Risdiplam for treating spinal muscular atrophy: A Single Technology Appraisal

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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		
EA5: Inclusion of drug wastage (0.50 bottles)	16.48		
EA6: ERG-preferred analysis	11.89		
ASA1: Additional utility gains for non-sitters and sitters	13.69		
ASA2a: Risdiplam worsening probability =1%	3.18		
ASA2b: Risdiplam worsening probability =2%	0.48		
ASA3a: Assumption of treatment plateau after 38 months	12.68		
ASA3b: Assumption of treatment plateau after 14 months	11.84		
ASA4: Initial period transition probabilities applied without adjustments until plateau timepoint	11.68		

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.

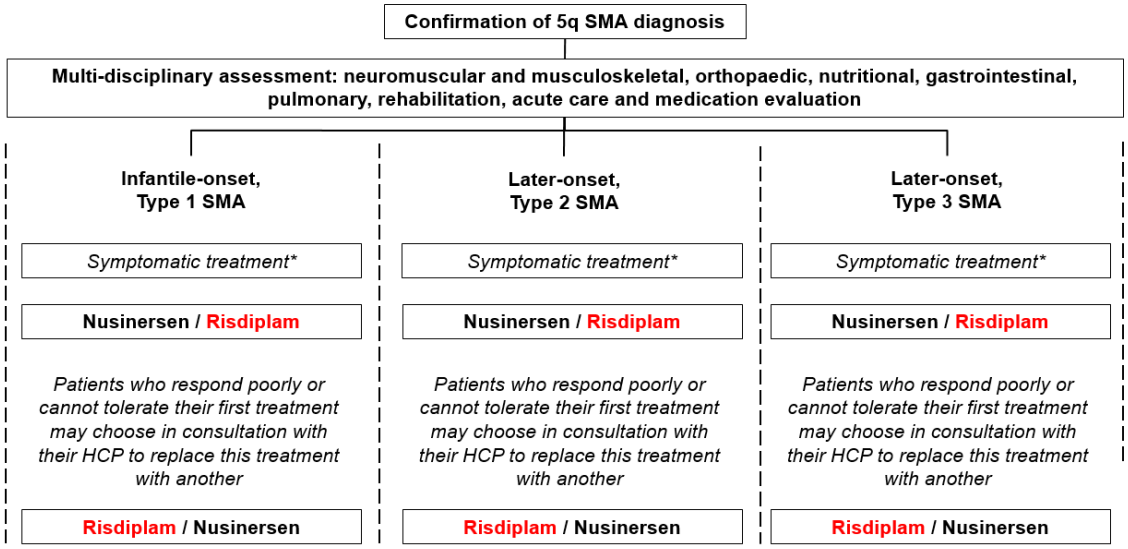
Providing a patient meets the entry criteria as specified above, due to equity considerations there is no upper limit of age on treatment initiation.

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)

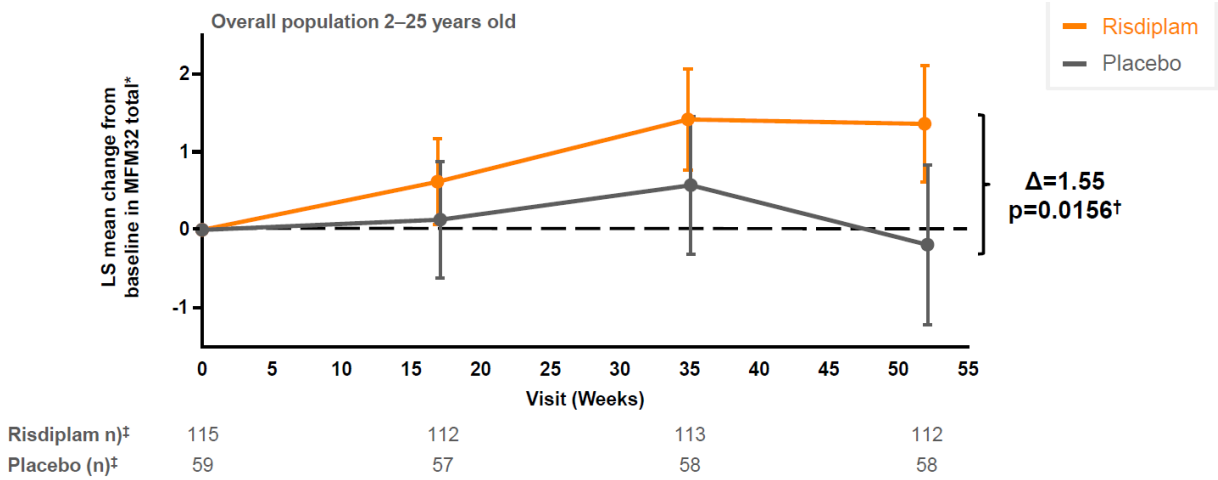
Outcome	Risdiplam n=120	Placebo n=60	Difference, risdiplam minus placebo (95% CI)	*p*-value
Primary endpoint				
Least squares mean change (SE) in MFM-32 Total Score from Baseline to Month 12	1.36 (0.38)	–0.19 (0.52)	1.55 (0.30, 2.81)	Unadjusted: 0.0156 Adjusted: 0.0156
Secondary endpoints				
Least 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 (≤25th percentile, >25th and ≤75th percentile, and >75th 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.

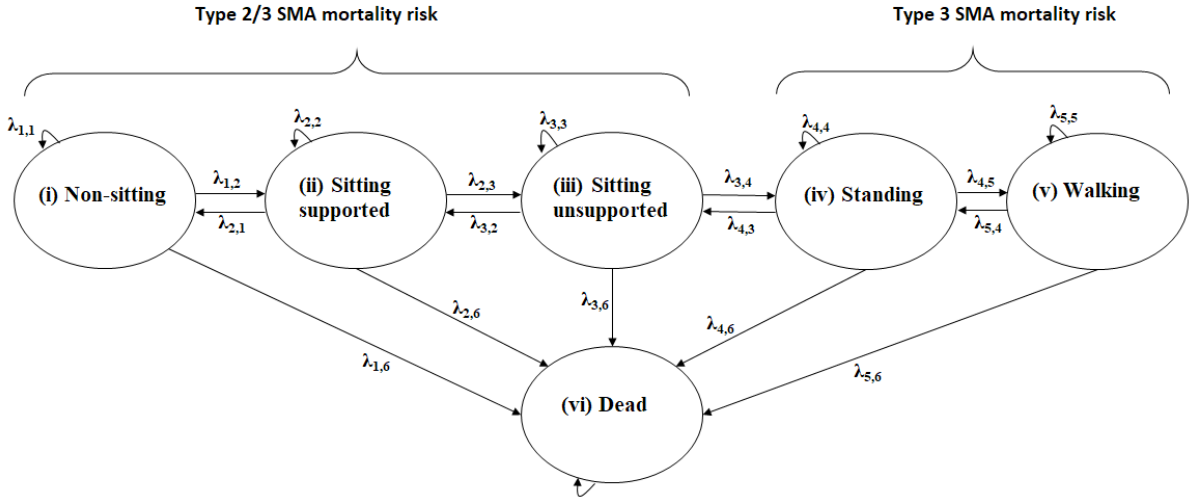
Whilst the comparator included in the company's models is consistent with the NICE scope, the ERG's clinical advisor commented that the majority of paediatric patients with Type 1 or 2 SMA who meet the entry criteria of the MAA are currently receiving nusinersen.

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)

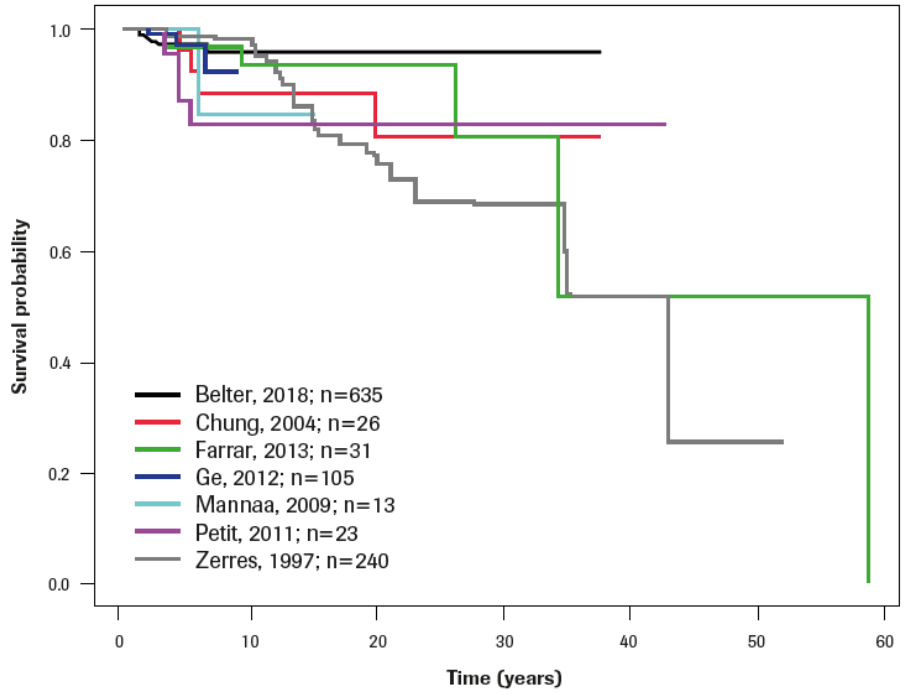


Figure 5: Modelled OS for Type 2 SMA based on pooled IPD from natural history studies (reproduced from CS Figure 13)

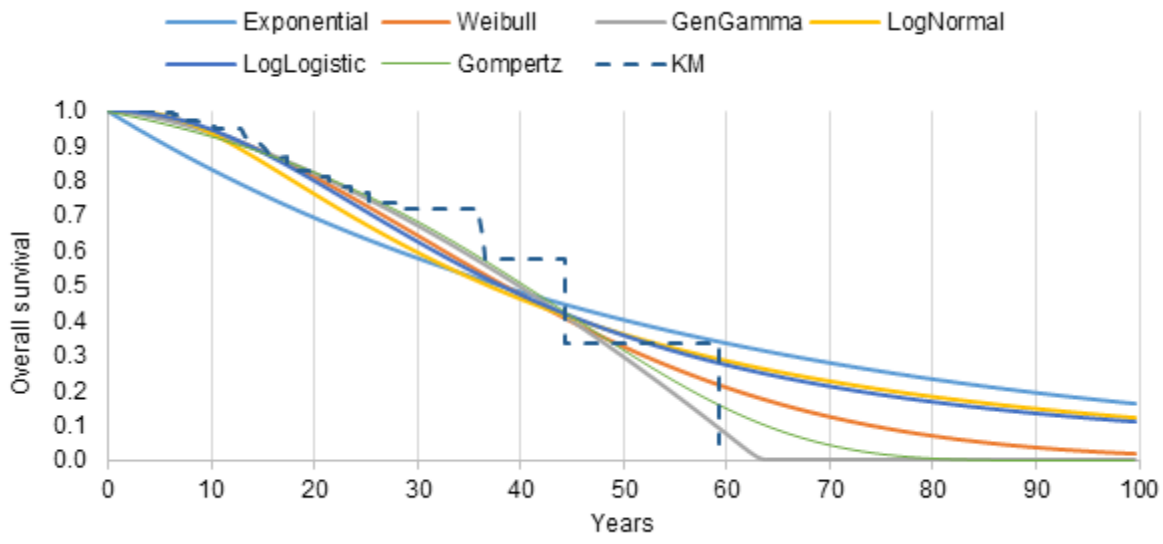


Table 27: AIC and BIC statistics, pooled OS for Type 2 SMA based on pooled IPD from natural history studies

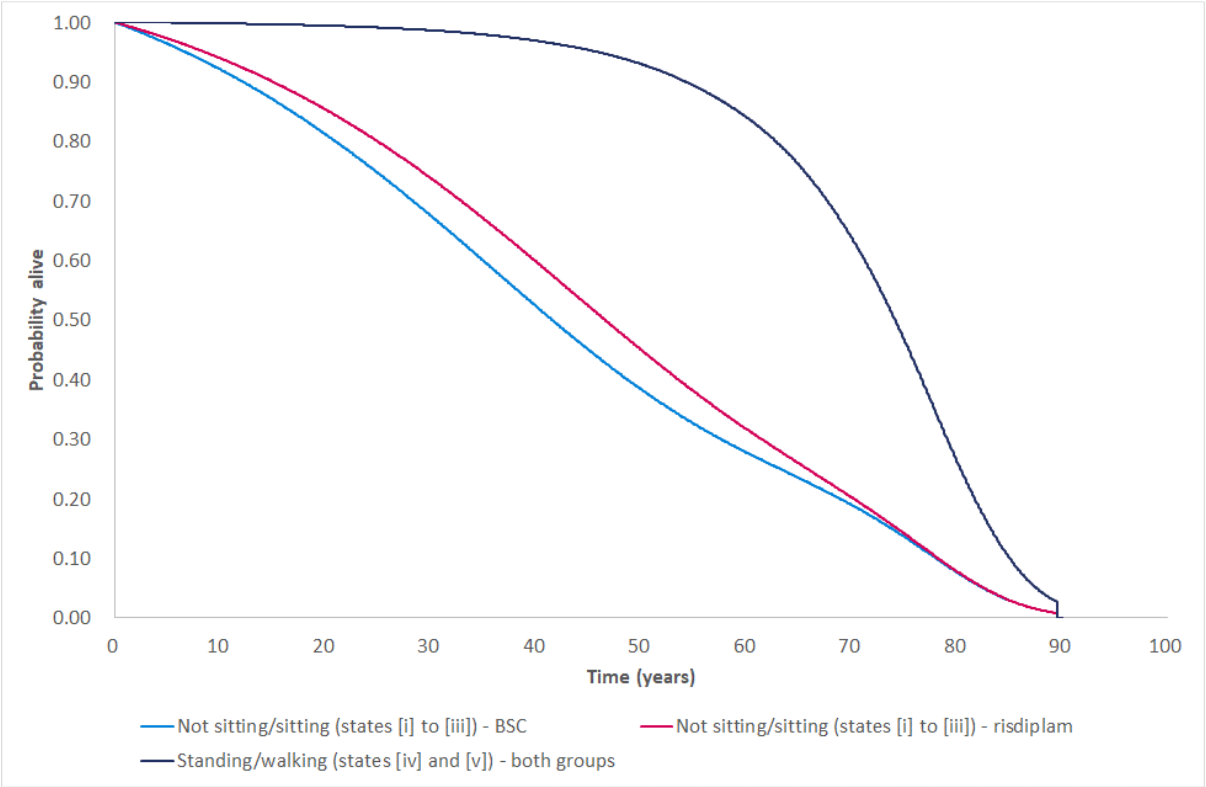
Model	AIC	BIC
Exponential	3434.1	3438.2
Weibull	3338.0	3346.1
Gompertz	3328.0	3336.1
Log-normal	3376.9	3385.1
Log-logistic	3363.9	3372.1
Generalised gamma	**3314.2**	**3326.5**

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			

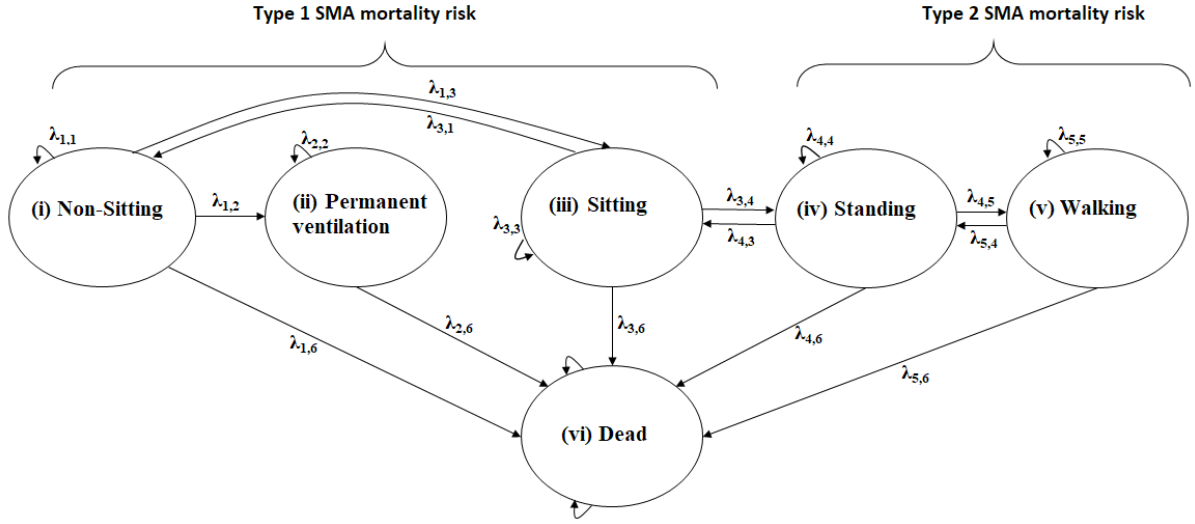
QALY - quality-adjusted life year; ITT - intention-to-treat; SMA - spinal muscular atrophy; MSM - multistate model; ICER - incremental cost-effectiveness ratio; Inc. - incremental
** Based on estimates provided by experts during company's advisory board meeting*

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

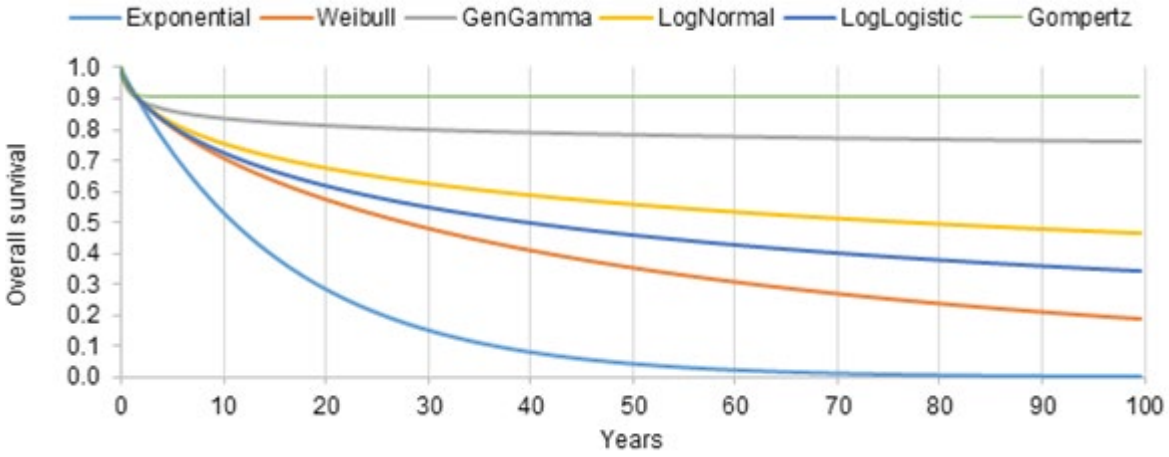
Health state	**Per cycle mortality risk applied whilst in health state**	
	BSC group	**Risdiplam group**
(i) Not sitting	Risdiplam group risk (from exponential model) raised to power of inverse HR derived from arm-based unadjusted indirect comparison of FIREFISH[23] and ENDEAR[25]	Exponential model fitted 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

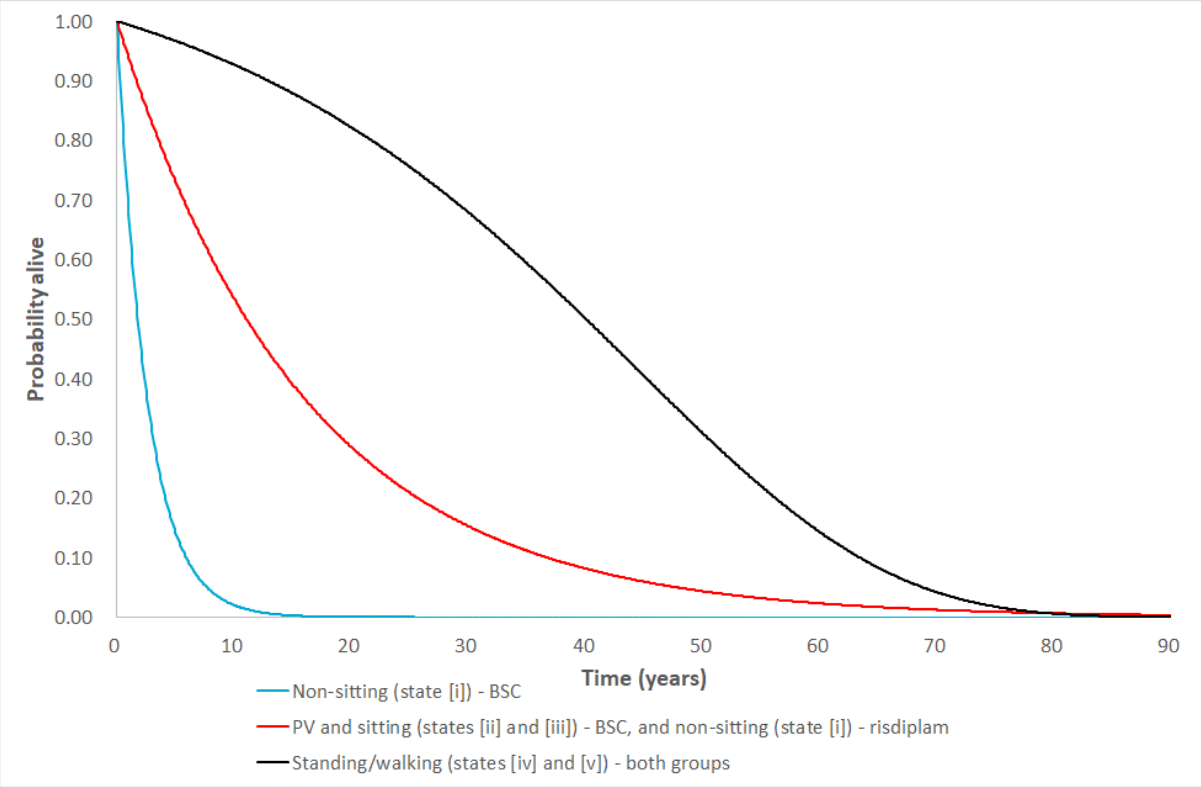
Model	AIC	BIC
Exponential	64.60	**66.60**
Weibull	65.70	69.80
Gompertz	64.30	68.40
Log-normal	65.10	69.20
Log-logistic	65.60	69.80
Generalised gamma	**62.50**	68.70

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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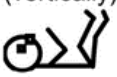
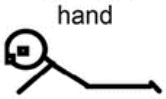
9 APPENDICES

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
15.33	0.00001109
15.42	0.00001109
15.50	0.00001109
15.58	0.00001109
15.67	0.00001109
15.75	0.00001109
15.83	0.00001109
15.92	0.00001109
16.00	0.00001530
16.08	0.00001530
16.17	0.00001530
16.25	0.00001530
16.33	0.00001530
16.42	0.00001530
16.50	0.00001530
16.58	0.00001530
16.67	0.00001530
16.75	0.00001530
16.83	0.00001530
16.92	0.00001530
17.00	0.00001918
17.08	0.00001918
17.17	0.00001918
17.25	0.00001918
17.33	0.00001918
17.42	0.00001918
17.50	0.00001918
17.58	0.00001918
17.67	0.00001918
17.75	0.00001918
17.83	0.00001918
17.92	0.00001918
18.00	0.00002484
18.08	0.00002484
18.17	0.00002484
18.25	0.00002484

18.33	0.00002484
18.42	0.00002484
18.50	0.00002484
18.58	0.00002484
18.67	0.00002484
18.75	0.00002484
18.83	0.00002484
18.92	0.00002484
19.00	0.00002527
19.08	0.00002527
19.17	0.00002527
19.25	0.00002527
19.33	0.00002527
19.42	0.00002527
19.50	0.00002527
19.58	0.00002527
19.67	0.00002527
19.75	0.00002527
19.83	0.00002527
19.92	0.00002527
20.00	0.00002527
20.08	0.00002827
20.17	0.00002827
20.25	0.00002827
20.33	0.00002827
20.42	0.00002827
20.50	0.00002827
20.58	0.00002827
20.67	0.00002827
20.75	0.00002826
20.83	0.00002826
20.92	0.00002826
21.00	0.00002826
21.08	0.00002899
21.17	0.00002899
21.25	0.00002899
21.33	0.00002899
21.42	0.00002899
21.50	0.00002898
21.58	0.00002898
21.67	0.00002898
21.75	0.00002898
21.83	0.00002898
21.92	0.00002898
22.00	0.00002898
22.08	0.00002875
22.17	0.00002875
22.25	0.00002875
22.33	0.00002875
22.42	0.00002875
22.50	0.00002875
22.58	0.00002875
22.67	0.00002875
22.75	0.00002875
22.83	0.00002875
22.92	0.00002875
23.00	0.00002875
23.08	0.00002779
23.17	0.00002779
23.25	0.00002779
23.33	0.00002779
23.42	0.00002779
23.50	0.00002779
23.58	0.00002779
23.67	0.00002779
23.75	0.00002779
23.83	0.00002779
23.92	0.00002779
24.00	0.00002779
24.08	0.00003032
24.17	0.00003032
24.25	0.00003032
24.33	0.00003031
24.42	0.00003031
24.50	0.00003031
24.58	0.00003031
24.67	0.00003031
24.75	0.00003031
24.83	0.00003031
24.92	0.00003031
25.00	0.00003031
25.08	0.00003244
25.17	0.00003244
25.25	0.00003244
25.33	0.00003244
25.42	0.00003244
25.50	0.00003244
25.58	0.00003244
25.67	0.00003244
25.75	0.00003244
25.83	0.00003244
25.92	0.00003244
26.00	0.00003244
26.08	0.00003328
26.17	0.00003328
26.25	0.00003328
26.33	0.00003328
26.42	0.00003328
26.50	0.00003328
26.58	0.00003328
26.67	0.00003328
26.75	0.00003328
26.83	0.00003328
26.92	0.00003328
27.00	0.00003328
27.08	0.00003502
27.17	0.00003502
27.25	0.00003502
27.33	0.00003501
27.42	0.00003501
27.50	0.00003501
27.58	0.00003501
27.67	0.00003501
27.75	0.00003501
27.83	0.00003501
27.92	0.00003501
28.00	0.00003501
28.08	0.00003871
28.17	0.00003871
28.25	0.00003871
28.33	0.00003871
28.42	0.00003871
28.50	0.00003871
28.58	0.00003871
28.67	0.00003871
28.75	0.00003871
28.83	0.00003871
28.92	0.00003871
29.00	0.00003871
29.08	0.00004007
29.17	0.00004007
29.25	0.00004007
29.33	0.00004007
29.42	0.00004007
29.50	0.00004006
29.58	0.00004006
29.67	0.00004006
29.75	0.00004006
29.83	0.00004006
29.92	0.00004006
30.00	0.00004006
30.08	0.00004436
30.17	0.00004436
30.25	0.00004436
30.33	0.00004436
30.42	0.00004436
30.50	0.00004436
30.58	0.00004436
30.67	0.00004436
30.75	0.00004436
30.83	0.00004436
30.92	0.00004436
31.00	0.00004436
31.08	0.00004733
31.17	0.00004733
31.25	0.00004733

31.33	0.00004733
31.42	0.00004733
31.50	0.00004733
31.58	0.00004733
31.67	0.00004733
31.75	0.00004733
31.83	0.00004733
31.92	0.00004733
32.00	0.00004733
32.08	0.00004946
32.17	0.00004946
32.25	0.00004946
32.33	0.00004946
32.42	0.00004946
32.50	0.00004946
32.58	0.00004946
32.67	0.00004946
32.75	0.00004946
32.83	0.00004946
32.92	0.00004946
33.00	0.00004946
33.08	0.00005445
33.17	0.00005445
33.25	0.00005445
33.33	0.00005445
33.42	0.00005445
33.50	0.00005445
33.58	0.00005445
33.67	0.00005445
33.75	0.00005445
33.83	0.00005445
33.92	0.00005445
34.00	0.00005445
34.08	0.00005885
34.17	0.00005885
34.25	0.00005885
34.33	0.00005885
34.42	0.00005885
34.50	0.00005885
34.58	0.00005885
34.67	0.00005885
34.75	0.00005885
34.83	0.00005885
34.92	0.00005885
35.00	0.00005885
35.08	0.00006316
35.17	0.00006316
35.25	0.00006316
35.33	0.00006316
35.42	0.00006316
35.50	0.00006316
35.58	0.00006316
35.67	0.00006316
35.75	0.00006316
35.83	0.00006316
35.92	0.00006316
36.00	0.00006315
36.08	0.00006779
36.17	0.00006779
36.25	0.00006779
36.33	0.00006779
36.42	0.00006779
36.50	0.00006779
36.58	0.00006779
36.67	0.00006779
36.75	0.00006779
36.83	0.00006779
36.92	0.00006779
37.00	0.00006779
37.08	0.00008130
37.17	0.00008130
37.25	0.00008130
37.33	0.00008130
37.42	0.00008130
37.50	0.00008130
37.58	0.00008130
37.67	0.00008130
37.75	0.00008130
37.83	0.00008130
37.92	0.00008130
38.00	0.00008130
38.08	0.00007812
38.17	0.00007812
38.25	0.00007812
38.33	0.00007812
38.42	0.00007812
38.50	0.00007812
38.58	0.00007812
38.67	0.00007812
38.75	0.00007812
38.83	0.00007812
38.92	0.00007812
39.00	0.00008555
39.08	0.00008555
39.17	0.00008555
39.25	0.00008555
39.33	0.00008555
39.42	0.00008555
39.50	0.00008555
39.58	0.00008555
39.67	0.00008555
39.75	0.00008555
39.83	0.00008555
39.92	0.00008555
40.00	0.00009376
40.08	0.00009376
40.17	0.00009375
40.25	0.00009375
40.33	0.00009375
40.42	0.00009375
40.50	0.00009375
40.58	0.00009375
40.67	0.00009375
40.75	0.00009375
40.83	0.00009375
40.92	0.00009375
41.00	0.00010175
41.08	0.00010175
41.17	0.00010175
41.25	0.00010174
41.33	0.00010174
41.42	0.00010174
41.50	0.00010174
41.58	0.00010174
41.67	0.00010174
41.75	0.00010174
41.83	0.00010174
41.92	0.00010174
42.00	0.00011227
42.08	0.00011227
42.17	0.00011227
42.25	0.00011227
42.33	0.00011227
42.42	0.00011227
42.50	0.00011227
42.58	0.00011227
42.67	0.00011227
42.75	0.00011227
42.83	0.00011227
42.92	0.00011226
43.00	0.00012246
43.08	0.00012246
43.17	0.00012246
43.25	0.00012246
43.33	0.00012246
43.42	0.00012245
43.50	0.00012245
43.58	0.00012245
43.67	0.00012245
43.75	0.00012245
43.83	0.00012245
43.92	0.00012245
44.00	0.00013379
44.08	0.00013379
44.17	0.00013379
44.25	0.00013379

44.33	0.00013379
44.42	0.00013379
44.50	0.00013379
44.58	0.00013378
44.67	0.00013378
44.75	0.00013378
44.83	0.00013378
44.92	0.00013378
45.00	0.00014882
45.08	0.00014882
45.17	0.00014881
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45.33	0.00014881
45.42	0.00014881
45.50	0.00014881
45.58	0.00014881
45.67	0.00014881
45.75	0.00014881
45.83	0.00014880
45.92	0.00014880
46.00	0.00015781
46.08	0.00015781
46.17	0.00015781
46.25	0.00015781
46.33	0.00015781
46.42	0.00015781
46.50	0.00015781
46.58	0.00015780
46.67	0.00015780
46.75	0.00015780
46.83	0.00015780
46.92	0.00015780
47.00	0.00017398
47.08	0.00017397
47.17	0.00017397
47.25	0.00017397
47.33	0.00017397
47.42	0.00017397
47.50	0.00017397
47.58	0.00017396
47.67	0.00017396
47.75	0.00017396
47.83	0.00017396
47.92	0.00017396
48.00	0.00018636
48.08	0.00018636
48.17	0.00018636
48.25	0.00018636
48.33	0.00018636
48.42	0.00018635
48.50	0.00018635
48.58	0.00018635
48.67	0.00018635
48.75	0.00018635
48.83	0.00018635
48.92	0.00018634
49.00	0.00020515
49.08	0.00020515
49.17	0.00020514
49.25	0.00020514
49.33	0.00020514
49.42	0.00020514
49.50	0.00020514
49.58	0.00020513
49.67	0.00020513
49.75	0.00020513
49.83	0.00020513
49.92	0.00020512
50.00	0.00022112
50.08	0.00022112
50.17	0.00022111
50.25	0.00022111
50.33	0.00022111
50.42	0.00022111
50.50	0.00022110
50.58	0.00022110
50.67	0.00022110
50.75	0.00022110
50.83	0.00022110
50.92	0.00022109
51.00	0.00023950
51.08	0.00023949
51.17	0.00023949
51.25	0.00023949
51.33	0.00023949
51.42	0.00023948
51.50	0.00023948
51.58	0.00023948
51.67	0.00023948
51.75	0.00023947
51.83	0.00023947
51.92	0.00023947
52.00	0.00025855
52.08	0.00025855
52.17	0.00025855
52.25	0.00025855
52.33	0.00025854
52.42	0.00025854
52.50	0.00025854
52.58	0.00025853
52.67	0.00025853
52.75	0.00025853
52.83	0.00025853
52.92	0.00025852
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53.17	0.00027418
53.25	0.00027418
53.33	0.00027417
53.42	0.00027417
53.50	0.00027417
53.58	0.00027416
53.67	0.00027416
53.75	0.00027415
53.83	0.00027415
53.92	0.00027415
54.00	0.00029407
54.08	0.00029406
54.17	0.00029406
54.25	0.00029405
54.33	0.00029405
54.42	0.00029405
54.50	0.00029404
54.58	0.00029404
54.67	0.00029403
54.75	0.00029403
54.83	0.00029402
54.92	0.00029402
55.00	0.00032105
55.08	0.00032104
55.17	0.00032104
55.25	0.00032104
55.33	0.00032103
55.42	0.00032103
55.50	0.00032102
55.58	0.00032102
55.67	0.00032101
55.75	0.00032101
55.83	0.00032101
55.92	0.00032100
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56.08	0.00035620
56.17	0.00035620
56.25	0.00035619
56.33	0.00035619
56.42	0.00035618
56.50	0.00035618
56.58	0.00035617
56.67	0.00035617
56.75	0.00035616
56.83	0.00035615
56.92	0.00035615
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57.08	0.00038885
57.17	0.00038885
57.25	0.00038884

57.33	0.00038883
57.42	0.00038883
57.50	0.00038882
57.58	0.00038881
57.67	0.00038881
57.75	0.00038880
57.83	0.00038879
57.92	0.00038879
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58.25	0.00042639
58.33	0.00042638
58.42	0.00042637
58.50	0.00042636
58.58	0.00042635
58.67	0.00042635
58.75	0.00042634
58.83	0.00042633
58.92	0.00042632
59.00	0.00046111
59.08	0.00046110
59.17	0.00046109
59.25	0.00046108
59.33	0.00046107
59.42	0.00046107
59.50	0.00046106
59.58	0.00046105
59.67	0.00046104
59.75	0.00046103
59.83	0.00046102
59.92	0.00046101
60.00	0.00050804
60.08	0.00050803
60.17	0.00050801
60.25	0.00050800
60.33	0.00050799
60.42	0.00050798
60.50	0.00050797
60.58	0.00050796
60.67	0.00050795
60.75	0.00050793
60.83	0.00050792
60.92	0.00050791
61.00	0.00055274
61.08	0.00055273
61.17	0.00055271
61.25	0.00055270
61.33	0.00055269
61.42	0.00055267
61.50	0.00055266
61.58	0.00055265
61.67	0.00055263
61.75	0.00055262
61.83	0.00055261
61.92	0.00055259
62.00	0.00062517
62.08	0.00062515
62.17	0.00062514
62.25	0.00062512
62.33	0.00062511
62.42	0.00062509
62.50	0.00062508
62.58	0.00062506
62.67	0.00062505
62.75	0.00062504
62.83	0.00062502
62.92	0.00062501
63.00	0.00067886
63.08	0.00067884
63.17	0.00067882
63.25	0.00067880
63.33	0.00067878
63.42	0.00067876
63.50	0.00067874
63.58	0.00067872
63.67	0.00067870
63.75	0.00067868
63.83	0.00067866
63.92	0.00067864
64.00	0.00073381
64.08	0.00073378
64.17	0.00073376
64.25	0.00073374
64.33	0.00073371
64.42	0.00073369
64.50	0.00073366
64.58	0.00073364
64.67	0.00073362
64.75	0.00073359
64.83	0.00073357
64.92	0.00073354
65.00	0.00080897
65.08	0.00080894
65.17	0.00080891
65.25	0.00080888
65.33	0.00080885
65.42	0.00080882
65.50	0.00080879
65.58	0.00080876
65.67	0.00080873
65.75	0.00080870
65.83	0.00080867
65.92	0.00080864
66.00	0.00087828
66.08	0.00087824
66.17	0.00087820
66.25	0.00087816
66.33	0.00087812
66.42	0.00087808
66.50	0.00087805
66.58	0.00087801
66.67	0.00087797
66.75	0.00087793
66.83	0.00087789
66.92	0.00087785
67.00	0.00095831
67.08	0.00095826
67.17	0.00095822
67.25	0.00095817
67.33	0.00095813
67.42	0.00095808
67.50	0.00095804
67.58	0.00095799
67.67	0.00095795
67.75	0.00095790
67.83	0.00095786
67.92	0.00095781
68.00	0.00105549
68.08	0.00105544
68.17	0.00105539
68.25	0.00105534
68.33	0.00105529
68.42	0.00105524
68.50	0.00105519
68.58	0.00105514
68.67	0.00105508
68.75	0.00105503
68.83	0.00105498
68.92	0.00105493
69.00	0.00114907
69.08	0.00114900
69.17	0.00114894
69.25	0.00114887
69.33	0.00114881
69.42	0.00114875
69.50	0.00114868
69.58	0.00114862
69.67	0.00114855
69.75	0.00114849
69.83	0.00114842
69.92	0.00114836
70.00	0.00123684
70.08	0.00123678
70.17	0.00123672
70.25	0.00123666

70.33	0.00123659
70.42	0.00123653
70.50	0.00123647
70.58	0.00123641
70.67	0.00123635
70.75	0.00123629
70.83	0.00123623
70.92	0.00123617
71.00	0.00135839
71.08	0.00135830
71.17	0.00135822
71.25	0.00135813
71.33	0.00135804
71.42	0.00135796
71.50	0.00135787
71.58	0.00135779
71.67	0.00135770
71.75	0.00135762
71.83	0.00135753
71.92	0.00135744
72.00	0.00151442
72.08	0.00151434
72.17	0.00151426
72.25	0.00151417
72.33	0.00151409
72.42	0.00151400
72.50	0.00151392
72.58	0.00151383
72.67	0.00151375
72.75	0.00151366
72.83	0.00151358
72.92	0.00151350
73.00	0.00174301
73.08	0.00174289
73.17	0.00174277
73.25	0.00174265
73.33	0.00174254
73.42	0.00174242
73.50	0.00174230
73.58	0.00174218
73.67	0.00174206
73.75	0.00174194
73.83	0.00174183
73.92	0.00174171
74.00	0.00190308
74.08	0.00190294
74.17	0.00190280
74.25	0.00190266
74.33	0.00190253
74.42	0.00190239
74.50	0.00190225
74.58	0.00190211
74.67	0.00190198
74.75	0.00190184
74.83	0.00190170
74.92	0.00190156
75.00	0.00212868
75.08	0.00212851
75.17	0.00212834
75.25	0.00212816
75.33	0.00212799
75.42	0.00212782
75.50	0.00212765
75.58	0.00212748
75.67	0.00212731
75.75	0.00212713
75.83	0.00212696
75.92	0.00212679
76.00	0.00240351
76.08	0.00240329
76.17	0.00240306
76.25	0.00240284
76.33	0.00240262
76.42	0.00240240
76.50	0.00240218
76.58	0.00240196
76.67	0.00240174
76.75	0.00240151
76.83	0.00240129
76.92	0.00240107
77.00	0.00240085
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'.