patients and those < 18 yrs with complex spinal anatomy of difficulty tolerating repeated LP The 'choice' of 1 treatment over another ie Risdiplam v Nusinersen v Onasemnogene may be difficult in some patient groups particular as there is little comparative data, in most instances the choice will be between Nusinersen and Risdiplam and will depend on efficacy/safety and ease of delivery together with the terms of access agreed by NICE/NHSE
• How does healthcare resource use differ between the technology and current care?	Those with preserved or improved motor skills require less medical, social and therapy input. In particular improved respiratory and bulbar function can reduce need for hospital admission and use of other technologies.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Risdiplam treatment should be initiated, prescribed and monitored in specialist NM centres with MDT expertise in management of SMA, to ensure that patients are given the best possible advice regarding treatment options and that the safety and efficacy of the drug can be accurately assessed However, given the restricted mobility in this condition and the varied geographical locaton of such specialist centres,

	facilities for drug delivery nearer to the patients home should be considered
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will be a need for training of NM teams, pharmacy and other personnel in drug management as per the EAMS process Not all UK NM centres are currently delivering Nusinersen or participating in SMA REACH so there may be some training needs to support effective physiotherapy assessment/medical care In SMA REACH centres managing children these systems are in place and the 'extra' costs' are likely to be minimal, however, this may be more of a challenge in an adult centre where patients may well 'return' to regular FU creating additional demands on existing resources. There are fewer adult REACH centres and it likely that expansion will be needed
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes definitely
• Do you expect the technology to increase length of life more than current care?	Yes - particularly in the weaker more severely affected patients whose life expectancy in natural history studies is very poor.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes as outlined above

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, the most severely affected type 0 patients have not been treated to date and are less likely to have 'rescuable' anterior horn cells on the basis of the mechanism of action and pathology The benefits of exon skipping drugs (and indeed gene therapy) are most marked in those treated early in their disease course, when nerves have the potential to recover and secondary complications of contractures, scoliosis, chest deformity etc that have an independently negative impact on function have not yet developed. Therefore the 'effects' in those with a long disease course secondary complications are likely to be less marked, though small differences in fine motor function can have a considerable impact on quality of life and most of the assessment tools do not capture these subtleties. Similarly the improvements in very weak patients on permanent ventilation are not known as these patients were excluded from the clinical trials and EAMS , but are likely to be less than in those without significant respiratory muscle weakness.
The use of the technology	
15. 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	The safety profile is relatively good and most AEs and SAEs in the clinical trials were disease rather than treatment related. The SmPC does not recommend particular monitoring The potential impact on fertility is a concern in the adult population and may affect uptake in certain groups The need to keep the drug in the fridge might be challenging in certain settings There may be compliance issues with a daily medication in an adolescent cohort - but generally patients are highly motivated to take disease modifying drugs

monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It would seem sensible to set some starting criteria around disease severity ie PV and in relation to stopping drug in face of lack of response ie on-going deterioration in muscle function despite treatment for a specific period (? similar to MAA ie across 2 assessments 6 months apart, allowing for potential variables) or if there is evidence of poor compliance Setting criteria about stopping in face of progressive decline will mean that these assessments need to be done by the NM MDT which may have implications for certain NM teams
17. 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?	Benefits to the individual and carers need to be taken into account Also capturing some meaningful QofL measure/ looking at PROMS as per the surveys submitted by Treat SMA and SMA UK is critical to understanding the real beenfits/impacts of treatment
18. 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	Yes, for reasons already stated Particular relevance in those who cannot access Nusinersen for both patient specific (complex spines, high risk GA) MAA criteria (those with type 3a who have lost ambulation) or service related (lack of treatment capacity or interventional radiology support)

is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes for some patients, but for others it may be a choice between Risdiplam and Nusinersen depending on final agreement with NICE/NHSE
• Does the use of the technology address any particular unmet need of the patient population?	Yes see above
19. 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 drug seems to be well tolerated with few AEs though the impact on fertility is likely to be significant in certain patient groups
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Trials were not conducted in the UK, but there is some evidence form the EAP and now the EAMS in UK and the nature of the patients, standards of care and outcome measures used are comparable with UK practice
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes,	Key Outcomes vary for different disease states/severity

and were they measured in the trials?	In SMA this is event free survival as well as improvements in motor function and acquisition of motor milestones In less severe disease states outcomes may relate to more maintenance/improvements of more subtle motor skills, independence, participation and quality of life
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The outcomes are motor states and survival and do not capture all the relevant issues as noted in the ERG report
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes there is further emerging data from the ongoing clinical trials, the EAMS for type 1 and 2 patients and in real world use in other countries
22. How do data on real-world experience compare with the trial data?	Reviewing data provided by PAGs responses in older type 2 and 3 patients seem more positive than in clinical trials, though the reports reflect 'relative' before and after improvements across different systems than specific functional scores as used in the trials.
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not specifically
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24a. Thinking about current NHS practice: would you expect any patients treated with best supportive care to reach the milestones of standing and walking in their lifetime (please answer separately for type 1 and type 2/3 disease)? b. Of these patients, how long (on average) would these milestones be retained?	No: type 1 patients treated with BSC will not sit independently and never acquire standing and walking Type 2 patients will not stand or walk without support, and the majoirty will lose their independent sitting balance before adulthood. Some may walk with aids and equipment in early childhood but this will usually be lost before 2nd decade Type 3 patients will stand independently and many will walk, though there are a group of 'borderline' patients who never achieve independent walking as defined by WHO but can walk with aids. The subgroup of type 3a patients are weaker and many will lose their ability to walk unaided in childhood

25. What is the average life expectancy for people with spinal muscular atrophy treated with best supportive care in the NHS? (please answer separately for type 1 and type 2/3 disease)	In type 1 , the natural history data suggests that 85% will die within the 1st year of life and very few will survive past 2 years of age. In recent times the supportive care has improved and with ventilation, enteral feeding and careful management of secretions, some infants may live up to 5 or more years, though motor function continues to decline and the majority will still die before their 2nd birthday The life expectancy in type 2 and 3 is dependent on overall disease severity and respiratory function, with more severely affected patients requiring permanent ventilation in childhood with a resulting life expectancy on 20-30, with some stronger type 3 patients never requiring ventilator support and having a relatively normal life expectancy, though all patients have steady decline
26. Thinking now about treatment with risdiplam: would you expect continued improvements that are maintained indefinitely over a patient's lifetime or is it clinically plausible to assume a plateau effect (similar to that assumed in the technology appraisal for nusinersen?)	It seems plausible to assume some kind of plateau effect similar to Nusinersen
27. Would you expect the long-term benefits of risdiplam to be greater than that observed in the	Potentially as the trial data is reported over a relatively short time frame and improvements from Nusinersen which has a similar mode of action, appear to be sustained for longer than 1 year. Also important to consider that preventing decline or plateauing is a benefit in a progressive disease

clinical trials? If so, why?	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients	This is true, but it is reasonable form the data available from clinical trials and 'real world' use that the greatest benefits are seen when treatment is initiated early and at a time when anterior horn cells have capacity to respond to additional SMN protein. The preliminary data from Rainbowfish and indeed from studies looking at other SMN increasing disease modifying drugs is that treatment of pre symptomatic infants is likely to yield the greatest benenfits. However, it is impossible to predict the 'type' of SMA from the SMN1 deletion alone and given the expense of the drug, and need for prolonged therapy, it should be targeted at preventing more severe disease in asymptomatic infants likely to develop type 1 or 2 SMA based on SMN2 copy number. Whilst there are exceptions, this would mean those with 2 or 3 SMN2 copies Data from trials of Risdiplam and other SMN protein increasing drugs suggests that treatment benefits are likely to be less marked in the most severe disease and so it is difficult to support 'routine' treatment in those with SMA type 0, though this might be an area where an MAA would be indicated though the

	numbers are very small I have little experience of managing type 4 patients, but the impact of the disease is less and so it is harder to justify high cost treatments
Key issue 2: Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA	This reflects the lack of a control group in the Firefish study and the fact that data reported is only for 12 months. The natural history of SMA 1 is well understood with untreated infants only losing motor milestones and function, resulting in significant reduced life expectancy dependent on the extent of the supportive care The baseline characteristics of the Firefish patients are clearly those of an SMA 1 population and given the 'hard' endpoints of survival without PV or need for feeding support as well as the improvements in motor milestones, I do not feel that there is likely to be significant sample bias or non treatment effects contributing to the outcome. The benefits are similar to those reported in the treated Endear group at 13months and given that both drugs have a similar mechanism of splice modification of SMN2, this is relevant. The benefits in respiratory and bulbar function appear to be sustained in further longitudinal data from Firefish with infants acquiring additional motor skills though this data has not yet been published
Key issue 3: Uncertainty surrounding long-term benefits of risdiplam	There is no published data to support long term benefits, but further data is emerging form the clinical trials and real world use to indicate continued benefit from treatment > 12 months In addition the benefits of the other SMN2 splice modifying drug Nusinersen have been shown to be sustained in type 1 SMA, so whilst the 'improvements in motor gains on Risdiplam may plateau depending on the infants disease severity and the degree of 'reversibility' of nerve damage, there is no biological reason why the drug should behave differently to Nusinersen where treatment effects seem to be maintained
Key issue 4: Caregiver QALY gain calculations implicitly	I am not an expert on this, but having read the ERG report, I agree that a caregivers quality of life may not equate to 0 after the death of an SMA patient, although clearly the loss of a child/loved one will have a significant impact on a carer's ' utility' which may be sustained

assume that caregivers die or survive with utility equal to zero after the SMA patient dies	
Key issue 5: The company's models do not include any discontinuation from risdiplam	I agree that this is an oversight. It is likely that there will be some non-responders where the condition continues to progress, some who may find side effects unacceptable and some where compliance is evidentially poor and does not justify continued treatment
Key issue 6: The company's models assume that in the subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely	In an infant the 'gains' in motor skills in the 2nd year of treatment could conceivably be more marked - as this coincides with a period of greater childhood development. For example a child with developmental delay may not sit until 1 year but could then learn to stand and walk before their 2nd birthday An infant with severe muscle weakness who is acquiring more muscle strength may take longer to acquire the power/skills to crawl, stand and walk and these skills may only develop after a loner period of treatment ie in the 2nd year In an older child, such continual improvements in motor skills are less likely - particularly if there are other disease complications such as contractures that have additional restrictions on movement. In this group the improvements in motor skills are likely to be more subtle and the treatment goal is likely to relate to stabilisation and prevention of decline which is clearly a more 'static' phenomenon that cannot improve year on year
Key issue 7: The company's models predict that a large proportion of patients will reach the milestones of standing or walking, which appears to be	This is particularly optimistic in later onset SMA with more chronic disease given the issues above Given the lack of long term data in Firefish the 'ceiling' effect is unknown, though it seems unlikely from parallel Nusinersen data that a 'large' proportion of type1patients, other than those treated pre symptomatically, although some will continue to develop skills. Some type 1 patients treated with Nusinersen and Onasemnogene have taken several years to achieve independent walking and this is likely to be the case with Risiplam given its mode of action

optimistic.	
Key issue 8: None of the patient utility values for SMA are ideal; caregiver utility values by motor milestone are not available	Again not my area of expertise except that motor milestones are not the sole determinant of level of care. Need for secretion clearance, suction, feeding, repositioning for pain, lack of ability to transfer independently - may be found to varying degrees in 'sitters' and these have a greater impact on carers than the fact that the individual cannot stand without support
Key issue 9: The company's modelling assumptions are inconsistent with those used to inform decision-making in TA588 (nusinersen for SMA)	
Key issue 10: The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills	Agree and this is supported by my clinical experience and the survey responses and documentation provided by the PAGs
Key issue 11: It is unclear	I agree that changes in supportive care have increased the life expectancy in infants with type 1 SMA,

whether NICE's End of Life criteria apply in Type 1 SMA	managed with BSC However the majority of infants with BSC will die within the 1st 2 years of life.
Are there any important issues that have been missed in ERG report?	The potential benefits of systemic administration of an SMN2 splice modifying drug to increase SMN production in the anterior horn cells throughout the spinal cord and corresponding improvements in nerves supplying the bulbar and respiratory muscles. This is relevant for those with type 2 and indeed type 3a SMA where respiratory decline is inevitable and likely to result in respiratory failure

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- There remains considerable unmet need in the UK SMA population despite implementation of MAA for Nusinersen and potential access to gene therapy in specific disease groups
- There are real benefits in HRQL and OS from improvements in respiratory and bulbar function. This is relevant for the later onset forms of SMA as well as infants with type 1
- Treatment early in the disease course is likely to yield the greatest benefit in motor milestones, but more subtle improvements later in life can be crucial in supporting independence and participation
- Given the costs of the medication and uncertainty about longer term benefits, setting some starting and stopping criteria would be helpful
- Whilst there may not be long term data regarding Risdiplam use, it would seem reasonable to expect a similar treatment profile to that seen with longer Nusinersen use, given its mode of action and comparable results in clinical trials

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

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Clinical expert statement & technical engagement response form

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with spinal muscular atrophy and current treatment options	
About you	
1. Your name	**Satvinder Mahal**
2. Name of organisation	**Great Ormond Street Hospital**
3. Job title or position	**Lead Pharmacist – Neurosciences**
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 spinal muscular atrophy? ☐ a specialist in the clinical evidence base for spinal muscular atrophy or technology? ☐ other (please specify):
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.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for spinal muscular atrophy	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Survival. The motor neurones most affected by this condition are those that allow walking, crawling, arm movement, head and neck movement, swallowing and breathing coupled with infants failing to achieve major motor milestones.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Survival, ventilation and swallowing ability.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in spinal muscular atrophy?	Treatment option compared to supportive. Yes, if current treatment (nusinersen) is not possible in patients develops severe scoliosis or increased difficulty for intrathecal access with or without IR support available.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Nusinersen intrathecal injections Supportive care.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Nusinersen TA Supportive care.
• 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.)	SMA networks within NHS
• What impact would the technology have on the current pathway of care?	Additional option to nusinersen injection.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes.
• How does healthcare resource use differ between the technology and current care?	Additional option.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist centres who have experience in treating SMA patients.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Initial baseline prior treatment. Treatment supply. Additional appointments to see response of treatment.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, alternative to current treatments particularly to patients not able to have intrathecal injections.
• Do you expect the technology to increase	Yes, treatment of SMA compared to supportive care.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, motor, bulbar, respiratory function and other complications.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Option should be available to clinician expert SMA for all SMA 1-3 patients.
The use of the technology	
15. 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	Will be easier. Additional appointments for baseline and response during treatment.

ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Initial criteria assessment and yearly review.
17. 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?	Yes, symptoms are subjective.
18. 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?	Yes, access to treatment for a condition otherwise managed by supportive care.

• Is the technology a 'step-change' in the management of the condition?	Yes, additional option.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, option for treatment.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Minot side effects not likely to affect QOL.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes,	Survival, ventilation and bulbar.

and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, likely.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Nothing outside defined.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Comparable for selected inclusion criteria.
Equality	
23a. Are there any potential equality issues that should be	No, if offered to proposed pathway.

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
24a. Thinking about current NHS practice: would you expect any patients treated with best supportive care to reach the milestones of standing and walking in their lifetime (please answer separately for type 1 and type 2/3 disease)? b. Of these patients, how long (on average) would these milestones be retained?	Not for either SMA1 or SMA 2 or 3, will supportive care provide advantage over risdiplam.
25. What is the average life expectancy for people with spinal	SMA1 sever forms within 2 years of age.

muscular atrophy treated with best supportive care in the NHS? (please answer separately for type 1 and type 2/3 disease)	SMA2/3 depending on symptom and spectrum of disease.
26. Thinking now about treatment with risdiplam: would you expect continued improvements that are maintained indefinitely over a patient's lifetime or is it clinically plausible to assume a plateau effect (similar to that assumed in the technology appraisal for nusinersen?)	Plateau effect similar to nusinersen.
27. Would you expect the long-term benefits of risdiplam to be greater than that observed in the clinical trials? If so, why?	Yes, open to wider range of SMA patients.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients	Some experience of trial use in patients previously treated by nusinersen.
Key issue 2: Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA	Not agree completely as not enough data at this moment.
Key issue 3: Uncertainty surrounding long-term benefits of risdiplam	Not agree completely as not enough data at this moment.

Key issue 4: Caregiver QALY gain calculations implicitly assume that caregivers die or survive with utility equal to zero after the SMA patient dies	No comment.
Key issue 5: The company's models do not include any discontinuation from risdiplam	Not enough data at this moment.
Key issue 6: The company's models assume that in the subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely	Not enough data at this moment.
Key issue 7: The company's models predict that a large proportion of patients will reach the milestones of standing or	Not enough data at this moment.

walking, which appears to be optimistic.	
Key issue 8: None of the patient utility values for SMA are ideal; caregiver utility values by motor milestone are not available	Not enough data at this moment.
Key issue 9: The company's modelling assumptions are inconsistent with those used to inform decision-making in TA588 (nusinersen for SMA)	Yes agree, as not enough data to support this.
Key issue 10: The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills	Yes agree.

Key issue 11: It is unclear whether NICE's End of Life criteria apply in Type 1 SMA	Will need SMA specialist clinician to interpret.
Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Proposed treatment provides patient access to treatment
- Review needed as more data from trials become available
- Suitability of being an oral treatment provides advantage over other treatments
- Treatment pathway needs review once gene therapy is approved
- Treatment accessibility to patients not meeting exact criteria needs to an option

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

✓**Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Thank you for agreeing to give us your views on this treatment 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.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Wednesday 10 March 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important 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 want 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 15 pages.

PART 1 – Living with or caring for a patient with spinal muscular atrophy and current treatment options	
About you	
1.Your name	**Andi Thornton**
2. Are you (please tick all that apply):	☒ a patient with spinal muscular atrophy? ☒ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with spinal muscular atrophy? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	TreatSMA
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☒ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: **I am Trustee of TreatSMA supporting and representing many with the condition** ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with spinal muscular atrophy? If you are a carer (for someone with spinal muscular atrophy) please share your experience of caring for them.	I am a 47 year old adult with SMA type 2, meaning I have never walked independently. Living with the condition is extremely difficult, not only because of the significant physical limitations, but the ongoing deterioration and the mental health conditions that this creates. Those with SMA are often of high intelligence and understand the condition and what it means, therefore the constant thought of losing functionality is a significant mentally challenging aspect of the condition. The relentless and constant need for assistance with every aspect of life is exhausting. It also makes having any kind of relationship or friendship extremely challenging. It's difficult when you need help with simple things such as feeding and drinking, largely removes your entire social life. For example, Christmas dinner celebrations with work colleagues is just not something I would ever consider attending because of the assistance I need. You kind of leave yourself in a bubble of a very small number of people who understand and are prepared to support the condition.

	I have been fortunate enough to be able to hold down a job with significant responsibility, but that is primarily down to the fact that I am at a level of experience where I am mostly providing leadership. Throughout my career I have felt my weakness increase and have always had that fear in my mind what would happen if I could no longer work. My employment means a lot to me, to a large extent it is the only independence that I really have, but should I lose the ability to use a mouse or even press a mouse button it would be gone overnight. These are the kind's of concerns that are on a your mind constantly.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for spinal muscular atrophy on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	After waiting 45 years with no treatment any treatment is essentially miraculous. While as an adult I am not eligible for Zolgensma, I believe this has the opportunity to completely change the way SMA is managed. In terms of treatments I am eligible for, the alternative to risdiplam is nusinersen, which although works scientifically in a very similar one, is significantly more difficult for administration. Most adults with SMA have had a spinal fusion, either partially or fully. This means that metal rods or plates are placed across the spine to correct scoliosis, another common complaint with SMA. Because nusinersen is delivered through intrathecal injection most adults do not have adequate access to the lower lumbar part of their spine to be able to receive such treatment. I for example am one of those. This means that if risdiplam was not available I would have no choice of treatment. As an adult, you also have issues with bone density. Often bones can be easily broken while being moved. This poses a significant risk to adults who would have to have spinal injections every 4 months, and from a personal perspective, the

	whole process feels somewhat degrading. We also cannot ignore the fact that with Covid 19 there are added risks of bringing those with SMA into a hospital environment. More generally, the NHS is focusing heavily on reducing hospital footfall and this is likely to be the case for some time to come. Inviting clinically extremely vulnerable patients into a hospital setting every 4 months is not the best way of managing these patients. We also need to remember that there is a significant cost in terms of administration with nusinersen, often the treatment requires interventional radiology to assist with guiding the injection. Risdiplam has an oral agent is much easier and cheaper to administer. As a Trustee of TreatSMA I have had the benefit of speaking to many patients of all ages, and my views reflect these..
8. If there are disadvantages for patients of **current NHS treatments** for spinal muscular atrophy (for example how the treatment is given or taken, side effects of treatment etc) please describe these	As described above the administration of nusinersen poses clinical risks as does any lumbar puncture. In addition to that we are asking clinically extremely vulnerable patients from Covid 19 to enter the hospital on a regular basis, when we should be looking at ways to treat patients closer to home. Parallel risks exist with regards to manual handling and the risks of a patient being injured. The intrathecal injection method for nusinersen is a large impediment to many people having access due to spinal fusions.
Advantages of this treatment	
9a. If there are advantages of risdiplam over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your	• As someone not able to receive nusinersen risdiplam has a major impact on my quality-of-life. • The improved mental health that goes along with knowing that I will no

ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does risdiplam help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	longer deteriorate from the condition • My ability to continue working for the NHS • Ease of administration, something that can be done at home by the patient or carers, without the need for hospital Intervention • The personal and emotional trauma of regular intrathecal injections • The significantly reduced risk of not having to attend hospital on regular basis for what is significantly invasive treatment, as well as reduced risk of additional infections such as Covid 19 • If I was to identify one of the above it would be the knowledge of not suffering continued deterioration
Disadvantages of this treatment	
10. If there are disadvantages of risdiplam over current treatments on the NHS please describe these? For example, are there any risks with risdiplam? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	

Patient population	
11. Are there any groups of patients who might benefit more from risdiplam or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	For many of the reasons I have stated above, risdiplam can often be the only option available to them in terms of receiving treatment. The large cohort of patients who have had spinal fusions will benefit significantly. Also, those elderly patients who it is difficult to get to hospitals and potentially the risks of being harmed or infected within hospital, risdiplam has a significant advantage. There are no real disadvantages to risdiplam to the best of my knowledge.
Equality	
12. Are there any potential equality issues that should be taken into account when considering spinal muscular atrophy and risdiplam? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race,	See above. Without having access to risdiplam those patients who are of an older age will be denied treatment.

religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	The committee needs to understand that inevitably many focus on improvements in the condition when it comes to treatment. The natural history of SMA is well known, and it is irrefutable that it is a degenerative condition. Therefore, it is important to note that stability of the condition is just as important as improvement. In fact, stability equals improvements in many areas because someone would have lost the ability to do something but they haven't, therefore that is an improvement. We need to move away from the constant expectation of improvements. For example, there is often much emphasis put on walking or standing. I have never walked or stood independently and nor do I feel the need to. I have had a pleasant and successful life and career without the ability to walk. However, if I was to be

	able to develop enough strength to be able to pick up a cup that would have a life changing impact on me. The ability to go to a pub and drink with friends, work colleagues, be healthier because I would be able to hydrate myself, it's these little things that need to be taken into account.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. Please describe the experience of those who live with spinal muscular atrophy (please specify type). Please also describe the experience prior to access of disease	

modifying drugs such as nusinersen.	
15. Please describe the experience of caregivers. This may include physical, emotional or financial burden, impact on the family etc.	
16. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Please don't think that because there is alternative treatment available that this is not required, it absolutely is due to the volume of patients who won't be able to tolerate intrathecal injections.
- This treatment is not about improvements, it's about halting the natural history of SMA, stabilisation is just, if not more so, important than improvements.
- Walking and standing should not be a consideration as to efficacy, lifestyle enhancements can be as small as being able to pick up a cup.

- There needs to be greater emphasis on the mental health of both the person suffering from SMA and those around them, including carers, family and wider family, all of whom often get involved in caring.
-

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.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Thank you for agreeing to give us your views on this treatment 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.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

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Completing this form

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Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

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- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with spinal muscular atrophy and current treatment options	
About you	
1.Your name	**Liz Ryburn**
2. Are you (please tick all that apply):	☐ a patient with spinal muscular atrophy? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with spinal muscular atrophy? ☐ X a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Spinal Muscular Atrophy UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ X Yes, I authored / was a contributor to my nominating organisations submission ☐ X I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with spinal muscular atrophy? If you are a carer (for someone with spinal muscular atrophy) please share your experience of caring for them.	
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for spinal muscular atrophy on the NHS?	

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for spinal muscular atrophy (for example how the treatment is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of risdiplam over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does risdiplam help to overcome/address any of the listed disadvantages of current treatment that you	

have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of risdiplam over current treatments on the NHS please describe these? For example, are there any risks with risdiplam? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from risdiplam or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	

Equality	
12. Are there any potential equality issues that should be taken into account when considering spinal muscular atrophy and risdiplam? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. Please describe the experience of those who live with spinal muscular atrophy (please specify type). Please	

also describe the experience prior to access of disease modifying drugs such as nusinersen.	
15. Please describe the experience of caregivers. This may include physical, emotional or financial burden, impact on the family etc.	
16. Are there any important issues that have been missed in ERG report?	
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • • •	

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Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Thank you for agreeing to give us your views on this treatment 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.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 30 April 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important 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 want 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 15 pages.

PART 1 – Living with or caring for a patient with spinal muscular atrophy and current treatment options	
About you	
1.Your name	**LUCY FROST**
2. Are you (please tick all that apply):	☐ a patient with spinal muscular atrophy? ☐ a patient with experience of the treatment being evaluated? ☒ a carer of a patient with spinal muscular atrophy? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	TREATSMA
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with spinal muscular atrophy? If you are a carer (for someone with spinal muscular atrophy) please share your experience of caring for them.	My son George is aged 9 and has Spinal Muscular Atrophy type 2. Spinal Muscular Atrophy is a devastating, soul destroying condition. As a parent or individual, how do you process the fact that your child or yourself is only going to get progressively weaker? Caring for George and living with the reality of SMA is emotionally, mentally, financially and physically exhausting. So, when George did receive Risdiplam, even knowing alone George would get treatment that would stop his decline at the very least impacted our family positively. The relief, the removed pressure and pure joy already had an effect on everyone's mental health in the home. George needed me for everything. This was exhausting for me and made George anxious of my contact whereabouts. The tables have turned since starting Risdiplam, George has become a very independent little boy. From opening doors, turning taps, cutting food, dropping a pencil and retrieving it, blowing his nose and

	turning on his own cough assist machine should he need it has made a massive impact on my life as a carer as George could do none of these things before. Our relationship has become more son and mother rather than son and carer.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for spinal muscular atrophy on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a. I have no personal experience with Spinraza, but I know George would find the lumbar puncture traumatic leading to anxiety and possible further mental problems down the line. Unlike Risdiplam, he would need hospital visits, which means time off school and at risk of infection in a hospital environment. 7b. Risdiplam is a universal treatment. It is far more accessible than other treatments. Those that take Risdiplam have a far less stressful experience, can remain at home, with no possible side effects from how it is administered. Work and school can continue as normal.
8. If there are disadvantages for patients of **current NHS treatments** for spinal muscular atrophy (for example how the treatment is given or taken, side effects of treatment etc) please describe these	There is no fully approved treatment and best supporting care will unequivocally lead to deterioration and for weaker patients to respiratory complications and death. Palliative care should not have a place where there are appropriate treatments must be in place. Palliative care has many disadvantages! But in a nutshell it inevitably leads to loss of function and in weaker patients, loss of life. Whilst Spinraza is assessed under MAA, it is not considered as an official treatment, however it is important to note that it has disadvantages: it is administered via lumbar puncture. This can cause headaches, poses a risk in itself, and additional risks if the individual needs sedation.

Advantages of this treatment	
9a. If there are advantages of Risdiplam over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does Risdiplam help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	9a. Risdiplam has improved my son's respiratory system. His lung capacity has improved giving him a stronger cough, this means he has the abilities to clear secretions and not need machines to clear airways. A simple cough does not lead to pneumonia or a lung collapse due to mucus remaining on the chest and not lifting due to weak cough. It also gives independence in school, more time in school due to better health and no hospital stays.. My son also no longer aspirates, all of the above means George no longer gets chest infections which means no hospital stays, weeks off school, time off work for his father, extended family not needed to help with his sister, and I am not putting my own health at risk doing such intense care, not to mention the additional equipment and medication that would be needed. George has gained phenomenal physical strength and is doing things he has never done. His mental and emotional health has improved as his confidence and independence has soared. From doing his own respiratory physio, wiping his bottom, getting onto the floor from the sofa, bum shuffling, cooking, emptying the dish washer, writing and playing the piano. All of the above he couldn't do. George helps me with housework – how amazing! Whilst I have first-hand experience with George as above, many parents and adults across the globe report similar improvements. Therefore, I can, with confidence, state that my family is not a unique case! 9b. Respiratory simply because, if compromised, could cost George his life. 9c. Yes because it is an oral treatment delivered to your home that can be taken at home.

Disadvantages of this treatment	
10. If there are disadvantages of Risdiplam over current treatments on the NHS please describe these? For example, are there any risks with Risdiplam? If you are concerned about any potential side effects you have heard about, please describe them and explain why.	No.
Patient population	
11. Are there any groups of patients who might benefit more from Risdiplam or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	All SMA patients will benefit from treatment. SMA is a progressive treatment for **everybody.**
Equality	
12. Are there any potential equality issues that should be taken into account when considering spinal	There will only be equality issues if Risdiplam is not approved for all ages and types. SMA is SMA, it does not pause for one type. For example, type 3s, who are still left without treatment, they are having to watch their child deteriorate or

muscular atrophy and Risdiplam? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	themselves get weaker, whilst other begin to access treatment. This must be very hard to watch, especially when your deterioration and strength then mirrors that of a weaker type. You are getting weaker as your SMA friends get stronger. This physical impact may be obvious, but the mental impact of getting progressively weaker as your friends and community get stronger is bound to cause great distress and mental health issues. I quote a type 3 parent, which mirrors the feelings of the whole community: "How is it fair to give some a treatment while others can't, and just sit by 'literally' and watch others progress and not deteriorate while they are a prisoner to their own body. They know others have the same condition, yet they still can't be treated the same right to receive treatment." SMA Types were designed by clinicians to allows them to describe diagnostics of patients more effectively for the purpose of record keeping. These were never meant to be a decisive label used to prevent access to the treatment and generate inequality based of the differences between standing and sitting.

Other issues	
13. Are there any other issues that you would like the committee to consider?	The effect SMA has on siblings who become young carers and their mental and academic wellbeing. The wider extended family who are drawn in to help. The cost of equipment and remembering that the equipment grows with the child. A piece of equipment is not bought and that's it, it is replaced constantly, and more support is needed with the equipment when the child or adult who is not on treatment get weaker e.g., head rests, lateral supports etc. The cost for more supportive equipment, core, respiratory devices, technology as the treatment progresses

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. Please describe the experience of those who live	SMA is a horrendous condition which progresses over time. It takes away independence, quality of life and is a constant threat to existing on this earth. The patient has quality of life and can contribute to

with spinal muscular atrophy (please specify type). Please also describe the experience prior to access of disease modifying drugs such as nusinersen.	society; imagine having so much to offer but not being able to do it simply because your muscles were weak. What a waste of life that someone has to experience and offer. Already George has gained so much strength that has seen him do better in school simply because he has the stamina and energy. I know he will go on to work, I am so pleased Risdiplam has enabled him to show his full potential. Treatment needs to be approved to all. It is unacceptable to allow someone to waste away within their body, with their loved ones helplessly looking on, when there is a treatment to prevent it.
15. Please describe the experience of caregivers. This may include physical, emotional or financial burden, impact on the family etc.	SMA causes a massive financial burden: equipment, time off work, unable to work, illness, adaptions and transport. Emotionally and physically, it is exhausting but has improved considerably since my son has been on treatment. Not having to worry about him declining in itself is massive. I feel like we are living and not existing. I know our future is bright, not just for George, for us as a family, especially my daughter who became a young carer, and the grandparents too. Risdiplam has changed our lives for the better.
16. Are there any important issues that have been missed in ERG report?	
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • Treatment for all.	

- Risdiplam has changed my son's life, and his family's.
- My son has not been ill once since starting treatment and no longer aspirates.
- Consider the quality of life of the patient, family and extended family.
- Risdiplam is an oral treatment and can be delivered and taken in your own home with no trauma of a lumbar puncture or risk with sedation.

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.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 10 March 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**For Spinal Muscular Atrophy UK and MDUK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients	**No**	**Type 0 and 4** Though we agree the company has not provided evidence of treatment for Type 0 and 4, and we are aware that the scope of this appraisal is for those with SMA Type 1, 2 and 3, we wish to strongly reiterate our view that access to treatment should not be defined by Type of SMA. The clinical classifications and 'Typing' of SMA were introduced in 1990 by a committee of clinicians and geneticists to promote collaborative studies between different centres and to identify the genes of SMA. Their classification was based primarily on the age of onset and the age of death, with the ability to sit unaided and stand and walk unaided added on. **The classifications were never meant as a way to make decisions about who should / should not have access to treatment** (V Dubowitz writing in 'SMA Disease Mechanisms and Therapy' edited by Summer, Paushkin & Ko, 2016). It is well recognised that SMA is a continuum and that there can be great variation in the impact of a person's SMA both between and within these so-called Types. More accurately termed 5q SMA, SMA Types 0,1,2,3 and 4 have the same genetic cause and are agreed to represent a spectrum. Most trials for all the new treatments for SMA were set up at a time when 'type' was not so strongly challenged. Most set out, at least initially and understandably, to trial treatment for the most severe SMA accounting for some 60% of the incident

		population where children rarely survived their second birthday. In doing so, the primary outcome was 'increased survival' together with the more easily measured outcomes of motor milestones and impact on respiratory function. As has subsequently been realised, this ignores other important but more difficult to measure outcomes. Added to this, an enrolment cut off for these most severely affected children may well have been selected as six months of age to protect trial integrity. This despite the 1990 classifications referring to this most severe SMA as occurring when a child shows **symptom onset** before the age of 6 months. This could therefore lead to misinterpretation of the results as meaning this treatment would only be suitable and have efficacy for children of this age range. As trials evolved and the realisation that these new treatments could impact on those who develop symptoms later, so they moved to the next group classification of type. This has invariably meant that those who develop symptoms from the age of 18 months onwards are left until last. Notably the traditional type 3 classification includes a huge range of ages up to 18 years with some children losing walking ability by the age of 3 years and others not until their teens; for some their SMA impacts their breathing, while for most this does not happen. Added to this we have the classification Type 4 and, as one person responding to our survey about access to risdiplam put it, "*In the past all research has been focusing on type 1 and 2 and 3. Nothing on type 4. Is type 4 not as important? Is my life over with nothing to look forward to except caregivers and an old folks' home?"* With respect to this classification, we note that: • young adults may 'deny' symptom onset or have symptoms dismissed; the road to diagnosis can be very delayed. • in some countries, where the clinical classification of Type 3b and Type 4 is viewed as less distinct, drug treatment may be possible for some individuals with SMA symptom onset over the age of 19 years of age. • numbers with this clinical classification are very small (1%)

		• life expectancy is normal and a treatment that could stabilise or improve progressive muscle weakness would greatly improve its quality; the health, wellbeing and independence benefits maintained by continued ability to stand and to carry out tasks of daily living which need upper body and limb strength are highly valued by survey respondents. So, although we agree issue 1 is a correct statement, we strongly suggest that it is time to move away from 'typing' SMA and to instead trust the judgement of our experienced clinicians to talk with families and adults. These discussions would, as they do now, focus on the severity of the impact of the individual's SMA, the length of time since their symptoms first appeared, the trials and real-world evidence, the science of the treatment and the likely impact of the treatment on the individual's SMA. If, as we argue, stabilisation of the condition is the agreed goal and the treatment is not achieving this, it can then be stopped. Only by adopting this approach can we avoid what has been the most distressing time for those who have been excluded from other treatment due to this arbitrary typing. **Pre-symptomatic treatment** In terms of pre-symptomatic treatment, a similar argument applies. Along with this we need to heed the science and clinical trial and real-world findings that with all the drugs developed to treat SMA, it is universally agreed that earlier treatment is leading to greater potential positive outcomes. The company is now conducting a study, RAINBOWFISH with primary completion date June 2021. By the time the committee meets in May, the European SMA Newborn Screening (NBS) Alliance will have published its paper summarising the powerful evidence of why and how this needs to be introduced. The UK NBS Alliance for SMA will have met with the UK Newborn Screening Committee with a view to this possibility being reviewed in the UK as early as later this year. There are already pilot projects

		underway in the UK and NBS is in place in the majority of States in the US and slowly being introduced in Europe. It is also important to note that this pre-symptomatic population is identifiable now during pregnancy and at birth in families who already have a history of SMA. Currently many families choose to terminate a pregnancy if SMA is identified, particularly if they have experienced caring for a child with SMA Type 1 before treatments started to become available. However, one father of a young child with SMA Type 1 whose beliefs would not allow the family to consider such an option, recently described, a pre symptomatic treatment would completely change their current decision not to embark on a future pregnancy. We imagine, that if treatments for SMA are shown to have similar positive outcomes to each other, parents with a newborn with pre-symptomatic SMA will elect for a one-time therapy. However, this will not be clinically possible for all as such a therapy is delivered by a virus. We understand that real world studies suggest this may naturally occur in some 5% of the newborn population. Also, some may not be willing for their child to undergo a gene therapy. Therefore, it is vital therefore that there is still a treatment choice for these families. We suggest that this should include this option of a lifetime treatment that may be delivered orally and daily as well as one that is more invasively delivered by intravenous or intrathecal administration.
Key issue 2: Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA	**Yes**	We agree that there is uncertainty. However, this needs to be countered by statements that cover the very reasonable reasons why this is including that: • it is unethical to have a placebo group, • it is too early in the development of the treatments to have any head-to-head studies which would also be challenging to conduct, • it is a rare condition, so numbers of patients entering clinical trials are inevitably small.

		• the science is sound and results to date are promising. • the method of administration is a huge breakthrough that makes it so much more accessible to the wider SMA population. We believe this uncertainty will be addressed by longer term collection of both clinical trial and real-world data. We also suggest that though the cost effectiveness models use the achievement of motor milestones and presumptions around this as proxies for the gains of treatment, these are far too blunt an instrument and fail to capture the outcomes that really matter to a family. Yes, walking would be a great outcome but to suggest this is the pinnacle of success also implicitly suggests that the life of someone who uses a powerchair to get around is of less value. It seems to fail to recognise that other extremely important outcomes are gained alongside those earlier motor milestones – the ability to sit and have head control opens up so many more possibilities for a child who can now join in with the family, be at a desk at school; the fine motor skills that will allow a child to touch a switch, manage a button, interact with family and friends, communicate non-verbally if this is needed. The possibility of greater stamina and less fatigue gives them more time to absorb their environment and learn; these are so often bright children. Increasing upper limb strength brings the possibility of lifting a cup, cleaning teeth, brushing hair, managing a keyboard. Achieving standing again brings so many benefits both physically (reduced constipation, stretching of muscles), socially and practically – at the same level as peers, able to access higher surfaces. Improvements in respiratory function means less reliance on machines to intervene, less fear about going out or to school for fear of chest infections and hospitalisations. The list goes on. We also need to remember that this is a relentlessly progressive condition in which prevention of loss of function and stabilisation is itself the most critical outcome for many who have SMA. To know that you will still be able to live life as now and

		perhaps also make some of these potential gains is so much more important than the isolated possibility of walking. We strongly suggest any final economic model needs to adequately reflect the value of these potential gains and the likely stage at which they may occur with treatment, as well as the importance of stabilisation of this progressive condition.
Key issue 3: Uncertainty surrounding long-term benefits of risdiplam	**No**	We agree that there is uncertainty. However, this needs to be countered by statements that cover the very reasonable reasons why this is (trials are at a relatively early stage, a rare condition so numbers of patients entering clinical trials is inevitably small), that the science is sound, that results to date are promising and the method of administration is a huge breakthrough that makes it so much more accessible to the wider SMA population than other treatments developed to date. We believe this uncertainty will also be addressed by wider longer-term collection of both clinical trial and real-world data. We are also keen to remind the committee that the importance of stabilisation or even the smallest benefit for people impacted by a progressive muscle wasting condition cannot be stressed enough. In 2019, **96.7% of 1,327 validated responses to SMA Europe's SMA Community survey** stated they would "*consider it to be progress if there was a drug to stabilize their current clinical state*."
Key issue 4: Caregiver QALY gain calculations implicitly assume that caregivers die or survive with utility equal to zero after the SMA patient dies	**No**	As far as we understand it, the company's model assumes caregivers only gain health while the 'patient' is alive while the ERG suggests they only incur health losses while the patient is alive. Though undeniably caregivers (especially parents), are themselves impacted significantly by their caregiving responsibilities (sleep deprivation, stress, fatigue, having to give up paid work, reduced social life, financial worries) which are in turn increased with the severity of the impact of their child's SMA, we are concerned that these models should also reflect the positives of this care. Parents will do anything

		for their child and for their child to continue to live. Many talk of the joy they bring, how much they have learned from them, their pride in their young child's achievements and courage when they are unwell and hospitalised. Yes, it's hard work but families adjust and value their disabled family member as much as any other. The issues arise with society, the barriers to inclusion and the lack of adequate health and social care support, not with the person. So, we are very keen to ensure that any final model does not implicitly assume a lesser value placed on the life of a disabled person or see the caregiver only as someone who sees themselves as 'burdened'. We also want to be assured that the final model takes into account the impact of the death of a child (who may be very young or a teenager or adult) on their caregivers (parents and others). Those we support talk of the gaping hole left in their lives, the sleepless nights of grief, going over whether they did all that they could, going over the anger they feel that they didn't get enough support and care. Many seek bereavement counselling. Many have broken relationships and may now find they are on their own. Many have given up careers that are challenging to pick up again. Many have lost confidence and social contacts. Yes, the hard physical work is over but the mental and other impacts continue. We suggest that any model that suggests a caregiver bounces back to full health following bereavement is simplistic, not evidence based and really does need further consideration.
Key issue 5: The company's models do not include any discontinuation from risdiplam	No	Discontinuation criteria agreed by the clinical and patient networks would seem wise. The ERG's clinical adviser's suggestions of progressions to permanent ventilation, the incidence of adverse reactions and the related loss of motor functions appear to have merit. The key is that stabilisation is the outcome allowing continuation of treatment. What specific aspects of stabilisation are critical for an individual need to be agreed with their clinician from the outset e.g., maintenance of movement in a finger that enables control of the person's powerchair.
Key issue 6: The company's models assume that in the	**No**	Again, looking at the discussion about the model, it talks about the trajectory that matters being one that reaches goals of standing and walking which we have questioned above in key issue 2 and 3.

subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely		What does 'more effective' mean? Ongoing stabilisation means an ability to continue to live life in a predictable way that does not require constant adjustments to home and work environments and equipment or frequent renegotiations of health and social care packages as needs increase; that relieves the emotional and psychological impact of forever anticipating life changing loss; that enables someone to continue with a social life where they are confident about who and how they are, not worrying that this might be the last time they can go out to a pub and sip on a beer without being embarrassed and without fear of choking. We hope the final model reflects the importance and value of sustainable stabilisation.
Key issue 7: The company's models predict that a large proportion of patients will reach the milestones of standing or walking, which appears to be optimistic.	**No**	Please see comments on key issues 2, 3 and 6.
Key issue 8: None of the patient utility values for SMA are ideal; caregiver utility values by motor milestone are not available	**No**	Over the last 4 years, the SMA community has been inundated with surveys. As one person said, "*I'm tired of filling out a million surveys explaining my view, my life, my experiences"* SMA UK has worked hard to help market researchers and pharma companies with their surveys and to set up focus groups that will ask the right questions of patients and caregivers so that appropriate utility values can be established. Despite all this we are still seeing hours of work, time and money going into yet more economic modelling and arguing which has the potential to creates delays in the appraisal and immense frustration in the community. We hope that there will soon be consensus and a final economic model that will be agreed and used by all for at least the foreseeable future.
Key issue 9: The company's modelling assumptions are inconsistent with those used to	**No**	See comment in key issue 2, 3 and 8.

inform decision-making in TA588 (nusinersen for SMA)		
Key issue 10: The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills	**No**	See comments in Key issue 2 and 6.
Key issue 11: It is unclear whether NICE's End of Life criteria apply in Type 1 SMA	**No**	We find this a perplexing comment. No matter the theory of the model there can be no doubt that end of life criteria apply with best supportive care for SMA Type 1. We strongly suggest that if it's not in there it should be.

Additional issues

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Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: **A Managed Access Agreement**	Referred to as a possibility in the Company's submission	**No**	We see the company has indicated a willingness for a Managed Access Agreement as a way to collect further evidence to address uncertainty. We would however question if this is necessary given the ongoing clinical trials and that the UK's skilled and experience clinical network will anyway monitor developments. We can trust them not to continue to prescribe treatments that are not delivering as expected. Additionally, we can trust our community which keenly follows treatment research and strongly suggest it is very unlikely that people will want to take a daily medication that isn't doing anything. Our limited experience of an MAA is that it is a complex time consuming and costly process that in itself creates ongoing stress and uncertainty. That said, if it would be the only way for NICE to feel comfortable about recommending the treatment, we would be supportive.

Additional issue 2: Population Statistics	**Consultation papers**	**Yes**	We noticed that statistics referred to in the consultation papers were prior to our website information being updated in September 2020. The following information (with references) is available at: https://smauk.org.uk/what-is-spinal-muscular-atrophy Approximately 1 in 40 people carry the faulty *SMN1* gene - that means there are around 1.67 million carriers in the UK. Recent studies indicate that approximately one in every 10,000 babies worldwide are born with a Type of SMA. In the UK in 2019, there were 712,699 live births. This suggests that in that year, approximately 71 babies were born with a Type of 5q SMA. Recent studies suggest between 1 and 2 people in every 100,000 worldwide have a Type of SMA. In 2019, the UK population was approximately 66.8 million. Based on this, it is estimated that between 668 and 1336 people have SMA in the UK at any one time. Previous estimates by clinicians have suggested an upper limit of about 2,500. As there is no central information source the exact numbers are unknown. In 2018, Public Health England (PHE) started to collect data about people diagnosed with SMA in **England**, through the National Congenital Anomaly and Rare Disease Register (NCARDRS). In their 2019 report,

			they estimated that 1 in 16,320 babies born in England have SMA Type 1 (around 42 babies per year).
Additional issue N: ***Economic Modelling***			We also note, again with limited understanding of the economic modelling debates that go on, that all models for all treatments for SMA Type 1 result in the finding that, even if the treatment is agreed to be clinically effective and delivered at zero cost for the drug, they do not meet NICE's ICER thresholds. We are very aware that this is a bigger issue than just for treatments for SMA and is an important topic that is part of the NICE Methods and Processes review. However, we are very concerned about this and hope that this counterintuitive outcome should not block the possibility of risdiplam being recommended for NHS funding.

NICE National Institute for Health and Care Excellence

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Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**TreatSMA**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 2: Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA	**NO**	The issue raised here is that there is no direct comparison. The mechanism and biology of the condition is very well understood and the fact remains that deterioration resulting in death is the best outcome in cases with BSC in place. There has never been any other outcome. The fact that stabilisation and any improvement is observed clearly shows that the treatment has clinical efficacy. The question here is often when the child is diagnosed and how many motor neurones are left to be saved at the time of diagnosis. The close to diagnosis the administration of the treatment is the more profound effect it will have. At the time when other treatments available worldwide to SMA patients type 1 it would be unethical to conduct clinical study with direct cohort comparison to for natural history as the cohort receiving no treatment will deteriorate and die very quickly.
Key issue 3: Uncertainty surrounding long-term benefits of risdiplam	**NO**	"The long-term benefits of risdiplam – the company's models assume indefinite treatment benefits whereas the ERG assumes a plateau after which risdiplam-treated patients cannot achieve additional motor milestones" – ERG must remember that stabilisation of the condition is just as important. In cases where additional milestones cannot be achieved one must not consider this as a plateau, but support of existing abilities. This makes the treatment effective indefinitely.

Key issue 4: Caregiver QALY gain calculations implicitly assume that caregivers die or survive with utility equal to zero after the SMA patient dies	**NO**	"The approach used to estimate caregiver QALYs – the company's models assume that caregivers only gain health whilst the SMA patient is alive, whereas the ERG believes it is more appropriate to assume that the caregivers only lose health whilst the SMA patient is alive." – We believe that that this is significantly over simplified! Caregivers lose health due to burden of SMA, however upon receiving treatment the caregivers will regain the health. For example: Child who has lost ability to self transfer becomes a burden on the caregivers back as they must now do the lifting. Equally, as the ability is reinstated the caregivers back gets in a better health. The same applies to long term sleeping patterns – children which are unable to turn in bed independently, keep caregivers in state of broken sleep (links to Dementia and all sorts of health problem).
Key issue 5: The company's models do not include any discontinuation from risdiplam	**NO**	This very much depends on the reason for having the discontinuation model. In principle nobody wants to spend huge sums of money on treatments that aren't working, but it's the desolation of "aren't working" which leads us to question the requirement. If we are talking about discontinuation criteria it needs to be based on what we expect the treatment to deliver, stabilisation. Discontinuation criteria MUST NOT be based on perceived improvements on random measurement scales such as the Hammersmith. The anticipation of the treatment is to avoid deterioration and therefore any discontinuation criteria needs to be based on that, e.g. if the patient is continuing to deteriorate.
Key issue 6: The company's models assume that in the subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely	**NO**	Long tern benefits: As highlighted earlier – even though no additional milestones are achieved it does not mean that the treatment is no longer effective. Maintenance of the milestones is equally important. It is like saying to the assessor – for 25 years you had your eyesight, lets remove it and see if that has no impact on your life. We must view these models with care. Again this comes down to similar comments to the discontinuation model. It depends on what "treatment effects" you are measuring. While the patient will at some point be unable to reach further milestones the issue here is one of stability and not improvements. If the treatment

		maintains stability then there is no reason why this wouldn't apply indefinitely, after all the science and natural history behind SMA is quite clear.
Key issue 7: The company's models predict that a large proportion of patients will reach the milestones of standing or walking, which appears to be optimistic.	**NO**	"The company's models predict that a large proportion of patients will reach the milestones of standing or walking, which appears to be optimistic" – The biology of the condition is well understood and it is plausible that the company prediction can be right. However, this indeed works on the assumption that the population has access to suitable physiotherapy centres. Our personal experience in this area in the real world clearly shows that children who have access early to the treatment and access to suitable physio regime show fantastic improvements. However we do agree that this may be optimistic. Saying that, we also must highlight that stabilisation is by far more important then getting new ability to walk independently.
Key issue 8: None of the patient utility values for SMA are ideal; caregiver utility values by motor milestone are not available	**NO**	Can we remember that the very groupings of SMA patients, e.g. type 1, 2, 3 et cetera, is incredibly arbitrary. Due to the nature of the condition there is limited natural history information documented.
Key issue 9: The company's modelling assumptions are inconsistent with those used to inform decision-making in TA588 (nusinersen for SMA)	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 10: The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills	**NO**	We agree with the comments from the ERG in terms of the gross motor milestones not taking into account quality-of-life improvements such as fine motor skills. There are many patients who have never had the opportunity to walk, and have no desire nor expectation to reach that milestone, but the ability to lift a cup to their mouth to ensure hydration is far more important to them. This kind of fine motor milestone has a far bigger impact on quality-of-life than walking, not to mention the associated illnesses which can be exasperated by malnutrition and dehydration.

Key issue 11: It is unclear whether NICE's End of Life criteria apply in Type 1 SMA	**NO**	"It is unclear whether NICE's End of Life criteria apply in Type 1 SMA" – The EoL criteria must be applied to Type 1 as it is well established that under BPC any type 1 child has life expectancy of 2 years. In the type 2 similar is applicable, however due to improvement in the standards of care the life expectancy for people with SMA type 2 now varies.

Additional issues

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Additional issue 1: Caregiver health gains	Page 17	**NO**	"This is incorrect as caregivers will continue to accrue health gains after the SMA patient has died" – This is a gross mis-understanding from ERG. Upon death of the children with SMA people have taken their own lives. People suffered complete emotional breakdowns resulting in health decline and death. Most of the families affected by child loss from SMA do not have excellent health (eating disorders, self-harm, self-abuse). Only a person who never lost their child can make such terrible assumption. It would be completely inappropriate and disrespectful to keep this in!
Additional issue 2: *Available treatments*	The whole document observation	**NO**	There are a number of comments comparing risdiplam to nusinersen but we must remember there is a significant proportion of the SMA community that have no access to nusinersen due to complexities with spinal access. There can be no direct comparison between the 2.
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Association of British Neurologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients	No	
Key issue 2: Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: Uncertainty surrounding long-term benefits of risdiplam	**Yes**	ERG 4.2.1.5 suggests longterm benefits of Risdiplam have been over estimated by the company.
Key issue 4: Caregiver QALY gain calculations implicitly assume that caregivers die or survive with utility equal to zero after the SMA patient dies	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 5: The company's models do not include any discontinuation from risdiplam	No	Stopping criteria would be essential to avoid unnecessary continuation of a non-effective treatment.
Key issue 6: The company's models assume that in the	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely		
Key issue 7: The company's models predict that a large proportion of patients will reach the milestones of standing or walking, which appears to be optimistic.	**Yes**	The analysis in ERG 5.3.4 is likely to be more realistic then the company's own predictions in respect of the milestones of standing and walking. However, it is entirely unclear what beneficial effect may result decades later from improving strength in very young children, whose musculoskeletal and neuromuscular systems are developing as this is a completely new field.
Key issue 8: None of the patient utility values for SMA are ideal; caregiver utility values by motor milestone are not available	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 9: The company's modelling assumptions are inconsistent with those used to inform decision-making in TA588 (nusinersen for SMA)	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 10: The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills	**Yes**	Further information on the effect of Risdiplam on fine motor skills would impact upon understanding of its benefits.
Key issue 11: It is unclear whether NICE's End of Life criteria apply in Type 1 SMA	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

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Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
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Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**SMA REACH UK (List of the colleagues who contributed BELOW):** [redacted]; **Adult SMA REACH UK contributors:** [redacted]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	FM: Ad Boards Biogen, Novartis, Roche, PTC Therapeutics, Sarepta, Dyne Therapeutics; Pfizer AMC: Ad boards Biogen, Avexis, Roche, PTC Therapeutics and Sarepta Min Ong: none EW: none ZA: none CG: Roche

Key issues for engagement

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients	**No**	The data from the ongoing presymptomatic study (RAINBOWFISH) has not been made public as yet. We expect this study should allow to assess efficacy of Risdiplam in pre-symptomatic group.
Key issue 2: Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA	**YES**	It is clear to us that that outcomes in Firefish study are considerably better than untreated controls, both for motor and also respiratory/bulbar outcomes, improving quality of life and life expectancy of treated infants. In the study the treated patients demonstrated acquisition of motor skills and event free survival that are not in keeping with the natural history of the condition and therefore provide clear evidence a treatment effect. As the natural history of SMA type 1 is very well defined, we consider entirely reasonable the use of natural history control for comparison Its relative clinical efficacy to nusinersen is not known at this time as matched case comparative analysis has not been performed. We notice that the treated patients in the Firefish study show continue improvement, suggesting that a ceiling effect has probably not been reached within the duration of the study. The prolonged period of response is in keeping with what observed also using nusinersen
Key issue 3: Uncertainty surrounding long-term benefits of risdiplam	**YES**	We firstly acknowledge that performing a longer term comparative study against standards of care alone is not feasible nor ethical given the licensing and approved use of Nusinesen and Zolgensma around the world and indeed the UK. While there is no long term data, we notice that there is no evidence of plateau in response in Firefish, with

		motor improvements and sustained benefits to respiratory /bulbar function in those treated for longer ie between 12 and 24 month analysis. 88% were event free, 59% of infants were sitting without support for at least 5 seconds, as measured by the BSID-III, 100% maintained swallow and 86% were exclusively orally fed at 24 months. This is completely uncharacteristic of SMA 1 patients, and the benefits in respiratory and oral / bulbar function should not be underestimated both in terms of health care costs and quality of life of the infants and families. Not being repeatedly admitted to hospital or indeed requiring treatment at home for chest infections represents considerable improvements in quality of life. We also stress that even stability would be a beneficial outcome and mechanistically it seems most likely that there would be at least stability with continuing treatment, or some further improvement. We consider unethical to suggest that long term studies would be needed and more appropriate to ensure there is a mechanism for continuing evaluation through real world data collection
Key issue 4: Caregiver QALY gain calculations implicitly assume that caregivers die or survive with utility equal to zero after the SMA patient dies	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 5: The company's models do not include any discontinuation from risdiplam	**No**	We suggest that this should be included. Firstly there may be some non-responders and including stopping criteria that this would be reasonable. However these must take into account the fact that stability is a benefit in a progressive disorder provided this can be assessed at the start of treatment. In type 2/3 patients this may require more sensitive tools that capture meaningful benefit to patients than those routinely used in practice. Secondly there may be some patients who, after a period of treatment, bearing in mind this is a daily self-administered drug, fail to comply with regular treatment either because treatment effects do not match expectations or because the balance between adverse effects and benefits is not sufficient.

		Having clear stopping criteria and palliative care route / best supportive care model will be helpful to the treating clinicians; the criteria need to be discussed at the time of initiation of treatment.7 Child bearing and reproductive choices will also need to be clear
Key issue 6: The company's models assume that in the subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely	**Yes**	The model needs to reflect the fact that the response to therapeutic intervention requires considerable time to be appreciated in its fullness, as the clinical trial data suggest and as- by analogy- other SMN enhancing drugs demonstrate The model needs to capture the capacity to make motor developmental progress in those in earlier disease phase where anterior horn cell function can still be rescued by treatment. It would be expected that in this group ie infants and younger children that gross motor and fine motor function may improve, whereas in those with more established and chronic disease the gains may be smaller but still functionally meaningful, for example more independence with eating/writing and operation of controls In addition benefits of stabilising respiratory and bulbar function should not be underestimated and the reduced health care costs do accrue over time. Natural history studies including the recent manuscript of the SMA REACH UK / ISMAc collaboration (Trucco et al, 2021) show that a high proportion of type 2 and type 3a patients (Trucco) will require intervention inc NIV, cough assist and hospital admission. However sufficient time is necessary to allow patients not to reach these milestones, so it is entirely reasonable to expect that thee benefits will continue to emerge with chronic therapy.
Key issue 7: The company's models predict that a large proportion of patients will reach the milestones of standing or walking, which appears to be optimistic.	**No**	Firefish does show that a greater proportion of infants achieve sitting and standing at 24 v 12 months of treatment. Children with SMA do not have cognitive delay that might delay their ability to achieve these tasks, unlike in some other disorders, so effects relate to treatment. We agree that the prediction of how many children will achieve some of these milestones is difficult to be predicted a priori as it will be very largely dependent on the age and timeline between symptom onset and access to therapy. The expectations are clearly different for presymptomatic Typ1 1 patients; symptomatic type 1 patients after a few weeks from onset; or after 6 months or more from onset, or after the age of 1 year.

		We agree that treatment effect will be greatest in those who start treatment at early stages of the disease and in these groups especially, given the continuing improvement seen in trials at 24 months it seems reasonable to infer that there will be continuing improvement with expectation of achieving milestones such as standing and walking. For a child with SMA2 and chronic contractures, standing may not be achievable; however improvement in upper limb function will have major impact on their function, independence and quality of life. Indeed, even if the patients who may not achieve to actually stand and walk, may still benefit in the domains of fine motor/ upper limb/ trunk/ respiratory function which are the issues that reduce hosp admission and health care costs and improve participation with reduced need for additional equipment/social/one ot one care in school/educational/workplace settings
Key issue 8: None of the patient utility values for SMA are ideal; caregiver utility values by motor milestone are not available	**No**	Motor milestones are only a small part of what determines caregiver utility and Qof L As above, if an individual can take the tops of pens, open packets of food, manipulate cutlery, raise arms to mouth, sit comfortably with no scoliosis, transfer using a transfer board, the need for one to one care reduces considerably - even though the patient hasn't 'moved' form the sitting to the standing group. Risdiplam improved independence in activities of daily living using the novel SMAIS measure; this was in caregivers and in children >12 years; including self-care such as brushing teeth and feeding themselves. Whilst none of the utility values are ideal, we have to appreciate that this is a new area of research and most of the studies do focus on the motor function and milestones as this is quantifiable and easy to demonstrate improvement and change in. However self-care, which involved motor function such as teeth brushing and also feeding yourself, is a huge benefit both to the child for their independence and well-being as well as care giver
Key issue 9: The company's modelling assumptions are inconsistent with those used to	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

inform decision-making in TA588 (nusinersen for SMA)		
Key issue 10: The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills	**YES/NO**	This is a crucial determinant of HRQoL. Newer tools are being developed and could be used to monitor these gains as part of an observational study, but, as stated, it is no longer ethical to leave an SMA patient who meets criteria for Nusinersen untreated, to do such a study. We also note that achievement in fine motor skills may have a greater impact on independent living than does the ability to stand/ walk. Indeed patients often find this the biggest change in their SMA treatment rather than gross motor improvements.
Key issue 11: It is unclear whether NICE's End of Life criteria apply in Type 1 SMA		. It is likely there will be some non responders and in the absence of a post natal screening programme, there will still be infants in clinical practice who present late or at the time of their 1st respiratory crisis, who may not see treatment benefits in time to prevent further respiratory compromise or decline. Some families may choose to discontinue treatment in SMA1 infant if they feel that their child's best interests are not being served by ongoing medical treatment. Parallel palliative care planning must remain part of the standards of care in type 1 and potentially some type 2 patients. In this context EoL criteria should still apply to children affected by type 1 SMA as for symptomatic children it is still a Life-threatening / limiting condition even with the current treatments. Regardless of the response to current treatments, it is important to discuss advanced care plans with families and set out plans for management of symptoms and acute illness. Advanced care plans for increasing number of patients with SMA1 now includes full escalation of care (in contrast to the practice a decade ago); this needs to have ongoing regular reviews as their condition progresses over time. As this group of patients often have many associated symptoms that need skilful management by a palliative care team; so, although ceiling of care could be the same as for an unaffected child (in particular when responding well to treatment in

		comparison to natural history); discussion about palliative care in the context of symptoms management will be an important part of their care

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

Risdiplam for treating spinal muscular atrophy: A Single Technology Appraisal

Addendum: ERG comments on company's technical engagement response

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1. Introduction

The company's technical engagement response includes a written technical engagement response document,[1] together with updated versions of the company's Type 2/3 and Type 1 SMA models. The updated models include amended assumptions and an updated PAS discount for risdiplam (updated discount = [redacted] reduction from the list price). The company's technical engagement response does not contain any additional clinical effectiveness evidence for risdiplam which has not previously been presented within the original company submission (CS).[2] Additional responses were received by the Association of British Neurologists, TreatSMA, SMA REACH, a joint submission from Spinal Muscular Atrophy UK and Muscular Dystrophy UK and a submission from a patient with SMA. These additional submissions provide useful insights into living with SMA and the value that patients and their families would place on a new effective treatment. The SMA REACH submission also refers to longer-term 24-month data from FIREFISH;[3] however, these data are not included in the company's technical engagement response and their source is unclear.

This ERG addendum provides a brief commentary on the company's technical engagement response[1] and the updated economic models for the Type 2/3 and Type 1 SMA populations. It does not include a critique of responses from other stakeholders; however, the issues raised in these submissions have been considered within the ERG's comments.

Section 2 of the ERG addendum summarises the characteristics of the company's updated models and presents the results of the company's updated base case and scenario analyses. Section 3 presents comments from the ERG on the company's technical engagement response. Section 4 presents the results of additional analyses undertaken by the ERG which explore the impact of some of the unresolved uncertainties within this appraisal.

2. Description of company's updated Type 2/3 and Type 1 SMA models and analyses presented

The company's updated models include a number of amendments which partially align them with the ERG's preferred analyses; however, there remain some important differences. Table 1 summarises the changes applied within the company's updated base case models. As shown in the table, there are five key differences between the company's updated base case models and the ERG's preferred analyses:[4]

(i) The company has increased the PAS discount for risdiplam from [redacted] to [redacted].

(ii) The company has retained their existing approach to valuing HRQoL impacts on caregivers, whereby caregiver utilities are counted only whilst the patient with SMA is still alive. The ERG believes that it would be more appropriate to value caregiver disutilities whilst the patient is alive, possibly including some valuation of the impact of bereavement.

(iii) The company has assumed that all Type 2/3 SMA patients have 2.2 caregivers, based on their burden of illness study. The ERG's preferred analysis assumed 3 caregivers for patients who are unable to sit, based on assumptions employed in the final iterations of the models used to inform NICE TA588 (nusinersen for treating SMA).[5]

(iv) The company's updated base case models assume that all Type 2/3 SMA patients will discontinue risdiplam after 30 years, whilst all Type 1 SMA patients will discontinue risdiplam after 50 years. Following discontinuation, the models assume a gradual loss of treatment benefit in terms of motor milestones, but no detrimental impact on survival outcomes. The ERG's preferred analyses did not include discontinuation assumptions; however, the ERG report[4] suggested that the development of discontinuation criteria may improve the cost-effectiveness of risdiplam.

(v) Utility gains associated with the achievement/maintenance of fine motor skills for patients who cannot stand are included in the company's updated base case models. These benefits were excluded from the ERG's preferred analyses, but were considered in additional sensitivity analyses.

The company's technical engagement response[1] also presents three additional scenario analyses for each SMA population:

- Company scenario analysis 1: Company's updated base case plus ERG-preferred caregiver disutility approach
- Company scenario analysis 2: Company's updated base case plus an [redacted] reduction from the list price for risdiplam after [redacted] years, which is intended to reflect a loss of exclusivity for risdiplam
- Company scenario analysis 3: Company's updated base case plus health outcomes and costs discounted at a rate of 1.5% per annum.

The ERG notes that whilst scenario analysis 3 may be informative, it does not reflect the discount rates included in the current NICE Reference Case.[6]

Table 1: Summary of company's updated base case and scenario analyses, Type 2/3 and Type 1 SMA models

Aspect of model	Amendment included in ERG preferred analysis[4]?	Amendment included in company's updated base case model[1]?
Amendments relating to ERG exploratory analyses[4]		
EA1: error 1(a) - subsequent period assumptions applied 1 cycle too early	Yes	Yes
EA1: error 1(b) - corrected general population mortality model	Yes	Yes
EA1: error 1(c) - BSC group contains insufficient cycles (Type 2/3 SMA model only)	Yes	Yes
EA1: error 1(d) - Caregiver QALYs assumed to be zero after patient dies	Yes	No. Company's original approach retained. ERG-preferred approach presented as additional scenario analysis.
EA3: Inclusion of Biogen's clinical advisors' utility values from TA588[5] (plus n=3 caregivers for non-sitters in Type 2/3 SMA)	Yes	Partially. Patient utilities amended. 2.2 caregivers assumed in Type 2/3 SMA.
EA4: Assumption of treatment plateau (Type 2/3 SMA - 26 months; Type 1 SMA – 66 months)	Yes	Yes. Implemented 1 cycle earlier than in the ERG's preferred analyses.
EA5: Inclusion of drug wastage (0.50 bottles)	Yes	Yes
ASA1: Additional utility gains for non-sitters and sitters	No. Included in ERG additional sensitivity analyses.	Yes
Other amendments included in company's technical engagement response[1]		
New PAS discount	No	Yes. Increased from [redacted] to [redacted]
Treatment effect discontinuation and subsequent loss of treatment benefit	No	Yes. Type 2/3 SMA: Treatment effects on transition probabilities assumed constant up to 30 years then constant waning effect applied to reach BSC values after 10 years. No survival impact assumed. Type 1 SMA: Treatment effects on transition probabilities assumed constant up to 50 years then constant waning effect to reach BSC values after 5 years. No survival impact assumed.
Price reduction due to loss of exclusivity ([redacted] reduction from list price after [redacted] years)	No	No. Presented as additional scenario analysis.
Discount rates for health outcomes and costs = 1.5% per annum	No	No. Presented as additional scenario analysis

EA - ERG exploratory analysis; ASA - ERG additional sensitivity analysis; SMA - spinal muscular atrophy; ERG - Evidence Review Group; BSC - best supportive care; QALY - quality-adjusted life year; PAS - Patient Access Scheme

2. Summary of updated results presented in the company's technical engagement response

The results of the company's updated base case and scenario analyses for the Type 2/3 and Type 1 SMA populations are summarised in Table 2 and Table 3, respectively. These results are based on the deterministic versions of the company's models. Within the Type 2/3 SMA population, the company's updated base case ICER is estimated to be [redacted] per QALY gained. Within the Type 1 SMA population, the company's updated base case ICER is estimated to be [redacted] per QALY gained. The company's scenario analyses around loss of exclusivity and alternative discount rates each lead to lower ICERs for risdiplam in both populations. The inclusion of the ERG's preferred caregiver disutility approach increases the ICER for risdiplam in both populations; the impact is substantial in the Type 1 SMA population (ICER increased from [redacted] to [redacted] per QALY gained).

Table 2: Results of updated base case model and scenario analyses including updated PAS, Type 2/3 SMA model, deterministic

Option	LYGs*	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
Company's updated base case						
Risdiplam	48.57	11.57	39.49	[redacted]	-	-
BSC	43.77	5.98	33.25	[redacted]	-	-
Incremental	4.79	5.59	6.23	[redacted]	[redacted]	[redacted]
Company's updated base case + ERG-preferred caregiver disutility approach						
Risdiplam	48.57	11.57	-4.22	[redacted]	-	-
BSC	43.77	5.98	-7.67	[redacted]	-	-
Incremental	4.79	5.59	3.46	[redacted]	[redacted]	[redacted]
Company's updated base case + lower prices due to loss of exclusivity						
Risdiplam	48.57	11.57	39.49	[redacted]	-	-
BSC	43.77	5.98	33.25	[redacted]	-	-
Incremental	4.79	5.59	6.23	[redacted]	[redacted]	[redacted]
Company's updated base case + 1.5% discount rates						
Risdiplam	48.57	16.69	58.57	[redacted]	-	-
BSC	43.77	8.14	48.34	[redacted]	-	-
Incremental	4.79	8.55	10.23	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care

** Undiscounted*

Table 3: Results of updated base case model and scenario analyses including updated PAS, Type 1 SMA model, deterministic

Option	LYGs*	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
Company's updated base case						
Risdiplam	21.90	5.11	18.43	[redacted]	-	-
BSC	4.88	0.02	3.56	[redacted]	-	-
Incremental	17.03	5.09	14.88	[redacted]	[redacted]	[redacted]
Company's updated base case + ERG-preferred caregiver disutility approach						
Risdiplam	21.90	5.11	-6.76	[redacted]	-	-
BSC	4.88	0.02	-3.14	[redacted]	-	-
Incremental	17.03	5.09	-3.61	[redacted]	[redacted]	[redacted]
Company's updated base case + lower prices due to loss of exclusivity						
Risdiplam	21.90	5.11	18.43	[redacted]	-	-
BSC	4.88	0.02	3.56	[redacted]	-	-
Incremental	17.03	5.09	14.88	[redacted]	[redacted]	[redacted]
Company's updated base case + 1.5% discount rates						
Risdiplam	21.90	7.08	24.76	[redacted]	-	-
BSC	4.88	0.01	4.32	[redacted]	-	-
Incremental	17.03	7.08	20.44	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care

** Undiscounted*

3. ERG comments on company's response to key issues for technical engagement

The ERG's comments on the company's technical engagement response are presented in Table 4. This table should be read in conjunction with the company's technical engagement response.[1]

Table 4: Summary of company's key points on issues for technical engagement and ERG comments

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
Key issue 1 No evidence is available for pre-symptomatic, Type 0, Type 4, or previously treated SMA patients	• The company agrees that there is no evidence for risdiplam in pre-symptomatic, Type 0 or Type 4 SMA • There is a clear unmet need in patients who cannot tolerate or respond poorly to nusinersen • Despite the absence of data, there is no plausible biological rationale why prior treatment with nusinersen should lead to different outcomes compared with those for untreated patients • Previously treated patients should have the option to receive risdiplam, else the only remaining option will be BSC • Despite the absence of data for pre-symptomatic patients, earlier treatment will improve the effectiveness and cost-effectiveness of risdiplam	As discussed in the ERG report[4] (Section 3.1), the available evidence for the clinical effectiveness of risdiplam is restricted to treatment-naïve patients with Type 1, 2 and 3 SMA. The company's technical engagement response does not present any additional evidence for patients with pre-symptomatic, Type 0 or Type 4 SMA. As such, the clinical effectiveness and cost-effectiveness of risdiplam in these populations remains unknown.
Key issue 2 Uncertainty surrounding the relative efficacy of risdiplam in Type 1 SMA	• The differences between populations enrolled in the FIREFISH[3] and ENDEAR[7] studies were small; hence, both the naïve indirect comparison and the matching-adjusted indirect comparison (MAIC) are potentially appropriate • The MAIC suggests a greater survival benefit for risdiplam versus BSC, which counterintuitively results in a less favourable ICER for risdiplam. This means that the cost-effectiveness analysis penalises an innovative treatment which extends patients' lives • Neither method accurately reflects the clinical benefit of risdiplam in Type 1 SMA patients • In line with the ERG's preferred analyses, the company's base case model has been amended to include the MAIC	The ERG's views regarding the company's indirect comparison of risdiplam versus BSC in Type 1 SMA remain unchanged; the ERG's critique of this indirect comparison can be found in Section 5.3.4 (critical appraisal point [5]) of the ERG report.[4] The key points are as follows: • The parametric survival model for OS applied in the risdiplam group was based on data from the single-arm FIREFISH study, which included only 5 deaths, whilst the HR was derived from an unanchored indirect comparison using FIREFISH and ENDEAR.[3, 7] As such, any estimate of the relative survival benefit of risdiplam versus BSC should be considered highly uncertain. • Whilst unanchored MAICs are associated with several problems and potential biases, the ERG considers that this approach should be preferred over naïve arm-based comparisons. • Within the company's economic model for Type 1 SMA, applying a more favourable treatment effect for OS increases the ICER for risdiplam because: (a) the inverse of the HR is applied to the risdiplam group OS model, hence applying a lower (better) HR reduces mean OS

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
		in the BSC group but does not affect OS in the risdiplam group, and (b) BSC is associated with high disease management costs and low patient utility. • Applying the HR derived from the company's naïve indirect comparison results in a mean OS duration of 10.1 years for BSC-treated patients.[2] The ERG does not consider this model prediction to be plausible. Applying the HR derived from the company's updated MAIC[8] leads to a lower expected survival duration of 4.88 years. This may still be an overestimate. • The ERG notes that relative treatment effects tend to be highly transportable across populations. The conventional approach to generating absolute survival functions is to apply the relative treatment effect to the survival function in patients treated with BSC in the target population, rather than applying inverse treatment effects to the intervention group for which less evidence exists. The ERG also notes that there is no reason why hazards should be proportional. The company's updated base case models include relative treatment effect estimates obtained from the MAICs. This is in line with the ERG's preferred analyses.
Key issue 3 Uncertainty surrounding long-term benefits of risdiplam	• The company agrees that there is uncertainty regarding the long-term treatment benefit of risdiplam • The company endeavoured to make informed assumptions within the model based on expert clinical opinion and the committee papers for TA588[9] • Additional data releases are expected in 2021 (open-label extension phases of SUNFISH[10] and FIREFISH[3]).	The company's technical engagement response[1] does not contain any additional evidence to inform the clinical effectiveness review or economic analyses. The ERG agrees that further data-cuts of FIREFISH[3] and SUNFISH[10] may provide valuable information regarding the plausibility of the long-term predictions of the company's models. The ERG understands that there will not be any further comparative data from SUNFISH, thus there will be no further data on the relative efficacy of risdiplam. However, the ERG also recognises the ethical issues relating to long-term placebo control and agrees that additional longer-term data, albeit non-comparative, will nevertheless be useful.

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
Key issue 4 Caregiver QALY gain calculations implicitly assume that caregivers die or survive with utility equal to zero after the SMA patient dies	• The company understands that the approach used to value caregiver QALYs in the risdiplam models is different to the approach used in TA588[5] • The approach used to value caregiver QALYs is particularly impactful on the ICER when a novel treatment extends patient survival. The ERG's preferred caregiver QALY loss approach penalises risdiplam for extending patient survival rather than rewarding it. This does not occur when using the company's preferred additive caregiver QALY approach because additional life years are gained by the caregiver whilst the patient is still alive. • A recent report by the NICE Decision Support Unit (DSU) identified the use of both the company's preferred additive caregiver utility approach and the ERG's preferred caregiver disutility approach in previous appraisals and concluded that "*in reality, it is likely that neither of these are realistic*."[11] The company suggests that neither approach is more appropriate than the other. • The choice of caregiver QALY valuation approach has a greater impact on the incremental QALY gains for the Type 1 SMA population compared with the Type 2/3 SMA population. This is partly driven by the poorer level of HRQoL assumed in the Type 1 SMA model population. Applying the caregiver disutility approach means that it is more favourable in the model to receive the intervention associated with poorer survival outcomes (BSC). • Under the caregiver disutility approach, applying a 100% PAS discount leads to an ICER for risdiplam of [redacted] per QALY gained (company scenario analysis 1 in Table 2 plus 100% discount). The company suggests that this high ICER means that the ERG's preferred caregiver disutility approach lacks face validity.	The ERG understands that patients' families and other caregivers would place considerable value on being able to spend additional time with patients with SMA. The ERG agrees that valuing the impact of risdiplam for caregivers is difficult and is subject to considerable uncertainty. This uncertainty is partly driven by a lack of evidence relating to HRQoL impacts on caregivers of SMA patients, but also the absence of clear guidance on whether and how caregiver HRQoL should be valued within economic evaluations undertaken for NICE. The ERG agrees that neither the company's additive approach nor the ERG's preferred caregiver disutility approach is ideal. The ERG believes that the company's additive caregiver utility approach is incorrect; this is because it implicitly assumes that the caregiver either dies or survives with zero utility when the SMA patient dies. This is not realistic and the approach artificially inflates the incremental net QALY gains for the risdiplam group, thereby lowering the ICER. The ERG further notes that excluding subsequent health gains accrued by caregivers after a patient with SMA has died implies a normative position that society places value on the HRQoL of caregivers of surviving SMA patients, but does not place any value on bereaved caregivers. This is unlikely to be considered a reasonable position. The ERG also agrees that the caregiver disutility approach applied in the ERG's preferred analyses is subject to a problematic assumption that caregivers' HRQoL rebounds to that of the general population after the patient dies. This is also not a realistic assumption as it ignores the impact of bereavement. The DSU report on modelling caregiver HRQoL[11] highlights that both the additive caregiver approach and the caregiver disutility approach have been considered in previous NICE appraisals. The additive caregiver approach has been proposed once in a manufacturer's model submitted to inform NICE TA217 (donepezil, galantamine, rivastigmine and memantine for Alzheimer's disease); however, this model was not used to inform final decision-making.[12] In line with other NICE appraisals in

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
	• The extension to life as a result of risdiplam treatment will be extremely valued by patients' families, and this benefit should be recognised in the economic analysis. This additional time will be immensely valued by patients and their carers, and the company asks that the Committee take this key factor into account in their decision-making.	which caregiver HRQoL impacts were included, the two previous NICE appraisals of SMA treatments both considered an approach based on caregiver disutilities: these impacts were included in the final base case models used to inform TA588 (nusinersen for SMA[9]), and in a scenario analysis in ID1473 (onasemnogene abeparvovec for Type 1 SMA).[13] The ERG believes that there is no precedent for the additive caregiver approach in informing NICE recommendations and that adopting this approach for risdiplam would deviate considerably from previous appraisals, including those of other SMA treatments. In response to comments contained in the technical engagement responses, the ERG has undertaken additional analyses which attempt to address the problematic assumption that caregiver HRQoL rebounds to general population levels immediately following the patient's death. This requires some valuation of the impact of bereavement on caregivers' HRQoL. Whilst there is some evidence through which to quantify this impact (for example, Song *et al*[14]), there is uncertainty about how long such impacts might apply. In Section 4 of this addendum, the ERG presents analyses which include the valuation of caregiver bereavement using two alternative sets of assumptions: • Approach 1: A fixed "lump-sum" QALY loss is applied to the incident number of new deaths in each model cycle. The analysis assumes: (i) a disutility of -0.04 for bereaved caregivers based on Song *et al*;[14] (ii) an arbitrary duration of disutility of 20 years and (iii) that each SMA patient has 2.2 caregivers. • Approach 2: An indefinite caregiver disutility is applied to the proportion of SMA patients who have died. This analysis assumes: (i) a disutility of -0.04 for bereaved caregivers and (ii) that each patient has 2.2 caregivers. The ERG's additional analyses are illustrative only and should be interpreted with caution due to the somewhat arbitrary nature of the assumptions required. They are also limited by the fact that the company's

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
		models do not include caregiver ageing or survival. In addition, the ERG notes that valuing caregiver bereavement is not explicitly mentioned in the NICE Methods Guide,[6] it is not included in the vast majority of NICE appraisals of other treatments for other conditions, and its impact on opportunity cost (i.e. health benefits forgone from displaced therapies) is unlikely to be reflected in the usual NICE thresholds for assessing cost-effectiveness. The company's technical engagement response[1] also comments on the results of the model if risdiplam is given with a 100% PAS discount. The ERG agrees that if the caregiver disutility approach is applied together with a 100% PAS discount for risdiplam, the ICER is [redacted] The ERG does not believe that the results of the model should be used as the basis for determining whether or how caregiver HRQoL impacts should be valued.
Key issue 5 The company's models do not include any discontinuation from risdiplam	• Following consultation with two practising NHS clinicians, the company believes that a 'hard-stop', time-based discontinuation rule for risdiplam would be more appropriate than an outcomes-based stopping rule • The company's updated base case models include the following assumptions: o Type 2/3 SMA: All patients remain on treatment for 30 years; risdiplam acquisition costs stop at 30 years; motor milestone transition probabilities wane to BSC values linearly over 10 years; no detrimental impact on survival assumed. o Type 1 SMA: All patients remain on treatment for 50 years; risdiplam acquisition costs stop at 50 years; motor milestone transition probabilities wane to BSC values linearly over 5 years; no detrimental impact on survival assumed.	As discussed in Section 5.3.4 of the ERG report[4] (critical appraisal point [4]), the application of treatment discontinuation criteria may improve the cost-effectiveness of risdiplam. It is important however that these criteria are clinically appropriate, acceptable to patients and operationally feasible. Overall, the ERG believes that the appropriateness of the proposed discontinuation approach is largely a matter for the company, NHS England and other stakeholders to consider, but notes the following: • The company's technical engagement response[1] does not provide any details regarding a formal Commercial Access Agreement (CAA) between the company and the NHS which includes this discontinuation rule. A formal CAA may be required to ensure that the discontinuation rule is adhered to in NHS practice. • There is uncertainty regarding the extent to which relative treatment effects would be lost following discontinuation of risdiplam. The company's assumptions are based on clinical input and might be reasonable; however, empirical evidence is absent.

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
	• Clinical input obtained by the company supports assumptions regarding sustained survival benefits employed in these analyses • Risdiplam is expected to lose exclusivity in [redacted]; a scenario analysis is presented in which the cost of risdiplam is assumed to be reduced by [redacted] • Per-cycle discontinuation is not included due to lack of data and complexity of assumptions required	• The company's scenario analyses around future price reductions resulting from the loss of exclusivity of risdiplam may be a relevant concern for decision-making, but are not related to discontinuation criteria. Within the company's model, this scenario analysis is implemented by reducing the acquisition cost of risdiplam to [redacted] of its current list price [redacted] years after model entry. The ERG considers that the results of this analysis would be more persuasive if the company had set out a CAA which would ensure that this price reduction is binding. • Further consideration of discontinuation criteria defined according to the loss of motor function milestones may be warranted, as these would likely also improve the cost-effectiveness of risdiplam.
Key issue 6 The company's models assume that in the subsequent phase (after 2 years), risdiplam is more effective than in the initial phase and that these treatment effects apply indefinitely	• The company's original base case model was informed by clinical expert input; however, the company agrees that their original base case could be perceived as optimistic • In line with the ERG's preferred analyses, the company's updated models include a treatment benefit plateau in the Type 2/3 and Type 1 SMA models at 26 and 66 months, respectively	The ERG's concerns regarding the assumptions of long-term treatment effects applied in the company's original model have not changed. These can be found in Section 5.3.4 of the ERG report[4] (critical appraisal points [7], [8] and [9]). In the absence of further evidence with which to corroborate the company's optimistic assumptions, the ERG's preferred analyses, which are intended to be consistent with the final models used in TA588,[5] represent a more reasonable starting point for discussions on the cost-effectiveness of risdiplam. In line with the ERG's preferred analyses, the company's updated base case Type 2/3 and Type 1 models include a treatment benefit plateau at months 26 and month 66, respectively. These are each applied one cycle earlier than in the ERG's preferred analyses,[4] which slightly disadvantages risdiplam. This issue is addressed within the ERG's additional analyses (see Section 4)
Key issue 7 The company's models predict that a large	• Despite the short 12-month data collection period of FIREFISH,[3] one patient acquired the ability to bounce, which is a key milestone towards walking	The ERG's view regarding the plausibility of the company's original model predictions remain unchanged. These can be found in Section 5.3.4 of the ERG report[4] (critical appraisal point [9]). The ERG considers these model predictions to be highly optimistic and clinically implausible. The

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
proportion of patients will reach the milestones of standing or walking, which appears to be optimistic.	• The company agrees that their original assumptions about risdiplam-treated patients reaching advanced milestones could be perceived as optimistic • The inclusion of a treatment benefit plateau reduces the proportion of risdiplam-treated patients reaching the standing and walking milestones in both models. This may be conservative [redacted] • The models do not adequately reflect other benefits of risdiplam e.g. improved bulbar function and feeding/swallowing, reductions in hospitalisations and improved upper limb function • As with TA588,[9] additional considerations and NICE decision modifiers should be recognised	ERG's preferred analyses, which include the assumption of a plateau in treatment benefit, lead to lower and potentially more plausible proportions of patients reaching the standing/walking health states. This is consistent with the assumptions made in the final iterations of the models used to inform TA588.[5] With respect to the arguments made in company's technical engagement response,[1] the ERG notes the following: • [redacted] The company's concerns regarding other benefits of risdiplam which are missing from the model is not directly relevant to this key issue, but do require consideration. The ERG's additional sensitivity analyses and the company's updated base case models include additional utility gains for non-sitters and sitters to reflect benefits associated with achieving/maintaining upper limb function (this is further discussed under Key Issue 10). It is unclear whether benefits associated with avoided hospitalisations are captured in the models or not - the ERG's preferred analyses and the company's updated models use non-preference-based estimates of utility obtained from clinical experts and it is unclear exactly which aspects of health the experts considered in their valuations. • The ERG agrees that considerations deemed relevant for informing decision-making in TA588[9] also apply to the appraisal of risdiplam
Key issue 8 None of the patient utility values for SMA are ideal;	• The company's original models unintentionally applied values which were different to those used in the final iterations of the models used to inform TA588[5] • The company agrees that the values obtained from Biogen's clinical experts in TA588 should be used in both	The ERG's concerns regarding health utility values for SMA patients and their caregivers can be found in Section 5.3.4 of the ERG report[4] (critical appraisal point [10].

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
caregiver utility values by motor milestone are not available	the Type 2/3 and Type 1 models instead. These have been included in the company's updated base case models • Whilst evidence for caregiver utilities is lacking, the company's approach is intended to align with the approach used in TA588.	In line with the ERG's preferred analyses, the company's updated base case models include health utility estimates for patients and caregivers which are consistent with the ERG's preferred analyses.
Key issue 9 The company's modelling assumptions are inconsistent with those used to inform decision-making in TA588 (nusinersen for SMA)	• The company made a conscious effort to align with the assumptions accepted by the Appraisal Committee in TA588,[9] where possible • Deviations from the approach taken in TA588 were generally informed by UK clinical expert opinion obtained via advisory boards • Not all uncertainties were resolved in TA588; as SMA is a complex disease to model, and differences between risdiplam and nusinersen may warrant alternative assumptions (e.g. discontinuation assumptions due to the different modes of administration of risdiplam and nusinersen) • The company's updated base case models are now aligned with the final TA588 models,[5] except for the approach used to model caregiver QALYs and the number of caregivers included in the Type 2/3 SMA model.	The assumptions employed in the company's updated base case models are partially consistent with those applied in the final iterations of the models used to inform TA588,[5] but with some important differences. As described in Table 1, the two sets of models are subject to the following differences: • The company's updated risdiplam models only count caregiver QALY gains whilst the SMA patient is still alive. The models used to inform TA588 only counted caregiver disutilities whilst the SMA patient is alive. As described in Key Issue 4, the approach used to value caregiver QALY impacts has a substantial impact on the ICER for risdiplam, particularly in the Type 1 SMA population. • The company's updated risdiplam models now assume that all surviving patients remain on treatment until some maximum treatment time (Type 2/3 – 30 years; Type 1 – 50 years), with some loss of previously achieved motor milestones following discontinuation (see Key Issue 5). The final TA588 models employed more complex discontinuation assumptions based on patients reaching certain milestones by specific timepoints, an assumption that some patients will worsen and discontinue treatment, and consideration of the patient's ability to receive intrathecal injections following scoliosis surgery. • The updated risdiplam Type 2/3 SMA model assumes that each SMA patient has 2.2 caregivers. The Type 2/3 SMA model in TA588 assumed 3 caregivers for SMA patients who are unable to sit. The ERG applied an assumption which was consistent with that used in TA588, which in turn reflects a plausible assumption that caregiver demands are greater for more severely disabled patients. There is no strong empirical evidence to support either the company's or the

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
		ERG's preferred approach. Consistency with previous appraisals may be preferred.
Key issue 10 The model structures account for gross motor milestones but may not fully account for HRQoL gains due to achievement of fine motor skills	• The company agrees that their original models did not capture utility gains associated with fine motor skills e.g. upper limb function • These benefits are particularly valuable to patients • There is evidence from SUNFISH[10] to support such gains (based on the RULM and the SMAIS), but limited evidence to quantify their impact • Additional utility gains have been included for non-sitters and sitters in the company's updated models • The additional utility gains included are conservative and do not fully capture the magnitude of the impact on quality of life that upper limb function brings to SMA patients and their carers	As described in Section 5.3.4 of the ERG report,[4] the company's original model structures are characterised in terms of gross motor milestones (sitting, standing and walking). However, SMA treatments, including risdiplam, may offer additional benefits in terms of achieving and maintaining fine motor skills and this may have a substantial impact on a patient's overall level of functioning, participation and independence, thereby leading to meaningful impacts on HRQoL. As part of the ERG's exploratory analyses,[4] an additional sensitivity analysis was presented in which additional patient utility gains of 0.05 and 0.10 were applied in the risdiplam group to the non-sitting and sitting states, respectively.[4] These additional utility estimates were taken from the previous model developed by Thokala *et al*.[15] This additional sensitivity analysis did not form part of the ERG's preferred analyses because the estimates of utility gains are not evidence-based. Whilst the ERG considers the achievement and maintenance of fine motor skills to be a relevant issue for consideration, there is uncertainty regarding: (i) how many risdiplam-treated patients would accrue these gains; (ii) how long those gains would last, and (iii) the impact of these gains on patient (and potentially caregiver) HRQoL. In the absence of any evidence, it is unclear whether the assumed values are conservative or optimistic. Longer-term follow-up of SUNFISH[10] and FIREFISH[3] may help to resolve uncertainty around the duration over which such benefits are maintained.
Key issue 11 It is unclear whether NICE's End of Life criteria apply in Type 1 SMA	• Owing to the single-arm design of FIREFISH,[3] modelling OS for BSC-treated patients is challenging • NICE's End-of-Life (EoL) criteria were applied to the Type 1 SMA population TA588,[9] despite the model predicting a mean OS of 2.14 years	The ERG's comments on whether risdiplam meets NICE's EoL criteria can be found in the ERG report[4] (Section 6). The key points are summarised below: • Without respiratory support, mean survival for BSC-treated patients reported in natural history studies is less than 2 years

Issue	Summary of main points discussed in the company's technical engagement response	ERG comments
	• Feedback from patient organisations consistently emphasised that the life expectancy of Type 1 SMA patients is 2 years or less • Expert clinical opinion obtained by the company indicates that respiratory care is increasingly used in recent years to artificially extend patients' lives. Without this respiratory support or active therapy, life expectancy is approximately 2 years • Given the precedents in previous SMA appraisals and the extremely poor levels of HRQoL associated with artificially extending survival, NICE's EoL criteria also apply for Type 1 SMA patients in the risdiplam appraisal.	• In TA588,[9] the Appraisal Committee considered it reasonable to accept that nusinersen could meet the short life-expectancy criterion for early-onset SMA • The availability of nusinersen is expected to increase mean survival in people with Type 1 SMA; however, nusinersen is not included as a comparator for risdiplam in this appraisal • The company's original Type 1 SMA model suggested that BSC-treated patients have a mean survival duration of 10.1 years (based on the naïve indirect comparison of OS from FIREFISH[3] and ENDEAR[16]). The ERG does not consider this to be plausible. The company's updated Type 1 SMA model suggests that BSC-treated patients have a shorter mean survival duration of 4.88 years. This difference is driven by the use of the HR obtained from the MAIC (see Key Issue 2). • The ERG considers it likely that risdiplam will extend OS by more than 3 months; however, model-predicted OS gains should be considered highly uncertain.

4. Additional analyses undertaken by the ERG

4.1 Description of additional exploratory analyses undertaken by the ERG.

The ERG undertook additional exploratory analyses using the company's updated models to assess the impact of key issues raised during technical engagement on the ICER for risdiplam versus BSC, together with the company's updated PAS for risdiplam. The following scenarios are presented using the company's models:

- **ERG additional analysis 1:** ERG-preferred model (caregiver disutility approach, no discontinuation, 3 caregivers for Type 2/3 SMA patients who cannot sit; equivalent to EA6 in the ERG report[4])
- **ERG additional analysis 2:** ERG-preferred model plus fine motor skills utility gains (equivalent to ASA1 in the ERG report)
- **ERG additional analysis 3:** ERG-preferred model plus 2.2 caregivers for all Type 2/3 SMA patients (Type 2/3 SMA model only)
- **ERG additional analysis 4:** ERG-preferred model plus company's new discontinuation assumptions
- **ERG additional analysis 5:** ERG-preferred model plus fine motor skills utility gains, 2.2 caregivers and company's new discontinuation assumptions
- **ERG additional analysis 6a:** ERG-preferred model plus "lump-sum" QALY loss associated with bereavement (disutility = -0.04, duration = 20 years, no. caregivers = 2.2 per SMA patient).
- **ERG additional analysis 6b:** ERG original preferred model plus indefinite caregiver disutility proportional to patient death (disutility = -0.04, no. caregivers = 2.2 per SMA patient).

4.2 Results of additional exploratory analyses undertaken by the ERG

Type 2/3 SMA model results

The results of the ERG's additional exploratory analyses for the Type 2/3 SMA population are shown in Table 5. The ERG's preferred analysis including the company's updated PAS leads to a deterministic ICER for risdiplam versus BSC of [redacted] per QALY gained (AA1). The inclusion of additional patient utility gains associated with achieving/maintaining fine motor skills (AA2) and the incorporation of the company's discontinuation assumptions (AA4) each reduce the ICER for risdiplam, whilst assuming 2.2 caregivers for all patients (AA3) increases the ICER. When all three amendments are included in the model (AA5), the ICER for risdiplam versus BSC is estimated to be [redacted] per QALY gained. Analyses AA6a and AA6b indicate that irrespective of how bereavement is modelled, the impact on the ICER is minimal.

Table 5: Results of additional exploratory analyses undertaken by the ERG, including updated PAS, Type 2/3 SMA model, deterministic

Option	LYGs*	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
AA1: ERG-preferred analysis with updated PAS for risdiplam*						
Risdiplam	50.30	11.42	-3.60	[redacted]	-	-
BSC	43.77	5.98	-10.06	[redacted]	-	-
Incremental	6.53	5.44	6.45	[redacted]	[redacted]	[redacted]
AA2: ERG-preferred analysis plus additional utility gains for fine motor skills						
Risdiplam	50.30	12.38	-3.60	[redacted]	-	-
BSC	43.77	5.98	-10.06	[redacted]	-	-
Incremental	6.53	6.40	6.45	[redacted]	[redacted]	[redacted]
AA3: ERG-preferred analysis plus 2.2 caregivers per SMA patient						
Risdiplam	50.30	11.42	-3.48	[redacted]	-	-
BSC	43.77	5.98	-7.67	[redacted]	-	-
Incremental	6.53	5.44	4.19	[redacted]	[redacted]	[redacted]
AA4: ERG-preferred analysis plus discontinuation						
Risdiplam	48.60	10.51	-4.67	[redacted]	-	-
BSC	43.77	5.98	-10.06	[redacted]	-	-
Incremental	4.83	4.53	5.39	[redacted]	[redacted]	[redacted]
AA5: ERG-preferred analysis plus additional utility gains, 2.2 caregivers per SMA patient, discontinuation						
Risdiplam	48.60	11.60	-4.19	[redacted]	-	-
BSC	43.77	5.98	-7.67	[redacted]	-	-
Incremental	4.83	5.62	3.48	[redacted]	[redacted]	[redacted]
AA6a: ERG-preferred analysis plus bereavement QALY loss (disutility=-0.04, duration=20 years; applied to 2.2 caregivers)						
Risdiplam	50.30	11.42	-4.04	[redacted]	-	-
BSC	43.77	5.98	-10.59	[redacted]	-	-
Incremental	6.53	5.44	6.55	[redacted]	[redacted]	[redacted]
AA6b: ERG-preferred analysis plus indefinite bereavement-related disutility (disutility=-0.04, applied indefinitely to cumulative mortality probability, 2.2 caregivers)						
Risdiplam	50.30	11.42	-4.12	[redacted]	-	-
BSC	43.77	5.98	-10.71	[redacted]	-	-
Incremental	6.53	5.44	6.59	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care
** Undiscounted*

Type 1 SMA model results

The results of the ERG's additional exploratory analyses for the Type 1 SMA population are shown in Table 6. The ERG's preferred analysis including the company's updated PAS leads to a deterministic ICER for risdiplam versus BSC of [redacted] per QALY gained (AA1). The inclusion of additional patient utility gains associated with achieving/maintaining fine motor skills (AA2) and the incorporation of the company's discontinuation assumptions (AA4) each reduce the ICER for risdiplam; combining these two amendments results in an ICER for risdiplam versus BSC [redacted] per QALY gained (AA5). Analyses AA6a and AA6b indicate that alternative assumptions surrounding bereavement-related caregiver QALY losses have markedly different impacts on the ICER; assuming a lifetime

bereavement-related caregiver disutility, the ICER for risdiplam is estimated to be [redacted] per QALY gained.

Table 6: Results of additional exploratory analyses undertaken by the ERG, including updated PAS, Type 1 SMA model, deterministic

Option	LYGs*	QALYs - patients	QALYs carers	Costs	ICER (patients)	ICER (patients + carers)
AA1: ERG-preferred analysis with updated PAS for risdiplam*						
Risdiplam	21.68	4.77	-6.68	[redacted]	-	-
BSC	4.88	0.02	-3.14	[redacted]	-	-
Incremental	16.80	4.75	-3.54	[redacted]	[redacted]	[redacted]
AA2: ERG-preferred analysis plus additional utility gains for fine motor skills						
Risdiplam	21.68	5.19	-6.68	[redacted]	-	-
BSC	4.88	0.02	-3.14	[redacted]	-	-
Incremental	16.80	5.17	-3.54	[redacted]	[redacted]	[redacted]
AA3: ERG-preferred analysis plus 2.2 caregivers per SMA patient						
Risdiplam	Same as ERG-preferred analysis					
BSC						
Incremental						
AA4: ERG-preferred analysis plus discontinuation						
Risdiplam	21.99	4.72	-6.75	[redacted]	-	-
BSC	4.88	0.02	-3.14	[redacted]	-	-
Incremental	17.11	4.70	-3.61	[redacted]	[redacted]	[redacted]
AA5: ERG-preferred analysis plus additional utility gains, discontinuation included						
Risdiplam	21.99	5.15	-6.75	[redacted]	-	-
BSC	4.88	0.02	-3.14	[redacted]	-	-
Incremental	17.11	5.13	-3.61	[redacted]	[redacted]	[redacted]
AA6a: ERG-preferred analysis plus bereavement QALY loss (disutility=-0.04, duration=20 years; applied to 2.2 caregivers)						
Risdiplam	21.68	4.77	-7.69	[redacted]	-	-
BSC	4.88	0.02	-4.70	[redacted]	-	-
Incremental	16.80	4.75	-2.98	[redacted]	[redacted]	[redacted]
AA6b: ERG-preferred analysis plus indefinite bereavement-related disutility (disutility=-0.04, applied indefinitely to cumulative mortality probability, 2.2 caregivers)						
Risdiplam	21.68	4.77	-8.06	[redacted]	-	-
BSC	4.88	0.02	-5.33	[redacted]	-	-
Incremental	16.80	4.75	-2.73	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care
** Undiscounted*

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