**Title:** Spinal muscular atrophy - Nusinersen (MAA review of TA588) and Risdiplam (MAA review of TA755) [ID6195]

**Produced by:** Warwick Evidence

Warwick Applied Health

Warwick Medical School, University of Warwick

Coventry, CV4 7AL

**Authors:** **Jo Parsons**, Assistant Professor in Health Science Research1

**Mehdi Yousefi**, Research Fellow in Health Economics1

**Mubarak Patel**, Research Fellow in Medical Statistics1

**Anna Brown**, Information Specialist1

**Amin Mehrabian**, Research Fellow1

**Janette Parr**, Research Associate1

**Furqan Butt,** Research Fellow1

**Jeremiah Donoghue,** Research Associate**1**

**Amy Grove**, Professor of Health Technology Assessment and Implementation Science1

**Peter Auguste**, Assistant Professor in Health Economics & Decision Modelling1

1 Warwick Evidence, Warwick Medical School, University of Warwick, Coventry

**Correspondence to:** Dr Peter Auguste

Warwick Evidence, Warwick Medical School,

University of Warwick, Coventry, CV4 7AL

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*None*

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**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme or the Department for Health and Social Care. Any errors are the responsibility of the authors.

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**Contributions of authors**

Jo Parsons: senior clinical effectiveness reviewer (designed and conducted the systematic review of the clinical literature, and critique of clinical evidence submitted by the companies), Mehdi Yousefi: cost-effectiveness reviewer (designed and conducted the systematic review of the cost-effectiveness literature, and critique of economic evidence submitted by the companies), Mubarak Patel: statistical analysis (critique of companies’ statistical analysis, network meta-analysis, write-up of results), Anna Brown: information specialist (designed search strategies, and critique of company’s searches). Amin Mehrabian: clinical effectiveness reviewer (conducted the systematic review of the clinical literature, and critique of clinical evidence submitted by the companies). Janette Parr: clinical effectiveness reviewer (conducted the systematic review of the clinical literature, and critique of clinical evidence submitted by the companies). Furqan Butt: clinical effectiveness reviewer (conducted the systematic review of the clinical literature). Jeremiah Donoghue: clinical effectiveness reviewer (conducted the systematic review of the clinical literature). Amy Grove: clinical effectiveness reviewer (supervised clinical effectiveness and write-up of summaries). Peter Auguste: Project and cost-effectiveness lead (designed and conducted the systematic review of the cost-effectiveness literature and critique of the economic evidence submitted by the companies). All authors contributed to drafting relevant sections of the report.

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**Please note that:**  *Sections highlighted in aqua and underlined are ‘commercial in confidence’ (CIC). Figures that are CIC have been bordered with blue.* Depersonalised Data (DPD) is highlighted in pink.

ABSTRACT

**Background**: The rare and genetic progressive disorder spinal muscular atrophy (SMA) is characterised by degeneration of alpha motor neurons in the spinal cord, resulting in progressive muscle atrophy, muscle weakness and paralysis. The most common type of SMA is caused by a defect in the survival motor neuron 1 (SMN1) gene. SMN1 is estimated to be found in approximately 1 in 11,000 births, making it the leading genetic cause of infant mortality. The availability of disease modifying therapies has improved the clinical prospect of SMA patients. Evidence suggests that these therapies have shown to be efficacious by improving the prognoses for SMA patients, but there is still uncertainty with regards to their cost-effectiveness, especially in the advent of little to no long-term information about their effectiveness.

**Aim**: The aim of the multiple technology appraisal was to assess the clinical and cost-effectiveness of nusinersen and risdiplam compared to each other and onasemnogene abeparvovec and best supportive care in treating 5q SMA.

**Methods**: We undertook a systematic review of the clinical and cost-effectiveness literature by searching key databases (e.g., Embase, Medline) from 25 to 31 January and using standard approaches. Additionally, we appraised clinical and economic evidence submitted on April 25, 2024, by Biogen and Roche, then undertook an independent economic assessment.

**Results**: The review of the clinical effectiveness evidence identified 105 studies described in 127 reports. Across all SMA types, nusinersen and risdiplam were seen to lead to significant improvements in motor function. Effectiveness on other outcomes varied by SMA type, with high survival rates and improvement in ventilation particularly apparent in type 1 and presymptomatic SMA. Adverse events were reported across all treatments and types.

The review of the cost-effectiveness literature identified 20 studies and reports. Often the reporting quality was satisfactory, and most studies appeared methodologically robust. However, we noted inconsistencies related to assumptions/uncertainty associated with the long-term treatment effects of these disease modifying therapies. The evidence assessment group undertook an independent economic analysis utilising the models provided by Roche. These models were chosen based on their scope, usability and flexibility. Applying the price discount for risdiplam, the EAG base-case results showed that for the presymptomatic population, onasemnogene abeparvovec \*\*\*\*\*\*\*\*\* risdiplam and nusinersen and had an incremental cost-effectiveness ratio (ICER) of \*\*\*\*\*\*\* per QALY when compared to BSC. In the type 1 and type 2/3 models, risdiplam compared to BSC resulted in ICERs of approximately, \*\*\*\*\*\*\* and \*\*\*\*\*\*\*\*, respectively. Across all models, at a £30,000 per willingness-to-pay threshold, treatment with risdiplam compared to BSC had a \*\*\*\* probability of being cost-effective.

In general, the EAG agrees with the companies’ assessment of these treatments’ impact on motor function and survival. However, discrepancies exist in the reported adverse events and other functional outcomes for risdiplam, which had mixed results and could not be fully interpreted.

Economic evaluations comparing nusinersen, risdiplam and onasemnogene abeparvovec across presymptomatic, type 1 and type 2/3 SMA populations were sparse. Drawing on the model submitted by Roche, in our independent assessment of these disease modifying therapies, we found that these treatments had increased survival, but the incremental cost-effectiveness ratios were \*\*\*\*\* the commonly used willingness-to-pay thresholds. Until more reliable direct comparative evidence becomes available and with an appropriate follow-up time, appropriate (and transparent) resource use and cost information for treating SMA and better information about patient and caregiver utility values by health state, the true cost-effectiveness of these DMTs remain unknown.

SCIENTIFIC SUMMARY

**Background**

Spinal muscular atrophy (SMA) is a rare genetically inherited disorder that leads to muscle weakness and progressive reduced mobility and movement. SMA is classified into several types (including presymptomatic and types 0 – 4 5q SMA) and different subgroups (inc. types a, b and c). Each SMA type presents differently as the severity of the genetic condition declines with age of onset. Full details of SMA types are presented in Section 1.2.

The prognosis of SMA varies between types with extensive evidence demonstrating a much lower survival rate between types 0-1 in babies and infants compared to types 2, 3 and 4 in children and adults. Type 1 SMA is the most prevalent, movement and mobility are severely affected as muscles weaken, and extremely low muscle tone (hypotonia) leads to an inability to move hands, fingers, arms and legs. Type 2 is less severe than type 1, and patients with type 2, and type 3 (where their condition has progressed), are able to sit but are not ambulatory. SMA can have a psychological burden on parents and caregivers.

There is no cure for SMA, however pharmacological treatments (disease modifying therapies [DMTs]) are available to patients in the NHS. See Section 1.4.3 for treatment pathway. A multiple technology appraisal was conducted to critically appraise the clinical and cost effectiveness of these treatments, nusinersen and risdiplam (complete details are provided in Section 1.4.1), in comparison with standard of care, established clinical management. The interventions were compared with each other and comparing to onasemnogene abeparvovec (where appropriate). The assessment decision problem is presented in Section 2.1. The EAG’s critique of the company’s conception of the decision problem is outlined in Sections 2.1.1through to 2.2.

**Aim**

To appraise the clinical and cost-effectiveness of nusinersen and risdiplam within their marketing authorisations for treating people with 5q spinal muscular atrophy (SMA).

**Objectives**

To achieve this aim we,

* undertook systematic reviews of the literature to ascertain the clinical and cost-effectiveness of nusinersen and risdiplam within their marketing authorisations,
* critically appraised the company submissions for these DMTs
* reviewed the economic evidence submitted by the companies (Biogen Idec Ltd and Roche), to undertake an independent assessment and generate cost-effectiveness results.

Methods

Clinical effectiveness assessment

A systematic literature review (SLR) was conducted of the clinical effectiveness evidence of nusinersen, and risdiplam for treating SMA. Full details are provided in Section 3.1. In brief, a comprehensive search was developed iteratively and undertaken in a range of relevant bibliographic databases and other sources on 29th January 2024. Date limits were used to identify relevant information on the clinical and cost-effectiveness of these DMTs for treating SMA. Two reviewers independently screened the titles and abstracts against pre-defined eligibility criteria. Studies that met the following criteria were considered relevant for inclusion in the SLR (see Section3.2.2:

Population

* People with types 0, 1, 2, 3 or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies

If the evidence is available, we will consider the following subgroup:

* Number of SMN2 gene copies in people with pre-symptomatic SMA
* Functional status (non-sitter, sitter, walker) and baseline motor function and level of motor function
* People who have had prior active treatment for SMA
* SMA type
* By age
* By prior treatment (naive or successful)
* Patients transition from childhood to adulthood

Intervention

* Nusinersen monotherapy
* Risdiplam monotherapy

Comparator

* Established clinical management.
* Best supportive care
* The interventions will be compared to each other.

In addition, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene.

* Onasemnogene abeparvovec

Outcomes

* Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills)
* Bulbar function (including, for example, swallowing and ability to communicate)
* Frequency and duration of hospitalisation
* Respiratory function
* Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures)
* Need for non-invasive or invasive ventilation
* Stamina and fatigue
* Mortality
* Adverse effects of treatment
* Health-related quality of life (for patients and carers).

Study design

* RCTs, and non-randomised trials, observational studies, will be included in the SLR, and the evidence base for each intervention, types of 5q SMA and outcomes of relevance to the NICE final scope will be reported.

Prioritisation for full-text assessment

* Inclusion was limited to single-arm studies if there were 20 or more participants, and if there was 12 months or more of available data.
* Systematic reviews and meta-analysis were not included in the SLR, however, the reference lists of identified reviews were screened for possible studies.

Data from all studies eligible for inclusion were extracted using a pre-defined extraction form. All included studies were extracted by one reviewer and validated by a second reviewer. Any conflicts were resolved by discussion, or with involvement from a third reviewer. See Section 3.2.3 for a description of all extracted data. Data were synthesised narratively, and a feasibility assessment for indirect treatment comparison to evaluate the relative effectiveness of risdiplam and nusinersen for SMA was conducted. The EAG were unable to conduct our own ITC due to the paucity of multi-arm trials and the unavailability of the Individual Patient Data (IPD) required to perform any matching-adjustment method. An ITC was feasible in the type 2/3 population between the nusinersen arm of CHERISH and the risdiplam arm of SUNFISH if the assumption of equivalence between placebo and sham-control was made, similar to the approach Roche took in their restricted NMAs, and resulting in the same conclusions as Roche’s analyses in this population. Quality assessment of was conducted on included studies using Cochrane risk of bias tool for RCTs and ROBINS-1 for non-randomised trials, quality assessment was not conducted on single-arm studies.

Results

Systematic review of the clinical effectiveness literature

We identified 105 studies described in 127 reports that examined the clinical effectiveness of nusinersen, risdiplam or both, for the treatment of SMA. Populations of interest were people with presymptomatic SMA, or types 1, 2, 3 and 4 SMA. No studies examined the clinical effectiveness of these disease modifying therapies for treating people with type 0. Type 4 was only included in a small number of studies, and always in addition to other SMA types (no study examined the effectiveness in type 4 SMA alone). A study flow diagram is presented in Section 3.3.1.

Most studies included in the SLR were single-arm studies, i.e., no comparator was present. In studies where comparators were present, these were most commonly control groups, or placebo/sham conditions. Most included studies examined populations with type 2 and 3 SMA, or where multiple or all SMA types were examined. Very few studies examined the clinical effectiveness amongst presymptomatic patients. Full SLR results are presented in Section 3.3. Quality assessment results are presented in Section 3.3.1.2, of the six included RCT studies, 4 had some risk of bias concerns, 1 was rated high, and 1 low risk of bias. Most of the non-randomised studies were at serious or moderate risk of bias.

* Summary of outcomes of effectiveness in presymptomatic SMA:

There are limited studies included that examine pre-symptomatic SMA, and often few of them reported the outcomes of interest. From the available evidence both nusinersen and risdiplam appear effective for improving or stabilising motor function and motor milestones, stabilising bulbar function, and there was 100% survival and no need for permanent ventilation amongst presymptomatic patients. Adverse events were reported for all interventions, with some being attributed to treatment, and others being considered as not being treatment related.

* Summary of outcomes of effectiveness of type 1 SMA:

Evidence of effectiveness was available in 15 studies, but the number of studies reporting each outcome varied. Overall improvements were seen in motor function, bulbar function amongst type 1 patients. Few studies measured hospitalisation amongst this population, and there was mixed effectiveness reported for respiratory function. Ventilation was generally improved, and there was a high rate of survival across treatment. There were generally less AEs reported in patients receiving treatment compared to control conditions.

* Summary of outcomes of effectiveness of type 1 and 2 SMA:

Evidence on the effectiveness in type 1 and 2 patients was only based on six studies. These did not report all outcomes, so many outcomes were based on very few, or no studies making it hard to conclude the effectiveness of nusinersen and risdiplam for Type 1 and 2 SMA. Acknowledging the small number of studies, studies reporting the effectiveness of Type 1 and 2 SMA improved respiratory function but showed small or non-significant improvements in bulbar function or need for ventilation. Overall motor function improved following treatment, apart from one study where control group showed a greater increase in the proportion of later-onset patients able to stand.

* Summary of outcomes of effectiveness of type 2 and 3 SMA:

23 studies examining the effectiveness of nusinersen or risdiplam in patients with type 2 and 3 SMA, however most outcomes were reported by very low numbers of studies. Type 2 and 3 SMA patients showed improvements or stabilisation of motor function, minimal improvement in respiratory function, worsening of complications of SMA, an increased need in ventilation, and where reported, the majority, or all patients reported at least one adverse event.

* Summary of outcomes of effectiveness of mixed SMA:

In studies where patients had a mixture of SMA types, there was generally an improvement in motor function, an increased need for ventilation, a worsening of scoliosis, increased hospitalisation and a worsening of feeding ability.

*SLR summary*

* Across all SMA types, nusinersen and risdiplam lead to significant improvements in motor function.
* Effectiveness on other outcomes varied by SMA type, with high survival rates and improvement in ventilation particularly apparent in type 1 and presymptomatic SMA.
* Adverse events were reported across all treatments and types.

**Key issues/ uncertainties: (full details presented in Section 4.8)**

* Evidence for the clinical effectiveness of nusinersen and risdiplam are largely based on single-arm studies- uncertainty around the robustness of this evidence.
* Bias in included studies is likely due to the lack of blinding in non-randomised studies (although it is acknowledged that this might partly be due in some cases to blinding not being reported rather than not completed).
* Limited evidence for the effectiveness of treatment for presymptomatic SMA patients.
* Limited evidence for the effectiveness of type 0 and type 4 SMA, but this is to be expected due to the dearth of research into these types. No included studies examined type 4 alone, but it was included in nine studies looking at multiple SMA types.
* Adverse events were present across all treatments, with some serious cases reported.
* Due to time restraints, the EAG acknowledge potential limitation of the review in relation to quality assessment. This was only completed by one researcher, rather than the preferable approach of two researchers completing this independently. However, the EAG is confident in their findings as quality assessment was completed by experienced systematic reviewers.

Review of company submissions

Company submissions were received from Biogen Idec Ltd. and Roche, which include systematic reviews of the literature on the clinical effectiveness of nusinersen and risdiplam to treat SMA of any type (full EAG critiques are provided in Section 4.1 and Section 4.1.2)

Biogen Idec Ltd

* In the company submission from Biogen Idec Ltd. presymptomatic evidence is largely obtained from NURTURE (a phase 2, open label, single arm study). NURTURE showed favourable results for nusinersen in presymptomatic patients in relation to overall survival and need for permanent ventilation, improvements in motor milestones, motor function and growth parameters. Improvements were also observed in bulbar function (particularly swallowing) and need for ventilation. No adverse effects were attributed to nusinersen amongst presymptomatic patients.
* Evidence on the clinical effectiveness evidence for Type 1 SMA comes from ENDEAR and SHINE. ENDEAR is a RCT comparing nusinersen with a sham arm. Participants were then invited to enrol into SHINE and all participants received nusinersen. Comparisons between those receiving nusinersen in ENDEAR were made with those receiving sham in ENDEAR and starting later with nusinersen in SHINE.

Patients previously receiving nusinersen in ENDEAR showed improvements in many outcomes, but particularly notable were \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Adverse events were generally attributed to treatment, but of note all adverse events that led to discontinuation during SHINE in infantile-onset patients were fatal.

* Evidence for the clinical effectiveness of nusinersen in type 1 and 2 patients comes from EMBRACE; a randomised, double-blind, sham-procedure study, followed by an unblinded amended open-label element. Improvements were seen in this population following nusinersen in motor milestones.
* Evidence for type 2 and 3 SMA following nusinersen comes from CHERISH (an RCT) and SHINE. Participants were categorised as previously receiving nusinersen (during CHERISH), or previously receiving sham (and then starting nusinersen during SHINE). \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. They also demonstrated more improvement in motor function measures.
* Evidence for nusinersen in studies reporting mixed SMA types comes from the company MAA and the REACH registry. Survival rates and the need for permanent ventilation were improved, and results largely suggest nusinersen prevents the worsening of symptoms rather than showing improvements on outcomes.

Biogen Idec Ltd. conducted matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) methods to using IPD on nusinersen and aggregate data for risdiplam and onasemnogene abeparvovec to make indirect comparisons. Nusinersen was compared solely to best supportive care. See Section 4.6.1 for EAG critique of the company ITC.

* ITC results were not included in the economic model.

Biogen’s ITC results resulted in \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\* \*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

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Roche

* In the company submission from Roche, presymptomatic evidence for risdiplam comes from RAINBOWFISH; an open-label, single-arm study. Risdiplam showed good overall survival, and improvements in motor function, growth, bulbar functioning and ventilation. Adverse events were reported in most patients, but no deaths, and small numbers of serious adverse events.
* Evidence for type 1 SMA patients comes from FIREFISH, a dose-finding phase (part 1) and a confirmatory phase (part 2). High proportions of patients were alive without the need for permanent ventilation throughout the study. Improvements were seen in motor function and rate of hospitalisation. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*
* Evidence for type 2 and 3 SMA patients come from SUNFISH; a two-part randomised placebo-controlled double-blind study. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*
* Evidence for type 1,2 and 3 SMA comes from JEWELFISH; an open-label study, currently reporting safety outcomes only. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, but the vast \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*
* Evidence of SMA in mixed types in clinical practice comes from the REACH registry. No patients were recorded as needing permanent ventilation, and two patients are reported as having died. Preliminary results suggest improvements in motor function, but small sample size hinders full and reliable analysis.

Roche conducted ITC analysis using IPD data from risdiplam, and aggregate date from nusinersen and onasemnogene abeparvovec trials. A naïve comparison was conducted for presymptomatic SMA due to limitations with the data, unanchored MAICs were used to indirectly compare risdiplam to nusinersen and onasemnogene abeparvovec. Analyses for the type 2/3 population used anchored MAICs or restricted NMAs to compare risdiplam to nusinersen.

* Roche’s analyses found no statistically significant differences between risdiplam and nusinersen in the presymptomatic and type 2/3 populations.
* In the type 1 population, ITC results favoured risdiplam over nusinersen for all outcomes, and found no statistically significant differences between risdiplam and onasemnogene abeparvovec.

Summary of company submission critique

The EAG generally agrees with the company’s positive assessment of these treatments’ impact on motor function and survival. However, discrepancies exist in the reported adverse events and other functional outcomes, which had mixed results and could not be fully interpreted.

Biogen and Roche approached the ITC in similar ways but with a few key differences, potentially impacting their economic models.

In both submissions, when Biogen and Roche modelled time-to-event outcomes such as overall survival and time to permanent ventilation using parametric survival curves, they opted for the more clinically plausible curves rather than the best statistically fitting curves. Whilst the choice to use clinically plausible curves can enhance the face validity and acceptance of the economic models, it also necessitates careful consideration of the potential biases and limitations introduced by this approach.

Cost-effectiveness assessment

*Systematic literature review of the economic evaluation studies*

An SLR of the economic evidence on the cost-effectiveness of DMTs (e.g., onasemnogene abeparvovec, nusinersen, and risdiplam) for treating SMA was performed using the same methodological approach as the clinical effectiveness SLR. Full details are provided in Section 5.1.

Objectives

* To summarise the modelling techniques, modelling structures, inputs (e.g., clinical inputs, survival analysis methods, resource use and costs, utility estimates) required to populate the models, assumptions, and report key results.
* To outline key issues to consider for the conduct of future model-based economic analyses.

Methods

A comprehensive search strategy was developed by an information specialist in collaboration with the review team. Searches were conducted on 30th-31st January 2024. Searches included terms for SMA, onasemnogene abeparvovec, nusinersen and risdiplam, with the addition of a validated search filter for economic evaluations where appropriate.

Study selection followed a two-step process: screening of titles/abstracts and reading of full texts. Two reviewers independently screened titles and abstracts of the records identified through the searches, with potentially relevant titles/abstracts progressing to the full text stage. Eligibility criteria included;

Population (and sub-groups where applicable)

People with types 0, 1, 2, 3 or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.

Intervention(s)

Nusinersen monotherapy and risdiplam monotherapy.

Comparator(s)

* Established clinical management.
* Best supportive care
* The interventions will be compared to each other.

In addition, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene.

• Onasemnogene abeparvovec

Outcome(s)

The outcomes of the studies should be reported in terms of life-years gained (LYG) or quality-adjusted life years (QALYs).

Study design

* All types of economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-consequence, or cost minimization analyses)
* Only full publications in the English language will be considered, although relevant non-English studies will be mentioned.

Data extraction was undertaken by one reviewer, then cross-checked by a second reviewer for accuracy. Any disagreements between the reviewers were resolved by discussion or by recourse to a third reviewer. The reporting and methodological quality of each economic evaluation were assessed using the consolidated health economic evaluation reporting standard (CHEERS) and appraised against the Philips’ checklists (details are provided in Section 5.2.4). Due to the context-specific nature of economic evaluation, the conduct and findings of studies included in the systematic review were summarised narratively.

Results

We identified 20 studies/reports that undertook an economic evaluation that assessed/evaluated different disease modifying therapies (e.g., nusinersen, onasemnogene abeparvovec, or risdiplam) for treatment of SMA. Full details on included study characteristics and model structures and inputs are provided in Section 5.3.

* In general, the populations of interest were people with presymptomatic SMA, and types 1,2,3 SMA.
* No studies evaluated these therapies in people with type 0 or type 4 SMA.
* All authors used a Markov model with health states centred around functional milestones (e.g., permanent ventilation, not sitting, sitting, standing and walking) and compared these therapies against best supportive care, onasemnogene versus nusinersen, nusinersen versus risdiplam or onasemnogene versus risdiplam.

Summary of the SLR of the economic evaluation studies

No study evaluated all three therapies in the same economic evaluation. We found that there was a lack of direct comparative clinical evidence between the different therapies and best supportive care. This limitation is compounded by the discrepancies (e.g., selection of health states, patient health state utility values, inclusion/exclusion of caregivers’ utility values, robust health state resource used and costs and simplifying assumptions) noted in the conduct of these economic analyses.

As a result of these complexities/challenges, the true cost-effectiveness of these therapies remains unanswered.

Company submissions

The EAG received company submissions from Biogen Idec Ltd. and Roche, which included SLRs, and economic evidence, inclusive of Markov models programmed in Microsoft Excel. Full EAG critiques of the company submissions are provided in Section 5.4.1 and 5.4.2.

Three models each were submitted to estimate the cost-effectiveness of their therapies in treating people with presymptomatic SMA, type 1 SMA and types 2/3 SMA.

* For the presymptomatic population, Biogen compared \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, which returned an incremental cost-effectiveness ratio of approximately \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.
* For type 1 and, types 2/3 SMA, \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* per QALY, respectively.
* For the presymptomatic population, at a £20,000 per QALY willingness-to-pay threshold nusinersen when compared BSC had a \*\*\*\* probability of being cost-effective.
* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.
* For the type 1 and types 2/3 analyses, risdiplam when compared to BSC resulted in ICERs of approximately \*\*\*\*\*\*\* and \*\*\*\*\*\*\*\*, respectively. All other therapies were \*\*\*\*\*\*\*\*\*.

Summary of EAG critique of submissions

The EAG noted that the companies’ models were logical and depicted the clinical pathways for treating people with SMA. The EAG did not identify any major errors in the companies’ models. The companies provided details about the conduct of their economic analyses. In general, the process of identifying and justifying the choice of key model inputs were transparent and robust. Most of the economic analyses conformed to the NICE reference case, but there were instances where the time horizon was not long enough to capture any important differences between the interventions being compared. Assumptions were clearly reported and appeared appropriate. In some instances, the EAG noted that there were inconsistencies in the inputs reported in the main report with those in the company’s electronic model. The results reported in the company submission reflected those in the model submitted. However, there were some areas of concern/uncertainty:

* No cost-effectiveness analyses for type 0 or type 4 submitted (Both companies)
* Nusinersen compared to BSC only across the presymptomatic, type 1 SMA and type 2/3 SMA (Biogen models).
* Company digitised parametric curves rather than Kaplan-Meier plots (Biogen presymptomatic model).
* Equal efficacy between risdiplam, nusinersen and onasemnogene abeparvovec is not supported by strong evidence (Roche presymptomatic model).
* Cost-effectiveness results for a total presymptomatic population, emphasising careful interpretation due to small subgroup sizes in SMA patients with two versus more than two SMN2 copies. Stratification is crucial, given newborns' potential to develop different SMA types and distinct differences in assessments like mean CHOP INTEND and HINE-2, as shown in the RAINBOWFISH trial (Roche presymptomatic model.)
* General population mortality applied to all model health states (Roche presymptomatic model).
* Lack of robust evidence for using the HR for determine the overall survival (OS) type 1 (Roche type 1 model)
* Event Free Survival (EFS): Lack of robust evidence for using HR (vs risdiplam) (Roche type 1 SMA model)
* Time horizon not long enough to capture/reflect all important differences in costs and benefits between the technologies being compared (Roche presymptomatic model).
* Severity modifier calculated based on patient and caregiver utility values (Roche models).
* Hazard ratio for nusinersen and OA, instead of survival curves as used for risdiplam (Roche models).
* Average of 2.2 caregivers required to provide care regardless of health status (permanent ventilation, not sitting, sitting, standing and walking) (Roche models).
* Roche type 2/3 model stated three caregivers required for not sitting health state, but this was not reported in the main CS document B; company reported 2.2 caregivers required.
* Double counting of utility occurs when both the patient incremental benefit and the caregiver incremental benefit are added to the main utility of some health states for all treatments.
* Double counting of utility occurs when Roche uses certain values for disease impacts and treatment-related events, including scoliosis, respiratory support, and bulbar dysfunction.
* Disease impact costs: Overlap with other categories of resource use and costs

EAG independent assessment

The EAG reviewed the economic evidence submitted by Biogen Idec Ltd and Roche, with our evaluation leading to the selection of the Roche models to undertake our independent assessment. We selected these models based on their scope and applicability and functionality/flexibility (*see* Section 6 for full details). Several changes were made to each model to before estimating the cost-effectiveness of these therapies in each population of interest.

EAG independent assessment results

The EAG’s results includes making the following changes in the Roche economic models for the presymptomatic, type 1 SMA and types 2/3 SMA populations, respectively. All analyses are based on the PAS prices for risdiplam and are presented as fully incremental results.

**For the presymptomatic population**:

In this population, Roche assumed equal efficacy between nusinersen, onasemnogene abeparvovec and risdiplam. We made changes to:

* Time horizon
* Utility decrements- disease impacts and treatment related events
* Severity modifier
* Caregiver utilities
* Patient: incremental benefit for risdiplam, nusinersen and onasemnogene abeparvovec
* Caregiver: incremental benefit for risdiplam, nusinersen and onasemnogene abeparvovec
* Disease impact costs
* Overall survival for permanent ventilation, not sitting, sitting
* Overall survival for BSC

**For type 1 SMA population**:

* Time horizon
* Utility decrements- disease impacts and treatment related events
* Caregiver utilities
* Patient: incremental benefit for risdiplam, nusinersen and onasemnogene abeparvovec
* Caregiver: incremental benefit for risdiplam, nusinersen and onasemnogene abeparvovec
* Disease impact costs
* Overall survival
* Event fee survival

**For the type 2/3 SMA population**:

* Utility decrement- disease impacts and treatment related events
* Patient: incremental benefit for risdiplam
* Number of caregivers
* Caregiver: incremental benefit for risdiplam

**Summary of EAG key results**

The EAG assessed the cost-effectiveness of risdiplam compared to nusinersen, onasemnogene abeparvovec and BSC in people with presymptomatic SMA, type 1 SMA and types 2/3 SMA.

Presymptomatic population

The EAG base-case results showed that treatment with onasemnogene abeparvovec \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* with risdiplam and nusinersen. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* strategies resulted in a comparison between \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, which resulted in an ICER of approximately \*\*\*\*\*\*\* per QALY. However, in the PSA, the ranking of the technologies has changed, with the \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* in the deterministic results The PSA central estimate was \*\*\*\*\*\*\* per QALY for the comparison between risdiplam and BSC, and at willingness-to-pay threshold of £30,000 per QALY has a \*\*\*\* probability of being cost-effective. Deterministic results were sensitive to the cost of risdiplam and scenario results showed that excluding caregivers utility values and the source of health state treatment costs were key drivers of the cost-effectiveness results.

Type 1 SMA

Risdiplam therapy \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. When \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, treatment with risdiplam is expected to yield and additional \*\*\*\* QALYs costing an additional \*\*\*\*\*\*,\*\*\*\*\*\*,which equated to an ICER of approximately \*\*\*\*\*\*\*. The PSA central estimate was \*\*\*\*\*\*\* for the comparison between \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, and at a WTP threshold of £30,000 per QALY has a \*\*\*\* probability of being cost-effective. Cost of risdiplam, excluding caregivers’ utility values, source of BSC information were key drivers of the cost-effectiveness analysis.

Type 2/3 SMA

Risdiplam therapy \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. When compared to BSC, risdiplam resulted in an ICER of approximately \*\*\*\*\*\*\*\* per QALY. The PSA central estimate was approximately \*\*\*\*\*\*\*\* per QALY, and at willingness-to-pay threshold of £30,000 per QALY has a \*\*\*\* probability of being cost-effective. The key influential model inputs to the ICER were comparative efficacy versus BSC, health state treatment costs, severity modifier and number of caregivers per health state

**Discussion**

Clinical effectiveness evidence

The aim of this MTA was to assess the clinical and cost effectiveness of nusinersen and risdiplam for treating SMA. Clinical evidence presented by both Biogen and Roche is largely in line with the evidence presented in the EAG systematic literature review.

Evidence is presented on clinical effectiveness amongst presymptomatic, type 1, 2, and type 3 SMA patients.

* The main source of evidence for clinical effectiveness of nusinersen comes from the following trials: NURTURE (presymptomatic SMA), ENDEAR (type 1), EMBRACE (type 1 and 2), CHERISH (type 2 and 3) and SHINE (type 1,2 and 3 following on from ENDEAR and CHERISH trials).
* The main source of evidence for clinical effectiveness of risdiplam is from RAINBOWFISH (Presymptomatic), FIREFISH (type 1), JEWELFISH (type 1,2,3), SUNFISH (type 2 and 3).

Overall, evidence for treatment of SMA patients with nusinersen has shown significant motor function improvements, better growth outcomes, high survival rates, and minimal adverse events. Early initiation of treatment optimizes effectiveness, though some data gaps, high discontinuation rates, and baseline differences pose challenges in fully assessing its long-term benefits.

Cost-effectiveness evidence

Evidence is presented on cost-effectiveness of DMTs for SMA. No study evaluated all three therapies in the same economic evaluation. We found that there was a lack of direct comparative clinical evidence between the different therapies and best supportive care.

* This limitation is compounded by the discrepancies (e.g., selection of health states, patient health state utility values, inclusion/exclusion of caregivers’ utility values, robust health state resource used and costs and simplifying assumptions) noted in the conduct of these economic analyses.
* As a result of these complexities/challenges, the true cost-effectiveness of these therapies remains unanswered.

PLAIN ENGLISH SUMMARY

Spinal muscular atrophy (SMA) is a rare condition causing muscle weakness and problems with spinal cord function and loss of body movement. SMA is usually caused by faults in the persons genes and affects motor neurones (cells in the brain that control crawling and movement). Motor neurones also support movement of arms, head and neck, and control swallowing and breathing. Across the world SMA affects one to two people in every 10,000. Approximately 70 people were born with SMA in 2021 in the UK. Type 1 SMA can develop between 2 to 6 months of age, but people can be diagnosed later in life (Types 2, 3 and 4 SMA). SMA causes disability and can cause death. SMA affects families and carers, due to the impact of caring for patients, need for specialist equipment and ongoing emotional, financial, and social support.

There is a new treatment available for people with SMA called onasemnogene aberparvovec. This is used for certain types of SMA, known as type 1 SMA and pre-symptomatic SMA. It can be used for babies who are 6 months or younger. Or babies aged 7 to 12 months when agreed by clinical experts. Onasemnogene aberparvovec is a gene therapy so it corrects faulty genes. Two other treatments for people with all SMA types are called nusinersen and risdiplam and are not gene therapies. These treatments appear to give short-term benefits to patients, but longer-term benefits are unclear. To help us understand long-term benefit of these, a treatment funding scheme was introduced. In this scheme (a Managed Access Agreement), the two treatments (nusinersen and risdiplam) were made available to patients in the NHS and longer-term data was collected to examine if the treatments continued to work.

We will examine data from the treatment funding scheme, and use a method called systematic review, to examine all scientific information about the treatments. We aim to understand long-term benefits, and harms, of the SMA treatments available. Medical treatments should also represent good value for money for the NHS. Therefore, we perform scientific methods to examine the value for money of medicines (known as health economics and economic modelling). Results from an economic analysis help health and care decisions on how to spend limited healthcare resources. In this study, economic models will compare different treatments and use cost information from many sources, to estimate costs and benefits of the treatments. This will be presented as a quality-adjusted life year (QALY). In the UK, this is the standard measure for valuing healthcare treatments over a person’s lifetime. QALYs help decision makers understand additional years a patient might gain from taking treatments. It provides information on the quality of the person’s life during those years. Previously, it was unclear if both nusinersen and risdiplam were considered good value for money for the NHS. It is important to update this economic modelling using the longer-term data we have collected. This will allow us to understand if these treatments offer good value for money as well as providing benefits to patients.

We will examine the patient benefit (clinical effectiveness) and value for money (cost-effectiveness) of the two treatments, nusinersen and risdiplam. We will compare this to standard care patients would receive if no treatment was given (best supportive care) and the new gene therapy onasemnogene abeparvovec. Results will be used to help health and care decision makers decide whether all the treatments can be made available for patients of different types.

TABLE OF CONTENTS

[ABSTRACT 4](#_Toc173414353)

[SCIENTIFIC SUMMARY 6](#_Toc173414354)

[PLAIN ENGLISH SUMMARY 25](#_Toc173414355)

[TABLE OF CONTENTS 27](#_Toc173414356)

[LIST OF TABLES AND LIST OF FIGURES 38](#_Toc173414357)

[LIST OF ABBREVIATIONS 43](#_Toc173414358)

[1 BACKGROUND 45](#_Toc173414359)

[1.1 Introduction 45](#_Toc173414360)

[1.2 Description of health problem 45](#_Toc173414361)

[1.2.1 Aetiology, pathology and prognosis 46](#_Toc173414362)

[1.2.2 Epidemiology 46](#_Toc173414363)

[1.2.3 Incidence and/or prevalence 46](#_Toc173414364)

[1.2.4 Impact of health problem 47](#_Toc173414365)

[1.2.5 Measurement of disease 48](#_Toc173414366)

[1.3 Current service provision 51](#_Toc173414367)

[1.3.1 Management of disease 51](#_Toc173414368)

[1.3.2 Current service cost 51](#_Toc173414369)

[1.3.3 Variation in services and/or uncertainty about best practice 52](#_Toc173414370)

[1.3.4 Relevant national guidelines, including National Service Frameworks 52](#_Toc173414371)

[1.4 Description of technology under assessment 53](#_Toc173414372)

[1.4.1 Summary of Intervention 53](#_Toc173414373)

[1.4.2 Identification of important sub-groups 54](#_Toc173414374)

[1.4.3 Current usage in the NHS 54](#_Toc173414375)

[1.4.4 Anticipated costs associated with intervention 54](#_Toc173414376)

[2 DEFINITION OF THE DECISION PROBLEM 55](#_Toc173414377)

[2.1 Decision problem 55](#_Toc173414378)

[2.1.1 Critique of Company adherence to the NICE Final Scope 55](#_Toc173414379)

[2.1.1.1 Biogen (nusinersen) 55](#_Toc173414380)

[2.1.1.1.1 Population 56](#_Toc173414381)

[2.1.1.1.2 Intervention 58](#_Toc173414382)

[2.1.1.1.3 Comparators 59](#_Toc173414383)

[2.1.1.1.4 Outcomes 60](#_Toc173414384)

[2.1.1.1.5 Economic analysis 62](#_Toc173414385)

[2.1.1.1.6 Special consideration including issues related to equity or equality 63](#_Toc173414386)

[2.1.1.2 Roche (risdiplam) 64](#_Toc173414387)

[2.1.1.2.1 Population 64](#_Toc173414388)

[2.1.1.2.2 Intervention 66](#_Toc173414389)

[2.1.1.2.3 Comparators 66](#_Toc173414390)

[2.1.1.2.4 Outcomes 67](#_Toc173414391)

[2.1.1.2.5 Economic analysis 69](#_Toc173414392)

[2.1.1.2.6 Special consideration including issues related to equity or equality 70](#_Toc173414393)

[2.2 Overall aims and objectives of assessment 70](#_Toc173414394)

[3 ASSESSMENT OF CLINICAL EFFECTIVENESS 70](#_Toc173414395)

[3.1 Systematic review of existing clinical-effectiveness evidence 70](#_Toc173414396)

[3.1.1 Objectives 71](#_Toc173414397)

[3.2 Methods for reviewing effectiveness 71](#_Toc173414398)

[3.2.1 Identification of studies 71](#_Toc173414399)

[3.2.2 Inclusion and exclusion criteria 72](#_Toc173414400)

[3.2.3 Data extraction strategy 74](#_Toc173414401)

[3.2.4 Critical appraisal strategy 75](#_Toc173414402)

[3.2.5 Methods of data synthesis 75](#_Toc173414403)

[3.2.5.1 Narrative synthesis 75](#_Toc173414404)

[3.2.5.2 Indirect Treatment Comparisons (ITC) 75](#_Toc173414405)

[3.3 Results 76](#_Toc173414406)

[3.3.1 Quantity and quality of research available 76](#_Toc173414407)

[3.3.1.1 Characteristics of included studies 77](#_Toc173414408)

[3.3.1.2 Assessment of study quality 78](#_Toc173414409)

[3.3.1.2.1 Cochrane risk of bias tool: 78](#_Toc173414410)

[3.3.1.2.2 ROBINS-1: 79](#_Toc173414411)

[3.3.1.3 Intervention(s), Comparator(s), Outcome(s), Study perspective and Location & Setting 81](#_Toc173414412)

[3.3.1.4 Number and type of studies excluded 83](#_Toc173414413)

[3.3.2 Assessment of effectiveness 83](#_Toc173414414)

[3.3.2.1 Critical review and synthesis of information 83](#_Toc173414415)

[3.3.2.1.1 Presymptomatic SMA 83](#_Toc173414416)

[3.3.2.1.2 Type 1 SMA 85](#_Toc173414417)

[3.3.2.1.3 Type 1 and 2 SMA 90](#_Toc173414418)

[3.3.2.1.4 Type 2 and 3 SMA 93](#_Toc173414419)

[3.3.2.1.5 Mixed Type SMA 98](#_Toc173414420)

[3.3.2.1.6 Unreported SMA Type 102](#_Toc173414421)

[3.4 Gaps in the evidence 104](#_Toc173414422)

[3.5 Discussion 105](#_Toc173414423)

[3.5.1 Summary of key results 105](#_Toc173414424)

[3.5.2 Generalisability 105](#_Toc173414425)

[3.5.3 Key issues/ uncertainties 105](#_Toc173414426)

[4 Summary and critique of clinical evidence (clinical trials, company’s statistical analyses) submitted by companies/sponsors 106](#_Toc173414427)

[4.1 Critique of the methods of the company reviews 106](#_Toc173414428)

[4.1.1 Biogen submission 106](#_Toc173414429)

[4.1.1.1 Search strategies 107](#_Toc173414430)

[4.1.1.2 Excluded studies 107](#_Toc173414431)

[4.1.1.3 Critique of company’s review 107](#_Toc173414432)

[4.1.1.4 Critical appraisal of company’s clinical effectiveness evidence 108](#_Toc173414433)

[4.1.2 Roche submission 109](#_Toc173414434)

[4.1.2.1 Search strategies 110](#_Toc173414435)

[4.1.2.2 Excluded studies 110](#_Toc173414436)

[4.1.2.3 Critique of company’s review 110](#_Toc173414437)

[4.1.2.4 Critical appraisal of company’s clinical effectiveness evidence 111](#_Toc173414438)

[4.2 Overview of evidence for the assessment of clinical effectiveness 113](#_Toc173414439)

[4.2.1 Intervention(s) 114](#_Toc173414440)

[4.2.2 Comparator(s) 114](#_Toc173414441)

[4.2.3 Population 115](#_Toc173414442)

[4.2.4 Outcomes reported from the pivotal trials 117](#_Toc173414443)

[4.2.5 Outcomes reported in the economic model 120](#_Toc173414444)

[4.2.6 Methods of data synthesis 127](#_Toc173414445)

[4.3 Biogen submission 127](#_Toc173414446)

[4.3.1 Summary of evidence for clinical effectiveness of nusinersen 127](#_Toc173414447)

[4.3.2 Critique of efficacy results (presymptomatic population) 129](#_Toc173414448)

[4.3.2.1 Outcomes of interest 129](#_Toc173414449)

[4.3.2.1.1 Overall survival/time to death or permanent ventilation 129](#_Toc173414450)

[4.3.2.1.2 WHO motor milestones 130](#_Toc173414451)

[4.3.2.1.3 Motor function 130](#_Toc173414452)

[4.3.2.1.4 Growth parameters 130](#_Toc173414453)

[4.3.2.1.5 Dysphagia/ bulbar function 131](#_Toc173414454)

[4.3.2.1.6 Need for ventilation 131](#_Toc173414455)

[4.3.2.1.7 Adverse events 131](#_Toc173414456)

[4.3.2.1.8 Summary of presymptomatic evidence 132](#_Toc173414457)

[4.3.3 Critique of efficacy results (type 1) 132](#_Toc173414458)

[4.3.3.1 Outcomes of interest 133](#_Toc173414459)

[4.3.3.1.1 Overall survival/ time to death or permanent ventilation 133](#_Toc173414460)

[4.3.3.1.2 WHO Motor Milestones 133](#_Toc173414461)

[4.3.3.1.3 Motor function 134](#_Toc173414462)

[4.3.3.1.4 Growth parameters 134](#_Toc173414463)

[4.3.3.1.5 Dysphagia/ bulbar function 134](#_Toc173414464)

[4.3.3.1.6 Need for ventilation 134](#_Toc173414465)

[4.3.3.1.7 Frequency and duration of hospitalisation 135](#_Toc173414466)

[4.3.3.1.8 Scoliosis and Contractures 135](#_Toc173414467)

[4.3.3.1.9 Quality of Life 136](#_Toc173414468)

[4.3.3.1.10 Adverse events 136](#_Toc173414469)

[4.3.3.1.11 Summary of type 1 evidence 136](#_Toc173414470)

[4.3.4 Critique of efficacy results (type 1 and 2) 136](#_Toc173414471)

[4.3.4.1 Outcomes of interest 137](#_Toc173414472)

[4.3.4.1.1 Motor milestones 137](#_Toc173414473)

[4.3.4.1.2 Growth 137](#_Toc173414474)

[4.3.4.1.3 Summary of type 1 and 2 evidence 137](#_Toc173414475)

[4.3.5 Critique of efficacy results (type 2 and 3) 138](#_Toc173414476)

[4.3.5.1 Outcomes of interest 138](#_Toc173414477)

[4.3.5.1.1 Overall survival/ time to death or permanent ventilation 138](#_Toc173414478)

[4.3.5.1.2 WHO Motor Milestones 138](#_Toc173414479)

[4.3.5.1.3 Motor function 139](#_Toc173414480)

[4.3.5.1.4 Scoliosis and contractures 140](#_Toc173414481)

[4.3.5.1.5 Dysphagia/ bulbar function 140](#_Toc173414482)

[4.3.5.1.6 Quality of life 141](#_Toc173414483)

[4.3.5.1.7 Frequency and duration of hospitalisation 141](#_Toc173414484)

[4.3.5.1.8 Ventilation support 142](#_Toc173414485)

[4.3.5.1.9 Adverse events 142](#_Toc173414486)

[4.3.5.1.10 Summary of type 2 and 3 evidence 142](#_Toc173414487)

[4.3.6 Critique of efficacy results (mixed SMA type) 142](#_Toc173414488)

[4.3.6.1 Outcomes of interest 143](#_Toc173414489)

[4.3.6.1.1 Overall survival/ mortality 143](#_Toc173414490)

[4.3.6.1.2 Motor milestones 143](#_Toc173414491)

[4.3.6.1.3 Motor function 144](#_Toc173414492)

[4.3.6.1.4 Bulbar function 144](#_Toc173414493)

[4.3.6.1.5 Quality of life 145](#_Toc173414494)

[4.3.6.1.6 Frequency and duration of hospitalisation 145](#_Toc173414495)

[4.3.6.1.7 Permanent ventilation 146](#_Toc173414496)

[4.3.6.1.8 Adverse events 146](#_Toc173414497)

[4.3.6.1.9 Summary of mixed SMA evidence 146](#_Toc173414498)

[4.3.7 Summary of Biogen’s ITC 147](#_Toc173414499)

[4.4 Roche submission 148](#_Toc173414500)

[4.4.1 Critique of efficacy results (presymptomatic population; RAINBOWFISH) 152](#_Toc173414501)

[4.4.1.1 Outcomes of interest 158](#_Toc173414502)

[4.4.1.1.1 Overall survival/time to death or permanent ventilation 158](#_Toc173414503)

[4.4.1.1.2 Motor function 159](#_Toc173414504)

[4.4.1.1.3 Growth parameters 159](#_Toc173414505)

[4.4.1.1.4 Dysphagia/bulbar function 159](#_Toc173414506)

[4.4.1.1.5 Need for ventilation 159](#_Toc173414507)

[4.4.1.1.6 Frequency and duration of hospitalization 160](#_Toc173414508)

[4.4.1.1.7 Quality of life 160](#_Toc173414509)

[4.4.1.1.8 Adverse Events 160](#_Toc173414510)

[4.4.1.1.9 Summary 160](#_Toc173414511)

[4.4.2 Critique of efficacy results (type 1; FIREFISH) 161](#_Toc173414512)

[4.4.2.1 Outcomes of interest 167](#_Toc173414513)

[4.4.2.1.1 Overall survival/time to death or permanent ventilation 167](#_Toc173414514)

[4.4.2.1.2 Motor function 167](#_Toc173414515)

[4.4.2.1.3 Growth parameters 168](#_Toc173414516)

[4.4.2.1.4 Dysphagia/bulbar function 168](#_Toc173414517)

[4.4.2.1.5 Frequency and duration of hospitalisation 168](#_Toc173414518)

[4.4.2.1.6 Quality of life 169](#_Toc173414519)

[4.4.2.1.7 Adverse Events 169](#_Toc173414520)

[4.4.2.1.8 Summary 169](#_Toc173414521)

[4.4.3 Critique of efficacy results (type 2 and 3; SUNFISH) 169](#_Toc173414522)

[4.4.3.1 Outcomes of interest 174](#_Toc173414523)

[4.4.3.1.1 Motor function 174](#_Toc173414524)

[4.4.3.1.2 Quality of life 174](#_Toc173414525)

[4.4.3.1.3 Adverse Events 174](#_Toc173414526)

[4.4.3.1.4 Summary 175](#_Toc173414527)

[4.4.4 Critique of efficacy results (type 1, 2 and 3; JEWELFISH) 175](#_Toc173414528)

[4.4.4.1 Outcomes of interest 176](#_Toc173414529)

[4.4.4.1.1 Adverse Eventss 176](#_Toc173414530)

[4.4.5 Critique of REACH registries results (SMA in clinical practice) 177](#_Toc173414531)

[4.4.5.1 Outcomes of interest 181](#_Toc173414532)

[4.4.5.1.1 Overall survival/time to death or permanent ventilation 181](#_Toc173414533)

[4.4.5.1.2 Motor function 181](#_Toc173414534)

[4.4.5.1.3 Dysphagia/bulbar function 181](#_Toc173414535)

[4.4.5.1.4 Scoliosis and contractures 182](#_Toc173414536)

[4.4.5.1.5 Quality of life 182](#_Toc173414537)

[4.4.5.1.6 Summary 182](#_Toc173414538)

[4.4.6 Summary of Roche’s ITC 182](#_Toc173414539)

[4.5 Critique of Biogen’s and Roche’s ITCs 184](#_Toc173414540)

[4.5.1 Indirect Treatment Comparisons (ITC) methods 184](#_Toc173414541)

[4.5.2 Differences between Biogen and Roche ITC methods 185](#_Toc173414542)

[4.5.3 Critical review and synthesis of information 186](#_Toc173414543)

[4.5.4 Comparison of treatment effect modifiers and prognostic factors 187](#_Toc173414544)

[4.5.5 Comparison of intervention responses 190](#_Toc173414545)

[4.5.6 Comparison of placebo/sham responses 193](#_Toc173414546)

[4.5.7 Comparison of relevant safety results 194](#_Toc173414547)

[4.6 EAG Quantitative Analyses 194](#_Toc173414548)

[4.6.1 EAG replication of ITC and EAG’s preference 194](#_Toc173414549)

[4.6.1.1 Presymptomatic population 195](#_Toc173414550)

[4.6.1.2 Type 1 population 196](#_Toc173414551)

[4.6.1.3 Type 2/3 population 197](#_Toc173414552)

[4.6.1.4 Summary 200](#_Toc173414553)

[4.6.2 EAG’s survival extrapolation analysis 201](#_Toc173414554)

[4.7 Conclusion of the clinical effectiveness section 202](#_Toc173414555)

[4.8 Key clinical effectiveness issues 204](#_Toc173414556)

[5 ASSESSMENT OF COST-EFFECTIVENESS 208](#_Toc173414557)

[5.1 Systematic review of existing cost-effectiveness evidence 208](#_Toc173414558)

[5.1.1 Objectives 208](#_Toc173414559)

[5.2 Methods for reviewing effectiveness 208](#_Toc173414560)

[5.2.1 Identification of studies 208](#_Toc173414561)

[5.2.2 Inclusion and exclusion criteria 209](#_Toc173414562)

[5.2.2.1 Population (and sub-groups where applicable) 209](#_Toc173414563)

[5.2.2.2 Intervention(s) 209](#_Toc173414564)

[5.2.2.3 Comparator(s) 209](#_Toc173414565)

[5.2.2.4 Outcome(s) 210](#_Toc173414566)

[5.2.2.5 Study design 210](#_Toc173414567)

[5.2.3 Data extraction strategy 210](#_Toc173414568)

[5.2.4 Critical appraisal strategy 211](#_Toc173414569)

[5.2.5 Methods of data synthesis 211](#_Toc173414570)

[5.3 Results 211](#_Toc173414571)

[5.3.1.1 Characteristics of included studies 213](#_Toc173414572)

[5.3.1.1.1 Intervention(s), Comparator(s), Outcome(s), Study perspective and Location & Setting 213](#_Toc173414573)

[5.3.1.1.2 Model structure and health states 213](#_Toc173414574)

[5.3.1.1.3 Time horizon, cycle length and discount rate 214](#_Toc173414575)

[5.3.1.1.4 Health-state utility values 215](#_Toc173414576)

[5.3.1.1.5 Health-state resource use and costs, currency and conversion 216](#_Toc173414577)

[5.3.1.1.6 Results of Engaging Patients and Affected Stakeholders 216](#_Toc173414578)

[5.3.1.1.7 Results of resource use and costs 217](#_Toc173414579)

[5.3.1.1.8 Results of survival modelling 217](#_Toc173414580)

[5.3.1.1.9 Assumptions used in studies/reports 218](#_Toc173414581)

[5.3.1.1.10 Model inputs used across studies 219](#_Toc173414582)

[5.3.1.1.11 Characterising uncertainty in different studies 220](#_Toc173414583)

[5.3.1.1.12 Limitations identified across studies 220](#_Toc173414584)

[5.3.1.2 Reporting and methodological quality assessment 221](#_Toc173414585)

[5.3.1.2.1 Reporting quality assessment 221](#_Toc173414586)

[5.3.1.2.2 Methodological quality assessment 222](#_Toc173414587)

[5.3.2 Assessment of cost-effectiveness 223](#_Toc173414588)

[5.3.2.1 Critical review and synthesis of information 223](#_Toc173414589)

[5.3.2.2 Discussion 223](#_Toc173414590)

[5.4 Summary and critique of economic evidence submitted by companies/sponsors 227](#_Toc173414591)

[5.4.1 Biogen 228](#_Toc173414592)

[5.4.1.1 EAG critique of company’s systematic literature review of economic evidence 228](#_Toc173414593)

[5.4.1.2 Presymptomatic population 229](#_Toc173414594)

[5.4.1.2.1 NICE reference case checklist 229](#_Toc173414595)

[5.4.1.2.2 Model structure 230](#_Toc173414596)

[5.4.1.2.3 Population 231](#_Toc173414597)

[5.4.1.2.4 Interventions and comparators 231](#_Toc173414598)

[5.4.1.2.5 Perspective, time horizon and discounting 232](#_Toc173414599)

[5.4.1.2.6 Treatment effectiveness and extrapolation 232](#_Toc173414600)

[5.4.1.2.7 Health-related quality of life 232](#_Toc173414601)

[5.4.1.2.8 Resource use and costs 234](#_Toc173414602)

[5.4.1.2.9 Mortality 235](#_Toc173414603)

[5.4.1.2.10 Discontinuation 237](#_Toc173414604)

[5.4.1.2.11 Decision modifier: Severity 238](#_Toc173414605)

[5.4.1.2.12 Company’s cost-effectiveness results (presymptomatic population) 239](#_Toc173414606)

[5.4.1.2.13 Deterministic sensitivity analysis (presymptomatic population) 242](#_Toc173414607)

[5.4.1.2.14 Company’s scenario analysis 243](#_Toc173414608)

[5.4.1.3 Type 1 SMA population 244](#_Toc173414609)

[5.4.1.3.1 Model structure 244](#_Toc173414610)

[5.4.1.3.2 Population 244](#_Toc173414611)

[5.4.1.3.3 Interventions and comparators 244](#_Toc173414612)

[5.4.1.3.4 Perspective, time horizon and discounting 244](#_Toc173414613)

[5.4.1.3.5 Health-related quality of life 245](#_Toc173414614)

[5.4.1.3.6 Resource use and costs 245](#_Toc173414615)

[5.4.1.3.7 Mortality 245](#_Toc173414616)

[5.4.1.3.8 Discontinuation 245](#_Toc173414617)

[5.4.1.3.9 Company’s cost-effectiveness results (type 1 SMA) 246](#_Toc173414618)

[5.4.1.3.10 Deterministic sensitivity analyses (type 1 SMA) 249](#_Toc173414619)

[5.4.1.3.11 Scenario analysis results (type 1 SMA) 250](#_Toc173414620)

[5.4.1.4 Type 2/3 SMA population 250](#_Toc173414621)

[5.4.1.4.1 Model structure 250](#_Toc173414622)

[5.4.1.4.2 Population 251](#_Toc173414623)

[5.4.1.4.3 Interventions and comparators 251](#_Toc173414624)

[5.4.1.4.4 Perspective, time horizon and discounting 252](#_Toc173414625)

[5.4.1.4.5 Health-related quality of life 252](#_Toc173414626)

[5.4.1.4.6 Resource use and costs 252](#_Toc173414627)

[5.4.1.4.7 Mortality 252](#_Toc173414628)

[5.4.1.4.8 Discontinuation 252](#_Toc173414629)

[ *out of 21 patients who could not sit discontinued (28.6%).* 252](#_Toc173414630)

[5.4.1.4.9 Company’s cost-effectiveness results (type 2 and 3 SMA) 253](#_Toc173414631)

[5.4.1.4.10 Deterministic sensitivity analysis (type 2/3 SMA) 256](#_Toc173414632)

[5.4.1.4.11 Scenario analysis results (type 2/3 SMA) 257](#_Toc173414633)

[5.4.1.4.12 Model validation and face validity check 257](#_Toc173414634)

[5.4.2 Roche 258](#_Toc173414635)

[5.4.2.1 EAG critique of company’s systematic review of the economic evidence 258](#_Toc173414636)

[5.4.2.2 Presymptomatic population 259](#_Toc173414637)

[5.4.2.2.1 NICE reference case checklist 259](#_Toc173414638)

[5.4.2.2.2 Model structure and transitions 260](#_Toc173414639)

[5.4.2.2.3 Population 262](#_Toc173414640)

[5.4.2.2.4 Interventions and comparators 263](#_Toc173414641)

[5.4.2.2.5 Perspective, time horizon and discounting 263](#_Toc173414642)

[5.4.2.2.6 Treatment effectiveness and extrapolation 264](#_Toc173414643)

[5.4.2.2.7 Health-related quality of life 265](#_Toc173414644)

[5.4.2.2.8 Resource use and costs 267](#_Toc173414645)

[5.4.2.2.9 Mortality 269](#_Toc173414646)

[5.4.2.2.10 Decision modifier: Severity 271](#_Toc173414647)

[5.4.2.2.11 Company’s cost-effectiveness results 271](#_Toc173414648)

[5.4.2.2.12 Company’s probabilistic sensitivity analysis results 273](#_Toc173414649)

[5.4.2.2.13 Deterministic sensitivity analysis (presymptomatic population) 276](#_Toc173414650)

[5.4.2.2.14 Scenario analysis results (presymptomatic population) 278](#_Toc173414651)

[5.4.2.3 Type 1 SMA population 280](#_Toc173414652)

[5.4.2.3.1 Model structure 280](#_Toc173414653)

[5.4.2.3.2 Population 281](#_Toc173414654)

[5.4.2.3.3 Intervention and comparators 281](#_Toc173414655)

[5.4.2.3.4 Perspective, time horizon and discount rate 281](#_Toc173414656)

[5.4.2.3.5 Treatment effectiveness and extrapolation 281](#_Toc173414657)

[5.4.2.3.6 Health-related quality of life 284](#_Toc173414658)

[5.4.2.3.7 Resource use and costs 284](#_Toc173414659)

[5.4.2.3.8 Mortality 285](#_Toc173414660)

[5.4.2.3.9 Discontinuation 286](#_Toc173414661)

[5.4.2.3.10 Company’s cost-effectiveness results (type 1 SMA) 287](#_Toc173414662)

[5.4.2.3.11 Company’s probabilistic sensitivity analysis (type 1 SMA) 288](#_Toc173414663)

[5.4.2.3.12 Company’s sensitivity analysis results (type 1 SMA) 290](#_Toc173414664)

[5.4.2.3.13 Company’s scenario analysis results (type 1 SMA) 292](#_Toc173414665)

[5.4.2.4 Type 2/3 SMA population 294](#_Toc173414666)

[5.4.2.4.1 Model structure 295](#_Toc173414667)

[5.4.2.4.2 Population 295](#_Toc173414668)

[5.4.2.4.3 Intervention and comparators 295](#_Toc173414669)

[5.4.2.4.4 Perspective, time horizon and discount rate 296](#_Toc173414670)

[5.4.2.4.5 Treatment effectiveness and extrapolation 297](#_Toc173414671)

[5.4.2.4.6 Health-related quality of life 297](#_Toc173414672)

[5.4.2.4.7 Resource use and costs 300](#_Toc173414673)

[5.4.2.4.8 Mortality 301](#_Toc173414674)

[5.4.2.5 Company’s cost-effectiveness results (type 2/3 SMA) 302](#_Toc173414675)

[5.4.2.6 Company’s probabilistic sensitivity analysis results (type 2/3 population) 303](#_Toc173414676)

[5.4.2.7 Company’s deterministic sensitivity analysis results 305](#_Toc173414677)

[5.4.2.8 Company’s scenario analyses for the type 2/3 SMA population 306](#_Toc173414678)

[5.5 Conclusion 308](#_Toc173414679)

[6 Independent EAG economic assessment 314](#_Toc173414680)

[6.1.1 EAG results 315](#_Toc173414681)

[6.1.1.1 Changes made to Roche’s presymptomatic model 315](#_Toc173414682)

[6.1.1.2 Results (pre-symptomatic population) 316](#_Toc173414683)

[6.1.1.2.1 Deterministic base-case results 317](#_Toc173414684)

[6.1.1.2.2 PSA results 318](#_Toc173414685)

[6.1.1.2.3 One-way sensitivity analysis results 320](#_Toc173414686)

[6.1.1.2.4 Scenario analysis results 320](#_Toc173414687)

[6.1.1.3 Changes made to Roche’s type 1 SMA model 323](#_Toc173414688)

[6.1.1.4 Results (type 1 SMA) 325](#_Toc173414689)

[6.1.1.4.1 Deterministic base-case results 325](#_Toc173414690)

[6.1.1.4.2 PSA results 326](#_Toc173414691)

[6.1.1.4.3 One-way sensitivity analysis results 328](#_Toc173414692)

[6.1.1.4.4 Scenario analysis results 329](#_Toc173414693)

[6.1.1.5 Changes made to Roche’s type 2/3 SMA model 332](#_Toc173414694)

[6.1.1.6 Results (types 2/3 SMA) 333](#_Toc173414695)

[6.1.1.6.1 Deterministic base-case results 333](#_Toc173414696)

[6.1.1.6.2 PSA results 334](#_Toc173414697)

[6.1.1.6.3 One-way sensitivity analysis results 336](#_Toc173414698)

[6.1.1.6.4 Scenario analysis results 337](#_Toc173414699)

[6.1.2 Model validation and face validity check 339](#_Toc173414700)

[6.1.3 Discussion 340](#_Toc173414701)

[6.1.3.1 Summary of key results 340](#_Toc173414702)

[6.1.3.1.1 Presymptomatic population 340](#_Toc173414703)

[6.1.3.1.2 Type 1 SMA 340](#_Toc173414704)

[6.1.3.1.3 Type 2/3 SMA 341](#_Toc173414705)

[6.1.3.2 Generalisability of results 341](#_Toc173414706)

[6.1.3.3 Strengths and limitations of analysis 342](#_Toc173414707)

[7 DISCUSSION 342](#_Toc173414708)

[7.1 Statement of principle findings 342](#_Toc173414709)

[7.2 Strengths and limitations of the assessment 345](#_Toc173414710)

[7.3 Uncertainties 346](#_Toc173414711)

[7.4 Patient and Public Involvement 346](#_Toc173414712)

[8 CONCLUSIONS 347](#_Toc173414713)

[8.1 Suggested research priorities 348](#_Toc173414714)

[9 REFERENCES 349](#_Toc173414715)

[10 APPENDICES 378](#_Toc173414716)

[Appendix 1: Literature search strategies 378](#_Toc173414717)

[Appendix 2: Data extraction sheet 392](#_Toc173414718)

[Appendix 3: Methodological quality assessment 398](#_Toc173414719)

[Appendix 4: Reporting quality assessment 423](#_Toc173414720)

[Appendix 5: Characteristics of included cost-effectiveness analysis studies 436](#_Toc173414721)

[Appendix 6: Changes made to economic model 467](#_Toc173414722)

LIST OF TABLES AND LIST OF FIGURES

**List of Tables**

[Table 1: Outcome measures used to monitor and evaluate people with SMA (adapted from Roche CS Document B, Table 4) 49](#_Toc173414723)

[Table 2: Motor function outcomes 61](#_Toc173414724)

[Table 3: Health-related quality of life measures 62](#_Toc173414725)

[Table 4: Motor function outcomes 67](#_Toc173414726)

[Table 5: Health-related Quality of Life 69](#_Toc173414727)

[Table 6: Inclusion and exclusion criteria 73](#_Toc173414728)

[Table 7: Risk of Bias for Randomised Controlled Trials (RCTs) 78](#_Toc173414729)

[Table 8: Risk of bias for non-randomised trials (ROBINS-1) 79](#_Toc173414730)

[Table 9: Summary of studies included in the economic modelling of nusinersen or risdiplam 113](#_Toc173414731)

[Table 10: Baseline characteristics of the nusinersen and risdiplam arms of the pivotal trials for SMA Type 1 which were presented in both submissions 115](#_Toc173414732)

[Table 11: Baseline characteristics of the nusinersen and risdiplam arms of the pivotal trials for SMA Types 2 and 3 which were presented in both submissions 116](#_Toc173414733)

[Table 12: Baseline characteristics of the nusinersen and risdiplam arms of the pivotal trials for presymptomatic SMA which were presented in both submissions 117](#_Toc173414734)

[Table 13: Results of the analysis of the primary and key secondary outcomes for SMA type 1 118](#_Toc173414735)

[Table 14: Results of the analysis of the primary and key secondary outcomes for SMA types 2 and 3 119](#_Toc173414736)

[Table 15: Results of the analysis of the primary and key secondary outcomes for presymptomatic SMA 120](#_Toc173414737)

[Table 16: Clinical effectiveness inputs into each company's economic models 123](#_Toc173414738)

[Table 17: Summary of main sources of clinical effectiveness evidence 127](#_Toc173414739)

[Table 18: Covariates adjusted for in Biogen's ITCs 148](#_Toc173414740)

[Table 19: Summary of clinical effectiveness evidence provided by the EAG 151](#_Toc173414741)

[Table 20: RAINBOWFISH primary efficacy and intention to treat populations' demographic and baseline characteristics 154](#_Toc173414742)

[Table 21: Key efficacy endpoints in RAINBOWFISH (paediatric, pre-symptomatic, genetically diagnosed SMA 157](#_Toc173414743)

[Table 22: FIREFISH Part 2 key demographic and baseline disease characteristics 162](#_Toc173414744)

[Table 23: Key efficacy endpoints in FIREFISH (infantile-onset type 1 SMA) 166](#_Toc173414745)

[Table 24: Summary of Motor Function Baseline Characteristics for SUNFISH 172](#_Toc173414746)

[Table 25: Covariates adjusted for in Roche's ITCs 183](#_Toc173414747)

[Table 26: Summary statistics of adjusted covariates in both company's ITCs for the presymptomatic population 188](#_Toc173414748)

[Table 27: Summary statistics of adjusted covariates in both company's ITCs for the SMA type 1 population 188](#_Toc173414749)

[Table 28: Summary statistics of adjusted covariates in both company's ITCs for the SMA type 2/3 population 190](#_Toc173414750)

[Table 29: Comparison of the responses to intervention treatments in the presymptomatic population 191](#_Toc173414751)

[Table 30: Comparison of the responses to intervention treatments in the SMA type 1 population 191](#_Toc173414752)

[Table 31: Comparison of the responses to intervention treatments in the SMA type 2/3 population 192](#_Toc173414753)

[Table 32: Placebo/sham response for the outcome RULM score in the SMA type 2/3 population 193](#_Toc173414754)

[Table 33: Key clinical effectiveness issues 204](#_Toc173414755)

[Table 34: NICE reference case checklist 229](#_Toc173414756)

[Table 35: Characteristics of presymptomatic population by SMN2 copies 231](#_Toc173414757)

[Table 36: Health state utility values used in company base-case 233](#_Toc173414758)

[Table 37: Health state utility values used in scenario analyses (based on TA755) 233](#_Toc173414759)

[Table 38: Resource use and caregiver utility values used in base-case analysis (obtained from CS document B, page 182) 234](#_Toc173414760)

[Table 39: Annual health state costs used in the company’s base-case analysis 235](#_Toc173414761)

[Table 40: Annual health state costs used in the company’s scenario analysis (obtained from CS document B, pg 184) 235](#_Toc173414762)

[Table 41: Summary of the QALY shortfall analysis across SMA populations 238](#_Toc173414763)

[Table 42: Company deterministic base-case results for the presymptomatic population 239](#_Toc173414764)

[Table 43: Company probabilistic base-case results for the presymptomatic population 240](#_Toc173414765)

[Table 44: Description of the company’s scenario analyses in comparison to the base-case (total presymptomatic population) 243](#_Toc173414766)

[Table 45: Description of the company’s scenario analyses in comparison to the base-case (presymptomatic population with 2 SMN2 copies) 243](#_Toc173414767)

[Table 46: Description of the company’s scenario analyses in comparison to the base-case (presymptomatic population with more than 2 SMN2 copies) 244](#_Toc173414768)

[Table 47: Company deterministic base-case results for people with type 1 SMA 246](#_Toc173414769)

[Table 48: Company probabilistic base-case results for people with type 1 SMA 246](#_Toc173414770)

[Table 49: Description of the company’s scenario analyses in comparison to the base-case (type 1 SMA population) 250](#_Toc173414771)

[Table 50: Company deterministic base-case results for people with type 2 or 3 SMA (later onset) 253](#_Toc173414772)

[Table 51: Company probabilistic base-case results for people with type 2 or 3 SMA (later onset) 253](#_Toc173414773)

[Table 52: Description of the company’s scenario analyses in comparison to the base-case (type 2/3 SMA population) 257](#_Toc173414774)

[Table 53: NICE reference case checklist 259](#_Toc173414775)

[Table 54: Risdiplam, nusinersen and onasemnogene abeparvovec motor milestone transition probabilities (Roche presymptomatic model base case) (obtained from CS document B Table 106, Page 224) 261](#_Toc173414776)

[Table 55: Summary of patient utility values for cost-effectiveness analysis (presymptomatic and type 1 base case model) (TA588 ERG report early onset model, Biogen clinical Advisors) (obtained from CS document B Table 121, Page 255) 265](#_Toc173414777)

[Table 56: Summary of carer utility values for cost-effectiveness analysis (presymptomatic and type 1 base case model) (Bastida et al. 2017 and Ara et al. 2010) (obtained from CS document B Table 124, Page 257) 266](#_Toc173414778)

[Table 57: Health care resource use for paediatric (per cycle costs) – (obtained from Roche health care resource use study) 267](#_Toc173414779)

[Table 58: Health care resource use for adults (per cycle costs) – (obtained from Roche health care resource use study) 268](#_Toc173414780)

[Table 59: Proportion of patients that using the resources (one number) as one-off in the beginning of treatment and their unit costs– (obtained from Roche HCRU Study) 268](#_Toc173414781)

[Table 60: One-off costs for different health states in presymptomatic SMA model (obtained from Roche health care resource use study) 269](#_Toc173414782)

[Table 61: Company deterministic base-case results for the presymptomatic population (using list prices) 272](#_Toc173414783)

[Table 62: Company deterministic base-case results for the presymptomatic population (using PAS price for risdiplam) 272](#_Toc173414784)

[Table 63: EAG ranking of the company’s deterministic base-case results for the presymptomatic population (using list prices) 273](#_Toc173414785)

[Table 64: EAG ranking of the company’s deterministic base-case results for the presymptomatic population (using PAS price for risdiplam) 273](#_Toc173414786)

[Table 65: Company PSA results for the presymptomatic population (using list prices) 274](#_Toc173414787)

[Table 66: Company PSA results for the presymptomatic population (using PAS price for risdiplam) 274](#_Toc173414788)

[Table 67: Scenario analysis results for the presymptomatic population (using the PAS price for aisdiplam) 278](#_Toc173414789)

[Table 68: Deterministic base-case results for the type 1 SMA population (using list prices) 287](#_Toc173414790)

[Table 69: Deterministic base-case results for the type 1 SMA population (using PAS price) 287](#_Toc173414791)

[Table 70: Probabilistic sensitivity analysis results for the type 1 SMA population (using list prices) 288](#_Toc173414792)

[Table 71: Probabilistic sensitivity analysis results for the type 1 SMA population (using PAS price) 288](#_Toc173414793)

[Table 72: Scenario analysis results for people with type 1 SMA (using PAS price for risdiplam) 292](#_Toc173414794)

[Table 73: Summary of patient utility values for cost-effectiveness analysis (type 2/3 base case model) (Obtained from CS Document B, Table 127, pg.259) 298](#_Toc173414795)

[Table 74: Summary of carer utility values for cost-effectiveness analysis (type 2/3 base case model) (TA588/TA755 ERG report) (Obtained from CS Document B, Table 130, pg.261) 299](#_Toc173414796)

[Table 75: Modified Delphi panel HCRU results applied to type 2/3 SMA (SUNFISH) model health states per monthly cycle (Obtained from CS Document B, Table 135, pg.283) 300](#_Toc173414797)

[Table 76: Real-world study (TA588) applied to type 2/3 SMA (SUNFISH) model health states per monthly cycle, with the one-off costs from the modified delphi panel (Obtained from CS Document B, Table 137, pg.283) 301](#_Toc173414798)

[Table 77: Deterministic base-case results for the type 2/3 SMA population (using list prices) 302](#_Toc173414799)

[Table 78: Deterministic base-case results for the type 2/3 SMA population (using PAS prices) 303](#_Toc173414800)

[Table 79: Probabilistic results for the type 2/3 SMA population (using list prices) 303](#_Toc173414801)

[Table 80: Probabilistic results for the type 2/3 SMA population (using PAS price) 304](#_Toc173414802)

[Table 81: Scenario analysis results for the type 2/3 SMA population (using PAS prices) 307](#_Toc173414803)

[Table 82: Key issues identified and EAG recommendations 309](#_Toc173414804)

[Table 83: EAG Base case inputs based on Roche presymptomatic SMA model 315](#_Toc173414805)

[Table 84: Deterministic base-case results for the presymptomatic population (using PAS price) 317](#_Toc173414806)

[Table 85: PSA results for the presymptomatic population (using PAS price) 318](#_Toc173414807)

[Table 86: Scenario analysis results for the presymptomatic SMA population (using PAS prices) 321](#_Toc173414808)

[Table 87: EAG Base case inputs based on Roche type 1 SMA model 323](#_Toc173414809)

[Table 88: Deterministic base-case results for the type 1 SMA population (using PAS price) 325](#_Toc173414810)

[Table 89: Probabilistic results for the type 1 SMA population (using PAS price) 326](#_Toc173414811)

[Table 90: Scenario analysis results for the type 1 SMA population (using PAS price) 329](#_Toc173414812)

[Table 91: EAG base-case inputs on Roche type 2/3 SMA model 332](#_Toc173414813)

[Table 92: Deterministic base-case results for the type 2/3 SMA population (using PAS price) 333](#_Toc173414814)

[Table 93: Deterministic base-case results for the type 2/3 SMA population (using PAS price) 334](#_Toc173414815)

[Table 94: Scenario analysis results for the type 2/3 SMA model (PAS price for risdiplam) 337](#_Toc173414816)

**List of Figures**

Figure 1: PRISMA flow of records in clinical effectiveness SLR 77

Figure 2: Study flow diagram 212

Figure 3: Illustrative model structure for the presymptomatic population 230

Figure 4: Overall survival curves for the presymptomatic population for people who received nusinersen treatment or BSC 237

Figure 5: Incremental cost-effectiveness scatterplot for the comparison between nusinersen versus BSC (presymptomatic population) 240

Figure 6: Cost-effectiveness acceptability curve for nusinersen at different willingness-to-pay thresholds 241

Figure 7: Tornado diagram for the impact of change to individual parameters on the ICER (cost per QALY) (presymptomatic population) 242

Figure 8: Incremental cost-effectiveness scatterplot for the comparison between nusinersen versus BSC (type 1 SMA) 247

Figure 9: Cost-effectiveness acceptability curve for nusinersen at different willingness-to-pay thresholds (type 1 SMA) 248

Figure 10: Tornado diagram for the impact of change to individual parameters on the ICER (cost per QALY) (type 1 SMA) 249

Figure 11: Illustrative model structure for the presymptomatic population 251

Figure 12: Incremental cost-effectiveness scatterplot for the comparison between nusinersen and BSC (type 2/3 SMA) 254

Figure 13: Cost-effectiveness acceptability curve for nusinersen at different willingness-to-pay thresholds 254

Figure 14: Tornado diagram for the impact of change to individual parameters on the ICER (cost per QALY) (type 2/3 SMA) 256

Figure 15: Incremental cost-effectiveness scatterplot for the comparisons between risdiplam and BSC, nusinersen and OA for the presymptomatic population (using PAS price for risdiplam) 275

Figure 16: Cost-effectiveness acceptability curve for the risdiplam compared to BSC, nusinersen and onasemnogene abeparvovec at different WTP thresholds (using PAS price for risdiplam) 275

Figure 17: Deterministic one-way sensitivity analysis for the comparison between risdiplam versus BSC (using the PAS price for risdiplam) 276

Figure 18: Deterministic one-way sensitivity analysis for the comparison between risdiplam versus nusinersen (using the PAS price for risdiplam) 277

Figure 19: Deterministic one-way sensitivity analysis for the comparison between risdiplam and onasemnogene abeparvovec (using the PAS price for risdiplam) 277

Figure 20: Type 1 OS parametric functions for risdiplam (Obtained from CS Document B, Figure 31, pg. 229) 285

Figure 21: Incremental cost-effectiveness plane for comparisons between risdiplam and BSC, nusinersen and onasemnogene abeparvovec (using PAS price) 289

Figure 22: Cost-effectiveness acceptability curves for the comparisons between risdiplam and BSC, nusinersen and onasemnogene abeparvovec at different WTP thresholds (using the PAS price for risdiplam) 290

Figure 23: Deterministic one-way sensitivity analysis for the comparison between risdiplam and BSC (using the PAS price for risdiplam) 291

Figure 24: Deterministic one-way sensitivity analysis for the comparison between risdiplam and nusinersen (using the PAS price for risdiplam) 291

Figure 25: Deterministic one-way sensitivity analysis for the comparison between risdiplam and onasemnogene abeparvovec (using the PAS price for risdiplam) 292

Figure 26: Incremental cost-effectiveness scatterplot for the comparison between risdiplam and BSC and nusinersen (using PAS price for risdiplam) 305

Figure 27: Cost-effectiveness acceptability curve for the comparison between risdiplam and BSC and nusinersen at different WTP thresholds (using the PAS price for risdiplam) 305

Figure 28: Deterministic one-way sensitivity analysis for the comparison between risdiplam and BSC (using the PAS price for risdiplam) 306

Figure 29: Deterministic one-way sensitivity analysis for the comparison between risdiplam and nusinersen (using the PAS price for risdiplam) 306

Figure 30: Incremental cost-effectiveness scatterplot for the comparisons between risdiplam and BSC, nusinersen and onasemnogene abeparvovec for the presymptomatic population (using PAS price for risdiplam) 319

Figure 31: Cost-effectiveness acceptability curve for the risdiplam compared to BSC, nusinersen and onasemnogene abeparvovec at different WTP thresholds (using PAS price for risdiplam) 319

Figure 32: Deterministic one-way sensitivity analysis for the comparison between risdiplam and BSC (using the PAS price for risdiplam) 320

Figure 33: Incremental cost-effectiveness scatterplot for the comparisons between risdiplam and BSC, nusinersen and onasemnogene abeparvovec for the type 1 SMA population (using PAS price for risdiplam) 327

Figure 34: Cost-effectiveness acceptability curve for the risdiplam compared to BSC, nusinersen and onasemnogene abeparvovec at different WTP thresholds (using PAS price for risdiplam) 327

Figure 35: Deterministic sensitivity analysis results for the type 1 SMA model (PAS price for risdiplam), ICER versus BSC 328

Figure 36: Incremental cost-effectiveness scatterplot for the comparisons between risdiplam, BSC and nusinersen for the type 2/3 SMA population (using PAS price for risdiplam) 335

Figure 37: Cost-effectiveness acceptability curve for the risdiplam compared to BSC and nusinersen at different WTP thresholds (using PAS price for risdiplam) 335

Figure 38: Deterministic sensitivity analysis results for the type 2/3 SMA model (PAS price for risdiplam), ICER versus nusinersen 336

Figure 39: Deterministic sensitivity analysis results for the type 2/3 SMA model (PAS price for risdiplam), ICER versus BSC 336

LIST OF ABBREVIATIONS

AE Adverse event

AR Assessment report

BNF British National Formulary

BSC Best supportive care

CEA Cost-effectiveness analysis

CHEERS Consolidated health economic evaluation reporting standards

EAG Evidence assessment group

eMIT Electronic marketing tool

HES Hospital Episode Statistics

HINE-2 Hammersmith Infant Neurological Examination Module 2

HFMSE Hammersmith functional motor scale

HRQoL Health-related quality of life

HSUV Health state utility values

ITC Indirect treatment comparison

LYG Life-year gained

MAA Managed Access Agreement

MAIC Matching-adjusted indirect comparison

MTA Multiple Technology Appraisal

MFM Motor function measure

NA Not applicable

NHB Net health benefit

NHS National Health Service

NMA Network meta-analysis

NR Not reported

NICE National Institute for Health and Care Excellence

PPI Patient and public involvement

PRISMA Preferred reporting items for systematic reviews and meta-analyses

PROM Patient reported outcome measure

PSA Probabilistic sensitivity analysis

PSSRU Personal social services research unit

QALY Quality-adjusted life year

ROB Risk of bias

RULM Revised upper limb module

RWE Real world evidence

SAE Severe adverse event

SLR Systematic literature review

SMA Spinal muscular atrophy

SMN Survival motor neurons

TA Technology appraisal

WHO World Health Organization

1. BACKGROUND
   1. Introduction

This multiple technology appraisal (MTA) was conducted to critically appraise the clinical and cost effectiveness of nusinersen and risdiplam in comparison to standard of care, established clinical management, comparing the interventions to each other, and comparing to onasemnogene abeparvovec (where appropriate).1 The population being studied is patients with spinal muscular atrophy (SMA) types 0, 1, 2, 3, and 4 5q SMA or presymptomatic 5q SMA confirmed by genetic testing. Nusinersen has a marketing authorisation in the UK for the treatment of pre-symptomatic and symptomatic 5q SMA, and risdiplam has a marketing authorisation in the UK for the treatment of 5q SMA in patients with a diagnosis of type 1 or 2 SMA, or patients with type 3 SMA with one to four SMN2 copies.1

* 1. Description of health problem

SMA is a rare genetically inherited disorder that leads to muscle weakness and progressive reduced mobility and movement.1 SMA is classified into several types including presymptomatic and types 0 – 4 5q SMA and different subgroups including type a, b and c. The main cause of SMA is defects in the SMN1 gene, leading to a decline of motor neurones in the spinal cord, consequently causing defects in the function of the motor neurone and respiratory system.1 However, each SMA type presents differently as the severity of the genetic condition declines with age of onset. Symptoms from type 0 affect babies prior to birth, where survival beyond the first few weeks is low. Type 1 affects babies < 6 months and presents with difficulty in movement, swallowing and breathing caused by very weak muscle tone and muscle strength. Type 2 SMA occurs between 7-18 months of age and causes difficulty in walking without assistance. Type 3 SMA affects individuals 18 months – 18 years old and whilst walking and sitting may improve from type 2, in many circumstances people lose the mobility over time.1 Type 4 SMA occurs in adults > 18 years and whilst it is less severe than previous types, it is typically associated with muscle weakness, particular in the deltoids, triceps and quadriceps.1, 2

* + 1. Aetiology, pathology and prognosis

In humans, the SMN protein comes from both SMN1 and SMN2 genes.3 The underlying cause of SMA is the mutation in the SMN1 gene (encoding survival motor neurone protein) that has a primary role of protein production for the motor neurons. Survival of cells permit this muscle movement, resulting in a lack of protein production, which in turn leads to low cell survival rate and consequently an inability to perform muscle action.4 The pathological process of the neurodegenerative disease is caused by homozygous deletion or mutation of the SMN1 gene resulting in the loss of lower survival motor neurones (SMN).

The prognosis of SMA varies between types with extensive evidence demonstrating a much lower survival rate between types 0-1 in babies and infants compared to types 2, 3 and 4 in children and adults. Despite the presence of both SMN1 and SMN2 in humans, research indicates that the SMN2 gene has limited protein production capabilities and cannot compensate for the loss of the SMN1. Therefore, patients with a higher SMN2 copy number progress to milder symptoms and effects.5

* + 1. Epidemiology

SMA is a rare condition, with global rates of one or two cases per 100,000 .6 The cause of the neurodegenerative disease is the mutation of the SMN1 gene in which 1 in 40 people carry, equivalent to 1.69 million people in the UK. If both parents carry this altered gene, there is a one in four chance of babies developing SMA.7 In addition, research demonstrates one in two chances of babies developing one faulty and one healthy copy of the SMN1 gene and a 25% chance of inheriting two healthy copies of the SMN1 gene and, therefore not developing SMA.8

* + 1. Incidence and/or prevalence

Prevalence of SMA was estimated in 2017 to be 1-2 per 100,000 people, when examining all types together,6 however variation of prevalence is observed between countries.6 Prevalence of type 1 SMA has been estimated to account for more than half of the total cases of SMA, with a prevalence of between 0.04 and 0.28 per 100,000 people. The prevalence of type 1 SMA is lower than prevalence for all types together, potentially due in part to the severity of type 1 and the associated short life expectancy.6 UK data shows approximately 1,350 people were living in the UK with SMA in 2022.7

Incidence of all types of SMA has been reported to be on average 8 per 100,000 live births globally.6 UK data suggests an incidence in 2022 of 1 in 14,000 births, equating to approximately 48 live births in 2022.7 An estimated 37 babies are born in England and Wales each year with type 1 SMA (Biogen CS, Document B, Section B.1.3.3).

According to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality and registration data that collects data from death certificates, the infant mortality rate of patients with SMA1 was reported as 4.2 per 100,000 births (1 per 16,350 births) in England between 2009 and 2016.9 Since 2017, the progression and development of disease-modifying therapies (including nusinersen) have reduced SMA related infant mortality rate.9 However since the development of disease modifying therapies, the prevalence of SMA is likely to be currently higher as Biogen estimates there are currently approximately 130 – 150 prevalent patients living with SMA type 1 in England and Wales. (Biogen CS, Document B, Section B.1.3.3).

* + 1. Impact of health problem

The effect of each SMA type varies depending on the age range of affected patients. For type 1 SMA (the most prevalent type), the burden of the disease ranges from various symptoms and complications that, if left untreated, can become life-threatening.10 Movement and mobility are severely affected as muscles weaken, and extremely low muscle tone (hypotonia) leads to an inability to move hands, fingers, arms and legs. Babies also experience difficulty breathing, coughing and increased susceptibility to chest infections. (Biogen CS, Document B Section B.1.3.4)

Type 2 SMA is not considered to be as severe as type 1, although complications such as joint subluxations, dislocations and scoliosis are quite common, often leading to significant concerns for the patient. These complications can result in mobility and respiratory issues which require extensive care and treatment (Roche CS, Document B, Section B.1.3.2). Type 2 SMA usually presents with milder symptoms. Patients with type 2, and type 3 patients where their condition has progressed, are able to sit but are not ambulatory (Biogen CS, Document B, Section B.1.3.4). Hence these patients’ mobility can be affected significantly and may require constant supervision to prevent falls and musculoskeletal injuries. With the progression of the disease, patients may attain ambulatory abilities, learning how to sit and walk independently. However supervision and support with daily activities remains significant since severe signs of muscle weakness on both sides of the body are often seen amongst SMA3 children.11 During growth development, patients may exhibit increased susceptibility to infections and illness compared to unaffected patients emphasising the need for urgent professional healthcare.11

SMA can have a psychological burden on parents and caregivers. As a result of numerous hospitals stays and ongoing supervision, patients and carers frequently bear a significant emotional and social burden as a result of difficulties including palliative care, nutrition and ventilatory needs (Roche CS, Document B, Section B.1.3.2). Additionally, parents frequently exhibit an excessive amount of optimism regarding newly developed therapies.12 At the same time, evidence shows that treatment may change the course of the disease, but a cure is still unattainable. Therefore, the worrisome nature of the child’s health can continue even with the initiation of treatments; for instance, uncertainty about long-term efficiency of the treatment heightens ethical and financial concerns for parents/caregivers.12

SMA is primarily managed by the NHS, often requiring a multidisciplinary team of healthcare professionals. SMA management can put additional burden on the healthcare system, as a result of the emotional, economic, and health-related burdens of the disease. Previous research has indicated the emotional well-being parents and families experience during the journey of SMA, yet clinicians and healthcare professionals may also need to consider their expectations.13 Careful counselling and discussions should revolve around the harms and benefits of treatment. If patients respond successfully to treatments, the effectiveness may not always be complete; for instance, children may still exhibit compromised neuromuscular performance. Furthermore, even when treatment is available, access to these treatments can represent a substantial barrier for many families.13 The cost burden associated with caring for someone with SMA may vary depending on type of disease; the more advanced the condition, the more intensive treatments are required, increasing the expense (Biogen CS, Document B, Section B.1.3.5).

* + 1. Measurement of disease

Several outcome measures are used to monitor and evaluate people affected by SMA; however, these vary according to the type of SMA (Roche CS, Document B, Table 4). Table 1 shows the outcomes of measurement (adapted from Roche CS, Document B, Table 4).

Table 1: Outcome measures used to monitor and evaluate people with SMA (adapted from Roche CS Document B, Table 4)

|  |  |  |
| --- | --- | --- |
| **Measurement** | **Description** | **Clinical meaningful improvement** |
| SMA Type 1 (Infantile onset) | | |
| CHOP INTEND | 16-item motor function measure, scores ranging from 0 – 4 in each item. Both assess both active and reflexive movements, such as upper and lower extremities, hand grasping, rolling, head control, and others | Improvement in CHOP-INTEND scores > 40 is clinically meaningful for infants with type 1. |
| HINE-2 | A measurement tool which assesses 8 developmental motor milestones (Head control, Sitting, voluntary grasp, ability to kick, rolling, crawling, standing and walking) | Achievement of important motor milestones and higher scores (> 2 point increase in the ability to kick and 1> point increase in head control, rolling, sitting, crawling, standing or walking) are clinically meaningful improvements. |
| BSID-III | * Validated tool to assess attainment of motor milestones, including static positioning (head control and sitting), dynamic movements such as crawling, quality of movement such as kicking balance and motor planning. * 72 items are scored on a 2-point scale to measure whether patients can perform in various domains, such as cognitive and motor language, with two scales conducted on parent questionnaires: social-emotional and adaptive behaviour. | The ability to achieve a sitting position unsupported at 12 months is considered a clinically meaningful and important milestone in SMA1 |
| SMA Type 2 and Type 3 (Later onset) | | |
| MFM32 | * Consists of 32 items measuring daily activities and assessing three domains (D1: standing and transfers, D2: axial and proximal motor function, D3: Distal motor function. * Scores are between 0 – 3 which are then summed and transformed onto a 0 – 100 scale to yield the MFM32 total score expressed as a %. | * A change of > 0 in MFM32 total score representing stabilisation or improvement of motor is clinically meaningful * > 3 points should be marked as improvements for patients |
| RULM | * Measures upper limb motor function * 19 items, scored on a scale between 0 – 2 for each item excluding one that is scored between 0 – 1). Areas of the body that are measured include elbow, wrist and hand function * A total score of 0 – 37 is estimated demonstrating higher scores will be equivalent to greater upper limb motor function | * According to natural history data, the mean change in RULM score -0.4 points in type 2 and 3 patients aged 2.7 – 49.7 years * A change of > 0 in RULM total score representing stabilisation or improvement in motor function is clinically meaningful * Change of > 2 un RULM represents an estimate of a meaningful improvement in motor function. |
| HFMSE | * Measures items consisting of sitting, rolling, crawling, kneeling and standing/stepping * Widely used in SMA 2 and 3 * Measures gross motor function in SMA 2 and 3 patients > 2 years. * Consists of 33 items to measure functional abilities such as standing transfers, ambulation and proximal and axial function scored on a range of 0 – 2 (max score 66 points) | * Stabilisation and small improvements on the HFMSE are considered meaningful improvement * Change of > 3 points in HFMSE demonstrates meaningful improvement in motor function |
| Additional disease measurement whilst the patient is still alive might include RHS, ATEND, EK2, SMAIS-ULM. | | |
| ATEND, Adapted Test of Neuromuscular Disorders; CHOP INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EK2, Egen Klassifikation scale version 2, HINE, Hammersmith Infant Neurological Examination; HFMSE, Hammersmith Functional Motor Scale Extended; MFM32, 32-item Motor Function Measure; RHS, Revised Hammersmith scale; RULM, revised upper limb module; SMA, spinal muscular atrophy; SMAI-ULM, SMA independence scale-upper limb module | | |

* 1. Current service provision
     1. Management of disease

Whilst there is no cure for SMA, advancements in medical interventions have been made. Nusinersen received marketing authorisation in 2017 and this contributed to the significant decline in infant mortality rate from 4.2 per 100,000 to 1.9 per 100,000. However, access was only available to SMA-type 1 patients through agreement of the parent/carer and clinical management team (Biogen CS Document B, Section B.1.3.7).

Onasemnogene abepravovec (Zolgensma) is a gene therapy that uses a modified, non-replicating adenovirus as a vector, which carries a functional copy of the human SMN gene, which when delivered begins production of the SMA protein. It is administered as a single-dose intravenous infusion for patients diagnosed with SMA1 or up to 3 copies of SMN2.14 Initially (in 2021) onasemnogene abepravovec treated patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and diagnosis of SMA1 among infants < 12 months old. This was later extended to all ages in patients weighing 21kg or less, and in 2023, NICE further recommended this treatment for presymptomatic individuals (Biogen CS Document B, Section B.1.3.7). Risdiplam was developed in 2021, targeting the faulty gene's backup copy. This is administered orally for 5q SMA patients > 2 months old. Risdiplam was made available to SMA type 1, 2 and 3 patients or presymptomatic with 1 – 4 SMN2 copies. In 2023, the medicines and Healthcare products regulatory agency approved a licence to lift the extension from patients > 2 months old to all ages.(Biogen CS, Document B, Section B.1.3.7)15

In addition to pharmacological medicines, the NHS recommended other supportive measures. Occupational therapists and physiotherapists prescribe assistive equipment for enabling movement and managing day-to-day activities, including walking farms, wheelchairs, splints and braces for lower limb support. Exercises and stretches are used to maintain strength and flexibility, and breathing assistance, for instance, a suction machine to clear the airways and throat of mucus.16

* + 1. Current service cost

For nusinersen, the total annual treatment cost is £450,000 for the first year and £225,000 for subsequent years (Biogen CS, Document B, Table 2). Over 5 years, the treatment costs for each patient are approximately £1.35 million.17

* + 1. Variation in services and/or uncertainty about best practice

Epidemiological data on SMA is limited to Europe. Approximately 66% of Global SMA patient registry data is based on patients from Europe. Possible reasons were reported to be the lack of healthcare infrastructure in some countries, primarily low socio-economic status areas that impact their access to genetic testing.6 Availability of treatment may vary internationally. Variations include access to treatment, funding and diagnostic capabilities. Prevalence and incidence may be influenced by the presence of specialised care centres. For instance, Sweden has been reported to have a higher prevalence of SMA and other neuromuscular disorders due to more reliable diagnosis of SMA.6

* + 1. Relevant national guidelines, including National Service Frameworks

England Rare Disease framework18 presents a national guideline for improving the lives of individuals living with a rare condition in the UK. Priority areas for this include ensuring a prompt diagnosis, increasing healthcare professional awareness of conditions, ensuring good coordination of care and increased access to relevant specialist care and treatment.18

The 2017 International Standards of Care for SMA were developed to address evolving care and management needs around treatment.19 Since publication of the standards of care, newly developed disease modifying therapies such as nusinersen, have emerged prompting updates to the guidelines to reflect the awareness around these advancements. Significant aspects include early diagnosis, elicited by the increased awareness of clinical signs and now the use of molecular genetic testing which enhances its reliability to confirm the diagnosis.20 Rehabilitation involves consistent regulation of physical therapy to help maintain mobility and physical function. Emerging research has shown that assistive technology and specialised equipment is recommended to enhance and sustain physical function. For instance, stretching can be performed through manual assistance and use of orthoses to support basic movements such as standing and sitting and the assistance of postural supports and seating systems to ensure correct positioning.20

* 1. Description of technology under assessment
     1. Summary of Intervention

Nusinersen (Spinraza) is an antisense oligonucleotide manufactured by Biogen.21 Nusinersen is authorised for the treatment of patients with 5q SMA. Nusinersen increases the production of functional survival of SMN protein by targeting the SMN2 gene displacing factors that suppress slicing. This leads to increased retention of exon 7 in the SMN2 gene, increasing the production of SMN protein (Biogen CS, Document B, Table 2). Nusinersen is administered via spinal injections (intrathecal bolus injections) over 1 – 3 minutes, via lumbar puncture (LP) directly into the cerebrospinal fluid (CSF). Injections are conducted every 4 months; with loading doses administered beforehand as soon as possible after diagnosis. Four loading doses are administered on days 0, 14, 28 and 63, with a recommended licenced dose of 12mg (5ml) per single dose. This should continue until the treating clinician and patient make an agreement to stop treatment.21 Administration is performed in a neuromuscular treatment centre by trained healthcare professionals. In some cases, sedatives or general anaesthetics are required for administration. The marketing authorisation for nusinersen includes all patients with confirmed pre-symptomatic SMA or type 1, 2, 3 and 4 SMA (CS, Document B, section B.1.1).

Risdiplam (Evrysdi®) is a is a SMN2 splicing modifier which increases production of the functional SMN protein by modifying the splicing of the SMN2 gene transcript. Risdiplam is administered orally in liquid form and is designed for patients with SMA types 1, 2 and 3 or with 1 – 4 SMN2 copies.22 Risdiplam has demonstrated efficacy for patients irrespective of their age, SMA type or physical status (Roche CS, Document B, Table 2). Treatment with risdiplam is ongoing with doses based on the patient’s age and weight. Risdiplam should be administered daily. Regular monitoring is required, however risdiplam is often administered at home daily by the patient or a caregiver orally. This eliminates the need for repeated clinical visits, invasive procedures or concomitant use of medications (CS, Document B, Section B.1.3.5), but decisions around where treatment is administered is made by a clinical team at a specialist neuromuscular centre.23

* + 1. Identification of important sub-groups

Sub-groups examined in the MTA, according to the NICE scope1 include (where possible):

* Number of SMN2 gene copies (the number of SMN2 copies impacts on the severity and symptoms presented)5
* Functional status (The functional status of a person with SMA is grouped into different categories, such as: sitting with support, sitting without support, standing with assistance, standing alone and walking with assistance alone (Roche CS, Document B, Section B.5.2.3.8).
* People with prior active treatment
  + 1. Current usage in the NHS

Nusinersen was recently adopted in July 2019, where NICE assessed patients with 5q SMA and presymptomatic SMA (Biogen CS, Document B, Section B.1.3.7). The current usage of SMA treatments within the NHS varies widely regarding availability and uptake of key therapeutic options. Nusinersen has been made available in England, Wales and Northern Ireland via a managed access agreement (MAA). In Scotland, nusinersen is routinely funded for all patients within the licenced indication (Roche CS, Document B, Section B.1.3.3). However, there may be some variation in usage across different parts of the UK. Across England, Wales and Northern Ireland, adults can be referred to specific treatment centres, whereas in Scotland, nusinersen is routinely available for children only as there are no centres that offer this service for adults in Scotland. However there is provision in the NHS agreement for adults only.24 England holds significantly more regional neuromuscular centres for both children and adults in comparison to Wales, Northern Ireland and Scotland that only hold very few treatment centres.25 In NHS England, clinicians prioritise individuals who have significant and recent declines in walking and feeding.7

* + 1. Anticipated costs associated with intervention

Costs associated with the interventions have been presented by the companies (Roche CS, Document B, Table 2)

Risdiplam

* Average cost of a course of treatment £7,900 per 60 mg/80 ml vial (Risdiplam).
* Patient access scheme – resulting net price per 60 mg/80 ml vial is \*\*\*\*\*\*

(Roche CS, Document B, Table 2)

.Nusinersen

* List price and average cost of a course of treatment is £75,000 per vial excluding value added tax (VAT)
* Total annual treatment cost is £450,000 for the first year and £225,000 for subsequent years
* Patient access scheme - total annual treatment cost is \*\*\*\*\*\*\*\* for the first year and \*\*\*\*\*\*\* for the subsequent years (Biogen CS, Document B, Table 2)

1. DEFINITION OF THE DECISION PROBLEM

This section will discuss the key factors to be addressed within this MTA, using the company decision problem.

* 1. Decision problem

This section will identify any differences between the NICE final scope. and the company decision problem.

* + 1. Critique of Company adherence to the NICE Final Scope
       1. Biogen (nusinersen)

Section B.1 of the Company Submission (CS) Document B discusses the company’s view of the decision problem and CS Document B Table 1 summarises this view and how it may or may not differ from that in the NICE final scope.

The company’s description of the decision problem (summarised in CS Document B, Table 1) defines the relevant population, intervention, comparator, and outcomes as follows:

**Population**: Presymptomatic SMA and SMA types 1, 2 and 3

**Intervention**: Nusinersen

**Comparator**: Established clinical management, best supportive care, risdiplam or onasemnogene abeparvovec

**Outcomes**: Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills), Bulbar function (including, for example, swallowing and ability to communicate), Frequency and duration of hospitalization, Respiratory function, Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures), Need for non-invasive or invasive ventilation, Stamina and fatigue, Mortality, Adverse effects of treatment, Health-related quality of life (for patients and carers).

The EAG’s critique of the company’s conception of the decision problem is outlined in sections 2.1.1 through to 2.2.

* + - * 1. Population

The NICE final scope defines the population as people with types 0, 1, 2, 3, or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.

The population addressed in the company submission is people with presymptomatic SMA and SMA types 1, 2 and 3. This is narrower than the NICE final scope because it excludes SMA type 0 and 4. The rationale given by the company for excluding these groups from the submission is that the evidence base is limited to people with presymptomatic SMA and SMA types 1, 2 and 3. The company state that SMA type 0 was excluded from the submission because treatment for these patients is futile. They also state that the evidence base on nusinersen for SMA type 4 is insufficient for cost-effectiveness modelling.

The EAG consulted clinical experts who confirmed that, due to the severity of the disease at birth, the treatment of SMA type 0 is regarded by professionals as futile and unlikely to happen in the UK. However, one expert suggested that there may be a small number of babies with less severe manifestations at birth who may benefit from treatment and that, in these cases, the SMN2 copy number should be established. According to this expert, rather than SMA ‘type’, it would be important to assess clinical severity.

The subgroups specified in the NICE final scope are included in the company’s description of the decision problem. These are: Number of SMN2 gene copies in people with pre-symptomatic SMA, Functional status (non-sitter, sitter, walker), and people who have had prior active treatment for SMA.

In the company submission, results are presented for the ENDEAR study. This study enrolled people with SMA type 1. The age at symptom onset in the ENDEAR study ranged from 1-20 weeks (CS Document B, Section B.2.4). This is in line with the definition of SMA type 1 in the NICE final scope.

The CHERISH study enrolled people with SMA types 2 and 3. The median age at symptom onset in this trial was ten months in the nusinersen group and 11 months in the control group (range of 6-20 months). This suggests that most people in this trial could be said to have SMA Type 2 using the definition in the NICE final scope. The EAG note that the term ‘later-onset’ SMA is used by the company to describe patients in this study who have SMA type 2 or 3.

The SHINE study included people who previously participated in other studies of nusinersen. The company submission focuses on people who were previously enrolled in the ENDEAR and CHERISH studies.

The NUTURE study enrolled people with clinically pre-symptomatic SMA with 2 or 3 SMN2 copies. This is a narrower population than specified in the NICE final scope which also includes people with 1 and 4 SMN2 copies. In the company submission results are presented by SMN2 copy number (a sub-group of interest as specified in the NICE final scope).

The company analysed paediatric data collected via the MAA (‘Real World’ data) in five cohorts based on SMA Type and motor function at baseline. These were:

* Type 1 enrolled in EAP
* Type 1 not enrolled in the EAP
* Type 2 and 3 non-sitters
* Type 2 and 3 sitters
* Type 2 and 3 walkers

These cohorts align with the ‘Functional Status’ NICE subgroup of interest.

The EAG note that the proportion of people with SMA type 3 in the MAA data is lower than types 1 and 2 (25.91% versus 36.82% and 37.27% respectively; CS Document B, Table 19, p94). Only one person was classified as SMA Type 3 and a non-sitter.

Data from the Adult SMA REACH Registry (‘Real World’ data) was analysed in cohorts that match the NICE subgroups of interest (non-sitter, sitters, walkers). Adult SMA REACH data largely relates to SMA type 3 (n=82 versus type 2 n=12). However, the EAG notes that some of the Type 2/3 cohort could be classified as SMA type 4 because the stated age-range at symptom onset was 1-30 years.

Although not included in this submission, the company note that efficacy of nusinersen in patients who received prior therapy is being assessed in the ongoing studies (ASCEND and RESPOND), which include patients previously treated with risdiplam and onasemnogene abeparvovec (CS Document B, Table 1).

* + - * 1. Intervention

The NICE final scope defines the intervention as nusinersen monotherapy in addition to existing clinical services and established clinical management. The company submission defines the intervention as nusinersen but gives no further detail.

The NICE final scope does not specify a dosage or dosing schedule for nusinersen. The approved dosage of nusinersen is 12 mg on days 0, 14, 28 and 63 then 12 mg every 4 months thereafter.26

The EAG notes that nusinersen is administered by intrathecal injection and the procedure can vary in terms of whether sedation or imaging guidance is needed, for example, experts confirm that spine deformity makes the procedure difficult, but not impossible (feasibility may depend on the severity of the deformity). Experts also confirm that sometimes, if a local anaesthetic cannot be tolerated, a general anaesthetic may be required. Co-morbidities may mean the risk of general anaesthetic is considered too great.

The dosage in the ENDEAR study was a scaled equivalent 12 mg dose. This was administered on days one, 15, 29, and 64, followed by maintenance dosing once every four months (on days 183 and 302) which aligns with the marketing authorisation (MA).

For the CHERISH study the dosage of nusinersen was 12 mg, however, the schedule differs from the MA. In the CHERISH study three loading doses were administered on days one, 29, 85, followed by a maintenance dose given 6 months later (day 274).

The data presented in the company submission from the SHINE study pertains to only those who were previously enrolled in ENDEAR and CHERISH so all would have received the 12 mg dose, but those from CHERISH were initially receiving nusinersen on the schedule described above but were then switched to a maintenance dose every four months.

In the NURTURE study of nusinersen for presymptomatic SMA, nusinersen was administered at a dose of 12 mg on days one, 15, 29, 64 with maintenance doses every four months thereafter. This matches the authorised dosing schedule.

No information is given in the company submission about the dosage and schedule of nusinersen the real-world data pertains to.

* + - * 1. Comparators

The NICE final scope describes comparators as: established clinical management, best supportive care (BSC), risdiplam and onasemnogene abeparvovec (for children aged ≤12 months with a biallelic mutation in the SMN1 gene and presenting with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene). The comparators listed in the company submission decision problem are the same as the NICE final scope.

The company state that direct evidence is only presented for established clinical management and BSC as comparators. Experts have confirmed that best supportive care (BSC) is required by all symptomatic (and probably the presymptomatic with 2 SMN2 copies) patients along with specific therapies. In CS Table 1 the company suggest the sham control used in the phase III ENDEAR and CHERISH trials can be considered to represent established clinical management/BSC.

The company justify focussing the submission on the comparison between nusinersen and BSC by highlighting limitations of indirect treatment comparisons (ITCs).

The company submission includes two comparative studies where the comparator is a sham procedure (ENDEAR and CHERISH) and two non-comparative studies (SHINE and NURTURE). No studies with a disease modifying therapy as a comparator are presented.

The company state that ITCs were undertaken to provide relative effectiveness estimates for nusinersen versus risdiplam and onasemnogene abeparvovec. However, after completion the analyses were viewed as having major limitations and possibly high levels of bias. The company therefore concluded that the ITC should not be used in the cost-effectiveness models (CS Document B, B.2.5., p111).

* + - * 1. Outcomes

The outcome measures identified in the NICE final scope and listed by the company in CS Document B Table 1 are identical and constitute the following: Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills), bulbar function (including, for example, swallowing and ability to communicate), frequency and duration of hospitalization, respiratory function, complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures), need for non-invasive or invasive ventilation, stamina and fatigue, mortality, adverse effects of treatment, health-related quality of life (for patients and carers).

Section B.2.4 of the company submission describes the efficacy data from the included studies. Key efficacy results for ENDEAR and CHERISH are summarised but the company refer the reader to TA588 for the full data.17

The following section details how the company submission addresses each type of outcome listed in the NICE final scope.

**Motor function** outcomes were available for all studies included in the submission. The specific measures presented by the company for each study are presented in Table 2.

Table 2: Motor function outcomes

|  |  |
| --- | --- |
| **Trial name** | **Motor function outcomes** |
| CHERISH | HFMSE  RULM score  WHO motor milestones |
| ENDEAR | CHOP INTEND  HINE-2  WHO motor milestones |
| NURTURE | Six-minute walking test (6MWT)  CHOP INTEND  HFMSE  WHO motor milestones (analysis available for 2 and 3 SMN2 copies) |
| SHINE | CHOP INTEND  WHO motor milestones |
| SMA REACH Registry (paediatric) | CHOP INTEND  HINE-2  RHS  RULM  WHO motor milestones |
| SMA REACH Registry (adult) | 6MWT  ATEND (Left and Right)  RHS  RULM  WHO motor milestones |

**Bulbar function** in terms of Parent Assessment of Swallowing Ability (PASA) is presented for the ENDEAR/SHINE, CHERISH/SHINE and NURTURE studies. And in terms of Gastrostomy tube placement for the NURTURE study.

**Hospitalisation** data is available for ENDEAR/SHINE and CHERISH/SHINE.

**Complications of spinal muscular atrophy** in terms of scoliosis and muscle contractures are available for the ENDEAR/CHERISH and CHERISH/SHINE

Studies.

Outcomes relating to the **need for non-invasive or invasive ventilation** are available for all the studies included in the submission except for the CHERISH study.

**Mortality** outcomes are available for all the included studies.

**Adverse effects of treatment** are available in the summary of product characteristics (CS, Appendix C) and in CS Document B section B.2.6.

**Health-related quality of life (for patients and carers)** is available for each study in Table 3.

Table 3: Health-related quality of life measures

|  |  |
| --- | --- |
| **Trial name** | **HRQoL measure** |
| CHERISH/SHINE | ACEND  PedsQL |
| ENDEAR/SHINE | ACEND  PedsQL |
| Real World (Paediatric) | EQ-5D  PGI-I  PGI-S  SMAIS |
| Real World (adult) | EQ-5D  PGI-I  PGI-S  SMAIS |

Information on **stamina and fatigue** has been included as measured by the 6-Minute Walk Test (6MWT).

Data on **respiratory function** outcomes, other than ventilation, is not included in the submission.

In addition to the outcomes listed in the NICE final scope the company has presented growth parameters (weight and length) for the ENDEAR, CHERISH, SHINE and NURTURE studies and CMAP responders for the ENDEAR study in their submission.

* + - * 1. Economic analysis

In CS Table 1, the NICE scope states:

* The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.
* The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
* Costs will be considered from an NHS and Personal Social Services perspective.
* The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.

The company submission states the economic analysis will be “*as per the reference case*” (CS, Document B, Table 1).

The EAG note that in accordance with the NICE final scope, the base-case results in the CS are presented in terms of incremental cost per quality-adjusted life year for all the models (presymptomatic, SMA type 1 and SMA types 2 and 3).

* + - * 1. Special consideration including issues related to equity or equality

In CS Document B Table 1 the NICE scope does not state any special considerations.

The company have highlighted that the assessment of nusinersen may have some features that are seen in the highly specialised technologies programme. More specifically they state that decision modifiers and flexibility in NICE’s decision making should be considered (CS Document B, Table 1, p14).

* + - 1. Roche (risdiplam)

Section B.1 of the company evidence submission Document B discusses the company’s view of the decision problem and CS Document B Table 1 summarises this view and how it may or may not differ from that in the NICE final scope.

The company’s description of the decision problem (summarised in CS Document B, Table 1, p11-13) defines the relevant population, intervention, comparator, and outcomes as follows:

**Population**: People with types 0, 1, 2 or 3 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies

**Intervention**: Risdiplam (monotherapy in addition to existing clinical services and established clinical management)

**Comparator**: Established clinical management, BSC, the interventions will be compared to each other. In addition, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene onasemnogene abeparvovec.

**Outcomes**: Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills); bulbar function (including, for example, swallowing and ability to communicate); frequency and duration of hospitalisation; respiratory function; complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures); need for non-invasive or invasive ventilation; stamina and fatigue; mortality; adverse effects of treatment; health-related quality of life (for patients and carers).

There are no differences to the NICE final scope.

The EAG’s critique of the company’s conception of the decision problem is outlined in sections 2.1.1.2.1 through to 2.1.1.2.6.

* + - * 1. Population

The population stated in the company submission decision problem (CS Table 1) is as per the NICE final scope. The NICE final scope defines the population as people with types 0, 1, 2 or 3 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.

In CS Table 1, p12, the company state that subgroups to be considered are as per the NICE final scope, namely: number of SMN2 gene copies in people with pre-symptomatic SMA; Functional status (non-sitter, sitter, walker) and People who have had prior active treatment for SMA.

A comparison of the study populations and sub-groups considered in the company submission and those specified in the NICE final scope follows.

In the FIREFISH study the median age at symptom onset was 1.5 months (range: 1.0–3.0 months). This population is in line with the definition of SMA Type 1 in the NICE final scope.

For the SUNFISH trial the median age of symptom onset was 12.3 (range 0-57) months for the risdiplam arm and 12.8 (range 6-135) months in the placebo arm. This population is in line with the definition of SMA Type 2 and 3 in the NICE final scope. However, it is noted that most participants were classified as having SMA Type 2 (70.0% of the risdiplam arm and 73.3% of the placebo arm).

The RAINBOWFISH study enrolled people aged from birth to 6 weeks who had been genetically diagnosed with SMA (SMN1 deletion and any SMN2 copies) but were not yet presenting with SMA symptoms. All participants had 2 SMN2 copies. This population is in line with the definition of presymptomatic SMA in the NICE final scope but excludes those with other SMN2 copy numbers (the decision problem in the NICE final scope includes 1 to 4 SMN2 copies).

The JEWELFISH study enrolled people with type 1, 2 and 3 SMA (6 months to 60 years) previously enrolled in Roche Study MOONFISH with the splicing modifier RO6885247 (development discontinued), or previously treated with nusinersen, onasemnogene abeparvovec or olesoxime (a Roche development molecule which has since been discontinued). Prior therapy is a sub-group of interest in the NICE final scope.

In the REACH paediatric registry data presented in the company submission, there were 25 people with SMA Type 1 (mean age at symptom onset 3.4 months), 36 people with SMA Type 2/3 non-sitters (mean age at symptom onset 13.5 months) and 65 people with SMA Type 2/3 able to sit or walk (mean age at symptom onset was 14.3 months).

The REACH adult registry data presented in the company submission includes 5 people with SMA Type 1 (mean age at symptom onset 0.42 years), 82 people with SMA Type 2/3 non-sitters (mean age at symptom onset 1.37 years) and 89 people with SMA Type 2/3 able to sit or walk (mean age at symptom onset 3.68 years).

The groups included align with the ‘Functional status (non-sitter, sitter, walker)’ sub-group to be considered.

In summary, the evidence submitted by the company diverges from the NICE decision problem in that it does not include evidence on risdiplam for SMA Type 0 or 4.

The EAG note that in addition to subgroups specified in the NICE final scope, the company presents ‘Permanently ventilated patients’ as a subgroup to consider (CS Document B, Table 1, p13).

* + - * 1. Intervention

The intervention stated in the company submission decision problem (CS Table 1) is as per the NICE final scope. The NICE final scope defines the intervention as risdiplam monotherapy in addition to existing clinical services and established clinical management.

The NICE final scope does not specify a dosage or dosing schedule for risdiplam. However, the approved dosage of risdiplam for adults is 5 mg once daily.27 No information is given in CS Document B, section B.2.2 about the dosage and schedule of risdiplam in the included studies.

* + - * 1. Comparators

The comparators stated in the company submission decision problem (CS, Document B, Table 1) are as per the NICE final scope. The NICE final scope describes comparators as: established clinical management, BSC, nusinersen and onasemnogene abeparvovec (for children aged ≤12 months with a biallelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene).

All five studies included in the company submission are non-comparative, except for the first 12 months of the SUNFISH study in which there was a placebo comparator.

In the company submission, results from the FIREFISH study are compared to natural history data although this is not a comparator listed in the NICE final scope.

An indirect treatment comparison was performed for risdiplam versus BSC, nusinersen and onasemnogene abeparvovec in patients with type 1 SMA (CS Document B, Section B.2.9).

* + - * 1. Outcomes

The outcomes stated in the company submission decision problem (CS Table 1) are as per the NICE final scope. The outcome measures identified in the NICE final scope constitute the following: motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills), bulbar function (including, for example, swallowing and ability to communicate), frequency and duration of hospitalization, respiratory function, complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures), need for non-invasive or invasive ventilation, stamina and fatigue, mortality, adverse effects of treatment, HRQoL (for patients and carers).

The following section discusses how the data included in the company submission address outcomes specified in the NICE final scope.

**Motor function** outcomes are available for all studies included in the submission. Measures can be found in Table 4.

Table 4: Motor function outcomes

|  |  |
| --- | --- |
| **Trial name** | **Motor function outcomes** |
| FIREFISH | BSID III  HINE-2  CHOP-INTEND |
| JEWELFISH | MFM-32  HFMSE  RULM  6MWT  BSID-III  HINE-2 |
| RAINBOWFISH | BSID-III  HINE-2  CHOP-INTEND  HFMSE |
| REACH paediatric | CHOP-INTEND  RHS  RULM,  HINE |
| REACH adult | RHS  RULM  ATEND  EK2 |
| SUNFISH | MFM32  RULM  HFMSE |

Data on **Bulbar function** in terms of the proportion of patients with the ability to swallow is available for two studies, FIREFISH and RAINBOWFISH.

**Hospitalisations** data is available for the FIREFISH study.

**Respiratory function** in terms of Forced Vital Capacity (FVC) is presented for the SUNFISH study.

**Complications of spinal muscular atrophy** in terms of spinal surgery is presented for the REACH registry (both adult and paediatric).

The **need for non-invasive or invasive ventilation** in terms of ventilation-free survival is presented for the FIREFISH, RAINBOWFISH and REACH registry (adult and paediatric).

**Mortality** data in terms of survival is presented for FIREFISH, RAINBOWFISH, JEWELFISH and the REACH registry (adult and paediatric).

**Adverse effects of treatment** are presented for the FIREFISH, SUNFISH and JEWELFISH studies.

**Health-related quality of life** is presented in Table 5

Table 5: Health-related Quality of Life

|  |  |
| --- | --- |
| Trial name | HRQoL measure |
| FIREFISH | ITQOL-SF47 |
| SUNFISH | SMAIS total score  Caregiver and patient reported |
| REACH adult registry | EQ-5DL  SMAIS  Patient-reported Global Impression of Change [P-GIC] |

The EAG note that data relating to stamina and fatigue is not available in the company submission. The company state “*currently available outcome measures do not capture other important features of life with SMA that are deemed to be important to patients and their families such as the ability to perform daily activities, respiratory function, swallowing, fatigue and endurance.*” (CS Document B, B.3.13, p320).

In addition to the outcomes listed in the NICE final scope, the company has presented development of clinically manifested SMA, growth measures (weight, length, height, head circumference, chest circumference), degree of innervation (CMAP amplitude) for the RAINBOWFISH study.

* + - * 1. Economic analysis

In terms of the economic analysis, the NICE final scope states:

* The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of an ICER of cost per QALY.
* The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
* Costs should be considered from an NHS and PSS perspective.
* The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered. The availability of any managed access arrangement for the intervention will be considered.

A difference between the NICE final scope and the decision problem addressed in the company submission is highlighted by the company. They state, “*In the presymptomatic population, a cost-comparison has been used to compare risdiplam to nusinersen and onasemnogene abeparvovec”*. The rationale given by the company for this difference is that equal efficacy had to be assumed given insufficient comparative efficacy data (CS Table 1, p12).

No subgroup analyses were performed.

* + - * 1. Special consideration including issues related to equity or equality

In CS Document B, Table 1 the NICE scope does not state any special considerations. In CS Document B, Table 1 (p13) the company state that the MAA for risdiplam excludes patients who are permanently ventilated or have a tracheostomy and that “*In the current situation, the decision to treat permanently ventilated patients must be taken to an NHSE panel, delaying treatment and potentially worsening prognosis*”.

* 1. Overall aims and objectives of assessment

The main aims of this assessment are:

To examine the clinical and cost effectiveness of nusinersen in treating Spinal Muscular Atrophy (SMA)

To examine the clinical and cost effectiveness of risdiplam in treating Spinal Muscular Atrophy (SMA).

1. ASSESSMENT OF CLINICAL EFFECTIVENESS
   1. Systematic review of existing clinical-effectiveness evidence

A systematic literature review (SLR) was conducted of the clinical effectiveness evidence of Disease-Modifying Therapies (DMTs) (nusinersen, and risdiplam) for treating Spinal Muscular Atrophy (SMA). The SLR was performed following the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions.28 A flow diagram illustrating the number of records identified, included, and excluded at each stage of the SLR (and reasons for exclusions at full text stage) will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.29

* + 1. Objectives
* To summarise the clinical effectiveness of disease modifying therapies nusinersen and risdiplam for the treatment of 5q Spinal Muscular Atrophy (SMA).
  1. Methods for reviewing effectiveness

Previous systematic reviews on the clinical effectiveness evidence for SMA have previously been published.30-40 These systematic reviews mostly examined efficacy of treatment for SMA, with the exception of one40 which analysed adverse events in treatment of SMA. These systematic reviews all differ to the current review, and limitations are noted within them all. Many of the previous reviews examined different treatment options, most were limited to examining SMA types 1,2 and 3, many examined children only and different study designs, sources searched, and outcomes were included.

This systematic review was conducted in line with the registered protocol (CRD42024512226)10 PRISMA guidelines29 and the Cochrane Handbook for Systematic Reviews of Interventions.28

Changes were made to the protocol regarding exclusion criteria of included studies. This was done for pragmatic reasons, due to the large volume of results initially eligible for inclusion in the review and was done prior to data extraction. Changes included the exclusion of conference abstracts, exclusion of case reports or case series (when n<20), and the exclusion of single-arm studies when n<20, or <12 months data from initiation of treatment was reported).

* + 1. Identification of studies

The search strategy comprised the following main elements:

* Searching of electronic bibliographic databases and other online sources,
* Contacting experts in the field,
* Scrutiny of references of included studies and a selection of recent, relevant systematic reviews
* Scrutiny of NICE company submissions for any additional data.

A comprehensive search strategy was developed by the research team, supported by an information specialist. Searches were built around terms for spinal muscular atrophy, nusinersen and risdiplam and used both free text keywords and, where available, thesaurus (MeSH/EMTREE) terms. Where possible, strategies to exclude animal studies, editorials/commentaries and similar publication types were applied. Searches were limited to studies published in English language, and to studies published since dates of relevant company submissions for TA588 (nusinersen, original submission 1st October 2017)41 and TA755 (risdiplam, literature search for company submission last updated in January 2020)42 The search was developed in Embase (via Ovid), and checked by a second information specialist for accuracy and completeness before being translated for other sources.

Searches were conducted in the following sources on 29th January 2024: Embase (Ovid); MEDLINE All (Ovid); Cochrane CENTRAL (Wiley); International HTA database (INAHTA); Science Citation Index and Conference Proceedings (Web of Science), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform. Email alerts were set up in Embase, MEDLINE, Web of Science and Cochrane Library to identify any relevant new publications and these were screened for potential inclusion in the review until 30th April 2024. Websites of selected international HTA and medicines approval agencies (NICE, Scottish Medicines Consortium, Canadian Agency for Drugs and Technologies in Health, Institute for Clinical and Economic Review, U.S. Food and Drug Administration, Medicines and Healthcare Products Regulatory Agency and European Medicines Agency) were searched on 25th January 2024. Records were exported to EndNote 21, where duplicates were systematically identified and removed. Full details of all searches are provided in Appendix 1.

* + 1. Inclusion and exclusion criteria

Inclusion and exclusion criteria are detailed in Table 6. Following deduplication, titles and abstracts were screened for all results by two reviewers independently, and any conflicts were resolved. Any discrepancies that were unresolved were resolved by a third reviewer. Full texts of all potentially eligible studies were retrieved and screened independently by two reviewers, and any conflicts resolved. Reasons for exclusions at full text stage were recorded and are available on request.

Table 6: Inclusion and exclusion criteria

|  |  |  |
| --- | --- | --- |
| **Factor** | **Inclusion criteria** | **Exclusion** **criteria** |
| **Design** | RCTs, and non-randomised trials, observational studies, SLRs and meta-analyses a | Editorials  Commentaries  Case reports  Case series (where n< 20)  Conference abstracts  Single-arm studies or studies with no comparator with a small sample-size (i.e. n<20) or those where no results were reported at 12 months or beyond from initiation of treatment. |
| **Interventions** | Nusinersen monotherapy  Risdiplam monotherapy | Concomitant or previous participation in any investigational drug  Any history of cell therapy |
| **Population** | People with types 0, 1, 2, 3 or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies | Received spinal fusion surgery following a diagnosis of scoliosis (prohibits safe administration of nusinersen)  Hospitalisation or respiratory conditions history or planned at the time of screening or tracheostomy.  History of surgery for scoliosis or hip fixation  Presence of clinically relevant ECG abnormalities before study drug administration  Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases |
| **Comparators** | * Established clinical management. * Best supportive care   The interventions will be compared to each other.   * In addition, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene. * Onasemnogene abeparvovec | No exclusion criteria |
| **Outcomes** | The outcome measures to be considered include:   * Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) * Bulbar function (including, for example, swallowing and ability to communicate) * Frequency and duration of hospitalisation * Respiratory function * Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) * Need for non-invasive or invasive ventilation. * Stamina and fatigue * Mortality * Adverse effects of treatment * HRQoL (for patients and carers). | No exclusion criteria |
| aSLRs and meta-analyses will be included past the abstract screening stage to enable bibliography searching but will be excluded at full-text stage.  ECG, electrocardiogram; HRQoL, health-related quality of life; RCT, randomised-controlled trial; SLR, systematic literature review | | |

* + 1. Data extraction strategy

Data from all studies eligible for inclusion were extracted using a pre-defined extraction form. All included studies were extracted by one reviewer and validated by a second reviewer. Any conflicts were resolved by discussion, or with involvement from a third reviewer. An example data extraction form (for Hahn et al. 2022) can be found in Clinical Appendix 1. All other extraction forms are available on request.

Extracted data included:

* Study characteristics (e.g., author’s name, year of publication, country, study design, study setting, sample size in each arm, funding source, duration of follow-up(s), and methodological features corresponding to the Cochrane risk of bias assessment tool)
* Patient baseline characteristics (e.g., trial inclusion/exclusion criteria; number of participants enrolled, and number of participants analysed; age, race, and gender; time from diagnosis of SMA to study entry; co-morbidities; prior active treatment; pre-symptomatic diagnosis; SMA type; number of SMN2 copies; relapse rate; age at symptom onset; age at treatment initiation; best motor function the person obtained).
* Treatment characteristics (e.g., type of drug, method of administration, dose, and frequency; definition of best supportive care as described by trialists, treatment duration); and follow-up; switch between treatments.43
* Outcome characteristics for each included outcome reported (e.g., definition of outcome measure; timing of measurement; scale of measurement; and effect size as presented, including mean difference, risk ratio, odds ratio, or hazard ratio, or arm-level data necessary to calculate an effect size). Measures of variability and statistical tests used will also be extracted (standard deviation, 95% confidence interval, standard error, p-values.
  + 1. Critical appraisal strategy

Studies were assessed for quality using the Cochrane risk of bias assessment tool for randomised controlled trials,44 and the ROBINS-I for non-randomised studies.45 Due to time limitations, quality assessment was conducted by one reviewer. Quality assessment was not performed for single-arm non-randomised studies, which were assumed to be at high risk of bias if used to inform relative treatment effects.

* + 1. Methods of data synthesis
       1. Narrative synthesis

Extracted data were tabulated to provide clinical evidence on the effectiveness of the treatments. A narrative synthesis accompanies each table to provide a comprehensive overview and critique of each study providing clinical effectiveness evidence, with special emphasis on the methodological quality and population diversity of the studies.

* + - 1. Indirect Treatment Comparisons (ITC)

Formal indirect Treatment comparisons were conducted to evaluate the relative effectiveness of risdiplam and nusinersen for SMA. Studies which included either risdiplam, nusinersen, or onasemnogene abeparvovec was included into the feasibility assessment to check the most appropriate method of data synthesis. There were two methods used in the absence of individualised patient data (IPD):

1. **Naïve comparison**

This method involves directly comparing outcomes from different studies without any adjustments for differences in study populations or designs. It is the simplest form of comparison but can be misleading due to potential biases and differences between the study groups. They are generally less reliable since they do not account for confounding variables or variations in study methodologies and designs.

1. **Network Meta-analysis (NMA)**

NMAs combine direct and indirect evidence across a network of studies to compare multiple treatments simultaneously, allowing for the estimation of relative treatment effects even when treatments have not been directly compared in head-to-head trials. It is usually considered the most comprehensive and statistically robust method for comparing multiple treatments, as it synthesises all available evidence and provides a holistic view of the relative effectiveness of different interventions. However, it requires enough high-quality studies, which can be challenging in rare diseases like SMA.

* 1. Results
     1. Quantity and quality of research available

Electronic database searches and searches of other sources, such as websites, yielded a total of 4,278 records. After removing duplicates, 2,538 records were screened for inclusion, of which 1,566 records were excluded based on title and abstract. The remaining 972 records were screened at full text, of which 845 studies were excluded, with the reasons for exclusion shown in Figure 1. 105 studies described in 127 reports were considered relevant for this systematic review.

Figure 1: PRISMA flow for clinical effectiveness review



Figure 1: PRISMA flow of records in clinical effectiveness SLR

* + - 1. Characteristics of included studies

Full characteristics of included studies can be found in Clinical Appendix 2. Across the included studies examining clinical effectiveness of treatment for SMA, the populations of interest were people with presymptomatic SMA, and types 1, 2, 3 and 4 SMA. Studies included a wide range of subgroups, including SMA type and SMN2 copy numbers.

* + - 1. Assessment of study quality

Quality assessment of included studies (using Cochrane risk of bias tool for RCTs and ROBINS-1 for non-randomised trials),44, 45 was conducted on included studies. As pre-defined in the protocol, quality assessment was not conducted on single-arm studies. Therefore, study quality was conducted on 29 studies.

Full outcomes of risk of bias assessments for each domain can be found in Table 7 and Table 8.

Cochrane risk of bias tool:

Six Randomised Controlled Trials (RCTs) (CHERISH,46 EMBRACE,47 ENDEAR,48 SUNFISH part 1,49 SUNFISH part 250, 51) were assessed using the Cochrane risk of bias tool.44 These were rated overall as high n=1 (ENDEAR),48 some concerns n=4 (CHERISH,46 EMBRACE,47 SUNFISH part 250, 51) and low risk of bias n=1 (SUNFISH part 1).49 The most common domain rated as having risk of bias was bias arising from the randomisation process rated as high in n=148 and some concerns in n=4 studies.46, 47, 50, 51

Table 7: Risk of Bias for Randomised Controlled Trials (RCTs)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author and year** | **Study design** | **Overall RoB rating** | **Bias arising from the randomization process** | **Effect of assignment to intervention** | **Effect of adhering to intervention** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported result** |
| CHERISH (Mercuri 2018) | Randomised parallel-group trial | Some Concerns | Some Concerns | Low | Low | Low | Low | Some Concerns |
| EMBRACE (Acsadi 2021) | Randomised, double-blind, sham procedure-controlled study. | Some Concerns | Some Concerns | n/a | Some concerns | Low | Low | Low |
| Finkel 2017 | Randomised parallel-group trial | High | High | Some Concerns | Low | Low | Low | Low |
| Mercuri 2022 | Randomised parallel-group trial | Some Concerns | Some Concerns | Low | Low | Low | Low | Low |
| SUNFISH Part 1 (Mercuri 2023) | Randomised parallel-group trial | Low | Low | Low | Low | Low | Low | Low |
| SUNFISH Part 2 (Oskoui 2023) | Randomised parallel-group trial | Some Concerns | Some Concerns | Low | Low | Some Concerns | Low | Low |

ROBINS-1:

23 non-randomised studies,52-74 including SHINE,69 were assessed using the ROBINS-1 tool.45 These were rated overall as serious n=1353, 54, 56, 59, 60, 62, 63, 65, 68, 69, 72-74 and moderate risk of bias n=10.52, 55, 57, 58, 61, 64, 66, 67, 70, 71 The most common domain rated as demonstrating risk of bias in non-randomised trials was selection of reported results (rated as serious in 4 studies53, 63, 69, 73 including SHINE69 and moderate in 7 studies55, 56, 58, 61, 62, 66, 68) and bias due to confounding (rated as serious in 8 studies54, 56, 59, 65, 67, 68, 72, 74 and moderate in 11 studies52, 53, 55, 57, 58, 62, 63, 70, 71, 73). Of note, due to the nature of non-randomised trials, the majority did not discuss the blinding of assessors and were therefore rated as moderate risk of bias on Bias in measurement of outcome. One study reported blinding68 and was rated as low risk of bias, and one study was rated as serious on this domain (SHINE).69

Table 8: Risk of bias for non-randomised trials (ROBINS-1)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author and year** | **study design** | **RoB tool used** | **Overall RoB rating** | **Bias due to confounding** | **Bias in selection of participants into the study** | **Bias in classification of interventions** | **Bias due to deviations from intended interventions** | **Bias due to missing data** | **Bias in measurement of outcomes** | **Bias in selection of the reported result** |
| Alruthia 2021 | "Cross sectional,  Questionnaire " | Robin | Moderate | Moderate | Low | Moderate | Low | Low | Moderate | Low |
| Alves 2021 | Longitudinal cohort study | Robin | Serious | Moderate | Low | Serious | Low | Low | Moderate | Serious |
| Chiriboga 2016 | Open-label, escalating dose phase 1 study | Robin | Serious | Serious | Low | Low | Low | Low | Moderate | Low |
| Duan 2022 | Non-randomised observational trial | Robin | Moderate | Moderate | Moderate | Low | Low | Low | Moderate | Moderate |
| Finkel 2021 | Phase 2, open-label, multicentre, dose-escalation clinical trial | Robin | Serious | Serious | Moderate | Low | Low | Moderate | Moderate | Moderate |
| Freigang 2021b | Prospective, multicenter observational study | Robin | Moderate | Moderate | Low | Low | Low | Low | Moderate | Low |
| Gaffar 2022 | Nonrandomised, two-part, phase 2-3, open-label interventional clinical trial: dose-escalation, dose-finding study | Robin | Moderate | Moderate | Low | Low | Low | Low | Moderate | Moderate |
| García de la Banda 2020 | Prospective study | Robin | Serious | Serious | Low | Low | Low | Low | Moderate | Low |
| Kroksmark 2023 | Prospective study | Robin | Serious | Low | Low | Moderate | Low | Low | Moderate | Low |
| Lee 2022 | Retrospective study | Robin | Moderate | NI | Low | Low | Low | Low | Moderate | Moderate |
| Li 2024 | Single-center retrospective case–control study | Robin | Serious | Moderate | Low | Serious | Low | Low | Moderate | Moderate |
| Mirea 2021 | observational study | Robin | Moderate | NI | Low | Low | Low | Low | Moderate | Low |
| Mirea 2022 | Retrospective observational study | Robin | Serious | Moderate | Low | Low | Low | Low | Moderate | Serious |
| Pane 2022 | Real-world data | Robin | Serious | Serious | Low | Low | Low | Low | Moderate | Low |
| Pechmann 2023 | SMArtCARE registry of longitudinal data used | Robin | Moderate | Moderate | Low | Low | Moderate | Low | Moderate | Moderate |
| Rich 2022 | "Retrospective analysis of samples collected during two trials (NCT04139343 and   NCT04591678) " | Robin | Moderate | Serious | Low | Low | Low | Low | Moderate | Low |
| Schneider 2021 | single-centre cross-sectional and longitudinal study | Robin | Serious | Serious | NI | Low | Low | Low | Low | Moderate |
| SHINE (Dunaway Young 2023) | Uncontrolled Before and After Study/Time Series | Robin | Serious | Low | Low | Low | Low | Low | Serious | Serious |
| Trancho 2024 | Observational study | Robin | Moderate | Moderate | NI | NI | NI | Low | Moderate | Low |
| Trucco 2023 | Multicentre cross-sectional prospective study | Robin | Moderate | Moderate | Moderate | Low | Low | Low | Moderate | Low |
| van der Heul 2020 | Prospective study | Robin | Serious | Serious | Serious | Moderate | Low | Low | Moderate | Low |
| Vazquez-Costa 2022 | Prospective observational study | Robin | Serious | Moderate | Low | Low | Low | Low | Moderate | Serious |
| Weaver 2021 | Observational cohort study | Robin | Serious | Serious | Serious | Moderate | Low | Low | Moderate | Low |

* + - 1. Intervention(s), Comparator(s), Outcome(s), Study perspective and Location & Setting

Characteristics of included studies can be found in Clinical Appendix 2. Included studies examined the clinical effectiveness of nusinersen and/or risdiplam. Risdiplam was the intervention being studied in n= 1049-51, 58, 75-80,81, 82 (including FIREFISH,75 JEWELFISH,76 RAINBOWFISH77 and SUNFISH part 1 and 249-51 and both nusinersen and risdiplam in n=2.61, 83 Onasemnogene abeparvovec was the intervention being studied in n=4 (SPR1NT 2 copies,84 SPR1NT 3 copies,85 STR1VE EU,86 STR1VE US.87) Nusinersen was examined in the remainer of the included studies n= 89.

Comparators were present in 29 of the included studies (the majority of included studies were single-arm or observational studies). Comparators included standard of care n=1,52 control groups n=1353, 55, 57, 59, 60, 62, 65, 67, 68, 70, 71, 73, 74 placebo or sham procedures n= 7 (EMBRACE,47 SHINE,69 ENDEAR,48 CHERISH,46 SUNFISH part 1 and 249-51), different doses of the intervention drug n=3,54, 56, 58 different interventions n=461, 63, 64, 72 and different cohorts n=1.66

Many studies examined multiple SMA types. Five studies examined presymptomatic SMA alone, NURTURE,88 RAINBOWFISH,77 SM201,89 SPR1NT 2 copies,84 SPR1NT 3 copies.85 15 studies examined type 1 SMA alone48, 58, 64, 72, 75, 86, 87, 90-97 (including ENDEAR,48 FIREFISH,75 STR1VE EU,86 STR1VE US87). Two studies examined type 276, 98 (including JEWELFISH76), 3 type 368, 99, 100 (including European Registries100), six studies examined type 1 and 247, 59, 79, 80, 101-103 (including EMBRACE47) and 25 type 2 and 346, 50, 54, 60, 62, 65, 71, 78, 81, 104-118 (including CHERISH,46 CS2/12,106 SUNFISH part 2,50). No studies examined type 4 alone. Many studies examined a mixture of SMA types: type 1,2,3 and presymptomatic was examined in four studies,53, 119-121 types 2,3 and 4 in two studies,73, 122 types 1,2,3 and 4 in six studies,123-128 types 2 and 4 in one study,129 type 3 and 4 in one study,130 types 1,2 and 3 in 23 studies52, 55, 57, 63, 69, 74, 83, 131-145 (including SHINE)69. All SMA types were examined in one study146 and SMA type was not reported in ten studies.56, 61, 66, 67, 70, 82, 147-150

Within the included studies, the majority (n=82) were conducted in one country: Germany n=17,57, 68, 78, 80, 103, 105, 108, 109, 114, 117, 118, 122, 123, 125, 140, 149, 151 US n=1353-55, 61, 67, 106, 135, 139, 148 STR1VE US74, 87 Italy n=8,65, 71, 90, 95-97, 99, 111 (including STR1VE US)87, Poland n=4,94, 119, 120, 152 UK n=3,79, 91, 150 Croatia n=3,81, 132, 143 France n=3,59, 101, 102 Japan n=3,126-128 Australia n=3,133, 136, 138 Romania n=3,63, 64, 131 Sweden n=2,60, 83 Korea n=2,110, 134 Netherlands n=2,72, 121 China n=2,55, 62 Turkey n=2,72, 142 Israel n=2,92, 107 Brazil n=293, 112 and one study from each of the following countries: Belgium,130 Hong-Kong,137 Hungary,144 Saudi- Arabia52 Spain,73 Switzerland145. The remaining studies were conducted in multiple countries, consisting of less than six countries n=1198, 147 EMBRACE47 European Registries56, 58, 66, 86, 100, 115, 124, 126, 146 (including EMBRACE47 and European Registries100) and six countries or over n=10 (CHERISH,46 ENDEAR,48 FIREFISH,75 JEWELFISH,76 NURTURE,88 RAINBOWFISH,77 SHINE,69 SPR1NT 2 copies,84 SPR1NT 3 copies,85 SUNFISH.50 Country was not reported in five studies70, 82, 89, 104, 113 (including SM201)89.

Setting of studies included Specific treatment centres for SMA n=24,55, 57, 61, 66, 71, 73, 80, 92, 93, 98, 101, 102, 108, 113-115, 119, 121, 131, 140, 141, 145, 151, 152 University hospitals n=18,54, 56, 64, 67, 68, 72, 86, 87, 105, 110, 117, 118, 125, 130, 139, 142, 143, 148 Hospitals or secondary care n=1946, 50, 60, 62, 69, 75, 78, 81, 84, 85, 88, 91, 93, 106, 109, 126, 137, 138, 150 (including CHERISH,46 CS/12,106 FIREFISH,75 NURTURE,88 SHINE,69 SPR1NT 2 copies,84 SPR1NT 3 copies,85 SUNFISH50), undefined clinical or health settings n=7,59, 95, 116, 120, 128, 144, 149 remote settings n=6,52, 79, 82, 83, 127, 132 Tertiary care setting n=4,133-136 medical schools or teaching centres n=4,63, 96, 122, 123 Registries n=365, 99, 146 EAP n=2,94, 97 outpatient settings n=2,58, 74 secondary/tertiary centre n=1,111 a medical centre n=1,107 and unspecified or un-reported setting n=1347, 48, 53, 70, 77, 89, 90, 100, 103, 104, 124, 129, 147 (including EMBRACE,47 ENDEAR,48 European Registries,100 RAINBOWFISH,77 SM20189).

* + - 1. Number and type of studies excluded

1,564 studies were excluded at full text stage. Full reasons for exclusion at full text stage are available on request.

* + 1. Assessment of effectiveness
       1. Critical review and synthesis of information

Included studies reported clinical effectiveness of nusinersen and risdiplam using several outcomes. These are taken in turn, grouped by SMA type. For more information on outcomes, please see Clinical Appendices 3 (motor function outcomes), 4 (other outcomes) and 5 (adverse events).

* + - * 1. Presymptomatic SMA

Five studies examined presymptomatic patients (NURTURE,88 RAINBOWFISH,77 SM201,89 SPR1NT 2 copies,84 SPR1NT 3 copies85).

***Motor function:***

Three studies examined motor function in presymptomatic patients (NURTURE,88 RAINBOWFISH77 and SM20189).

***CHOP INTEND:***

Improvements were seen on CHOP INTEND following nusinersen with mean scores of 62.1 (2 copies) and 63.4 (3 copies) in NURTURE88 and 7/18 patients achieving maximum scores in SM201.89 Risdiplam led to 57.1% achieving the maximum score, and 100% patients achieving 40 or more points (RAINBOWFISH)77.

***Hammersmith Infant neurological examination (HINE-2):***

Two studies examined scores of HINE-2. Following nusinersen, all patients had age-appropriate motor development, and 5/5 developed additional milestones at day 302. At the last study visit 13/18 had achieved maximum score SM201.89 Following risdiplam, 28.6% achieved the maximum score, and all developed complex motor abilities during the study (RAINBOWFISH)77.

***WHO motor milestones:***

Two studies examined WHO motor milestones following nusinersen treatment. All patients were able to sit without support, and all children who achieved milestones retained them at the last visit (NURTURE).88 Additionally, 5/7 patients were able to sit independently, 1/5 was able to stand unaided and one was able to walk with support. Amongst younger patients, two were able to stand with support (SM201)89.

***Compound Muscle Action Potential (CMAP):***

Amongst studies examining the effectiveness of nusinersen, CMAP score remained stable (NURTURE)88 and increased in 3/5 patients at day 302 (SM201)89. One study examining risdiplam showed increased CMAP in 5/7 patients (RAINBOWFISH)77.

***Bulbar function:***

Two studies examining presymptomatic SMA reported bulbar function. One examining the effectiveness of nusinersen (NURTURE)88 and one risdiplam (RAINBOWFISH)77. The majority of participants with presymptomatic SMA maintained their ability to swallow (NURTURE,88 RAINBOWFISH77) and feed orally (RAINBOWFISH)77. One study examined choking, with 76% (19/25) parents or caregivers not being concerned about their child choking at final assessment (NURTURE)88.

***Frequency or duration of hospitalisation:***

Only one presymptomatic SMA study reported frequency or duration of hospitalisation. RAINBOWFISH77 reported no hospitalisations during receipt of risdiplam during the study.

***Complications of SMA:***

***Weight:***

Of the five studies examining presymptomatic SMA, one reported weight (SPR1NT 2 copies).84 The majority of participants 13/14 (93%) were able to retain body weight during the study. No other growth parameters were reported for presymptomatic SMA.

***Need for ventilation:***

Two studies examining presymptomatic SMA (NURTURE88 and RAINBOWFISH77) reported the need for ventilation. No patients required permanent ventilation, and four patients receiving nusinersen required temporary ventilation following a short illness (NURTURE)88.

***Mortality/ survival:***

Of the five studies examining presymptomatic SMA, three assessed survival or mortality. Two of these examined nusinersen (NURTURE,88 SM20189) and one onasemnogene abeparvovec (SPR1NT 2 copies)84. All three studies reported 100% survival (NURTURE,88 SM201,89 SPR1NT 2 copies84) following treatment.

***Adverse events:***

Adverse events (AEs) were reported in four studies. One examining nusinersen (NURTURE),88 one examining risdiplam (RAINBOWFISH)77 and two examining onasemnogene abeparvovec (SP1NT 2 copies,84 SPR1NT 3 copies85). For nusinersen, 100% patients reported AEs, and 48% reported Serious Adverse Events (SAEs) (NURTURE)88. In risdiplam, 38.9% reported AEs related to skin/ tissue disorder and 50% related to gastrointestinal disorders. No SAEs or death were reported for presymptomatic patients receiving risdiplam (RAINBOWFISH).77 In patients receiving onasemnogene abeparvovec, 36% (SPR1NT 2 copies)84 and 20% (SPR1NT 3 copies)85 reported serious TRAEs. No AEs were definitely attributed to treatment in NURTURE,88 but AEs were related to treatment in SPR1NT 284 and 3 copies85.

***Summary of outcomes of effectiveness in presymptomatic SMA:***

There are limited studies included that examine pre-symptomatic SMA, and often few of them reported the outcomes of interest. From the available evidence both nusinersen and risdiplam appear effective for improving or stabilising motor function and motor milestones, stabilising bulbar function, and there was 100% survival and no need for permanent ventilation amongst presymptomatic patients. AEs were reported for all interventions, with some being attributed to treatment, and others being considered as not being treatment related.

* + - * 1. Type 1 SMA

15 studies examined type 1 SMA48, 58, 64, 72, 75, 86, 87, 90-97 (including ENDEAR,48 FIREFISH,75 STR1VE EU86 and STR1VE US87).

***Motor function:***

***Hammersmith Functional Motor Scale Expanded (HFMSE):***

Two studies examined HFMSE in Type 1 patients following nusinersen treatment. Both showed a significant increase in scores, one a mean increase from 14.7 to 18.8 at 48 months,97 and the other an increase of 1.60 points compared to mean decline in control group (-3.93 points) at 24 months.93

***CHOP INTEND:***

Seven studies including ENDEAR,48, 64, 93-97 examined the effect of nusinersen on CHOP INTEND in Type 1 patients. Overall scores on CHOP INTEND increased amongst the majority of patients but some also showed stabilisation of scores.64, 96, 97

Two studies examining effect of risdiplam on Type 1 CHOP INTEND scores showed an increase in scores (FIREFISH,75 Gaffar et al, 202258), with higher increases shown by patients receiving higher doses of risdiplam.58

***Six Minute Walk Test (6MWT):***

One study examined the effectiveness of nusinersen in the 6MWT. One participant improved and was able to walk 165m at 48 months.97

***Hammersmith Infant neurological examination (HINE-2):***

Four studies examined HINE-2 in Type 1 patients following nusinersen treatment. Amongst these studies, the majority of patients remained stable,95 21/68 patients reached the ability to sit,96 44.5% patients improved from baseline to 48 months97 and patients receiving nusinersen were classified as a responder (41%) on HINE-2 compared to control group (0%) (ENDEAR).48

Two studies examined HINE-2 in Type 1 patients following risdiplam. Patients demonstrated an overall increase in score, with higher doses leading to higher proportions of responders, and more patients with greater head control.58 An increased number of patients were recorded as achieving the highest motor milestone category (FIREFISH).75

***WHO motor milestones:***

Two studies examined WHO milestones following treatment with onasemnogene abeparvovec. In both, treatment groups performed better than control groups with 44% of the ITT cohort able to sit independently for 10 seconds compared to 0% in control group (STR1VE EU),86 and 59% in treatment group able to sit independently for 30 seconds compared to 0% in natural history group (STR1VE, US).87

***Compound Muscle Action Potential (CMAP):***

One study examined CMAP in Type 1 patients following nusinersen. 36% treatment group were classified as responders compared to 5% of the control group (ENDEAR).48

***Egen Klassification (EK2):***

One study examined EK2 in Type 1 patients following nusinersen, and reported 5/41 patients showed a change of at least 2 points.93

***Manual muscle testing (MMT):***

One study examined MMT in Type 1 patients following risdiplam, and reported a greater improvement in patients receiving risdiplam compared to placebo in patients aged between 2 and less than 6 years (FIREFISH).75

***Bayley Scales of Infant and Toddler Development III (BSID-III) gross motor subscale:***

One study examined BSID-III in Type 1 patients following risdiplam and showed 60% could sit without support for 5 or more seconds, and 40% could sit without support for 30 or more seconds (FIREFISH).75

***Bulbar function:***

Of the 15 studies examining type 1 SMA, eight measured bulbar function. In relation to feeding, eight reported this outcome, with three showing some improvement in feeding, one following nusinersen97 and two following risdiplam (Gaffar et al, 202258 and FIREFISH75).

Two studies examining nusinersen treatment showed no change90 or stability93 and three (all examining nusinersen) showing a decline in the ability to feed orally following treatment.72, 92, 96

Three of the seven studies reported swallowing, with one showing improved swallowing following risdiplam treatment,58 one showing a reduced deterioration following nusinersen90 and one showing a decline following nusinersen72 in swallowing following treatment.

***Frequency or duration of hospitalisation:***

One study reported frequency of hospitalisation in type 1 patients following treatment with risdiplam. The rate of hospitalisations per person per year was 0.94, and median duration was 17 nights (FIREFISH).75

***Respiratory function:***

Three studies examined the effectiveness of nusinersen on respiratory function in Type 1 patients. One study reported improvements in most patients,91 whilst one reported all patients needing to use respiratory support.92 A further study reported reduction in time on ventilatory support in the majority of patients.93

***Complications of SMA:***

***Scoliosis:***

One examined scoliosis in patients receiving nusinersen and showed worsening of scoliosis.92

***Growth:***

One study examining growth in patients with type 1 following onasemnogene abeparvovec reported more patients thriving than the natural history group (STR1VE US).87 One study examined growth in patients with type 1 following risdiplam. The median change from baseline in length- or height-for-age percentiles was -11 (FIREFISH).75

***Weight:***

One study examined weight in patients with Type 1 following risdiplam. The median change from baseline in weight-for-age percentiles was 3 (FIREFISH).75

***Need for ventilation:***

Seven studies examined type 1 patients’ need for ventilation. Amongst the two studies examining onasemnogene abeparvovec, treatment conditions showed higher rates of survival without the need for permanent ventilation than control conditions 97% vs 26% (STR1VE EU)86 and 91% vs 26% (STR1VE US)87. In two studies most participants did not need permanent ventilation following treatment, one when patients were treated with nusinersen (ENDEAR),48 where less patients receiving nusinersen than control patients needed permanent ventilation, and one when patients were treated with risdiplam (FIREFISH)75. Improvements were seen in patients receiving nusinersen64 where hours on ventilation reduced. Most patients receiving non-invasive ventilation remained stable in patients receiving nusinersen.97 Almost a quarter of patients receiving risdiplam (19-25%) did not require ventilation support.58

***Mortality:***

Four studies examined mortality or survival in type 1 patients. All studies showed most patients to be alive at follow-up. Amongst patients receiving nusinersen, 7/68 patients died96 and 84% patients survived (versus 61% in sham condition) (ENDEAR)48. Amongst patients receiving risdiplam, 93% were alive at follow-up (FIREFISH)75 and 4/21 died.58

***Adverse events:***

Ten studies reported adverse events (AEs) in Type 1 patients. In studies examining nusinersen, there were 96% patients reporting an AE compared to 98% in control (ENDEAR),48 2.4% patients,93 no patients compared to two in control,64 12 patients94 and 20.8% patients reported a SAE.97 In patients receiving onasemnogene abeparvovec, 100% patients reported AEs (STR1VE US)87 and 97% (STR1VE EU).86 In patients receiving risdiplam, 78% patients reported AEs (FIREFISH)75 and 202 AEs were reported.58

Eight studies examined serious AEs (SAEs). Of patients receiving nusinersen, 76% patients reported SAE compared to 95% in the sham condition (ENDEAR),48 one patient64 and seven patients96 died. Of patients receiving onasemnogene abeparvovec, 58% (STR1VE EU)86 and 45.45% (STR1VE US)87 reported SAEs. Of patients receiving risdiplam, 68% patients reported SAEs (FIREFISH)75 and 24 SAEs were reported.58

The most common AEs reported amongst nusinersen patients were headache,93, 97 fever, vomiting and loss of appetite,64 post lumbar puncture syndrome and respiratory problems.94 The most common AEs amongst risdiplam patients were respiratory related AEs (FIREFISH75 and Gaffar et al, 202258).

***Health related quality of life (HRQoL):***

Only one study examining the effectiveness of risdiplam on type 1 SMA examined HRQoL (FIREFISH).75 The Infant and Toddler Quality of Life Questionnaire (ITQOL-SF47) was used, and showed improvement in emotional health, temperament and mood, growth and development domains, no change in bodily pain/discomfort, parent impact on time limitation, family cohesion, overall health domains and a decline in physical abilities and general health perceptions.

***Summary of outcomes of effectiveness of Type 1 SMA:***

Evidence of effectiveness was available in 15 studies, but the number of studies reporting each outcome varied. Overall improvements were seen in motor function and bulbar function amongst type 1 patients. Few studies measured hospitalisation amongst this population, and there was mixed effectiveness reported for respiratory function. Ventilation was generally improved, and there was a high rate of survival across treatment. There were generally less AEs reported in patients receiving treatment compared to control conditions.

* + - * 1. Type 1 and 2 SMA

Seven studies,47, 59, 79, 80, 101-103 including EMBRACE,47 reported the effectiveness of type 1 and 2 SMA and two including JEWELFISH,76, 98 reported Type 2 alone.

***Motor function:***

***Hammersmith Functional Motor Scale Expanded (HFMSE):***

One study examining Type 2 patients only following nusinersen reported a significant increase in mean HFMSE scores, and a significant difference between the number of clinically meaningful increases in treated and untreated patients.98

***Revised upper limb module (RULM):***

One study examining Type 2 only following nusinersen reported a significant increase in scores between baseline and 12 months on RULM, and a significant difference between the number of clinically meaningful increases in treated and untreated patients.98

***CHOP INTEND:***

One study examining the effectiveness of nusinersen in Type 1 and SMA showed improvement on CHOP INTEND, with mean total scores increasing from 35.1 to 50.3.101

***Hammersmith Infant neurological examination (HINE-2):***

Three studies examined the effectiveness of nusinersen in Type 1 and 2 patients using the HINE-2. Two showed significant improvements in scores of more than 2 points in 7 patients,59 and significant improvements in head control, sitting, voluntary grasp, ability to kick supine, rolling, crawling and standing.101 Improvements were seen in infantile-onset patients receiving Nusinersen (78%) compared to sham (0%) responders, but in later-onset patients, more sham patients were able to stand (40% compared to 66% sham) (EMBRACE).47

***WHO Motor milestones:***

One study examined WHO milestones in Type 1 and 2 patients following nusinersen and reported 93% patients gained new milestones, two patients lost a motor ability and one remained stable.102

***Clinical Global Impressions of Improvement (CGI-I):***

One study examined CGI-I following nusinersen in Type 1 and 2 patients. More patients receiving nusinersen improved compared to those initially in the sham condition (EMBRACE).47

***Motor Function Measurement (MFM):***

Two studies examined MFM in patients with Type 1 and 2 following nusinersen. In one study one subscale showed a non-significant increase from 55-61%.59 The other study showed an increase in the median total score by 6 points.101

***Bulbar function:***

One study examining bulbar function in patients with type 1 and 2 SMA following treatment with nusinersen reported a non-significant increase in number of patients needing feeding support.101

***Respiratory function:***

One study examining respiratory function in patients with Type 1 and 2 following treatment with nusinersen, reported better respiratory muscle strength and significantly better forced vital capacity (FVC) in patients with type 2 SMA compared to control.59

***Need for ventilation:***

Three studies examined the effectiveness of nusinersen on type 1 and 2 patients’ need for ventilation. No change was seen in the number of patients needing ventilation support overall, but there was a non-significant increase in the number of patients needing ventilation support amongst patients with type 1 SMA.101 A further study showed an increase in the number of patients needing ventilation support in patients with 2 SMN2 copies, and a decrease in patients with 3 SMN2 copies.102 When examining time on ventilation in patients receiving nusinersen, longer time was spent receiving support in patients receiving sham condition (infantile-onset: 11.1%, later-onset: 43.8%) or sham then nusinersen (infantile-onset: 8.5%, later-onset 48.6%) compared to those receiving nusinersen (infantile-onset: 0%, later-onset: 17.6%) (EMBRACE).47

***Complications of SMA:***

***Growth:***

One study examined growth in patients with type 1 and 2 following nusinersen treatment. Mean weight, body length, head circumference, and chest circumference increased over time for participants in all groups (EMBRACE).47

***Adverse events:***

Four studies report adverse events in patients with type 1 and 2 SMA. Two examined the effectiveness of nusinersen and reported 95 AEs in 25 patients.101 A further study reported the most common AE as vomiting, reported by 29% patients receiving nusinersen and 14% patients receiving sham following nusinersen (EMBRACE).47 Two studies reported AEs following risdiplam, with more AEs reported amongst type 2 patients (85% vs 15% in type 179 and 100 AEs reported in type 2 vs 30 AEs reported in type 1).80 SAEs are reported in nusinersen with six patients dying,101 four SAEs79 and ten SAEs80 reported following risdiplam. One further study reported AEs in type 2 patients, with 92% reporting at least one AE, and 14% reporting SAEs (JEWELFISH).76

The most common AEs following nusinersen were AEs related to lumbar puncture procedure and headache,101 and following risdiplam treatment were respiratory, gastrointestinal, skin issues and headache.79, 80

***Health related quality of life* *(HRQoL):***

Only one study reported HRQoL in patients with type 1 and 2 SMA following nusinersen. Family/ caregiver HRQoL was measured, and there was no significant difference between treated and untreated patients. Fathers of treated children reported more negative impact on productivity at work and daily activities than fathers of untreated patients.103

***Summary of outcomes of effectiveness of type 1 and 2 SMA:***

Evidence on the effectiveness in type 1 and 2 patients was only based on six studies. These did not report all outcomes, so many outcomes were based on very few, or no studies making it hard to conclude the effectiveness of nusinersen and risdiplam for Type 1 and 2 SMA. Acknowledging the small number of studies, studies reporting the effectiveness of Type 1 and 2 SMA improved respiratory function but showed small or non-significant improvements in bulbar function or need for ventilation. Overall motor function improved following treatment, apart from one study where control group showed a greater increase in the proportion of later-onset patients able to stand.

* + - * 1. Type 2 and 3 SMA

23 studies examined type 2 and 3 SMA46, 49-51, 54, 60, 62, 65, 71, 78, 81, 104-113, 115-118 (including CHERISH,46 CS2/12,106 SUNFISH part 1 and 249, 50) and three studies examined type 3 only.68, 99, 100

***Motor function:***

***Hammersmith Functional Motor Scale Expanded (HFMSE):***

15 studies examined HFMSE in type 2 and 3 patients following treatment with

nusinersen. Four studies showed no change, or a stabilisation in scores of HFMSE following nusinersen,105, 113, 117, 118 and one showed initial improvements which were not sustained at 12 months.78 Improvements were observed in the remaining 11 studies, with treated patients showing more improvements than control groups (CHERISH46 and two other studies60, 112) and improvements reported following Nusinersen (eight studies, including CS2/12).54, 62, 65, 104, 106, 111, 115, 116

Two studies examined HFMSE in type 3 patients only following treatment with nusinersen. Treated patients showed significantly higher scores100 and significant improvements from baseline.99

Three studies examined HFMSE in type 2 and 3 patients following treatment with risdiplam. Both showed an increase, with 22.6% patients improving on at least one motor scale81 and a mean increase of 0.95 in favour of risdiplam (SUNFISH part 1 and 2).49-51

***Revised upper limb module (RULM):***

Eight studies examined RULM in Type 2 and 3 patients following nusinersen. No significant increase was observed in two studies.105, 118 One study showed a significant increase in type 2 patients, but not in type 3,65 and remaining studies, including CS2/12,106 showed an increase in RULM scores, or an increase in clinically meaningful improvements.106, 111, 115, 117 One study showed improvements of treated patients (4.2) compared to controls (0.5) (CHERISH).46

Two studies examined RULM in Type 3 only following nusinersen. Scores amongst treated patients increased whilst untreated decreased,100 and some studies showed increases up to 12 months of treatment.99

Three studies examined RULM in Type 2 and 3 following risdiplam. One showed significant improvements in RULM score (SUNFISH part 1 and 2),49-51 one showed no significant improvements,78 and one showed increases of more than 1 point in 5 patients, and decreases in one patient.81

***CHOP INTEND:***

One study examined CHOP INTEND scores in type 2 and 3 following nusinersen treatment and reported an overall mean increase of 2.37 points.112

***6 Minute Walk Test (6MWT):***

Three studies reported 6MWT in type 2 and 3 following nusinersen. In one study, 78% of patients showed a clinically meaningful improvement.104 A further study reported that 100% patients achieved a clinically meaningful improvement by day 1050, but 1/11 type 2 patients gained the ability to walk independently, and in type 3, 2/4 lost the ability to walk at baseline and regained it during treatment (CS2/12).106 Distance walked in the 6MWT increased significantly, with the rate of patients achieving a clinically meaningful increasing from 53% to 69% of patients.111

One study reported 6MWT in Type 3 only following nusinersen and showed no significant increase in scores.99

***WHO Motor Milestones:***

Two studies examined WHO milestones in type 2 and 3 following nusinersen, showing improvement in motor milestones. 20% gained at least one motor milestone compared to 6% in the control group (CHERISH)46 and 14.9% of young sitters and 1.3% of older sitters gained the ability to walk independently following treatment. Furthermore, no motor milestones were lost during nusinersen treatment.115

***Revised Hammersmith Scale (RHS):***

One study examining RHS in type 2 and 3 patients receiving nusinersen observed a significant increase at six months, but not beyond.107 One study examining RHS following risdiplam reported an increase in 2/6 patients, meaningful improvement in three patients and a decrease of one point by one patient.81

***Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R):***

Three studies reported on ALSFRS-R in type 2 and 3 patients following nusinersen. All three reported an increase of one point.104, 107, 117 In one of these, the increase was observed in type 3 only,104 and one the increase was observed in type 2 only.107

***Medical Research Council sum score (MRC-SS):***

Three studies examined MRC-SS in type 2 and 3 patients following nusinersen. Increases were seen in type 3 patients only,104 an average change of 3.9 points at 24 months in treated patients113 and significant increases in ambulatory patients only.116

***Compound Muscle Action Potential (CMAP):***

Two studies examined CMAP in type 2 and 3 following nusinersen. One showed an increase of 0.4mV in type 2 patients and 0.3 mV in type 3 patients (CS2/12),106 whilst the other showed no significant changes post nusinersen.62

One study examined CMAP in Type 3 only patients following nusinersen and found no significant differences between SMA patients and healthy individuals.68

***Egen Klassification (EK2):***

One study examined EK2 in patients with type 2 and 3 following nusinersen and showed improvement by at least two points in five patients.112

***Manual muscle testing (MMT):***

One patient examined MMT in type 2 and 3 following nusinersen and showed a significant increase at six and 14 months, but then no further increase.107

***Motor unit number estimation (MUNE):***

One study examined MUNE in type 2 and 3 following nusinersen and showed an increase for type 2 patients by 2.0 points, and a decrease for type 3 patients by 29.6 points (CS2/12).106

One study examined MUNE in type 3 only following nusinersen showed no significant differences overall.68

***Motor Function Measurement (MFM):***

One study examining MFM in type 2 and 3 patients following risdiplam showed improvements in 32% patients and stabilisation in 58% patients (SUNFISH part 1 and 2).49-51

***Grip Force Feedback System (GFFS):***

Two studies reported GFFS in type 2 and 3 patients following nusinersen. GFFS increased in all cohorts at follow-up118 and three patients reported increased hand strength.113

***Bulbar function:***

Five studies reported bulbar function in type 2 and 3 SMA patients. Four studies examined swallowing. In studies examining nusinersen, six patients improved whilst six worsened and no new swallowing impairments developed105 and minimal nusinersen patients needed treatment compared to all untreated patients.71 Two studies examined effectiveness of risdiplam on swallowing, similar numbers of patients improved and worsened following risdiplam.78, 81 One study examined feeding following nusinersen treatment with an increased need for tube feeding after treatment.115

***Frequency or duration of hospitalisation:***

Two studies examined the rate of hospitalisation in nusinersen. One patient needed hospitalisation104 and the rate of hospitalisation was 0.1 per patient in patients treated with nusinersen compared to 0.49 in the control group.112

***Respiratory function:***

Five studies examined respiratory function in type 2 and 3 patients. No significant improvement was seen in two studies of nusinersen107, 111 and one of risdiplam (SUNFISH part 1 and 2).49-51 FVC remained stable following nusinersen treatment109 and 10/15 patients reported improvement following risdiplam.81

***Complications of SMA:***

***Scoliosis:***

Scoliosis was examined in one study measuring effectiveness of nusinersen in type 2 and 3 patients. Worsening of scoliosis was seen in 12 non-ambulant patients following nusinersen treatment.112

***Weight:***

One study examined weight in patients receiving risdiplam in patients with type 2 and 3 SMA. 9/31 patients gained more than 5% body weight.81

***Hip and Knee motion:***

Hip and knee motion was examined in one study, and showed worsened motion in one type 2 and one Type 3 patient receiving nusinersen.60

***Need for ventilation:***

One study examined the need for ventilation amongst patients with type 2 and 3 receiving nusinersen. During treatment, 9% started occasional ventilation, none needed permanent ventilation and one discontinued ventilation.115

***Stamina and fatigue:***

One study examined fatigue in type 2 and 3 SMA patients receiving risdiplam, and showed reduction in fatigue after treatment.81

***Adverse events:***

Nine studies reported AEs in patients with type 2 and 3 SMA and two patients reported AEs in patients with type 3 only. Amongst patients with type 2 and 3, eight reported effectiveness of nusinersen. The majority, or all patients reported at least one AE in three papers (89%,54 100% (CS2/12),106 93% vs 100% in control group in CHERISH46), but low rates of AE were reported in other studies examining the effectiveness of nusinersen (reported in 3/37 patients,107 in 41.4% patients,111 in 4.2% patients,112 nine AEs reported,113 and AES reported in 64/256115). SAEs were reported by two studies, with 17% patients receiving nusinersen reporting a SAE vs 29% in control group in CHERISH,46 and 18% reporting a SAE in CS2/12.106

In studies examining AEs following nusinersen in type 3 only, there was a 1.3% discontinuation rate because of AEs,100 and no SAEs reported.99

One study reported effectiveness of risdiplam in type 2 and 3. 92.5% patients reported an AE compared to 91.7% in placebo group (SUNFISH part 1 and 2).49-51

The most common AEs reported for type 2 and 3 patients were post lumbar procedure syndrome (CS2/12),106 headache (six studies including CS2/12),54, CHERISH,46, 106, 107, 111-113 back pain including CHERISH,46, 54, 112 and respiratory and gastrointestinal difficulties.115 In one study examining type 3 only, headache, nausea and back pain were most reported.99

***Health related quality of life* *(HRQoL):***

HRQoL was reported in three studies of patients with type 2 or 3 SMA. Patients receiving nusinersen showed no significant change in the PedsQL GCS,54, 110 improvement in financial burden and decline on burden on time on ACEND.110 Patients receiving risdiplam showed no worsening in QoL following treatment.81

***Summary of outcomes of effectiveness of Type 2 and 3 SMA:***

23 studies examining the effectiveness of nusinersen or risdiplam in patients with Type 2 and 3 SMA, however most outcomes were reported by very low numbers of studies. Type 2 and 3 SMA patients showed improvements or stabilisation of motor function, minimal improvement in respiratory function, worsening of complications of SMA, an increased need in ventilation, and where reported, the majority, or all patients reported at least one AE.

* + - * 1. Mixed Type SMA

39 studies (including SHINE)69 reported the effectiveness of nusinersen on a mixture of SMA types52, 53, 55, 57, 63, 69, 73, 74, 104, 114, 119-146, 151, 152 and one reported the effectiveness of both nusinersen and risdiplam.83

***Motor function:***

***Hammersmith Functional Motor Scale Expanded (HFMSE):***

27 studies examined HFMSE in mixed SMA type following nusinersen. Six showed stabilisation of scores amongst most or all of patients.126, 130, 131, 136, 138, 146 One study showed both improvements and decline in HFMSE scores.145 The remaining studies (including SHINE)69 showed increases in HFMSE scores.63, 69, 73, 114, 119, 121, 124, 125, 127, 128, 132-134, 137, 139, 141-144, 152

***Revised upper limb module (RULM):***

13 studies examined RULM in mixed SMA types following nusinersen. One study showed improvement amongst paediatric patients and stabilisation in adult patients146 and one study showed increases in five type 2 patients and decreases in five patients, and increases in two type 3 patients, stabilisation in two patients and decreases in one.145 One study showed decrease of -2.40 points amongst patients that discontinued.114 The remaining studies (including SHINE)69 showed increases in RULM.69, 73, 124, 125, 130, 133, 137, 139, 144, 152

***CHOP INTEND:***

19 studies examined CHOP INTEND amongst patients with mixed SMA types following nusinersen. Two studies showed varied results with some unclear effectiveness126 and 67% patients remaining clinically stable.138 Patients receiving higher doses of nusinersen showed higher increases in CHOP INTEND scores,143 scores in non-sitters increased by six points,139 and significant increases were observed in type 1 and 2 patients, but not type 3 patients.141 Remaining studies (including SHINE)69 observed increased CHOP INTEND scores.63, 69, 119, 121, 129, 131-133, 136, 137, 142, 144, 145, 152

***Six Minute Walk Test (6MWT):***

12 studies examined 6MWT in mixed SMA type following nusinersen treatment. The majority of these studies showed improvement. Studies reported no significant increase in ambulatory patients,130 no significant increase in four patients,132 a worsening in 33% patients (along with a clinically meaningful increase of 50%).152 One study showed an increase amongst later-onset patients.128 The remaining studies reported increases in 27.2% paediatric patients and 26.5% adult walkers,146 and overall improvements or clinically meaningful increases.73, 124, 125, 127, 137, 144, 145

***Hammersmith Infant neurological examination (HINE-2):***

Eight studies examined HINE-2 in patients with mixed SMA type following nusinersen. Of these, scores were unchanged in two.121, 136 Scores were increased or the same137 and scores significantly increased in the first year, followed by stabilisation in years 2 and 3.134 Increased HINE-2 scores were seen,126-128 and increased numbers of patients reported head control and independent sitting (SHINE).69

***WHO Motor Milestones:***

Two studies examined motor milestones in mixed SMA types following nusinersen. Significant increases136 and stable or higher milestones in all patients (SHINE)69 were observed.

***Revised Hammersmith Scale (RHS):***

RHS was examined in one study of mixed SMA type following nusinersen and showed no significant increase in 12/17 type 3 patients.132

***Clinical Global Impressions of Improvement (CGI-I):***

Two studies examined CGI-I in mixed type SMA following nusinersen treatment. 62.3% patients’ scores improved and 37.7% were unchanged.127 64.1% and 61.5% treated patients improved.73

***Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R):***

Two studies examined ALSFRS-R in mixed SMA types following nusinersen. 67.3% improved scores and 32.7% remained unchanged.128 Treated patients experienced clinically meaningful improvements.73

***Medical Research Council sum score (MRC-SS):***

One study examined MRC-SS in mixed SMA type following nusinersen. There was a significant increase by 2.4-2.5 points, with type 3 or 4 patients scoring higher than type 2.130

***Compound Muscle Action Potential (CMAP):***

Three studies examined CMAP in mixed type patients following nusinersen treatment. Increases were seen across all three.53, 131, 138 Scores were higher in patients with 4 SMN2 copies compared to 2 or 3 SMN2 copies.53 Most significant increases were observed in type 1 patients.131

***Egen Klassification (EK2):***

One study examined EK2 in mixed type studies following nusinersen, and demonstrated a significant increase.73

***Timed Up and Go (TUG):***

One study examined TUG in mixed type SMA following nusinersen and showed that scores were faster over time.129

***Motor unit number estimation (MUNE):***

One study examined MUNE scores in mixed type SMA following nusinersen, and showed increased scores.138

***Grip Force Feedback System (GFFS):***

One study examined GFFS in mixed type SMA following nusinersen showed a significant increase in scores, and a significant higher dominant hand score.130

***Bulbar function:***

Bulbar function was reported in four studies of nusinersen, indicating a general worsening in relation to feeding, with more patients needing tube feeding or more support following nusineren treatment.55, 121, 132, 145

***Frequency or duration of hospitalisation:***

Two studies reported hospitalisation following nusinersen treatment. There was a slight increase in the rate of hospitalisation104, 136 and an increase in duration of hospitalisation from 2.88 days pre-treatment to 11.23 days post treatment.104

***Respiratory function:***

Eight studies reported respiratory function following nusinersen treatment. Four studies reported improvements in FVC and general respiratory function,73, 129, 130, 136 three reported no change following nusinersen treatment123, 133, 146 and one reported a decline in one patient following treatment.132

***Complications of SMA:***

***Scoliosis:***

Two studies examined the effectiveness of nusinersen on scoliosis, both showing worsening following nusinersen treatment.137, 141

***Weight:***

One study examined weight, and reported higher BMI in patients reporting weaning off nusinersen.122

***Need for ventilation:***

Eight studies reported the need for ventilation following nusinersen treatment. Seven of these reported an increase in the need for ventilation support during or following nusinersen treatment.55, 120, 121, 127, 136, 141, 145 Some studies reported patients being able to stop ventilation support during or following nusinersen treatment, but numbers were often low.121, 127, 128, 136

***Stamina and fatigue:***

Two studies reported fatigue following nusinersen. One reported increased fatigue during treatment,123 whilst one reported improvements in fatigue.146

***Mortality:***

Two studies reported survival/ time to death following nusinersen treatment. Median survival was 823 days, with ten patients dying during the study period,120 and median time to death was 73.0 weeks in patients receiving nusinersen compared to 22.6 weeks in patients receiving sham or sham then nusinersen. 58% of patients alive at SHINE baseline, were alive at the end of SHINE.69

***Adverse events:***

19 studies of mixed SMA types reported AEs during or following nusinersen treatment. Of these, the number of AEs reported varied, but some reported high rates of AEs (91% patients,124 77% patients,73 whilst others reported more moderate or low rates.104, 121, 125, 127-130, 132, 135, 139, 145, 146, 152 Seven studies report the presence of SAEs, although these are generally low incidents.73, 119, 127, 128, 132, 135, 141

The most common AEs reported in studies examining the effectiveness of nusinersen in studies with mixed SMA types were headache,104, 121, 124, 125, 127-130, 139, 152 back pain,73, 121, 124, 125, 130, 142, 152 lumbar puncture site pain104, 129 and post lumbar puncture syndrome.73, 124, 146

***Health related quality of life HRQoL:***

Nine studies reported HRQoL following nusinersen. Of these, four showed no significant difference as a result of nusinersen treatment on HRQoL,52, 74, 114, 122, 130 three showed improvements compared to before nusinersen or to control group55, 140, 151 and one study showed a change of -4.8 points on the SF36 scale.123

One study reported HRQoL following nusinersen and risdiplam.83

***Summary of outcomes of effectiveness of mixed SMA:***

In studies where patients had a mixture of SMA types, there was generally an improvement in motor function, an increased need for ventilation, a worsening of scoliosis, increased hospitalisation and a worsening of feeding ability.

* + - * 1. Unreported SMA Type

Eight studies examined the effectiveness of nusinersen in patients where SMA type was not reported.56, 66, 67, 70, 147-150 One examined the effectiveness of risdiplam82 and one examined nusinersen, risdiplam and onasemnogene abeparvovec.61

***Motor function:***

***CHOP INTEND:***

Four studies examined CHOP INTEND in patients with unreported SMA type following nusinersen. All four studies showed an improvement.56, 66, 149, 150

***Six Minute Walk Test (6MWT):***

Two studies examined 6MWT in unreported SMA type following nusinersen. One study showed a variable increase in distance walked,148 whilst the other reported that SMA patients achieved half the distance walked than control patients.70

***Hammersmith Infant neurological examination (HINE-2):***

Three studies examined HINE-2 in patients where SMA type is not reported, following nusinersen treatment. Sitters had more improvement than non-sitters (3 vs 1 point increase).147 In patients with 2 SMN2 copies, 63% patients showed incremental improvements in scores.56 Additionally, amongst patients with 2 SMN2 copies, all showed improvement, eight presymptomatic patients remained symptom free, and those with 3 SMN2 copies, one patient had delayed milestones, whilst all other patients remained asymptomatic with normal milestones.149

***WHO Motor Milestones:***

Two studies examined motor milestones in patients where SMA type was unreported, following nusinersen treatment. 25% patients achieved developmental motor milestones in cohort 1 compared to 53% in cohort 2.56 In a further study, 33% in the younger cohort and 10.9% in the older cohort gained the ability to sit independently, and no milestones were lost in any patients.66

***Compound Muscle Action Potential (CMAP):***

Three studies examined CMAP in patients with unreported SMA type following nusinersen treatment. All studies reported some increase in CAMP,56, 148, 149 with scores plateauing after day 568,56 and increases in symptomatic patients not reaching levels of asymptomatic patients.149

***Timed Up and Go (TUG):***

One study reported TUG following nusinersen where SMA type was unreported. SMA patients completed TUG in 21.3 seconds compared to control patients completing in 4.3 seconds.70

***Bulbar function:***

Two studies examined feeding in patients with unreported SMA type receiving nusinersen. The need for feeding tube increased during treatment,66 and one showed a decline in feeding score.150

***Frequency or duration of hospitalisation:***

One study examined hospitalisation in patients receiving nusinersen. 74.9% patients were admitted to hospital as a result of AEs.66

***Need for ventilation:***

Two studies examined the need for ventilation following nusinersen treatment. The number of patients needing ventilation increased from baseline.66, 150

***Mortality:***

Four studies examined the rate of death during nusinersen treatment in patients where SMA type was unreported. Two patients died in one study.149 Three patients died in each of two studies,66, 147 and five patients died.56 Mean age at death was reported as 46.3 months.66

***Adverse events:***

Four studies reported AEs in patients with unreported SMA type. Three of these were reporting AEs or SAEs in patients receiving nusinersen.56, 66, 147 A total of 239 AEs were reported in 74 patients,66 and the incidence of AEs reduced during treatment.56 SAEs were reported in two studies, with 3 SAEs147 and 101 SAEs56 reported.

One study reported 1588 AEs and 703 SAEs following treatment with risdiplam.82

The most common AEs following nusinersen were respiratory related AEs56, 66, 147 and gastroenteritis.66 The most common AEs in studies reported risdiplam treatment were gastrointestinal, procedural complications and disorders of the nervous system.82

***Summary of outcomes of effectiveness of mixed SMA:***

Only ten studies did not report the type of SMA in patients. There was a worsening of feeding ability and an increased need for ventilation. Motor function generally increased, but 6MWT and TUG were performed better in control patients. These results are limited in their contribution within this review, as it is not clear, or reported which SMA types these are referring to.

* 1. Gaps in the evidence

The EAG note there is limited evidence on the following areas:

Type 0 SMA

Type 4 SMA

Presymptomatic SMA

RCT evidence (for all SMA types).

The included literature revealed less available evidence/ publications on the clinical effectiveness of risdiplam.

Some outcomes were not reported as often (mortality, SMA complications, Stamina and Fatigue), making it difficult to make any conclusions about the effectiveness of treatment in relation to these outcomes.

There were not many studies eligible for inclusion in the SLR that examined relevant comparators. Most included studies were single arm studies, resulting in limited comparative evidence for different drugs (e.g. nusinersen vs risdiplam, or either nusinersen or risdiplam vs onasemnagene abeparvovec).

* 1. Discussion
     1. Summary of key results

The findings from the EAG’s systematic literature review on the effectiveness of nusinersen and risdiplam in treating SMA across various SMA types indicate significant improvements in motor function and milestones, with high survival rates and minimal need for permanent ventilation in presymptomatic and Type 1 patients. However, adverse events were common across all treatments and SMA types, with some serious cases reported. While motor function improvements were largely consistent, other health outcomes such as bulbar function, respiratory function, and the need for ventilation showed mixed results.

* + 1. Generalisability

Very few studies were based in the UK, with no studies focusing solely on UK patients. This creates some uncertainty around the generalisability of findings from this SLR, to UK patients. However clinical experts consulted on this have informed the EAG that standards of care for SMA and prognosis for SMA is similar across the countries involved in the trials, and so it is likely this is not a serious concern.

* + 1. Key issues/ uncertainties
* Evidence for the clinical effectiveness of nusinersen and risdiplam are largely based on single-arm studies- uncertainty around the robustness of this evidence.
* Bias in included studies is likely due to the lack of blinding in non-randomised studies (although it is acknowledged that this might partly be due in some cases to blinding not being reported rather than not completed).
* Limited evidence for the effectiveness of treatment for presymptomatic SMA patients.
* Limited evidence for the effectiveness of type 0 and type 4 SMA, but this is to be expected due to the dearth of research into these types. No included studies examined type 4 alone, but it was included in 9 studies looking at multiple SMA types.
* Adverse events were present across all treatments, with some serious cases reported.
* Due to time restraints, the EAG acknowledge potential limitation of the review in relation to quality assessment. This was only completed by one researcher, rather than the preferable approach of two researchers completing this independently. However, the EAG is confident in their findings as quality assessment was completed by experienced systematic reviewers.

1. Summary and critique of clinical evidence (clinical trials, company’s statistical analyses) submitted by companies/sponsors

This section will provide critique of the evidence used to assess the clinical effectiveness of nusinersen and risdiplam provided by each company. It will highlight any concerns regarding the methodology of the systematic literature reviews completed by the companies.

* 1. Critique of the methods of the company reviews
     1. Biogen submission

A systematic literature review (SLR), reported in detail in CS Appendix D, was conducted to identify published clinical studies of nusinersen, risdiplam or onasemnogene abeparvovec to treat SMA of any type, in any age group. Randomised and non-randomised, interventional and observational studies were included, however non-comparative observational studies with fewer than 100 participants were excluded. The eligibility criteria (CS Appendix D.1.5, Table 1) broadly match those in the NICE scope.

* + - 1. Search strategies

The searches were originally run in January 2023 and updated in October/November 2023. The search strategies were comprehensive and accurate. A good range of bibliographic databases and other sources were searched, including trials registers, websites of HTA and regulatory agencies, recent conferences and reference lists of recent systematic reviews (CS, Appendix D.2.1).

* + - 1. Excluded studies

The EAG checked the list of studies excluded at full-text screening (CS, Appendix D, Table E.1) against the eligibility criteria (CS, Appendix D.1.5, Table 1). Four published papers55, 71, 120, 153 and 1 conference abstract154 were identified that may have been wrongly excluded and may potentially have provided useful data for the review.

* + - 1. Critique of company’s review

The company SLR included 52 studies in 282 reports and reported outcomes for different SMA types separately (CS, Document B, Section B.2.1). The EAG note that there is limited evidence for the clinical effectiveness of pre-symptomatic SMA, with one study (NURTURE) available for the effectiveness of nusinersen in pre-symptomatic SMA (CS, Document B, Section B.2.1).

The EAG note concerns around study designs of included studies. There were in total five RCTs included in the company’s review, consisting of one for type 1 nusinersen, one for type 1 and 2 nusinersen, one for type 2 and 3 nusinersen and two for type 2 and 3 risdiplam. There were no RCTs for presymptomatic SMA eligible for inclusion in the review (CS, Appendix D, Section 3.1). The reliance on single-arm studies, or non-comparative observational studies raises some uncertainty around the results.

Included outcomes also varied. The only common outcomes for nusinersen and risdiplam trials were overall survival, treatment-related serious adverse events and mean change of HFMSE score. For overall survival and treatment- related SAEs there were no events in either trial- very limited RCT evidence for each type (CS, Appendix D, Section 3.2).

The EAG also notes that there are no studies included in the SLR that were conducted exclusively in the UK (CS, Appendix D, Section 5.1), but after consultation with clinical experts the EAG acknowledge that standards of care for SMA and prognosis for SMA is similar across the countries involved in the trials, and so it is likely this is not a serious concern. Also, there is limited information on baseline ventilation and baseline motor milestones in studies included in the review for type 1 and 2 SMA (CS, Appendix D, Section 5.1.3.2).

* + - 1. Critical appraisal of company’s clinical effectiveness evidence

The EAG note some concern around the risk of bias (RoB) of studies included in the SLR. All studies in the review (apart from three non comparative observational studies that were low risk) showed some RoB and most were rated as moderate-high risk of bias (CS, Appendix D, Section 5.2.1). This creates some uncertainty around the reliability of the reports of the clinical effectiveness of nusinersen.

RCTs were assessed using the Cochrane Risk of Bias Tool. All five RCTs were judged as having ‘some concerns.’ All five (ENDEAR, EMBRACE, SUNFISH 1, SUNFISH 2 and CHERISH) showed concern on *‘Bias arising from the randomisation process’* (CS, Appendix D, Section 5.2.1.1). Specifically, ENDEAR had an imbalance across arms relating to receiving ventilatory support, tending to favour placebo. EMBRACE showed an imbalance across arms receiving ventilatory support, median age at first dose, sex, ethnicity and SMN2 copy number varied between groups (this bias was deemed to be a consequence of small sample size). Time on ventilator at baseline was lower in nusinersen group (this bias was deemed to likely favour nusinersen group). CHERISH showed apparent baseline differences but a lack of statistical evidence of this. There were slight differences in age, sex, race, disease duration and motor milestones achieved (CS, Appendix D, Section 5.2.1.1).

Single-arm trials were assessed using the Joanna Briggs Institute (JBI) case series checklist. All 20 single-arm trials showed unclear risk of bias. The main area of concern was around the inclusion of participants. Unclear in all trials if participants were included consecutively. It was also apparent that if there was insufficient data, if patients were lost to follow-up or some clinical features were not included, they were not included. Statistical concerns included that historical controls were compared to study population, with differences often being observed between groups (CS, Appendix D, Section 5.2.1.2).

Cohort studies were assessed using ROBIN-I tool. Three cohort studies were rated as moderate, one as serious and one as critical risk of bias. Four were at risk of confounding due to differences in intervention and control groups at baseline, whilst the other was rated moderate due to poor reporting and excluded patients without follow-up data (CS, Appendix D, Section 5.2.1.3).

Non-comparative observational studies were assessed using the JBI tool. 15 were rated as high risk, four were unclear and three low risks. Patient inclusion (insufficient follow-up or adherence) or reasons for exclusions were unclear and contributed to the risk of bias rating. (CS, Appendix D, Section 5.2.1.4) D).

The EAG have replicated the company’s RoB conducted on five included RCTs in the SLR, using the Cochrane RoB tool. The EAG agree with the company’s ratings of risk of bias, except for one domain (Risk of bias due to deviations from the intended interventions) in one RCT,47 where the EAG consider there to be some concern over blinding of key trail personnel, but this does not affect the overall rating given to this study as ‘some concerns’. For five cohort studies, neither rated any as low risk, but the EAG rated three higher due to confounding and selection concerns. In single-arm studies, EAG and Biogen mostly agreed, differing in 4/11 cases due to EAG’s stricter view on statistical analysis with historical controls. For observational and case-series studies, the JBI tool was used by Biogen. The EAG replicated these studies, and their overall appraisals matched the company’s, though there were some discrepancies.

* + 1. Roche submission

An SLR of *“all published and ongoing trials in SMA Types 1, 2 and 3”* was undertaken in January 2018 and updated in January 2020, June 2021 and February 2023 (CS Appendix D.1). The review is therefore more than a year out of date. However, HTA documentation and grey literature was hand searched in October 2023 to identify anything new (CS Appendix D.1).

The SLR eligibility criteria (CS Appendix D.1, Table 3) differ from the NICE scope in that more interventions are included, and specific outcome measures tend to be listed rather than general outcomes. Sham is not listed as a comparator in the eligibility criteria, though trials with sham control are included (CS Appendix D.1, ‘Overview of the included studies’). Only English language studies were included. There was no limit on the size of eligible observational studies but “cross-sectional studies” and “case series/case reports” were excluded, however these study types are not clearly defined (CS Appendix D.1, Table 3).

* + - 1. Search strategies

A broad, appropriate range of bibliographic databases and other sources were searched for the clinical SLR, including conferences, HTA and regulatory agencies’ websites and trial registries (CS, Appendix D.1, Table 1). The search strategies are not reported, presumably they are the same as those run in January 2020 for TA755, however they are not available in the online CS report for TA755.155 The ERG report for TA755 identified some shortcomings in the company’s search strategies (section 4.1.1) but concluded that no relevant studies had been missed from the submission (section 4.2.2).42 Likewise, for the current submission, the company is likely to be aware of the main studies of SMA treatment appropriate for treatment comparisons, and this, alongside the range of sources searched, should have ensured that no important, relevant studies were missed. However, as the searches have not been re-run since February 2023, there is the possibility that more recent publications or conference presentations providing additional relevant data for key studies were missed.

* + - 1. Excluded studies

The EAG checked the list of studies excluded at full-text screening (CS, Appendix D.1, Table 3) against the eligibility criteria (CS, Appendix D.1, pages 11-12). One published paper153 and one conference abstract156 were identified that may have been wrongly excluded and may potentially have provided useful data for the review.

* + - 1. Critique of company’s review

According to Figure 2 of CS Appendix D, 2050 records were identified, with 143 duplicates. After screening and exclusion, 230 primary studies remained, comprising 37 trials and 193 observational studies. The trials were classified by SMA type: three presymptomatic, eight SMA type 1, 12 type 2/3, and 14 mixed. The observational studies, however, lacked presymptomatic studies and were mostly mixed SMA types. The EAG noted limited evidence for the clinical effectiveness of pre-symptomatic SMA and nusinersen, with two-thirds of the studies unfinished. The 37 clinical trials included 18 single-arm studies, 11 RCTs, seven DC/DE trials, and one non-RCT trial. The reliance on single-arm or non-comparative observational studies introduces uncertainty around the results. Most studies focused on nusinersen, with a few evaluating risdiplam, raising concerns about the conclusiveness of risdiplam’s efficacy due to limited evidence. The studies were conducted primarily in North and South America, with some in Europe and Asia, including the UK. The EAG noted the lack of studies specifically investigating the UK population, including ethnicity and the potential impact on treatment efficacy and metabolism. The company reported that only 23/37 trials and 8/193 observational studies were treatment-naive, raising concerns about the reliability of the results due to potential accumulation effects of the drug molecules and possible adverse effects or biased treatment effects. The company also asserted that the well-documented clinical phenotype of Type 1 SMA was used to contextualize the key efficacy results from the FIREFISH study. However, no data or information was provided regarding other main trials such as RAINBOWFISH or JEWELFISH. In the FIREFISH Part 2 study for infantile-onset, Type 1 SMA, 52 patients were screened, with 11 failing to meet the criteria. At the time of the CCOD, 38 of 41 patients (92.7%) were still in study. In the SUNFISH Part 2 study for later-onset, Type 2/3 SMA, a total of 180 patients were enrolled across 14 different countries. 120 patients were randomized to treatment with risdiplam and 60 patients to placebo treatment. At the time of the CCOD, 4 patients had discontinued the study during the placebo-controlled period: 3 patients (2.5%) in the risdiplam arm, and 1 patient (1.7%) in the placebo arm. The EAG did not consider the discontinuation rate to be a significant concern.

* + - 1. Critical appraisal of company’s clinical effectiveness evidence

The company offers a concise table of the risk of bias tool for clinical trials in Table 16 B.2.5. The comprehensive version of the risk of bias, which is identical to the one used for Health Technology Assessments (HTAs), is provided in the CS appendix D.3 Table 4. This table addresses several crucial aspects of a study, including the randomisation process and its appropriateness, ensuring that each participant had an equal opportunity of being assigned to any group.

The table also briefly and superficially covers other aspects such as the concealment of treatment allocation, baseline imbalances and similarities of groups, blinding, and dropouts. The risk of bias tool, with the mentioned questions, serves as an instrument for evaluating the internal validity of a clinical trial. However, it has limitations and cannot cover all aspects of a study.

The tool does not assess the generalizability of the results to other populations or settings, the reliability of the data collection methods used in the study, and all aspects of study designs, such as the appropriateness of the study type for the research question or the adequacy of the sample size. Some items, like the adequacy of blinding or the handling of missing data, can be somewhat subjective and may vary between reviewers.

Moreover, while the tool provides a list of potential sources of bias, it does not offer detailed guidance on how to assess each item, which can be challenging for less experienced reviewers. The EAG acknowledges these points and suggests that the following tools should be used in conjunction with other tools and considerations, or the company should have followed more thorough and detailed tools such as Cochrane's Risk of Bias tool.44 The company only applied the risk of bias tool for the trials and did not provide an evaluation for other types of studies.

According to the details of clinical trials quality assessment in D.3.Table 4, information on the RoB was provided for seven trials. All of them were considered incomplete, and the company provided no further information or details in this regard. There were imbalances in dropouts in two studies, including the SUNFISH, which leads to a high risk of bias.

Regrettably, the scant and insufficient data that the company provided, along with a very poor tool, calls into question the reliability of the quality assessment presented. It is highly biased and not concrete enough to be considered as a source by the EAG. Furthermore, the FIREFISH, RAINBOWFISH, and the JEWELFISH are not reported. No conclusion of the RoB is reported.

The EAG intended to replicate the Risk of Bias conducted in the Roche submission, however this was not possible as it was unclear which studies the appraisal related to. Two RCTs stated author surnames of the included study, but these were not able to be located within the reference pack, and others were listed by trial name. It was not clear which specific publications were appraised for each of these trials. Therefore, the EAG has not replicated the RoB conducted by the company.

* 1. Overview of evidence for the assessment of clinical effectiveness

The sources of evidence for the assessment of the clinical effectiveness of relevant treatments are the following.

For nusinersen: ENDEAR, CHERISH, SHINE, NURTURE, and real-world evidence (RWE).

For risdiplam: FIREFISH, SUNFISH, RAINBOWFISH, and REACH registries.

Table 9 presents the study designs of these pivotal trials that supported the application for marketing authorisation. ENDEAR, CHERISH, and SUNFISH were phase III RCTs comparing either nusinersen or risdiplam to placebo at a sample size ratio of 2:1. The population of ENDEAR was type 1, for CHERISH and SUNFISH it was types 2 and 3. The remaining were single-arm studies looking at a combination of efficacy, safety, and tolerability of the active treatments.

The designs of the present studies are slightly narrower compared to the final NICE scope as both submissions exclude evidence for type 0 and type 4 SMA. Both submissions have justified the omissions; the life-expectancy of type 0 SMA is less than six months and the paucity of evidence for type 4 SMA.

Table 9: Summary of studies included in the economic modelling of nusinersen or risdiplam

|  |  |  |  |
| --- | --- | --- | --- |
| **Trial** | **Type** | **Trial population** | **Sample size** |
| **Nusinersen** | | | |
| ENDEAR | Phase III sham-controlled RCT | Type 1 | Nusinersen = 80  Sham-control = 41 |
| CHERISH | Phase III sham-controlled RCT | Type 2 and 3 | Nusinersen = 84  Sham-control = 42 |
| SHINE | Open-label extension of ENDEAR and CHERISH single-arm | Type 1, 2, 3 | Type 1 from ENDEAR: Nusinersen = 65; sham = 24  Type 2/3 from CHERISH: nusinersen = 83; sham = 42 |
| NURTURE | Phase II open-label single-arm | Pre-symptomatic | 2 SMN2 gene copies = 15  3 SMN2 gene copies = 10 |
| MAA | Real-world evidence single-arm | Type 1, 2, 3 | Type 1 EAP enrolled = 46  Type 1 not EAP enrolled = 32  Type 2/3 non-sitters = 21  Type 2/3 sitters = 88  Type 2/3 walers = 30 |
| **Risdiplam** | | | |
| FIREFISH | Phase II/III single-arm | Type 1 | Risdiplam = 41 |
| SUNFISH | Phase II/III placebo-controlled RCT | Type 2 and 3 | Risdiplam = 120  Placebo = 60 |
| RAINBOWFISH | Open-label extension single-arm | Pre-symptomatic | Per-protocol  SMN2 copy number 2 = 5  Intent-to-treat  SMN2 copy number 2 = 8  SMN2 copy number 3 = 13  SMN2 copy number >= 4 = 5 |
| MAA, managed access agreement; RCT, randomised-controlled trial | | | |

* + 1. Intervention(s)

ENDEAR, CHERISH, and SHINE used nusinersen. In ENDEAR, 12 mg doses of nusinersen were administered as a single intrathecal lumbar puncture (LP) injection, with loading doses administered on study days 1, 15, 29, and 64, followed by maintenance dosing once every four months. In CHERISH, there were three loading doses for nusinersen on days 1, 29, and 85 followed by a maintenance 12 mg dose on day 274 administered as a single intrathecal LP injection. In SHINE, nusinersen 12 mg was administered every four months if they were already on nusinersen from ENDEAR or CHERISH. For sham-control patients joining SHINE, they were put on a loading phase before joining the above regimen.

FIREFISH, SUNFISH, and RAINBOWFISH used risdiplam. Risdiplam is taken orally once a day using a reusable oral syringe at around the same time each day.

* + 1. Comparator(s)

As noted previously, ENDEAR, CHERISH, and SUNFISH were the only studies with comparators, which was placebo in these three trials. After the placebo-controlled parts of ENDEAR and CHERISH were completed, the final dose being on day 302 and 274 respectively, both control groups joined SHINE. SUNFISH was placebo-controlled for the first 12 months of the study before becoming a single-arm open-label extension from months 13 to 60 where the placebo group was administered risdiplam.

* + 1. Population

The NICE final scope specified the population of this appraisal as “people with types 0, 1, 2, 3, or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies”.  The population in both submissions addressed the presymptomatic SMA and SMA types 1, 2, and 3 only. Type 0 was not included as the treatment of type 0 SMA was deemed ‘futile’ by clinical experts consulted by Biogen and since they have an untreated lifespan of under six months with no achieved motor milestone. Type 4 was omitted due to the paucity of evidence surrounding this type.

The evidence for the clinical effectiveness of nusinersen and risdiplam for the type 1 SMA population came from ENDEAR and FIREFISH, respectively. The mean age at SMA diagnosis in ENDEAR was 12.6 weeks in the nusinersen arm and 17.5 weeks in the control group. The median age at SMA diagnosis in FIREFISH was 2.79 months, which is roughly 12.1 weeks, similar to the intervention group of ENDEAR. Patients were enrolled to the nusinersen arm of ENDEAR around day 163, and to FIREFISH at around 5.32 months, or 162 days – again, similar between trials. Disease duration was slightly higher in FIREFISH compared to the nusinersen arm of ENDEAR (14.7 weeks vs 13.2 weeks). Both intervention arms had a similar proportion of women and proportion on ventilation. There were differences in baseline CHOP-INTEND score and the mean HINE-2 score of ENDEAR was similar to the median HINE-2 score of FIREFISH. ENDEAR reported both peroneal and ulnar CMAP amplitude compared to FIREFISH which reported ulnar CMAP amplitude. Comparing the ulnar CMAP amplitudes, the value from FIREFISH is slightly smaller than that of ENDEAR. Table 10 presents the common baseline characteristics of the nusinersen and risdiplam arms of ENDEAR and FIREFISH. Full baseline characteristics for ENDEAR are presented in the Biogen submission Table 9, and for FIREFISH in the Roche submission Table 6.

Table 10: Baseline characteristics of the nusinersen and risdiplam arms of the pivotal trials for SMA Type 1 which were presented in both submissions

|  |  |  |
| --- | --- | --- |
|  | **ENDEAR** | **FIREFISH** |
| Treatment | **Nusinersen** | **Risdiplam** |
| Sample size | 80 | 41 |
| Age at enrolment (days) |  | 162A |
| Age at first dose (days) | 163 |  |
| Age at SMA diagnosis (weeks) | 12.6 | 12.1B |
| Disease duration (weeks) | 13.2 | 14.7B |
| Female (%) | 54 | 53.7 |
| CHOP-INTEND score | 26.63 | 11 |
| HINE-2 score | 1.29 | 1 |
| CMAP amplitude | 0.371 / 0.226C | 0.19D |
| Use of ventilation (%) | 26 | 26.8 |
| A converted from months to days  B converted from months to weeks  c Peroneal and ulnar CMAP amplitude, respectively  0 Ulnar CMAP amplitude  ENDEAR reported means while FIREFISH reported median values. | | |

The evidence for the effectiveness of nusinersen and risdiplam for SMA types 2 and 3 came from CHERISH and SUNFISH, respectively. The median age of participants was younger in CHERISH compared to SUNFISH. The oldest participant in CHERISH was 9 years old compared to 25 years in SUNFISH, however the median age of symptom onset was similar between both groups. More than half of the participants in both arms were female, and the most frequently occurring SMN2 copy number was copy number 3 at almost 90% for both groups. Table 11 presents the common baseline characteristics of the nusinersen and risdiplam arms of CHERISH and SUNFISH. Full baseline characteristics for ENDEAR are presented in the Biogen submission Table 11, and for FIREFISH in the Roche submission Table 7.

Table 11: Baseline characteristics of the nusinersen and risdiplam arms of the pivotal trials for SMA Types 2 and 3 which were presented in both submissions

|  |  |  |
| --- | --- | --- |
|  | **CHERISH** | **SUNFISH** |
| Treatment | Nusinersen | Risdiplam |
| Sample size | 84 | 120 |
| Age at screening (years) | 4 | 9 |
| Age at symptom onset (months) | 10 | 12.3 |
| Age at SMA diagnosis (months) | 18 |  |
| Disease duration (months) | 39.3 |  |
| Female (%) | 55 | 50.8 |
| SMN2 copy number (%) |  |  |
| 2 | 7 | 2.5 |
| 3 | 88 | 89.2 |
| 4 | 2 | 8.3 |
| Unknown | 2 |  |
| Continuous variables presented as medians in both submissions | | |

NURTURE and RAINBOWFISH were used for the clinical effectiveness of nusinersen and risdiplam, respectively, in the presymptomatic population. These were presented by SMN2 copy number with RAINBOWFISH also presenting results of the primary efficacy set and the ITT set separately. The only common characteristics presented in both submissions for this population were age at first dose and gender. Table 12 presents the common baseline characteristics of the nusinersen and risdiplam arms of NURTURE and RAINBOWFISH. Full baseline characteristics for NURTURE are presented in the Biogen submission table 18, and for RAINBOWFISH in the Roche submission Table 8 (primary efficacy population) and Table 9 (ITT population).

Table 12: Baseline characteristics of the nusinersen and risdiplam arms of the pivotal trials for presymptomatic SMA which were presented in both submissions

| **Trial** | **NURTURE** | | **RAINBOWFISH** | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **SMN2 copy number** | 2 | 3 | 2 | 2 | 3 | 4+ |
| **Treatment** | Nusinersen | Nusinersen | Risdiplam | Risdiplam | Risdiplam | Risdiplam |
| **Population** | ITT | ITT | Primary efficacy | ITT | ITT | ITT |
| **Sample size** | 15 | 10 | 5 | 8 | 13 | 5 |
| **Age at first dose (days)** | 19.5 | 22.3 | 25.8 | 23.9 | 29.9 | 32.4 |
| **Female (%)** | 47 | 60 | 60 | 50 | 69.2 | 60 |
| Continuous variables presented as means in both submissions | | | | | | |

* + 1. Outcomes reported from the pivotal trials

Table 13 presents the results of the statistical analysis of the primary outcomes and common secondary outcomes from ENDEAR and FIREFISH. The primary outcomes of ENDEAR were proportion of motor milestone responders, assessed using HINE-2, and event-free survival. The final analysis, over half of the nusinersen group achieved a motor milestone compared to zero patients in the control group. Although the numbers of participants who achieved event-free survival per group in ENDEAR were not reported in document B, treatment with nusinersen led to a 47% reduction in odds of death or permanent ventilation. The primary outcome of FIREFISH was the proportion of participants on risdiplam who achieved sitting without support and tested this proportion against a pre-determined 5% criterion. At 24 months, the proportion of participants who achieved this outcome was 61%, translating to a statistically significant p-value of less than 0.0001 compared to the pre-determined criterion.

Key secondary outcomes which could be compared between the two groups include event-free survival from FIREFISH, and CHOP-INTEND responders, both of which significantly favour the intervention groups against either placebo or a pre-determined criterion. Full results are presented in section B.2.4.1 in the Biogen submission and section B.2.6.1 in the Roche submission.

Table 13: Results of the analysis of the primary and key secondary outcomes for SMA type 1

|  | **ENDEAR** | **FIREFISH** |
| --- | --- | --- |
| **Treatment** | Nusinersen | Risdiplam |
| **Primary outcomes** |  |  |
| **Motor milestone responders (%)** |  |  |
| Interim analysis | 41% vs 0% (p<0.0001) |  |
| Final analysis | 51% vs 0% |  |
| **Event-free survival** |  |  |
| Final analysis | HR = 0.530 (p=0.0046) |  |
| 12 months |  | 85.37% |
| 24 months |  | 82.93% |
| **Sitting without support (vs 5% criterion)** |  |  |
| 12 months |  | 29.3% (p<0.0001) |
| 24 months |  | 61.0% (p<0.0001) |
| **Secondary outcomes** |  |  |
| **CHOP-INTEND (4+ score change from baseline)** |  |  |
| Day 394 | 71% vs 3% (p<0.0001) |  |
| 12 months |  | 90.20% |
| 24 months |  | 90.20% |
| **Survival** |  | 38/41 |

Table 14 presents the results of the statistical analysis of the primary outcomes and common secondary outcomes from CHERISH and SUNFISH. The primary outcome of CHERISH was the change from baseline in HFMSE score at 15 months. The score in the nusinersen group increased by a mean of 4 points, compared to a decrease of almost 2 points in the control group. This outcome was a secondary outcome in SUNFISH. At 52 weeks, there was no significant difference between groups but there was a significant difference at 104 weeks, with a mean difference of 2.15 points in the risdiplam arm compared to control. The primary outcome of SUNFISH is the change form baseline in MFM32 score with a mean difference of 1.83 favouring risdiplam. The other common outcome between the two trials was the change in baseline in RULM score. At 15 months, the mean difference was between the nusinersen and control arms was 3.7, and at 52 weeks for the comparison between risdiplam and control, the mean difference was 1.59. Both results were statistically significant. Full results are presented in B.2.4.2 in the Biogen submission and section B.2.6.2 in the Roche submission.

Table 14: Results of the analysis of the primary and key secondary outcomes for SMA types 2 and 3

|  |  |  |
| --- | --- | --- |
| **Primary** | **CHERISH** | **SUNFISH** |
| **HFMSE score CFB** |  |  |
| 15 months | 4.0 vs -1.9 (p<0.0001) |  |
| 52 weeks |  | Mean diff = 0.58 (p=0.3902) |
| 104 weeks |  | Mean diff = 2.15 |
| **MFM32 score CFB** |  |  |
| Week 104 |  | Mean diff = 1.83 |
| **Secondary** |  |  |
| **RULM score CFB** |  |  |
| 15 months | Mean diff = 3.7 (p<0.0001) |  |
| 52 weeks |  | Mean diff = 1.59 (p=0.0469) |

Table 15 presents the results of the statistical analysis of the primary outcomes and common secondary outcomes from NURTURE and RAINBOWFISH. The primary outcome of NURTURE was time to death or respiratory intervention, of which there were no events in either of the SMN2 2- or 3-copy number groups. The primary outcome of RAINBOWFISH in the primary efficacy population was the proportion achieving sitting without support for five seconds. 80% (4 out of 5) of patients achieved this outcome. Both studies used CHOP-INTEND. Those with 3 or 4 SMN2 copy numbers achieved a score of 60. Of the SMN2 2-copy numbers in NURTURE, four participants achieved a maximum score of 64, but only three of the eight participants from RAINBOWFISH achieved a score over 60.

Table 15: Results of the analysis of the primary and key secondary outcomes for presymptomatic SMA

| **Trial** | **NURTURE** | | **RAINBOWFISH** | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **SMN2 copy number** | 2 | 3 | 2 | 2 | 3 | 4+ |
| **Population** | ITT | ITT | Primary efficacy | ITT | ITT | ITT |
| Primary outcome |  |  |  |  |  |  |
| Time to death or respiratory intervention (Feb 21 data-cut) | No events | No events |  |  |  |  |
| Sitting without support for 5 seconds |  |  | 80% (p<0.0001 vs 5% criterion) |  |  |  |
| **CHOP-INTEND** |  |  |  |  |  |  |
| Achieved maximum score of 64 | 80% | 100% |  |  |  |  |
| Achieved score >= 40 |  |  |  | \*\*\* | \*\*\* | \*\*\* |
| Achieved score >= 50 |  |  |  | \*\*\* | \*\*\* | \*\*\* |
| Achieved score >= 60 |  |  |  | \*\*\* | \*\*\* | \*\*\* |

* + 1. Outcomes reported in the economic model

Both submissions fitted parametric survival models to time-to-event data in order to enable long-term extrapolations estimations. Biogen fitted parametric survival curves to overall survival (presymptomatic and SMA type 1) and time-to-permanent ventilation (SMA type 1). Roche fitted survival curves to ventilation-free survival (SMA type 1), and overall survival (SMA Type 1 and 2/3). These are discussed further in section 4.6.2. Table 16 reports the clinical effectiveness inputs used in the economic model, by SMA population, and the source of each result. The Biogen models were used to compare the cost effectiveness of nusinersen to BSC, thus they did not include clinical effectiveness inputs for risdiplam and onasemnogene abeparvovec. On the other hand, the Roche models compared risdiplam to nusinersen, onasemnogene abeparvovec, and BSC, thus had inputs for all three comparators.

The baseline characteristics used in each model for each population were from the pivotal trials discussed previously, except for the SMA type 3 model for nusinersen which used baseline characteristics from Wadman et al,38 which investigated muscle strength, motor function, and patterns of muscle weakness in 180 patients with SMA types 1-4 in The Netherlands between 2010 and 2016.

In the Biogen models, the clinical effectiveness of nusinersen versus BSC mainly came from the pivotal trials included in the submission, except for BSC for the presymptomatic population. The distribution of SMA types came from Calcuho et al.157 and data on motor milestones were calculated using a weighted average of the BSC data applied to SMA types 1, 2, and 3 in the other economic models. This was done because the presymptomatic population will end up having one of these types of SMA.

In the Roche models, the clinical effectiveness of risdiplam came from the results of the pivotal trials. For the SMA type 2/3 population, this included the results of all SUNFISH participants excluding Asian participants, due to potential differences in standard of care in Asian regions. These models included the effectiveness of BSC from the same pivotal trials except for the presymptomatic population where BSC was excluded. The clinical effectiveness of nusinersen and onasemnogene abeparvovec were also included in some of these models. In the presymptomatic model, nusinersen and onasemnogene abeparvovec were assumed to have equal efficacy to risdiplam. In the SMA type 1 model, the effectiveness of nusinersen was based on the results of the MAIC on the HINE-2 endpoint, and for onasemnogene abeparvovec on the unanchored MAIC on the BSID-III endpoint of STR1VE-EU. In the SMA type 2/3 model, only the effectiveness of nusinersen was included, which was based on the results of the MAIC conducted on RULM.

The per-cycle probability of decline for nusinersen in the presymptomatic model was based on data from NURTURE, with BSC using data from ENDEAR and CHERISH. In the type 1 and 2/3 models, probability of decline for BSC was based on results from Wadman et al. with the probability of decline for treatment with nusinersen based on results from ENDEAR or CHERISH. The probability of decline for risdiplam treatment came from the respective pivotal trials. Only in the SMA type 1 model did it include probabilities for the other comparators. The probabilities of decline for nusinersen and onasemnogene abeparvovec were based on results from the ITC provided in document B, and for BSC the probability came from TA755.

Time-to-permanent ventilation was included in presymptomatic and SMA type 1 models only.  Results from ENDEAR and SHINE were used for this endpoint in the type 1 model for both nusinersen and BSC, and results from HST24 using Wijnigaarde et al.158 were used for BSC in the presymptomatic model. FIREFISH was used for this endpoint for the type 1 model for risdiplam. In the presymptomatic model, data from national life tables were used for risdiplam and all three comparators were assumed to have the same time-to-permanent ventilation.

In the Biogen models, overall survival was assumed to be the same between nusinersen and BSC. The presymptomatic model used data from HST24, the type 1 model used data from ENDEAR and SHINE, and the type2/3 model used data from Wijngaarde at al.158 The Roche models used the same sources for this endpoint as the time-to-permanent ventilation outcome. The type 2/3 Roche models reconstructed survival IPD from six studies which were pooled and applied a HR of 0.75 in favour of risdiplam for survival when treated with BSC.

There was no discontinuation assumed when treated with risdiplam. The Biogen models used data from the MAA for discontinuation from nusinersen for all SMA types, except the type 1 model, which used the MAA data for not sitting or sitting without support but used an assumption for standing with support and walking independently. This assumption was because of discontinuation data for this population not being presented by motor milestone achievement, unlike for the other populations.

Finally, the Roche models also included inputs for additional time-to-event outcomes, such as time-to-scoliosis. The inputs were sourced from PNCR analysis (presymptomatic), natural history (type 1 model), and Ribero et al. (type 2/3 model).

Both submissions fitted parametric survival models to time-to-event data in order to enable long-term extrapolations estimations. Biogen fitted parametric survival curves to overall survival (presymptomatic and SMA type 1) and time-to-permanent ventilation (SMA type 1). Roche fitted survival curves to ventilation-free survival (SMA type 1), and overall survival (SMA type 1 and 2/3). These are discussed further in section 4.6.2.

Table 16: Clinical effectiveness inputs into each company's economic models

| **Population** | **Presymptomatic** | | **SMA Type 1** | | **SMA Type 2** | | **SMA Type 3** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Company** | **Biogen** | **Roche** | **Biogen** | **Roche** | **Biogen** | **Roche** | **Biogen** | **Roche** |
| **Input** | **Source** | **Source** | **Source** | **Source** | **Source** | **Source** | **Source** | **Source** |
| **Baseline characteristics** | NURTURE | RAINBOWFISH | ENDEAR | FIREFISH | CHERISH and SHINE | SUNFISH | Wadman et al. | SUNFISH |
| **Clinical effectiveness of** | | | | | | | | |
| Nusinersen | Distribution: ENDEAR (2 SNM2 copies), CHERISH (3 SMN2 copies)  Total: weighted average  Motor milestones: NURTURE | Equal efficacy to Risdiplam (HR=1) | ENDEAR and SHINE | Based on results of MAIC on the HINE-2 endpoint | CHERISH and SHINE | RULM MAIC | CHERISH and SHINE | RULM MAIC |
| Risdiplam |  | RAINBOWFISH |  | FIREFISH |  | SUNFISH (excluding Asian patients) |  | SUNFISH (excluding Asian patients) |
| Onasemnogene abeparvovec (OA) |  | Equal efficacy to Risdiplam (HR=1) |  | Based on the results of the unanchored MAIC conducted on the BSID-III endpoint from STR1VE-EU |  |  |  |  |
| Best supportive care | Distribution: Calucho et al.  Motor milestones: weighted average of BSC data applied to types 1,2,3 | PNCR | ENDEAR | FIREFISH | CHERISH | SUNFISH | CHERISH | SUNFISH |
| **Per-cycle probability of decline**  *In the Biogen submission, the studies showed durability over long-term, therefore a probability of decline was applied after 6.25 years (presymptomatic), 5 years (type 1), and 8 years (type 2/3). For the BSC models, these probabilities were applied after 1.5 years (presymptomatic), 1 year (type 1), and 15 months (type 2/3).*  *These were similarly applied in the long-term (after 24 months) for all SMA types in the Risdiplam model.* | | | | | | | | |
| Nusinersen | NURTURE |  | RR of \*\*\* applied to that of BSC (ENDEAR) | ITC | Applied RR of \*\*\* to that of BSC (CHERISH) |  | Applied RR of \*\*\* to that of BSC (CHERISH) |  |
| Risdiplam |  | RAINBOWFISH |  | FIREFISH |  | SUNFISH |  | SUNFISH |
| Onasemnogene abeparvovec |  |  |  | ITC |  |  |  |  |
| Best supportive care | ENDEAR and CHERISH |  | Wadman et al. | TA755 | Wadman et al. |  | Wadman et al. |  |
| **Permanent ventilation** | | | | | | | | |
| Nusinersen |  | Assumed same as Risdiplam | ENDEAR and SHINE |  |  |  |  |  |
| Risdiplam |  | National life tables |  | FIREFISH |  |  |  |  |
| Onasemnogene Abeparvovec |  | Assumed same as Risdiplam |  |  |  |  |  |  |
| Best supportive care | Wijngaarde et al. (HST24) |  | ENDEAR and SHINE |  |  |  |  |  |
| **Overall survival** | | | | | | | | |
| Nusinersen | HST24 | Assumed same as Risdiplam | ENDEAR and SHINE |  | Wijngaarde et al. |  | Wijngaarde et al. |  |
| Risdiplam |  | National life tables |  | FIREFISH |  | Pooled from 6 studies\* |  | Pooled from 6 studies\* |
| Onasemnogene Abeparvovec |  | Assumed same as Risdiplam |  |  |  |  |  |  |
| Best supportive care | HST24 (same as Nusinersen) |  | ENDEAR and SHINE |  | Wijngaarde et al. | Applied a HR of 0.75 in favour of Risdiplam in line with TA588 | Wijngaarde et al. | Applied a HR of 0.75 in favour of Risdiplam in line with TA588 |
| **Discontinuation** | | | | | | | | |
| Nusinersen | MAA |  | Not sitting/sitting without support: MAA  Standing with support/walking independently: Assumption |  | MAA |  | MAA |  |
| Risdiplam | Company assumed that there was no discontinuation regardless of the treatment received. | | | | | | | |
| **Time-to-event outcomes** | | | | | | | | |
| Nusinersen |  |  |  | Natural history |  |  |  |  |
| Risdiplam |  | Data from a PNCR analysis |  | Natural history |  | Ribero et al. 2023 |  | Ribero et al. 2023 |

* + 1. Methods of data synthesis

Due to the lack of head-to-head trials comparing the safety and efficacy between any combination of risdiplam, nusinersen or onasemnogene abeparvovec, and long-term studies investigating either nusinersen or risdiplam against BSC, meta-analyses were considered unfeasible. Therefore, the two submissions considered other indirect treatment comparison methods. Both companies performed matching adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) analyses, Roche also performed NMAs whilst Biogen deemed NMAs as inappropriate. Details of each company’s ITC are discussed in section 4.5.

* 1. Biogen submission
     1. Summary of evidence for clinical effectiveness of nusinersen

Table 17 outlines the main sources of evidence used to assess the clinical effectiveness of nusinersen.

Table 17: Summary of main sources of clinical effectiveness evidence

| **Trial name** | **Study design** | **Intervention drug** | **Comparators** | **SMA type** | **Population** | **Primary efficacy end points** |
| --- | --- | --- | --- | --- | --- | --- |
| CHERISH (NCT02292537) | Phase 3, multicenter, randomized, double-blind, sham-procedure controlled study | Nusinersen | Sham procedure control group | Type 2 and 3 | Children between the ages of 2–12 years with symptomatic SMA | Change from baseline to month 15 in Hammersmith Functional Motor Scale-Expanded (HFMSE) score. |
| Embrace  (NCT02462759) | A Phase 2, Randomized, Double-blind, Sham-procedure Controlled Study | Nusinersen | Sham procedure | Type 1 and 2 | All ages eligible. | Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs) [ Time Frame: Part 1 and 2: From first dose/sham procedure to end of study (up to 1080 days)]  Changes in Clinical Laboratory Parameters, Electrocardiograms,  vital signs, head circumference, chest circumference, arm circumference, weight, weight for age, head to chest circumference, body length, neurological exam outcomes, etc. |
| Endear (NCT02193074) | Phase 3, randomized, double-blind, sham-procedure controlled study | Nusinersen | Sham procedure control group | Type 1 | Symptomatic infants diagnosed with SMA (with clinical features consistent with Type I SMA) (infants aged up to 210 days) | Motor milestones (Hammersmith Infant Neurological Examination)  Event-free survival  Time to death/ Respirator ventilation |
| MAA | Real-world data | Nusinersen | n/a | Type 1, 2 and 3 | Paediatric patients | Motor function and motor milestones |
| Nurture (NCT02386553) | Ongoing phase 2, open-label, single-arm study | Nusinersen | n/a | Pre-syptomatic | Presymptomatic babies. Age 6 weeks or younger | Time to death or respiratory intervention |
| REACH registry | Real- world data | Nusinersen | n/a | Type 3 | Adults with SMA (largely Type 3) | Motor function |
| Shine (NCT02594124) | Phase 3, open-label extension for participants in previous Nusinersen studies. Non-randomised, open label | Nusinersen | Sham procedure from previous CHERISH or ENDEAR study | Type 1, 2 or 3 | participants with infantile or later-onset SMA | Safety/ tolerability of treatment.  Number of participants experiencing AEs |

* + 1. Critique of efficacy results (presymptomatic population)

Evidence of the effectiveness of nusinersen for presymptomatic SMA comes from the NURTURE study (NCT02386553). NURTURE is a phase 2, open-label, single-arm, multinational study so there is no comparator. There are no randomised controlled trials examining the effectiveness in a presymptomatic SMA population. NURTURE was conducted across ten countries (Argentina, Australia, Germany, Israel, Italy, Qatar, Taiwan, Turkey, UK, US) and consists of a five-year treatment period and a post-treatment follow-up evaluation. A total of 25 participants were analysed in NURTURE. Presymptomatic infants enrolled to the NURTURE study had 2 or 3 SMN2 copies and were expected to develop type 1 or 2 SMA. Presymptomatic treatment (before number of motor neurons have fallen below critical threshold) is optimal (CS, Document B, Section B.2.3.3).

The EAG have concerns over the small sample size, and the lack of a comparator in the NURTURE study.

* + - 1. Outcomes of interest
         1. Overall survival/time to death or permanent ventilation

The primary endpoint of NURTURE was overall survival/time to death or permanent ventilation. The company report that no patients died or required permanent ventilation as of the Feb 15th, 2021, data cut, at a mean age of 4.9 years (in contrast to expected end points where SMA is untreated), and 4/25 patients met the endpoint of death or ventilation throughout the NURTURE study (CS, Doc B, Section B.2). All patients in NURTURE had 100% event-free survival at follow-up (CS, Appendix D, section 5.3.2.1).

* + - * 1. WHO motor milestones

Following treatment with nusinersen, 84% could sit without support and 64% could walk independently at follow-up of median 34 months. (CS, Appendix D, section 5.3.3.2). In infants with 2 SMN2 copies, 73% could sit without support and 40% could walk independently, an in infants with 3 SMN2 copies 100% could sit and walk independently at follow-up (CS, Appendix D, section 5.3.3.2). All ten patients with 3 SMN2 copies achieved highest WHO motor milestones- walking independently within normal timeframes. Of 15 patients with 2 SMN2 copies 15/15 achieved sitting without support and standing with assistance, 14/15 achieved hands and knee crawling and walking with assistance, 13/15 achieved standing alone and walking alone (some of these were achieved within normal timeframes) (CS, Doc B, section B.2). All children who achieved a WHO motor milestone retained it at the last visit (CS, Doc B, section B.2.4.4.2). WHO motor milestones are reported in the company submission.

* + - * 1. Motor function

Motor function in presymptomatic patients was measured using CHOP INTNED and HFMSE. Most infants in NURTURE (22/25) achieved maximum CHOP INTEND score of 64, with scores increasing steadily from baseline (CS, Doc B, section B.2.4.4.3).

Overall HFMSE mean and individual scores showed continued improvement in NURTURE, with predicted mean total scores and improvements higher in NURTURE with 2 or 3 SMN2 copies than CHERISH with symptomatic later-onset SMA in nusinersen or control groups. 11 children in NURTURE had a valid 6-minute walk test, showing presymptomatic infants can achieve and sustain independent walking (CS, Doc B, section B.2.4.4.4).

* + - * 1. Growth parameters

All children in NURTURE grew and gained weight. The mean weight for age stabilised over time. The mean weight for age was higher in NURTURE than in ENDEAR/SHINE (where patients were treated with nusinersen after symptom onset). (CS, Doc B, section B.2.4.4.5). At 4.9-year follow-up, 48% were within 25th percentile and 40% were within 75th percentile at weight and length for age (CS Appendix D, section 5.3.7).

* + - * 1. Dysphagia/ bulbar function

Dysphagia was assessed using the Parent Assessment of Swallowing Ability (PASA) questionnaire developed by Biogen. Patients in NURTURE consistently rated never to rarely experiencing difficulty swallowing (over mean of 2.6 years). At last assessment 23 (92%) maintained ability to swallow and caregivers had no concerns about swallowing (regardless of SMN2 copy number). Pre-symptomatic patients expected to develop type 1 or 2, 22/25 (88%) achieved maximum score of 3 for ability to suck and swallow on HINE-1 at data cut (median 34 months). In risdiplam, all patients with 12 months or more follow-up could swallow and feed orally (CS B.2.4.4.6).

Regarding choking, at last assessment 19/25 (76%) disagreed/ strongly disagreed being concerned about child aspirating whilst eating. For feeding tube use, at interim analysis (mean age 4.9 years), 5/25 (20%) patients (all with 2 SMN2 copies) were receiving some tube feeding. (App D. 5.3.6.3.1.1). Of five patients in NURTURE with 2 SMN2 copies ever identified as tube fed, two were always tube fed, three often tube fed in seven days before last assessment. (CS B.2.4.4.6).

* + - * 1. Need for ventilation

At a mean of 4.9 years follow-up, 27% of NURTURE patients with 2 SMN2 copies and 0% 3 SMN2 copies required continuous ventilation six or more hours a day (CS Appendix D, section 5.3.4.1).

No data was available on the impact of nusinersen in presymptomatic patients for frequency or duration of hospitalisation, or Health Reported Quality of Life.

* + - * 1. Adverse events

No adverse events were attributed to nusinersen for pre-symptomatic patients at median follow-up of 4.9 years (CS, Document B, Section B.2.6). No serious treatment related adverse events (TRAEs) (CS, Appendix D, Section 5.4.2) and no discontinuation was reported in NURTURE due to adverse events (CS, Appendix D, Section 5.4.3.1).

* + - * 1. Summary of presymptomatic evidence

The evidence presented suggests that initiating treatment at the presymptomatic stage, optimises the effectiveness of treatment. However, the EAG suggests some caution should be taken when interpreting the results of the presymptomatic evidence due to the lack of a comparator arm, and the small sample size available for analysis.

* + 1. Critique of efficacy results (type 1)

Efficacy results for type 1 SMA comes from the ENDEAR and SHINE trials. ENDEAR was a randomised controlled trial, comparing patients with infantile-onset SMA treated with nusinersen compared to control patients receiving a sham procedure. ENDEAR was conducted across 13 countries (Australia, Belgium, Canada, France, Germany, Italy, Japan, Korea, Spain, Sweden, Turkey, United Kingdom, United States) and consisted of planned follow-up of 13 months. Participants had 2 SMN2 copies and were classified as most likely type 1. Patients either received nusinersen or a sham procedure.

Type 1 efficacy results also come from the SHINE study. To overcome critique of ENDEAR in relation to short-term follow-up, participants previously enrolled in ENDEAR were eligible to enrol into SHINE; an ongoing open-label extension study of nusinersen in participants who were enrolled in previous nusinersen trials. Participants that had received either nusinersen in ENDEAR (previous nusinersen) or a sham procedure in ENDEAR (previous sham) were included, and all received nusinersen in SHINE.

The SHINE trial provides longer follow-up from participants enrolled in previous nusinersen trials, however the EAG note that there was a high discontinuation rate in ENDEAR/SHINE- only \*\*/121 completed both (CS, Document B, Section B.2.4.3.1). The EAG also note that SHINE is a single-arm study, and therefore no comparator is available for the period patients are enrolled in SHINE, other than the difference between time that nusinersen was started. Therefore, comparisons can be made regarding length of time of treatment, rather than treatment versus no treatment. The EAG also note that within SHINE, all the adverse events that led to discontinuation had fatal outcomes (n=31) (CS, Document B, Section B.2.4.3.1.1).

* + - 1. Outcomes of interest
         1. Overall survival/ time to death or permanent ventilation

In ENDEAR, the rate of death was 16% over 13 months, with a lower risk of death for participants receiving nusinersen than those receiving sham (CS, Appendix D, Section 5.3.1.2). Evidence from observational studies of nusinersen in type 1 SMA show the rate of death as 3.4% at ten months, and 2.1% at three years (CS, Appendix D, Section 5.3.1.2). The EAG note that this is quite a high rate of death, but also note that it is comparable to studies of risdiplam in type 1 SMA (14% at 12-month follow-up in FIREFISH part 1) (CS, Appendix D, Section 5.3.1.2).

In SHINE, where ENDEAR patients were enrolled and followed-up, earlier initiation of treatment (participants in the previous nusinersen group) \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\* previous nusinersen patients \*\*\*\*\*\*\*\*\*\*\* died or needed permanent ventilation in ENDEAR/SHINE than previous control \*\*\*\*\*\*\*\*\*\*\*\* Furthermore, 28 patients in previous sham arm died or needed permanent ventilation during ENDEAR and a further \*\*\*\*\*\*\*\*\*\* during SHINE (CS, Document B, Section B.2.4.3.1.2). Overall, \*\*\*\* previous nusinersen participants in ENDEAR or SHINE died \*\*\*\*\*\*\*\*\*\*\* compared to those in the sham arm \*\*\*\*\*\*\*\*\*\*\* (CS, Document B, Section B.2.4.3.1.3).

* + - * 1. WHO Motor Milestones

In ENDEAR/ SHINE, the HINE-2 was used to assess motor milestones amongst type 1 patients, and showed \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* (CS, Document B, Section B.2.4.3.1.4). Despite milestones showing little difference between previous nusinersen and previous sham at approximately six-month follow-up, at day 818, previous sham patients had \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* (CS Document B, Section B.2.4.3.1.4). At the last HINE-2 measurement \*\*\*\*\*\*\*\*\* previous sham had full head control vs \*\*\*\*\*\*\*\*\*\*\* previous nusinersen. Furthermore\*\*\* previous sham patients could sit or pivot vs \*\*\*\*\*\*\*\* previous nusinersen patients (CS, Document B, Section B.2.4.3.1.4).

* + - * 1. Motor function

Motor function in type 1 SMA patients was measured using CHOP-INTEND and HINE-2. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* (CS, Document B, Section B.2.4.3.1.5) showing earlier initiation of nusinersen to be more effective. At \*\*\*\*\*\*\*\*, previous nusinersen patients showed a mean score of \*\*\*\*\*\*\*\*\*\*\* (an \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, compared to previous sham patients who had mean score of \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*; an initial mean \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*) (CS, Document B, Section B.2.4.3.1.5). More previous nusinersen patients showed a HINE-2 response 37/73 (51%) than previous sham patients 0/37 (CS, Appendix D, Section 5.3.3.6.2). Increased CHOP-INTEND and HINE-2 scores were seen amongst previous nusinersen patients than previous sham patients in single-arm studies and non-comparative observational studies of nusinersen in type 1 SMA patients (CS, Appendix D, Section B.3.3.6.2).

* + - * 1. Growth parameters

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Previous control mean weight for age percentile at day 2102 was \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* vs previous nusinersen \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

* + - * 1. Dysphagia/ bulbar function

Dysphagia was assessed using the Parent Assessment of Swallowing Ability (PASA). Assessments were taken on the day that all patients received nusinersen at licenced dose. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\* (CS, Document B, Section B.2.4.3.1.7).

* + - * 1. Need for ventilation

The rate of permanent ventilation in ENDEAR was lower for previous nusinersen (23%) than for previous sham (32%) at six and nine months but this result was not significant. The CS-3A single-arm study showed that at 37-month follow-up, 31% patients with 2 SMN2 copies and 0% with 3 copies needed invasive ventilation.

Further evidence on the need for ventilation in type 1 SMA patients comes from five non comparative observational studies. Results were varied, but in one study of early onset SMA, the amount of respiratory support increased over 24-month follow-up, with a greater increase in children aged 2 years or younger (CS, Appendix D, Section 5.3.4.2).

* + - * 1. Frequency and duration of hospitalisation

A non-comparative observation study showed that of US administrative claims data 52% patients with type 1 SMA had been admitted to hospital at least once in a 24-month period (CS, Appendix D, Section 5.3.8.2). In contrast to this, ENDEAR/ SHINE showed that annualised hospitalisation rate for serious respiratory events \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* in ENDEAR/SHINE. First year rates after treatment were \*\*\*\*\* per patient per year in previous sham compared to \*\*\*\*\* per person per year in previous nusinersen patients. By year eight, \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* were admitted to hospital (CS, Document B, Section B.2.4.3.1.10).

* + - * 1. Scoliosis and Contractures

Information about scoliosis and contractures in type 1 SMA patients in ENDEAR/SHINE is taken from CS, Document B, Section B.2.4.3.1.8. Patients aged 2 or over had annual X-rays of thoracolumbar region to assess cobb angel (scoliosis). The EAG notes that assessments were only taken in SHINE (following a protocol amendment Jan 2017), and assessments were not taken at any German sites.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. Median cobb angel of previous \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*). \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.

Contractures were assessed from January 2017. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* XX \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* had at least one contracture. Previous nusinersen patients had \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* of scoliosis and contractures (CS, Document B, Section B.2.4.3.1.8).

* + - * 1. Quality of Life

Quality of life was only assessed in type 1 SMA following a protocol amendment in January 2017. Mean PedsQL scores of patients with infantile onset previously in ENDEAR \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* and \*\*\*\*\*\* for previous nusinersen patients than previous sham patients.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* (CS, Document B, Section B.2.4.3.1.9).

* + - * 1. Adverse events

No treatment related adverse events (TRAEs) were reported during 14 months of ENDEAR, although 9/80 (11%) participants in the nusinersen arm, and 6/41 (15%) participants in the sham arm reported possible TRAEs (CS, Appendix D, Section 5.4.1). At 13-month follow-up there were no reported serious TRAEs in ENDEAR (CS, Appendix D, Section 5.4.2), 13/80 (16%) in nusinersen arm and 16/41 (39%) in sham arm discontinued treatment due to adverse events over 13 months, including death n=1 and brain injury n=1) (CS, Appendix D, Section 5.4.3.1). AEs were consistent with SMA type 1 (CS, Document B, Section B.2.4.3.1.1). In infantile- onset patients in SHINE, all adverse events that led to discontinuation had fatal outcomes (n=31) (CS, Document B, Section B.2.4.3.1).

* + - * 1. Summary of type 1 evidence

For many of the outcomes, the longer-term follow-up achieved by the SHINE trial of SMA type 1 patients shows promise of the effectiveness of nusinersen. Patients that received nusinersen during ENDEAR went on to have better outcomes in SHINE than those that received sham in ENDEAR, and then started nusinersen later (during SHINE). However, the EAG note the high rate of discontinuation, the fairly high rate of death and fatal adverse effects amongst this patient group receiving nusinersen.

* + 1. Critique of efficacy results (type 1 and 2)

Evidence for SMA type 1 and 2 is available from one RCT: EMBRACE. EMBRACE was a randomised, double-blind, sham procedure–controlled study, followed by an unblinded amended open-label protocol. Additionally, evidence for type 1 and 2 SMA comes from one single-arm study (RESPOND), one cohort study and one non-comparative observational study for patients with type 1 and 2. Studies predominantly include infants and children, and most patients had 2 or 3 SMN2 copy numbers, some non-comparative observational studies included patients with 4 SMN2 copies.

In the EMBRACE study, there were no patients on invasive or permanent ventilation at baseline, but many were receiving some form of ventilation support. This was higher in the sham arm (57%) compared to the nusinersen arm (21%), suggesting the presence of differences in baseline characteristics (CS, Appendix D, Section 5.1.3.2).

* + - 1. Outcomes of interest
         1. Motor milestones

In composite motor milestone scores, more patients showed improvement in nusinersen arm (79%) compared to sham arm (29%) at 14 months, however the significance of the difference was not reported. In the DEVOTE part A single arm trial in type 2 SMA, 83% of patients maintained motor milestones at follow-up (302 days). However, the EAG note that the reliability of a single-arm trial is uncertain (CS, Appendix D, Section 5.3.3.4).

* + - * 1. Growth

It is noted that for EMBRACE patients with type 1 or 2, some growth outcomes were not reported for sham arm, only in nusinersen or previous sham arms. This makes comparisons of effectiveness difficult. Changes in body length, chest circumference, and head circumference were generally better in nusinersen arm. Furthermore, weight and head to chest circumference ratio favoured nusinersen after the sham arm but this was not significant (CS, Appendix D, Section 5.3.7.2).

* + - * 1. Summary of type 1 and 2 evidence

There are limited outcomes examining type 1 and 2 together, and those that are evident are not complete - some outcomes for the sham arm are missing, making comparison of the effectiveness difficult. There is also some evidence of baseline differences between the sham and nusinersen arms particularly around the baseline need for ventilation support.

* + 1. Critique of efficacy results (type 2 and 3)

Evidence for type 2 and 3 SMA patients comes predominantly from the CHERISH and SHINE trials. CHERISH was a multinational randomised controlled trial, conducted in 11 countries (Canada, China, France, Germany, Italy, Japan, Korea, Spain, Sweden, US, Hong Kong). Participants were randomised to either nusinersen arm or the sham procedure arm. CHERISH was a 15-month study, and to overcome the limitations of a short-duration study, participants from CHERISH were eligible to enrol on SHINE. Within SHINE, participants all received nusinersen, and were categorised as previous nusinersen (received nusinersen during CHERISH), or previous sham (received sham during CHERISH). Information and critique of SHINE can be found in section 4.3.3 (Page 132).

Additional evidence for nusinersen in type 2 and 3 SMA come from one single-arm study, one cohort study, and four non-comparative observational studies. Only one cohort study in patients with only type 2 and two non-comparative observational studies of nusinersen in patients with type 3 exist. For nusinersen type 2 studies were in children and type 3 in children and adults. For mixed type 2 and 3, most were in children only. The majority of patients in type 2 and 3 had 3 or 4 SMN2 copies. (CS, Document B, Section 5.1.3.1).

* + - 1. Outcomes of interest
         1. Overall survival/ time to death or permanent ventilation

\*\*\*\*\*\*\*\*\*\*\*\* with later-onset SMA from the CHERISH trial \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* in previous sham and \*\*\*\*\*\*\*\*\* in previous nusinersen patients. The company report that \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* (CS, Document B, Section 2.4.3.2.2).

* + - * 1. WHO Motor Milestones

Participants in CHERISH were non-ambulant and able to sit unassisted. Similar achievement was seen for nusinersen and sham patients on milestones. Stand without support was achieved in 1/66 (2%) nusinersen arm compared to 1/34 (3%) in the sham arm. Walk with support was achieved by 1/66 (2%) in nusinersen arm compared to 0/34 in sham arm at 15 months (CS, Appendix D, Section 5.3.3.5). In CHERISH, more participants achieved one or more new WHO motor milestone for nusinersen (20%) compared to sham (6%), although the difference was not significant.

One further nusinersen trial (CS-2/ CS-12) showed that 1/11 (9%) patients with type 2 SMA gained the ability to walk independently by 34 months (compared to 0% at baseline). Non-comparative observational studies examining the effectiveness of nusinersen in patients with type 2 and 3 SMA in ambulant patients reported 99% maintenance of independent walking at 38 months, and another showed new achievement of independent walking in 7% of patients at 38 months (CS, Appendix D, Section 5.3.3.5).

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* (CS, Document B, Section B.2.4.3.2.3). This demonstrates starting treatment earlier leads to better outcomes on motor milestones achieved.

* + - * 1. Motor function

Motor function in type 2 and 3 SMA are assessed using HFMSE and RULM.

**HFMSE**

Clinically meaningful differences in HFMSE were seen in patients receiving nusinersen than Sham in CHERISH (CS, Document B, Section B. 2.4.2). Mean HFMSE scores in CHERISH/SHINE \*\*\*\*\*\*\*\*\*\*\* in previous nusinersen patients than previous sham patients, however baseline mean scores between previous nusinersen \*\*\*\*\*\* and previous sham \*\*\*\*\*\* were different.\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* (CS, Document B, Section B.2.4.3.2.4).

**RULM**

Clinically meaningful increase in RULM seen in patients treated with nusinersen compared to sham in CHERISH (CS, Document B, Section B.2.4.2). \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. At day 2790, more previous sham patients \*\*\*\*\*\*\*\*\*\*\* than previous nusinersen patients \*\*\*\*\*\*\*\*\*\*\* were responders on RULM (CS, Document B, Section B.2.4.3.2.5).

Other evidence on the effectiveness of motor function in type 2 and 3 includes the CS-2/CS-12 trial, showing high response on HFMSE (78%) and RULM (56%) for type 2 patients, but lower rates for type 3 patients at 35 months (CS, Appendix D, Section 5.3.3.6.3). Some cohort studies showed greater improvement in HFMSE in nusinersen patients compared to untreated controls at 24 months, but other studies did not show this difference (CS, Appendix D, Section 5.3.3.6.3). In non-comparative observational studies, 7/10 studies reporting HFMSE showed significant improvements from baseline. In studies reporting HFMSE, 23-66% achieved 3 or more-point increases in HFMSE score and 51-90% achieved 1 or more point increase., 15-38% showed 2 or more and 17% showed 3 or more-point increase (CS, Appendix D, Section 5.3.3.6.3).

* + - * 1. Scoliosis and contractures

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* At day \*\*\*\* median increases in Cobb angle were higher in previous sham patients. Median cobb angles in previous sham patients were \*\*\*\* \*\*\*\*\*\*\* (\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*) compared to previous nusinersen \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* (CS, Document B, Section B.2.4.3.2.6).

During the follow-up of \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* had growing rod or spinal fixation surgery. Overall, \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* . At day 1800, \*\*\*\*\*\*\*\*\*\*\* previous sham patients and \*\*\*\*\*\*\*\*\*\*\* previous nusinersen patients had at least one contracture (CS, Document B, Section B.2.4.3.2.6).

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

* + - * 1. Dysphagia/ bulbar function

Dysphagia was measured using the PASA questionnaire. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Feeding tube use at baseline was only reported in one non-comparative observational nusinersen study (4-14%) (CS, Appendix D, Section 8.1.3.2).

* + - * 1. Quality of life

Quality of life was assessed during CHERISH using the Paediatric Quality of Life Inventory (PedsQL). Nusinersen patients scored 5 points higher on PedsQL than sham patients, but significance was not reported (CS, Appendix D, Section 5.3.9.1). Evidence from a single arm trial of type 2 and 3 patients showed an increase in patient PedsQL of 9.8%, and an increase in parent reported PedsQL of 8.4% (CS, Appendix D, Section 5.3.9.1).

During CHERISH/SHINE, \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Mean scores for feeding/grooming/dressing, transfers and mobility were higher for previous nusinersen patients than previous sham patients.

Mean scores for feeding/grooming/dressing at day 2070, \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* for previous nusinersen patients compared to \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* for previous sham patients. Mean scores for transfers at day 2070 were \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* for previous nusinersen compared to \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* for previous sham patients. Finally, mean scores for mobility at day 2070 were \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* for previous nusinersen compared to \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* for previous sham patients (CS, Document B, Section B.2.4.3.2.8).

* + - * 1. Frequency and duration of hospitalisation

CHERISH showed a reduction in the rate of hospitalisation over 24 months in patients receiving nusinersen compared to sham patients, however, this result was not significant. One non-observational study showed that over 24 months, 51% of patients with type 2, and 25% of patients with type 3 were admitted to the hospital at least once (CS, Appendix D, Section 5.3.8.3).

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \* \*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\* \*\*\*\*\*\*\*\*. The annualised rate of hospitalisation for serious respiratory events during the first year of CHERISH/SHINE was \*\*\*\* admissions per patient per year in previous sham patients, compared to \*\*\*\* admissions per patient per year in previous nusinersen patients. The rate of hospitalisation \*\*\*\*\*\*\*\*\*\* \*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* and was \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\* over the eight-year follow-up (CS, Document B, Section B.2.4.3.2.9).

* + - * 1. Ventilation support

Ventilatory support was not reported in CHERISH, but it was reported in four non-comparative observational studies. Ventilatory support was needed in 15% of type 2 patients and 17% of type 3 patients at 24 months. 2% of patients with type 1-4 SMA needed new ventilation support at a mean 324-day follow-up (CS, Appendix D, Section 5.3.4.3).

* + - * 1. Adverse events

No serious TRAEs were reported in CHERISH or SHINE (CS, Appendix D, Section 5.4.2).

* + - * 1. Summary of type 2 and 3 evidence

Some secondary outcomes (WHO milestones) revealed no differences between nusinersen and sham groups in CHERISH, but in SHINE (where a longer follow-up was available), those receiving nusinersen earlier had better motor milestone achievements.

At day 2790, results based on the RULM scale showed that the response rate was in favour of sham group when compared to nusinersen which questions the applicability of nusinersen for long-term..

There was no improvement from nusinersen for proportions of children who achieve standing alone or walking with assistance at month 15.

It was noted by the EAG that there were baseline HFMSE differences between previous nusinersen and previous sham patients. All patients HFMSE scores decreased during CHERISH/ SHINE suggesting for motor function, starting nusinersen earlier did not improve outcomes.

There were gaps in the reporting of the need for ventilation support at baseline in CHERISH, and this was not often reported in other studies.

* + 1. Critique of efficacy results (mixed SMA type)

Eight studies reporting the effectiveness of nusinersen enrolled participants with mixed SMA type. Two studies enrolled infants and children, four enrolled infants, children and adults and two enrolled adults. Participants were mainly type 1-3 SMA, and the majority of patients had 3 SMN2 copies (CS, Appendix D, Section 5.1.3.1). Data from the MAA provides real-world evidence of the effectiveness of nusinersen for mixed types of SMA amongst paediatric patients in the UK, and data from the REACH registry provides real-world evidence of the effectiveness of nusinersen for adult patients in the UK. Caution should always be employed when examining real-world evidence due to the lack of comparators available.

* + - 1. Outcomes of interest
         1. Overall survival/ mortality

No patients in final analysis cohort of the MAA died. Since the introduction of nusinersen, more than 90% of patients with type 1 SMA receiving nusinersen treatment survive beyond two years. However, some deaths occurred in patients ineligible for analysis (Five type 1 non-EAP patients, and one type 1 patient who previously participated in EAP died) (CS, Document B, Section B.2.4.5.1.3). There were low rates of death, or no deaths in observational studies of mixed type SMA over 1-to-38-month follow-ups (CS, Appendix D, Section 5.3.1.3).

* + - * 1. Motor milestones

Amongst nusinersen treated Paediatric patients in the MAA, 70.8% of patients achieved new WHO motor milestones, or maintained current milestones (CS, Document B, Section B.2). At most timepoints up to 80% of type 1 non-EAP patients, up to 72.7% type 2/3 non sitters, and up to 30% type 2/3 sitters achieved new milestones. Almost all ambulant type 2/3 patients at baseline maintained the ability to walk independently up to four years (one patient lost ambulation during this time). At baseline, 22% of type 1 EAP patients achieved the ability to sit, however it is noted that approximately 30% of patients had unknown motor milestone at baseline (CS, Document B, Section B.2.4.5.1.2).

The proportion of type 1 EAP patients gaining new milestones from baseline was lower among type 1 EAP patients (up to 33.3%), with most demonstrating stabilisation of milestones. This stabilisation was expected as this group included many chronic patients, many suffering with SMA for a long time. It was noted by the company that some maintenance or achievement of milestones may have been affected by SMA-related comorbidities, especially in non-ambulant type 2/3 SMA patients (CS, Document B, Section B.2.4.5.1.2).

From data in the REACH registry of adult SMA patients, at 42 months, 87.5% or more adult patients attained new or maintained motor milestones. The majority of these achieved stabilisation rather than gained new milestones (CS, Document B, Section B.2.4.5.2.2). It was noted that ambulant patients could not achieve any more as walking without assistance is the final milestone that can be achieved.

* + - * 1. Motor function

Evidence for paediatric patients from the MAA data shows a general improvement from baseline in motor function scales across SMA type. This improvement contrasts with the decline in SMA if left untreated (CS, Document B, Section B.2).

Only small improvements were seen in upper limb function (RULM), with no other significant changes from baseline in any scales. Nusinersen prevents worsening of motor function compared to natural history of SMA (compared to mean decline of 0.6 points from baseline to 12 months in untreated later-onset adult patients) (CS, Document B, Section B.2).

There were two timed motor function tests (10 min run test and Rise from Floor test) assessed in ambulant paediatric SMA patients. Both tests showed long-term stability but limited number of participants available for each of these, making it impossible to run statistical models (CS, Document B, Section B.2.4.5.1.2). Amongst patients with type 1 SMA, the proportion of CHOP INTEND and HINE-2 responders was lower in the EAP cohort (including patients with longer disease duration at treatment initiation) showing the benefits of early treatment. Data for type 2/3 patients are limited.

Motor function in adult SMA patients from the REACH registry was assessed using RULM, 6MWT, ATEND and RHS. There were small improvements in upper limb function on RULM, but otherwise there were no statistically significant changes from baseline. This shows that in adult patients, nusinersen prevented disease-worsening of condition but did not lead to improvements (CS, Document B, Section B.2.4.5.2.2).

* + - * 1. Bulbar function

Data on bulbar function in paediatric patients comes from the MAA. One non comparative observational study (from US administrative claims) reported tube feeding in patients with type 2 and 3 SMA. 32% type 2 and 34% type 3 required nutritional support at up to 24 months. A further study showed that the use of feeding tube was 13% at year 1, 65% at year 2 and 58% at year 4 (CS< Appendix D, Section 5.3.6.3.1.3).

* + - * 1. Quality of life

Paediatric quality of life evidence in the MAA was limited, and patient reported outcomes were not separated by type or by baseline motor function. Only two patients completed the EQ-5D-5L so the results were not presented. Available patient reported outcome (PRO) data shows stability and improvement compared to baseline. No patients reported severe or extreme problems in any EQ-5D Y domains at baseline or final assessment, EQ-5D VAS scores were stable, SMAIS scores showed some improvement and of PGI-S scores, six had no change in severity at follow-up, and four had reduction of 1 unit. At final follow-up seven reported no change, two reported reductions and three reported improvements (CS, Document B, Section B.2.4.5.1.5).

Adult quality of life evidence from the REACH registry was limited, and patient reported outcomes were not separated by type or by baseline motor function. Available PRO data showed improvement or stability at last follow-up, and at the final follow-up, proportion of patients reporting extreme self-care problems declined from 35.3% at baseline to 29.0%. The proportion of patients with no problems with mobility, usual activity and anxiety/depression increased at last follow-up compared to baseline. Mean scores on EQ-5D-VAS, SMAIS, PGI-S and PGI-I remained stable at last follow-up, median EQ-5D-VAS and SMAIS scores increased, showing improvement in general health and greater independence (CS, Document B, B.2.4.5.2.3).

In one non-comparative observational study, Patient Global Impression of Improvement (PGI-I) showed that patients that were very much, or much improved was 14% at six months, 25% at 14 months, 36% at 22 months and 51% at 30-month follow-ups (CS, Appendix D, Section 5.3.9.2).

The EAG note that comparisons of real-world data to clinical trials should be treated with caution.

* + - * 1. Frequency and duration of hospitalisation

One non-comparative observational study of nusinersen reported the mean duration of medical visits (days per patient per year) was 50.9 to 92.4, and mean inpatient days were 2.0 to 6.4 amongst type 1 to 3 SMA patients (CS, Appendix D, Section 5.3.8.4).

* + - * 1. Permanent ventilation

Data on paediatric patients from the MAA showed that no patients in the non-EAP group needed permanent ventilation at data-cut, and three patients with type 1 SMA required permanent ventilation (all enrolled in the nusinersen EAP prior to the MAA, which included chronic type 1 patients). Two patients with type 1 enrolled in the EAP had tracheostomy at baseline, and no additional procedures were required during the study.

Permanent ventilation was only required for four patients with type 1 SMA enrolled in the EAP (this group consisted of more chronic type 1 patients). Median treatment initiation age of EAP was 2.91 years compared to 0.28 years in the non-EAP group. This shows substantial improvement from natural history of SMA in relation to permanent ventilation. The company note a high rate of missing data (approx. 30% was missing) so time to permanent ventilation not available (CS, Document B, Section B.2.4.5.1.4).

* + - * 1. Adverse events

Within the adult population in the REACH Registry, four patients (4.3%) discontinued nusinersen treatment. Reasons for discontinuation included adverse events related to nusinersen or the administration procedure (CS, Document B, Section B.2.4.5.2.1).

* + - * 1. Summary of mixed SMA evidence

There are some limitations with the mixed SMA type evidence. Including limited long-term data within the MAA. There is limited data at 48-month follow-up (CS, Document B, Section B.2.4.5.1.2), a limited number of studies reporting baseline ventilation characteristics. There was unknown baseline WHO motor milestones in 30% patients.

The high rate of discontinuation amongst MAA data of paediatric patients should be noted. A total of 78 patients stopped before final data cut of 2023: 75 (96.2%) switched treatment. Reasons included increased difficulty performing lumbar puncture, spinal fusion surgery and changing preference (CS, Document B, Section B.2.4.5.1).

Some outcomes appear to reflect nusinersen preventing worsening of SMA symptoms rather than improvements. The EAG noted some missing data on weight (CS, Document B, Section B.2.3.4.3), however the exact percentage of data missing and reasons for missing data are unknown.

Some outcomes have insufficient patients included at some time points making them unable to be used in analysis, and limited data is also available of some outcomes, such as PROs, making it difficult to fully assess the effectiveness of nusinersen on these outcomes.

Overall, some caution should be taken with real-world data, due to the lack of a comparator and not comparable to more robust results in clinical trials.

* + 1. Summary of Biogen’s ITC

Individualised patient data (IPD) were available for the nusinersen trials and aggregate data (AgD) were available for the trials of the two comparators included in Biogen’s ITC, risdiplam and onasemnogene abeparvovec. The company employed MAIC (12 of 14 comparisons) and STC methods to make the indirect comparison between nusinersen, risdiplam, and onasemnogene abeparvovec, making full use of the IPD at hand. MAICs reweight IPD to align it with the AgD of the comparator, while STCs adjust the outcome models to estimate the treatment effects as if they were compared within the same study population. Both methods were unanchored as the available data did not allow anchored comparisons. Appendix D of the company submission details the methods used for all 18 comparisons. nusinersen was compared to only onasemnogene abeparvovec in the presymptomatic population, comparing the NURTURE and SPR1NT trials using unanchored MAICs. Five comparisons apiece were done between nusinersen and either risdiplam or onasemnogene abeparvovec in the type 1 population, again using MAICs. In the type 2/3 population, STCs were used to compare nusinersen vs risdiplam. The covariates adjusted for in the comparisons for each SMA type are presented in Table 18. It should be noted that the company “attempted to adjust for all available covariates without attempting to classify them as prognostic/effect modifiers”, meaning that the analysis may include variables that do not influence the treatment effect, potentially leading to over-adjustment and less precise estimates.

In the presymptomatic population, nusinersen was indirectly compared to onasemnogene abeparvovec for two outcomes: WHO motor milestones achieved at 18 months of age for standing with support and walking alone. In both analyses, there were no statistically significant differences between nusinersen and onasemnogene abeparvovec although point estimates did favour the latter treatment.

In the type 1 population, nusinersen was compared to onasemnogene abeparvovec for three BSID-III domains as well as overall survival (OS) and permanent ventilation (PV) and compared to risdiplam for three HINE-2 domains as well as OS and PV. There were \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

In the type 2/3 populations, nusinersen was compared to risdiplam for outcome of change from baseline to 12 months in HFMSE and RULM scores. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

None of the ITC results were included in Biogen’s economic modelling. The full critique of Biogen’s ITC is presented in sections 4.5 and 4.6.

Table 18: Covariates adjusted for in Biogen's ITCs

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Presymptomatic** | **SMA type 1** | **SMA type 2/3** |
| Age at first dose | Included |  |  |
| Age at screening |  | Included | Included |
| Age at symptom onset |  | Included | Included |
| CHOP-INTEND total score at baseline | Included | Included |  |
| Feeding issues at baseline |  | Included |  |
| RULM score at baseline |  |  | Included |
| Sex | Included | Included | Included |
| SMN2 copy number | Included | Included | Included |
| Ventilation support at baseline |  | Included |  |
| Weight | Included | Included |  |

* 1. Roche submission

Risdiplam’s clinical effectiveness is backed by a wide array of research studies and clinical trials. These trials aim to provide data that supports the safety and effectiveness of risdiplam in treating various stages of SMA, from pre-symptomatic to infantile and later-onset stages. The risdiplam clinical program is one of the most comprehensive ever undertaken for SMA, covering a diverse patient population, which supports its broad use in SMA treatment.

Two key studies, SUNFISH (BP39055) and FIREFISH (BP39056), offer strong, long-term clinical evidence. Each study is split into two parts: Part 1 focuses on determining the appropriate dosage, while Part 2 confirms the effectiveness and safety of the chosen dosage over a 5-year period. Currently, the FIREFISH study provides data up to 4 years, but this will be extended to 5 years. The final report will be provided during the consultation phases of the NICE evaluation procedure.

The FIREFISH study is tailored for infants with type 1 SMA, while the SUNFISH study targets paediatric and adult patients with type 2 or 3 SMA. Each study part involves different patients with similar characteristics, with the SUNFISH study also including a small number of ambulant patients.

The RAINBOWFISH study is an open-label, single-arm, multicentre study that investigates the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) in patients from birth to 6 weeks at first dose, who are genetically diagnosed but asymptomatic.

The JEWELFISH study strengthens the findings of the SUNFISH and FIREFISH trials. It’s an open-label, non-comparative study involving patients with type 1, 2, and 3 SMA, aged from 6 months to 60 years. The patient cohort includes various sources, including those previously treated with nusinersen, onasemnogene abeparvovec, and olesoxime. The study primarily focuses on safety, with efficacy outcomes considered exploratory.

Following the initial NICE appraisal [TA755], risdiplam was recommended as a potential SMA treatment under specific conditions, known as MAA. The MAA included a Data Collection Agreement (DCA) to gather necessary data to address uncertainties identified in the initial submission. This data comes from four risdiplam clinical trials (FIREFISH, SUNFISH, RAINBOWFISH, and JEWELFISH) and real-world usage data from the SMA REACH UK registry database. The goal was to understand risdiplam’s real-world application and support its long-term use and cost-effectiveness.

The company explains that due to the diverse patient populations in the studies, different scales were used to assess motor function, preventing the combination of efficacy data. Risdiplam, with its extensive clinical development program, is claimed to benefit all types of SMA, including pre-symptomatic and those with infantile- and adult-onset groups.

Towards the end, the company argues that comparing the clinical and economic aspects is challenging due to significant evidence gaps in nusinersen’s clinical trials and restrictions. For instance, there’s no data for nusinersen in patients over 9 years old or those with type 3 SMA. It’s also noted that the nusinersen-treated population generally has less severe SMA compared to the risdiplam population, suggesting a likely better prognosis.

The EAG disputes the company’s claim of adequately addressing the data gaps for nusinersen, particularly the lack of data for patients over 9 years old and those with type 3 SMA. Existing evidence shows nusinersen’s application in patients aged over nine years and those diagnosed with type 3 SMA. A comprehensive review and meta-analysis of real-world data on motor function in Type 2 and 3 SMA patients treated with nusinersen revealed positive changes in all functional measures at each time point, contrasting with negative changes observed in untreated cohorts.32 This suggests that nusinersen has a beneficial impact on motor function across a broad spectrum of SMA type 2 and 3 patients over a 10–14-month observation period. Other studies have shown sustained improvement in motor function in type 2 and 3 SMA patients treated with nusinersen for at least two years. These studies suggest that nusinersen may benefit older patients and those diagnosed with type 3 SMA.65, 99, 121, 159

The EAG agrees with the company’s assertion that a lower incidence of spinal complications typically indicates a more favourable prognosis. However, the prognosis can significantly vary based on the specific type of SMA, the age at symptom onset, and the individual’s overall health status. SMA is a hereditary neuromuscular condition that affects motor neurons in the spinal cord, leading to progressive muscle atrophy and weakness.

The company has depicted the synopsis of the experiments and investigations in Table 5 of CS Document B, located in section B.2.2. The EAG perceives the company’s Table 5 as lacking in comprehensiveness and detail, hence, it has furnished Table 19. This table encompasses the aims, time span, structure, and demographics, in addition to the comparators and disclosed outcomes that were specified in the decision problem.

Of the methodology of the pertinent clinical evidence in the B.2.3 of CS document B, the company indicated that, unless otherwise stated, data on the clinical trials were derived from the clinical study reports (unpublished).

Table 19: Summary of clinical effectiveness evidence provided by the EAG

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Objectives** | **Design** | **Population** | **Comparator** | **Reported outcomes specified in the decision problem** |
| **FIREFISH** | Part 1: safety, tolerability, PK and PD, dose selection for Part 2  Part 2: efficacy, safety and tolerability, PK and PD | Open-label, two-part seamless, multicentre, single-arm study | Type 1 (infantile onset);   Aged ≥1 month and ≤7 months at the time of enrolment | No | Motor function (BSID III, HINE-2, CHOP-INTEND)  Bulbar function;  Survival and ventilation-free survival;  Healthcare utilisation;  Adverse events,  HRQoL |
| **SUNFISH** | Part 1: safety, tolerability, PK and PD, dose selection for Part 2   Part 2: efficacy, safety and tolerability, PK and PD | Two-part seamless, randomised, multicentre, placebo-controlled, double-blind study | Type 2 SMA and non-ambulant type 3 SMA;   People aged 2–25 years | Placebo for the first 12 months  Single-arm OLE for the remaining 4 years | Motor function (MFM32, RULM, HFMSE);  Adverse events;  HRQoL |
| **RAINBOWFISH** | Efficacy, safety for presymptomatic patients | Open-label, single-arm, multicentre study | Pre-symptomatic   Aged from birth to 6 weeks at first dose,   Diagnosed genetically | No | Development of clinically manifested SMA,  Growth measures (weight, length, height, head circumference, chest circumference),  Degree of innervation (CMAP amplitude) |
| **JEWELFISH** | Safety and efficacy | Multicentre, open-label, non-comparative, single-arm, exploratory study | Type 1, 2 and 3   Aged 6 months to 60 years | No | Motor function (MFM-32, HFMSE, RULM, 6MWT, BSID-III, HINE-2),  Adverse events, HRQoL,  survival and ventilation-free survival |
| **REACH registries** | Safety and efficacy (were used for scenario analysis in the economic model) | Adult and paediatric SMA registry datasets,  Observational data | Patients treated with risdiplam under the MAA | No | Motor function (CHOP-INTEND, RHS, RULM, HINE, Adult registry; ATEND, EK2),  Survival and ventilation-free survival |
| HRQoL, health-related quality of life; MAA, managed access agreement | | | | | |

* + 1. Critique of efficacy results (presymptomatic population; RAINBOWFISH)

RAINBOWFISH study design that is presented at the CS B.2.3.3 is a continuing, open-label, single-arm, multicentre clinical trial designed to examine the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in pre-symptomatic patients aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA (SMN1 deletion and any SMN2 copies). Following this period, participants have the option to partake in an open-label extension phase (OLE) projected to last a minimum of three additional years. OLE phase of at least 36 months (month 24 to month 60) and a follow-up, consequently, the cumulative treatment period for each participant is anticipated to be no less than five years. In the current company’s submission, only 12 months of data from 26 patients is reported as part of the primary analysis and the ITT. The study is composed of a screening phase, a treatment period, an OLE phase, and a follow-up.

In the primary efficacy analysis, the company included a small sample of five patients, all of whom were white. These patients were evaluated across four countries: Australia, Brazil, Poland, and the Russian Federation. The absence of the United Kingdom from this list potentially undermines the validity of assumptions based on this population. All patients had two SMN2 copies and a baseline CMAP amplitude of ≥ 1.5 mV.

The company's submission, detailed in Tables 8 and 9 of Document B, provides data for both the primary efficacy (PE) population, comprising only five patients aged between 22 and 35 days, and the ITT population, which includes a total of 26 patients with varying SMN2 copy numbers.

The EAG has concerns about the small number of participants in the PE group. This could potentially undermine the study’s statistical strength and increase the likelihood of a Type II error. The company has enrolled 26 patients for the ITT analysis, but the PE group only consists of five participants. The results obtained from such a small group may have difficulty reaching statistical significance and could be imprecise. This could diminish the reliability and robustness of the findings. Furthermore, it raises questions about whether this subgroup is truly representative.

Conversely, the ITT analysis, which includes all randomized patients, maintains the advantages of randomization and offers a more conservative estimate of the treatment effect. An ITT population of 26 patients is more substantial and is likely to produce more robust and generalizable results.

The EAG has questioned the lack of reported CMAP amplitude for the ITT population, despite its inclusion in the RAINBOWFISH PE and FIREFISH baseline data. The CMAP is a crucial component of the RAINBOWFISH study, yet its reporting is incomplete. Understanding the range, median, mean, and standard deviation of the patients' CMAP amplitude could assist in identifying any imbalances between the ITT and PE analyses.

Despite these challenges, such as the small PE population and the absence of CMAP amplitude data, the EAG conducted a comparison of the ITT and PE baseline characteristics. Additionally, the EAG compiled a combined table of baseline characteristics (*see* Table 20) for both populations, as presented by the company in Tables 8 and 9 of Document B.

Table 20: RAINBOWFISH primary efficacy and intention to treat populations' demographic and baseline characteristics

|  | ***SMN2 Copy Number*** | | | | |
| --- | --- | --- | --- | --- | --- |
| **2  (N=8)** | **3**  **(N=13)** | **>=4**  **(N=5)** | **All Patients**  **(N=26)** | **PE population with 2 SMN2 copies (N=5)** |
| **Age at enrolment (Days)**  Mean (SD)  Median  25%-75%-ile  Min – Max | 22.8 (5.0)  22.5  21 – 24  15 – 33 | 28.9 (7.5)  27.0  23 – 36  19 – 40 | 31.2 (6.1)  31.0  28 – 36  23 – 38 | 27.5 (7.1)  24.0  22 – 36  15 – 40 | 24.6 (4.8)  23.0  22 – 24  21 – 33 |
| **Age at First Dose (Days)**  Mean (SD)  Median  25%-75%-ile  Min – Max | 23.9 (5.3)  23.5  22 – 25  16 – 35 | 29.9 (7.5)  28.0  24 – 37  20 – 41 | 32.4 (6.3)  32.0  29 – 37  24 – 40 | 28.5 (7.2)  25.0  23 – 37  16 – 41 | 25.8 (5.3)  24.0  23 – 25  22 – 35 |
| **Sex**  Male  Female | 4 (50.0%)  4 (50.0%) | 4 (30.8%)  9 (69.2%) | 2 (40.0%)  3 (60.0%) | 10 (38.5%)  16 (61.5%) | 2 (40.0%)  3 (60.0%) |
| **Ethnicity**  Hispanic or Latino  Not Hispanic or Latino  Not stated | 3 (37.5%)  5 (62.5%)  0 | 0  12 (92.3%)  1 (7.7%) | 0  5 (100%)  0 | 3 (11.5%)  22 (84.6%)  1 (3.8%) | 2 (40.0%)  3 (60.0%) |
| **Race**  Asian  White  Unknown | 0  8 (100.0%)  0 | 1 (7.7%)  11 (84.6%)  1 (7.7%) | 2 (40.0%)  3 (60.0%)  0 | 3 (11.5%)  22 (84.6%)  1 (3.8%) | 5 (100.0%) |
| **Country**  Australia  Belgium  Brazil  Poland  Russian Federation  Taiwan  United States | 1 (25.0%)  0  3 (37.5%)  1 (12.5%)  2 (25.0%)  0  0 | 6 (46.2%)  1 (7.7%)  0  1 (7.7%)  3 (23.1%)  0  2 (15.4%) | 0  2 (40.0%)  0  1 (20.0%)  0  2 (40.0%)  0 | 8 (30.8%)  3 (11.5%)  3 (11.5%)  3 (11.5%)  5 (19.2%)  2 (7.7%)  2 (7.7%) | 1 (20.0%)  2 (40.0%)  1 (20.0%)  1 (20.0%) |
| **Region**  Europe  Rest of the World  US | 3 (37.5%)  5 (62.5%)  0 | 5 (38.5%)  6 (46.2%)  2 (15.4%) | 3 (60.0%)  2 (40.0%)  0 | 11 (42.3%)  13 (50.0%)  2 (7.7%) | 2 (40.0%)  3 (60.0%) |
| **Weight (g)**  Mean (SD)  Median  25%-75%-ile  Min – Max | 3820.5 (435.1)  3999.0  3538 – 4073  3076 – 4270 | 4060.1(647.5)  4000.0  3560 – 4345  3400 – 5726 | 4190.0(902.9)  4170.0  3585 – 4300  3275 – 5620 | 4011.3(635.6)  4015.0  3560 – 4270  3076 – 5726 | 4049.6(151.6)  4045.0  3968 – 4100  3865 – 4270 |
| **Height / Length (cm)**  Mean (SD)  Median  25%-75%-ile  Min – Max | 53.88 (3.72)  53.0  52.5 – 54.5  49.0 – 62.0 | 53.46 (2.73)  53.0  51.0 – 55.0  50.0 – 59.0 | 54.60 (2.70)  53.0  53.0 – 57.0  52.0 – 58.0 | 53.81 (2.97)  53.0  52.0 – 55.0  49.0 – 62.0 | 55.40 (3.78)  54.0  53.0 – 55.0  53.0 – 62.0 |
| **Head Circumference (cm)**  Mean (SD)  Median  25%-75%-ile  Min – Max | 36.26 (1.44)  36.00  35.5 – 37.3  34.0 – 38.6 | 36.82 (1.21)  36.80  36.0 – 37.4  35.0 – 38.8 | 37.00 (1.77)  36.50  36.0 – 38.0  35.0 – 39.5 | 36.68 (1.37)  36.50  36.0 – 37.5  34.0 – 39.5 | 37.02 (1.10)  37.00  36.0 – 37.5  36.0 – 38.6 |
| **Chest Circumference (cm)**  Mean (SD)  Median  25%-75%-ile  Min – Max | 35.10 (2.23)  35.40  33.0 – 37.0  32.0 – 38.0 | 36.18 (2.24)  36.10  35.5 – 37.8  33.0 – 40.5 | 37.22 (3.38)  36.0  35.0 – 40.0  33.6 – 41.5 | 36.05 (2.49)  36.00  33.6 – 37.8  32.0 – 41.5 | 36.20 (1.92)  37.0  36.0 – 37.0  33.0 – 38.0 |
| **Chest to Head Circumference Ratio**  Mean (SD)  Median  25%-75%-ile  Min – Max | 0.9675(0.0342)  0.9775  0.942 – 0.994  0.914 – 1.000 | 0.9825(0.0489)  0.9740  0.963 – 1.014  0.904 – 1.066 | 1.0046(0.0500)  1.0000  0.986 – 1.051  0.933 – 1.053 | 0.9822(0.0452)  0.9810  0.963 – 1.000  0.904 – 1.066 | 0.9776(0.0347)  0.9870  0.984 – 1.000  0.917 – 1.000 |

In the ITT group, eight patients possess 2 SMN2 copies. However, three of these patients are absent from the PE population, with no rationale provided for this exclusion. These excluded patients include two males and one female, one of whom is Hispanic, while the others are not. All three are white, with one from Europe and the remaining two from other global regions. Regrettably, the company has disclosed the countries of origin for only seven of the eight patients in the ITT population with 2 SMN2 copies, leaving one patient's nationality undisclosed. It is discernible that one patient is from Brazil and another from Russia, but the third patient's country remains unknown. This unidentified patient might be part of the group excluded from the PE population and could potentially be European.

The ITT group's weight standard deviation (435.1) significantly exceeds that of the PE group (151.6), indicating a broader dispersion of values from the mean in the ITT group. Moreover, the PE group's minimum value (3865) surpasses that of the ITT group (3076), while the maximum value is consistent across both groups (4270). This suggests a more restricted range of values in the PE group, implying that some data points falling outside the range have been excluded from the PE group's lower data range. Given these removed data points and the disparities in standard deviation, potential imbalances exist that the company should have addressed. These imbalances could affect the study's validity and reliability.

The PE group's elevated mean and median values suggest that this group may generally exhibit higher values than the ITT group. Concurrently, minor discrepancies in the standard deviation and interquartile range suggest potential non-equivalence between the two groups concerning their variability and distribution of values. The PE group's standard deviation (0.0347) slightly exceeds that of the ITT group (0.0342), indicating a marginally broader dispersion of values from the mean in the PE group. The trends observed in the minimum-maximum and 25%-75% percentile range for the Chest-to-head Head Circumference Ratio align with those noted for the weight measurements. This suggests that the three excluded patients might be grappling with nutritional challenges or difficulties with feeding and swallowing. These patients might be contending with muscle weakness and skeletal abnormalities for the chest-to-head circumference ratio. All these factors could potentially contribute to a poorer prognosis.

The RAINBOWFISH trial aims to evaluate if infants with two SMN2 copies and a baseline CMAP amplitude ≥1.5 mV can sit unassisted after a year of treatment, surpassing the 5% performance criterion. This benchmark is based on the natural progression of Type 1 SMA.

The RAINBOWFISH trial is designed for a specific group of SMA patients with two SMN2 copies and a baseline CMAP amplitude of ≥1.5 mV. However, the EAG questions its relevance to the broader Type 1 SMA population due to the lack of additional data justifying the selected CMAP range. This study shows significant variability in CMAP among SMA patients. The trial’s criteria exclude patients with a severe prognosis, introducing bias. The study also reveals that pretreatment CMAP amplitudes increased six months post-treatment. Notably, patients with a pretreatment CMAP amplitude ≥2 mV showed a significant increase in CMAP post-treatment, aligning with normal motor development. This supports the EAG’s view that the trial’s criteria may not reflect real-world patient characteristics.148, 160, 161

The trial’s primary outcome is the patient’s ability to sit unassisted, but this may not reflect all potential benefits or side effects of the treatment. The EAG suggests adding performance criteria at 7.5% and 10% for a more comprehensive understanding of the treatment’s efficacy. Additionally, using a range of performance criteria could offer a nuanced view of treatment effectiveness and align with the goal of finding the most effective treatment for SMA patients. Multiple thresholds could provide insights into different levels of treatment effectiveness. A higher performance criterion could enhance the perceived impact of the trial results but may also make achieving the trial’s objectives more challenging. Conversely, a lower criterion could simplify achieving the trial’s objectives but may lessen the perceived impact of the results. The performance criterion should be both challenging and achievable to provide meaningful information about the treatment’s effectiveness.

The study involves two key populations: the ITT population and the PE analysis population. The primary endpoint of the study is the proportion of infants who can sit without support after 12 months of treatment. If the one-sided p-value is <5% (Type 1 error rate), then the null hypothesis will be rejected. Please refer to Table 21, which shows the key efficacy endpoint of the RAINBOWFISH study. This table is a replica of Table 14 from CS Document B.

The primary analysis was conducted once the last patient enrolled had reached 12 months of treatment. All infants enrolled will continue to receive treatment to provide unbiased estimates of the secondary and exploratory endpoints. Analyses of the secondary efficacy endpoints will be performed using all data available at the time of the 12-month, 24-month, and further analysis reporting events. For the primary efficacy population only, the proportion of patients who are alive and have achieved the motor milestone δ 5% (null) versus p > 5% (alternative) will be analysed.

Table 21: Key efficacy endpoints in RAINBOWFISH (paediatric, pre-symptomatic, genetically diagnosed SMA

|  |
| --- |
| ***Development of clinically manifested SMA*** |
| * Proportion of patients developing clinically manifested SMA at month 12 and month 24 |
| ***Survival and ventilation-free survival*** |
| * Time to death or permanent ventilationa (from enrolment) * Proportion of patients who are alive without permanent ventilation at month 12 and 24 * Proportion of patients who are alive at month 12 and 24 |
| ***Motor function and development milestones*** |
| * Proportion of patients who achieve the attainment levels of the motor milestones as assessed in the HINE-2 (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) at month 12 and 24 * Proportion of patients sitting without support for 5 seconds, sitting without support for 30 seconds, standing alone, walking alone at month 24 as assessed in Item 22, 26, 40 and 42 of the BSID-III Gross Motor Scale, respectively * Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of chronological reference standard at Months 24 and 42 (as assessed through the use of the BSID-III Gross Motor Scale) * Change from baseline score in the CHOP INTEND motor function scale at Month 12 * Proportion of patients who achieve a score of ≥40, ≥50, and ≥60 or higher in the CHOP INTEND motor function scale at Month 12 * Proportion of patients who meet CHOP INTEND stopping criteria at any point up to Month 24 * Change from baseline (Month 24) in the HFMSE at Month 60 of treatment |
| ***Growth measures*** |
| * Number and proportion of patients within 3rd percentile of normal range for weight-for-age, length/height-for-age, weight-for-length/height, and head circumference-for-age at Month 12, 24, 36, 48 and 60 o, based on the WHO Child Growth Standards (WHO 2019) * Change from baseline percentiles for weight-for-age, length/height-for-age, weight-for-length/height, and head circumference-for-age at Month 12, 24, 36, 48, 60 * Change from baseline in chest circumference at Month 12 and 24 * Ratiob between chest and head circumferences at Month 12 and 24 |
| ***Nutrition*** |
| * Proportion of patients with the ability to swallow at month 12, 24, 36, 48 and 60 * Proportion of patients with the ability to feed orally at month 12, 24, 36, 48 and 60 |
| ***Muscle electrophysiology*** |
| * Change from baseline in CMAP amplitude at month 12 and 24 |

aPermanent ventilation is defined as 16 hours of non-invasive ventilation per day or intubation for  21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy, bHead circumference will be the denominator of the ratio

* + - 1. Outcomes of interest
         1. Overall survival/time to death or permanent ventilation

By the time of the CCOD, no patient required permanent ventilation, and all patients were alive without permanent ventilation at month 12. One patient with 2 SMN2 copies developed clinically manifested SMA at month 12 and withdrew from the study.

* + - * 1. Motor function

The clinical trial of risdiplam treatment for 12 months showed significant improvements in patients' motor functions. The primary goal of patients being able to sit without support for 5 seconds was achieved by 80% of patients, surpassing the predefined success rate of 5%. Notably, patients developed more complex abilities like standing and walking.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

At month 12, all but one patient (96%) were sitting without support, and of those, 92% achieved the highest level of sitting. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, 52% could stand unaided, and 48% were walking independently.

Patients achieved high levels of motor function, with a median CHOP-INTEND score near the maximum. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

* + - * 1. Growth parameters

A significant proportion of patients who underwent 12-month treatment with risdiplam demonstrated steady progress. This growth, which aligns with their age-related expectations, was observed across all assessed parameters of growth and development from the initiation of treatment to the 12-month mark.

* + - * 1. Dysphagia/bulbar function

Patients maintained their ability to feed orally and swallow, with no patients requiring tube feeding. At month 12, all patients could swallow, and 96.2% could feed orally.

* + - * 1. Need for ventilation

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

* + - * 1. Frequency and duration of hospitalization

As per the company’s analysis of the clinical efficacy and safety data outlined in section B.2.12 of the CS, no hospitalizations were necessary during the 12-month outcome period.

* + - * 1. Quality of life

Within the RAINBOWFISH and FIREFISH studies, the ITQOL Questionnaire was used as company stated in the B.3.4 of CS. However, utility data were not collected in either study, as company considers that the EQ-5D is not validated in children and there are well-known limitations in conceptualising, collecting and measuring utility data in infants and young children.

* + - * 1. Adverse Events

A total of 26 patients received at least one dose of study treatment. The median duration of treatment exposure was \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. Out of 26 patients, 92.3% had at least one AE and no death has been reported for the RAINBOWFISH. Only four patients had SAEs. Most of the reported AEs in the total population are categorized as Grade 1 AEs. The company states that only \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* The company’s assumption has not been validated by the EAG. The sole basis for this conclusion is attributed to the investigators’ decision. Given that the data reported by RAINBOWFISH is confined to a limited number of participants, it is imperative to conduct further studies to gain a more comprehensive understanding of the AEs. This will enable a more robust and reliable assessment of the safety of risdiplam in pre-symptomatic patients.

* + - * 1. Summary

The data and evidence presented by the company suggest its effectiveness in various assessments of patient motor functions, bulbar functions, respiratory metrics, and growth measurements. However, the EAG expressed concerns and comments about the methodologies employed, the number of patients evaluated, and the diverse approaches taken. While the effectiveness appears promising, the ambiguity in certain sections and interpretations warrants a more thorough and comprehensive discussion to arrive at a robust conclusion.

* + 1. Critique of efficacy results (type 1; FIREFISH)

The company’s B.2.3.1 section provides details on the FIREFISH trial and study design. FIREFISH is a two-part, multicentre study that evaluates the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in infants with Type 1 SMA. The study consists of an exploratory dose-finding phase (Part 1) and a confirmatory phase (Part 2) to assess the safety and efficacy of risdiplam. After selecting the dose for Part 2, 21 participants from Part 1 continued receiving risdiplam, leading to a total treatment duration of 24 months. Part 2 also lasted 24 months, with the primary analysis conducted at the 12-month mark.

Both phases were followed by an open-label extension (OLE) phase, lasting 3 years. A total of 52 patients participated in the OLE phase. The company’s submission indicates that 21 patients from Part 1 continued their treatments into Part 2. Risdiplam’s peak plasma time is between 1-4 hours, and it primarily binds to serum albumin. When administered daily, it results in a three-fold accumulation of peak plasma concentration and the area under the plasma concentration-time curve from 0 to 24 hours. Steady-state exposures are achieved within 7 to 14 days. This information is based on studies conducted in healthy individuals.162-164

The washout period for risdiplam is not explicitly stated in the literature. However, considering its terminal elimination half-life of approximately 50 hours, it would typically take around 10 to 12 days for risdiplam to be nearly eliminated from the body. A study mentioned a minimum treatment-free period of 120 days before starting risdiplam therapy following the administration of nusinersen, or of ≥ 12 weeks following onasemnogene abeparvovec therapy.80, 165 These are general estimates, and the exact timing can vary based on individual factors such as age, metabolism, and other health conditions. The data of the 21 patients’ clinical effectiveness and safety is influenced by their previous enrolment, which could potentially bias the findings of the confirmatory Part 2 of the study. The company should have justified the variances between distinct time intervals of physical and effectiveness evaluations, considering the OLE phase and the 24-month treatment duration. In conclusion, it is important to highlight that the previous paragraphs raise questions about the company’s strategy of combining patients from Phase 1 and Phase 2 without any scientific justification and considering possible biases, and then extending all to the OLE phase. The dosages received by Phase 1 patients varied, being either higher or lower than the final dose. This approach is being questioned for its validity.

In the FIREFISH Part 2 study, 41 patients were enrolled, with a slight female majority (53.7%). The median age at enrolment was 5.3 months, ranging from 2.2 to 6.9 months. Most patients were either White (53.7%) or Asian (34.1%), with a small percentage of unknown ethnicity (12.2%). The median age at symptom onset was 1.45 months, and the median age at diagnosis was 2.79 months. The patient distribution was primarily from Europe (58.5%) and China (26.8%), with no specific data for UK patients.

The disease duration, defined as the time from symptom onset to treatment initiation, was less than 3 months for 65.9% of patients and 3 months or more for 34.1%, resulting in a median disease duration of 3.4 months.

All patients had 2 SMN2 copies and none had received a tracheostomy before the study. The median baseline scores for CHOP-INTEND, BSID-III, HINE-2, and CMAP amplitude were 22.0, 2.0, 1.0, 0.2 mV, respectively. The range of motor function scores is not wide, with CHOP-INTEND having a wider range compared to others. The data distribution is generally normal, with other motor function scores slightly skewed to the right. This confirms the company’s statement that all patients had well-established diseases by the time of study enrolment.

Most of the enrolled patients (70.7%) did not require respiratory support, while the rest may have used non-invasive respiratory support for less than 16 hours per day. Almost all patients were able to swallow (97.6%) and were primarily fed liquids. Most were fed orally, with nearly 10% fed via a feeding tube. The company has provided the essential baseline characteristics of Part 2 of the FIREFISH study in section B.2.3.5. Additionally, these details are reported in Table 22 of the EAG’s report, which is a replica of Table 6 in Document B of the CS.

Table 22: FIREFISH Part 2 key demographic and baseline disease characteristics

|  |  |
| --- | --- |
|  | **Risdiplam**  **N=41** |
| Median age at enrolment, months (range) | 5.32 (2.2–6.9) |
| Median age at onset of symptoms, months (range) | 1.45 (1.0–3.0) |
| Median age at diagnosis, months (range) | 2.79 (0.9–6.1) |
| Sex, n (%)  Male  Female | 19 (46.3)  22 (53.7) |
| Race, n (%)  White  Asian  Unknown | 22 (53.7)  14 (34.1)  5 (12.2) |
| Region, n (%)  Europe  North America  China  Japan  Rest of world | 24 (58.5)  1 (2.4)  11 (26.8)  1 (2.4)  4 (9.8) |
| Median disease duration, months (range)  ≤3 months, n (%)  >3 months, n (%) | 3.38 (1.0–6.0)  14 (34.1)  27 (65.9) |
| *SMN2* copy number, n (%)  2 | 41 (100) |
| Tracheostomy, n (%)  Yes  No | 0  41 (100) |
| Median CHOP-INTEND score (range) | 22.0 (8.0–37.0) |
| Median BSID-III gross motor scale total raw sore (range) | 2.0 (0.0–8.0) |
| Median HINE-2 score (range) | 1.0 (0.0–5.0) |
| Median CMAP negative peak amplitude, mV (range) | 0.19 (0.0–0.8) |
| Current level of motor function, n (%)  Head control carried upright  Head control ventral  No appropriate function listed | 1 (2.4)  1 (2.4)  39 (95.1) |
| Highest motor function achieved, n (%)  Controls head upright  Kicking horizontally  Kicking vertically  No appropriate function listed | 2 (4.9)  2 (4.9)  2 (4.9)  35 (85.4) |
| ***Baseline level of respiratory support*** | |
| Current level of respiratory support, n (%)  No pulmonary care  BiPAP support <16 hours per day  BiPAP support ≥16 hours per day  Cough assist – used daily for therapy, not illness related  Cough assist – used with an illness | 29 (70.7)  10 (24.4)  0  3 (7.3)  1 (2.4) |
| Ventilation provided prophylactically, n (%)  Yes  No  Awake assisted ventilation  Night-time assisted ventilation  Nap-time assisted ventilation  >16 h assisted ventilation  Airway clearance through cough assistance | 11 (26.8)  20 (73.2)  0  9 (22.0)  2 (4.9)  0  3 (7.3) |
| BiPAP support ≥16h per day for >21 consecutive days, n (%)  Yes  No | 0  41 (100) |
| Intubation for >21 consecutive days, n (%)  Yes  No | 0  41 (100) |
| ***Baseline nutritional check up*** | |
| Able to swallow, n (%)  Yes  No  Missing | 40 (97.6)  1 (2.4)  0 |
| Median age ability to swallow lost, months (range) | n=1  1.58 (1.6–1.6) |
| Primary food intake type, n (%)  Oral fluid (milk) food intake  Mixed (fluid/pureed food) oral intake  Modified oral food intake  Solid food  Nasogastric food intake  Gastrostomy tube fed  Missing | 30 (73.7)  4 (9.8)  0  0  6 (14.6)  1 (2.4)  0 |
| Feeding route, n (%)  Fed orally  Fed via a feeding tube  Fed via a combination of oral and tube feeding  Missing | 33 (80.5)  4 (9.8)  2 (4.9)  2 (4.9) |

According to Roche’s description, the second phase of the FIREFISH study aimed to determine if the proportion of infants who could sit unassisted after a year of treatment exceeded a predefined performance criterion of 5%. This benchmark was based on the natural history of type 1 SMA, where infants are typically unable to sit independently. The study targeted a sample size of 40 infants, ensuring at least 90% power to test the null hypothesis (p≤0.05) against the alternative (p>0.05), assuming a true sitting proportion of 20%. Early withdrawals were classified as non-responders and included in the primary analysis. After a 24-month treatment period, patients could opt to enter the OLE to continue receiving risdiplam for up to five years, allowing for the evaluation of long-term efficacy outcomes.

The company cites references and asserts that historical studies of natural history indicate that type 1 SMA infants have never achieved major motor milestones such as independent rolling or sitting and have a median age of death (or a requirement of at least 16 hours/day of non-invasive ventilation) of 10.5 months. However, due to the lack of long-term natural history data, no formal statistical comparisons with natural history data were possible.166-168

The company’s claim that historically, infants with type 1 SMA have been unable to reach significant motor milestones such as independent rolling or sitting is not entirely consistent with the EAG’s evaluation of this issue. The EAG partially supports this claim, noting that recent therapeutic advancements have allowed a subset of infants with SMA type 1 to achieve these milestones.168, 169 However, the median age of death among this population varies. One research study suggests a median age of approximately 7.3 months for reaching death or the need for permanent ventilation. In contrast, another source indicates that in the absence of medical intervention, the average lifespan of infants with SMA type 1 is approximately two years.170, 171 Yet another source cites the median survival age as being between 8 and 10 months.20, 172, 173

Regarding non-invasive ventilation, it is commonly used in infants with type 1 SMA, often before the onset of respiratory difficulties. This strategy can assist in preparing for respiratory failure and reducing chest deformities.174 It has been reported that nearly all children with type 1 SMA experience improved respiration during sleep when some form of ventilation is utilised.173, 175

In the second phase of the FIREFISH study, all enrolled participants were included in the Intent-to-Treat (ITT) analysis, serving as the main group for efficacy analyses. However, weight-for-age and length/height-for-age percentiles were analysed based on the safety population. These metrics, typically classified as clinical data, can also provide safety information under certain circumstances. The company incorporated these outcomes into their safety analysis, but it would be beneficial to include them in the efficacy and ITT analysis as well.

The study’s second phase provided efficacy results compared with the natural progression of untreated infants with type 1 SMA. Additionally, a comparison was made between risdiplam and other treatments in patients with type 1 SMA. The study aimed to see if more than 5% of infants could sit without support after 12 months of treatment. However, due to traditionally poor outcomes for type 1 SMA infants, no formal statistical comparisons were possible for the long-term study data. The key efficacy endpoints of FIREFISH are compiled by the company in Table 12 of CS Document B and reported by the EAG in Table 23.

The EAG has commented on the efficacy assessment section provided by the company. The Infant Toddler Quality of Life Questionnaire (ITQOL-SF47) is a reliable tool for capturing patient/caregiver-reported outcomes, but it has limitations. Other robust tools are available for assessing health-related quality of life in infants and toddlers.176-178

The company reports using a hierarchical testing approach to control for multiplicities across different time points. While the hierarchical testing approach is valid and robust for controlling the familywise error rate, it may overlook potentially meaningful effects at secondary time points if the primary endpoint is not significant.

The approach of using independent central readers to analyse the results of the main study, and site clinical advisors to evaluate the outcomes of the OLE, has its pros and cons. The central readers, not being part of the patient’s care, are less likely to be biased in their evaluations. They can also ensure a consistent method of assessing outcomes across different sites. On the other hand, site clinical advisors, who are involved in patient care, might have biases that could influence their evaluations in the OLE. In an OLE context, the awareness of the treatment given to both investigators and patients could lead to bias. From a statistical perspective, this method does not inherently cause problems, but the potential for bias should be acknowledged and mitigated where possible. No steps were taken in the OLE to lessen the impact of the bias due to the central and on-site readers. To mitigate this, apply blinding where possible, standardise training and protocols, use mixed-effects models, conduct sensitivity analyses, and consider secondary confirmation by central readers. Clear documentation of these procedures is crucial for maintaining reliability and validity.

Table 23: Key efficacy endpoints in FIREFISH (infantile-onset type 1 SMA)

|  |
| --- |
| ***Motor function and development milestones*** |
| * Proportion of patients sitting without support for at least 5 seconds, as assessed by Item 22 of the BSID‑III gross motor scale a * Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline * Proportion of motor milestone responders as assessed by the HINE-2b * Proportion of patients able to support weight or stand with support as assessed by the HINE-2 * Proportion of patients able to bounce while assessing the walking item of the HINE-2 |
| ***Survival and ventilation-free survival*** |
| * Proportion of patients alive without permanent ventilation (≥16 hours of 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)   * Proportion of patients alive |
| ***Nutrition*** |
| * Proportion of patients with the ability to feed orally * Proportion of patients with the ability to swallow |
| ***Healthcare utilisation*** |
| * Number of hospitalisations per patient-year * Proportion of patients with no hospitalisations |
| ***Patient/caregiver reported outcomes*** |
| * Change from baseline in the ITQOL-SF47 Questionnaire domains and single item scores |

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

* + - 1. Outcomes of interest
         1. Overall survival/time to death or permanent ventilation

The percentage of infants who were alive without the need for permanent ventilation was 85.4% after a year. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\* The median time to death or the need for permanent ventilation could not be estimated due to the low number of events. However, when compared with historical data, the treatment with risdiplam significantly improved survival without events.

* + - * 1. Motor function

The FIREFISH part 2 results show that after 12 months of risdiplam treatment, 29.3% of patients could sit without support, surpassing the 5% performance criterion based on natural history data. Also, 56.1% achieved a CHOP-INTEND total score of 40 or higher, and 90.2% saw an increase of at least 4 points from their initial score.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

At Month 24, 43.9% of patients were sitting without support for 30 seconds, more than double the number at Month 12. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*

After a year of treatment, more than half of the patients achieved a CHOP-INTEND total score of 40 or more. These improvements were sustained and enhanced at the 24-month mark and maintained up to the 48-month mark.

Initially, only 4.9% of patients could control their heads. This increased to 53.7% after a year and 70.7% after two years. After a year, 78.0% of patients were classified as motor milestone responders.

* + - * 1. Growth parameters

As for the analysis populations of CS B.2.4.1.2, company assets that with the exception of the weight-for-age and length/height-for-age percentiles which have been analysed in the safety section, no other growth measurements have been found or reported. The EAG has evaluated the approach taken by the company and has thoroughly discussed it in the context of critiquing the statistical interpretations. The EAG was unable to locate any additional data related to this matter.

* + - * 1. Dysphagia/bulbar function

At Month 12, 82.9% of patients had the ability to feed orally. This remained relatively stable at Month 24, with 85.4% able to feed orally.

* + - * 1. Frequency and duration of hospitalisation

The rate of hospitalisations decreased over time. There was a total of 50 hospitalisations by month 12, resulting in a rate of 1.30 (90% CI: 1.02, 1.65) hospitalisations per patient-year. \*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\* \*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.

* + - * 1. Quality of life

According to company’s submission section B.3.4, in the FIREFISH and RAINBOWFISH studies, the ITQOL Questionnaire was utilized. However, neither of the studies collected utility data, as the EQ-5D is not validated for use in children according to the references provided. There are recognized challenges in conceptualizing, gathering, and measuring utility data in infants and young children. While parents or caregivers might be able to provide proxy assessments of a patient’s HRQoL, these assessments may not accurately reflect the HRQoL in SMA patients.

* + - * 1. Adverse Events

According to the company’s B.2.10.1 section regarding the AEs of FIREFISH, they have provided data about the exposure to risdiplam. Accordingly, in Part 2 of the FIREFISH study up to the CCOD of 22 November 2022, the median duration of exposure to risdiplam was \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* All patients had received at least \*\*\* of the total number of prescribed doses (dose intensity). \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. \*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*; their mean and median are reported in Table 87 of CS document B. In total, \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\* \*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*

* + - * 1. Summary

The company has shared the long-term results of using risdiplam on patients with SMA type 1, administered through the FIREFISH program. The EAG has expressed some doubts about the methods used. Despite these concerns, the overall results of risdiplam indicate progress in various areas, including motor functions and respiratory outcomes.

* + 1. Critique of efficacy results (type 2 and 3; SUNFISH)

The SUNFISH study is a two-part, multicenter, randomized, placebo-controlled, and double-blind investigation. It aims to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in adult and pediatric patients with later-onset (type 2 and type 3) SMA. Like the FIREFISH study, SUNFISH consists of a dose-finding part (Part 1) and a confirmatory part (Part 2) to evaluate the safety and efficacy of risdiplam at the dose level determined from Part 1. Part 2 investigates the efficacy and safety of risdiplam over a 24-month treatment period in patients aged 2-25 years with type 2 and non-ambulant type 3 SMA. After the dose for Part 2 was selected, patients in Part 1 transitioned to the chosen dose as part of an OLE phase. Efficacy outcome measures were assessed throughout Part 1, including the OLE phase. After week 104, all patients could join the OLE for 3 years.

A total of 168 patients were randomized in a 2:1 ratio to receive either risdiplam or placebo. These patients were then stratified by age group. Patients in Part 2 who initially received placebo switched to active treatment at week 52. Notably, the initial treatment assignment remained blinded to patients and clinical site staff until all patients completed the week 104 study visit.

According to Table 7 in Document B, 120 patients were allocated to the risdiplam group and 60 to the placebo group. The median age during the screening phase was 9.0 years for both groups, with a range of 2–25 years for the risdiplam group and 2–24 years for the placebo group. The median age at symptom onset was 12.3 and 12.8 years for the risdiplam and placebo groups, respectively. However, CADTH data179 shows a higher mean age at symptom onset for the placebo group (18.5 vs 14.1), suggesting more variability in this group. Despite similar medians, the placebo group showed a larger standard deviation and range, indicating a greater data spread and potential outliers.

The data sets appear imbalanced, contradicting the company’s claim of balance. The placebo group shows more variability, which could affect statistical results and data interpretation.

Both groups have the same mean (111.3), but the intervention group’s median is higher (106.6 vs 96.6), suggesting a positive effect on at least half of the population, assuming normal distribution. The intervention group’s data is less spread out and more consistent, as indicated by a narrower range (17-275 vs 1-271) and slightly lower standard deviation (67.1 vs 70.2).

Discrepancies in the data sets are suggested by differences in median and range regarding the time from symptom onset to first treatment. The intervention appears to eliminate extremely low values and increase the median without affecting the mean, indicating a significant effect on a subset of the population. The difference in ranges suggests minor imbalances, with the placebo group showing a wider range, potentially indicating outliers or larger population variability. The narrower range in the intervention group suggests more consistent outcomes.

Most of the population were white (67.2%) in both groups, with most having 3 and 4 SMN2 copies. The company added one unknown patient to the 3 SMN2 copies subgroups without explanation.

Patients in SUNFISH Part 2 represent a broad range of late-onset SMA, including both type 2 and non-ambulant type 3 SMA. People with contractures were not excluded.

Baseline data favours risdiplam for patients who could stand or walk, although differences are small and insignificant. More patients with scoliosis were allocated to the risdiplam group.

The risdiplam group had a lower degree of curvature at baseline, suggesting imbalances in this section favouring risdiplam. The placebo group had a higher proportion of patients with severe curvature, potentially biasing the study results.

Data on scoliosis surgery before screening is incomplete. The company has not provided all data in this regard. The unknown patients are allocated almost 6.6% more to the risdiplam arm.

In the FIREFISH baseline characteristics table (Table 6, Document B), the company provided details on baseline motor function, respiratory support level, and nutritional status. However, in the SUNFISH data, these details are only briefly mentioned. Regrettably, the company has not provided extensive data on baseline motor function outcomes, despite more comprehensive reporting for FIREFISH Part 2.

According to the CADTH submission, the company has included this data in a subsequent table, but the information is not thoroughly explained. The EAG has merged the data from the CADTH179 and EMA180 submissions in Table 24. There are minimal differences between the risdiplam and placebo groups, none of which are likely to cause imbalances.

Despite the lack of comprehensive and more detailed explanation, the EAG has identified potential bias in this section and expected that the company provide a more acceptable data set for this section.

Table 24: Summary of Motor Function Baseline Characteristics for SUNFISH

|  |  |  |
| --- | --- | --- |
| MFM-32 total score | **Risdiplam** | **Placebo** |
| Number of patients with a valid MFM- 32 observation at baseline, n | 115 | 59 |
| Mean (SD) | 45.48 (12.09) | 47.35 (10.12) |
| Median (range) | 46.88 (16.7−71.9) | 47.92 (17.7−71.9) |
| RULM total score | | |
| Number of patients with a valid RULM observation at baseline, n | 119 | 58 |
| Mean (SD) | 19.65 (7.22) | 20.91 (6.41) |
| Median (range) | 19.00 (3.0−36.0) | 20.00 (9.0−38.0) |
| HFMSE total score | | |
| Number of patients with a valid HFMSE observation at baseline, n | 120 | 60 |
| Mean (SD) | 16.10 (12.46) | 16.62 (12.09) |
| Median (range) | 14.00 (0.0−48.0) | 1. (2.0−43.0) |

The SUNFISH study's second phase aimed to determine if the mean change from baseline in total MFM32 score at Month 12 was significant, with a target sample size of 168 participants. After 12 months, all patients initially on placebo switched to active treatment, making subsequent efficacy endpoints exploratory.

The ITT population, including all randomized patients, was the primary group for efficacy analyses. The primary efficacy was based on a hypothetical treatment strategy, assuming no other treatments for SMA were available and patients continued their randomised treatment until the primary analysis timepoint.

Motor function was evaluated using three validated scales: MFM32, RULM, and HFMSE. The MFM32 scale was selected to assess the primary endpoint. The primary analysis was conducted on the change from baseline in the total MFM32 score using all data collected in the second phase up to 12 months.

The SMA Independence Scale (SMAIS) was developed to evaluate function-related independence, a crucial aspect for individuals with type 2 and type 3 SMA. The SMAIS has been validated through quantitative analysis using SUNFISH data and an independent US survey.

The EAG acknowledges the company's rationale in developing the SMAIS for SMA patients, a strategy often used when existing scales don't fully capture specific outcomes of interest.181-183 The SMAIS, designed to assess function-related independence, measures the level of assistance needed for daily activities. This provides valuable insights into a patient’s functional status and the disease's impact on their life.184, 185

Key considerations in developing a new scale are its reliability (consistency) and validity (ability to measure what it's intended to).181-183 The SMAIS has proven capable of detecting significant changes in the level of assistance required for daily activities in individuals with type 2 SMA and non-ambulant individuals with type 3 SMA.183

While this approach is valid and reasonable, the company should provide comprehensive details about its specifics, context, and methodology. This could have allowed the EAG to evaluate its appropriateness, validity, reliability, reproducibility, convenience for patients and caregivers, and consistency across all types of SMA patients. However, the EAG questions the reliability of the references in the last paragraph of B.2.4.2.3, as they are primarily authored by individuals financially supported by the company. Independent reviews analysing a larger patient population could offer a valuable critique of the SMAIS's efficacy and reliability.

To control the type I error rate due to multiple testing of risdiplam versus placebo for the primary and five key secondary efficacy endpoints in the ITT population, a gatekeeping approach was applied to the six null hypotheses, which were grouped into five families. While this method reduces the risk of false positives and prioritises key hypotheses, it may decrease power for secondary endpoints and adds complexity to the analysis. The study's conclusions about secondary outcomes depend on the primary results, impacting the overall interpretation.

Following the initial 12-month placebo-controlled period of the SUNFISH clinical trial, all patients had the opportunity to switch to risdiplam. Therefore, only summary descriptive statistics were possible for long-term data collected after the primary analysis (24 – 60 months). The EAG deems it statistically rational and defensible to employ summary descriptive statistics for the analysis of long-term data collected post-primary analysis.

* + - 1. Outcomes of interest
         1. Motor function

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* The MMRM analysis of the MFM32 total score at month 12 showed a significant improvement in patients treated with risdiplam compared to those on placebo. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

In an analysis of the RULM total score, the average change from the start of the study to Month 12 was significantly higher in patients receiving risdiplam compared to those receiving a placebo. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*

In the analysis of the HFMSE total score during the placebo-controlled period, the average change from the start of the study to Month 12 was higher in patients receiving risdiplam than in patients receiving placebo. Of patients who started the study with risdiplam treatment, \*\*\*\*\* achieved a ≥2 improvement in HFMSE total score at week 260.

* + - * 1. Quality of life

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

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* + - * 1. Adverse Events

Based on the data of treatment duration, \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. The treatment’s safety summary is reported. \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. All AEs reported as related to study medication by the investigator resolved except for \*\* AEs. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.

* + - * 1. Summary

The SUNFISH trial part 2 evaluated risdiplam's effectiveness in type 2 and 3. The primary and several key secondary endpoints were met, indicating improvement or stabilisation in a broad SMA population. Specifically, there was a significant improvement in the MFM32 total score at Month 12 with risdiplam compared to placebo.

* + 1. Critique of efficacy results (type 1, 2 and 3; JEWELFISH)

JEWELFISH is an open-label study that examined the safety, tolerability, PK, and PD of risdiplam in patients with type 1,2 and 3 SMA who had previously undergone treatment. These individuals had received therapies such as nusinersen, onasemnogene abeparvovec, olesoxime, or were participants in the MOONFISH study. The body’s reaction to a new treatment could be influenced by these prior treatments, resulting in variability in efficacy and safety outcomes, and the potential development of resistance or tolerance to certain adverse effects.186, 187

Investigating patients who have not received treatment before can offer a more transparent view of the drug’s efficacy and safety, as there are no confounding influences from previous treatments. This can be advantageous in comprehending the actual pharmacological effect of the drug and can act as a reference point for comparing the effectiveness of various treatments. Early intervention with potent therapies in patients who have not received treatment before may inhibit disease progression and result in improved long-term outcomes.188-190

The main goal of the JEWELFISH study was to evaluate safety, with efficacy data serving only as exploratory endpoints. As a result, this submission only includes safety outcomes. The efficacy results will be shared once the study is concluded.

* + - 1. Outcomes of interest

The company has disclosed AEs related to JEWELFISH in section B.2.10.3 of the CS, which are summarized in the present section. However, exploratory results and outcomes are also available. The company states that after a 24-month treatment period for the ITT population, the company reports that preliminary efficacy data suggests stability in motor function, as assessed by MFM-32 and RULM, across a diverse patient cohort aged 2-60 years. The HFSMA total score remained unchanged from the baseline.

The EAG evaluated Table 63 of the company's appendices, the only data provided on JEWELFISH's efficacy. Regrettably, none of the efficacy endpoints appeared statistically satisfactory among the various subcategories based on previously administered treatments. While there have been improvements in clinical efficacy, the statistical analysis, with a confidence interval including zero, did not yield any statistically significant results.

The only significant statistical improvement reported for the onasemnogene abeparvovec (AVXS-101) was for the motor function milestones, and the mean (SD) change from baseline in SMAIS-ULM caregiver-reported total score. Other outcomes were deemed non-evaluable for this group, possibly due to the small sample size of 11 patients (ITT population). Other treatment groups rarely showed statistically significant improvements with more patients and better power of study.

It's noteworthy that despite the lack of statistical significance in treatment effects, some improvements have been observed. The JEWELFISH EAG report concludes that risdiplam could be a valuable treatment option for patients, provided the company uses a standard sample size and addresses the concerns raised by the EAG regarding the effects of previous treatments on the patients included in the JEWELFISH study.

* + - * 1. Adverse Eventss

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* The median total duration of risdiplam in all patients was \*\*\*\*\*\*\*\*\*\*\*. The patients who received risdiplam were all participating in the JEWELFISH following previous therapeutic groups of nusinersen (\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*), AVXS-101 (\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*), olesoxime (\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*), and BP29420 (\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*). The EAG expresses concerns regarding the impact of prior treatments on the effectiveness of risdiplam and the reliability of the reported AEs. These concerns have not been adequately addressed by the company. For example, there are inconsistencies toward the AEs in different subcategories based on the company’s provided Table 95 of CS document B. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* According to the company, \*\*\*\*\*\*of events had maximum intensity Grade 1 or 2 and only \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

* + 1. Critique of REACH registries results (SMA in clinical practice)

The company's statements on the REACH registries are reported in CS, Document B, B.2.3.4. To provide additional longitudinal data on risdiplam's use in a clinical setting, address uncertainties highlighted in the initial NICE appraisal (TA755), and inform this updated NICE submission, the company has used data from the SMA UK's REACH registry for both children and adults. This data is collected from SMA patients who have participated in neuromuscular clinics across the UK. SMA REACH UK is part of an international initiative, the International SMA Consortium (ISMAC), which collects anonymized natural history data of SMA patients across the full spectrum of SMA severity. The data includes safety and efficacy data for current and future treatments, some of which may be provided to NICE, NHS England, and companies developing the treatments in an anonymized format. According to the company's submission, data on the specified outcomes of interest for all patients are reported at baseline and recorded by the patient's healthcare team within six months of starting treatment. Outcomes are then assessed and reported within 3 months of each routine 6-month follow-up clinical appointment.

In the company's submission (section B.5.2.3.8) regarding the REACH registries, it is noted that nusinersen was approved and funded in the UK prior to risdiplam. As a result, most patients who began risdiplam treatment were not eligible for nusinersen, as eligible patients had already started treatment. Consequently, risdiplam patients typically presented more severe initial symptoms, including scoliosis, compared to those treated with nusinersen. This difference in initial patient characteristics complicates the comparison of clinical outcomes between the two treatments.

The EAG acknowledges that the initial differences in scoliosis prognosis between the risdiplam and nusinersen groups make direct comparisons challenging. However, these differences do not preclude comparisons entirely. Advanced statistical methods, such as stratification, matching, regression adjustment, or propensity score methods, can adjust for these initial differences and focus on treatment effects. Nonetheless, results should be interpreted cautiously, considering the potential impact of these initial characteristics on the outcomes.

In the REACH registries, 126 paediatric patients were categorised based on their SMA type. The company reported the mean, median, standard deviation (SD), and range for these groups. For SMA type 1, most patients had 2 SMN2 copies, while other subtypes predominantly had 3 copies. However, the number of SMN2 copies was unknown for nearly half of all patients with type 2/3 SMA, introducing uncertainties regarding disease severity, progression, and risdiplam effectiveness across different subgroups.

The company states that 64.29% of the entire cohort exhibited scoliosis, making these patients ineligible for nusinersen treatment. However, risdiplam could be a viable alternative. This assertion is supported by the EAG, given that 70.29% of type 2/3 patients had scoliosis.

Regarding the CHOP-INTEND test scores, the baseline data for type 1 SMA revealed a mean of 28.85 and a median of 25.00 among a group of 13 patients. After rescaling the scores, the mean and median for the same group became 32.33 and 35.00, respectively, indicating a possible left skew in the distribution.

The adult registry comprised 176 patients, the majority of whom had type 2/3 SMA. If a patient from the paediatric cohort transitions to the adult dataset during the data collection period, new baseline patient characteristic data will be collected at the first routine visit scheduled after they turn 18 years of age. Consequently, their adult dataset baseline data may not accurately reflect their true baseline data prior to beginning treatment, potentially skewing the data. However, a sensitivity analysis is planned to assess the impact of removing any transitioning patients.

The company has reported the baseline characteristics of the adult cohort in Table 11 of CS Document B, which is incorrectly captioned for paediatrics when it is for adults. Unlike the paediatric cohort, the company has not reported the total data measurements for the 176 patients in the adult cohort. These measurements have been assessed only for each subgroup. All five patients with SMA type 1 have an unknown number of SMN2 copies. The SD for most of the reported outcomes at baseline for the type II/III- Sitters/Walkers is higher than other subgroups, indicating a wider spread and variation in the data. Possible outliers could significantly impact the following column of patients.

The company conducted a statistical analysis on eligible patients in the SMA REACH UK and Adult SMA REACH registries to supplement ongoing, long-term clinical trial data for risdiplam. The analysis was descriptive and used mixed-effects modelling for two cohorts: SMA type 1 and SMA type 2 or 3.

The company asserts that registry data, collected from patients receiving a drug through managed access, is not expected to include a comparator group. However, the EAG questions this approach, as it differs from the company's single-arm studies, SUNFISH and JEWELFISH. The EAG also raises concerns about the company's assumptions for this analysis and the lack of adjustment for multiple comparisons.

The company reported incomplete data due to differences between populations that prevent comparison. However, the EAG believes these differences could be adjusted, evaluated, and compared using alternative methods such as generalised linear models, generalised estimating equations, or propensity score matching.

The analysis included both paediatric and adult data. Patients who transitioned during the data collection period have new baseline data collected after they turn 18, which may not reflect their true baseline data. A sensitivity analysis is planned to assess the impact of removing transitioning patients.

The analysis populations included both paediatric and adult data stored in SMA REACH UK and Adult SMA REACH respectively. Both registries report data from centres in England only. The EAG acknowledges the company’s strategy to conduct a sensitivity analysis concerning the transitioning patients. Techniques such as propensity score matching could be utilised to pair patients who transitioned with comparable patients who did not transition, based on observed characteristics. This would establish a comparison group that could be used to estimate the impact of the transition and could be of help while providing more information.

An alternative beneficial approach could be to employ a mixed model instead of excluding patients who transitioned. This would account for the correlation between repeated measurements on the same patient. Furthermore, the transition could be incorporated into the analysis as a time-varying covariate, enabling the model to account for temporal changes. Or instead of removing transitioning patients, a longitudinal analysis could track the same patients over time as they transition from paediatrics to adulthood. This would provide a more continuous perspective on the patient’s progression and the treatment’s effectiveness over different life stages.

For key motor function outcomes, only the appropriate measurement scales were collected and reported for each patient. Additional data items captured by SMA REACH UK and Adult SMA REACH are of interest but are not included in the main analysis. The company's strategy allows for the alteration of scales in response to changes in a patient’s condition. However, the EAG raises concerns about potential data inconsistency and gaps.

Supplementary data items such as the EK2 scale, Vignos, and ATEND were gathered but are not incorporated in the primary analysis. The EAG suggests considering these items, as they offer a broader spectrum of functional states and incorporate nonmotor elements significant to patients. However, both the bedside and motor scales demonstrated only low to moderate internal responsiveness in patients.191, 192

The Vignos scale, a single-item assessment with 10 options, is used to evaluate lower limb function and has a strong correlation with other functional scales.193 The ATEND is a functional motor outcome assessment for individuals with a neuromuscular disorder who can't sit or transfer out of a wheelchair. It was developed based on the CHOP ATEND, a modified version of the CHOP INTEND.192, 194, 195 The ATEND includes 14 items ranging from cervical and trunk strength to distal strength, including arm and hand function. It considers contractures and the changing phenotype from older, weaker individuals with neuromuscular disease. These three tools could provide valuable insights if collected by the company as mandated data items.192, 194, 195

* + - 1. Outcomes of interest
         1. Overall survival/time to death or permanent ventilation

In terms of mortality, one type 1 patient and one type 2/3 non-sitter died. No patients have been recorded as being on permanent ventilation. Two patients discontinued risdiplam. Six patients underwent spinal surgery during the MAA.

In the time-to-event analysis, no patients experienced an event (death, permanent ventilation, or spinal surgery) after starting risdiplam treatment.

* + - * 1. Motor function

For SMA type 1 patients, preliminary observations suggest motor function improvement, but the small sample size complicates interpretation. For the SMA type 2/3 cohort, mixed effect modelling suggests an improvement in motor function, relative stabilization at 12 months, and a slight decline at 18 months.

The adult REACH registry included patients who had baseline data collected upon entering Adult SMA Reach UK. MMRM modelling for SMA type 1 and type 2/3 cohorts provided statistical estimates of longitudinal mean scores and changes from baseline for RHS and RULM. However, due to low patient numbers, there was insufficient data to fit MMRM models for the type 1 cohort.

Additional outcome measures were collected for type 2/3 patients. The ATEND was used to track changes in the older, chronic, wheelchair-bound population. The EK2 was used to assess changes in non-ambulant patients.

* + - * 1. Dysphagia/bulbar function

The company has not covered comprehensive data concerning the nutritional condition of the REACH group in their submission. However, the EAG was able to identify some information related to the adult registry, as documented in Table 71 of the company’s appendices. This includes data on bulbar function at baseline, and at 6, 12, and 18 months. Even though the reported results show percentages of improvements, there is a significant decrease in the number of patients from baseline to 18 months. This raises doubts about the interpretation of bulbar efficacy and the improvements attributed to risdiplam in the adult registry population.

* + - * 1. Scoliosis and contractures

In the CS, Document B, Section 5.2.3.8, the company states that, at baseline, their patients exhibited higher percentages of scoliosis and fractures. This is because many patients with better scoliosis conditions had already been receiving nusinersen, which is administered intrathecally, before starting risdiplam. This situation leads to a poor prognosis, as previously confirmed by the EAG. According to Table 72 in the company's appendices, 91.95% of type 2/3 non-sitters and 61% of type 2/3 sitters/walkers had scoliosis, and over 56% of both groups had contractures. The reduction in the number of patients has impacted the reported figures for scoliosis and contractures. Therefore, the presented data are not significantly valuable for interpreting the effect of risdiplam on scoliosis and contractures.

* + - * 1. Quality of life

According to the company, PROMs were not incorporated in the initial MAA. However, they were included in a pilot study that aimed to enrol 50 paediatric patients from two institutions, namely GOSH and Leeds. The EAG acknowledges that the PROMs were gathered across various metrics: EQ-5DL, SMAIS, P-GIC – severity, P-GIC – improvement, and feedback from adult patients. The company further clarifies that due to the lack of sufficient data for separate group analysis or formal analysis, the results are not interpreted. Given the company’s data limitations, the EAG concurs that the findings should be interpreted with caution due to the data insufficiency.

* + - * 1. Summary

The paediatric REACH registry included patients treated with risdiplam, with a low discontinuation rate indicating its real-world tolerance. However, due to the brief follow-up period since the start of the MAA in 2022, data interpretation is challenging.

* + 1. Summary of Roche’s ITC

In these ITCs, IPD were available from the risdiplam trials, and only AgD from the nusinersen and onasemnogene abeparvovec trials. The ITC for the presymptomatic population were all done using a naïve comparison as the three trials for this population formed a disconnected network and due to the small sample size and substantial differences at baseline between these studies. The comparison for the type 1 population used unanchored MAICs to indirectly compare risdiplam to nusinersen and onasemnogene abeparvovec. Analyses for the type 2 and 3 population used anchored MAICs or restricted NMAs to compare risdiplam to nusinersen. Table 25 presents the covariates adjusted for in this analysis.

In the presymptomatic population, the naive comparison of risdiplam with nusinersen and onasemnogene abeparvovec “demonstrated similar outcome progression trajectories” and t-tests which assessed the mean difference at each timepoint between the different populations results in no statistically significant differences between the two groups being compared.

In the type 1 population, results significantly favoured risdiplam over nusinersen for OS, event-free survival, CHOP-INTEND response, HINE-2 response, and adverse events. There were no significant differences between risdiplam and onasemnogene abeparvovec for any outcome in this population.

In the type 2/3 population, there were no significant differences between risdiplam and nusinersen.

Roche included the following results from the ITC in the economic model. The results of the presymptomatic ITC which resulted in no difference between risdiplam and nusinersen were used to justify the assumption in the presymptomatic economic model that the clinical effectiveness of nusinersen and onasemnogene abeparvovec are equivalent to risdiplam. In the type 1 model, the clincial effectiveness of nusinersen was taken from the results of the MAIC on the HINE-2 endpoint, and for onasemnogene abeparvovec from the results of the MAIC on the BSID-III endpoint from STR1VE-EU. In the type 2 and 3 model, the effectiveness of nusinersen was taken from the results of the RULM MAIC. The full critique of Roche’s ITC is presented in sections 4.5 and 4.6.

Table 25: Covariates adjusted for in Roche's ITCs

|  |  |  |  |
| --- | --- | --- | --- |
| **Covariate** | **Presymptomatic** | **SMA type 1** | **SMA type 2/3** |
| Age at first dose | Included | Included |  |
| Age at screening |  |  | Included |
| CHOP-INTEND total score at baseline | Included | Included |  |
| Disease duration at baseline |  | Both\* |  |
| HFMSE score at baseline |  |  | Included |
| RULM score at baseline |  |  | Included |
| SMN2 copy number | Included |  | Included |
| \*Included for comparison to ENDEAR, not for SPR1NT as was not reported | | | |

* 1. Critique of Biogen’s and Roche’s ITCs
     1. Indirect Treatment Comparisons (ITC) methods

Formal indirect treatment comparisons were conducted to evaluate the relative effectiveness of risdiplam and nusinersen for SMA by both companies. Studies which included either risdiplam, nusinersen, or onasemnogene abeparvovec were included into the feasibility assessment to check the most appropriate method of data synthesis. There were four methods used by Roche and Biogen:

1. **Naïve comparison**

This method involves directly comparing outcomes from different studies without any adjustments for differences in study populations or designs. It is the simplest form of comparison but can be misleading due to potential biases and differences between the study groups. They are generally less reliable since they do not account for confounding variables or variations in study methodologies and designs.

1. **Matching-adjusted indirect comparison (MAIC)**

MAICs adjust for differences in baseline characteristics between study populations by weighting individual patient data from one study to match the aggregate data from another study. In this submission, Roche used the IPD from the risdiplam trials and Biogen used the IPD from the nusinersen trials. This helps to reduce the bias by creating a more comparable study population. Although MAICs improve the reliability of comparisons by ensuring similar populations, it can lead to a significant reduction in effective sample size, especially in the context of SMA, a rare disease with already small study populations. This reduction can decrease the statistical power of the comparison and increase the uncertainty in the results.

1. **Simulated treatment comparison (STC)**

STCs use statistical modelling to simulate what the outcomes of one treatment would be if it were applied to the patient population of another study. This approach allows for adjustments based on differences in patient characteristics and study designs, enabling more accurate comparisons between treatments that have not been directly compared in head-to-head trials. For rare diseases like SMA, where studies often have small sample sizes, the use of STC can provide a more nuanced and accurate comparison of treatments by leveraging the available IPD. However, the effectiveness of STC in this context is limited by the availability and quality of detailed patient-level data, and the necessity of robust statistical modelling to account for small sample sizes and rare event data. These factors must be carefully considered to ensure the reliability and validity of the comparisons.

1. **Network Meta-analysis (NMA)**

NMAs combine direct and indirect evidence across a network of studies to compare multiple treatments simultaneously, allowing for the estimation of relative treatment effects even when treatments have not been directly compared in head-to-head trials. It is usually considered the most comprehensive and statistically robust method for comparing multiple treatments, as it synthesises all available evidence and provides a holistic view of the relative effectiveness of different interventions. However, it requires a sufficient number of high-quality homogeneous studies, which can be challenging in rare diseases like SMA.

* + 1. Differences between Biogen and Roche ITC methods

Roche include the risdiplam trial RAINBOWFISH in the ITC for the presymptomatic population whereas Biogen do not. Whilst Roche have access to the IPD from RAINBOWFISH and can, therefore, adjust the data from RAINBOWFISH to match NURTURE and SPR1NT, Biogen excluded it in the comparison based on Biogen only having access to RAINBOWFISH abstracts only, meaning that Biogen could not extract the data necessary to include it in the ITC. Roche, of course, did not have this issue. Moreover, Biogen excluded RAINBOWFISH from the ITC analyses due to it having a looser definition of the respiratory intervention used in the primary endpoint of NURTURE.

In the SMA type 2/3 population, Roche performed restricted NMAs whereas Biogen did not perform any type of NMA as they deemed them infeasible given the available data, namely due to heterogeneity between studies and a lack of common outcomes. The implications of the companies taking different approaches are arguable significant. Roche believed there was enough homogeneity and common outcomes among the available studies to justify this approach, unlike Biogen. This indicates a fundamental disagreement on the suitability of the data for an NMA. This also means results are not comparable. If Biogen’s concerns of heterogeneity are founded, then the validity of Roche’s NMA could be compromised, and vice-versa.

In the presymptomatic population, both companies adjusted for age at first dose, baseline CHOP-INTEND score and SMN2 copy number. However, Biogen also adjusted for sex and weight. In the type 1 population, both companies adjusted for age at first dose and CHOP-INTEND score, however Roche also adjusted for disease duration while Biogen adjusted for SMN2 copy number, age at symptom onset, feeding issues, sex, ventilation support, and weight. For the type 2/3 population, both companies adjusted for age at screening, baseline RULM score and SMN2 copy number. Roche also adjusted for baseline HFMSE score and Biogen adjusted for age at symptom onset, HINE-2 score and sex. The inconsistency in choosing and adjusting for the same treatment effect modifiers (TEMs), or covariates in Biogen’s case, can lead to differences in estimated treatment effects, making it difficult to directly compare findings. The analyses which omit important TEMs are liable to producing biased or confounded results, leading to incorrect conclusions of the ITCs. This can also affect generalisability, undermining the robustness of the analysis.

* + 1. Critical review and synthesis of information

Both company’s ITCs were comprehensive and were conducted on a myriad of outcomes. However, Biogen did not include any of the ITC results in the economic model, while Roche included a few. The differing approaches taken by the companies regarding their economic models have significant implications. Biogen’s decision to compare nusinersen solely to BSC and excluding ITC results with other treatments, may be perceived as less thorough. This limited perspective potentially underestimates or overestimates nusinersen’s cost-effectiveness relative to other active therapies like risdiplam or onasemnogene abeparvovec. In contrast, Roche’s inclusion of the ITC results in their economic model provides a more robust and holistic analysis. This approach offers a clearer understanding of risdiplam’s value in the SMA treatment landscape.

This section will largely focus on the results brought forward in the Roche economic model and briefly cover the remainder of the ITCs.

* + 1. Comparison of treatment effect modifiers and prognostic factors

Both companies undertook unadjusted and adjusted ITC analyses, adjusting for important effect modifying variables to satisfy the assumption that the relative effect of each treatment is consistent across populations. This section compares the distribution of important variables used in both ITCs to this assumption is met. Roche included tables which gave reasons as to why certain covariates were included or excluded in the ITC (tables 54-56 in CS doc B), whereas Biogen listed the covariates without justification.

The EAG requested the companies to include explanations of how these covariates were chosen, whether they were considered treatment effect modifiers in the usual sense or not, providing justification for their inclusion or exclusion. Biogen provided a table in their response to CQ A2 which explained the reasons for excluding covariates in the ITC, but not for the included covariates. The main reason for exclusion of key covariates in the ITC was that it was unavailable in the comparator studies.

Roche provided explanations to these in the publication by Baranello et al 2022.196

**Presymptomatic population**

A summary of these variables is presented in Table 26. The distribution of covariates is similar between studies within the same submission and across the two submissions, except for age at first dose. When comparing NURTURE to RAINBOWFISH, participants in RAINBOWFISH were significantly older at first dose compared to NURTURE participants by a mean of 6.99 months (95% CI = 1.83 to 12.15). X

**SMA type 1 population**

Table 27 summarises the variables that were adjusted for in either ITC for this population. The percentage of participants with feeding issues were higher in ENDEAR than the others and 0% were on ventilation support in FIREFISH and STR1VE-US, otherwise the distribution of the covariates were similar across studies and submissions.

Comparing ENDEAR to FIREFISH, ENDEAR participants had significantly higher baseline CHOP-INTEND scores, longer disease duration, higher proportions of patients with feeding issues and on ventilation, and were significantly older at symptom onset.

**SMA type 2/3 population**

Table 28 summarises the variables that were adjusted for in either of the two ITCs for this population. The distributions of the variables are similar (i.e., no statistically significant difference) except for baseline HFMSE score which is significantly higher in CHERISH than in SUNFISH and age at screening which is significantly higher in SUNFISH.

Table 26: Summary statistics of adjusted covariates in both company's ITCs for the presymptomatic population

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Submission** | **Biogen** | **Biogen** | **Roche** | **Roche** | **Roche** |
| Study | NURTURE | SPR1NT | RAINBOWFISH | NURTURE | SPR1NT |
| Type of data | Individual | Aggregate | Individual | Aggregate | Aggregate |
| Treatment | Nusinersen | OA | Risdiplam | Nusinersen | OA |
| Sample size | 25 | 14 | 21 | 25 | 29 |
| Covariates adjusted for in either model |  |  |  |  |  |
| Age at first dose in monthsA | 20.6 (10.5) | 20.7 (7.9) | 27.6 (7.3) | 20.6 (10.5) | 24.8 (10.0) |
| Baseline CHOP-INTEND score; mean (SD) | 49.0 (8.9) | 49.0B | 50.3 (7.4)C | 49.0 (8.9) | 46.0 (8.8)D |
| SMN2 copy number (%) |  |  |  |  |  |
| Two | 60% | 100% | 38% | 60% | 48% |
| Three | 40% | 0% | 62% | 40% | 52% |
| Sex (% males) | 48% | 29% | 38% | 48% | 35% |
| Weight; mean (SD) | NR | 3.6 (0.4) | 4.0 (0.6) | NR | 3.9 (0.5) |
| Source | Table 18 | Table 8.6 | Table 9E | Table 48/49 | Table 48/49 |
| A Converted SPR1NT results in the Biogen ITC from months to days  B Median  C From RAINBOWFISH CSR Table 7  D Only available for the 14 participants with 2 SMN2 copy numbers  E Combined SMN2 2/3 groups  Values from Roche’s document B for NURTURE and SPR1NT are weighed means based on SMN2 copy number | | | | | |

Table 27: Summary statistics of adjusted covariates in both company's ITCs for the SMA type 1 population

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Submission** | **Biogen** | **Biogen** | **Biogen** | **Roche** | **Roche** | **Roche** | **Roche** |
| **Study** | ENDEAR | FIREFISH | STR1VE EU/US | FIREFISH | ENDEAR | STR1VE-EU | STR1VE-US |
| **Type of data** | Individual | Aggregate | Aggregate | Individual | Aggregate | Aggregate | Aggregate |
| **Treatment** | Nusinersen | Risdiplam | OA | Risdiplam | Nusinersen | OA | OA |
| **Raw sample size** | 80 | 41 | 55 | 41 | 80 | 23 | 22 |
| **Covariates adjusted for in either model** |  |  |  |  |  |  |  |
| Age at first dose in months; mean (SD) | 5.4 (1.7 to 8.0)\* | NR | NR | NR | 5.4 (NR) | 4.4 (1.3) | 3.7 (1.6) |
| Age at screening; mean (SD) | 4.8 (1.4) | 5.3\* | 3.9 (1.4) | NR | NR | NR | NR |
| Baseline CHOP-INTEND score | 26.6 (8.1) | 22.0\* | 29.5 (8.9) | 22.0 (8.0 to 37.0)\* | 26.6 (8.1) | 27.9 (8.3) | 32.0 (9.9) |
| Disease duration at baseline in weeks; median (range) | 13.2 (0.0 to 25.9)\* | 3.40\* |  | 3.4 (1.0 to 6.0)\* | 13.2 (NR) | NR | NR |
| SMN2 copy number (%) |  |  |  |  |  |  |  |
| Two | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| Age at symptom onset in months; median (range) | 1.8 (0.5 to 4.1) | 1.50\* | 1.7 (NR) | 1.5 (1.0 to 3.0)\* | 2.0 (NR) | 1.7 (0.7) | 1.9 (NR) |
| Feeding issues at baseline | 51% | NR | 16% | 15%A | 9% | 27% | 0% |
| Sex (% males) | 46% | 46% | 44% | 46% | 46.00% | 42.00% | 45.00% |
| Ventilation support at baseline (%) | 26% | NR | 16% | 0%B | 26% | 27% | 0% |
| Weight; mean (SD) | NR | NR | 5.8 (1.0) | NR | NR | 5.8 (1.0) | 5.8 (1.1) |
| **Source** | Table 9 | Table 8.24 | Table 8.12 | Table 6 | Table 50 | Table 52 | Table 51 |
| \* Median (range) where reported  A N = 4 via feeding tube, N = 2 via a combination of oral and feeding tube  B BiPAP ≥ 16 hours per day | | | | | | | |

Table 28: Summary statistics of adjusted covariates in both company's ITCs for the SMA type 2/3 population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Submission** | **Biogen** | **Biogen** | **Roche** | **Roche** |
| **Study** | CHERISH | SUNFISH | SUNFISH | CHERISH |
| **Type of data** | Individual | Aggregate | Individual | Aggregate |
| **Treatment** | Nusinersen | Risdiplam | Risdiplam | Nusinersen |
| **Raw sample size** | 84 | 120 | 120 | 83 |
| **Covariates adjusted for in either model** |  |  |  |  |
| Age at screening; median years (range) | 4.0 (2.0 to 9.0) | 9.0 (NR) | 9.0 (2.0 to 25.0) | 4.0 (2.0 to 9.0) |
| HFMSE score at baseline; mean (SD) | 22.4 (8.3) | 16.1 (12.5) | 16.1 (12.5) | 22.4 (8.3) |
| RULM score at baseline; mean (SD) | 19.4 (6.2) | 19.7 (7.2) | 19.6 (7.2) | 19.4 (6.2) |
| SMN2 copy number (%) |  |  |  |  |
| Two | 7% | 3% | 3% | 7% |
| Three | 88% | 89% | 89% | 88% |
| Four | 2% | 8% | 8% | 2% |
| Unknown | 2% | 0% | 0% | 2% |
| Age at symptom onset; month (range) | 10.0 (6.0 to 20.0) | 14.10A | 12.3 (0.0 to 57.0) | 10.0 (6.0 to 20.0) |
| Sex (% male) | 45% | 49% | 49% | 45% |
| **Source** | Table 11 | Table 8.39 | Table 7 | Table 52 |
| Areported mean | | | | |

* + 1. Comparison of intervention responses

**Presymptomatic**

The Roche model included the clinical effectiveness of risdiplam from motor milestone achievement items used in RAINBOWFISH as an input in the presymptomatic model. The inputs for nusinersen and onasemnogene abeparvovec assumed equal efficacy to risdiplam. To check the appropriateness of this assumption, the EAG compared treatment responses from the respective trials, and also considered the results of previously published SLRs.

Table 29 presents the comparison of treatment responses in the intervention groups of the studies included in the Roche ITC for the presymptomatic population. Although the items used across studies that are presented in the table below differ slightly, they are all related to the proportion of children sitting without support. In NURTURE and SPR1NT, all children achieve this milestone, and in RAINBOWFISH only one child does not achieve this milestone. The overlapping confidence intervals also support this.

Table 29: Comparison of the responses to intervention treatments in the presymptomatic population

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment (N)** | **RAINBOWFISHA** | **NURTUREB** | **SPR1NTC** |
| Risdiplam (N=5) | Nusinersen (N=25) | OA (N = 15) |
| **MM: Sitting without support** | 80.0 (34.3 to 99.0) | 100.0 (84.3 to 100.0)\* | 100 (76.2 to 100.0)\* |
| A BSID-III item 22 analysed at 52 weeks  B WHO motor milestone analysed at 15 months  C BSID-III item 26 all achieved at 10 months of age  \*95% confidence interval calculated using Wilson score interval method | | | |

SMA type 1

For the SMA type 1 model, Roche used results from FIREFISH as the input for the clinical effectiveness of risdiplam. The effectiveness of nusinersen was based on the results of the MAIC conducted on the HINE-2 endpoint and the effectiveness of onasemnogene abeparvovec was based on the MAIC conduced on the BSID-III endpoint.

Table 30 presents the intervention responses for the instruments used in the company’s ITC and then were used in the economic model. The effectiveness input for nusinersen were based on results of the MAIC on the HINE-2 endpoint. When comparing the HINE-2 results from FIREFISH to ENDEAR, there is a statistically significant difference between the two studies in favour of risdiplam, irrespective of timepoints compared, suggesting heterogeneity between studies. OA was included in the model using results of the MAIC on BSID-III from STR1VE-EU only and, although risdiplam performs worse, the result is not significantly different.

Table 30: Comparison of the responses to intervention treatments in the SMA type 1 population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **FIREFISH** | **ENDEAR** | **STR1VE-EU** | **STR1VE-US** |
| **MM achievers (%): Sitting without support** | Risdiplam (N=41) | Nusinersen (N=80) | OA (N = 33) | OA (N = 22) |
| **BSID-III** | 29.3  (17.8 to 43.1) |  | 48.0  (31.0 to 65.1) | 59.0  (36.0 to 100.0) |
| **HINE-2** | 78.0  (64.8 to 88.0) | 41.0  (30.2 to 51.8) |  |  |
| 85.4  (73.2 to 93.4) | 51.0  (0.40 to 0.62) |  |  |
| **WHO** |  |  | 44.0  (26.0 to 100.0) |  |
| BSID-III: FIREFISH item 22, STR1VE-EU and -US item 26  HINE-2: FIREFISH presented 12/24m, ENDEAR presented interim/final analysis results | | | | |

**SMA type 2**

For the type 2/3 model, Roche used results from SUNFISH as the input for the effectiveness of risdiplam but excluded the results of Asian participants of SUNFISH. The effectiveness of nusinersen was based on the results of the MAIC based on the RULM endpoint.

Table 31 presents a comparison of the RULM outcomes between SUNFISH and CHERISH as these were used in the company’s ITC. Both groups had similar mean RULM score at baseline. However, the response to nusinersen is significantly higher than that of risdiplam which is also reflected in the estimated RULM score at 15 months, with CHERISH participants having a statistically significant 2.4-point increase compared to those of SUNFISH. This implies potential underlying heterogeneity between the study populations or differences in the efficacy profiles of these treatments in this patient cohort.

Table 31: Comparison of the responses to intervention treatments in the SMA type 2/3 population

|  |  |  |
| --- | --- | --- |
|  | **SUNFISH\*** | **CHERISH** |
| **RULM** | Risdiplam (N=120) | Nusinersen (N=45) |
| **Baseline** | 19.65 (7.22) | 19.40 (6.20) |
| **Change from baseline 15 months** | 1.61 (0.31) | 4.20 (0.40) |
| **Estimated at 15m by EAG** | 21.26 (7.23) | 23.60 (6.22) |
| \*Roche’s economic model excluded Asian patients of SUNFISH, the results here presents all SUNFISH participants | | |

* + 1. Comparison of placebo/sham responses

Only the SMA type 2/3 population included more than one study with a control group, CHERISH and SUNFISH. The presymptomatic population included only single-arm trials or open-label extensions which included only active treatments. The SMA type 1 population included open-label studies for risdiplam and onasemnogene abeparvovec with a single arm. The ENDEAR trial does contain a control group but, as no other studies included in the ITC for this population, a comparison between placebo responses could not be done. Therefore, only a comparison between the sham-control group from CHERISH and the placebo group from SUNFISH will be presented. Furthermore, as only the results from the MAIC for the RULM outcome were used in the economic model, the comparison of this outcome will be presented only in Table 32.

Table 32: Placebo/sham response for the outcome RULM score in the SMA type 2/3 population

|  |  |  |
| --- | --- | --- |
| **RULM score** | **CHERISH** | **SUNFISH** |
| Group (sample size) | Sham-control (42) | Placebo (58) |
| At baseline (SD) | 18.40 (5.70) | 20.91 (6.41) |
| Mean change from baseline at 12m (CHERISH) or 52w (SUNFISH) (SD) | 0.50 (0.56) | 0.02 (0.43) |
| EAG’s estimated score at 12m/52w (SD) | 18.90 (0.88) | 20.93 (0.84) |

Using the mean and SD values presented in the company submissions, the baseline RULM scores are similar (confidence intervals overlap). When considering the mean change from baseline to 12 months in CHERISH and 52 weeks in SUNFISH, there is a statistically significant difference between the sham-control group of CHERISH and the placebo group of SUNFISH (CHERISH: 0.33 to 0.67; SUNFISH: -0.09 to 0.13), suggesting that the placebo responses over time differ substantially between the groups.

The MAIC procedure adjusted the placebo score of SUNFISH to the pooled score of CHERISH (nusinersen and sham combined), so despite aligning the groups between studies, this was not done between placebo groups themselves. If the placebo response differs significantly between the groups, it can affect the relative treatment effect estimates. The true treatment effect could be confounded by differing placebo responses that were not fully accounted for during the MAIC. A larger placebo response in one trial compared to another can make the active treatment appear less effective or more effective, depending on the direction of the difference in placebo responses.

* + 1. Comparison of relevant safety results

The ITC presented in the Roche submission evaluated adverse events, adverse events leading to discontinuation, and severe adverse events for SMA type 1 and 2/3. In the SMA type 1 population, AE data from FIREFISH were compared with ENDEAR-SHINE and STR1VE-EU/US, while the type 2/3 population ITC compared AE data from SUNFISH to CHERISH. However, none of these results were used in the economic models. A detailed summary of safety outcomes is presented in section 4.4 (Page 148).

* 1. EAG Quantitative Analyses

The EAG requested anonymised individual-level patient data from Roche and Biogen to replicate the results both companies presented. As both companies employed slightly different methods and adjusted for different sets of covariates in their respective ITCs, the EAG would use the IPD to perform a harmonised comparison between risdiplam and nusinersen using consistent methodologies. This could only be done if both companies provide the IPD requested. Furthermore, a thorough examination of data quality, including the handling of missing data and assessing how different methods of dealing with missingness, outliers, and potential biases affect the overall results.

* + 1. EAG replication of ITC and EAG’s preference

The EAG were not provided with IPD from either company. Consequently, we could only critique the analyses based on the information presented in the submissions. Additionally, the EAG performed its own feasibility assessment for an independent ITC, the results of which are as follows. Due to time constraints, this was not done in any significant detail and was only performed to provide an illustrative comparison of the efficacy between treatments in this submission. Thus, the results of any potential EAG ITC should not be interpreted as definitive.

The EAG began a systematic literature review of SMA treatments prior to receiving the company submissions and used the results of this search to explore the possibility of conducting an ITC using published aggregate data for nusinersen, risdiplam, or onasemnogene abeparvovec. If it was considered infeasible, the EAG assessed the methods both Biogen and Roche employed for their respective ITCs to choose the most appropriate method given the available data for each population. Due to the EAG not having access to any individualised patient data, we only considered studies or publications which reported the results of trials with more than one arm, all single-arm trials were not considered.

* + - 1. Presymptomatic population

The EAG found three potential studies for this population:

* Alves 2021
* SPR1NT (2 SMN2 copies)
* SPR1NT (3 SMN2 copies)

Alves 2021 compared nusinersen to sham whilst the SPR1NT studies compared onasemnogene abeparvovec to natural history. Therefore, forming a network was not possible. Sham controls and natural history controls are not inherently equivalent, as sham involves participants who received a sham treatment which helps control for the placebo effect and participant expectations. Conversely, natural history data involves observational data from untreated patients. Assuming an equivalence between the two is likely to introduce bias and result in a weak network.

**EAG’s preference**

The results from both companies in the presymptomatic population resulted in non-significant differences between treatment and comparator. Biogen compared nusinersen to onasemnogene abeparvovec using a MAIC and made no comparison to risdiplam, while Roche used naïve comparisons to compare risdiplam with nusinersen and onasemnogene abeparvovec. A MAIC is typically more robust since it accounts for differences between studies, while naïve comparisons do not adjust for differences between studies.

Both companies included NURTURE and SPR1NT in the analysis, but Biogen excluded RAINBOWFISH from the ITC analyses due to it having a looser definition of the respiratory intervention used in the primary endpoint of NURTURE, while Roche kept RAINBOWFISH in the analysis.

Considering both approaches, Biogen’s approach using MAIC appears to be the more methodologically sound one in this population due to its adjustment for confounding variables and exclusion of a study with a significantly different endpoint definition. This approach likely provides a more accurate comparison despite the smaller sample sizes, the noted differences in age at first dose and the absence of a comparison to risdiplam.

* + - 1. Type 1 population

The EAG found the following potential studies for this population:

* Mirea 2021
* EMBRACE
* ENDEAR

EMBRACE and ENDEAR compared nusinersen to sham, while Mirea 2021 compared nusinersen to no treatment. A network is not possible as the only treatment included in the NICE scope is nusinersen.

**EAG’s preference**

Both companies conducted MAICs on the same studies for the SMA Type 1 population: ENDEAR, FIREFISH, and STR1VE. Comparing the variables that were adjusted for, there were significant differences in baseline CHOP-INTEND score, disease duration, age at symptom onset, and proportion with feeding issues and on ventilation support. There were no differences in SMN2 copy number or participant’s sex. Both companies adjusted for different sets of variables, and the set of variables Roche adjusted for were significantly different between studies; age at first dose, CHOP-INTEND, and disease duration at baseline. Thus, Biogen adjusted for more variables which had significant differences at baseline, and the matching method would have accounted for these differences.

Biogen noted a difference in the outcome measures used for the motor milestone attainment account and the small sample sizes. Roche noted the ESS reduction in FIREFISH after the matching procedure bringing the effective sample size down to 40.6 from 58 (a 30% reduction). Biogen also notes the ESS for each outcome analysed in their appendices, with the ESS decreasing from 46 to 12.61 (a 73% reduction) as was the case for the BSID-III sitting without support comparison with STR1VE.

In Biogen’s MAIC results, there were no significant differences between nusinersen and onasemnogene abeparvovec, and between nusinersen and risdiplam due to the large confidence intervals, except for the comparison with onasemnogene abeparvovec for the outcome BSID-III walks alone at 18 months of age where the proportion who took onasemnogene abeparvovec were significantly higher, albeit by a small number. Roche took a different approach post-matching, such as calculating the hazard ratios for OS and EFS and other outcomes, where the risdiplam groups performed significantly better compared to the nusinersen groups across all outcomes. There were no significant differences when comparing risdiplam to onasemnogene abeparvovec.

Considering both approaches, Biogen's approach may be more reliable due to its adjustment for a broader set of baseline variables, which can provide a more balanced comparison. The broader adjustment helps mitigate confounding factors better, despite the lack of significant findings except for one outcome. Roche's findings, while showing significant benefits for risdiplam, are potentially less robust due to the significant reduction in ESS and the more limited set of adjusted variables.

* + - 1. Type 2/3 population

The EAG found the following potential studies for this population:

* Freigang 2021
* Kolbel 2022
* CHERISH
* EMBRACE
* SUNFISH

Freigang 2021 compared nusinersen to age-matched controls, CHERISH and EMBRACE compared nusinersen to sham, SUNFISH compared risdiplam to placebo, and Kolbel 2022 compared a combination of nusinersen plus onasemnogene abeparvovec to no treatment, or “watchful waiting” as stated in this paper.

An indirect comparison is potentially possible using the results of these three studies and two publications. The EAG performed a feasibility assessment to undertake an NMA with the following assumptions:

* Nusinersen can be indirectly compared to risdiplam through common comparators (sham and placebo) with the assumption that sham-control and placebo are broadly similar (like Roche’s approach).
* The effect of onasemnogene abeparvovec may be inferred from Kolbel 2022 via the combination with nusinersen.
* Age-matched controls and no treatment are similar as they can be considered as untreated or minimal intervention controls.

However, once relevant data were extracted, which included study design, the same covariates that Roche and Biogen adjusted for in their type 2/3 comparisons, and outcomes, we ruled out Freigang 2021, Kolbel 2022, and EMBRACE. The primary outcome measured in Freigang 2021 was the inflammatory marker chitotriosidase 1 (CHIT1) in patients before and after nusinersen treatment. This was not a relevant outcome stipulated in the NICE scope and is not included in the other studies mentioned. This study did measure motor function and disease severity but did not present the results of the change in these pre and post treatment. Instead, they presented the correlation between CHIT1 and motor function which is not relevant to the decision problem. Kolbel 2022 measures the psychosocial burden for parents of children with SMA. This is a relevant outcome in the NICE scope, but the outcome presented was unable to link to any of the other studies. EMBRACE included patients across SMA types 1, 2, and 3 and did not report the type 2 and 3 results specifically. That, alongside the small sample size meant it was also excluded. A similar justification was given by Roche for exclusion in their ITC. Biogen excluded EMBRACE based on use of invasive or permanent ventilation.

Therefore, the only two studies that could be used in this ITC are CHERISH and SUNFISH, which is the same as Roche and Biogen. Both companies performed MAICs or STCs since they had the IPD for their respective trials. Since the EAG does not have access to this, the only feasible ITC is the NMA with the assumption that sham-control and placebo are similar, like what Roche did as a scenario analysis.

**EAG’s preference**

Biogen performed unanchored STCs for the comparison between nusinersen and risdiplam for SMA type 2 and 3 population using IPD from CHERISH. The outcomes analysed were change in HMFSE and RULM score from baseline and the results were presented as mean difference. Roche performed anchored analyses using the equivalence assumption between sham-control and placebo, with MAICs on the same outcomes but also included the proportion with ≥3-point improvement in HFMSE score and with a ≥2-point improvement in RULM score, presented as odds ratios. Roche also included restricted NMAs for safety outcomes and performed restricted NMAs as sensitivity analyses for the RULM and HFMSE outcomes, and anchored MAICs as sensitivity analyses for the safety outcomes. Biogen’s STC method does not rely on a common comparator and the assumption that Roche made to do an anchored comparison which relied on the validity of the equivalence assumption. However, if this assumption is reasonable, the anchored MAIC’s ability to reduce bias and prove more reliable comparisons by utilising a common reference point and matching accordingly can offer more robust and interpretable results.

Of the covariates adjusted for in either of the analyses, there were no differences between CHERISH and SUNISH for the following variables: baseline RULM score, SMN2 copy number, age at symptom onset and sex. There were differences in age at screening where SUNFISH participants were significantly older, and for HFMSE score, where CHERISH participants had significantly higher baseline scores. Both companies adjusted for age at screening, baseline RULM score and SMN2 copy number. Roche also adjusted for baseline HFMSE score while Biogen also adjusted for age at symptom onset, HINE-2 score and sex.

The results of Biogen’s STC varied when comparing the adjusted to the unadjusted (or crude) results. The unadjusted results significantly favoured nusinersen over risdiplam, while the adjusted results significantly favoured risdiplam over nusinersen. Roche’s results found no significant differences between risdiplam and nusinersen.

Considering both approaches, Roche's anchored MAICs, despite the ESS reductions (43 to 28.3), appear to offer a more reliable and interpretable comparison due to the common reference point, provided the equivalence assumption between sham-control and placebo holds. This method's ability to reduce bias and provide clinically meaningful results is a significant advantage. On the other hand, Biogen's unanchored STCs, while valuable for their broader covariate adjustments, showed variability between adjusted and unadjusted results, which can complicate clinical interpretation. Therefore, if the equivalence assumption is reasonable, Roche's anchored approach is preferred for providing more robust and clinically actionable insights into the comparative effectiveness and safety of nusinersen and risdiplam in the SMA type 2 and 3 population.

* + - 1. Summary

The EAG were unable to conduct our own ITC due to the paucity of multi-arm trials and the unavailability of the IPD required to perform any matching-adjustment methods. The EAG believe that both Biogen’s and Roche’s ITCs were high quality with differences in the covariates that were adjusted for, the availability of IPD from certain studies, and the primary efficacy outcome differences, to be the main factors that differentiate the two IPD approaches.

For the presymptomatic and type 1 population, the EAG prefers Biogen’s approach. Biogen’s method included a broader set of baseline variables, potentially providing a more balanced comparison by mitigating confounding factors. Although there were significant reductions in ESS, Biogen’s comprehensive adjustment for multiple variables makes their findings more robust for this population.

For the type 2 and 3 population, the EAG prefers Roche’s approach. Roche’s anchored analyses, despite the necessity of assuming equivalence between sham-control and placebo groups, offer a more reliable and interpretable comparison by using a common reference point. This method’s ability to reduce bias through MAICs and the inclusion of additional clinically significant outcome measures (such as the proportion of patients with significant improvements in HFMSE and RULM scores) makes their findings more robust and clinically meaningful for this population.

Given these considerations, the EAG recommends Biogen’s approach for the presymptomatic and type 1 population and Roche’s approach for the type 2 and 3 population.

* + 1. EAG’s survival extrapolation analysis

As mentioned in Table 16, both companies fitted parametric survival curves to shorter-term Kaplan-Meier data to extrapolate long-term estimates of time-to-death (overall survival) and permanent ventilation.

In both submissions the companies chose the parametric curves with the most plausible long-term estimates of survival and ventilation based on clinical expert opinion, and not based on best statistical fit using Akaike’s information criterion (AIC) or Bayesian information criterion (BIC). The EAG digitised and fit curves as a sense check.

To do this, the EAG digitised the curves and used the methods from Guyot et al197 to reconstruct the Kaplan-Meier pseudo-IPD. The best statistically fitting curves from the EAG’s analyses aligned with the best-fitting curves from both company’s survival analyses. This was also based on the plausibility of long-term survival estimates. The curves with the best statistical fit, based on AIC or BIC, had unlikely survival estimates, thus were discarded.

The only case where the EAG’s approach differed to the company was for the overall survival outcome in the presymptomatic population. Biogen reconstructed the parametric survival curves shown in figures 14, 16, and 17, which were presented in HST24. The EAG retrieved the original Kaplan-Meier plots for these curves from Gregoretti 2013 and Wijnigaarde 2020 as referenced in HST24, fitted survival curves to the reconstructed KM plots and reconstructed survival curves, and then compared both approaches. For the populations modelled in figures 14 and 16, the exponential curves were chosen by Novartis, the company representing onasemnogene abeparvovec in HST24, and the EAG for HST24. The EAG concludes that the exponential model is the best fitting, consistent with Biogen, Novartis, and the EAG of HST24, based on plausible long-term survival extrapolations.

It should be noted that Novartis, were unable to use fit long-term survival curves to the overall survival of patients with type 2a and 2b SMA in the sitting health state due the data in Wijnigaarde 2020 being too immature. Instead, they fitted curves to this data and compared it with the general population survival curves for The Netherlands to produce a hazard ratio, and then applied this hazard ratio to the general UK population to get an estimate for the UK sitter population with type 2a/2b SMA. The method described raises generalisability issues due to differences between the Netherlands and UK populations, potential inconsistencies in the hazard ratio application, and the limited deaths in the original dataset. These factors undermine the robustness of the survival estimates, as the populations may differ significantly in healthcare, demographics, and specific health state conditions. The EAG for HST24 did not raise any concerns with Novartis’ choice of parametric curves.

Roche provided monthly transition probabilities in their model while Biogen provided quarterly probabilities. To keep them consistent, the EAG digitised the relevant plots in HST24 (figures 14, 16, and 17) as referenced in the Biogen submission related to overall survival in the presymptomatic population. Once the same models were fitted, we plotted these overlaid with Biogen’s curves to ensure that both models closely aligned, then extracted the monthly transition probabilities.

* 1. Conclusion of the clinical effectiveness section

Based on the company submission, the nusinersen treatment in SMA patients, including presymptomatic, type 1, type 2, and type 3, has shown significant motor function improvements, better growth outcomes, high survival rates, and minimal adverse events. Early initiation of treatment optimizes effectiveness, though some data gaps, high discontinuation rates, and baseline differences pose challenges in fully assessing its long-term benefits. Moreover, the risdiplam treatment led to significant motor function improvements and high survival rates in presymptomatic and type 1 SMA patients, with steady growth and minimal adverse events. In type 2 and 3 SMA patients, motor and upper-limb function improved or stabilized, with increased independence in daily activities. Preliminary data from the JEWELFISH study showed motor function stability over 24 months, though statistical significance was not achieved. The REACH registries indicated motor function improvements or stabilization, but small sample sizes and limited data on bulbar function, scoliosis, and contractures raise concerns. Further studies are needed to fully assess the safety and efficacy of risdiplam.

The EAG’s SLR findings on the effectiveness of nusinersen and risdiplam in treating SMA across various types indicate significant improvements in motor function and milestones, with high survival rates and minimal need for permanent ventilation in presymptomatic and Type 1 patients. However, adverse events were common across all treatments, with some serious cases reported. While motor function improvements were consistent, other health aspects such as bulbar function, respiratory function, and the need for ventilation showed mixed results.

The EAG generally agrees with the company’s positive assessment of these treatments’ impact on motor function and survival. However, discrepancies exist in the reported adverse events and other functional outcomes, which had mixed results and could not be fully interpreted.

**Indirect treatment comparison**

Biogen and Roche approached the ITC in similar ways but with a few key differences, potentially impacting their economic models. Roche included RAINBOWFISH data in the presymptomatic population and conducted restricted NMAs for the SMA type 2 and 3 population, providing a comprehensive but potentially biased analysis. In contrast, Biogen excluded RAINBOWFISH data and avoided NMAs due to data heterogeneity, offering a narrower yet potentially more reliable perspective. Both companies adjusted for treatment effect modifiers, with Biogen's extensive adjustments introducing complexity and Roche's fewer adjustments streamlining the model but risking oversimplification. These methodological differences would have shaped the robustness and generalisability of each company's economic model had both companies included these results in their models. However, Roche included some results and Biogen included none of the ITC results, the implications of which being that Roche's economic model may reflect a broader but potentially less accurate range of treatment effects, while Biogen's model may be more conservative and reliable but limited in scope.

**Survival extrapolations**

In both submissions, when Biogen and Roche modelled time-to-event outcomes such as overall survival and time to permanent ventilation using parametric survival curves, they opted for the more clinically plausible curves rather than the best statistically fitting curves. This decision has significant implications for the robustness and reliability of their economic models. Choosing clinically plausible curves over statistically best-fitting ones can provide a more realistic projection of patient outcomes, aligning with clinical expectations and expert opinions. This approach can enhance the credibility of the model among clinicians and stakeholders who are familiar with the disease progression and treatment effects.

However, this method also introduces a degree of subjectivity and potential bias into the modelling process. By prioritising clinical plausibility, there is a risk of underestimating or overestimating certain outcomes if the chosen curves do not accurately reflect the true statistical distribution of the data. This can lead to either overly optimistic or overly conservative long-term estimates, impacting the perceived cost-effectiveness and overall value of the treatments. Furthermore, the reliance on clinical judgment rather than statistical rigor can complicate the validation and reproducibility of the models. Other researchers or decision-makers may find it challenging to replicate the findings if they rely on different clinical judgments or if new data emerges that alters the clinical understanding of the disease.

Overall, while the choice to use clinically plausible curves can enhance the face validity and acceptance of the economic models, it also necessitates careful consideration of the potential biases and limitations introduced by this approach. Balancing clinical insight with statistical accuracy remains a critical challenge in health economic modelling.

* 1. Key clinical effectiveness issues

The key issues with the clinical effectiveness evidence identified by the EAG are presented in Table 33.

Table 33: Key clinical effectiveness issues

| **Key issue** | **Description of concern** |
| --- | --- |
| Key issue 1:  Concerns regarding lack of evidence for the effectiveness of nusinersen or risdiplam on presymptomatic patients | There are few studies providing clinical evidence for patients with presymptomatic SMA, and no RCTs exist. This creates some uncertainty of the effectiveness of the interventions on this type of SMA. The main trials examining the efficacy of presymptomatic SMA are based on small sample sizes (NURTURE n=25. RAINBOWFISH n=26 with the primary efficacy consisting of only 5 patients). Questions arise about the reliability and robustness of this evidence. |
| Key issue 2:  Lack of RCT evidence on the clinical effectiveness of nusinersen and risdiplam for all SMA types. | There are very few RCTs published on the clinical effectiveness of nusinersen and risdiplam on patients across all types of SMA, both within the review conducted by the companies, and within the EAG conducted review. The reliance on single-arm studies, and non-comparative observational studies creates some uncertainty around the clinical effectiveness of nusinersen and risdiplam, based on the potential limitations and bias often found in single-arm studies. |
| Key issue 3:  Inconsistencies in ITC methodology: | Each company conducted the ITCs using different approaches. Biogen compared their treatment to BSC only, justifying this approach by saying indirect comparisons between nusinersen and risdiplam are not feasible due to small sample sizes and heterogeneity between studies. Roche compared their drug to the other active treatments listed in the NICE scope. The EAG acknowledge that this might be due to the nature of this disease since it is classified as rare, but given the paucity of data, both companies still did their ITCs in different ways. |
| Key issue 4:  Lack of evidence for the clinical effectiveness of SMA type 0 or 4. | The EAG acknowledge that there is limited evidence on type 4 SMA, and survival beyond a few weeks in type 0 is rare, but evidence for any effectiveness on these types is missing. The EAG note that several studies of type 4 SMA were included in the EAG systematic literature review, and inclusion of available evidence for type 0 and 4 would be appropriate given the marketing authorisation covers these SMA types. |
| Key issue 5:  Concerns about the clinical evidence presented for JEWELFISH (Risdiplam) | The EAG has some concerns around the evidence generated from the JEWELFISH study. The details of patients participating in phases 1 and 2, and their involvement in the JEWELFISH trial from other trials, should have been scrutinized for pharmacokinetics and potential effects of dose accumulation. The results of phase 2 effectiveness and AEs could be biased due to the impact of dose accumulation. The JEWELFISH trial recruited patients from other trials without reporting washover timings, which could skew the interpretation of its efficacy.  The company has not provided a complete set of efficacy results for JEWELFISH. The efficacy results of the JEWELFISH trial have been partially and briefly reported in supplementary materials and do not demonstrate promising effectiveness to support FIREFISH and SUNFISH as company stated. |
| Key issue 6:  Reporting of adverse events (AEs): | A significant number of AEs have been reported in the risdiplam submission, and some in the nusinersen submission. However, the companies primarily attribute these to the nature of the disease and asserts that the treatment-related AEs are mild. This interpretation, solely reported by the company’s experts, may not be valid. A more thorough evaluation might have been necessary. |
| Key issue 7:  Differences in baseline characteristics | Baseline characteristics are reported as well-balanced in the risdiplam submission, however the EAG note some concerns in the report about some variations between baseline characteristics which raise some uncertainty about this.  Reports of baseline characteristics in the nusinersen submission note some differences. For example, there are differences in baseline ventilation and motor milestones for type 1 and 2 evidence, an imbalance in arms of ENDEAR in ventilatory support, and differences in EMBRACE between baseline characteristics of median age at first dose, sex, ethnicity and SMN2 copy number and time on ventilator. These differences raise some uncertainty around the reliability of the clinical evidence presented. |
| Key issue 8:  Inconsistencies and varied outcomes | The outcomes reported in the trials lacked consistency. There was a noticeable variation in the outcomes across different trials, or perhaps the company did not comprehensively report them for different trials. This means that effectiveness for many outcomes is based on very few studies each. |

1. ASSESSMENT OF COST-EFFECTIVENESS
   1. Systematic review of existing cost-effectiveness evidence

A systematic literature review (SLR) of the economic evidence on the cost-effectiveness of Disease-Modifying Therapies (DMTs) (e.g., onasemnogene abeparvovec, nusinersen, and risdiplam) for treating SMA was performed following the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions.28 A flow diagram illustrating the number of records identified, included, and excluded at each stage of the SLR will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.29

* + 1. Objectives
* To summarise the modelling techniques, modelling structures, inputs (e.g., clinical inputs, survival analysis methods, resource use and costs, utility estimates) required to populate the models, assumptions, and report key results.
* To outline key issues to consider for the conduct of future model-based economic analyses.
  1. Methods for reviewing effectiveness
     1. Identification of studies

The searches comprised the following elements:

1. Searching of electronic bibliographic databases and other online sources
2. Contacting experts in the field, and
3. Scrutiny of references of studies included and a selection of recent, relevant systematic reviews.

A comprehensive search strategy was developed by an information specialist in collaboration with the review team. Searches included terms for SMA, onasemnogene abeparvovec, nusinersen and risdiplam, with the addition of a validated search filter for economic evaluations where appropriate. The search used both free text keywords and, where available, thesaurus (MeSH/EMTREE) terms. The search was initially developed in Embase (via Ovid) and checked by a second information specialist not otherwise involved in the project before being translated for other sources.

Searches were conducted in the following databases on 30th-31st January 2024: Embase (Ovid); MEDLINE All (Ovid); International HTA database (INAHTA); Science Citation Index and Conference Proceedings (Web of Science), CEA Registry (Tufts Medical Center) and EconPapers (RePec). Email alerts were set up in Embase, MEDLINE and Web of Science to identify any relevant new publications and these were screened for potential inclusion in the review until 8th July 2024. Database searches were supplemented by a targeted internet (Google) search on 31st January and checking websites of selected international HTA and medicines approval agencies (NICE, Scottish Medicines Consortium, Canadian Agency for Drugs and Technologies in Health, Institute for Clinical and Economic Review, U.S. Food and Drug Administration, Medicines and Healthcare Products Regulatory Agency and European Medicines Agency) on 25th January 2024. Full details of all searches are provided in Appendix 1.

Search results was exported to EndNote 21, where duplicates were systematically identified and removed.

* + 1. Inclusion and exclusion criteria

Reviewers piloted a screening form based on a predefined inclusion criterion. Study selection followed a two-step process: screening of titles/abstracts and reading of full texts. Two reviewers (PA and MY) independently screened titles and abstracts of the records identified through the searches, with potentially relevant titles/abstracts progressing to the full text stage.

* + - 1. Population (and sub-groups where applicable)

People with types 0, 1, 2, 3 or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.

* + - 1. Intervention(s)

Nusinersen monotherapy and risdiplam monotherapy.

* + - 1. Comparator(s)
* Established clinical management.
* Best supportive care
* The interventions will be compared to each other.

In addition, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene.

* Onasemnogene abeparvovec
  + - 1. Outcome(s)

The outcomes of the studies should be reported in terms of life-years gained (LYG) or quality-adjusted life years (QALYs).

* + - 1. Study design
* All types of economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-consequence, or cost minimization analyses)
* Only full publications in the English language will be considered, although relevant non-English studies will be mentioned.

The full text of all agreed abstracts was read, of which those accepted by both reviewers was included in the systematic review. Any disagreements between the reviewers were resolved by discussion or by recourse to a third reviewer. The study flow and reasons for exclusion of full text articles were documented using the PRISMA flow diagram.29

* + 1. Data extraction strategy

Information was extracted from the relevant studies using an a priori pre-piloted data extraction sheet (see Appendix 2) based on items outlined by Wijnen et al.198 Relevant information was extracted on study details (e.g., title, author, and year of study), characteristics (e.g., population and age), treatment strategies (e.g., onasemnogene abeparvovec, nusinersen and risdiplam), analytical methods (e.g., type of economic analysis, type of economic model, study perspective, resource use and costs and assumptions), results (e.g., base-case and sensitivity analysis results), discussion (e.g., study findings, comparison with other studies and limitations), and other (e.g., source of funding). For data being missing or not being clearly reported, efforts have been made to contact the corresponding author. A request for the missing information was sent, allowing authors a two-week period to respond. If no response was received within the specified timeframe, we assumed that the requested information was not available.

Data extraction was undertaken by one reviewer (MY), then cross-checked by a second reviewer (PA) for accuracy. Any disagreements between the reviewers were resolved by discussion or by recourse to a third reviewer.

* + 1. Critical appraisal strategy

All published economic evaluations included in this systematic review, along with any economic evaluations submitted to NICE by companies, would undergo a comprehensive appraisal. The reporting and methodological quality of each economic evaluation were assessed using the consolidated health economic evaluation reporting standard (CHEERS) and appraised against the Philips’ checklists, respectively (*see* Appendix 3).199, 200 The CHEERS checklist emphasises the study's relevance to policy and practice, as well as its transparency and reporting of results. The risk of bias/methodological quality was assessed using the Philips’ checklist, which comprises 57 items under two domains structure and data. Each economic analysis was assessed by one reviewer (MY) and cross-checked by a second health economist (PA). Any disagreements between the reviewers were resolved by discussion or by recourse to a third reviewer.

* + 1. Methods of data synthesis

Information extracted from the included studies was summarised and presented in a tabular form. Due to the context-specific nature of economic evaluation, the conduct and findings of studies included in the systematic review were summarised narratively. The results were organised in texts and summary tables. We highlighted issues/concerns related to the applicability to a UK setting, outlined the key drivers of cost-effectiveness, identified sources of uncertainty, provided a comprehensive overview of the cost-effectiveness evidence, and discussed recommendations for the conduct of future economic modelling.

* 1. Results

Electronic database searches and exploration of various sources, such as agency websites, yielded a total of 920 records. After removing duplicates, 694 records were screened for inclusion, of which 623 records were excluded based on title and abstract. The remaining 71 records were screened at full text, of which 51 studies were excluded, with the reasons for exclusion shown in Figure 2. 20 studies were considered relevant for this systematic review.

Records identified through database searching   
(n = 920)

**Screening**

**Included**

**Eligibility**

**Identification**

Records screened

(after duplicates removed)   
(n = 694)

Full-text articles assessed for eligibility   
(n = 71)

Studies included in qualitative synthesis (n = 20)

* Journal paper (n=7)
* Report funded by government (n=12)
* Thesis (n=1)

Records excluded at title and abstract level   
(n = 623)

Full-text articles excluded with reasons.

(n = 51)

* Conference abstract (n=27)
* Covered by another study (n=6)
* Letter to editor (n=5)
* Non-economic evaluation (n=5)
* Full-text not in English Language (n=3)
* Insufficient study design description (n=2)
* Intervention not of interest (n=2)
* Comparator not of interest (n=1)

Duplicate records removed   
(n = 226)

Additional records identified through other sources   
(n = 0)

Records identified

(total before deduplication)   
(n = 920)

Figure 2: Study flow diagram

* + - 1. Characteristics of included studies

The characteristics of the studies included are summarised in Appendix Table 7. Across the 20 economic analyses, the populations of interest were people with presymptomatic SMA, and types 1,2 and 3 SMA. No economic analyses were undertaken in people with type 0 or type 4 SMA. Subgroup categorisation based on onset age and disease duration, particularly distinguishing infantile-onset and later-onset types, showcases efforts to capture SMA's complexity.1, 15, 201-203 Noteworthy, variability includes focus on pre-symptomatic newborns,204 emphasis on infants with SMA type I at 3.4 Mean age (months),205 and diverging aims concerning SMA type I subjects.206, 207 These differences reflect varied research objectives, designs, and patient selection contributing to defined subgroup delineations.

* + - * 1. Intervention(s), Comparator(s), Outcome(s), Study perspective and Location & Setting

Studies compared onasemnogene abeparvovec versus BSC,14, 201, 204, 208 nusinersen versus BSC,17, 203, 207, 209-211 risdiplam versus BSC/SoC,15, 179 onasemnogene abeparvovec versus nusinersen,205, 206, 212-215 risdiplam versus nusinersen,202 by focussing on life-years gained (LYG) and quality adjusted life-years (QALY) outcomes. Majority of studies adopted the viewpoint of the health system or societal perspective.14, 15, 17, 179, 202-213, 215, 216 The geographical settings varied widely, with studies being undertaken in the USA, Canada, the UK, The Netherlands, Australia, and Sweden, showcasing a global perspective in SMA research with distinctive healthcare system nuances and perspectives.

* + - * 1. Model structure and health states

All studies included an economic model to assess the cost-effectiveness of therapies to treat SMA. Across all analyses, analysts used Markov models to capture SMA progression in the diverse patient populations, with health states definitions often centred on functional milestones (e.g., sitting, standing, walking, and ventilation support), emphasising a collective effort to encompass the breadth of functional abilities and disease severity in SMA patients. While the recurring inclusion of death as an absorbing state underscores its significance in SMA modelling.

We noted several differences in health state definitions, structures, and modelling techniques across the studies, showcasing varied interpretations of disease progression and outcomes in SMA. Distinctions in the number of states, milestone criteria, and approaches highlight the individualised nature of each economic model, influenced by study objectives, patient cohorts, available data, and modelling assumptions. The different studies employed various Markov models. Ten studies utilised a single Markov model to evaluate the cost-effectiveness of treatments,14, 201, 205, 206, 208, 211-215 while seven studies employed two Markov models for assessing type 1 and type 2/3 SMA.15, 17, 179, 202, 203, 207, 210 ICER 2019216 utilised three Markov models for presymptomatic, type 1, type 2/3 SMA patients. In the NICE HST24,204 two Markov models were utilised for short-term and long-term analyses. For the CADTH Nusinersen-2019,209 three Markov models were used to evaluate type 1, type 2, and type 3 SMA patients.

* + - * 1. Time horizon, cycle length and discount rate

Several studies’ economic analyses covered a long-term time horizon, spanning 60 to 100 years or even a lifetime, indicating a shared goal of capturing the long-term costs and benefits of interventions used to treat people living with SMA. Most studies utilised annual discount rates to modify costs incurred and benefits accrued over the modelled time horizon, with analyses using 1.5%, 3.5% and 5%, showcasing a consistent method to adjust for the time value of money in economic assessments. Cycle lengths varied between analyses, which ranged from monthly to multitudes of months, reflecting the necessity to model disease progression and treatment effects over specific time intervals to evaluate intervention impacts.

The range in time horizons, from short-term (e.g., 36 months) to long-term (e.g., a lifetime or 100 years), indicates diverse viewpoints on SMA modelling and intervention cost-effectiveness assessment.202, 206, 208 Discrepancies in discount rates, like 1.5%, 3%, and 5% yearly, suggest differing valuations of future costs and benefits among the studies, potentially influencing economic evaluations dissimilarly (Studies 6, 15, 17). Variations in cycle lengths, encompassing monthly intervals to specific trial follow-up points, illustrate differing strategies for capturing the dynamic nature of SMA progression and treatment effects in modelling.203, 207, 209 SMC studies(nusinersen, onasemnogene abeparvovec and risdiplam),202, 210, 215 with unclear cycle lengths or discount rates, could be collectively analysed to assess the impact of these methodological uncertainties on the credibility and transparency of economic evaluations in SMA research.

Analysing the commonalities, differences, and potential groupings based on time horizons, cycle lengths, and discount rates in the studies can advance researchers' understanding of the diverse modelling approaches utilized in assessing the economic implications of SMA interventions.

* + - * 1. Health-state utility values

Several sources of information were used to inform health state utility values, which included expert opinions, literature reviews, and clinical data to determine utility values for patients and caregivers. Data obtained from clinical trials or health-related quality-of-life studies were regularly mapped to standard utility measures like EQ-5D to evaluate SMA-related health states, highlighting a standardised approach to converting diverse data into a common utility metric.

However, we noted that in assigning utility values for specific health states, with some studies leaning on expert opinions and assumptions while others cited published literature and trial data, demonstrating varying levels of empirical backing for utility assessments. Variations in caregiver disutility calculations were evident, with some studies incorporating caregiver-specific data from diverse sources including surveys and population scores, indicating differences in valuing caregiving impacts on utility estimates.

TA588 and TA755 adjusted utility values based on caregiver disutilities for different SMA types, shared similarities in acknowledging caregiving impacts on utility estimates.15, 17 TA588 HST24 and CADTH- Nusinersen derived patient utility values from expert analyses and trial data in a multi-model SMA context, illustrated similarities in relying on expert opinions and clinical findings.17, 204, 209 Comparing how these studies translate complex clinical data into utility values could spotlight the effectiveness of utilizing expert insights in utility determination across various SMA types.

Through an examination of commonalities and methodological differences in sourcing utility values, researchers can enhance their comprehension of diverse approaches and considerations in utility estimation for SMA analysis.

* + - * 1. Health-state resource use and costs, currency and conversion

Resource use and cost information were obtained mainly from real-world data sources (e.g., national health services), clinical trials, and healthcare resource utilisation studies to determine SMA health state costs, emphasising a reliance on empirical evidence. External sources such as literature reviews and expert insights were commonly consulted for cost determinations.

Variability existed in the sources of cost data, with studies drawing from national health services, pharmaceutical company studies, and expert opinions, reflecting diversity in data sources for cost estimation. Variation in the granularity of cost breakdowns was observed, with some studies providing detailed cost itemisations and others presenting more aggregated estimates, indicating differing levels of detail in reporting resource use and cost information.

CADTH-OA, 2021 and Wang et al. both utilised national health services data for cost assessments, exhibit similarities in leveraging local healthcare system information for cost estimations.201, 206 Comparing specific cost components from these studies could reveal insights into the consistency of cost structures within national health service contexts. SMC -OA, 2021 and Zuluaga et al., 2019, referenced specific European studies for cost data, demonstrate similarities in relying on region-specific studies for cost estimations.203, 215 By comparing health state cost sources and currency conversion practices across the studies, researchers can enhance their understanding of the various methodologies and factors influencing cost estimations for managing SMA treatments.

A summary table of included cost-effectiveness studies can be found in Appendix 5

* + - * 1. Results of Engaging Patients and Affected Stakeholders

In the evaluation of TA588 and TA755, no patients were involved in determining utility values, while patient and carer groups actively participated in the study process. For SMC-Risdiplam-2022, patient involvement in utility value estimation was not specified, but patient group representatives and clinicians were engaged in assessing the value of risdiplam. Similarly, in HST15 and HST24, patients did not contribute to utility value estimation, but patient and carer groups were involved in the study process. In ICER-2019, patients participated in preliminary discussions. CADTH reviews of Risdiplam-2021 and OA-2021 involved patients through the CADTH review process and semi-structured interviews and surveys, respectively. Additionally, SMC-Nusinersen-2018 and SMC-OA-2021 included patient group representatives in evaluating additional benefits. These findings underscore the varied approaches employed in engaging with patients and stakeholders across different assessments, demonstrating a commitment to incorporating the perspectives and experiences of those impacted by spinal muscular atrophy treatments.

* + - * 1. Results of resource use and costs

The findings from different studies highlight diverse approaches to assessing resource use and costs in the context of SMA treatments. For instance, TA588 distributed cost items among various care categories and included a wide range of resource use categories such as drugs, medical tests, hospitalizations, and social services. Similarly, Zuluaga‑Sanchez et al. 2019 and NCPE-2017 delved into specific health-state costs, drug-acquisition costs, and other related expenses. Thokala et al. 2020 focused on treatment costs and healthcare resource allocation for different health states, while Wang et al. 2022 concentrated on drug acquisition and monitoring across health states. Each study, including SMC-Risdiplam-2022, SMC-OA-2021, Malone et al. 2019, provided unique perspectives on resource utilization and cost implications, underscoring the intricate nature of economic evaluations for SMA therapies. These varied analyses illuminate the specific costs and resources essential for disease management and treatment administration within distinct study contexts.

* + - * 1. Results of survival modelling

In the assessment of TA588, unique approaches were taken for type 1 SMA and type 2/3 SMA. For type 1 SMA, Weibull models were separately applied to each treatment group, incorporating a proportional hazards assumption with a gradual decrease in hazard ratio over 120 months. Additionally, a mortality adjustment factor of 0.75 was implemented in favourable health states. Conversely, for type 2/3 SMA, a flexible spline model with two knots was utilized, along with the same mortality adjustment factor in better health states.

In the evaluation of NICE-TA755-Risdiplam, distinct strategies were adopted for type 1 SMA and type 2/3 SMA. For type 1 SMA, varied models were established for the risdiplam and standard care groups based on trial data, employing exponential models or indirect hazard ratio comparisons for different health conditions. On the other hand, type 2/3 SMA survival modelling drew upon data from natural history studies, constructing a weighted survival model that considered general population mortality and differing prognoses between type 2 and type 3 patients.

Within the examination of HST24, survival modelling at the pre-symptomatic stage involved the use of Weibull and gamma models tailored to specific data cohorts. General population mortality data was adjusted using hazard ratios associated with different gene copies.

These observations showcase the diverse methods and models utilized in survival modelling for varying types of SMA among the studies. Each investigation tailored its approach to address the unique characteristics of disease stages, treatment cohorts, and health statuses, underscoring the nuanced considerations in predicting survival outcomes for individuals affected by SMA.

* + - * 1. Assumptions used in studies/reports

TA588 encompassed assumptions regarding treatment response, mortality adjustments, trial duration, scoliosis surgery, utility values, milestones, and data sources. Scenario analyses were performed for within-trial hazard ratios and caregiver ratios. Zuluaga Sanchez et al. 2019 postulated indefinite continuation of treatment effects and assumptions on milestones, mortality risk, motor milestones' impact, and treatment outcomes. Thokala et al. 2020 assumed the maintenance of motor function milestones until death, utilizing short-term model data for motor function milestones and ventilation while making assumptions about patient transitions, utility benefits, and disease progression.

SMC-Nusinersen-2018 assumed the persistence of treatment effects beyond the study's follow-up period on scores. Wang et al. 2022 made assumptions about treatment effects, sustainability of motor milestones, mortality risks, utility values, and administration duration. TA755 presented various assumptions about caregiver disutilities, utility values, treatment costs, and complications. CADTH-Nusinersen-2019 incorporated assumptions on treatment discontinuation, mortality risk, and comparisons among patient groups. ICER-2019 maintained consistent assumptions on motor milestone sustainability, transitions, comparisons, morbidity costs, and survival rates. CADTH-Risdiplam-2021 constructed modelling assumptions related to transitions, treatment discontinuations, permanent ventilation, and mortality.

Broekhoff et al. 2021 considered assumptions regarding motor milestone survival, reversibility, quality of life, and health states maintenance. Malone et al. 2019 integrated assumptions about lifelong treatment effects, milestone maintenance, treatment continuity, and symptom progression. CADTH-OA-2021 outlined detailed assumptions on transitions, ventilation, treatment discontinuation, treatment effects, and milestone maintenance. Meijer et al. 2023 relied on Markov model-based assumptions on transitions, milestone sustainability, and health state progression. SMC-OA-2021 established assumptions on pre-symptomatic scenarios, treatment efficacy, regression, and treatment discontinuation restrictions.

These findings exemplify the diverse range of assumptions made in different studies, impacting treatment outcomes, disease progression, clinical results, and healthcare resource utilization in SMA assessments.

* + - * 1. Model inputs used across studies

In the analysis of various studies exploring treatments for SMA, it is evident that similar parameters are recurrently addressed. For instance, study parameters such as health state distribution, utilities for patients and caregivers, costs by health state, transition probabilities, age at surgery, and overall survival appear consistently in studies like NICE-TA588-Nusinersen and Malone et al. 2019. Similarly, elements like time horizon, mean age, mortality risk, drug and administration costs, and health-state utility values are shared between Zuluaga Sanchez et al. 2019 and HST24. Furthermore, aspects like utility values for different health states, monthly costs, and administration costs are examined in studies including Thokala et al. 2020 and Meijer et al. 2023. These study parameters collectively offer a comprehensive understanding of the key factors considered in economic assessments of SMA therapies, shedding light on model structures, health state costs, utility values, and other significant variables.

* + - * 1. Characterising uncertainty in different studies

Results from various studies demonstrate the utilization of diverse analytical methods to assess uncertainty and characterize scenarios impacting cost-effectiveness outcomes in the realm of SMA therapies. For example, TA588 and Zuluaga Sanchez et al. 2019 both utilized PSA and explored scenario analyses to reveal key parameters affecting ICER values. Thokala et al. 2020 and Dean et al., 2021 delved into OWSA and demonstrated the dominance of specific treatments through scenario analyses. Similarly, SMC-Risdiplam-2022 showcased the dominance of a treatment over another in scenario analyses, while SMC-Nusinersen-2018 highlighted the sensitivity of ICER values to various factors. TA755 and Wang et al. 2022 employed both PSA and DSA to assess different scenarios affecting cost-effectiveness outcomes. Furthermore, studies like HST15, HST24, CADTH-Nusinersen-2019, and CADTH-Risdiplam-2021 conducted various sensitivity and scenario analyses to explore the impacts of assumptions on cost-effectiveness outcomes. Broekhoff et al. 2021 and Malone et al. 2019 investigated sensitivity and scenario analyses to understand the influence of key model parameters on cost-effectiveness outcomes, while CADTH-OA-2021 and SMC-OA-2021 assessed multiple scenarios to evaluate cost-effectiveness considering different parameters. Overall, these studies underline the importance of considering uncertainties and exploring varied scenarios when evaluating the cost-effectiveness of treatments for SMA.

* + - * 1. Limitations identified across studies

Across different research studies addressing economic evaluations of therapies for SMA, several common limitations emerge. For instance, the uncertainty in clinical data poses challenges affecting the reliability of cost-effectiveness estimates in studies like NICE-HST15-OA-TypeI, while Zuluaga Sanchez et al. 2019 faces limitations due to limited resource and cost data impacting accuracy. Thokala et al. 2020 highlights uncertainties in survival, disease progression, and treatment effectiveness, attributed to a lack of long-term follow-up. In Wang et al. 2022, small sample sizes in clinical trials and inadequate long-term clinical data lead to limitations in assessments.

Dean et al., 2021 raises concerns about incomplete follow-up impacting uncertainties in survival improvements, and bias potential impacting ICER calculations in SMC-Risdiplam-2022. Similarly, SMC-Nusinersen-2018 contends with assumptions potentially overestimating benefits and uncertainties due to a lack of long-term survival data. The NICE-HST24-OA-Pre-symptomatic study faces limitations with a limited age range in clinical trials affecting effectiveness uncertainties. ICER-2019 report limitations such as a lack of robust data leading to assumptions and structural assumptions impacting treatment relationships.

Moreover, Connock et al. 2020 relies on accessible public data for straightforward calculations but faces potential limitations in data availability. Malone et al. 2019 struggles with data limitations and relies on preliminary AVXS-101 data. CADTH-Nusinersen-2019 encounters issues with utility values reliability and inappropriate assumptions. CADTH-Risdiplam-2021 navigates uncertainties in clinical benefits comparisons and assumptions affecting model outcomes. Broekhoff et al. 2021 and CADTH-OA-2021 also grapple with limitations in clinical data evaluation and utility value assignment challenges.

Meijer et al. 2023 faces challenges with variable patient characteristics contributing to model uncertainty, while SMC-OA-2021 encounters uncertainties in data, assumptions, and utility values. These limitations underscore the complexities and challenges inherent in economic evaluations of SMA therapies, emphasizing the need for robust data, careful assumptions, and thorough evaluations to draw valid conclusions.

* + - 1. Reporting and methodological quality assessment
         1. Reporting quality assessment

We present a summary of the reporting quality of the 20 studies included in the current systematic review which was assessed using the CHEERS II checklist199 in Appendix 4.

In general, the reporting quality of the included studies were satisfactory, with most studies reporting information on their title, introduction, methods, results and discussion. Whilst majority of the published papers provided a structured summary in the form of an abstract, this was not the same for the reports, which might have been a result of it not being a requirement when preparing these reports. However, we found that majority of these reports provided more details on the conduct of the economic analyses compared to the published papers. Conversely, some reports did not provide this detailed information.202, 207, 210, 215 We noted that majority of studies reported details about the methods used (e.g., characteristics of the study population, setting and location, comparators, viewpoint of the economic analysis, time horizon, discount rate and selection, measurement and valuation of outcomes) in the economic analyses, but none had developed a health economics plan (HEAP), considered distributional effects or engagement with a patient population. Studies might have not scored on these criteria as they were recently added to the update of the CHEERS I appraisal tool,217 so this result was expected. Surprisingly, we found that the SMC reports202, 210, 215 have not provided details about description and rationale for selecting the model, the discount rate used in the analyses or described methods for analysis or statistical transformation of data or extrapolation processes, and characterising heterogeneity.

With regards to the results, we noted that some studies202, 209, 210, 212, 213, 215 have not adequately discussed study parameters and the effect of uncertainty.

Overall, the studies displayed varying levels of adherence to the CHEERS II criteria, indicating that there is need for enhancements in specific areas to improve the reporting quality.

* + - * 1. Methodological quality assessment

The methodological quality assessment for the 20 studies was conducted using the Philips checklist,200 which evaluates structure, data, and consistency. The assessment was based on qualitative methods as the checklist does not provide quantitative evaluations. The assessment was undertaken using available information from the main papers/reports and electronic supplementary material, if available.

In general, several studies/reports, including TA588,17 HST24,204 and ICER Spinraza and zolgensma 2019,216 demonstrated the best overall quality in methodology and low risk of bias. Conversely, SMC Onasemnogene -2021215 and NCPE-2017207 showed weaker methodological quality.

When looking at specific sections, Zuluaga‑Sanchez et al.203 and Malone et al. 2019214 excelled in structural aspects, while TA58817 and NICE-Onasemnogene HST24-pre-symptomatic204 were highlighted for strong data quality. In terms of consistency, HST24204 and Meijer 2023208 stood out for their robustness.

Overall, most studies adequately addressed methodological and structural uncertainties; however, some inconsistencies were found in considering alternative assumptions about treatment effects and uncertainties related to data incorporation as distributions. The studies generally demonstrated thorough testing of mathematical logic, comparison with previous models, and explanation of any counterintuitive results. Moving forward, addressing these inconsistencies and uncertainties would further enhance the methodological quality and reliability of the studies.

* + 1. Assessment of cost-effectiveness
       1. Critical review and synthesis of information
       2. Discussion

Our assessment of the studies that undertook an economic evaluation of treatments for people living with SMA highlighted some notable differences with regards to target population, interventions and comparators, outcomes, models, resource use and costs, health-state utility values, time horizons, assumptions, analyses, limitations, and patient engagement. Studies predominantly focused on people with type 1, 2, and 3 SMA, with subgroups identified based on age of onset and disease characteristics. Interventions (onasemnogene abeparvovec, nusinersen, risdiplam) were mainly compared against best supportive care across various global settings, with the results reported in terms of an ICER expressed as cost per LYG or cost per QALY. Markov models captured SMA progression by defining health states based on functional milestones and ventilation support. We noted the differences in model time horizons, discount rates, and sources of utility values, which could potentially impact on the base-case results. There was some engagement of patients and stakeholders, but this varied between studies. Our evaluation provides critical insights on the complexities and considerations in an economic evaluation of assessment of treatments for SMA.

**Consensus in Markov models and health states**

When we examined the Markov models and their health states, there were some noticeable differences. The models differed in terms of their illustrative structures, health states included, and assumptions about disease progression, treatment efficacy, and mortality. For example, the TA58817 study used two Markov models to differentiate between infantile and later-onset SMA, featuring distinct health states reflecting milestone achievements (e.g., standing and walking). In contrast, the HST24204 used short-term and long-term models to capture different disease phases and milestones by using transitions between sitting, walking, and death. Among the studies, assumptions on disease modification, treatment discontinuation, and survival were common factors influencing health state selection and transitions. For example, assumptions in the Thokala et al.211 assumed that patients maintained their motor function milestones until death, with treatment effects sustained post-trial. Conversely, the Broekhoff et al.205 assumed progression to specific health states based on disease severity and treatment outcomes, aligning survival rates with corresponding SMA types. In comparing the studies, there are clear disparities between the studies’ health state selection and progression, emphasizing the need for robust data, transparent methodologies, and comprehensive sensitivity analyses to ensure accurate and reliable assessments of SMA treatments' clinical efficacy and cost-effectiveness.

**Long‑Term Modelling Implications**

Examining economic evaluations from various studies highlights several key considerations in evaluating the long-term impact of SMA treatments. The identified limitations stress the necessity for robust long-term efficacy and safety data to fully capture the benefits of SMA treatments over an extended period. Challenges related to treatment sustainability, including motor function milestones and HRQoL are evident especially in the NICE, ICER and CADTH reports. These challenges encompass uncertainties in projecting treatment outcomes over a lifetime due to factors like uncertain long-term data, assumptions around sustained milestones, and varying patient characteristics. Tailored economic evaluations are crucial to address the diverse responses within SMA patient populations of different subtypes.14, 15, 17, 179, 208, 209, 216 Adjusting ICERs to account for these differences is crucial in accurately reflecting treatment outcomes across various patient groups with distinct disease progression rates. Efforts towards extended monitoring and real-world evidence collection are essential to bridge the gap in long-term data, enhancing the precision of evaluations and decision making for SMA treatments.

**Source of utility values**

The evaluations of utility values for patients with SMA highlights the challenges encountered in measuring robust utility values for rare conditions. Various studies assessed by organisations (e.g., NICE, ICER, and CADTH) revealed the complexities and variations in determining utility values for different health states in SMA patients, especially in the absence of long-term clinical data. The findings from the current review highlighted that there is a lack of robust utility data for SMA, a similar finding in a recent systematic literature, indicating a lack of consensus on the most appropriate estimation method.218

Furthermore, the scarcity of validated measures for paediatric patients, considering utility measurement instruments are primarily designed for adults, complicates the assessment of SMA.219 The TA588 report acknowledged the difficulties in obtaining comprehensive utility data for SMA, emphasising the absence of robust utility values and the challenges associated with utilizing generic preference-based measures to estimate HRQoL in paediatric patients. Similarly, the CADTH-Nusinersen and onasemnogene abeparvovec, 2019 studies address uncertainties surrounding the long-term effectiveness of treatments like nusinersen and onasemnogene abeparvovec, impacting on the accuracy of cost-effectiveness evaluations. Moreover, both the NICE-Nusinersen TA588 study and the CADTH-Nusinersen & onasemnogene abeparvovec, 2019 studies expressed concerns about the validity and reliability of assumptions in economic models due to factors such as limited clinical data, small sample sizes, and the absence of direct treatment comparisons, like nusinersen and risdiplam.

Additionally, we found that there was a tendency to use clinical expert opinion as a proxy utility values for modelling SMA.15, 17 Notably, NICE guidelines stipulate that in cases where it is challenging to measure HRQoL in patients, data should be gathered from caregivers rather than clinicians.220 Furthermore, NICE recommends that the valuation of health states should align with public preferences, which is not fulfilled when estimates from clinical experts are employed in economic modelling.220

Overall, while these studies yield crucial insights into the challenges of assessing utility values for SMA patients, they highlight the significance of continued research, robust data collection, and transparent reporting to improve the precision and reliability of economic evaluations in the context of rare diseases.

**Sources of resource use and costs**

Several sources and methods were used to collect and quantify resource use data. For example, some studies15, 17, 179, 208, 209, 211 relied on real-world evidence (RWE) surveys, Hospital Episode Statistics (HES) data, literature reviews, NHS Reference Costs, clinical trials data and clinical expert opinion to obtain information.

In TA588 and TA755 appraisals, resource use and cost data were specific to the UK healthcare system,15, 17 while in the CADTH-Nusinersen and CADTH-Risdiplam appraisal resource use and costs were obtained from studies undertaken in Germany and Canada, respectively.179, 209 The diversity in data sources could potentially lead to variations in the estimation of costs and resource utilisation, impacting the comparability of results across different studies.

Meijer et al. and Thokala et al. adjusted costs to reflect the economic impact of SMA treatment on different age groups.208, 211 The consideration of age-adjusted costs allows for a more nuanced understanding of the financial burden associated with treating SMA patients across various stages of life.

Assumptions regarding costs varied across studies, influencing the projection of financial implications related to SMA treatment. For instance, some studies assumed lifelong treatment efficacy, predefined discontinuation rates, and assumptions on disease progression, caregiver disutilities, and additional costs for SMA complications.15, 17, 179, 208, 209, 211 The different assumptions made in each study could contribute to discrepancies in cost estimates and affect the overall economic evaluations.

In TA588 and CADTH-Risdiplam reports they provided distinct definitions of BSC or standard of care, highlighting the variations in approaches to determine the baseline for cost-effectiveness comparisons.17, 179 Differences in defining BSC or standard of care could impact the evaluation of the incremental benefits and costs of newer treatment options for SMA.

The lack of direct comparative data between different treatments and best supportive care presents a significant challenge in conducting robust cost-effectiveness analyses. Variability in assumptions, data sources, and methodological approaches among studies further complicate the comparison of resource use data and cost estimates.

In summary, the collection and quantification of resource use data in studies related to SMA treatment involve a variety of sources, age-adjusted costs, assumptions about costs, definitions of best supportive care, and challenging comparisons due to the complexity and heterogeneity of the disease and treatments. Interpretation of the results from these studies should consider the nuances in data sources, methodologies, and assumptions used in conducting economic evaluations for SMA management.

* 1. Summary and critique of economic evidence submitted by companies/sponsors

This section focuses on the economic evidence submitted by Biogen Idec Ltd. and Roche, and additional information received from the companies in response to the EAG’s clarification questions. The EAG critically appraised the economic evidence submitted and examined the companies’ electronic models.

The chapter starts with the companies’ systematic reviews, methods, and results (base-case, sensitivity and scenario analyses) as reported in the CS. The EAG then compares the economic analysis to the NICE reference case, then provide a critique using frameworks on best practices for reporting economic evaluation and economic modelling to assess the overall reporting quality and validity of these analyses. In the subsequent chapter, where possible, the ERG has addressed their concerns in the form of additional analyses undertaken by the ERG.

The submissions received by the EAG included from Biogen Idec Ltd and Roche are as follows:

* A systematic literature review of the economic evidence for the management of people diagnosed with presymptomatic, type 1 and type 2 and 3 SMA.
* Methods used to undertake the economic analysis, and the company’s base-case and sensitivity analysis results.
* Electronic version of the Markov models built in Microsoft Excel.
  + 1. Biogen

In this section, the EAG reviewed economic evidence submitted by Biogen, and additional information received from the company in response to the EAG’s clarification question. The EAG critically appraised the economic evidence submitted and examined the company’s electronic model. This section is structured as follows. First, we present a critique of the company’s systematic literature review of the economic evidence. Second, we present the technology against the NICE reference case checklist. Third, we present an overview, then a critique of the economic models submitted, which describes in detail the model structure and evaluated the clinical evidence (e.g., treatment efficacy, treatment discontinuation, mortality) and economic evidence (e.g., health-related quality of life, resource use and costs) used to parameterise the model for nusinersen by population of interest.

* + - 1. EAG critique of company’s systematic literature review of economic evidence

Three SLRs for economic evaluations, utilities data and costs and resource use studies are reported in detail in CS Appendix G. The literature searches were originally run in January-February 2022 and were updated in October-November 2023.

A broad range of bibliographic databases and other sources were searched for all three SLRs, including HTA agencies’ websites, conferences and reference lists (CS Appendix G, Table 2.2).

The search strategies (reported in CS Appendix G, appendices A-C) are accurate and thorough, incorporating terms for SMA and sensitive filters for economic evaluations, utilities/HRQoL and costs/healthcare resource use. A date limit was applied to exclude studies published before 1998. The company identify a potential limitation of their resource use search terms, in that the only specific non-monetary resource use outcomes included were hospitalisation, visits/appointments and length of stay, and this may have missed some eligible. However, general resource use search terms are used, minimising this risk, and terms for missing school/preschool are also included, which is appropriate in the SMA population.

* + - 1. Presymptomatic population
         1. NICE reference case checklist

The EAG undertook an evaluation of the CS in relation to the NICE reference case, with the findings reported in Table 34.

Table 34: NICE reference case checklist

| **Attribute** | **Reference case and TA Methods guidance** | **Does the *de novo* economic evaluation match the reference case** |
| --- | --- | --- |
| **Defining the decision problem** | The scope developed by NICE | Decision problem clearly stated and is in line with the scope developed by NICE |
| **Comparator(s)** | Therapies routinely used in the NHS, including technologies regarded as current best practice for this population | No. Nusinersen was compared to BSC. |
| **Patient group** | As per NICE final scope, the population refers to:  People living with presymptomatic SMA, types 0 to 4 SMA | No. Due to the lack of evidence for type 0 and type 4 SMA, the company reported results separately for presymptomatic, type 1 SMA and types 2/3 SMA. |
| **Perspective costs** | NHS & Personal Social Services | Yes |
| **Perspective benefits** | All health effects on individuals | Yes |
| **Form of economic evaluation** | Cost-effectiveness analysis | Cost-effectiveness analysis |
| **Time horizon** | Sufficient to capture differences in costs and outcomes between the technologies being compared | 100-year time horizon |
| **Synthesis of evidence on outcomes** | Systematic review | Systematic review was undertaken by the company |
| **Outcome measure** | Quality adjusted life-years | Results reported in terms of quality adjusted life-years |
| **Health states for QALY** | Described using a standardised and validated instrument | Yes |
| **Benefit valuation** | Time-trade off or standard gamble | The standard UK EuroQol five dimensions [EQ-5D] tariff is used, which is based upon time-trade off |
| **Source of preference data for valuation of changes in HRQoL** | Representative sample of the public | Yes |
| **Discount rate** | An annual rate of 3.5% on both costs and health effects | Yes |
| **Equity** | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes |
| **Probabilistic modelling** | Probabilistic modelling | The company undertook PSA and reported these results |
| **Sensitivity analysis** |  | The company undertook a range of sensitivity and scenario analyses. |
| BSC, best supportive care; EQ-5D, EuroQol five dimensions; HRQoL; health-related quality of life; IFN, interferon; NHS; National Health Service; NICE; National Institute for Health and Care Excellence; PSA; probabilistic sensitivity analysis; QALY, quality-adjusted life years; | | |

* + - * 1. Model structure

The company used a cohort-based Markov model to depict the natural history of people living with presymptomatic SMA (*see* Figure 3).

A diagram of a diagram

Description automatically generated

Figure 3: Illustrative model structure for the presymptomatic population

**ERG summary**: The illustrative model used by the company captures the key features (i.e., health states and transitions) of people diagnosed with presymptomatic SMA. However, it should be noted that the model does not capture subsequent costs/benefits following discontinuation of nusinersen treatment. Instead, it is assumed that once treatment is discontinued people with follow the transitions associated with treatment with BSC.

* + - * 1. Population

The population included in the economic analysis for the presymptomatic population is reflective of the participants in the NURTURE trial. For the presymptomatic population, the company considered a total presymptomatic population, a population with two SMN2 copies and three SMN2 copies (*see* Table 35).

Table 35: Characteristics of presymptomatic population by SMN2 copies

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Two SMN2 copies** | **Three SMN2 copies** | **Total presymptomatic population** |
| Average age (years) | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Sex (female, %) | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Average weight (KG) | \*\*\*\* | \*\*\*\* | \*\*\*\* |

**ERG summary**: The EAG agrees with the approach taken by the company to provide results based on a total presymptomatic population, a population with two SMN2 copies and three SMN2 copies. With regards to the population of interest outlined in the NICE scope, the evidence submitted by the company is narrower. The company has not presented any clinical or cost-effectiveness evidence of nusinersen in treating people with type 0 or types 4 SMA.

* + - * 1. Interventions and comparators

The cost-effectiveness analysis compared nusinersen against BSC in a population with similar characteristics to participants in the NURTURE trial. The company did not compare nusinersen against onasemnogene abeparvovec or risdiplam, with a justification that the results of the ITC were not considered appropriate for use in the cost-effectiveness analysis.

*Intervention*

The company modelled nusinersen as a first-line therapy in accordance with the marketing authorisation. In the model, people received the four loading doses in the first four cycles of the model and in subsequent 4-monthly cycles received one administration of 12mg of nusinersen per cycle, which is based on the treatment schedule in the ENDEAR study and consistent with the marketing authorisation. The company stated that the same dose was administered intrathecally regardless of age.

*Comparator*

The final NICE scope outlines the comparators (established clinical management, BSC, the interventions compared to each other, and ‘for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene- onasemnogene abeparvovec’) to be considered by the companies. Across all populations, the company compared nusinersen against BSC. BSC reflected gastrointestinal, respiratory, nutritional and orthopaedic care/management delivered by a multidisciplinary team.

* + - * 1. Perspective, time horizon and discounting

The perspective/viewpoint of the analysis is that of the NHS and PSS, which is in line with the NICE Guide to the Methods of Technology Appraisal.220 The model assumes a 100-year time horizon, which is long enough to capture the long-term costs and benefits of treatment. Costs incurred and benefits accrued were discounted based on an annual rate of 3.5%. Several sensitivity and scenario analyses were undertaken by the company.

**EAG summary**: The EAG considers the approach taken by the company appropriate.

* + - * 1. Treatment effectiveness and extrapolation

Details of the treatment effectiveness are presented in Section 4.3.2 through to 4.3.7

* + - * 1. Health-related quality of life

The company stated that EQ-5D-5L information was collected as part of the MAA, but due to the limited number of participants and short follow-up, this information was not used to derive health state utility values. Hence, health state utility values were obtained from another source, HST24.204 In Table 36, the company provided the health state utility values used in the base-case, as well as in scenario analysis (*see* Table 37). Additionally, they provided their rationale for using these values, but stated that these values were not contested by the EAG for HST24. It should be noted that these values have been applied to all three models, assuming that they are reflective of the health state and not the type of SMA.

Table 36: Health state utility values used in company base-case

|  |  |  |
| --- | --- | --- |
| **Health state** | **Utility value** | **Notes** |
| Permanent ventilation | 0.00 | Based on HS1 (non-sitter, PAV) health state |
| Not sitting | 0.19 | Based on HS1 (non-sitter, no PAV) health state |
| Sitting | 0.60 | Based on HS2 (sitter) health state |
| Standing | 0.77 | Assumed to be equivalent to HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking) |
| Walking | Equivalent to general population utility | Assumed to be equivalent to HS-BRND health state |
| Permanent ventilation | 0.00 | Based on HS1 (non-sitter, PAV) health state |
| PAV, permanent assisted ventilation; SMA, spinal muscular atrophy | | |

Table 37: Health state utility values used in scenario analyses (based on TA755)

|  |  |  |
| --- | --- | --- |
| **Health state** | **Utility value (Type 1)** | **Utility value (Type 2)** |
| Permanent ventilation | -0.02 | N/A |
| Not sitting | 0.10 | 0.10 |
| Sitting | 0.20 | 0.20 |
| Standing | 0.70 | 0.70 |
| Walking | 0.85 | 0.85 |

The company further included an ‘on-treatment’ utility values of 0.10 for all people being treated. Their rationale is based on clinical expert opinion at an advisory board that there would be other health-related quality of life gains associated with gross motor milestones that are not captured. Namely, additional upper limb function when on active treatment, which can help people undertake some daily activities.

In Table 38, we report the caregiver utility values used in the company’s base-case. The company’s approach to capturing the impact of carers was to apply a caregiver utility increment rather than a decrement, which causes the QALYs in the model to decrease regardless of if people are in a better or worse health state.

Table 38: Resource use and caregiver utility values used in base-case analysis (obtained from CS document B, page 182)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Health state** | **Number of caregivers** | **Mean utility** | **Reference** | **Justification** |
| Permanent ventilation | 2 | 0.484 | Table 3 (number of caregivers) and Table 58 (caregiver utility). | Based on the preferred base case for the EAG in TA755.43 |
| Not sitting | 2 | 0.484 |
| Sitting without support | 2 | 0.628 |
| Standing with assistance | 1 | 0.771 |
| Walking independently | 1 | Population norm |

* + - * 1. Resource use and costs

Cost assessment was based on assigning resource use and costs for nusinersen, comprising drug acquisition costs, administration costs and health state management costs, all from the perspective of the NHS and PSS. The company provided justification for not including costs associated with treating adverse events or concomitant medication.

The list price of a dose (12mg/5ml) of nusinersen is £75,000. Nusinersen is administered intrathecally by lumbar puncture, using the cost of £836 for diagnostic spinal puncture as a proxy.221 The cost of nusinersen in the first cycle of treatment, which includes four loading doses is £300,000, with an additional intrathecal administration cost of £3,899. Costs thereafter for maintenance doses are £75,000 with an intrathecal administration cost of £836 per cycle. In the base-case the company applied a \*\*\* PAS to the cost of nusinersen, which reduces it to \*\*\*\*\*\*\*.

Table 39: Annual health state costs used in the company’s base-case analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Resource category | Permanent ventilation | Non-sitter | Sitting | Standing and Walking |
| Drugs | £619 | £810 | £781 | £1,012 |
| Medical tests | £880 | £1,152 | £917 | £ 675 |
| Medical visits | £3,669 | £4,801 | £2,805 | £2,461 |
| Hospitalisations | £218,987 | £70,829 | £40,577 | £276 |
| Accident and Emergency | £375 | £490 | £201 | £80 |
| Health material | £3,590 | £4,400 | £2,274 | £652 |
| Social services | £55,590 | £30,019 | £20,013 | £3,177 |
| **Total** | **£283,710** | **£112,500** | **£67,567** | **£8,333** |

Table 40: Annual health state costs used in the company’s scenario analysis (obtained from CS document B, pg 184)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Health state** | **Annual cost reported in TA588** | **Inflated annual cost (applied in CEM)** ¥ | **Inflated cost per 4-month cycle** | **Source** |
| Permanent ventilation\* | £136,444 | £150,989 | £50,330 | Burden of illness and resource utilisation in SMA survey, 2017. |
| Not sitting | £77,968 | £86,280 | £28,760 |
| Sitting | £55,185 | £61,068 | £20,356 |
| Standing | £20,229 | £22,385 | £7,462 |
| Walking | £20,229 | £22,385 | £7,462 |
| \* The annual cost for ‘permanent ventilation’ is assumed to be equivalent to the cost of ‘not sitting’ as per TA588 with a 175% increase in costs as applied in TA577  ¥ Costs are inflated from cost year 2016/17 to 2021/22 using an inflation index of 1.11 using indices derived from PSSRU 2022, NHSCII pay and prices. | | | | |

Resource use and costs associated with adverse reaction and miscellaneous costs were not considered in the economic analyses.

* + - * 1. Mortality

Mortality was required in the model to estimate the rate at which people died within each cycle over the model time horizon. People could transition from any health state to the dead health state. The company stated that time-to-death data were not available from the NURTURE trial because at the latest data cut, all participants were alive and free of permanent ventilation. Hence, they obtained time-to-death information from an alternative source; namely, HST24.204 The company digitised the parametric curves, rather than the generating IPD from the Kaplan-Meier plots, which is the more conventional approach, then fitting various parametric curves to the IPD generated. The company stated that they took this approach to remain consistent with the curves reported in HST24. The company selected specific curves/figures from HST24 for the permanent ventilation, not sitting and sitting health states to model survival. These curves were reflective of the EAG’s preferred assumptions for HST24, which were exponential for people with permanent ventilation, and gamma for not sitting and sitting without support health states.

For people occupying the standing and walking health states, the company assumed that these people would have the same mortality as the general population, an assumption that we confirmed with our clinical advisors. General population mortality was based on the national life tables for the 2017-2019 duration.

Due to the lack of information on the long-term overall survival for people who received treatment for SMA, the company assumed that overall survival did not differ between treatment and people who received BSC. Any gain in life expectancy would be a result of the additional time spent in the standing and walking health states.

Other simplifying assumptions with regards to mortality is that people with two copies of SMN2 will have the same overall survival as people with three copies of SMN2.

In Figure 4, we present the overall survival curves by health states included in the presymptomatic model, which were used for people treated with nusinersen and those treated with BSC.

Figure 4: Overall survival curves for the presymptomatic population for people who received nusinersen treatment or BSC

**ERG summary**: The company’s approach to digitising the parametric curves reported in HST24 to model overall survival indirectly assumes that the analyst who developed the curves did so without any major errors. Also, the curves reported reflects a full range of parametric curves fitted and extrapolated to the KM plots and the one chosen is the most appropriate, adhering to the NICE DSU standards. In the EAG’s digitising of the original figures reported in HST24 to generate individual patient data (IPD), we were satisfied that that correct parametric curves had been fitted to these data and that the company chose an appropriate parametric curve to extrapolate beyond the observed data.

* + - * 1. Discontinuation

The company stated that only five pre-symptomatic participants were included in the MAA, which would have been insufficient to estimate discontinuation rates. Hence, they utilised discontinuation rates based on participants in the MAA with types 2/3 SMA, as the prognosis of presymptomatic and type 2/3 are similar.

* + - * 1. Decision modifier: Severity

The company’s base-case does not include a severity modifier. Instead, the company included caregiver utility ‘increments’ and in scenario analyses excluded caregiver utility increments but included a severity modifier (*see* Table 41). The company rationale was that according to the ‘*NICE TSD23 states that proportional severity estimates cannot be included when caregiver increments are applied’*.

Table 41: Summary of the QALY shortfall analysis across SMA populations

| **Factor** | **SMA Type** | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Presymptomatic** | | **Type 1 SMA** | | **Type 2/3 SMA** | |
| Sex distribution (female, %) | 50% | | 46% | | \*\*\*\* | |
| Starting age | 20.6 days | | 55.4 days | | \*\*\*\* | |
| QALYs of population without the disease | 70.27 (undiscounted); 24.30 (discounted) | | 70.07 (undiscounted); 24.2 (discounted) | | 66.42 (undiscounted); 23.97 (discounted) | |
|  | With caregiver utility increments | Without caregiver utility increments | With caregiver utility increments | Without caregiver utility increments | With caregiver utility increments | Without caregiver utility increments |
| QALYs | 8.67 | 7.99 | 0.25 | 0.20 | 13.72 | 12.60 |
| Absolute QALY shortfall | 15.63 | \*\*\*\*\* | 24.03 | \*\*\*\*\* | 10.26 | \*\*\*\*\* |
| Proportional QALY shortfall | 0.64 | \*\*\*\* | 0.99 | \*\*\*\* | 0.43 | \*\*\*\* |
| QALY weight based on proportional QALY shortfall | 1.2 | 1.2 | 1.7 | 1.7 | 1.0 | 1.0 |
| QALY weight based on absolute QALY shortfall | 1.0 | 1.0 | 1.7 | 1.7 | 1.0 | 1.0 |
| QALY, quality adjusted life year; SMA, spinal muscular atrophy | | | | | | |

**EAG summary**: The EAG understands the importance of capturing the impact of caregiver quality of life for caring for people with SMA in an economic analysis. TSD23 states that ‘*Carer impacts should be excluded from the calculation of AS and PS. Severity weights should be applied only to the incremental QALYs for patients*.’ (TSD23 pg 19)222 It is our understanding that severity weights can still be applied but only based on the incremental QALYs for patients. Hence, we propose calculating the absolute and proportional shortfall based on patients, then adding the caregiver utility increments.

* + - * 1. Company’s cost-effectiveness results (presymptomatic population)

The company reported deterministic and probabilistic results, as well as scenario analyses results for the comparison between nusinersen versus best supportive care. Main outcomes are reported in terms of life years and QALYs gained; results are reported in the form of an ICER expressed as cost per QALY gained.

Company’s base-case results

The results in Table 42 show that in the total presymptomatic population nusinersen is approximately \*\*\*\*\*\*\* more expensive than BSC and is expected to yield 5.92 more QALY, which equates to an ICER of approximately, \*\*\*\*\*\* per QALY. In a population or people with two SMN2 copies and more than two SMNs copies, resulted in \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, and an ICER of approximately \*\*\*\*\*\*\* per QALY, respectively.

Table 42: Company deterministic base-case results for the presymptomatic population

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
| BSC | \*\*\*\*\*\*\*\*\*\* | 19.91 | 8.67 | \* | - | - | \* |
| Nusinersen | \*\*\*\*\*\*\*\*\*\* | 20.84 | 14.59 | \*\*\*\*\*\*\* | 0.92 | 5.92 | \*\*\*\*\*\* |
| BSC, Best supportive care; LYG, Life years gained; QALYs, Quality-adjusted life years | | | | | | | |

PSA results were undertaken based on the cost per QALY. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are calculated based on randomly selecting variables from each distribution. Probability distributions were applied to key model input parameters. Table 43 we report the results of the company’s PSA for the total presymptomatic population, which are similar to the deterministic results.

Table 43: Company probabilistic base-case results for the presymptomatic population

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
| BSC | \*\*\*\*\*\*\*\*\*\* | 19.92 | 8.67 | \* | - | - | \* |
| Nusinersen | \*\*\*\*\*\*\*\*\*\* | 20.88 | 14.58 | \*\*\*\*\*\*\* | 0.97 | 5.91 | \*\*\*\*\*\* |
| BSC, Best supportive care; LYG, Life years gained; QALYs, Quality-adjusted life years | | | | | | | |

Each simulation of the incremental costs and incremental QALYS for nusinersen versus BSC were plotted on an incremental cost-effectiveness plane (*see* Figure 5), along with the respective cost-effectiveness acceptability curve (CEAC) (*see* Figure 6). The CEAC shows the proportion of simulations in which nusinersen compared to BSC are cost-effective at different willingness-to-pay thresholds for a QALY. These results show that at a WTP threshold of £20,000 per QALY nusinersen compared to BSC had a \*\*\*\* probability of being cost-effective.

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Figure 5: Incremental cost-effectiveness scatterplot for the comparison between nusinersen versus BSC (presymptomatic population)

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Figure 6: Cost-effectiveness acceptability curve for nusinersen at different willingness-to-pay thresholds

* + - * 1. Deterministic sensitivity analysis (presymptomatic population)

The company undertook one-way sensitivity analysis by varying key input parameters using their 95% CI to assess the impact on the several outcomes, with the results presented in the form of a tornado diagram (see Figure 7). In the absence of 95% CI, the company used an arbitrary ±20% around the point estimates.

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Figure 7: Tornado diagram for the impact of change to individual parameters on the ICER (cost per QALY) (presymptomatic population)

The results in Figure 7 shows that the per cycle health state costs for not sitting was a key driver of the economic analysis for the presymptomatic population.

* + - * 1. Company’s scenario analysis

Total presymptomatic population

The company undertook a range of scenario analyses to assess the impact of each change to the base-case results. In Table 44 through to Table 46, we present the scenario analyses results for the total presymptomatic population, presymptomatic population with 2 SMN2 copies and more than 2 SMN2 copies, respectively.

Table 44: Description of the company’s scenario analyses in comparison to the base-case (total presymptomatic population)

|  |  |  |  |
| --- | --- | --- | --- |
| **Scenario** | **Scenario analysis** | **Results** | **Impact** |
| **0** | **Reference** | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 1 | Assumption that nusinersen cohort does not decline | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 2 | The rate of decline for BSC is halved | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 3 | Remove carer utility increments | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 4 | Remove active treatment increments | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 5 | Remove all increments | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 6 | Alternate utility source: TA588 | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 7 | Costs from TA588 | \*\*\*\*\*\* | \*\*\*\*\*\* |

Presymptomatic population with 2 SMN2 copies

Table 45: Description of the company’s scenario analyses in comparison to the base-case (presymptomatic population with 2 SMN2 copies)

|  |  |  |
| --- | --- | --- |
| **Scenario** | **Scenario analysis** | **Results** |
| **0** | **Reference** | \*\*\*\*\*\* |
| 1 | Assumption that nusinersen cohort does not decline | \*\*\*\*\*\* |
| 2 | The rate of decline for BSC is halved | \*\*\*\*\*\* |
| 3 | Remove carer utility increments | \*\*\*\*\*\* |
| 4 | Remove active treatment increments | \*\*\*\*\*\* |
| 5 | Remove all increments | \*\*\*\*\*\* |
| 6 | Alternate utility source: TA588 | \*\*\*\*\*\* |
| 7 | Costs from TA588 | \*\*\*\*\*\* |

Presymptomatic population with 2 SMN2 copies

Table 46: Description of the company’s scenario analyses in comparison to the base-case (presymptomatic population with more than 2 SMN2 copies)

|  |  |  |  |
| --- | --- | --- | --- |
| **Scenario** | **Scenario analysis** | **Results** | **Impact** |
| **0** | **Reference** | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 1 | Assumption that nusinersen cohort does not decline | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 2 | The rate of decline for BSC is halved | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 3 | Remove carer utility increments | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 4 | Remove active treatment increments | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 5 | Remove all increments | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 6 | Alternate utility source: TA588 | \*\*\*\*\*\* | \*\*\*\*\*\* |
| 7 | Costs from TA588 | \*\*\*\*\*\* | \*\*\*\*\*\* |

**EAG summary**: The EAG consider that the scenario analyses undertaken by the company all appears to be necessary/appropriate, with the results showing that across all models in these populations the base-case results were robust to all changes except with the use of health state costs from TA588.

* + - 1. Type 1 SMA population
         1. Model structure

Same illustrative model structure to the presymptomatic population. See Figure 3

* + - * 1. Population

The population included in the economic analysis for the presymptomatic population is reflective of the participants in the ENDEAR trial.

* + - * 1. Interventions and comparators

In this population, the cost-effectiveness analysis compared nusinersen against BSC in a population with similar characteristics to participants in the ENDEAR trial. The company did not compare nusinersen against onasemnogene abeparvovec or risdiplam, with a justification that the results of the ITC were not considered appropriate for use in the cost-effectiveness analysis. Additionally, a naïve comparison was considered inappropriate given the differences between study populations.

* + - * 1. Perspective, time horizon and discounting

See Section 5.4.1.2.5

* + - * 1. Health-related quality of life

See Section 5.4.1.2.7

* + - * 1. Resource use and costs

See Section 5.4.1.2.8

* + - * 1. Mortality

Patient-level data from ENDEAR and SHINE trials was used to inform time to all-cause mortality for the permanent ventilation, not sitting and sitting without support health states. Participants who were allocated to the sham treatment switched to treatment with nusinersen at the beginning of the SHINE trial, so the analysis drew on appropriate methods (e.g., rank preserving structure failure time model) for treatment switching. To the Kaplan-Meier data, several parametric curves were fitted and used to extrapolate beyond the observed period, with company selecting the Weibull due to model fit and clinical plausibility. The Weibull model was bounded to ensure that life expectancy did not exceed general population mortality. The company further assumed that there was no increased risk of mortality for people who were in the standing with support and walking health states.

**EAG summary**: The EAG considers the RPSFTM used by the company plausible given that participants switched treatments within the trial. To the resulting KM plot, the company fitted different parametric curves to the survival data and chose the most plausible by considering goodness-of-fit measures and clinical expert opinion.

* + - * 1. Discontinuation

The probability of discontinuation of nusinersen treatment was determined by the MAA, where 44 of the 81 participants discontinued over the 3.5-year period, of which 32 participants switched to onasemnogene abeparvovec therapy. The company stated that it is expected that people who are eligible for onasemnogene abeparvovec therapy are likely to receive that treatment prior to commencing nusinersen. Hence, the high numbers of people switching the onasemnogene abeparvovec seen in the MAA are not reflective of true discontinuation, so, it was further assumed that participants who switched to onasemnogene abeparvovec would have remained on nusinersen. The discontinuation data used in the model are based on those participants that stopped treatment as they were unable to receive nusinersen safely and due to scoliosis.

* + - * 1. Company’s cost-effectiveness results (type 1 SMA)

The results in Table 47 show that in the type 1 SMA population nusinersen is approximately \*\*\*\*\*\*\*\* more expensive than BSC and is expected to yield 4.74 more QALY, resulting in an ICER of approximately, \*\*\*\*\*\*\*\* per QALY. PSA results were in line with the deterministic results (*see* Table 48).

Table 47: Company deterministic base-case results for people with type 1 SMA

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
| BSC | \*\*\*\*\*\* | 2.91 | 0.25 | \* | - | - | \* |
| Nusinersen | \*\*\*\*\*\* | 8.38 | 5.03 | \*\*\*\*\*\*\*\* | 5.47 | 4.74 | \*\*\*\*\*\*\*\* |
| BSC, Best supportive care; LYG, Life years gained; QALYs, Quality-adjusted life years | | | | | | | |

Table 48: Company probabilistic base-case results for people with type 1 SMA

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
| BSC | \*\*\*\*\*\* | 3.05 | 0.25 | \* | - | - | \* |
| Nusinersen | \*\*\*\*\*\* | 8.37 | 4.95 | \*\*\*\*\*\*\*\* | 5.32 | 4.70 | \*\*\*\*\*\*\*\* |
| BSC, Best supportive care; LYG, Life years gained; QALYs, Quality-adjusted life years | | | | | | | |

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Figure 8: Incremental cost-effectiveness scatterplot for the comparison between nusinersen versus BSC (type 1 SMA)

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Figure 9: Cost-effectiveness acceptability curve for nusinersen at different willingness-to-pay thresholds (type 1 SMA)

Each simulation of the incremental costs and incremental QALYS for nusinersen versus BSC were plotted on an incremental cost-effectiveness plane (see Figure 8), along with the respective cost-effectiveness acceptability curve (CEAC) (see Figure 9). The scatterplot showed that majority of the simulations were above the WTP threshold, indicating that nusinersen compared to BSC was not cost-effective in this patient population. The CEAC shows the proportion of simulations in which nusinersen compared to BSC are cost-effective at different willingness-to-pay thresholds for a QALY. These results show that at a WTP threshold of £20,000 per QALY nusinersen compared to BSC had a \*\*\*\* probability of being cost-effective.

* + - * 1. Deterministic sensitivity analyses (type 1 SMA)

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Figure 10: Tornado diagram for the impact of change to individual parameters on the ICER (cost per QALY) (type 1 SMA)

The results in Figure 10 shows that varying health state utility values by ±20% and per cycle health state costs for treating people requiring permanent ventilation had the greatest impact to the ICER (cost per QALY).

* + - * 1. Scenario analysis results (type 1 SMA)

In Table 49, we report the scenario analyses undertaken with regards to the type 1 SMA population. These results show that base-case results are sensitive to the scenarios analyses run by the company, with results ranging from approximately \*\*\*\*\*\*\* to \*\*\*\*\*\*\*\*.

Table 49: Description of the company’s scenario analyses in comparison to the base-case (type 1 SMA population)

|  |  |  |  |
| --- | --- | --- | --- |
| **Scenario** | **Scenario analysis** | **Results** | **Impact** |
| **0** | **Reference** | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 1 | Alternate utility source: TA588 | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 2 | Exclude caregiver utility increments | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 3 | Exclude active treatment utility increments | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 4 | Costs from TA588 (Wickenstones) | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 5 | Health state costs for active treatments set to 0 GBP (£) at total discounted BSC LYs | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 6 | Assumption that nusinersen cohort does not decline | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 7 | The rate of decline for BSC is halved | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |

* + - 1. Type 2/3 SMA population
         1. Model structure

For the type 2/3 SMA population the gross motor milestones achieved are captured in the not sitting, sitting without support, standing with support and walking independently health states and the absorbing health state, dead. Health states and possible transition can be seen in Figure 11.

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Figure 11: Illustrative model structure for the presymptomatic population

**EAG summary**: The EAG consider that the approach taken by the company to model captures the key features (i.e., health states and transitions) of people diagnosed with type 2/3 SMA. Of note, the company provided rationale for not including a permanent ventilation health state, suggesting that this health state is rare in people with type 2/3 SMA.

* + - * 1. Population

The population included in the economic analysis for the type 2/3 population is reflective of the participants in the CHERISH and SHINE trials. Baseline characteristics for the type 2 population reflected the CHERISH trial and type 3 SMA population was based on a natural history study undertaken by Wadman et al. The company assumed that 100% of the type 3 cohort was walking at baseline. The type 2/3 population was taken as the mean of the type 2 and type 3 population.

* + - * 1. Interventions and comparators

See Section 5.4.1.2.4

* + - * 1. Perspective, time horizon and discounting

See Section 5.4.1.2.5

* + - * 1. Health-related quality of life

See Section 5.4.1.2.7.

* + - * 1. Resource use and costs

See Section 5.4.1.2.8.

* + - * 1. Mortality

Given the lack of immature data from the SHINE extension study, the company opted to use information from a Dutch natural history study158 to model overall survival by health state. For people in the not sitting health state the company fitted a gamma parametric curve to the data for people with type 1c SMA as used in HST24. For people in a sitting without support health state, the company fitted an exponential distribution based on data from people in the Wijingaarde et al study with participants with type 2a and 2b SMA. A hazard ratio was applied to these data to reflect an England and Wales setting.

* + - * 1. Discontinuation

The probability of discontinuation for the type 2/3 SMA population is based on data obtained from the MAA, which is based on the number of participants who discontinued treatment by health state. From the MAA, over the 3.5-year duration:

* *out of 21 patients who could not sit discontinued (28.6%).*
* *22 out of 88 patients who could sit without support discontinued (28.41%).*
* *3 out of 30 patients who walk independently discontinued (10%).*
* *No data were available for patients who could stand and, therefore, the discontinuation rate for walkers was applied to this health state (10%).*

Rates of discontinuation were converted to transition probabilities, which assumed a constant hazard over time.

**EAG summary**: The EAG considers that the approach taken by the company to be feasible.

* + - * 1. Company’s cost-effectiveness results (type 2 and 3 SMA)

The results in Table 50 show that in the type 2/3 SMA population nusinersen is approximately \*\*\*\*\*\*\*\* more expensive than BSC and is expected to yield 2.85 more QALYs, resulting in an ICER of approximately, \*\*\*\*\*\*\*\* per QALY. PSA results were in line with the deterministic results (*see* Table 51).

Table 50: Company deterministic base-case results for people with type 2 or 3 SMA (later onset)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
| BSC | \*\*\*\*\*\*\*\*\*\* | 22.86 | 13.72 | \* | - | - | \* |
| Nusinersen | \*\*\*\*\*\*\*\*\*\* | 23.14 | 16.56 | \*\*\*\*\*\*\*\* | 0.29 | 2.85 | \*\*\*\*\*\*\*\* |
| BSC, Best supportive care; LYG, Life years gained; QALYs, Quality-adjusted life years | | | | | | | |

Table 51: Company probabilistic base-case results for people with type 2 or 3 SMA (later onset)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
| BSC | \*\*\*\*\*\*\*\*\*\* | 22.86 | 13.67 | \* | - | - | \* |
| Nusinersen | \*\*\*\*\*\*\*\*\*\* | 23.16 | 16.45 | \*\*\*\*\*\*\*\* | 0.30 | 2.78 | \*\*\*\*\*\*\*\* |
| BSC, Best supportive care; LYG, Life years gained; QALYs, Quality-adjusted life years | | | | | | | |



Figure 12: Incremental cost-effectiveness scatterplot for the comparison between nusinersen and BSC (type 2/3 SMA)

![A black background with a black square

Description automatically generated with medium confidence]()

Figure 13: Cost-effectiveness acceptability curve for nusinersen at different willingness-to-pay thresholds

Each simulation of the incremental costs and incremental QALYs for nusinersen versus BSC were plotted on an incremental cost-effectiveness plane (see Figure 12), along with the respective cost-effectiveness acceptability curve (CEAC) (see Figure 13). The scatterplot showed that all the simulations were above the WTP threshold, indicating that nusinersen compared to BSC was \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* in this patient population. Correspondingly, the CEAC shows that at a WTP threshold of £20,000 per QALY nusinersen compared to BSC had a \*\*\*\* probability of being cost-effective.

* + - * 1. Deterministic sensitivity analysis (type 2/3 SMA)

![A black background with a black square

Description automatically generated with medium confidence]()

Figure 14: Tornado diagram for the impact of change to individual parameters on the ICER (cost per QALY) (type 2/3 SMA)

* + - * 1. Scenario analysis results (type 2/3 SMA)

In Table 52, we report the scenario analyses undertaken with regards to the type 2/3 SMA population. These results show that base-case results are sensitive to the scenarios analyses run by the company, with results ranging from approximately \*\*\*\*\*\*\* to \*\*\*\*\*\*\*\*.

Table 52: Description of the company’s scenario analyses in comparison to the base-case (type 2/3 SMA population)

|  |  |  |  |
| --- | --- | --- | --- |
| **Scenario** | **Scenario analysis** | **Results** | **Impact** |
| **0** | **Reference** | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 1 | The rate of decline for BSC is halved | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 2 | Remove carer utility increments | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 3 | Remove active treatment increments | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 4 | Assumption that nusinersen cohort does not decline | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 5 | Alternate utility source: TA588 | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 6 | Costs from TA588 | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| 7 | Type 2 sub-population standing with support and walking independently as per CHERISH / SHINE | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| BSC, best supportive care; TA, Technology Appraisal | | | |

* + - * 1. Model validation and face validity check

The company stated that a technical validation of the three models were undertaken with a focus on checking of formulae within the models were correct and appropriately applied. As part of the process, a quality assurance checklist was used comprising a range of tests sense checks, ad hoc checks. The internal validation process was undertaken by a health economist who was not directly involved in the health economic modelling.

Additionally, the company stated that the economic models were validated during ‘the UK Advisory Board’, which involved describing the model structure and inputs to UK clinical experts and health economists, where necessary revisions were made based on the advice/feedback provided.

**EAG summary**: The methods used to validate the clinical benefit does not appear to be optimal. However, on inspection of the Microsoft Excel economic models, the EAG did not find any major errors and believe that the model is methodological robust.

* + 1. Roche

In this section, the EAG reviewed economic evidence submitted by Roche, and additional information received from the company in response to the EAG’s clarification question. The EAG critically appraised the economic evidence submitted and examined the company’s electronic model. This section is structured as follows. First, we present the technology against the NICE reference case checklist. Second, we present an overview, then a critique of the economic models submitted, which describes in detail the model structure and evaluated the clinical evidence (e.g., treatment efficacy, treatment discontinuation, mortality) and economic evidence (e.g., health-related quality of life, resource use and costs) used to parameterise the model for risdiplam by population of interest.

* + - 1. EAG critique of company’s systematic review of the economic evidence

The company undertook SLRs for published cost-effectiveness studies (reported in CS Appendix G), health-related quality of life studies (CS Appendix H) and cost and healthcare resource identification, measurement and valuation studies (CS Appendix I). Searches were originally undertaken in 2019 (for TA755) and updated in January 2024. Only the SLR updates are reported in full in this submission. The search strategies and eligibility criteria were changed between the original and update searches, to exclude broader neuromuscular disease terms and focus on SMA (CS Appendix G.1); the EAG considers this a reasonable approach.

For the update of all three SLRs in 2024, records not from a UK setting were “deprioritised” (CS Appendix G.2, Table 22). This “deprioritisation” is effectively an exclusion criterion added post-hoc, which is not best practice, and presumably means that some international studies were included in the original SLRs which would have been excluded from the updates.

A good selection of bibliographic databases and other sources were searched for all the SLRs, including two recent conferences, UK HTA agency websites, additional economics sources and reference lists (CS Appendix G.1). Separate database search strategies were devised for each SLR but results of these and of general “grey literature” searches were pooled for deduplication and screening (CS Appendix G.1). No errors in the search strategies have been identified by the EAG. Whilst a few potentially useful search terms were missed (for example, terms for economic models, expenditure, and the Emtree heading ‘‘hereditary spinal muscular atrophy”), the pooling of all results from different searches and the use of free text searching in multiple fields will have minimised the risk of missing relevant publications. The search strategies for conferences and additional websites (CS Appendix G.1, Tables 16 and 18) are very pragmatic, searching only for ‘spinal muscular atrophy’; there is a small risk that some eligible studies were missed that didn’t describe the disease using exactly this phrase.

* + - 1. Presymptomatic population

The presymptomatic SMA model refers to infants aged 1-42 days who, without treatment, would likely develop a phenotype of type 1 SMA.

* + - * 1. NICE reference case checklist

The EAG undertook an evaluation of the presymptomatic SMA model in Roche’s CS in relation to the NICE reference case, with the findings are summarised in the Table 53.

Table 53: NICE reference case checklist

| **Attribute** | **Reference case and TA Methods guidance** | **Does the de novo economic evaluation match the reference case** |
| --- | --- | --- |
| Defining the decision Problem | The scope developed by NICE | Decision problem clearly stated and is in line with the scope developed by NICE |
| Comparator(s) | Therapies routinely used in the NHS, including technologies regarded as current best practice for this population | Risdiplam is being compared to nusinersen, BSC and onasemnogene abeparvovec (in presymptomatic and type 1 SMA), |
| Patient group | As per NICE final scope, the population refers to: People living with SMA | As per NICE final scope |
| Perspective costs | NHS & Personal Social Services | Yes |
| Perspective benefits | All health effects on individuals | Yes |
| Form of economic Evaluation | Cost-effectiveness analysis | Cost-effectiveness analysis |
| Time horizon | Sufficient to capture differences in costs and outcomes between the technologies being compared | \*\*-year time horizon for presymptomatic and type 1 SMA model, and \*\*-year time horizon for type 2/3 SMA |
| Synthesis of evidence on outcomes | Systematic review | Systematic review was undertaken by the company |
| Outcome measure | Quality adjusted life-years | Results reported in terms of quality adjusted life-years |
| Health states for QALY | Described using a standardised and validated instrument | Patients-(presymptomatic and type 1: HSUVs provided by Biogen’s clinical advisors in the TA588 ERG report  Patients- type 2/3: Utility values from the Lloyd et al. 2019 EQ-5D vignette study  Carer HSUVs in both models: Bastida et al. 2017 and general population utility. |
| Benefit valuation | Time-trade off or standard gamble | Unclear |
| Source of preference data for valuation of changes in HRQoL | Representative sample of the public | Yes |
| Discount rate | An annual rate of 3.5% on both costs and health effects | Yes |
| Equity | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes |
| Probabilistic modelling | Probabilistic modelling | The company undertook PSA and reported these results |
| Sensitivity analysis |  | The company undertook a range of sensitivity analyses. |
| BSC, best supportive care; ERG, evidence review group; HRQoL; health-related quality of life; HSUV, health state utility values; NHS; National Health Service; NICE; National Institute for Health and Care Excellence; PSA; probabilistic sensitivity analysis; QALY, quality-adjusted life years; SMA, spinal muscular atrophy | | |

* + - * 1. Model structure and transitions

The presymptomatic SMA (RAINBOWFISH) model is designed to accurately represent disease progression and the impact of treatments in presymptomatic SMA patients. Developed through literature reviews, clinical guidelines, HTA reports, and consultations with experts, the model focuses on motor milestone achievements, a critical indicator of patient development. It includes four health states ('not sitting', 'sitting', 'standing', 'walking') based on the HINE-2 scale, validated by clinical experts. The model also features 'permanent ventilation' and 'death' states to account for the severe prognosis of SMA. Patients start in the 'not sitting' state and can transition monthly, reflecting their progression or deterioration. The rationale for the model is to provide a structured approach to understanding and improving patient outcomes, despite inherent limitations in fully capturing all aspects of SMA's impact. It aims to evaluate the cost-effectiveness and clinical benefits of treatments like risdiplam.

Roche used data from the RAINBOWFISH study at one year (CCOD 20 Feb 2023) to calculate motor milestone transition probabilities for presymptomatic patients treated with risdiplam. The single-arm nature of RAINBOWFISH precluded direct estimation for BSC, and an indirect treatment comparison (ITC) was not feasible due to sample size and baseline differences. Consequently, a naïve comparison suggested similar progression for risdiplam, nusinersen, and onasemnogene abeparvovec, assuming equal efficacy (hazard ratio of 1). A continuous time Markov multi-state model with HINE-2 scores was used for transition probabilities, disallowing non-sequential transitions. The transition probabilities are outlined in Table 54. As equal efficacy between treatments is assumed, the transition probabilities are the same for risdiplam, nusinersen and onasemnogene abeparvovec.

Table 54: Risdiplam, nusinersen and onasemnogene abeparvovec motor milestone transition probabilities (Roche presymptomatic model base case) (obtained from CS document B Table 106, Page 224)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Health states** | | **From** | | | |
| **Non-sitting** | **Sitting** | **Standing** | **Walking** |
| **To** | **Non-sitting** | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **Sitting** | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **Standing** | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **Walking** | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |

**EAG summary**: The chosen Markov model for the presymptomatic phase is deemed appropriate in light of its adherence to NICE guidelines, robust validation, and incorporation of clinical expertise. However, interpretations must be cautious due to assumptions of uniform efficacy and high uncertainty arising from small sample sizes, despite its ability to capture distinct SMA types' natural history, severity, and prognosis.

The structure of the presymptomatic SMA (RAINBOWFISH) model aligns with a comprehensive understanding of SMA, integrating literature, guidelines, and expert input. It accurately represents patients' motor abilities and recognises disease severity, emphasizing the necessity for permanent ventilation in severe cases. Nonetheless, it acknowledges limitations in fully encompassing all complexities of the condition.

In evaluating the appropriate data source for transition probabilities in a presymptomatic model base-case analysis, several factors were considered across the NURTURE, RAINBOWFISH, and SPR1NT trials. Each trial has unique attributes and methodological designs that impact their suitability for deriving transition probabilities. The NURTURE trial, which assessed the efficacy of nusinersen in people with presymptomatic SMA, appears to be the most appropriate for several reasons: longer study duration, patient distribution and sample size, gender balance. Hence, the EAG considers the NURTURE trial data to be a better source to derive monthly transition probabilities for the base-case for the presymptomatic model.

* + - * 1. Population

The presymptomatic population comprises infants aged 1 to 42 days (6 weeks) with no prior treatment, expected to develop type 1 SMA. This aligns with RAINBOWFISH trial criteria, consistent with risdiplam's marketing authorisation and NICE scope.

**EAG summary**: The presymptomatic population demonstrates unique characteristics compared to other SMA types. Given the possibility of newborns evolving into type 1, 2, or 3 SMA patients, it's imperative to classify them based on potential SMA types. This stratification becomes particularly pertinent when considering the distinct differences observed between patients with two versus more than two SMN2 copies, as evidenced in the RAINBOWFISH trial. These discrepancies, notably in assessments such as mean CHOP-INTEND, mean HINE-2, or Ulnar CMAP amplitude, underscore the necessity for a nuanced approach. The EAG proposes dividing presymptomatic patients into two primary categories: those with two SMN2 copies and those with more than two SMN2 copies. Such categorisation is predicated on the observation that patients with two SMN2 copies exhibit characteristics akin to type 1 SMA patients, while those with more than two SMN2 copies resemble type 2/3 SMA patients. The EAG maintains that despite potential misalignment with the current project's scope, this division provides advantages when evaluating the cost-effectiveness or effectiveness of interventions aimed at the presymptomatic population, compared to considering all presymptomatic individuals as a single population.

* + - * 1. Interventions and comparators

For the presymptomatic population, the company compared risdiplam against nusinersen and BSC. For children aged 12 months and under with a biallelic mutation in the SMN1 gene and presenting with a clinical diagnosis of type 1 5q SMA or presymptomatic with up to 3 copies of the SMN2 gene: onasemnogene abeparvovec.

**EAG summary**: All feasible and practical options, including onasemnogene abeparvovec, nusinersen, and BSC have been clearly specified and are under evaluation. The EAG agrees with Roche's rationale that BSC reflects patients who are not being treated with risdiplam, nusinersen, or onasemnogene abeparvovec, comparing to a world without these treatments. The EAG, in alignment with Roche, believes 'established clinical management' includes all treatments and BSC, thus shouldn't be a standalone comparator. EAG considers BSC comparison appropriate and feasible, unlike 'established clinical management'.

* + - * 1. Perspective, time horizon and discounting

The EAG acknowledges the thorough identification of relevant costs and consequences, ensuring alignment with the NHS and PSS perspective. The clear delineation of patient groups and evaluated strategies in the report underscores the model's scope, thus enhancing its transparency and justification. Additionally, the comprehensive coverage of all potential outcomes related to SMA, consistent with the final scope, further strengthens the study's relevance and applicability to decision-making processes.

The time horizon for the presymptomatic SMA model is set at a lifetime (\*\* years), reflective of patients' potential lifespan. This choice aligns with NICE's reference case and aims to capture all costs and benefits associated with risdiplam or BSC. The rationale behind the \*\*-year horizon is to ensure that all costs and benefits are accounted for, considering that patients in both treatment arms would likely have deceased by the end of this period. Similar to type 1 SMA, the time horizon is chosen to accommodate the generally reduced life expectancy of patients, although Roche acknowledges the potential for some patients in the active treatment arms to survive beyond \*\* years due to limited data on treated patients' survival.

In the base-case, the costs incurred, and benefits accrued are discounted at a rate of 3.5% per annum.

**EAG summary**: The EAG acknowledges the thorough identification of relevant costs and consequences, which are in line with the NHS and Personal Social Services perspective.

The EAG propose a longer time horizon of 90 years for babies diagnosed with presymptomatic SMA. The recommendation for a 90-year time horizon for presymptomatic SMA is further supported by the understanding that a significant proportion of patients receiving treatment can survive for the long term. This consideration aligns with the observed trend in clinical practice, where advancements in treatments have led to improved survival outcomes for SMA patients. Longer time horizon has been utilised in previous NICE technologies appraisals,15, 17 ensuring consistency and comparability across evaluations. Additionally, a longer time horizon allows for a more comprehensive examination of the costs and benefits associated with treatments, particularly important in chronic conditions like SMA. The analyses of two NICE technology appraisals14;204 economic analyses concluded at a 100-year horizon, which captured the lifetime impact of onasemnogene abeparvovec. Therefore, extending the time horizon to 90 years may enable a more accurate assessment of the long-term cost-effectiveness of these interventions for the presymptomatic population.

* + - * 1. Treatment effectiveness and extrapolation

Roche's approach to presymptomatic treatment effect centred on equal efficacy assumptions among risdiplam, nusinersen, and onasemnogene abeparvovec. Despite limited observed events in the RAINBOWFISH study, they derived overall survival data from national life tables. Comparing mean scores, for example HINE-2, CHOP-INTEND, and BSID-III across treatments showed no significant differences, leading to an assumed equal efficacy (hazard ratio of 1). This approach, while acknowledging small sample sizes and high uncertainty, allowed for a comprehensive assessment within their cost-effectiveness models, ensuring consistency across treatment durations.

**EAG summary**: Roche's approach to presymptomatic treatment effect relies on an overly simplified assumption of equal efficacy among risdiplam, nusinersen, and onasemnogene abeparvovec. This assumption overlooks potential efficacy differences. Additionally, comparing mean scores like HINE-2, CHOP-INTEND, and BSID-III without matching patient characteristics is methodologically weak, failing to account for confounding variables. The EAG acknowledges that small sample sizes and differing trial populations hinder robust ITC. The EAG recommends reassessing with more comprehensive data in the future. While Roche's methodology aims for thorough cost-effectiveness assessments, the reliance on equal efficacy assumptions and unadjusted mean score comparisons necessitate a more rigorous approach for valid and reliable findings.

* + - * 1. Health-related quality of life

Roche considered the quality of life of both SMA patients and their caregivers in the presymptomatic model. For the presymptomatic population, Roche obtained HSUVs from TA588, which were obtained from Biogen’s clinical advisors in the TA588 EAG report. These values were chosen based on their face validity and clinical plausibility. EAG reviewed Roche’s patient utility aspects, noting a range of -0.02 (permanent ventilation) to 0.850 (walking independently) (*see* Table 55).

Table 55: Summary of patient utility values for cost-effectiveness analysis (presymptomatic and type 1 base case model) (TA588 ERG report early onset model, Biogen clinical Advisors) (obtained from CS document B Table 121, Page 255)

|  |  |  |  |
| --- | --- | --- | --- |
| State | Utility value (mean) | 95% confidence interval | Justification |
| Permanent ventilation | -0.020 | NA | Based on TA755 and UK clinical experts |
| Not sitting | 0.100 | NA |
| Sitting | 0.200 | NA |
| Standing | 0.700 | NA |
| Walking | 0.850 | NA |
| NA, not applicable; TA, technology appraisal | | | |

Caregiver HSUVs, in the model were informed by Bastida et al. 2017 and general population utility. For scenario analyses, EQ-5D-5L utility values were additionally collected from caregivers of SMA patients in both the initial Roche UK BoI study, and a recently run Roche UK utility study. For both studies, the values have been cross-walked to the EQ-5D-3L and valued using UK tariffs. Roche has stated that based on the company’s UK BOI study, across all health states, an average of 2.2 caregivers would be required to care for people with SMA.

Table 56: Summary of carer utility values for cost-effectiveness analysis (presymptomatic and type 1 base case model) (Bastida et al. 2017 and Ara et al. 2010) (obtained from CS document B Table 124, Page 257)

|  |  |  |  |
| --- | --- | --- | --- |
| State | Utility value: mean | 95% confidence interval | Justification |
| Permanent ventilation | 0.484 | NA | Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. study and general population utility223 possessed the greatest clinical validity for carers of SMA patients |
| Not sitting | 0.484 | NA |
| Sitting | 0.628 | NA |
| Standing | 0.771 | NA |
| Walking | 0.915 | NA |
| HSUV, health-state utility values; NA, not applicable; SMA, spinal muscular atrophy | | | |

In the presymptomatic model, Roche incorporates the following items affecting patient and caregiver utilities:

Patient: Incremental benefits for risdiplam, nusinersen, and onasemnogene abeparvovec: using 0.20 for not sitting and sitting health states

Caregiver: Incremental benefits for risdiplam, nusinersen, and onasemnogene abeparvovec: using 0.05 for not sitting and sitting health states

Additionally, utility decrements due to disease impacts and treatment-related events are included, such as scoliosis (-0.0717), respiratory support (-0.0852), and bulbar dysfunction (-0.17).

**EAG summary**: The EAG is satisfied with the utility sources used by Roche for patients and caregivers. However, the EAG considers that incorporating patient and caregiver incremental benefits, along with utility decrements due to disease impacts and treatment-related events, leads to double counting. Each utility value for a specific health state already covers the overall situation of patients in that state, so adding other utilities results in double counting. The inclusion of caregiver utilities in the model has been a contentious issue in various studies. The EAG assumes the patient utilities in the model are calculated with caregiver presence, thus justifying the inclusion of caregiver utilities. EAG also assume the caregivers are unpaid.

Regarding the number of caregivers per health state, the EAG is not satisfied with Roche's use of an average number across all health states due to varying patient distributions. This can cause discrepancies between the results and the actual patient distribution in each health state. Consequently, the EAG is satisfied with Biogen’s caregiver numbers, which specify two caregivers for more severe health states and one for standing and walking health states.

* + - * 1. Resource use and costs

Roche conducted research on healthcare resource use in SMA by utilising a modified Delphi panel methodology. They aimed to gather expert opinions on types 1 and 2/3 SMA in the UK. The study involved iterative rounds to achieve consensus among the experts. The eligibility criteria ensured the inclusion of various healthcare professionals. The questionnaire design was rigorous and focused on healthcare resource use. The analysis method included a consensus threshold of 70%. Roche's study provided valuable insights into the economic impact of SMA. The costs in Roche healthcare resource use study categorises in three sections including r\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. Further details about these costs can be found in Table 57 through to Table 60.

Table 57: Health care resource use for paediatric (per cycle costs) – (obtained from Roche health care resource use study)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Health States** | **Hospitalisations** | **Specialist visits** | **Tests and investigations** | **Surgeries and procedures** | **Specialist equipment** | **Total** |
| **Permanent ventilation** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Unable to sit** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Sitting** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Standing** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Walking** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |

Table 58: Health care resource use for adults (per cycle costs) – (obtained from Roche health care resource use study)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Health States** | **Hospitalisations** | **Specialist visits** | **Tests and investigations** | **Surgeries and procedures** | **Specialist equipment** | **Total** |
| **Permanent ventilation** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Unable to sit** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Sitting** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Standing** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Walking** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |

Table 59: Proportion of patients that using the resources (one number) as one-off in the beginning of treatment and their unit costs– (obtained from Roche HCRU Study)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Resource** | **PV** | **Unable to sit** | **Sitting** | **Standing** | **Walking** | **Unit Costs** |
| **Standing frame** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Specialist buggy** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Seating for home** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Sleep system** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Portable bed/cot hoist** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Ceiling or electronic bed hoist** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Specialist toilet seat** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Specialist bath seat** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Specialist bath/shower** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **BiPAP ventilator machine** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Cough assist machine** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Nebuliser** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Humidifier** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Suction machine for controlling saliva** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Home adaptations** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| PV, permanent ventilation | | | | | | |

Table 60: One-off costs for different health states in presymptomatic SMA model (obtained from Roche health care resource use study)

|  |  |
| --- | --- |
| **Health States** | **One-off costs** |
| Permanent ventilation | \*\*\*\* |
| Unable to sit | \*\*\*\* |
| Sitting | \*\*\*\* |
| Standing | \*\*\*\* |
| Walking | \*\*\*\* |

**EAG summary**: The costs incorporated into the model are partly justified. Drug acquisition and administration costs for risdiplam, onasemnogene abeparvovec, and nusinersen are clear and appropriate. However, there are issues with one-off costs and end-of-life costs. Health state costs include detailed categories, for example, hospitalisations, specialist visits, and equipment. End-of-life care costs are inconsistently referenced across studies (TA588, HST24). One-off costs are imported from Roche's healthcare resource use study without clear validation in TA588 and HST24.

The study provides detailed descriptions of the sources for risdiplam, onasemnogene abeparvovec, and nusinersen acquisition and administration costs, but it lacks clarity on the sources for drug wastage calculations of risdiplam and nusinersen. While some cost categories are well-defined, inconsistencies and uncertainties in others undermine the model's justification. Health state costs, specialist visits, and resource utilisation for various SMA health states are well-outlined, but there are gaps in clarity and transparency, especially regarding end-of-life and one-off costs. The Delphi panel methodology used to derive healthcare resource use data adds robustness but still leaves some cost sources ambiguous, particularly for the permanent ventilation health state. Roche has included certain costs under the heading "Disease impact costs." The EAG is not convinced by the justification for these costs and is satisfied with their exclusion from the base case analysis. EAG recommend including these costs in the model only as a scenario analysis.

* + - * 1. Mortality

Due to the lack of observed mortality events in the RAINBOWFISH study, the company to the following approach to model mortality:

1. Overall survival for people treated with risdiplam

* For all health states other than permanent ventilation, the overall survival in the model is informed by national life tables for England and Wales. This implies that for patients on risdiplam, the model uses general population mortality rates from these national statistics to estimate survival probabilities. For people in the permanent ventilation health state, in the CS document B, the company assumed mortality based on BSC. However, on inspection of the model, it appears that the general population mortality rates had been applied to the permanent ventilation health state, albeit with no one transitioning to the permanent ventilation health state.

1. Overall survival for people treated with nusinersen and onasemnogene abeparvovec.

* Survival data for nusinersen and onasemnogene abeparvovec is informed by the NURTURE and SPR1NT studies, respectively.
* For the permanent ventilation health state, it was assumed that the general population mortality rate is applied across all treatments

1. Overall survival for people who received BSC

* The model allows for BSC-specific mortality rate as an option

**EAG summary**: We have raised concerns about Roche’s approach to population mortality in the presymptomatic model for SMA. Roche’s model uses general population mortality rates for England and Wales to estimate overall survival for risdiplam in all states. The EAG noted that in CS document B the company stated that for the permanent ventilation health state overall survival was based on BSC; however, in the model it appeared that overall survival was based on general population mortality rates, albeit no one progressed to this health state. The same general mortality rates are applied across all treatments (risdiplam, nusinersen, and onasemnogene abeparvovec). We consider that using the general population mortality rates may overestimate survival in the more severe health states (e.g., permanent ventilation, not sitting and sitting). Hence, the EAG propose using the KM plots in figure 14 of HST24 for permanent ventilation, figure 16 of HST24 for the not sitting health states to model survival. For the sitting health state, we will take the approach used by Novartis in HST24.204 It is our understanding that the company fitted curves to data reported in Wijnigaarde 2019224 and compared it with the general population survival curves for the Netherlands to produce a hazard ratio, and then applied this hazard ratio to the general UK population to get an estimate for the UK sitter population with type 2a/2b SMA.

* + - * 1. Decision modifier: Severity

Roche applies adjustments to QALYs when there is a shortfall in QALYs for individuals with SMA compared to those without it over their remaining lifetime. Baseline characteristics from risdiplam trials inform expected total discounted QALYs for the general population receiving current treatment. Roche conducts a QALY shortfall analysis specific to presymptomatic, type 1, and type 2/3 populations (considering both patient and caregiver utility). An adjustment of 1.7 to the value of risdiplam QALYs is applied across all populations.

**EAG summary**: EAG addresses Roche's method of calculating severity weight and incorporating it into the model alongside caregiver disutility. TSD23 outlines that severity weighting pertains to the direct impact on the patient’s quality of life and should be used for calculating patient-specific QALYs; thus, excluding carer utility to focus on patient outcomes. However, EAG highlights the importance of considering caregiver disutility (as noted in TSD23,222 especially for SMA patients in permanent ventilation, not sitting, and sitting health states, as they require full-time care. EAG agrees with Roche that caregiver disutility should be calculated separately, but recommends deriving severity weighting from patient utility values, then adding carer utility values. In scenario analyses, EAG suggests either excluding all caregiver utility and using only severity weighting or excluding both carer utility and severity weighting.

* + - * 1. Company’s cost-effectiveness results

In Table 61, we report the company’s deterministic base-case results, which shows that using the list price for risdiplam it is approximately £3,838,800 more costly than BSC and expected to yield an additional 30.48 QALYs (inclusive of the 1.7 severity weighting) equating to an ICER of approximately £125,900 per QALY.

Table 61: Company deterministic base-case results for the presymptomatic population (using list prices)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER incremental (£/QALY)** |
| Risdiplam | £4,166,372 | 18.64 | 14.51 | - | - | - | - |
| Nusinersen | £4,785,969 | NA | NA | -£619,597 | NA | NA | NA |
| Onasemnogene abeparvovec | £1,747,146 | NA | NA | £2,419,226 | NA | NA | NA |
| BSC | £327,582 | 13.95 | -3.42 | £3,838,791 | 4.70 | 30.48 | £125,936 |

Incorporating the PAS discount of \*\*% for risdiplam, for the comparison between BSC results in an ICER of approximately \*\*\*\*\*\*\* per QALY (*see* Table 62).

Table 62: Company deterministic base-case results for the presymptomatic population (using PAS price for risdiplam)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER incremental (£/QALY)** |
| \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |

In Table 63 and Table 64, we report the fully incremental analysis using the list price and PAS for risdiplam, respectively. In Table 63, using the list price for risdiplam, treatment with onasemnogene abeparvovec dominates risdiplam and nusinersen. Excluding all dominated strategies, onasemnogene abeparvovec compared to BSC resulted in an ICER of approximately £79,200 per QALY.

Table 63: EAG ranking of the company’s deterministic base-case results for the presymptomatic population (using list prices)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER incremental (£/QALY)** |
| BSC | 327,600 | 13.59 | -3.42 | - | - | - | - |
| Onasemnogene Abeparvovec | 1,747,100 | 18.60 | 14.51 | 1,419,600 | 5.01 | 17.93 | 79,200 |
| Risdiplam | 4,166,400 | 18.60 | 14.51 | 2,419,300 | - | - | Dominated |
| Nusinersen | 4,786,000 | 18.60 | 14.51 | 3,038,900 | - | - | Dominated |

Under the PAS, \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* \*\*\*\*\*\*\* (*see* Table 64).

Table 64: EAG ranking of the company’s deterministic base-case results for the presymptomatic population (using PAS price for risdiplam)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER incremental (£/QALY)** |
| \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |

* + - * 1. Company’s probabilistic sensitivity analysis results

Roche's PSA of the presymptomatic SMA model involved 2,000 iterations according to the CS document B (in the presymptomatic model shows 1000) to assess cost and outcome uncertainties. The cost-effectiveness plane (with a willingness-to-pay threshold of £30,000 per QALY) shows that all iterations of the PAS price versus BSC are \*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\* \*\*\*\* \*\*\*\*\*\*\*\*\*, and the iterations versus x\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, suggesting risdiplam is \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. However, it should be noted that a considerable number of iterations for the comparison between risdiplam and onasemnogene abeparvovec and nusinersen are in the \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. The probability of risdiplam being cost-effective at PAS price is XX\*.(*see* Table 66 and Figure 15 and Figure 16)

Table 65: Company PSA results for the presymptomatic population (using list prices)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER per QALY** |
| Risdiplam | £4,149,533 | 14.23 | - | - | - |
| Nusinersen | £4,768,367 | 14.23 | -£618,834 | NA | NA |
| Onasemnogene abeparvovec | £1,754,558 | 14.22 | £2,394,976 | NA | NA |
| BSC | £336,678 | -2.47 | £3,812,855 | 28.38 | £134,340 |

Table 66: Company PSA results for the presymptomatic population (using PAS price for risdiplam)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment** | **Costs** | **QALYs** | **Costs** | **QALYs** | **ICER per QALY** |
| \*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | - | - | - |
| \*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* |
| \*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* |
| \*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* |



Figure 15: Incremental cost-effectiveness scatterplot for the comparisons between risdiplam and BSC, nusinersen and OA for the presymptomatic population (using PAS price for risdiplam)



Figure 16: Cost-effectiveness acceptability curve for the risdiplam compared to BSC, nusinersen and onasemnogene abeparvovec at different WTP thresholds (using PAS price for risdiplam)

* + - * 1. Deterministic sensitivity analysis (presymptomatic population)

The company undertook one-way sensitivity analysis by varying key input parameters using their 95% CI to assess the impact on the several outcomes, with the results presented in the form of a tornado diagram. In Figure 17 through to Figure 19, show the impact to the pairwise ICERs for the comparison between risdiplam versus BSC, nusinersen and onasemnogene abeparvovec, using the PAS price for risdiplam.

The inputs with the greatest impact to the ICER versus BSC is the cost of risdiplam, followed by the health state utility values for patients in the walking health state, caregivers of patients in the walking health state and the number of carers per patients. When compared to nusinersen and onasemnogene abeparvovec, across both the biggest drivers to the ICER are the carer utility values in the not sitting and sitting health states as well as the patient utility values in the not sitting and sitting health states.



Figure 17: Deterministic one-way sensitivity analysis for the comparison between risdiplam versus BSC (using the PAS price for risdiplam)



Figure 18: Deterministic one-way sensitivity analysis for the comparison between risdiplam versus nusinersen (using the PAS price for risdiplam)



Figure 19: Deterministic one-way sensitivity analysis for the comparison between risdiplam and onasemnogene abeparvovec (using the PAS price for risdiplam)

* + - * 1. Scenario analysis results (presymptomatic population)

The company undertook a range of scenario analyses to assess the impact of each change to the deterministic results. In Table 67, we report the scenario analyses undertaken with regards to the presymptomatic population. These results show that impact to the pairwise ICER when risdiplam is compared to BS, nusinersen and onasemnogene abeparvovec. Key findings include changing BSC efficacy source to PNCR data with SMN2 copies matched to RAINBOWFISH increased ICER by \*\*\*\*\*\*%; applying UK Burden of Illness caregiver utility values raised the ICER by \*\*\*\*\*\*%; VAT savings impacted the ICER for risdiplam versus nusinersen and onasemnogene abeparvovec by \*\*\*\*\*\*% and \*\*\*\*\*\*%, respectively; and a discount rate of 1.5% for benefits and 3.5% for costs reduced ICER by \*\*\*\*\*\*%.

Table 67: Scenario analysis results for the presymptomatic population (using the PAS price for risdiplam)

| **Scenario** | **ICER (vs BSC)** | **% ICER change from the base case** | **ICER**  **(vs nusinersen)** | **% change from base case** | **ICER**  **(vs onasemnogene abeparvovec)** | **% change from base case** |
| --- | --- | --- | --- | --- | --- | --- |
| Base case | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | - |
| **Efficacy scenarios** | | | | | | |
| Comparative efficacy vs. BSC: Source for BSC set to PNCR data with SMN2 copies matched to RF | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for % scoliosis: change to Wijngaarde et al. 2019 | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for % bulbar dysfunction: change to Wadman et al. 2017 | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for % respiratory support: change to van der Heul et al. 2019 | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| **HCRU scenarios** | | | | | | |
| Alignment with TA588 source for HCRU | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Alignment with TA588 source for HCRU and PV health state costs:  175% increase from the “Not Sitting” health state | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| **Utility values scenarios** | | | | | | |
| Source for patient utility values: EQ-5D-3L (NICE ERG TA588) | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for patient utility values: EQ-5D-Y (Lloyd et al, 2019) | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for caregiver utility values: Roche utility survey | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for caregiver utility values: UK Burden of Illness Study | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| **Other Scenarios** | | | | | | |
| Inclusion of VAT saving from risdiplam homecare | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Number of carers lowered to 2 | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Number of carers increased to 3 | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Discount rate for both costs and benefits is lowered to 1.5% | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5% | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| BSC, best supportive care; EQ-5D-5L, EuroQoL 5 Dimensions 3 Levels; EQ-5D-Y, European Quality of Life-5 Dimensions – Youth version; ERG, Evidence Review Group; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; LY, life year; NICE, National Institute for Health and Care Excellence; PV, permanent ventilation; QALY, quality-adjusted life year; RF, RAINBOWFISH | | | | | | |

* + - 1. Type 1 SMA population

In this section, the EAG reviewed Roche's economic evaluation of a type 1 SMA model against NICE standards. The EAG summarised the model structure and evaluated clinical evidence (e.g., efficacy, treatment discontinuation, mortality) and economic evidence (e.g., drug costs, health state resource use and costs, utilities). The EAG also critiqued the methods and inputs used in the analysis.

* + - * 1. Model structure

The type 1 SMA (FIREFISH) model is a Markov model developed in Microsoft Excel, structured around key motor milestones ('not sitting', 'sitting', 'standing', and 'walking'), a 'permanent ventilation' health state, and an absorbing 'death' state. This model, similar in terms of health states to the presymptomatic SMA model, was validated by clinical experts and designed to capture the progression and treatment outcomes for type 1 SMA patients. The inclusion of the 'permanent ventilation' state addresses the severe prognosis of type 1 SMA, reflecting current clinical practices where advanced therapies have increased the use of permanent ventilation despite its associated poor quality of life. Patients start in the 'not sitting' state and transition monthly, potentially improving or deteriorating by one health state at a time, based on clinician input.

**EAG summary**: The Markov model for the Type 1 SMA (FIREFISH) model is appropriate given its alignment with NICE guidelines, rigorous validation, and inclusion of clinical expertise. It integrates literature, guidelines, and expert input, accurately representing patients' motor abilities and emphasizing the need for permanent ventilation in severe cases.

* + - * 1. Population

The patient population for the type 1 SMA model mirrors that of the FIREFISH, ENDEAR, and STR1VE-EU trials for risdiplam, nusinersen, and onasemnogene abeparvovec, respectively. ENDEAR-SHINE’s overall population lacks reported mean characteristics, so weighting uses the original ENDEAR population. Patient populations are similar in age and disease duration but differ in severity. ENDEAR patients have higher mean CHOP INTEND (4.1 points) and HINE-2 scores (0.36 points). Ventilatory support use differs and comparability with FIREFISH is uncertain.

EAG Summary: The EAG is generally satisfied with the reference trials for the population in the type 1 SMA model for risdiplam, nusinersen, and onasemnogene abeparvovec, despite some differences in disease severity and treatment initiation age among the FIREFISH, ENDEAR, and STR1VE-EU trials.

* + - * 1. Intervention and comparators

Same as presymptomatic SMA model.

* + - * 1. Perspective, time horizon and discount rate

Same as presymptomatic SMA model.

* + - * 1. Treatment effectiveness and extrapolation

Roche conducted a comprehensive analysis of the efficacy of risdiplam for treating type 1 SMA using data from the FIREFISH trial. The following summarises their approach and findings:

Cost-Effectiveness Analysis:

* An artificial plateauing of treatment effect for risdiplam, nusinersen, and onasemnogene abeparvovec was applied at 66 months. Transitions between health states were deactivated from this point, assuming patients in active treatment would remain in their current health state until death. This was aligned with EAG-preferred analysis in TA755 and committee preference in TA588.

FIREFISH Trial Data:

* Initial efficacy data up to 24 months showed clinically meaningful improvements in complex motor function, sustained through the 5-year study extension.
* Updated 5-year data supported long-term benefits, with some patients showing further improvements.

Efficacy Endpoints (FIREFISH Study):

* Proportion of patients sitting without support for 5 seconds improved from 29.3% at 12 months to \*\*\*\*\* at 60 months.
* Proportion sitting without support for 30 seconds improved from 17.1% at 12 months to \*\*\*\*\* at 60 months.
* CHOP-INTEND scores of 50 or higher improved from 19.5% at 12 months to \*\*\*\*\* at 60 months.
* CHOP-INTEND scores of 60 or higher improved from \*\*\*\* at 12 months \*\*\*\* at Month 24 and to \*\*\*\*\* at 60 months.
* HINE-2 scores showed motor milestone responders maintained at \*\*\*\*\* from 12 months to 60 months.

Transition Probabilities and Long-Term Assumptions:

* Transition probabilities in the type 1 SMA model were derived from FIREFISH trial data.
* A continuous time Markov multi-state model estimated transitions between motor milestone health states, using baseline HINE-2 scores as covariates.
* Long-term assumptions included stability or improvement for patients treated with risdiplam, while those on best supportive care were not expected to improve post follow-up.
* Parametric survival analysis informed transitions to permanent ventilation.

Indirect Treatment Comparisons (ITC):

* Despite challenges from single-arm studies, Roche performed a population matching technique (unanchored MAIC) to compare the relative efficacy and safety of risdiplam with nusinersen and onasemnogene abeparvovec.
* Alignments with guidelines and expert opinions were maintained.
* For the FIREFISH and ENDEAR-SHINE comparison, matching factors are age at first dose, baseline motor function (CHOP-INTEND score), and disease duration at baseline. For FIREFISH and STR1VE-US/EU, matching factors are age at first dose and baseline motor function. Disease duration is a strong predictor of treatment efficacy, but it is not reported in STR1VE-US/EU, so it cannot be included.
* For type 1 SMA, the ITC between risdiplam and onasemnogene abeparvovec, despite comparisons to two STR1VE studies, lacks sufficient evidence to conclude relative efficacy or safety due to limited baseline characteristic overlap and high uncertainty in point estimates, rendering the comparisons inconclusive.
* After four years, children treated with risdiplam (FIREFISH) showed a 79% reduction in death rates (95% CI 53–98%) and a 79% reduction in death or permanent ventilation (95% CI 63–90%) compared to nusinersen (ENDEAR). children treated with risdiplam also had a 43% higher rate of achieving a HINE-2 motor milestone response (95% CI 20–74%) and a 172% higher rate of ≥4-point improvement on the CHOP-INTEND scale (95% CI 100–210%).
* For STR1VE-US, an ITC analysis using STC was conducted due to insufficient baseline characteristic overlap for MAIC. For STR1VE-EU, STC was considered but not performed due to large baseline differences, which could bias conclusions.

**EAG Summary:** Roche's assessment of risdiplam for Type 1 SMA, based primarily on the FIREFISH trial data, presents a thorough analysis with both strengths and areas for improvement:

**Treatment Effects:**

* The FIREFISH trial data utilised by Roche demonstrates significant improvements in motor function over five years, supporting the sustained efficacy of risdiplam in treating type 1 SMA.
* Roche's approach to long-term assumptions and transition probabilities using Markov multi-state models ensures a robust projection of treatment outcomes, providing valuable insights into the potential clinical benefits of risdiplam.

**ITC Methods:**

* Roche employed ITC, including unanchored MAIC and other matching techniques, to assess the relative efficacy and safety of risdiplam against nusinersen, onasemnogene abeparvovec, and BSC.
* Despite methodological rigor, limitations such as small sample sizes and disparities in baseline characteristics across studies, particularly in STR1VE-US/EU, impact the certainty of comparative effectiveness assessments.

**Critiques and Solutions:**

* The use of unanchored MAIC and other matching techniques addresses challenges from single-arm studies but requires careful consideration of baseline characteristic overlap. Future studies could benefit from enhanced standardization of data collection protocols to improve comparability.
* To mitigate biases from unadjusted characteristics, increased transparency in reporting study differences and comprehensive sensitivity analyses would enhance the reliability of comparative effectiveness assessments.
* The limited availability of data and shorter follow-up duration in some studies, such as STR1VE, pose challenges in assessing risdiplam's long-term effectiveness against standard care. Future research with extended follow-up periods would strengthen these comparisons.
  + - * 1. Health-related quality of life

Same as presymptomatic SMA model.

* + - * 1. Resource use and costs

Same as presymptomatic SMA model.

* + - * 1. Mortality

Roche approached mortality in the type 1 SMA model by integrating data from the FIREFISH and ENDEAR-SHINE trials through an unanchored MAIC approach. They assessed OS and event-free survival (EFS) using Kaplan-Meier curves up to four years and 4.9 years, respectively. The analysis focused on hazard ratios (HR) to compare risdiplam and nusinersen, considering age at first dose, duration of symptoms, and baseline CHOP-INTEND scores as matching factors.

Roche used general population mortality rates for patients achieving standing or walking milestones in SMA types 2 and 3. For type 1 SMA patients reaching similar health states, mortality assumptions aligned with type 2 SMA based on systematic literature reviews and expert consensus.

For OS, Roche conducted parametric survival analysis. Parametric survival functions for overall survival are shown in Figure 20, and the goodness-of-fit statistics indicated that the Gompertz curve provided the best fit. However, due to the short timeframe of available data, the emphasis was placed on long-term clinical plausibility. UK clinical experts considered the exponential curve most plausible, consistent with TA755, and it was selected for the base case analysis. Other parametric models were not considered viable by clinicians and thus were not explored in scenario analyses.

A graph of different colored lines

Description automatically generated

Figure 20: Type 1 OS parametric functions for risdiplam (Obtained from CS Document B, Figure 31, pg. 229)

**EAG Summary**: EAG acknowledges Roche's rigorous approach in integrating FIREFISH and ENDEAR-SHINE trial data via MAIC for type 1 SMA mortality analysis. They approve of the overall survival data source, parametric survival analysis, and selection of the exponential curve, supported by UK clinical experts for its clinical plausibility and alignment with TA755, ensuring robustness in long-term projections despite data limitations. The EAG recommends that given the limitations in conducting the ITC and the lack of long-term data, using parametric survival analysis and choosing the exponential curve (same overall survival values for all treatments) is consistent with TA755, and Section 4.5—is a suitable approach for evaluating OS and EFS for all treatments, including risdiplam, nusinersen, and onasemnogene.

* + - * 1. Discontinuation

Roche's strategy for treating type 1 SMA with risdiplam is grounded in several key elements. They project that after 24 months of treatment, patients will either exhibit improvements or remain stable in terms of motor milestones achieved. This assumption is supported by clinical expert validation and literature findings, consistent with precedents set in healthcare assessments like NICE decision TA588.

Regarding treatment duration, Roche anticipates that risdiplam's beneficial effects will persist over the long term. This expectation is bolstered by data from the FIREFISH trial, which showed sustained improvements in motor function up to 60 months. Within their modelling, Roche sets specific milestones such as not sitting and permanent ventilation at 66 months, underscoring their commitment to long-term efficacy.

Roche has also identified a treatment effect plateau at 66 months post-treatment initiation. This decision, supported by cost-effectiveness analyses and alignment with health authority recommendations (TA755 and TA588), assumes that patients will stabilize in their health state without further transitions until death after this point.

Furthermore, Roche acknowledges a gradual waning of treatment benefits post-completion of the treatment duration, extending up to 60 months. This reflects their interpretation of FIREFISH trial data and expert clinical opinions on the gradual decline in therapeutic impact after treatment cessation.

**EAG summary**: The EAG acknowledges Roche's strategic approach in treating type 1 SMA with risdiplam, particularly focusing on the duration of treatment, plateau in treatment effect, waning of treatment effect, and underlying assumptions. However, we have identified one principal consideration that merit further exploration and potential adjustment.

With respect to comparators nusinersen and onasemnogene abeparvovec, the EAG currently has no access IPD Biogen or Novartis. The EAG proposes using this data for both nusinersen and onasemnogene abeparvovec to refine assumptions about treatment effects across therapies. The inclusion of this data in an independent economic assessment would supplement the model's robustness, ensuring a more nuanced comparison of treatment outcomes and supporting informed decision-making.

* + - * 1. Company’s cost-effectiveness results (type 1 SMA)

Table 68: Deterministic base-case results for the type 1 SMA population (using list prices)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER incremental (£/QALY) |
| Risdiplam | £3,048,405 | 13.48 | 1.89 | - | - | - | - |
| Nusinersen | £2,915,805 | 11.26 | -0.33 | £132,600 | 2.22 | 3.77 | £35,160 |
| Onasemnogene abeparvovec | £1,919,785 | 12.92 | 0.49 | £1,128,620 | 0.56 | 2.38 | £474,048 |
| BSC | £219,069 | 6.79 | -4.97 | £2,829,336 | 6.69 | 11.67 | £242,519 |

Table 69: Deterministic base-case results for the type 1 SMA population (using PAS price)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER incremental (£/QALY) |
| Risdiplam | \*\*\*\*\*\*\*\*\*\* | 13.48 | 1.89 | - | - | - | - |
| Nusinersen | £2,915,805 | 11.26 | -0.33 | \*\*\*\*\*\*\*\*\*\* | 2.22 | 3.77 | \*\*\*\*\*\*\*\*\*\* |
| Onasemnogene abeparvovec | £1,919,785 | 12.92 | 0.49 | \*\*\*\*\*\*\*\*\*\* | 0.56 | 2.38 | \*\*\*\*\*\*\*\*\*\* |
| BSC | £219,069 | 6.79 | -4.97 | \*\*\*\*\*\*\*\*\*\* | 6.69 | 11.67 | \*\*\*\*\*\*\*\*\*\* |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality adjusted life year | | | | | | | |

* + - * 1. Company’s probabilistic sensitivity analysis (type 1 SMA)

Table 70: Probabilistic sensitivity analysis results for the type 1 SMA population (using list prices)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER per QALY (£)** |
| Risdiplam | £3,335,374 | 3.48 | - | - | - |
| Nusinersen | £3,461,649 | 2.02 | -£126,274 | 2.50 | -£50,596 |
| Onasemnogene abeparvovec | £1,944,207 | -2.11 | £1,391,167 | 9.57 | £145,391 |
| BSC | £285,855 | -6.25 | £3,049,520 | 16.55 | £184,258 |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year | | | | | |

Table 71: Probabilistic sensitivity analysis results for the type 1 SMA population (using PAS price)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER per QALY (£)** |
| Risdiplam | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\* | - | - | - |
| Nusinersen | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* |
| Onasemnogene abeparvovec | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* |
| BSC | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\* |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year | | | | | |



Figure 21: Incremental cost-effectiveness plane for comparisons between risdiplam and BSC, nusinersen and onasemnogene abeparvovec (using PAS price)



Figure 22: Cost-effectiveness acceptability curves for the comparisons between risdiplam and BSC, nusinersen and onasemnogene abeparvovec at different WTP thresholds (using the PAS price for risdiplam)

* + - * 1. Company’s sensitivity analysis results (type 1 SMA)



Figure 23: Deterministic one-way sensitivity analysis for the comparison between risdiplam and BSC (using the PAS price for risdiplam)



Figure 24: Deterministic one-way sensitivity analysis for the comparison between risdiplam and nusinersen (using the PAS price for risdiplam)



Figure 25: Deterministic one-way sensitivity analysis for the comparison between risdiplam and onasemnogene abeparvovec (using the PAS price for risdiplam)

* + - * 1. Company’s scenario analysis results (type 1 SMA)

Table 72: Scenario analysis results for people with type 1 SMA (using PAS price for risdiplam)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Scenario** | **ICER (vs BSC)** | **% ICER change from the base case** | **ICER (vs nusinersen)** | **% ICER change from the base case** | **ICER (vs onasemnogene abeparvovec)** | **% ICER change from the base case** |
| **Base-case** | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| **Efficacy scenarios** |
| Comparative efficacy vs. onasemnogene abeparvovec: Source for onasemnogene abeparvovec set to STC STR1VE-US | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Risdiplam transition probabilities informed by bootstrapped multi-state model 5 | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for % scoliosis: based on fixed proportions over time based on FIREFISH | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for % respiratory support: on fixed proportions over time based on FIREFISH | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for % bulbar dysfunction: on fixed proportions over time based on FIREFISH | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| **HCRU scenarios** |
| Alignment with TA588 source for HCRU | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Alignment with TA588 source for HCRU and PV health state costs:  175% increase from the “Not Sitting” health state | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| **Utility values scenarios** |
| Source for patient utility values: EQ-5D-3L (NICE ERG TA588) | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for patient utility values: EQ-5D-Y (Lloyd et al, 2019) | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for caregiver utility values: Roche utility survey | \*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* |
| Source for caregiver utility values: UK Burden of Illness Study | \*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| **Other Scenarios** |
| Changing time horizon to 20 years | \*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Changing time horizon to 40 years | \*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Inclusion of VAT saving from risdiplam homecare | \*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Changing baseline characteristics to REACH UK patient population | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Number of carers lowered to 2 | \*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Number of carers increased to 3 | \*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Discount rate for both costs and benefits is lowered to 1.5% | \*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5% | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |

* + - 1. Type 2/3 SMA population

In this section, the EAG reviewed Roche's economic evaluation of a type 2/3 SMA model. The type 2/3 SMA model refers to both ambulant and non-ambulant patients aged 2–25 years at the time of enrolment with type 2 and 3 SMA. The EAG summarised the model structure and evaluated clinical evidence (e.g., efficacy, treatment discontinuation, mortality) and economic evidence (e.g., drug costs, health state resource use and costs, utilities). The EAG critiqued the methods and inputs used in the analysis.

* + - * 1. Model structure

The type 2/3 SMA model, developed through collaboration with clinical experts and guided by literature reviews and prior HTA reports, aims to accurately represent the disease's progression and treatment outcomes. The company used a Markov model structure in Excel, delineating five motor milestone health states ('not sitting', 'sitting with support', 'sitting unsupported', 'standing' (with or without support), and 'walking' (with or without support) for type 2/3 SMA. By incorporating milestones from the MFM-32 scale and data from the SUNFISH trial, the model accounts for the diverse motor abilities of type 2/3 patients. Treatment options risdiplam, nusinersen, or best supportive care are considered within the model framework, acknowledging limitations in capturing the full impact of SMA and treatment benefits.

**EAG summary**: The Markov model for the type 2/3 SMA is suitable given its adherence to NICE guidelines, thorough validation, and inclusion of clinical expertise. The model effectively captures the natural history, severity, and prognosis of distinct SMA types.

* + - * 1. Population

Roche's evaluation of the type 2/3 SMA population for risdiplam and nusinersen considered a broad spectrum of patients, mirroring the SUNFISH trial's diverse age range and functional abilities, aligning with risdiplam's marketing authorisation. The CHERISH-SHINE study provided the evidence for nusinersen, but comparisons with risdiplam were challenging due to differences in study populations. SUNFISH included a wider range of patients, such as adults, those with severe scoliosis, and those with longer disease durations. Attempts to define a subset more similar to CHERISH were made (age ≤9 years, HFMSE score ≥10, no scoliosis), but this subset represented less than 40% of the SUNFISH Part 2 population. Differences in baseline characteristics, such as age, disease duration, and motor function, resulted in substantial uncertainty in the relative effect estimates.

* + - * 1. Intervention and comparators

For type 2/3 SMA, the cost-effectiveness model compares risdiplam to BSC and nusinersen, as per the final NICE scope. Efficacy and safety for risdiplam are informed by the SUNFISH clinical trial. nusinersen data are derived from CHERISH-SHINE. BSC comparisons are included to meet NICE scope but are considered less relevant due to the availability of DMTs.

During the consultation on the draft scope, Roche and stakeholders argued that BSC should be a comparator instead of 'established clinical management.' BSC includes various clinical pathways and resources. Roche asserts that 'established clinical management' encompasses all listed treatments and should not be standalone. BSC represents patients not on these treatments and could reflect the scenario if risdiplam and nusinersen are not recommended. Roche believes comparing to BSC is appropriate, while comparing to 'established clinical management' is not feasible or suitable.

**EAG summary**: All feasible and practical options, including nusinersen and BSC, have been clearly specified and are under evaluation. The EAG agrees with Roche's rationale that BSC reflects patients not on risdiplam, nusinersen, comparing to a world without these treatments. The EAG, in alignment with Roche, believes 'established clinical management' includes all treatments and BSC, thus shouldn't be a standalone comparator.

* + - * 1. Perspective, time horizon and discount rate

The EAG acknowledges the thorough identification of relevant costs and consequences, ensuring alignment with the NHS and PSS. The clear delineation of patient groups and evaluated strategies in the report underscores the model's scope, thus enhancing its transparency and justification. Additionally, the comprehensive coverage of all potential outcomes related to SMA, consistent with the final scope, further strengthens the study's relevance and applicability to decision-making processes.

Roche has opted for a lifetime horizon of 80 years for the type 2/3 SMA model, aligning with NICE guidelines and the typical life expectancy of patients with this condition. Although the NICE reference case suggests a 90-year horizon, Roche has adjusted this to 80 years, considering the mean baseline age in the model, which is 10 years. This time frame is deemed sufficient to encompass all relevant costs and benefits associated with both risdiplam and BSC.

In the base-case, the costs incurred, and benefits accrued are discounted at a rate of 3.5% per annum.

**EAG summary**: The EAG agrees with an 80-year time horizon for types 2/3 SMA. This aligns with patient life expectancy and NICE standards, ensuring comprehensive coverage of long-term costs and benefits.

* + - * 1. Treatment effectiveness and extrapolation

Roche evaluated the treatment effect of risdiplam compared nusinersen and BSC using three validated motor function scales (MFM32, RULM, and HFMSE). Each scale was chosen based on its clinical relevance to assess different aspects of motor function in patients with SMA. Roche undertook a MAIC to compare risdiplam against nusinersen.

**EAG summary**: In their analysis of Roche’s approach to treatment effects and ITCs in type 2/3 SMA models, the EAG critiques Roche's rationale for exclusively selecting the RULM without conducting scenario analysis for the HFMSE. The EAG highlights that the utilisation of different motor function scores, including HFMSE (RR = \*\*\*\*\*\*\*) or RULM (RR= \*\*\*\*\*\*\*), impacts the based-case ICER. The EAG recommends conducting scenario analyses that incorporate HFMSE to comprehensively assess treatment impacts across various functional abilities, particularly in SMA patients with diverse disease severities and age ranges.

* + - * 1. Health-related quality of life

The primary source for patient HSUVs was the Lloyd et al. (2019) EQ-5D vignette study. This study was selected because it was previously deemed acceptable by the ERG in the TA588 appraisal and was considered clinically plausible by UK clinical experts. Utility values collected from the SUNFISH study were used in scenario analyses but not in the base-case due to concerns about their clinical validity, as they did not reflect the broad range of HRQoL levels observed between motor milestones.

The utility values from the SUNFISH study were cross-walked from the EQ-5D-5L to the EQ-5D-3L and valued using UK tariffs. A repeated measures model with fixed and random effects was applied to the EQ-5D-5L data from the SUNFISH study to understand the effects of motor milestone achievement on utility values. Disutilities for scoliosis and respiratory support were calculated and additional utility improvements were applied for patients old enough to self-report (12 years and older).

Table 73: Summary of patient utility values for cost-effectiveness analysis (type 2/3 base case model) (Obtained from CS Document B, Table 127, pg.259)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| State | Utility value: mean | 95% confidence interval | Reference in submission | Justification |
| Not sitting | −0.170 | NA | Section B.3.4.5 | Feedback from UK clinical experts was that HSUVs sourced from the Lloyd et al. study possessed the greatest clinical validity for type 2/3 patients (Section B.3.14). |
| Sitting (supported) | 0.040 | NA |
| Sitting (unsupported) | 0.040 | NA |
| Standing | 0.555 | NA |
| Walking | 0.555 | NA |
| Disutilities | | | | |
| Bulbar function | -0.170 | NA |  |  |
| HSUV, health state utility value; NA, not applicable | | | | |

For the base case, carer HSUVs were informed by the Bastida et al. (2017) study and general population utility values, as these were considered to demonstrate greater face validity by UK clinical experts. Additional utility values were collected from caregivers in Roche UK studies and used in scenario analyses. Roche has stated that based on the company’s UK BOI study, across all health states, an average of 2.2 caregivers would be required to care for people with SMA. (CS document b, pg 262, However, economic model inputs worksheet suggests 3 caregivers- cell H206)

Table 74: Summary of carer utility values for cost-effectiveness analysis (type 2/3 base case model) (TA588/TA755 ERG report) (Obtained from CS Document B, Table 130, pg.261)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| State | Utility value: mean | 95% confidence interval | Reference in submission | Justification |
| Not sitting | 0.700 | NA | Section B.3.4.5 | Feedback from UK clinical experts was that HSUVs sourced from the TA588/TA755 ERG report possessed the greatest clinical validity for carers of SMA patients (see Section B.3.14.1) |
| Sitting (supported) | 0.772 | NA |
| Sitting (unsupported) | 0.843 | NA |
| Standing | 0.915 | NA |
| Walking | 0.915 | NA |
| HSUV, health state utility value; NA, not applicable | | | | |

In the type 2/3 model, Roche incorporates the following items affecting patient and caregiver utilities:

Patient: Incremental benefits for risdiplam and nusinersen: using 0.20 for not sitting, sitting without support, and sitting with support health states

Caregiver: Incremental benefits for risdiplam and nusinersen: using 0.05 for not sitting, sitting without support, and sitting with support health states

Additionally, utility decrements due to disease impacts and treatment-related events are included, such as scoliosis (\*\*\*\*\*\*\*), respiratory support (\*\*\*\*\*\*\*), and bulbar dysfunction (\*\*\*\*\*).

**EAG summary**: The EAG is satisfied with Roche's selection of utility sources for the base case analysis in type 2/3 SMA, consistent with the ERG's stance in TA755. Patient utility values from the Lloyd et al.225 EQ-5D vignette study were endorsed for their clinical plausibility, contrasting with SUNFISH study values deemed less reflective of HRQoL variability.

Regarding caregiver utility, EAG has two main comments: Firstly, EAG is generally satisfied with the set of utilities Roche used for caregivers, including HSUVs from Lopez-Bastida et al.226 general population utility, and EQ-5D-5L values from Roche UK studies. These utilities align with previous STA studies and show general agreement across different health states. Secondly, the number of caregivers needed for SMA patients varies with disease severity. Roche uses an average of 2.2 caregivers for all SMA patients, but EAG recommends using different caregiver numbers based on health states, as suggested by Biogen’s submission, for more accurate disutility estimation. The EAG considers that incorporating patient and caregiver incremental benefits, along with utility decrements due to disease impacts and treatment-related events, leads to double counting. Each utility value for a specific health state already covers the overall situation of patients in that state, so adding other utilities results in double counting.

* + - * 1. Resource use and costs

The items for resource use and cost in the type 2/3 SMA model are the same as in the type 1 and presymptomatic SMA models. Roche uses the resource use and costs derived from the modified Delphi study for the base-case analysis and the costs from TA588 with the one-off costs from the modified Delphi panel for the scenario analysis (*see* Table 75 and Table 76).

Table 75: Modified Delphi panel HCRU results applied to type 2/3 SMA (SUNFISH) model health states per monthly cycle (Obtained from CS Document B, Table 135, pg.283)

|  |  |  |  |
| --- | --- | --- | --- |
| **Health state** | **Total costs per cycle** | | **One-off costs** |
| **Paediatric patient** | **Adult patient** |
| Unable to sit | £1,581 | £697 | £15,586 |
| Sitting with support | £1,315 | £521 | £9,456 |
| Sitting without support | £1,315 | £521 | £9,456 |
| Standing | £660 | £189 | £2,372 |
| Walking | £222 | £121 | £715 |

Table 76: Real-world study (TA588) applied to type 2/3 SMA (SUNFISH) model health states per monthly cycle, with the one-off costs from the modified delphi panel (Obtained from CS Document B, Table 137, pg.283)

|  |  |  |
| --- | --- | --- |
| Health state | Total costs per cycle\* from TA588 | One-off costs |
| Not sitting | £13,284 | £15,586 |
| Sitting with support | £13,284 | £9,456 |
| Sitting without support | £9,704 | £9,456 |
| Standing | £1,951 | £2,372 |
| Walking | £1,951 | £715 |

**Footnotes:** \*costs have been inflated from 2018/19 using NHSCII Pay and Price Index

**EAG summary:** EAG's comments on resource use and costs fall into three main categories: risdiplam, and nusinersen acquisition and administration costs, Health Care Resource Use, and Specialist Equipment (one-off). EAG is satisfied with Roche's approach in all three categories. The EAG received feedback from a patient representative regarding additional specialist equipment (e.g., powered wheelchair) provided as one-off costs by the NHS/PSS. To address this, EAG suggests that a scenario analysis increasing the one-off healthcare costs by 20% for the 'Not sitting', 'Permanent ventilation', and 'Sitting' health states could manage this uncertainty. To further address uncertainty around HCRU, the recommend undertaking a scenario analysis using HCRU data from TA588 (including PV health state costs from different sources) and HST24, incorporating the one-off costs from the Modified Delphi panel HCRU results.

In the specialist equipment (one-off) category, EAG considers Roche's approach and recommends using this category for all options included in the base case analysis.

* + - * 1. Mortality

Roche's considerations regarding mortality for patients with type 2 and type 3 SMA are informed by both literature evidence and clinical expert opinions.

1. General population mortality for type 3 SMA: For patients with type 3 SMA, and for type 2 patients who achieve the health states of standing or walking, Roche assumes mortality rates equivalent to the general population (data from the ONS).
2. Type 2 SMA Mortality: Mortality for type 2 SMA patients who do not reach the advanced motor milestones of standing or walking is treated separately. Roche used a SLR to identify survival curves specific to type 2 SMA. After reviewing multiple studies, data from six selected studies were pooled to create a comprehensive survival dataset. Parametric survival functions were fitted to this pooled data, with the Gompertz model selected for the base case based on goodness-of-fit statistics and clinical expert feedback.
3. Hazard ratio for risdiplam: A HR of 0.75 is applied to reflect the anticipated reduced mortality risk associated with risdiplam treatment compared to BSC. This aligns with the approach taken in previous assessments.17

In terms of survival analysis, Roche employed an extensive survival analysis process using data from six studies on type 2 SMA. Kaplan-Meier curves from these studies were digitised to create IPD, which were then pooled. Various parametric survival functions were assessed, with the Gompertz model selected based on AIC/BIC and long-term plausibility as confirmed by clinical experts.

**EAG summary**: The EAG generally supports Roche's methodology regarding mortality assumptions for type 2/3 SMA. A 0.75 HR for risdiplam reflects Roche's strategy to account for potential mortality reduction. The EAG suggests alternative hazard ratios (HR) of 0.90 or 0.60 due to limited robust evidence.

* + - 1. Company’s cost-effectiveness results (type 2/3 SMA)

In Table 77 we report the company’s deterministic results for the type 2/3 SMA population, using the list prices. These results show that risdiplam dominate treatment with nusinersen. When compared to BSC results in an ICER of approximately £343,700 per QALY.

Table 77: Deterministic base-case results for the type 2/3 SMA population (using list prices)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER incremental (£/QALY)** |
| **Risdiplam** | £4,504,435 | 21.63 | 2.39 | - | - | - | - |
| **Nusinersen** | £4,599,047 | 21.51 | 1.55 | -£94,612 | 0.13 | 1.44 | Risdiplam is dominant |
| **BSC** | £305,448 | 20.29 | -4.79 | £4,198,986 | 1.34 | 12.22 | £343,682 |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality adjusted life years | | | | | | | |

Under PAS agreements, the ICER reduced to approximately \*\*\*\*\*\*\*\* per QALY for the comparison between risdiplam and BSC (*see* Table 78).

Table 78: Deterministic base-case results for the type 2/3 SMA population (using PAS prices)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER incremental (£/QALY)** |
| **Risdiplam** | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| **Nusinersen** | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| **BSC** | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |

* + - 1. Company’s probabilistic sensitivity analysis results (type 2/3 population)

In Table 79, we report the company’s PSA results, which shows that total costs for risdiplam and nusinersen are underestimated compared to the deterministic results, while the expected QALYs yielded are overestimated. Conversely, the total costs for BSC are overestimated compared to the deterministic results and QALYs underestimated, resulting in reduction to the ICER of approximately \*\*\*\*\*\*\*\* per QALY, using list prices.

Table 79: Probabilistic results for the type 2/3 SMA population (using list prices)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER per QALY** |
| Risdiplam | £4,215,781 | 2.49 | - | - | - |
| Nusinersen | £4,344,519 | 1.67 | -£128,738 | 1.41 | -£91,294 |
| BSC | £309,195 | -4.50 | £3,906,587 | 11.87 | £329,084 |

In Table 80, we report the company’s PSA results using the commercial agreements. These results show that the ICER reduces to approximately \*\*\*\*\*\*\*\* per QALY.

Table 80: Probabilistic results for the type 2/3 SMA population (using PAS price)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER per QALY (£)** |
| Risdiplam | \*\*\*\*\* | \*\*\*\*\* | - | - | - |
| Nusinersen | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| BSC | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |

PSA results indicate that at a willingness-to-pay threshold of £30,000 per QALY, risdiplam when compared to BSC is generally \*\*\*\*\* the cost-effectiveness threshold. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.



Figure 26: Incremental cost-effectiveness scatterplot for the comparison between risdiplam and BSC and nusinersen (using PAS price for risdiplam)



Figure 27: Cost-effectiveness acceptability curve for the comparison between risdiplam and BSC and nusinersen at different WTP thresholds (using the PAS price for risdiplam)

* + - 1. Company’s deterministic sensitivity analysis results

Based on the deterministic sensitivity analysis results for the type 2/3 SMA (SUNFISH) model (PAS price), the inputs with the greatest impact on the ICER versus BSC are the caregiver utilities for patients in the sitting without support health state and the drug acquisition cost of risdiplam. When compared to nusinersen, the utility benefit for patients and caregivers in the sitting without support health state are the greatest drivers of the ICER (*see* Figure 28 and Figure 29).



Figure 28: Deterministic one-way sensitivity analysis for the comparison between risdiplam and BSC (using the PAS price for risdiplam)



Figure 29: Deterministic one-way sensitivity analysis for the comparison between risdiplam and nusinersen (using the PAS price for risdiplam)

* + - 1. Company’s scenario analyses for the type 2/3 SMA population

In Table 81 we present the company’s scenario analyses results for the type 2/3 SMA population. These results show the impact on the ICER for risdiplam versus BSC and versus nusinersen. For the comparison between BSC, changing the source for caregiver utility values to Roche utility survey resulted in an increase in by \*\*\*\*\*\*\*\*, while applying TA588 as the source of HCRU lowered the ICER by \*\*\*\*\*\*\*. However, the ICER for the comparison between risdiplam and nusinersen remained robust, with \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.

Table 81: Scenario analysis results for the type 2/3 SMA population (using PAS prices)

| **Scenario** | **ICER**  **(vs BSC)** | **% ICER change from the base case** | **ICER (vs nusinersen)** | **% ICER change from the base case** |
| --- | --- | --- | --- | --- |
| **Base-case** | \*\*\*\*\*\*\*\* | \* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| **Efficacy scenarios** | | | | |
| Comparative efficacy vs. BSC: set to Natural history study | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Risdiplam efficacy informed by non-imputed 5-year SUNFISH (excl. Asia) | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Risdiplam efficacy post follow-up set to the extrapolations as seen in the SUNFISH trial period | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Weibull used for Type 2 OS extrapolation | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Source for % scoliosis: change to Wijngaarde et al. 2019 | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Source for % bulbar dysfunction: change to Wadman et al. 2017 | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Source for % respiratory support: change to van der Heul et al. 2019 | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| **HCRU scenarios** | | | | |
| Alignment with TA588 source for HCRU | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Utility values scenarios | | | | |
| Source for patient utility values: TA588 ERG clinical advisors | \*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Source for patient utility values: EQ-5D-3L values from SUNFISH | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Source for caregiver utility values: Roche utility survey | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Source for caregiver utility values: UK Burden of Illness Study | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| **Other Scenarios** | | | | |
| Inclusion of VAT saving from risdiplam homecare | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Changing baseline characteristics to REACH UK patient population | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Number of carers lowered to 2 | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Number of carers increased to 3 | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Discount rate for both costs and benefits is lowered to 1.5% | \*\*\*\*\*\*\*\* | \*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5% | \*\*\*\*\*\*\* | \*\*\*\*\*\*\* | \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | \* |
| BSC, best supportive care; EQ-5D-5L, EuroQoL 5 Dimensions 3 Levels; EQ-5D-Y, European Quality of Life-5 Dimensions – Youth version; ERG, Evidence Review Group; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; LY, life year; NICE, National Institute for Health and Care Excellence; PV, permanent ventilation; QALY, quality-adjusted life year. | | | | |

* 1. Conclusion

The EAG noted that the companies’ models were logical and depicted the clinical pathways for treating people with SMA. The EAG did not identify any major errors in the companies’ models. The companies provided details about the conduct of their economic analyses. In general, the process of identifying and justifying the choice of key model inputs were transparent and robust. Most of the economic analyses conformed to the NICE reference case, but there were instances where the time horizon was not long enough to capture any important differences between the interventions being compared. Assumptions were clearly reported and appeared appropriate. In some instances, the EAG noted that there were inconsistencies in the inputs reported in the main report with those in the company’s electronic model. The results reported in the company submission reflected those in the model submitted. However, there were some areas of concern/uncertainty outline in Table 82:

Table 82: Key issues identified and EAG recommendations

| **Model** | **Company** | **Key issue** | **EAG recommendation** |
| --- | --- | --- | --- |
| Type 0 and type 4 | Biogen and Roche | Cost-effectiveness analyses: No cost-effectiveness analyses for type 0 or type 4 submitted | None |
| Presymptomatic, type 1 and type 2/3 | Biogen | Comparator: Company compared nusinersen to BSC only | Using the Roche models as preferred models for conducting EAG base-case and scenario analysis. |
| Presymptomatic | Biogen | Survival analysis: company digitised parametric curves rather than KM plots for modelled health states | EAG to digitise KM plots from the original source to validate company’s model fitting and extrapolations. |
| Presymptomatic | Roche | Treatment effectiveness: Roche's assumption of equal efficacy among risdiplam, nusinersen, and onasemnogene abeparvovec is not backed by strong evidence. | EAG acknowledges that the small sample size and differences in trial population characteristics are the main barriers to conducting the ITC among these three treatments. However, EAG suggests that this should be reconsidered and reassessed with new and more comprehensive data in the future. |
| Type 2/3 | Roche | Treatment effects: There are marked differences between the results from the MAIC - RULM and MAIC - HFMSE scores. These differences are not included in the scenario analysis | Scenario analysis: Using the transition probabilities derived from the MAIC - HFMSE score for nusinersen. |
| Presymptomatic | Roche | Transition probabilities: Roche's assumption of equal efficacy for all treatments, based on one-year data from the RAINBOWFISH trial, oversimplifies the analysis. | EAG preferred using the transition probabilities from the NURTURE trial over those from the RAINBOWFISH trial for the base case analysis. However, to generate the monthly transition probability, EAG needs the clinical trial data on nusinersen (IPD) used in the NURTURE trial. This data has been requested, but EAG has not yet received it. |
| Presymptomatic | Roche | Duration of treatment and plateau: The EAG criticizes the assumption of a uniform 10-year treatment duration and plateau period for presymptomatic SMA patients and for all treatments, questioning the adequacy of supporting evidence. |
| Type 1 | Roche | Plateau: Uncertainty around efficacy data, particularly long-term efficacy, is not considered | Scenario analysis: a) Using the 66-month plateau with possibility of deterioration for all treatment, b) Use different plateaus for different treatments (66 months for risdiplam, 60 months for nusinersen, and 36 months for OA) with the possibility of deterioration, improvement, or staying at the current health state |
| Type 2/3 | Roche | Plateau: Uncertainty around efficacy data, particularly long-term efficacy, is not considered | Scenario analysis: Using different plateaus for different treatments (26 months for risdiplam, 15 months for nusinersen) with the possibility of deterioration, improvement, or staying at the current health state. |
| Presymptomatic | Roche | Population: The company reported cost-effectiveness results for a total presymptomatic population, emphasising careful interpretation due to small subgroup sizes in SMA patients with two versus more than two SMN2 copies. Stratification is crucial, given newborns' potential to develop different SMA types and distinct differences in assessments like Mean CHOP-INTEND and HINE-2, as shown in the RAINBOWFISH trial. | EAG notes that patients with two SMN2 copies who show symptoms will resemble those with type 1 SMA, while presymptomatic patients with more than two SMN2 copies will, after showing symptoms, resemble those with type 2/3 SMA. This difference is evident at the end of the treatment in the RAINBOWFISH and NURTURE trials. Based on this observation, EAG prefers using different models for presymptomatic patients with two SMN2 copies and those with more than two SMN2 copies. EAG believes this approach will better align with the population's nature and more accurately reflect treatment effectiveness. EAG acknowledges that, due to the sample size in these two categories in the RAINBOWFISH trial, a reliable subgroup analysis is currently not feasible. However, EAG recommend reassessing these two populations of presymptomatic SMA patients with new and more comprehensive data in the future. |
| Presymptomatic | Roche | Survival analysis: Company assumed general population mortality applied to all model health states | Base case analysis: Apply general population mortality to the standing without support and the walking independently health states, and for the other health states, use overall survival transitions (need to change to monthly probability) obtained from HST24, if possible.  Scenario analysis: Apply general population mortality rates to all health states in overall survival transitions |
| Type 1 | Roche | Survival analysis and event-free survival: Better support from UK clinical experts (based on Roche submission), but the HR is used to determine the overall survival (OS) in nusinersen, and onasemnogene | Base case analysis: Using the survival curve (Exponential)  Scenario analysis: using the HR for determine the overall survival (OS) Type 1 |
| Type 3 | Roche | Survival analysis: The uncertainty around the hazard ratio (HR) of 0.75, which reflects the anticipated reduced mortality risk associated with risdiplam treatment compared to best supportive care (BSC), is not considered. | Scenario analysis: using two options: a) HR=0.90, and b) HR=0.60 |
| Presymptomatic and type 1 | Roche | Time horizon: Not long enough to capture all costs and benefits accrued | Base case analysis: Run the model using a long-term time horizon (90-year).  Scenario analysis: Run the model using a Roche preferred time horizon(\*\*-year). |
| Presymptomatic, type 1 and type 2/3 | Roche | Severity modifier: Derived based on patient and carer utility values, then multiplied by the total value, including patient and carer utility | Base-case analysis: Derived based on patient utility values, then multiplied by the patient utility value, then add carers utility values  Scenario analysis: Excluding the severity modifier |
| Presymptomatic, type 1 and type 2/3 | Roche | Caregiver utility: Based on the company’s UK BOI study across all health states an average of 2.2 caregivers would be required to care for people with SMA. | Base-case analysis: The caregiver numbers from Biogen's submission are preferred by the EAG, with two caregivers needed in more severe health states and one caregiver in standing and walking health states.  Scenario analysis: a) Excluding the Carers' utilities, b) Excluding caregiver utilities for SMA patients who are in standing and walking health states, c) using the 2.2 carer for 'Not sitting', 'Sitting with support' and 'Sitting without support' health states and 1.5 carer for 'Standing' and 'Walking', d) using the 3 carers for 'Not sitting', 'Sitting with support' and 'Sitting without support' health states and 1.5 carer for 'Standing' and 'Walking' |
| Presymptomatic, type 1 and type 2/3 | Roche | Incremental benefit: Double counting of utility occurs when both the patient incremental benefit and the caregiver incremental benefit are added to the main utility of some health states for all treatments. | Base case analysis: EAG has excluded this incremental benefit.  Scenario analysis: Including these incremental benefits. |
| Presymptomatic, type 1 and type 2/3 | Roche | Utility decrements: Double counting of utility occurs when Roche uses certain values for disease impacts and treatment-related events, including scoliosis, respiratory support, and bulbar dysfunction. | Base case analysis: EAG has excluded the utility decrements due to disease impacts and treatment-related events.  Scenario analysis: Including the utility decrements due to disease impacts and treatment-related events. |
| Presymptomatic, type 1 and type 2/3 | Roche | Health Care Resource Use (HCRU): Uncertainty regarding various sets of HCRU, especially HST24, and potential increases in one-off healthcare costs are not considered. | Scenario analysis: a) Using the cost from HST24 with adding the one-off costs from Modified Delphi panel HCRU results, b) Alignment with TA588 source for HCRU and PV health state costs from Roche HCRU study with adding the one-off costs from Modified Delphi panel HCRU results, c) Alignment with TA588 source for HCRU and PV health state costs is equal to 'Not sitting' health state with adding the one-off costs from Modified Delphi panel HCRU results, d) Increasing the one-off health care costs by 20% in 'Not sitting', 'Permanent ventilation', and 'Siting' health states |
| Presymptomatic, type 1 | Roche | Disease impact costs: Overlap with other categories of resource use and costs | Base-case analysis: EAG has excluded disease impact costs  Scenario analysis: Including the disease impact costs |

1. Independent EAG economic assessment

The EAG evaluated six different models submitted by Biogen and Roche for presymptomatic, type 1, and type 2/3 SMA populations. These evaluations led to the selection of Roche's models for presymptomatic, type 1, and type 2/3 SMA as more suitable for independent EAG economic assessments. When selecting an appropriate model (in Excel format) for an independent economic assessment, especially in the context of evaluating treatments for various types of SMA patients, the following criteria were considered:

1. **Model scope and applicability:** Both companies provided models for people with presymptomatic, type 1 and type 2/3 SMA. For treatment comparisons, Roche's models include all relevant treatment options and comparators, including risdiplam, nusinersen, onasemnogene abeparvovec, and BSC, whereas Biogen's models only analysed nusinersen and BSC.
2. **Flexibility and customisability:** EAG found that Roche's models allow for easier adjustment of key parameters and assumptions than Biogen's models. Additionally, Roche's models are more adaptable to new data or emerging treatments.
3. **Usability and accessibility:** EAG determined that Roche's models are more user-friendly and easier to navigate than Biogen's models.
4. **Cost and resource use:** EAG found that Roche's models are superior for assessing the impact of varying costs in specific categories (e.g., hospitalisations, specialist visits, tests and investigations, specialist equipment) compared to Biogen's models.
5. **Outcomes measurement:** In terms of clinical outcomes and the ability to assess different scores' impact on the ICER, Roche's model offers a better opportunity than Biogen's models.

Regarding other criteria such as outcomes measurement, methodological rigor, validation and credibility, sensitivity analysis, and perspective and discounting, there are advantages and disadvantages in both companies' submissions, with no clear preference between Roche and Biogen.

* + 1. EAG results

Here, we present the EAG’s results, which includes making the following changes in the Roche economic models for the presymptomatic, type 1 SMA and types 2/3 SMA populations, respectively. All analyses are based on the PAS prices for risdiplam and are presented as fully incremental results.

Tables detailing the changes made to the company’s economic models based on the EAG’s amendments are presented in Appendix 6.

* + - 1. Changes made to Roche’s presymptomatic model

The EAG selected the Roche type presymptomatic model for the basis of our independent economic assessment for this population, by making changing to address the key issues identified (*see* Table 83).

Table 83: EAG Base case inputs based on Roche presymptomatic SMA model

| **Input** | **Roche Value** | **EAG Value** | **Section** |
| --- | --- | --- | --- |
| **Time horizon** | | | |
| Time horizon, years | \*\* | 90 | 5.4.2.2.5 |
| **Utility decrements - disease impacts and treatment related events** | | | |
| Scoliosis | \*\*\*\*\*\* | 0 | 5.4.2.2.7 |
| Respiratory support | \*\*\*\*\*\* | 0 |
| Bulbar dysfunction | \*\*\*\*\*\* | 0 |
| **Severity modifier** | | | |
| QALY weight | 1.7 (Derived based on patient and carer utility values, then multiplied by the total value, including patient and carer utility) | 1.7 (Derived based on patient utility values, then multiplied by the patient utility value, then add carers utility values) | 5.4.2.2.10 |
| **Caregiver utilities** | | | |
| Permanent ventilation | 2.2 | 2 | 5.4.2.2.7 |
| Not sitting | 2.2 | 2 |
| Sitting | 2.2 | 2 |
| Standing | 2.2 | 1 |
| Walking | 2.2 | 1 |
| **Patient: Incremental benefit for risdiplam, nusinersen, and onasemnogene abeparvovec** | | | |
| Not sitting | 0.20 | 0 | 5.4.2.2.7 |
| Sitting | 0.20 | 0 |
| **Caregiver: Incremental benefit for risdiplam, nusinersen, and onasemnogene abeparvovec** | | | |
| Not sitting | 0.05 | 0 | 5.4.2.2.7 |
| Sitting | 0.05 | 0 |
| **Disease impact costs** | | | |
| Respiratory support | £523 | 0 | 5.4.2.2.8 |
| Severe scoliosis | £2,167 | 0 |
| Bulbar dysfunction | £1,715 | 0 |
| **Overall Survival** | | | |
| Overall survival source for risdiplam, nusinersen, and onasemnogene abeparvovec | General population mortality | Obtained from HST24 for ‘Not sitting’, ‘Sitting’, and ‘Permanent ventilation’ health states | 5.4.2.2.9 |
| Overall survival for BSC | Weighted by SMN2 copies | Using the Probability of death from exponential (2 SMN2 copies only) for health states with more severity and Probability of death from exponential (>2 SMN2 copies only) for Sitting/standing/walking health states | 5.4.2.2.9 |

* + - 1. Results (pre-symptomatic population)

In this section we report the EAG results (deterministic, probabilistic, sensitivity and scenario analyses) for the presymptomatic population.

* + - * 1. Deterministic base-case results

The EAG’s base-case results for the presymptomatic population compares risdiplam against nusinersen, onasemnogene abeparvovec and BSC. These results are presented in Table 84, which shows that treatment \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. When compared to \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* results in an ICER of approximately, \*\*\*\*\*\*\* per QALY.

Table 84: Deterministic base-case results for the presymptomatic population (using PAS price)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER (£/QALY) without severity modifier** | **ICER with severity modifier** |
| BSC | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \* | \* | \* | \* | \* |
| Onasemnogene abeparvovec | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| Risdiplam | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| Nusinersen | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality adjusted life years | | | | | | | | |

* + - * 1. PSA results

PSA results were undertaken based on the cost per QALY. In Table 85 we report the results of the company’s PSA for the total presymptomatic population, which are not similar to the deterministic results. The ranking of the technologies has changed with risdiplam compared to BSC resulting in an ICER of approximately \*\*\*\*\*\*\* per QALY.

Table 85: PSA results for the presymptomatic population (using PAS price)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER incremental (£/QALY) without severity modifier** |
| BSC | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| Risdiplam | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| Onasemnogene abeparvovec | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| Nusinersen | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* | \*\*\*\*\* |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality adjusted life years | | | | | |

Each simulation of the incremental costs and incremental QALYs for risdiplam versus nusinersen, onasemnogene abeparvovec and BSC were plotted on an incremental cost-effectiveness plane (see Figure 30), along with the respective cost-effectiveness acceptability curve (CEAC) (see Figure 31). The CEAC shows the proportion of simulations in which nusinersen compared to BSC are cost-effective at different willingness-to-pay thresholds for a QALY. These results show that at a WTP threshold of £30,000 per QALY risdiplam compared to BSC had a \*\*\*\* probability of being cost-effective.



Figure 30: Incremental cost-effectiveness scatterplot for the comparisons between risdiplam and BSC, nusinersen and onasemnogene abeparvovec for the presymptomatic population (using PAS price for risdiplam)



Figure 31: Cost-effectiveness acceptability curve for the risdiplam compared to BSC, nusinersen and onasemnogene abeparvovec at different WTP thresholds (using PAS price for risdiplam)

* + - * 1. One-way sensitivity analysis results

The results in Figure 32 shows that the was a key driver of the economic analysis for the presymptomatic population is the \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.



Figure 32: Deterministic one-way sensitivity analysis for the comparison between risdiplam and BSC (using the PAS price for risdiplam)

* + - * 1. Scenario analysis results

The EAG undertook scenario analyses to assess the impact of each change to the deterministic results. In Table 86, we report the scenario analyses undertaken with regards to the presymptomatic population. These results show that impact to the pairwise ICER when risdiplam is compared to BSC, nusinersen and onasemnogene abeparvovec.

Table 86: Scenario analysis results for the presymptomatic SMA population (using PAS prices)

| **Scenario** | **ICER Risdiplam vs BSC (£)** | **% ICER change from the base case** | **ICER nusinersen vs BSC(£)** | **% change from base case** | **ICER OA vs BSC(£)** | **% change from base case** |
| --- | --- | --- | --- | --- | --- | --- |
| **Base case** | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Efficacy scenarios** | | | | | | |
| Comparative efficacy vs. BSC: Source for BSC set to PNCR data with SMN2 copies matched to RF | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Apply general population mortality rates to all health states in overall survival transitions | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **HCRU scenarios** | | | | | | |
| Alignment with TA588 source for HCRU and PV health state costs from Roche HCRU study | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| using the cost from HST24 with adding the one-off costs from Modified Delphi panel HCRU results | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Alignment with TA588 source for HCRU and PV health state costs is equal to 'Not sotting' health state | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Including the NHSE additional treatment costs proportion (applied to discounted drug costs) | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Increasing the one-off health care costs by 20% in 'Not sitting', 'Permanent ventilation', and 'Siting' health states | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Including the disease impact costs | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Utility values scenarios** | | | | | | |
| Including the Utility decrements due to disease impacts and treatment-related events. (respiratory support, severe scoliosis, and bulbar dysfunction)- source from PNCR survival (time- and treatment dependent) | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Excluding the Carers' utilities | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Excluding the severity modifier | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Excluding both carers' utility and severity modifier | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Excluding caregiver utilities for SMA patients who are in standing and walking health states | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| using the 2.2 carer for 'Not sitting', 'Sitting with support' and 'Sitting without support' health states and 1.5 carer for 'Standing' and 'Walking' | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| using the 3 carers for 'Not sitting', 'Sitting with support' and 'Sitting without support' health states and 1.5 carer for 'Standing' and 'Walking' | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Source for patient utility values: EQ-5D-3L, UK (NICE ERG TA588) | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Source for patient utility values: EQ-5D-Y, UK (Lloyd et al , 2019) | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Source for caregiver utility values: Roche utility survey | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Source for caregiver utility values: UK Burden of Illness Study | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| **Other Scenarios** | | | | | | |
| Discount rate for both costs and benefits is lowered to 1.5% | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5% | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Changing time horizon to 30 years | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |

* + - 1. Changes made to Roche’s type 1 SMA model

The EAG selected the Roche type 1 model for the basis of our independent economic assessment for this population, by making changing to address the key issues identified (*see* Table 87*)*.

Table 87: EAG Base case inputs based on Roche type 1 SMA model

| **Input** | **Roche Value** | **EAG Value** | **Section** |
| --- | --- | --- | --- |
| **Time horizon** | | | |
| Time horizon, years | \*\* | 90 | 5.4.2.2.5 |
| **Utility decrements - disease impacts and treatment related events** | | | |
| Scoliosis | \*\*\*\*\*\* | 0 | 5.4.2.2.7 |
| Respiratory support | \*\*\*\*\*\* | 0 |
| Bulbar dysfunction | \*\*\*\*\*\* | 0 |
| **Severity modifier** | | | |
| QALY weight | 1.7 (Derived based on patient and carer utility values, then multiplied by the total value, including patient and carer utility) | 1.7 (Derived based on patient utility values, then multiplied by the patient utility value, then add carers utility values) | 5.4.2.2.10 |
| **Caregiver utilities** | | | |
| Permanent ventilation | 2.2 | 2 | 5.4.2.2.7 |
| Not sitting | 2.2 | 2 |
| Sitting | 2.2 | 2 |
| Standing | 2.2 | 1 |
| Walking | 2.2 | 1 |
| **Patient: Incremental benefit for risdiplam, nusinersen, and onasemnogene abeparvovec** | | | |
| Not sitting | 0.20 | 0 | 5.4.2.2.7 |
| Sitting | 0.20 | 0 |
| **Caregiver: Incremental benefit for risdiplam, nusinersen, and onasemnogene abeparvovec** | | | |
| Not sitting | 0.05 | 0 | 5.4.2.2.7 |
| Sitting | 0.05 | 0 |
| **Disease impact costs** | | | |
| Respiratory support | £523 | 0 | 5.4.2.2.8 |
| Severe scoliosis | £2,167 | 0 |
| Bulbar dysfunction | £1,715 | 0 |
| **Overall Survival (OS) type 1** | | | |
| Nusinersen, onasemnogene abeparvovec | Using the HR | Survival curve  (Exponential) | 5.4.2.3.5 and 5.4.2.3.8 |
| **Event Free Survival (EFS)** | | | |
| Nusinersen, onasemnogene abeparvovec | Using HR (vs risdiplam) | Survival curve  (Exponential) | 5.4.2.3.5 and 5.4.2.3.8 |
| BSC, best supportive care; HR, hazard ration; OS, overall survival; QALY, quality adjusted life-year | | | |

* + - 1. Results (type 1 SMA)

In this section we report the EAG results for the types 1 SMA population.

* + - * 1. Deterministic base-case results

In Table 88 we report the EAG results for the type 1 SMA population. These results show that treatment with risdiplam \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. Excluding all \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, which resulted in an ICERs of approximately \*\*\*\*\*\*\*\* and \*\*\*\*\*\*\* per QALY, without and with severity modifier, respectively.

Table 88: Deterministic base-case results for the type 1 SMA population (using PAS price)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER (£/QALY) without severity modifier** | **ICER with severity modifier** |
| BSC | \*\*\*\* | \*\*\*\* | \*\*\*\* | \* | \* | \* | \* | \* |
| Risdiplam | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Onasemnogene abeparvovec | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Nusinersen | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality adjusted life years | | | | | | | | |

* + - * 1. PSA results

The PSA results are reported in Table 89, which show that in general the total costs and the total QALYs are overestimated and resulted in an ICER less than the deterministic results.

Table 89: Probabilistic results for the type 1 SMA population (using PAS price)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER witho**ut **severity modifier** |
| BSC | \*\*\*\* | \*\*\*\* | \* | \* | \* |
| Risdiplam | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Onasemnogene abeparvovec | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| Nusinersen | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* | \*\*\*\* |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality adjusted life years | | | | | |



Figure 33: Incremental cost-effectiveness scatterplot for the comparisons between risdiplam and BSC, nusinersen and onasemnogene abeparvovec for the type 1 SMA population (using PAS price for risdiplam)



Figure 34: Cost-effectiveness acceptability curve for the risdiplam compared to BSC, nusinersen and onasemnogene abeparvovec at different WTP thresholds (using PAS price for risdiplam)

In Figure 33, the PSA results are reported on a scatterplot. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* In Figure 34, the PSA results are reported on a CEAC, and these show that at a WTP of £30,000 per QALY, risdiplam when compared to BSC has a \*\*\*\* probability of being cost-effective.

* + - * 1. One-way sensitivity analysis results

In Figure 35, the one-way sensitivity analysis results show that the \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* is the most influential input when risdiplam is compared to BSC.



Figure 35: Deterministic sensitivity analysis results for the type 1 SMA model (PAS price for risdiplam), ICER versus BSC

* + - * 1. Scenario analysis results

In Table 90, we present the scenario analyses results for the type 1 SMA population. These results show that \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.

Table 90: Scenario analysis results for the type 1 SMA population (using PAS price)

| **Scenario** | **ICER Risdiplam vs BSC** | **% ICER change from the base case** | **ICER Risdiplam vs nusinersen** | **% change from base case** | **ICER Risdiplam vs OA** | **% change from base case** |
| --- | --- | --- | --- | --- | --- | --- |
| **Base case** | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Efficacy scenarios | | | | | | |
| Comparative efficacy vs. OA: Source for OA set to STC STR1VE-US | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Comparative efficacy vs. BSC: Source for BSC set to PCNR Analysis MCM, stratified by SMA type: SMA type I | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Comparative efficacy vs. BSC: Source for BSC set to Naïve - HINE | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Risdiplam transition probabilities informed by bootstrapped multi-state model 5 | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Using the 66-month plateau with possibility of deterioration for all treatment | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Use different plateaus for different treatments (66 months for risdiplam, 60 months for nusinersen, and 36 months for OA) with the possibility of deterioration, improvement, or staying at the current health state | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **HCRU scenarios** | | | | | | |
| using the cost from HST24 with adding the one-off costs from Modified Delphi panel HCRU results | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Alignment with TA588 source for HCRU and PV health state costs from Roche HCRU study | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Alignment with TA588 source for HCRU and PV health state costs is equal to 'Not sitting' health state | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Alignment with TA588 source for HCRU and PV health state costs: 175% increase from the “Not Sitting” health state | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Including the NHSE additional treatment costs proportion (applied to discounted drug costs)-VAT | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Increasing the one-off health care costs by 20% in 'Not sitting', 'Permanent ventilation', and 'Siting' health states | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Including the disease impact costs | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **Utility values scenarios** | | | | | | |
| Including the Utility decrements due to disease impacts and treatment-related events. (respiratory support, severe scoliosis, and bulbar dysfunction)- source from PNCR survival (time- and treatment dependent) | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Excluding the Carers' utilities | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Excluding the severity modifier | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Excluding both carers' utility and severity modifier | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Excluding caregiver utilities for SMA patients who are in standing and walking health states | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| using the 2.2 carer for 'Not sitting', 'Sitting with support' and 'Sitting without support' health states and 1.5 carer for 'Standing' and 'Walking' | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| using the 3 carers for 'Not sitting', 'Sitting with support' and 'Sitting without support' health states and 1.5 carer for 'Standing' and 'Walking' | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Source for patient utility values: EQ-5D-3L, UK (NICE ERG TA588) | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Source for patient utility values: EQ-5D-Y, UK (Lloyd et al, 2019) | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Source for caregiver utility values: Roche utility survey | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Source for caregiver utility values: UK Burden of Illness Study | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **Other Scenarios** | | | | | | |
| Changing time horizon to 30 years | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Discount rate for both costs and benefits is lowered to 1.5% | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5% | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Changing baseline characteristics to REACH UK patient population | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |

* + - 1. Changes made to Roche’s type 2/3 SMA model

The EAG selected the Roche type 2/3 model for the basis of our independent economic assessment for this population, by making changing to address the key issues identified (*see* Table 91).

Table 91: EAG base-case inputs on Roche type 2/3 SMA model

|  |  |  |  |
| --- | --- | --- | --- |
| **Input** | **Roche Value** | **EAG Value** | **Section** |
| **Utility decrements - disease impacts and treatment related events** | | | |
| Scoliosis | \*\*\*\*\*\* | 0 | 5.4.2.4.6 |
| Respiratory support | \*\*\*\*\*\* | 0 |
| Bulbar dysfunction | \*\*\*\*\*\* | 0 |
| **Severity modifier** | | | |
| QALY weight | 1.7 (Derived based on patient and carer utility values, then multiplied by the total value, including patient and carer utility) | 1.7 (Derived based on patient utility values, then multiplied by the patient utility value, then add carers utility values) | 5.4.2.2.10 |
| **Caregiver utilities** | | | |
| Not sitting | 2.2 (CS document b, pg 262)  However, economic model inputs worksheet suggests 3 caregivers (cell H206) | 2 | 5.4.2.4.6 |
| Permanent ventilation | 2 |
| Sitting | 2 |
| Standing | 1 |
| Walking | 1 |
| **Patient: Incremental benefit for risdiplam and nusinersen** | | | |
| Not sitting | 0.20 | 0 | 5.4.2.4.6 |
| Sitting with support | 0.20 | 0 |
| Sitting without support | 0.20 | 0 |
| **Caregiver: Incremental benefit for risdiplam and nusinersen** | | | |
| Not sitting | 0.05 | 0 | 5.4.2.4.6 |
| Sitting (supported) | 0.05 | 0 |
| Sitting (unsupported) | 0.05 | 0 |

* + - 1. Results (types 2/3 SMA)

In this section we report the EAG results for the types 2/3 SMA population. First, we report the EAG deterministic base-case results, then PSA results based on the cost per QALY. We then report one-way sensitivity and scenario analyses results, all using the PAS price for risdiplam.

* + - * 1. Deterministic base-case results

Results in Table 92 show that \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. Risdiplam compared to BSC resulted in an ICER of approximately \*\*\*\*\*\*\*\* per QALY.

Table 92: Deterministic base-case results for the type 2/3 SMA population (using PAS price)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER (£/QALY) without severity modifier** | **ICER with severity modifier** |
| BSC | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \* | \* | \* | \* | \* |
| Risdiplam | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Nusinersen | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality adjusted life years | | | | | | | | |

* + - * 1. PSA results

Table 93: Deterministic base-case results for the type 2/3 SMA population (using PAS price)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total QALYs** | **Incremental costs (£)** | **Incremental QALYs** | **ICER incremental (£/QALY) without severity modifier** |
| BSC | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \* | \* | \* |
| Risdiplam | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Nusinersen | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality adjusted life years | | | | | |

In Figure 36 and Figure 37, we report the results for the PSA in the form of the incremental scatterplot and CEAC. In Figure 36, it can be seen that a considerable number of iterations are in the south-west quadrant for the comparison between risdiplam and nusinersen, indicating that considering joint uncertainty in model inputs there is a possibility that risdiplam is likely to be less effective and less costly than treatment with nusinersen. From Figure 37, at a WTP of £30,000 per QALY risdiplam when compared to BSC has a \*\*\* probability of being cost-effective.



Figure 36: Incremental cost-effectiveness scatterplot for the comparisons between risdiplam, BSC and nusinersen for the type 2/3 SMA population (using PAS price for risdiplam)



Figure 37: Cost-effectiveness acceptability curve for the risdiplam compared to BSC and nusinersen at different WTP thresholds (using PAS price for risdiplam)

* + - * 1. One-way sensitivity analysis results

In Figure 38 and Figure 39 we report the results of the one-way sensitivity analyses, for the comparison between risdiplam versus nusinersen and versus BSC. These results show that the annual HSUV for a caregiver caring for a patient in a not sitting health state and the annual HSUV for a caregiver caring for a patient in a sitting without support health state, respectively were the most influential inputs in the type 2/3 model.



Figure 38: Deterministic sensitivity analysis results for the type 2/3 SMA model (PAS price for risdiplam), ICER versus nusinersen

****

Figure 39: Deterministic sensitivity analysis results for the type 2/3 SMA model (PAS price for risdiplam), ICER versus BSC

* + - * 1. Scenario analysis results

The EAG undertook scenario analyses to assess the impact of each change to the deterministic results. In Table 94 we report the scenario analyses undertaken with regards to the type 2/3 SMA population. These results in show that impact to the pairwise ICER (cost per QALY) when risdiplam is compared to BSC and nusinersen, respectively.

Table 94: Scenario analysis results for the type 2/3 SMA model (PAS price for risdiplam)

| **Scenario** | **ICER vs BSC (£)** | **% ICER change from the base case** | **ICER vs nusinersen (£)** | **% ICER change from the base case** |
| --- | --- | --- | --- | --- |
| Roche's Base case (PAS price for risdiplam) | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **Efficacy scenarios** | | | | |
| Using the transition probabilities derived from the MAIC - HFMSE score for nusinersen | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Choosing the hazard ratio (HR) of 0.90 to reflect the anticipated reduced mortality risk associated with risdiplam treatment compared to best supportive care (BSC). | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Choosing the hazard ratio (HR) of 0.60 to reflect the anticipated reduced mortality risk associated with risdiplam treatment compared to best supportive care (BSC). | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Use different plateaus for different treatments (26 months for risdiplam, 15 months for nusinersen) with the possibility of deterioration, improvement, or staying | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Comparative efficacy vs. BSC: set to Natural history study | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Risdiplam efficacy informed by non-imputed 5-year SUNFISH (excl. Asia) | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Risdiplam and nusinersen efficacy post follow-up set to the extrapolations as seen in the trial period | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Weibull used for Type 2 OS extrapolation | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **HCRU scenarios** | | | | |
| Using the cost from HST24 with adding the one-off costs from Modified Delphi panel HCRU results | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Excluding the Disease impact costs | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Using the costs from TA588 Base Case (RWE Study) | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **Utility values scenarios** | | | | |
| Excluding the Carers' utilities | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Excluding the severity modifier | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Excluding both carers' utility and severity modifier | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Excluding caregiver utilities for SMA patients who are in standing and walking health states | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Including the Utility decrements due to disease impacts and treatment related events | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| using the 2.2 carer for 'Not sitting', 'Sitting with support' and 'Sitting without support' health states and 1.5 carer for 'Standing' and 'Walking' | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| using the 3 carers for 'Not sitting', 'Sitting with support' and 'Sitting without support' health states and 1.5 carer for 'Standing' and 'Walking' | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Source for patient utility values: TA588 ERG clinical advisors | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Source for patient utility values: EQ-5D-3L values from SUNFISH | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Source for caregiver utility values: Roche utility survey | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Source for caregiver utility values: UK Burden of Illness Study | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| **Other Scenarios** | | | | |
| Discount rate for both costs and benefits is lowered to 1.5% | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5% | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |
| Changing baseline characteristics to REACH UK patient population | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* | \*\*\*\*\*\*\*\* |

* + 1. Model validation and face validity check

The EAG undertook model validation checks by independently running the models based on suggested changes and cross-checking results. Additionally, we completed several checks by changing key model inputs using extreme values, confirming that the observed results are what we expected. In some instances, we noted that the PSA results overestimated benefits associated with treatment and their corresponding expected total costs were underestimated, which resulted in inconsistencies with the deterministic results. On further inspection, it appeared to the EAG that this discrepancy between the PSA and deterministic results might have been a result of the distribution around the transition probabilities. Excluding these from the PSA resulted in central estimates that were more in line with the deterministic results.

Other checks undertaken by the EAG included, comparing the survival between the different types of SMA. We found that people with presymptomatic and type 2/3 SMA had a better prognosis than people with type 1 SMA.

* + 1. Discussion
       1. Summary of key results

The EAG assessed the cost-effectiveness of risdiplam compared to nusinersen, onasemnogene abeparvovec and BSC in people with presymptomatic SMA, type 1 SMA and types 2/3 SMA.

* + - * 1. Presymptomatic population

The EAG base-case for the presymptomatic population involved making changes to Roche’s base-case model by increasing the time horizon to 90 years, overall survival for health states (permanent ventilation, not sitting and sitting) based on survival curves obtained from HST24. Full details of changes made can be found in Section 6.1.1.1 \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

* + - * 1. Type 1 SMA

The EAG base-case for the type 1 SMA population excluded utility decrements for disease impacts and treatment related events, patient incremental benefit for risdiplam and caregiver incremental benefit for risdiplam and nusinersen, number of caregivers, and severity modifier based on patient utility values. Full details of the changes made can be found in Section 6.1.1.3. \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.

* + - * 1. Type 2/3 SMA

The EAG base-case for the type 2/3 SMA population excluded utility decrements for disease impacts and treatment related events, patient incremental benefit for risdiplam and caregiver incremental benefit for risdiplam and nusinersen, number of caregivers, and severity modifier based on patient utility values. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.

* + - 1. Generalisability of results

A key limitation of the Roche’s presymptomatic model is the inability to undertake an economic analysis with sub-populations of presymptomatic people with two or more than two copies of the SMN2 gene, separately. While we acknowledge the importance of these subpopulations, the applicability of our presymptomatic results for these populations will be compromised and therefore, will have to be interpreted with caution to assist with decision making.

Second, in the presymptomatic SMA model, we assumed equal efficacy among different treatments due to limitations related to sample size and heterogeneity among trial populations. This assumption may lead to discrepancies between our assessment results and real-world outcomes, necessitating careful consideration and caution in interpretation.

Third, the presymptomatic model includes assumptions about treatment duration and plateau time due to the lack of long-term efficacy data for different treatments. These assumptions may affect the generalisability of the results, especially regarding long-term outcomes. Similar assumptions are made in other models for type 1 and type 2/3 SMA patients concerning plateau time and the possibility of deterioration. These assumptions can limit the generalisability of the results, particularly over the long term.

Fourth, in our assessment, due to data limitations and availability, the transition probabilities used in the economic model were derived from treatment effectiveness measured by a single score or scale. Using different scores to obtain a unified set of transition probabilities was not feasible in this assessment, which posed challenges for some types of SMA. This issue is critical for type 2/3 and presymptomatic patients with more than two SMN2 copies. For patients in severe health states, some scales perform better than others, while different scales may be more appropriate for those in standing and walking health states. However, we had to use the same scale consistently.

* + - 1. Strengths and limitations of analysis

The companies’ models were logical and depicted the clinical pathways for treating people with SMA. The EAG did not identify any major errors in the models. The companies provided details about the conduct of their economic analyses, which in general adhered to the NICE reference case.

A key weakness of the economic analysis is the unavailability of the IPD for the EAG to conduct their own ITC. With both companies using different methods and adjusting for a different set of covariates, the EAG would have liked to assess the consistency, replicability, and appropriateness of the methodologies used. Analyses with both sets of IPD will allow for a more detailed comparison and evaluation of the different statistical approaches and assumptions used, as well as being able to test both sets of IPD under the same conditions, performing harmonised comparisons using consistent methodologies to ensure that the comparative analysis between nusinersen and risdiplam is fair and unbiased. Additionally, this might have been enhanced by the availability of IPD from Novartis for onasemnogene aberparvovec.

1. DISCUSSION
   1. Statement of principle findings

The aim of this MTA was to assess the clinical and cost-effectiveness of nusinersen and risdiplam for treating SMA. Clinical evidence presented by both Biogen and Roche is largely in line with the evidence presented in the EAG systematic literature review.

Evidence is presented on clinical effectiveness amongst presymptomatic, type 1, 2, 3 SMA patients. The main source of evidence for clinical effectiveness of nusinersen comes from the following trials: NURTURE (presymptomatic SMA), ENDEAR (type 1), EMBRACE (type 1 and 2), CHERISH (type 2 and 3) and SHINE (type 1,2 and 3 following on from ENDEAR and CHERISH trials).

The main source of evidence for clinical effectiveness of risdiplam is from RAINBOWFISH (Presymptomatic), FIREFISH (type 1), JEWELFISH (type 1,2,3), SUNFISH (type 2 and 3).

Overall, evidence for treatment of SMA patients with nusinersen has shown significant motor function improvements, better growth outcomes, high survival rates, and minimal adverse events. Early initiation of treatment optimizes effectiveness, though some data gaps, high discontinuation rates, and baseline differences pose challenges in fully assessing its long-term benefits.

Overall, evidence for the clinical effectiveness of risdiplam led to significant motor function improvements and high survival rates in presymptomatic and type 1 SMA patients, with steady growth and minimal adverse events. In type 2 and 3 SMA patients, motor and upper-limb function improved or stabilized, with increased independence in daily activities. Preliminary data from the JEWELFISH study showed motor function stability over 24 months, though statistical significance was not achieved. The REACH registries indicated motor function improvements or stabilization, but small sample sizes and limited data on bulbar function, scoliosis, and contractures raise concerns.

We assessed the cost-effectiveness of these DMTs in treating people with presymptomatic, type 1, 2/3 SMA using separate economic models. In the presymptomatic population, which assumed equal efficacy between nusinersen, risdiplam and onasemnogene abeparvovec and extending the model time horizon, the results of the fully incremental analysis showed that treatment with onasemnogene abeparvovec \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. In scenario analyses, we found that the base-case ICER changed markedly by changing the source of BSC data to PNCR, health state treatment costs, excluding caregivers’ utility values or excluding the severity weighting.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.. In scenario analyses, we found that the base-case ICER changed markedly in response to using the HR for nusinersen, onasemnogene abeparvovec, and BSC in survival analysis, excluding caregivers’ utility values, excluding the severity weighting or health state treatment costs.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. The model input for the \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* health state was found to be a key driver of cost-effectiveness. In the EAG exploratory analyses in the type 2/3 population, the ICERs were found to be robust to changes made to the comparative efficacy versus BSC, if set to Natural history study, health state treatment costs, excluding caregivers’ disutility or excluding severity weighing.

The findings of the EAG independent assessment align with the systematic literature review, indicating that \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. For example, HST24 suggests onasemnogene abeparvovec is cost-effective for presymptomatic SMA in infants under 12 months, and ICER (2019) reported an ICER of $243,000 per QALY for onasemnogene abeparvovec . \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. This is \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* CADTH (2021),179 which reported an ICER of $1,203,100 for risdiplam versus BSC for types 2/3. Broekhoff et al.205 and TA75515 also \*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. Drug costs, utility values, and treatment durations are key economic drivers across studies, underscoring the high costs and limited cost-effectiveness of SMA treatments.

* 1. Strengths and limitations of the assessment

We undertook a comprehensive and systematic search of the relevant clinical literature. Rigorous systematic reviewing methods were followed or adhered to for study inclusion, critical appraisal and evidence synthesis.

Limitations associated with the study design of clinical effectiveness evidence of nusineren and risdiplam is acknowledged by the EAG. Evidence is largely based on single-arm studies, leading to uncertainty around the robustness of this evidence due to lack of a comparator. Additionally, the EAG SLR suggested that bias in included studies is likely due to the lack of blinding in non-randomised studies.

There is limited evidence for the effectiveness of treatment for presymptomatic SMA patients, and on the effectiveness of type 0 and type 4 SMA, but this is to be expected due to the dearth of research into these types. No included studies examined type 4 alone, but the EAG note that type 4 was included in nine studies looking at multiple SMA types within the EAG SLR. Our assessment of nusinersen, risdiplam and onasemnogene abeparvovec faced challenges due to limited access to IPD from either company included in this appraisal as well as access to IPD from the comparator company, which restricted further analysis of treatment efficacy and the feasibility of ITC.

We undertook a comprehensive systematic review of the economic evaluations for SMA treatments, as well as an appraisal and assessment of the presymptomatic, type 1 and type 2/3 SMA. It included a thorough examination of TA588, TA755, HST24, and HST15. Our assessment benefited from effective communication with clinical advisers and valuable feedback from patient representatives.

* 1. Uncertainties

Uncertainties about the clinical effectiveness of nusinersen and risdiplam arise largely from the study design. As discussed in Section 7.2, there are uncertainties around the lack of RCTs, and the reliance on single-arm studies.

The EAG notes some uncertainties around imbalances of baseline characteristics in trials providing evidence for clinical effectiveness. Imbalances particularly in baseline ventilation and motor milestones cause some uncertainty.

Uncertainties regarding the cost-effectiveness analysis of various treatments mainly stem from parameters such as the price of these DMTs, if caregiver utilities should be captured in these appraisals and if so, which caregiver utility values should be used in the model, and moreover, the number of caregivers by health state. Additionally, the costs associated with permanent ventilation and non-sitting health states, and inclusion of the severity modifier. Further uncertainty relates to the transition probabilities derived from different scores, particularly for nusinersen in type 2/3 SMA, contribute to these uncertainties. The EAG also highlights ongoing uncertainties about the long-term effectiveness, especially concerning presymptomatic SMA.

* 1. Patient and Public Involvement

In our assessment, we have made efforts to consider the perspectives of SMA patients and their caregivers to ensure a more thorough analysis of the various treatment options available for SMA patients. To achieve this, we have posed several queries to a representative of SMA patients regarding the number of caregivers required in different health states, resource utilisation, and patient utilities, with a particular focus on the patients' experiences between two primary health states: sitting and standing. The EAG met with a patient representative to discuss these questions in detail. Overall, the input from patient representatives has been instrumental in helping us select the most appropriate set of costs and utilities for the base-case analysis. Additionally, some of the information provided offered insights for scenario analysis, especially concerning the number of caregivers and one-off costs.

1. CONCLUSIONS

Clinical effectiveness evidence of nusinersen and risdiplam has shown significant motor function improvements, better or stabilised growth outcomes, high survival rates, and minimal adverse events in SMA patients. The EAG generally agrees with the company’s assessment of these treatments’ impact on motor function and survival. However, discrepancies exist in the reported adverse events and other functional outcomes for risdiplam, which had mixed results and could not be fully interpreted.

Limitations of study designs, variations in baseline characteristics and small sample sizes within the main sources of clinical evidence has raised some uncertainty in findings (particularly evidence regarding presymptomatic SMA).

In our evaluation, we considered the ITC approaches for each population and acknowledged the strengths of Biogen’s ITC approach for the presymptomatic and type 1 populations, as well as Roche’s approach for the type 2/3 population. However, the selection of Roche’s economic models for our base-case analyses was driven by several factors beyond ITC preferences. Roche’s models offer a broader comparative scope, including risdiplam, nusinersen, onasemnogene abeparvovec, and best supportive care, which was essential for a comprehensive assessment. Moreover, the flexibility and adaptability of Roche’s model make it a robust tool to undertake sensitivity and scenario analyses. This flexibility is crucial given the limitations in our ability to conduct ITCs due to the lack of IPD. Thus, while the ITC approach is a significant component, our choice reflects a holistic view of the model's overall robustness and adaptability in economic evaluation.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*.

* 1. Suggested research priorities
* Large RCTs with a long-term follow-up, which include presymptomatic SMA participants with 2 SMN2 copies and more than 2 SMN2 copies.
* Collect real-world evidence on the resource use and costs associated with treating people with SMA to validate the modified Delphi study undertaken by Roche.
* Future studies to capture the number of caregivers required and their utility values by health state. Also, capturing the effect of the caregiver on SMA patients’ utility values.
* If possible, using appropriate scales for assessing motor function improvement based on the age and the health state of patients, especially type 3 SMA, to derive transition probabilities to be used in economic models.

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237. Zorginstituut Nederland. *Pakketadvies sluisgeneesmiddel onasemnogene abeparvovec (Zolgensma®) bij de behandeling van spinale musculaire atrofie (SMA)*. 2021. URL: <https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/05/06/pakketadvies-sluisgeneesmiddel-onasemnogene-abeparvovec-zolgensma> (Accessed 02 July 2024).

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1. APPENDICES

Appendix 1: Literature search strategies

Appendix Table 1: Overview of literature searches undertaken

|  |  |  |
| --- | --- | --- |
| *Clinical effectiveness review: bibliographic databases and trials registers* | | |
| **Database** | **Date searched** | **Number of records** |
| Embase (Ovid) | 29/01/24 | 1,837 |
| MEDLINE All (Ovid) | 29/01/24 | 700 |
| Science Citation Index and Conference Proceedings (Web of Science) | 29/01/24 | 1,072 |
| Cochrane CENTRAL and Cochrane Database of Systematic Reviews (Cochrane Library, Wiley) | 29/01/24 | 124, of which:   * 122 CENTRAL * 2 CDSR |
| International HTA database (INAHTA) | 29/01/24 | 4 |
| ClinicalTrials.gov | 29/01/24 | 73 |
| WHO International Clinical Trials Registry Platform | 29/01/24 | 85 |
| **Total number of records retrieved: 3,895**  **Duplicates removed (EndNote): 1,684**  **Final number for screening: 2,211** | | |
| *Clinical effectiveness review: other sources* | | |
| Websites (NICE, SMC, CADTH, ICER, FDA, MHRA, EMA) | 25/01/24 | 31 documents + 1 web page (ongoing project) from 21 projects/reviews |
| **Total number sought for retrieval: 32**  **Reports not retrieved/available: 0**  **Final number for screening: 32** | | |
| *Cost effectiveness review: bibliographic databases* | | |
| **Database** | **Date searched** | **Number of records** |
| Embase (Ovid) | 30/01/24 | 514 |
| MEDLINE All (Ovid) | 30/01/24 | 116 |
| Science Citation Index and Conference Proceedings (Web of Science) | 31/01/24 | 195 |
| International HTA database (INAHTA) | 30/01/24 | 33 |
| CEA Registry (Tufts Medical Center) | 30/01/24 | 13 |
| EconPapers (RePec) | 30/01/24 | 9 |
| **Total number of records retrieved: 880**  **Duplicates removed (EndNote): 220**  **Final number for screening: 660** | | |
| *Cost effectiveness review: other sources* | | |

|  |  |  |
| --- | --- | --- |
| Internet (Google) | 31/01/24 | 9 |
| Websites (NICE, SMC, CADTH, ICER, FDA, MHRA, EMA) | 25/01/24 | 31 documents + 1 web page (ongoing project) from 21 projects/reviews |
| **Total number sought for retrieval: 41**  **Reports not retrieved/available: 0**  **Final number for screening: 41** | | |

**Search strategies: clinical effectiveness review**

Embase (Ovid)

Date searched: 29/01/24

Embase <1974 to 2024 January 26>

1 exp hereditary spinal muscular atrophy/ or spinal muscular atrophy/ 14233

2 (spinal muscul\* atroph\* or SMA).kf,tw. 50728

3 (Werdnig adj Hoffman\*).kf,tw. 423

4 (Kugelberg adj Welander\*).kf,tw. 216

5 1 or 2 or 3 or 4 [disease terms] 55864

6 Nusinersen/ 1913

7 (Nusinersen or spinraza\* or isis smn\* or isis 396443).kf,tn,tw. 1699

8 6 or 7 2087

9 Risdiplam/ 566

10 (Risdiplam or evrysdi\* or RG 7916 or RG7916).kf,tn,tw. 484

11 9 or 10 630

12 5 and 8 1879

13 5 and 11 576

14 limit 12 to dc=20171001-20241231 1814

15 limit 13 to dc=20200101-20241231 504

16 (exp animal/ or exp animal experiment/) not (exp human/ or exp human experiment/ or conference abstract.pt.) 5077905

17 editorial.pt. 794403

18 14 or 15 1980

19 18 not (16 or 17) 1908

20 limit 19 to english language 1837

Lines 1-4 are adapted from the search strategy used in: Wadman RI, van der Pol WL, Bosboom WMJ, Asselman FL, van den Berg LH, Iannaccone ST, et al. Drug treatment for spinal muscular atrophy types II and III. Cochrane Database of Systematic Reviews 2020;2020(1):CD006282. <https://dx.doi.org/10.1002/14651858.CD006282.pub5>

The Embase search strategy was peer reviewed by Naila Dracup, Information Specialist, Warwick Medical School before translation to the other databases and registers, which was undertaken by Rachel Court, Senior Information Specialist, Warwick Medical School.

MEDLINE (Ovid)

Date searched: 29/01/24

Ovid MEDLINE(R) ALL <1946 to January 26, 2024>

1 exp Muscular Atrophy, Spinal/ 6593

2 (spinal muscul\* atroph\* or SMA).mp. 33123

3 (Werdnig adj Hoffman\*).mp. 399

4 (Kugelberg adj Welander\*).mp. 210

5 1 or 2 or 3 or 4 [disease terms] 34967

6 (Nusinersen or spinraza\* or isis smn\* or isis 396443).mp. 772

7 (Risdiplam or evrysdi\* or RG 7916 or RG7916).mp. 163

8 5 and 6 731

9 5 and 7 149

10 (201710\* or 201711\* or 201712\* or 2018\* or 2019\* or 2020\* or 2021\* or 2022\* or 2023\* or 2024\*).dt,ez,da,cb. 9960713

11 8 and 10 712

12 limit 8 to yr="2017 -Current" 723

13 11 or 12 724

14 (2020\* or 2021\* or 2022\* or 2023\* or 2024\*).dt,ez,da,cb. 7036354

15 9 and 14 141

16 limit 9 to yr="2020 -Current" 141

17 15 or 16 141

18 (exp Animals/ or exp Animal Experimentation/) not (Humans/ or exp Human Experimentation/) 5191116

19 Editorial.pt. 680347

20 13 or 17 769

21 20 not (18 or 19) 731

22 limit 21 to english language 700

Science Citation Index and Conference Proceedings (Web of Science)

Date searched: 29/01/24

Database: Web of Science Core Collection

Editions searched/Entitlements: WOS.SCI: 1970 to 2024, WOS.ISTP: 1990 to 2024

|  |  |  |
| --- | --- | --- |
|  | Search Query | Results |
| #1 | TS=(("spinal muscul\*" NEAR/0 atroph\*) OR SMA) | 49238 |
| #2 | TS=(Werdnig NEAR/0 Hoffman\*) | 413 |
| #3 | TS=(Kugelberg NEAR/0 Welander\*) | 113 |
| #4 | #1 OR #2 OR #3 | 49409 |
| #5 | TS=(Nusinersen OR spinraza\* OR "isis smn\*" OR "isis 396443") | 1231 |
| #6 | #4 AND #5  #Timespan: 2017-10-01 to 2024-12-31 (Index date) | 1061 |
| #7 | TS=(Risdiplam OR evrysdi\* OR "RG 7916" OR RG7916) | 257 |
| #8 | #4 AND #7  Timespan: 2020-01-01 to 2024-12-31 (Index date) | 208 |
| #9 | #6 OR #8 | 1163 |
| #10 | #9 and Editorial Material (Exclude – Document Types) | 1102 |
| #11 | (#10) AND (LA==("ENGLISH")) | 1072 |

The Ovid Medline search strategy was translated for use in Web of Science with the aid of the Polyglot Search Translator: Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. J Med Libr Assoc 2020;108(2):195-207. <http://dx.doi.org/10.5195/jmla.2020.834>

Cochrane CENTRAL and Cochrane Database of Systematic Reviews (Cochrane Library, Wiley)

Date searched: 29/01/24

ID Search Hits

#1 [mh "Muscular Atrophy, Spinal"] 128

#2 ((spinal NEXT muscul\* NEXT atroph\*) OR SMA):ti,ab,kw 1180

#3 (Werdnig NEXT Hoffman\*):ti,ab,kw 23

#4 (Kugelberg NEXT Welander\*):ti,ab,kw 45

#5 #1 OR #2 OR #3 OR #4 1212

#6 ((Nusinersen OR spinraza\* OR ("isis" NEXT smn\*) OR "isis 396443")):ti,ab,kw 86

#7 (Risdiplam OR evrysdi\* OR "RG 7916" OR RG7916):ti,ab,kw 63

#8 #5 AND #6 86

#9 #5 AND #7 63

#10 #5 AND #6 with Cochrane Library publication date Between Oct 2017 and Dec 2024 84

#11 #5 AND #7 with Cochrane Library publication date Between Jan 2020 and Dec 2024 50

#12 #5 AND #6 with Publication Year from 2017 to 2024, in Trials 73

#13 #5 AND #7 with Publication Year from 2020 to 2024, in Trials 47

#14 #10 OR #12 85

#15 #11 OR #13 50

#16 #14 OR #15 in Cochrane Reviews, Trials 124

The Ovid Medline search strategy was translated for use in the Cochrane Library with the aid of the Polyglot Search Translator: Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. J Med Libr Assoc 2020;108(2):195-207. <http://dx.doi.org/10.5195/jmla.2020.834>

International HTA database (INAHTA) <https://database.inahta.org/>

Date searched: 29/01/24

(("Muscular Atrophy, Spinal"[mhe]) OR ("spinal muscular atrophy" OR "spinal muscular atrophies" OR SMA OR "Werdnig Hoffman" OR "Kugelberg Welander"))

Year: 2017 to 2024

Language: English 4 results

ClinicalTrials.gov (classic website) <https://classic.clinicaltrials.gov/ct2/home>

Date searched: 29/01/24

search box on home page:

Other terms: Nusinersen OR spinraza OR Risdiplam OR evrysdi 73 studies found

WHO International Clinical Trials Registry Platform <https://trialsearch.who.int/Default.aspx>

Date searched: 29/01/24

search box on home page:

Nusinersen OR spinraza OR Risdiplam OR evrysdi 85 trials found

Websites

Date searched: 25/01/24

**National Institute for Health and Care Excellence (NICE)** <https://www.nice.org.uk/guidance/published?sp=on>

*Search for published guidance*

*Filter: Type: Guidance*

Filter by title or keyword:

Spinal muscular atrophy 4 results

* <https://www.nice.org.uk/guidance/ta755> 6 documents downloaded
* <https://www.nice.org.uk/guidance/hst15> 1 document downloaded
* <https://www.nice.org.uk/guidance/hst24> 1 document downloaded
* <https://www.nice.org.uk/guidance/ta588> 2 documents downloaded

SMA 0 results

Nusinersen 1 result (already identified above)

Risdiplam 1 result (already identified above)

Onasemnogene 2 results (already identified above)

Total: 4 technology assessments identified; 10 potentially relevant documents downloaded

**Scottish Medicines Consortium (SMC)** <https://www.scottishmedicines.org.uk/>

*Search box on homepage*

spinal muscular atrophy 6 results, of which 3 relevant

* [https://www.scottishmedicines.org.uk/medicines-advice/Nusinersen-spinraza-fullsubmission-131818/](https://www.scottishmedicines.org.uk/medicines-advice/nusinersen-spinraza-fullsubmission-131818/)
* [https://www.scottishmedicines.org.uk/medicines-advice/Risdiplam-evrysdi-full-smc2401/](https://www.scottishmedicines.org.uk/medicines-advice/risdiplam-evrysdi-full-smc2401/)
* [https://www.scottishmedicines.org.uk/medicines-advice/Onasemnogene -abeparvovec-zolgensma-full-smc2311/](https://www.scottishmedicines.org.uk/medicines-advice/onasemnogene-abeparvovec-zolgensma-full-smc2311/)

Nusinersen 2 results (already identified above)

Risdiplam 2 results (already identified above)

Onasemnogene 2 results (already identified above)

Total: 3 technology assessments identified; 3 potentially relevant documents downloaded

**CADTH: Canada’s Drug and Health Technology Agency** <https://www.cadth.ca/search>

*All searches limited to ‘Reports’*

Spinal muscular atrophy 23 results, of which 8 projects potentially relevant:

* Nusinersen, reimbursement review 2022 [https://www.cadth.ca/Nusinersen-1](https://www.cadth.ca/nusinersen-1) (combined clinical and pharmacoeconomic review)
* Health Technology Assessment Recommendations and Managed Entry Agreements Related to Optimizing the Treatment for Pediatric Spinal Muscular Atrophy. *In progress but effective finish date was January 2023 so keep an eye out* <https://www.cadth.ca/health-technology-assessment-recommendations-and-managed-entry-agreements-related-optimizing>
* Risdiplam, reimbursement review 2021 [https://www.cadth.ca/Risdiplam](https://www.cadth.ca/risdiplam) (combined clinical and pharmacoeconomic review)
* Onasemnogene abeparvovec, Reimbursement review 2021 [https://www.cadth.ca/Onasemnogene -abeparvovec](https://www.cadth.ca/onasemnogene-abeparvovec)
  + clinical report
  + pharmacoeconomic report
* Nusinersen for Adolescents and Adults with Spinal Muscular Atrophy: A Review of Clinical Effectiveness. Rapid review 2020. [https://cadth.ca/Nusinersen-adolescents-and-adults-spinal-muscular-atrophy-review-clinical-effectiveness](https://cadth.ca/nusinersen-adolescents-and-adults-spinal-muscular-atrophy-review-clinical-effectiveness)
* Nusinersen, reimbursement review 2018. [https://www.cadth.ca/Nusinersen](https://www.cadth.ca/nusinersen)
  + clinical report
  + pharmacoeconomic report
* Nusinersen for Adults with Spinal Muscular Atrophy: Clinical Effectiveness. Rapid response report; reference list. 2020. [https://www.cadth.ca/Nusinersen-adults-spinal-muscular-atrophy-clinical-effectiveness](https://www.cadth.ca/nusinersen-adults-spinal-muscular-atrophy-clinical-effectiveness)
* Nusinersen, reimbursement review 2019. [https://www.cadth.ca/Nusinersen-0](https://www.cadth.ca/nusinersen-0)
  + clinical report
  + pharmacoeconomic report

SMA 17 results, of which 0 relevant and not already identified above

Nusinersen 10 results (all already identified above)

Risdiplam 3 results (already identified above)

Onasemnogene 6 results (already identified above)

Total: 8 projects identified; 10 potentially relevant reports downloaded, 1 ongoing project web page bookmarked

**Institute for Clinical and Economic Review (ICER)** <https://icer.org/explore-our-research/assessments/>

*search by keyword; no filters applied*

spinal muscular atrophy 1 result

* An assessment of Onasemnogene Abeparvovec and Nusinersen for Spinal Muscular Atrophy (SMA). 2019 <https://icer.org/assessment/spinal-muscular-atrophy-2019/> (evidence report includes clinical and cost effectiveness)

SMA 10 results, of which 0 relevant and not already identified above

Nusinersen 1 result (already identified above)

Risdiplam 0 results

Onasemnogene 1 result (already identified above)

Total: 1 technology assessment identified; 1 report downloaded

**Drugs@FDA , U.S. Food & Drug Administration** <https://www.accessdata.fda.gov/scripts/cder/daf/>

Nusinersen 1 review found, approval date 2016: <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000TOC.cfm>

(separate medical, pharmacology, statistical, etc review documents but no pharmacoeconomic / cost effectiveness data). Medical review downloaded.

Risdiplam 1 review found, approval date 2020: <https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213535Orig1s000TOC.cfm> (separate clincial, statistical, etc review documents but no pharmacoeconomic / cost effectiveness data). Clinical review downloaded.

Onasemnogene 0 results

zolgensma 0 results

Total: 2 drug reviews; 2 documents downloaded

**MHRA products, Medicines & Healthcare products Regulatory Agency** <https://products.mhra.gov.uk/>

Nusinersen 5 results (SPCs for Nusinersen, Risdiplam & Onasemnogene ; 2 x PARs for Risdiplam (that appear to be identical)

Risdiplam 5 results, as above.

Total: 1 drug review; 1 document downloaded (Risdiplam PAR)

**European Medicines Agency (EMA)** <https://www.ema.europa.eu/en/homepage>

*search box on homepage*

Nusinersen 3 results, of which 1 relevant *downloaded 2 EPAR reports*

Risdiplam 3 results, of which 1 relevant *downloaded 2 EPAR reports*

Total: 2 drug reviews; 4 documents downloaded

**Total:**

**21 technology assessments, reviews or other projects identified**

**31 documents downloaded**

**1 webpage bookmarked (ongoing project)**

**Search strategies: cost effectiveness review**

Embase (Ovid)

Date searched: 30/01/24

Embase <1974 to 2024 January 29>

1 exp hereditary spinal muscular atrophy/ or spinal muscular atrophy/ 14240

2 (spinal muscul\* atroph\* or SMA).kf,tw. 50753

3 (Werdnig adj Hoffman\*).kf,tw. 423

4 (Kugelberg adj Welander\*).kf,tw. 216

5 1 or 2 or 3 or 4 [disease terms] 55889

6 Nusinersen/ 1915

7 (Nusinersen or spinraza\* or isis smn\* or isis 396443).kf,tn,tw. 1701

8 Risdiplam/ 567

9 (Risdiplam or evrysdi\* or RG 7916 or RG7916).kf,tn,tw. 485

10 Onasemnogene abeparvovec/ 928

11 (Onasemnogene or zolgensma\* or AVXS-101).kf,tn,tw. 850

12 6 or 7 or 8 or 9 or 10 or 11 2860

13 Economics/ 245379

14 Cost/ 63913

15 exp Health Economics/ 1055902

16 Budget/ 34254

17 budget\*.ti,ab,kw. 48761

18 (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. 322778

19 (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 553765

20 (cost\* adj2 (effective\* or utilit\* or benefit\* or minimi\* or analy\* or outcome or outcomes)).ab,kw. 295295

21 (value adj2 (money or monetary)).ti,ab,kw. 4226

22 Statistical Model/ 176325

23 economic model\*.ab,kw. 6445

24 Probability/ 151208

25 markov.ti,ab,kw. 37781

26 monte carlo method/ 52474

27 monte carlo.ti,ab,kw. 63410

28 Decision Theory/ 1861

29 Decision Tree/ 23267

30 (decision\* adj2 (tree\* or analy\* or model\*)).ti,ab,kw. 54152

31 or/13-30 [Economic Evaluations & Models - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/15] 2053618

32 socioeconomics/ 164905

33 exp Quality of Life/ 676846

34 quality of life.ti,kw. 179076

35 ((instrument or instruments) adj3 quality of life).ab. 5526

36 Quality-Adjusted Life Year/ 36559

37 quality adjusted life.ti,ab,kw. 27304

38 (qaly\* or qald\* or qale\* or qtime\* or life year or life years).ti,ab,kw. 46217

39 disability adjusted life.ti,ab,kw. 6856

40 daly\*.ti,ab,kw. 6736

41 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw. 51145

42 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw. 3036

43 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw. 1047

44 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw. 12605

45 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw. 71

46 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw. 537

47 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw. 40632

48 (hye or hyes).ti,ab,kw. 189

49 (health\* adj2 year\* adj2 equivalent\*).ti,ab,kw. 53

50 (pqol or qls).ti,ab,kw. 764

51 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw. 620

52 nottingham health profile\*.ti,ab,kw. 1688

53 nottingham health profile/ 670

54 sickness impact profile.ti,ab,kw. 1299

55 sickness impact profile/ 2405

56 health status indicator/ 3549

57 (health adj3 (utilit\* or status)).ti,ab,kw. 122035

58 (utilit\* adj3 (valu\* or measur\* or health or life or estimat\* or elicit\* or disease or score\* or weight)).ti,ab,kw. 26395

59 (preference\* adj3 (valu\* or measur\* or health or life or estimat\* or elicit\* or disease or score\* or instrument or instruments)).ti,ab,kw. 19792

60 disutilit\*.ti,ab,kw. 1323

61 rosser.ti,ab,kw. 141

62 willingness to pay.ti,ab,kw. 13671

63 standard gamble\*.ti,ab,kw. 1226

64 (time trade off or time tradeoff).ti,ab,kw. 2452

65 tto.ti,ab,kw. 2300

66 (hui or hui1 or hui2 or hui3).ti,ab,kw. 3241

67 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. 39842

68 duke health profile.ti,ab,kw. 121

69 functional status questionnaire.ti,ab,kw. 180

70 dartmouth coop functional health assessment\*.ti,ab,kw. 14

71 or/32-70 [ Economic - Health Utilities / Quality of Life - Standard - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2022: https://searchfilters.cadth.ca/link/18.] 1025897

72 5 and 12 and 31 390

73 5 and 12 and 71 235

74 72 or 73 514

The Embase search strategy was peer reviewed by Naila Dracup, Information Specialist, Warwick Medical School.

Lines 13-31 and 32-72 are search filters developed by CADTH:

Economic Evaluations & Models - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2024: <https://searchfilters.cadth.ca/link/15> . Accessed 2024-01-30, and

Economic - Health Utilities / Quality of Life - Standard - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2024: [https://searchfilters.cadth.ca/link/18 . Accessed 2024-01-30](https://searchfilters.cadth.ca/link/18%20.%20Accessed%202024-01-30).

MEDLINE (Ovid)

Date searched: 30/01/24

Ovid MEDLINE(R) ALL <1946 to January 29, 2024>

1 exp Muscular Atrophy, Spinal/ 6595

2 (spinal muscul\* atroph\* or SMA).mp. 33145

3 (Werdnig adj Hoffman\*).mp. 399

4 (Kugelberg adj Welander\*).mp. 210

5 1 or 2 or 3 or 4 [disease terms] 34989

6 (Nusinersen or spinraza\* or isis smn\* or isis 396443).mp. 773

7 (Risdiplam or evrysdi\* or RG 7916 or RG7916).mp. 164

8 (Onasemnogene or zolgensma\* or AVXS-101).mp. 269

9 6 or 7 or 8 [intervention or comparator terms] 961

10 Economics/ 27523

11 exp "Costs and Cost Analysis"/ 268504

12 Economics, Nursing/ 4013

13 Economics, Medical/ 9269

14 Economics, Pharmaceutical/ 3126

15 exp Economics, Hospital/ 25795

16 Economics, Dental/ 1921

17 exp "Fees and Charges"/ 31454

18 exp Budgets/ 14187

19 budget\*.ti,ab,kf. 37307

20 (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. 290781

21 (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 397747

22 (cost\* adj2 (effective\* or utilit\* or benefit\* or minimi\* or analy\* or outcome or outcomes)).ab,kf. 219322

23 (value adj2 (money or monetary)).ti,ab,kf. 3152

24 exp models, economic/ 16261

25 economic model\*.ab,kf. 4374

26 markov chains/ 16079

27 markov.ti,ab,kf. 30218

28 monte carlo method/ 32637

29 monte carlo.ti,ab,kf. 62092

30 exp Decision Theory/ 13553

31 (decision\* adj2 (tree\* or analy\* or model\*)).ti,ab,kf. 40912

32 or/10-31 [Economic Evaluations & Models - MEDLINE. In: CADTH Search Filters Database. Ottawa: CADTH; 2024: https://searchfilters.cadth.ca/link/16] 929288

33 "Value of Life"/ 5821

34 Quality of Life/ 281310

35 quality of life.ti,kf. 121344

36 ((instrument or instruments) adj3 quality of life).ab. 3996

37 Quality-Adjusted Life Years/ 16108

38 quality adjusted life.ti,ab,kf. 18209

39 (qaly\* or qald\* or qale\* or qtime\* or life year or life years).ti,ab,kf. 29608

40 Disability-Adjusted Life Years/ 227

41 disability adjusted life.ti,ab,kf. 5837

42 Healthy Life Expectancy/ 71

43 (daly\* or disability free life expectanc\* or haly\* or health\* life expectanc\*).ti,ab,kf. 6974

44 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf. 31483

45 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf. 2723

46 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf. 640

47 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf. 7960

48 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf. 41

49 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf. 467

50 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. 25339

51 (hye or hyes).ti,ab,kf. 77

52 (health\* adj2 year\* adj2 equivalent\*).ti,ab,kf. 48

53 (pqol or qls).ti,ab,kf. 476

54 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf. 509

55 nottingham health profile\*.ti,ab,kf. 1249

56 sickness impact profile.ti,ab,kf. 1100

57 exp health status indicators/ 344631

58 (health adj3 (utilit\* or status)).ti,ab,kf. 95721

59 (utilit\* adj3 (valu\* or measur\* or health or life or estimat\* or elicit\* or disease or score\* or weight)).ti,ab,kf. 16607

60 (preference\* adj3 (valu\* or measur\* or health or life or estimat\* or elicit\* or disease or score\* or instrument or instruments)).ti,ab,kf. 15044

61 disutilit\*.ti,ab,kf. 658

62 rosser.ti,ab,kf. 109

63 willingness to pay.ti,ab,kf. 9157

64 standard gamble\*.ti,ab,kf. 918

65 (time trade off or time tradeoff).ti,ab,kf. 1695

66 tto.ti,ab,kf. 1458

67 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2049

68 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. 23932

69 duke health profile.ti,ab,kf. 94

70 functional status questionnaire.ti,ab,kf. 133

71 dartmouth coop functional health assessment\*.ti,ab,kf. 14

72 or/33-71 [Economic - Health Utilities / Quality of Life - MEDLINE. In: CADTH Search Filters Database. Ottawa: CADTH; 2024: https://searchfilters.cadth.ca/link/19. Accessed 2024-01-26.] 775631

73 5 and 9 and 32 70

74 5 and 9 and 72 69

75 73 or 74 116

Science Citation Index and Conference Proceedings (Web of Science)

Date searched: 31/01/24

Database: Web of Science Core Collection

Editions searched/Entitlements: WOS.SCI: 1970 to 2024, WOS.ISTP: 1990 to 2024

|  |  |  |
| --- | --- | --- |
| # | Search Query | Results |
| 1 | TS=(Nusinersen OR spinraza\* OR "isis smn\*" OR "isis 396443") | 1232 |
| 2 | TS=(Risdiplam OR evrysdi\* OR "RG 7916" OR RG7916) | 257 |
| 3 | TS=(Onasemnogene or zolgensma\* or "AVXS-101") | 435 |
| 4 | #1 OR #2 OR #3 | 1653 |
| 5 | TS=(("spinal muscul\*" NEAR/0 atroph\*) OR SMA) | 49264 |
| 6 | TS=(Werdnig NEAR/0 Hoffman\*) | 413 |
| 7 | TS=(Kugelberg NEAR/0 Welander\*) | 113 |
| 8 | #5 OR #6 OR #7 | 49435 |
| 9 | TS=(cost\* or economic\* or pharmacoeconomic\* or pharmaco-economic\* or price or prices or pricing or expenditure\* or expense\* or financial or finance or finances or financed or budget\* or (value NEAR/1 (money OR monetary)) or (economic NEAR/1 model\*) or markov or monte carlo or (decision NEAR/1 (tree\* or analy\* or model\*))) | 3676686 |
| 10 | TS=("value of life" or "quality of life" or qol or hrql or hrqol or (("quality adjusted life" OR "disability adjusted life") NEAR/0 year\*) or qaly\* or qald\* or qale\* or qtime\* or "life year" or "life years" or daly\* or ("disability free life" NEAR/0 expectanc\*) or haly\* or (health\* NEAR/0 ("life expectance" or "life expectancy") or icer or "euro-qol" or euroqual or "euro qual" or utilit\* or disutilit\* or (net NEAR/0 benefit\*) or (contingent NEAR/0 valuation\*) or (preference\* NEAR/2 (valu\* or measur\* or health or life or estimat\* or elicit\* or disease or score\* or instrument or instruments)) or euroqol or "euro qol" or eq5d or eq-5d or "short-form 36" or "shortform 36" or sf-36 or sf36 or sf-6d or sf6d or sf-12 or sf12 or "health utilities index" or hui or hui1 or hui2 or hui3 or (time NEAR/0 trade\*) or tto or "standard gamble" or sg or markov or (decision NEAR/1 model\*) or (visual NEAR/0 analog\*) or "discrete choice" or ((health\* NEAR/0 year\*) NEAR/0 equivalen\*) or (health NEAR/0 stat\*) or (willing\* NEAR/1 pay) or resource\* or wellbeing or well-being)) | 2483907 |
| 11 | #4 AND #8 AND #9 | 107 |
| 12 | #4 AND #8 AND #10 | 132 |
| 13 | #11 OR #12 | 195 |

International HTA database (INAHTA) <https://database.inahta.org/>

Date searched: 30/01/24

(("Muscular Atrophy, Spinal"[mhe]) OR ("spinal muscular atrophy" OR "spinal muscular atrophies" OR SMA OR "Werdnig Hoffman" OR "Kugelberg Welander"))

33 results

CEA Registry (Tufts Medical Center) <https://cear.tuftsmedicalcenter.org/>

Date searched: 30/01/24

Advanced search screen, Methods:

Keyword is spinal muscular atrophy

OR Keyword is SMA 14 results (1 duplicate)

Keyword is Nusinersen

OR Keyword is spinraza

OR Keyword is Risdiplam

OR Keyword is evrysdi

OR Keyword is Onasemnogene

OR Keyword is zolgensma 8 results (all already identified above)

Total unique results: 13

EconPapers (RePEc) <https://econpapers.repec.org/scripts/search.pf>

Date searched: 30/01/24

Advanced search screen; Free text search box

Nusinersen OR spinraza OR Risdiplam OR evrysdi OR Onasemnogene OR zolgensma 9 results

Internet (Google) <https://www.google.co.uk/>

Date searched: 31/01/24

*Records were retrieved (added to EndNote library) only if potentially relevant to the review, and not already found via the database/other searches*

economic evaluation Nusinersen OR Risdiplam OR Onasemnogene OR spinraza OR evrysdi OR zolgensma browsed first 50 results; 8 records retrieved.

cost effectiveness Nusinersen OR Risdiplam OR Onasemnogene OR spinraza OR evrysdi OR zolgensma browsed first 50 results; 1 record retrieved.

health technology assessment Nusinersen OR Risdiplam OR Onasemnogene OR spinraza OR evrysdi OR zolgensma browsed first 50 results; 0 records retrieved.

Total: 9 records retrieved.

Websites

see Websites above

Appendix 2: Data extraction sheet

Here we report an example of a completed data extraction sheet (*see* Appendix Table 2). Furter completed sheets are available on request.

**Date: 04/03/2024**

**Study ID:**

**Name of first reviewer: MY**

**Name of second reviewer: PA**

Appendix Table 2: Completed data extraction sheet of an economic analysis

|  |  |
| --- | --- |
| Study details | |
| Study title | Pharmacoeconomic Review Report(Resubmission): Nusinersen (Spinraza): (Biogen Canada Inc): Indication: Treatment of patients with 5q SMA |
| First author | Canadian Agency for Drugs and Technologies in Health (CADTH) |
| Co-authors | - |
| Source of publication  Journal yy;vol(issue):pp | Version: Final (With Redactions)  Publication Date: April 2019  Report Length: 35 Pages |
| Publication link | <https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/sr0576-spinraza-resubmission-pharmacoeconomic-report.pdf> |
| Language | English |
| Publication type | HTA Report |
| Inclusion criteria/study eligibility/PICOS | |
| Population | Patients with SMA (type 1, 2 and 3) |
| Intervention(s) | Nusinersen (Spinraza) |
| Comparator(s) | standard of care (real-world care) |
| Outcome(s) | Life-years (LYs), and quality-adjusted life-years (QALYs) |
| Study design | Economic Evaluation (cost-utility analyses) |
| Methods | |
| Target population and subgroups | Patients with 5q SMA — stratified by SMA type — type I, II, and III |
| Setting and location | Canada |
| Approach to engagement with patients and others affected by the study | It is not clear |
| Study perspective | Canadian public health care system |
| Comparators | Standard of care (or real-world care, which includes supportive symptomatic treatment of respiratory, nutritional, and orthopaedic function decline) for patients with 5q SMA. |
| Time horizon | Time horizon:   * SMA type 1: 25 years * SMA type 2: 50 years * SMA type 3: 80 years   Cycle length:   * SMA type 1: patients could transition between health states at 2, 6, 10, 13, and 14 months. Subsequent cycles were every four months, which conformed to the timing of dosages of Nusinersen. * SMA type 2: For the first 15 months of the model, the cycle length was three months conforming to the timing of clinical assessment in the CHERISH study. Subsequent cycles were every four months. * SMA type 3: 3 months (for the first 27 months, subsequent cycles every 4 months) |
| Discount rate | 1.5% costs and benefits per annum |
| Outcome(s) | Life-years (LYs), and quality-adjusted life-years (QALYs) |
| Measurement of effectiveness | Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores  Hammersmith Functional Motor Scale – Expanded (HFMSE) scores |
| Measurement and valuation of preference-based outcomes | Patient: Types 1 and 3 SMA: unpublished utility value analyses by five experts in SMA  Type 2 SMA: QoL data from CHERISH mapped to EQ-5D  For long-term survival, data were used that were derived from a survival analysis of observational data from Zerres and Rudnik-Schoneborn. |
| Methods for identifying resource use | According to Klug et al. study  Focus groups with input from clinicians, health-economists and patient representatives |
| Resource use and costs | According to Klug et al. study  direct medical COI (Outpatient medical costs, Inpatient medical costs, Rehabilitation costs (in-/outpatient), Drug treatment costs, Costs for use of rehabilitation services, Costs for artificial nutrition, Costs for medical aids, Costs for respiratory management)  direct non-medical COI (Costs for housing, Costs for personal assistance for school and work attendance, Travel expenses, Informal care costs, Costs for legal advice, Costs for constructional modifications to house, Costs for constructional modifications to automobile, Other expenditures) |
| Data source of resource use | Health costs appear to be derived from a study of SMA costs in Germany |
| Currency, price date and conversion | All cost reported in Canadian dollars- Costs (currency, year): CAD, 2017 |
| Analytic approach and model type (if applicable) | Model:   * Three distinct Markov models were developed for three SMA types: type I, type II, and type III   States:   * In the SMA type I model, health states included baseline clinical status; whether clinical status improved, worsened, or had no improvement; milestones consistent with SMA type II (e.g., sits without support, stands with assistance, walks with assistance, and stand/walks unaided); and death. * In the SMA type II model, health states included baseline clinical status; whether clinical status worsened, had no improvement, had mild improvement, or had moderate improvement; whether the patient could stand or walk with assistance and milestones consistent with SMA type III (e.g., stand unaided and walks unaided); and death. * In the SMA type III model, health states included non-ambulatory, ambulatory, and death.   Other points:   * expected values of costs, QALYs, and Lys were obtained through probabilistic analysis.   Transition probabilities:   * For SMA type I, the transition probabilities for Nusinersen and real-world care (RWC) were obtained from the ENDEAR trial. * For SMA type II, the transition probabilities for Nusinersen and RWC were obtained from the CHERISH trial. * For SMA type III, Transition probabilities during the study period (first 24 months) between non-ambulatory and ambulatory for patients receiving Nusinersen were obtained from the CS2 and CS12 studies. [CONFIDENTIAL manufacturer's submission] |
| Assumptions | For treatment discontinuation, it was assumed that individuals would stop treatment after scoliosis surgery or after entering the worsening state.  It was assumed that patients receiving Nusinersen would have a reduced risk of mortality up to 50 months beyond the trial follow-up period. In addition, it was assumed that all patients who reached milestones consistent with SMA type II would experience mortality rates associated with SMA type II.  Long-term mortality was assumed to be the same as for the general population. |
| Results | |
| Study parameters | Disease progression during study period, Disease progression after study period, Mortality during study period, Mortality post study period, Utility values, Cost data |
| Total costs and outcomes  (Manufacturer’s Base Case) | |  |  |  | | --- | --- | --- | | Total QALYs | Total LYs | Total costs | | SMA type 1:  o Nusinersen: 3.919  o RWC: -0.881  SMA type 2:  o Nusinersen: 23.278  o RWC: 19.602  SMA type 3:  o Nusinersen: 12.053  o RWC: 10.490 | SMA type 1:  o Nusinersen: 8.373  o RWC: 3.583  SMA type 2:  o Nusinersen: 28.527  o RWC: 26.348  SMA type 3:  o Nusinersen: 44.155  o RWC: 44.155 | SMA type 1:  o Nusinersen: $3,534,854  o RWC: $339,683  SMA type 2:  o Nusinersen: $8,336.271  o RWC: $708,620  SMA type 3:  o Nusinersen: $5,554,707  o RWC: $1,091,307 | |
| Characterising uncertainty | * Probabilistic sensitivity analysis * Some scenarios about Alternative Utility Values, Alternative Progression Assumptions, Alternative Survival Assumptions and Additional Price Analyses. |
| Discussion | |
| Study findings  (Manufacturer’s Base Case) | ICER/QALY:   * SMA type 1: Nusinersen vs RWC: $665,570 * SMA type 2: Nusinersen vs RWC: $2,075,435 * SMA type 3: Nusinersen vs RWC: $2,855,818   The manufacturer reported that the probability that Nusinersen was cost-effective assuming a willingness-to-pay threshold of $300,000 per QALY was 0% for all SMA types. The manufacturer reported a number of scenario analyses; however, for all SMA types, the incremental cost per QALY gained for Nusinersen exceeded $500,000 in all analyses. |
| Limitations | 1. Utility values were derived from unpublished studies provided for Biogen Idec, which the CADTH Common Drug Review (CDR) did not consider had appropriate methodology for the estimation of utility. 2. The manufacturer made inappropriate assumptions relating to disease progression for patients with SMA types I, II, and III receiving Nusinersen. 3. The manufacturer made inappropriate assumptions relating to mortality within SMA types I and II. 4. Certain health states within the model were inappropriate as they were reflective relative rather than absolute health states. 5. The manufacturer’s submission did not allow further stratification by disease status within SMA type, which would have been highly informative. 6. The CDR clinical expert has raised a number of concerns with the clinical trial data for Nusinersen, which undermines the ability to facilitate the economic evaluation. This particularly relates to the lack of appropriate clinical data for assessing the effectiveness of Nusinersen in SMA type III. 7. The manufacturer did not provide new economic information as part of their resubmission and did not further address the previously cited limitations. |
| Generalisability | 1. Limited Population Representation in Clinical Trials: The lack of representation of the entire spectrum of patients with SMA in the clinical trials, especially for SMA type III, raises concerns about the generalizability of the study findings to real-world clinical practice. The subset of patients included in the trials may not fully reflect the diverse population that would receive Nusinersen. 2. Inadequate Comparative Clinical Trial Data: The absence of comprehensive comparative clinical trial data for SMA type III limits the ability to generalize the effectiveness of Nusinersen across all subtypes of 5q SMA. The relevance and applicability of the study conclusions may be compromised due to this lack of specific data for certain patient groups. 3. Potential Age-Related Treatment Effectiveness Variability: Subgroup analysis indicating varying effectiveness of Nusinersen based on age categories suggests the importance of considering age-related factors in evaluating treatment outcomes. Generalizing the cost-effectiveness of Nusinersen without stratifying by age may overlook significant variations in treatment response within different age groups. |
| Other | |
| Source of funding | Canada’s federal, provincial, and territorial governments |
| Conflicts of interest | The majority of information came from the company submission. There are some possibilities regarding conflicts of interest. |
| Comments | 1. Need for Absolute Health States: The economic model's reliance on relative states linked to patients' baseline status creates ambiguity in assessing actual functional improvements. Shifting towards absolute states representing current functioning levels could enhance the model's accuracy and relevance. 2. Questionable Utility Value Sources: The utilization of unpublished analyses and mapping exercises to derive utility values for different SMA types raises concerns about data transparency and validity. Clear and specific sources are crucial to ensuring the reliability of the economic evaluation. 3. Biased Assumptions in Disease Progression and Mortality: Biased assumptions favoring Nusinersen in disease progression post-clinical studies and mortality based on reached milestones undermine the objectivity of the economic model. Unfounded biases can skew cost-effectiveness outcomes and should be rectified. 4. Inadequate Representation of Population in Clinical Trials: Critically evaluating the lack of representation of the entire SMA population in clinical trials, particularly for SMA type III, is essential. Diverse patient demographics must be considered to obtain a comprehensive understanding of Nusinersen's effectiveness in real-world scenarios. 5. Importance of Stratified Analysis by Age and Disease Status: Conducting further stratified analyses based on age and disease status, as indicated by subgroup analysis findings, can provide valuable insights into Nusinersen's effectiveness across different patient groups. Enhancing stratification can lead to more informative and targeted cost-effectiveness assessments. |
| Authors conclusion | |
| In alignment with the manufacturer’s results of its pharmacoeconomic submission, CDR found that Nusinersen was not a cost-effective treatment for patients with 5q SMA types I, II, or III.  This finding has not been affected by the clinical information provided within the manufacturer’s resubmission. | |
| Reviewer’s conclusion | |
| The limitations in the economic model, including relative states and questionable utility value sources, along with biases in disease progression assumptions, cast doubt on the cost-effectiveness evaluation of Nusinersen for 5q SMA. Concerns raised by clinical experts about trial data discrepancies highlight the need for further stratified analysis and data refinement. Despite reanalysis aligning with non-cost-effectiveness, substantial uncertainties remain, particularly in assessing SMA type III. Given these challenges, Nusinersen's cost-effectiveness across SMA types I, II, and III is dubious. Continued research and data accuracy improvements are vital for reliable pharmacoeconomic assessments in 5q SMA treatment. | |

Appendix 3: Methodological quality assessment

Appendix Table 3: Critical appraisal of the economic models using an adapted Philips checklist (Philips et al., 2004)

| **Philips criteria** | | **NICE-Nusinersen TA588** | | **NICE-Risdiplam TA755** | **NICE-Onasemnogene HST15-type1** | | **NICE-Onasemnogene HST24-pre-symptomatic** | | **ICER Spinraza and zolgensma 2019** | **CADTH Nusinersen-2019** | **CADTH Risdiplam**  **2021** | **CADTH Onasemnogene -2021** | **Meijer et al.,**  **2023** | **Broekhoff et al., 2021** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Structure | | | | | | | | | | | | | | |
| 1 | Is there a clear statement of the decision problem? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 2 | Is the objective of the model specified and consistent with the stated decision problem? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 3 | Is the primary decision maker specified? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Unclear | Unclear |
| 4 | Is the perspective of the model stated clearly? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 5 | Are the model inputs consistent with the stated perspective? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 6 | Has the scope of the model been stated and justified? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Unclear | Unclear |
| 7 | Are the outcomes of the model consistent with the perspective, scope and overall objective of the model? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 8 | Is the structure of the model consistent with a coherent theory of the health condition under evaluation? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | No |
| 9 | Are the sources of the data used to develop the structure of the model specified? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 10 | Are the causal relationships described by the model structure justified appropriately? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Yes | Yes | Yes | Yes |
| 11 | Are the structural assumptions transparent and justified? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 12 | Are the structural assumptions reasonable given the overall objective, perspective and scope of the model? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 13 | Is there a clear definition of the options under evaluation? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 14 | Have all feasible and practical options been evaluated? | No | | No | No | | No | | No | No | No | No | No | No |
| 15 | Is there justification for the exclusion of feasible options? | Unclear | | Unclear | Unclear | | Unclear | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 16 | Is the chosen model type appropriate given the decision problem and specified casual relationships within the model? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | No |
| 17 | Is the time horizon of the model sufficient to reflect all important differences between the options? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 18 | Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Unclear | Yes | No | Yes |
| 19 | Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | No |
| 20 | Is the cycle length defined and justified in terms of the natural history of disease? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| DATA | |  |  | | |  | |  | |  |  |  |  | |
| 21 | Are the data identification methods transparent and appropriate given the objectives of the model? | Yes | | Unclear | Yes | | Yes | | Unclear | Unclear | Unclear | Unclear | Yes | Unclear |
| 22 | Where choices have been made between data sources are these justified appropriately? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Yes | Yes | Yes | Yes |
| 23 | Has particular attention been paid to identifying data for the important parameters of the model? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Yes | Yes | Yes | Yes |
| 24 | Has the quality of the data been assessed appropriately? | Yes | | Yes | Yes | | Yes | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 25 | Where expert opinion has been used are the methods described and justified? | Yes | | Yes | Unclear | | Unclear | | Yes | Yes | Unclear | Unclear | No | No |
| 26 | Is the data modelling methodology based on justifiable statistical and epidemiological techniques? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Yes | Yes | No | Unclear |
| 27 | Is the choice of baseline data described and justified? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 28 | Are transition probabilities calculated appropriately? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Yes | Yes | No | Yes |
| 29 | Has a half-cycle correction been applied to both costs and outcomes? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Unclear | Unclear | Yes | Unclear |
| 30 | If not, has the omission been justified? | - | | - | - | | - | | - | Unclear | Unclear | Unclear | - | Unclear |
| 31 | If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Unclear | Unclear | Unclear |
| 32 | Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Yes | Yes | Yes | Yes |
| 33 | Have alternative extrapolation assumptions been explored through sensitivity analysis? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 34 | Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 35 | Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis | No | | No | No | | No | | No | No | No | No | No | Yes |
| 36 | Are the costs incorporated into the model justified? | Yes | | Unclear | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 37 | Has the source for all costs been described? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 38 | Have discount rates been described and justified given the target decision maker? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 39 | Are the utilities incorporated into the model appropriate? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Yes | Yes | Yes | Yes |
| 40 | Is the source of utility weights referenced? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 41 | Are the methods of derivation for the utility weights justified? | Yes | | Yes | Yes | | Yes | | Unclear | Yes | Yes | Yes | Yes | Yes |
| 42 | Have all data incorporated into the model been described and referenced in sufficient detail? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Unclear | Unclear | Unclear | Unclear |
| 43 | Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?) | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Unclear | Unclear |
| 44 | Is the process of data incorporation transparent? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 45 | If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified? | Yes | | Unclear | Yes | | Yes | | Yes | Unclear | Unclear | Unclear | Yes | Yes |
| 46 | If data have been incorporated as distributions, is it clear that second order uncertainty is reflected? | Yes | | Unclear | Yes | | Yes | | Yes | Unclear | Unclear | Unclear | Yes | Yes |
| 47 | Have the four principal types of uncertainty been addressed? | Yes | | Yes | Yes | | Yes | | Yes | No | No | No | No | No |
| 48 | If not, has the omission of particular forms of uncertainty been justified? | - | | - | - | | - | | - | No | No | No | No | No |
| 49 | Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 50 | Is there evidence that structural uncertainties have been addressed via sensitivity analysis? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 51 | Has heterogeneity been dealt with by running the model separately for different sub-groups? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | No |
| 52 | Are the methods of assessment of parameter uncertainty appropriate? | Yes | | Yes | Yes | | Yes | | Yes | Unclear | Yes | Yes | Yes | Yes |
| 53 | If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified? | Yes | | Yes | Yes | | Yes | | Yes | No | No | No | Yes | Yes |
| 54 | Is there evidence that the mathematical logic of the model has been tested thoroughly before use? | Unclear | | Unclear | Unclear | | Unclear | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 55 | Are any counterintuitive results from the model explained and justified? | Yes | | Yes | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 56 | If the model has been calibrated against independent data, have any differences been explained and justified? | Unclear | | Unclear | Unclear | | - | | - | - | - | - | - | - |
| 57 | Have the results been compared with those of previous models and any differences in results explained? | Yes | | Yes | Yes | | Yes | | Unclear | No | No | No | Yes | Yes |
| N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear | | | | | | | | | | | | | | |

Appendix Table 4: Critical appraisal of the economic models using the Philips checklist (cont’d)

| **Philips criteria** | | **SMC Nusinersen- 2018** | **SMC Onasemnogene -2021** | | **SMC Risdiplam-2022** | | **Connock et al., 2020** | | **Dean et al. 2021** | **Malone et al. 2019** | **Wang et al. 2022** | **Zuluaga‑Sanchez et al. 2019** | **Thokala et al. 2020** | **NCPE-2017** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Structure | | | | | | | | | | | | | | |
| 1 | Is there a clear statement of the decision problem? | Unclear | Unclear | | Unclear | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 2 | Is the objective of the model specified and consistent with the stated decision problem? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 3 | Is the primary decision maker specified? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 4 | Is the perspective of the model stated clearly? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 5 | Are the model inputs consistent with the stated perspective? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 6 | Has the scope of the model been stated and justified? | Unclear | Unclear | | Unclear | | Unclear | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 7 | Are the outcomes of the model consistent with the perspective, scope and overall objective of the model? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 8 | Is the structure of the model consistent with a coherent theory of the health condition under evaluation? | Yes | Yes | | Yes | | No | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 9 | Are the sources of the data used to develop the structure of the model specified? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 10 | Are the causal relationships described by the model structure justified appropriately? | Yes | Yes | | Yes | | Unclear | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 11 | Are the structural assumptions transparent and justified? | No | No | | No | | Unclear | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 12 | Are the structural assumptions reasonable given the overall objective, perspective and scope of the model? | No | No | | No | | Unclear | | Unclear | Yes | Yes | Yes | Yes | Unclear |
| 13 | Is there a clear definition of the options under evaluation? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 14 | Have all feasible and practical options been evaluated? | Yes | No | | No | | Yes | | Yes | Yes | No | Yes | No | Yes |
| 15 | Is there justification for the exclusion of feasible options? | - | Unclear | | Unclear | | - | | - | - | Unclear | - | Unclear | - |
| 16 | Is the chosen model type appropriate given the decision problem and specified casual relationships within the model? | Yes | Yes | | Yes | | Unclear | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 17 | Is the time horizon of the model sufficient to reflect all important differences between the options? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 18 | Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified? | Yes | Yes | | Yes | | No | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 19 | Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions? | Yes | Yes | | Yes | | No | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 20 | Is the cycle length defined and justified in terms of the natural history of disease? | Unclear | Yes | | Yes | | No | | Unclear | Yes | Yes | Yes | Yes | Yes |
| Data | |  | |  | |  | |  | |  |  |  |  | |
| 21 | Are the data identification methods transparent and appropriate given the objectives of the model? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 22 | Where choices have been made between data sources are these justified appropriately? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 23 | Has particular attention been paid to identifying data for the important parameters of the model? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 24 | Has the quality of the data been assessed appropriately? | Unclear | Unclear | | Unclear | | Unclear | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 25 | Where expert opinion has been used are the methods described and justified? | Unclear | Unclear | | Unclear | | Unclear | | - | - | - | Unclear | - | - |
| 26 | Is the data modelling methodology based on justifiable statistical and epidemiological techniques? | Unclear | Unclear | | Unclear | | Unclear | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 27 | Is the choice of baseline data described and justified? | Unclear | Unclear | | Unclear | | Yes | | Unclear | Yes | Yes | Yes | Yes | Unclear |
| 28 | Are transition probabilities calculated appropriately? | Unclear | Unclear | | Yes | | Unclear | | Unclear | Yes | Yes | Yes | Yes | Unclear |
| 29 | Has a half-cycle correction been applied to both costs and outcomes? | Unclear | Unclear | | Unclear | | Unclear | | Unclear | Unclear | Yes | Yes | Unclear | Unclear |
| 30 | If not, has the omission been justified? | - | - | | - | | - | | - | - | - | - | - | - |
| 31 | If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques? | Unclear | Unclear | | Yes | | Unclear | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 32 | Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified? | Unclear | Unclear | | Unclear | | Unclear | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 33 | Have alternative extrapolation assumptions been explored through sensitivity analysis? | Unclear | Unclear | | Unclear | | No | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 34 | Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified? | Yes | Yes | | Yes | | Unclear | | Unclear | Yes | Unclear | Yes | Unclear | Unclear |
| 35 | Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis | Unclear | Unclear | | Unclear | | Unclear | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 36 | Are the costs incorporated into the model justified? | Unclear | Yes | | Unclear | | Yes | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 37 | Has the source for all costs been described? | Unclear | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 38 | Have discount rates been described and justified given the target decision maker? | Unclear | Unclear | | Unclear | | Unclear | | Yes | Yes | Yes | Yes | Yes | Yes |
| 39 | Are the utilities incorporated into the model appropriate? | Yes | No | | No | | Yes | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 40 | Is the source of utility weights referenced? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 41 | Are the methods of derivation for the utility weights justified? | Unclear | Unclear | | Unclear | | Unclear | | Yes | Yes | Unclear | Yes | Yes | Yes |
| 42 | Have all data incorporated into the model been described and referenced in sufficient detail? | No | No | | No | | Unclear | | Unclear | Yes | Yes | Yes | Yes | Unclear |
| 43 | Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?) | No | No | | No | | Yes | | No | No | No | No | No | Unclear |
| 44 | Is the process of data incorporation transparent? | Unclear | Unclear | | Unclear | | Yes | | Unclear | Yes | Yes | Yes | Yes | Unclear |
| 45 | If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified? | Unclear | Unclear | | Unclear | | Unclear | | Unclear | Unclear | Yes | Yes | Unclear | Unclear |
| 46 | If data have been incorporated as distributions, is it clear that second order uncertainty is reflected? | Unclear | Unclear | | Unclear | | Unclear | | Unclear | Unclear | Unclear | Yes | Unclear | Unclear |
| 47 | Have the four principal types of uncertainty been addressed? | Unclear | Unclear | | Unclear | | No | | No | Yes | Yes | Yes | Yes | Unclear |
| 48 | If not, has the omission of particular forms of uncertainty been justified? | - | - | | - | | Unclear | | No | - | - | - | - | Unclear |
| 49 | Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions? | Yes | Yes | | Yes | | Yes | | Yes | Yes | Yes | Yes | Yes | Yes |
| 50 | Is there evidence that structural uncertainties have been addressed via sensitivity analysis? | Unclear | Unclear | | Unclear | | Yes | | Yes | Unclear | Unclear | Unclear | Unclear | Unclear |
| 51 | Has heterogeneity been dealt with by running the model separately for different sub-groups? | Unclear | Unclear | | Unclear | | No | | No | No | No | Yes | No | Unclear |
| 52 | Are the methods of assessment of parameter uncertainty appropriate? | Yes | Yes | | Yes | | No | | Yes | Yes | Yes | Yes | Yes | Unclear |
| 53 | If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified? | Unclear | Unclear | | Unclear | | Unclear | | No | No | Yes | Yes | Yes | Unclear |
| 54 | Is there evidence that the mathematical logic of the model has been tested thoroughly before use? | Unclear | Unclear | | Unclear | | Unclear | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 55 | Are any counterintuitive results from the model explained and justified? | No | No | | No | | Yes | | Yes | Yes | Yes | Yes | Yes | No |
| 56 | If the model has been calibrated against independent data, have any differences been explained and justified? | Unclear | Unclear | | Unclear | | Unclear | | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| 57 | Have the results been compared with those of previous models and any differences in results explained? | No | No | | No | | Yes | | Yes | Yes | Yes | Yes | Yes | No |
| N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear | | | | | | | | | | | | | | |

Appendix 4: Reporting quality assessment

In Appendix Table 5 and Appendix Table 6 we report the reporting quality of studies against best practice guidelines.199

Appendix Table 5: Critical appraisal using the CHEERS checklist (Part I)

| **CHEERS criteria** | **Study and location where item is reported (page for location refer to PDF page)** | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NICE-Nusinersen TA588** | **NICE-Risdiplam TA755** | **NICE-Onasemnogene HST15-type1** | **NICE-Onasemnogene HST24-pre-symptomatic** | **ICER Spinraza and zolgensma 2019** | **CADTH Nusinersen-2019** | **CADTH Risdiplam**  **2021** | **CADTH Onasemnogene -2021** | **Meijer**  **2023** | **Broekhoff- 2021** |
| ***Title*** | | | | | | | | | | |
| Identify the study as an economic evaluation and specify the interventions being compared | Yes | Yes | Yes | Yes | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:1 |
| ***Abstract*** | | | | | | | | | | |
| Provide a structured summary that highlights context, key methods, results, and alternative analyses. | No | No | No | No | Yes  P:8 | Yes  P:6-7 | Yes  P:168-169 | Yes  P:7-9 | Yes  P:3 | Yes  P:1 |
| ***Introduction*** | | | | | | | | | | |
| Give the context for the study, the study question, and its practical  relevance for decision making in policy or practice. | No | Yes | Yes | Yes | Yes  P:49-61 | Yes  P:8-10 | Yes  P:25-30, 44-47 | No | Yes  P:8-13 | Yes  P:1-2 |
| ***Methods*** | | | | | | | | | | |
| Health economic analysis plan: Indicate whether a health economic analysis plan was developed and where available. | No | No | No | No | No | No | No | No | No | No |
| Study population: Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics). | Yes | Yes | Yes | Yes | Yes  P:101 | Yes  P:12 | Yes  P:168 | Yes  P:11 | Yes  P:14 | Yes  P:4 |
| Setting and Location: Provide relevant contextual information that may inﬂuence ﬁndings. | Yes | Yes | Yes | Yes | Yes  P:57 | Yes  P:2 | Yes  P:2 | Yes  P:2 | Yes  P:14 | Yes  P:4 |
| Comparators: Describe the interventions or strategies being compared and why chosen. | Yes | Yes | Yes | Yes | Yes  P:55 | Yes  P:9 | Yes  P:168 | Yes  P:7 | Yes  P:14 | Yes  P:4 |
| Perspective: State the perspective(s) adopted by the study and why chosen. | Yes | Yes | Yes | Yes | Yes  P:27 | Yes  P:12 | Yes  P:172 | Yes  P:7 | Yes  P:14 | Yes  P:4 |
| Time Horizon: State the time horizon for the study and why appropriate. | Yes | Yes | Yes | Yes | Yes  P:29 | Yes  P:12 | Yes  P:168 | Yes  P:7 | Yes  P:15 | Yes  P:4 |
| Discount Rate: Report the discount rate(s) and reason chosen. | Yes | Yes | Yes | Yes | Yes  P:27 | Yes  P:12 | Yes  P:172 | Yes  P:11 | Yes  P:15 | Yes  P:4 |
| Selection of outcomes: Describe what outcomes were used as the measure(s) of beneﬁt(s) and harm(s). | Yes | Yes | Yes | Yes | Yes  P:56 | Yes  P:12 | Yes  P:168 | Yes  P:7 | Yes  P:15 | Yes  P:4-5 |
| Measurement of outcomes: Describe how outcomes used to capture beneﬁt(s) and harm(s) were measured. | Yes | Yes | Yes | Yes | Yes  P:11 | Yes  P:15-16 | Yes  P:174-175 | Yes  P:13 | Yes  P:22-23 | No |
| Valuation of outcomes: Describe the population and methods used to measure and value outcomes. | Yes | Yes | Yes | Yes | Yes  P: 11 | Yes  P:15-16 | Yes  P:174 | Yes  P:13 | Yes  P:22-23 | Yes  P:4-5 |
| Measurement and valuation of resources and costs: Describe how costs were valued. | Yes | Yes | Yes | Yes | Yes  P: 111-115 | Yes  P:13 | Yes  P:174-175 | Yes  P:13 | Yes  P:23-25 | Yes  P:5 |
| Currency, price date, and conversion: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion. | Yes | No | Yes | Yes | Yes  P:11-115 | Yes  P:14 | No | No | Yes  P:23 | Yes  P:5 |
| Rationale and description of model: If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed. | yes | yes | Yes | Yes | Yes  P:99-101 | No | Yes  P:171 | Yes  P:11 | Yes  P:15-16 | No |
| Analytics and assumptions: Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used. | Yes | Yes | Yes | Yes | Yes  P:102-103 | No | Yes  P:171-174 | Yes  P:20 | Yes  P:36-37 | Yes  P:5 |
| Characterizing heterogeneity: Describe any methods used for estimating how the results of the study vary for subgroups. | Yes | Yes | Yes | Yes | Yes  P:106-109 | Yes  30-31 | Yes  P:171 | Yes  P:11 | Yes  P:12-13 | No |
| Characterizing distributional effects: Describe how impacts are distributed across different individuals or adjustments made to reﬂect priority populations. | Yes | Yes | Yes | Yes | Yes  P:106-109 | Yes  P:14 | Yes  P:171 | No | No | No |
| Characterizing uncertainty: Describe methods to characterise any sources of uncertainty in the analysis. | Yes | Yes | Yes | Yes | Yes  P:115 | No | Yes  P:176-181 | Yes  P:14 | Yes  P:24-26 | Yes  P:5-6 |
| Approach to engagement with patients and others affected by the study: Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study. | Yes | Yes | Yes | Yes | Yes  P:31 | No | Yes  P:30-34 | Yes  P:10 | No | No |
| ***Results*** | | | | | | | | | | |
| Study parameters: Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions. | Yes | Yes | Yes | Yes | Yes  P: 117-136 | No | No | Yes  P:38 | Yes  P:25 | Yes  P:7 |
| Summary of main results: Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure. | Yes | No | Yes | No | Yes  P:141-143 | Yes  P:14, 20 | Yes  P:182 | Yes  P:7, 24 | Yes  P:29 | Yes  P:5 |
| Effect of uncertainty: Describe how uncertainty about analytic judgments, inputs, or  projections affect ﬁndings. Report the effect of choice of discount rate and time horizon, if applicable. | Yes | Yes | Yes | Yes | Yes  P: 117-136 | No | Yes  P:176-181 | Yes  P:25-26 | Yes  P:29-32 | Yes  P:6-7 |
| Effect of engagement with patients and others affected by the study: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or ﬁndings of the study | Yes | Yes | Yes | Yes | No | No | No | No | No | No |
| ***Discussion*** | | | | | | | | | | |
| Study ﬁndings, limitations, generalizability, and current knowledge: Report key ﬁndings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice. | Yes | Yes | Yes | Yes | Yes  P:139-141 | Yes  P: 6, 15-19 | Yes  P: 169 | Yes  P:15-19, 26 | Yes  P:35-36 | Yes  P:9-10 |
| ***Other*** | | | | | | | | | | |
| Source of Funding: Describe how the study was funded and any role of the funder in the identiﬁcation, design, conduct, and reporting of the analysis | No | No | No | No | Yes  P:3 | Yes  P: 2 | Yes  P: 2 | Yes  P: 2 | No | Yes  P:10 |
| Conflicts of Interest: Report authors conﬂicts of interest according to journal or International Committee of Medical Journal Editors requirements. | Yes | Yes | Yes | Yes | Yes  P:270-272 | Yes  P: 2 | Yes  P: 2 | Yes  P: 2 | No | Yes  P:10 |

Appendix Table 6: Critical appraisal using the CHEERS checklist (Part II)

| **CHEERS criteria** | **Study and location where item is reported (page for location refer to PDF page)** | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SMC Nusinersen- 2018** | **SMC Onasemnogene -2021** | **SMC Risdiplam-2022** | **Connock et al., 2020** | **Dean et al. 2021** | **Malone et al. 2019** | **Wang et al. 2022** | **Zuluaga‑Sanchez et al. 2019** | **Thokala et al. 2020** | **NCPE-2017** |
| ***Title*** | | | | | | | | | | |
| Identify the study as an economic evaluation and specify the interventions being compared | No | No | No | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:1 |
| ***Abstract*** | | | | | | | | | | |
| Provide a structured summary that highlights context, key methods, results, and alternative analyses. | No | No | No | Yes  P:2 | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:1 | No |
| ***Introduction*** | | | | | | | | | | |
| Give the context for the study, the study question, and its practical  relevance for decision making in policy or practice. | Yes  P:3-9 | Yes  P:2-8 | Yes  P:2-9 | Yes  P:2-3 | Yes  P:1-3 | Yes  P:1-2 | Yes  P:1-3 | Yes  P:1-3 | Yes  P:1-2 | No |
| ***Methods*** | | | | | | | | | | |
| Health economic analysis plan: Indicate whether a health economic analysis plan was developed and where available. | No | No | No | No | No | No | No | No | No | No |
| Study population: Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics). | Yes  P:11 | Yes  P:9 | Yes  P:10 | Yes  P:3 | Yes  P:1 | Yes  P:2 | Yes  P:2 | Yes  P:5 | Yes  P:2 | No |
| Setting and Location: Provide relevant contextual information that may inﬂuence ﬁndings. | Yes  P:1 | Yes  P:1 | Yes  P:1 | Yes  P:3 | Yes  P:1 | Yes  P:2 | Yes  P:2 | Yes  P:5 | Yes  P:2 | Yes  P:2 |
| Comparators: Describe the interventions or strategies being compared and why chosen. | Yes  P:11 | Yes  P:9 | Yes  P:10 | Yes  P:3 | Yes  P:3 | Yes  P:2 | Yes  P:3 | Yes  P:5 | Yes  P:2 | Yes  P:6 |
| Perspective: State the perspective(s) adopted by the study and why chosen. | Yes  P:11 | Yes  P:10 | No | Yes  P:3 | Yes  P:1 | Yes  P:2 | Yes  P:3 | Yes  P:5 | Yes  P:2 | **Yes**  **P:5** |
| Time Horizon: State the time horizon for the study and why appropriate. | Yes  P:11 | Yes  P:10 | Yes  P:10 | Yes  P:3 | Yes  P:7 | Yes  P:2 | Yes  P:3 | Yes  P:5 | Yes  P:2 | **Yes**  **P:5** |
| Discount Rate: Report the discount rate(s) and reason chosen. | No | No | No | No | Yes  P:7 | Yes  P:3 | Yes  P:3 | Yes  P:5 | Yes  P:2 | **Yes**  **P:6** |
| Selection of outcomes: Describe what outcomes were used as the measure(s) of beneﬁt(s) and harm(s). | Yes  P:11 | Yes  P:11 | Yes  P:13 | Yes  P:3 | Yes  P:1 | Yes  P:2-3 | Yes  P:6 | Yes  P:5 | Yes  P:2 | **Yes**  **P:1** |
| Measurement of outcomes: Describe how outcomes used to capture beneﬁt(s) and harm(s) were measured. | Yes  P:12 | Yes  P:10 | Yes  P:11 | Yes  P:3 | Yes  P:3 | Yes  P:6-7 | Yes  P:3 | Yes  P:13-14 | Yes  P:5-6 | **Yes**  **P:5** |
| Valuation of outcomes: Describe the population and methods used to measure and value outcomes. | Yes  P:12 | Yes  P:10-11 | Yes  P:11 | Yes  P:3 | Yes  P:3-4 | Yes  P:6-7 | Yes  P:3 | Yes  P:13-14 | Yes  P:5-6 | **Yes**  **P:5** |
| Measurement and valuation of resources and costs: Describe how costs were valued. | No | Yes  P:11 | Yes  P:11 | Yes  P:3 | Yes  P:3-4 | Yes  P:6 | Yes  P:3-4 | Yes  P:12-13 | Yes  P:6 | **No** |
| Currency, price date, and conversion: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion. | Yes  P:16 | Yes  P:16 | Yes  P:16 | Yes  P:3 | Yes  P:5 | No | Yes  P:4 | Yes  P:12 | Yes  P:6 | **No** |
| Rationale and description of model: If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed. | No | No | No | No | No | Yes  P:2-4 | No | No | No | No |
| Analytics and assumptions: Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used. | No | No | No | No | No | Yes  P:3 | Yes  P:3 | Yes  P:5 | Yes  P:2 | No |
| Characterizing heterogeneity: Describe any methods used for estimating how the results of the study vary for subgroups. | Yes | No | No | No | No | No | No | No | Yes  P:7 | No |
| Characterizing distributional effects: Describe how impacts are distributed across different individuals or adjustments made to reﬂect priority populations. | No | No | No | No | No | No | No | No | No | No |
| Characterizing uncertainty: Describe methods to characterise any sources of uncertainty in the analysis. | No | No | No | No | No | Yes  P:7 | Yes  P:5-6 | Yes  P:14 | Yes  P:7 | Yes  P:6 |
| Approach to engagement with patients and others affected by the study: Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study. | Yes  P:10 | Yes  P:8-9 | Yes  P:9-10 | No | No | No | No | No | No | No |
| ***Results*** | | | | | | | | | | |
| Study parameters: Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions. | No | No | No | No | No | No | Yes  P:4 | Yes  P:4-10 | No | No |
| Summary of main results: Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure. | Yes  P:12-13 | Yes  P:11 | Yes  P:12 | Yes  P:2 | Yes  P:7 | Yes  P:9 | Yes  P:6 | Yes  P:15 | Yes  P:7 | Yes  P:6 |
| Effect of uncertainty: Describe how uncertainty about analytic judgments, inputs, or  projections affect ﬁndings. Report the effect of choice of discount rate and time horizon, if applicable. | Yes  P:12-13 | Yes  P:12 | Yes  P:12 | Yes  P:4 | Yes  P:8 | Yes  P:10-11 | Yes  P:6-7 | Yes  P:14-17 | Yes  P:8-9 | Yes  P:6 |
| Effect of engagement with patients and others affected by the study: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or ﬁndings of the study | No | No | No | No | No | No | No | No | No | No |
| ***Discussion*** | | | | | | | | | | |
| Study ﬁndings, limitations, generalizability, and current knowledge: Report key ﬁndings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice. | Yes  P:12-13 | Yes  P:13 | Yes  P:12-13 | Yes  P:4-5 | Yes  P:9-11 | Yes  P:11-12 | Yes  P:6, 8-9 | Yes  P:15-18 | Yes  P:9-10 | No |
| ***Other*** | | | | | | | | | | |
| Source of Funding: Describe how the study was funded and any role of the funder in the identiﬁcation, design, conduct, and reporting of the analysis | No | No | No | Yes  P:5 | Yes  P:11 | Yes  P:13 | Yes  P:9 | Yes  P:18 | Yes  P:11 | No |
| Conflicts of Interest: Report authors conﬂicts of interest according to journal or International Committee of Medical Journal Editors requirements. | No | No | No | Yes  P:5 | Yes  P:11 | Yes  P:12-13 | Yes  P:9 | Yes  P:18 | Yes  P:11 | No |

Appendix 5: Characteristics of included cost-effectiveness analysis studies

Appendix Table 7: Characteristics of the economic analyses included in the systematic review

| **Study, year** | **Target population and subgroup(s)** | **Intervention(s), Comparator(s)**  **Outcome(s), Study perspective,**  **Location & Setting** | **Model structure and health states** | **Time horizon, cycle length and discount rate** | **Source of utility values used** | **Sources of Health state costs, currency and conversion** |
| --- | --- | --- | --- | --- | --- | --- |
| NICE-Nusinersen TA588, 201917 | **Target population:** Paediatric patients with 5q SMA (Types 1,2 and 3)  **Subgroups:**  1- infantile Infantile-onset (type 1)  • ≤12 weeks disease duration  • >12 weeks disease duration  2- Later-onset ((types II and III) SMA.)  • <25 months disease duration  • ≥25 months disease duration | **Intervention:** Nusinersen  **Comparator:** BSC  **Outcomes:** LYG, QALYs  **Study perspective:** NHS and PSS of UK  **Location (Setting):** UK (relevant settings (e.g. inpatient, outpatient/clinic)) | **Two Markov models:**  • Infantile onset (type 1)  • Later-onset (type 2/3)  **Health states:**  Type 1: Eight health states based on HINE-2 including: No milestone achieved, mild milestones, moderate milestones, sits without support, stands with assistance, walks with assistance, stands/walks unaided and dead.  Type 2/3: Seven states based on HMFSE and WHO including: Sits without support but does not roll, sits and rolls independently, sits and crawls with hands and knees, stands/walks with assistance, stands unaided, walks unaided and dead. | **Time horizon:**   * Type 1: 60 years * Type 2/3: 80 years   **Cycle length:**   * Type 1: new cycle after 2, 6, 10, 13 and 14 months and every 4 months thereafter * Type 2/3: new cycle after 3, 6, 9, 12 and 15 months and every 4 months thereafter   **Discount rate:**   * 3.5% per year for both costs and benefits | Patients:  Patients (type 1 and type 2/3) had utility values determined by manufacturer experts.  Caregiver:  Caregiver disutilities were based on Spanish caregiver data and UK population EQ-5D scores. It was assumed that type 1 patients had 3 caregivers, while type 2/3 patients had 2 caregivers, with 3 for those unable to sit. | **Sources of costs:**  • Real-World Evidence (RWE) survey to validate the direct expenses linked to SMA within the UK healthcare system (2017 RWE survey involving pediatric neurological consultants from nine UK centers).  • Analyzed data from the Hospital Episode Statistics (HES) in the UK  **Currency and conversion:** UK pound (£) |
| NICE-Risdiplam TA755, 202115 | **Target population:**  • Paediatric patients with 5q SMA (Types 1,2 and 3)  **Subgroups:**  • Type 2/3: included both ambulant and non-ambulant patients aged 2–25 years at the time of enrolment with type 2 and 3 SMA.  • Type 1: included infants with symptomatic type 1 SMA aged 1–7 months at the time of enrolment. | **Intervention:** Risdiplam  **Comparator:** BSC  **Outcomes:** LYG, QALYs  **Study perspective:** NHS and PSS of UK  **Location (Setting):** UK (relevant settings (e.g. inpatient, outpatient/clinic)) | Two Markov models:  • Type 2/3 model  • Type 1 model  **Health states:**  Type 2/3: Six states based on MFM-32 and HMFSE (‘not sitting’, ‘sitting with support’, ‘sitting unsupported’, ‘standing (with or without support)’ and ‘walking (with or without support)’ and ‘death’. (Plateau at 26 months)  Type 1: Six states based on HINE-2 (‘not sitting’, ‘sitting’, ‘standing’, ‘walking’) and ‘permanent ventilation’ and ‘death’. (Plateau at 66 months) | **Time horizon:**  • Type 1and Type 2/3: 90 years  **Cycle length:**  • Type 1and Type 2/3: one month.  **Discount rate:**  • 3.5% per year for both costs and benefits | Patients:  Utility values same as NICE-nusinersen TA588. Caregiver (type 1): Adjusted disutility assumption with no QALY losses post 10.23 years. Bereavement considered after 30.58 years. Assumed 2.2 caregivers per patient.    Caregiver (type 2/3): Disutility linked to patient health states, caregiver utility returns to normal after patient death. Disutility of -0.04 applied for 20 years (scenario 1) and 90 years (scenario 2) after patient's death. | **Sources of costs:**  • Health state resource use for NICE-nusinersen TA588.  • Costs for permanent ventilation are 175% higher than non-sitting health states.  • SMA complication costs apply universally in BSC and half in risdiplam groups in severe health states.  • The costs per unit and occurrence rates for each complication were obtained from the NHS Reference Costs of 2019/20.  **Currency and conversion:** UK pound (£) |
| NICE-OA HST15-type1, 202114 | patients with 5q SMA- Infantile-onset (type 1) | **Intervention:** Onasemnogene abeparvovec  **Comparator:** BSC  **Outcomes:** LYG, QALYs  **Study perspective:** NHS and PSS of UK  **Location (Setting):** UK (relevant settings (e.g. inpatient, outpatient/clinic)) | **One Markov model**  **Health states:**  Six states: not sitting, permanent assisted ventilation, sits unassisted, walks unassisted, within a broad range of normal development and dead. | **Time horizon:** 100 years  **Cycle length:**  6-month cycles for first 3 years, 12-month cycles for remainder of model  Discount rate:  • 3.5% per year for both costs and benefits | PAV: Assumption based on the ERG interim report  Not sitting – BSC and onasemnogene abeparvovec: Thompson et al. 2017227  Sits unassisted – BSC and onasemnogene abeparvovec: Tappenden et al. 2018228  Walks unassisted and Broad range of normal development: Ara and Brazier 2010223 | **Sources of costs:**  Inpatient and outpatient costs: NHS  pharmacological therapy resources: PCA  **Currency and conversion:** pound (£)-2019 |
| NICE-OA HST24-pre-symptomatic, 2023204 | Newborn infants with genetically confirmed, pre-symptomatic SMA with two or three copies of the *SMN2* gene who were age ≤6 weeks (≤42 days) at time of treatment. | **Intervention:** Onasemnogene abeparvovec  **Comparator:** BSC  **Outcomes:** LYG, QALYs  **Study perspective:** NHS and PSS of UK  **Location (Setting):** UK (relevant settings (e.g. inpatient, outpatient/clinic)) | **Two Markov model:**  • Short-term model  • Long-term extrapolation model  **Health states:**  Short-term: Six states including: ‘Sitting and walking independently’, ‘non-sitter, no PAV’, ‘non-sitter, PAV’’ , ‘sitter’, ‘delayed walker’, ‘death’  Long-term: Seven states including six states from short term and ‘experiences later onset SMA’ | **Time horizon:**  100 years  **Cycle length:**  One month  **Discount rate:**  • 3.5% per year for both costs and benefits | PAV: Assumption based on the ERG interim report  Not sitting and Patients in the walking & experiencing later onset SMA state who lase the ability to walk: Thompson et al. 2017227  Sitting: EAG’s clinical experts in TA588  Walking and broad range of normal development: Ara and Brazier 2010223 | **Sources of costs:**  Costs sourced from NHS 2019/20, the NHS Business Services Authority prescription cost analysis 2021/22, and the literature.  **Currency and conversion:** UK pound (£) inflated to 2021 |
| ICER- Nusinersen & OA, 2019216 | SMA patients of all ages and types including:  • symptomatic patients with infantile-onset (Type I) SMA  • symptomatic patients with later-onset (Type II/III) SMA  • presymptomatic SMA patients | **Intervention:** Nusinersen and onasemnogene abeparvovec  **Comparator:** BSC  **Outcomes**: LYG, QALYs  **Study perspective:** USA health care sector  **Location (Setting):** USA (inpatient, outpatient/clinic, office, and home settings) | Three de novo Markov models in accordance with target population.  **Health states:**  • Type I and Pre-symptomatic models:  ‘Not sitting’, ‘PV’, ‘sitting’, ‘walking’, ‘death’  • Type II/III: ‘sitting’, ‘walking’, ‘death’  Absorbing states For long-term extrapolation model:  Type I : ‘PV’ and ‘death’  Type II/III: ‘death’ | **Time horizon:**  Lifetime  **Cycle length:**  One month  **Discount rate:**  3.0% for costs and benefits | PAV for both arms, Not sitting for BSC arm:Thompson et al. 2017227  Not sitting for treatment arm:Assumption  Sitting for BSC arm:Tappenden et al. 2018228  Sitting for treatment arm:Assumption  Walking for both arms:General populationutility | **Sources of costs:**  Nusinersen:  Drug:Redbook 2018;229 Magellan 2016230  Inpatient Cost:Nationwide Children’s Hospital Price Information List 2018  Onasemnogene abeparvovec Drug cost:Market analystEstimate231  Administration costs for both arms:Physician fee schedule  2018;232facility price  Redbook 2018229  **Currency and conversion**: $**US** inflated to 2017 |
| CADTH- Nusinersen, 2019209 | Patients with SMA (type 1, 2 and 3) | **Intervention:** Nusinersen  **Comparator:** RWC  **Outcomes:** LYG, QALYs  Study perspective: Canadian public health care system  **Location (Setting):** Canada | **Three Markov models:** type I, type II, and type III  **Health states:**  • Type I: ‘baseline’; ‘improved baseline’, ‘worsened baseline’, ‘no improvement’; ‘sits without support’, ‘stands with assistance’, ‘walks with assistance’, **‘**stand/walks unaided’, ‘loss of type II/III motor function’, and ‘death’.  • Type II: ‘baseline’, ‘worsened , ‘no’, ‘mild’ and ‘moderate’ improvement, ‘stand/walk with assistance’, ‘stand unaided’, ‘walks unaided’, ‘loss of ambulation with/without assistance’ and ‘death’.  • Type III: ‘baseline’, ‘non-ambulatory**’**, **‘**ambulatory**’**, and **‘**death**’**. | **Time horizon:**  • type 1: 25 years  • type 2: 50 years  • type 3: 80 years  **Cycle length:**  • type 1: At 2, 6, 10, 13, and 14 months. Subsequent cycles were every four months.  • type 2: three months (For the first 15 months). Subsequent cycles were every four months.  • type 3: three months (for the first 27 months), subsequent cycles every 4 months.  **Discount rate**: 1.5% costs and benefits per annum | Patient:  Types 1 and 3 SMA: unpublished utility value analyses by five experts in SMA  Type 2 SMA: QoL data from CHERISH mapped to EQ-5D | **Sources of costs:**  Health costs appear to be derived from a study of SMA costs in Germany **(**Klug et al.)233  **Currency and conversion**: Canadian dollars for 2017 |
| CADTH-risdiplam , 2021179 | population was divided into two subgroups evaluated separately:  • patients with SMA type I  • patients with SMA type II or SMA type III | **Intervention:** Risdiplam  **Comparator:** BSC  **Outcomes**: QALYs  **Study perspective:** Canadian publicly funded health care payer  **Location (Setting):** Canada | **Two Markov models in accordance with target population.**  **Health states:**  **• Type I:**  six states including ‘not sitting’, ‘sitting,’ ‘standing’, ‘walking,’ ‘permanent ventilation’, and ‘death’  **• Type II/III:** ‘not sitting’, ‘supported sitting’, ‘unsupported sitting’, ‘standing’, ‘walking’, and ‘death’ | **Time horizon:**  • Type I: 25 years  • Type II/III: 80 years  **Cycle length:**  For both models one month  **Discount rate**: 1.5% costs and benefits per annum. | Health state utility values were obtained from a sponsor-commissioned Canadian burden-of-illness survey. (included a EuroQol 5-Dimensions 5-Levels health utility questionnaire). In the absence of available data for the “PV” and “not sitting” states, the value identified in the survey for sitting supported was applied to both health states. | **Sources of costs:**  Outpatient, hospitalizations, Medical equipment and medications identified from a Canadian burden-of-illness study. health care resource utilization come from the Alberta Hospital, the Ontario Ministry of Health 2020. End-of-life costs were obtained from Widger et al.234 and Seow et al.235  **Currency and conversion:** Canadian dollars |
| CADTH-OA, 2021201 | Patients with SMA type 1 with an onset of symptoms at ≤ 6 months of age, and with 2 copies of the SMN2 gene. | **Intervention:** Onasemnogene abeparvovec  **Comparator:** BSC and Nusinersen  **Outcomes**: QALYs  **Study perspective:** Canadian publicly funded health care payer  **Location (Setting):** Canada | **One Markov model**  **Health states:**  **six states including:** ‘within a broad range of normal development’, ‘walking unassisted’, ‘sitting unassisted’, ‘unable to sit unassisted’, ‘PAV’ and ‘death’ | **Time horizon:**  60 years  **Cycle length:**  Six 6 months in the early phase and yearly in the extrapolation phase.  **Discount rate**:  1.5% costs and benefits per annum. | Utility for the ‘unable to sit unassisted’ and ‘sitting unassisted‘ health states was identified from the literature (Tappenden et al. (2018))228  utility of the general population for the ‘walking unassisted’ and ‘within broad range of normal development’ health states were derived from (Ara et al, 2010)223 | **Sources of costs:**  • Administration costs: Ontario Schedule of Benefits for physician services.  • Screening costs: expert opinion.  • Health state costs: unpublished health care resource utilization study conducted by the sponsor.    **Currency and conversion:**  Canadian dollars |
| Meijer et al., 2023208 | Patients with SMA Type I, SMN1 mutation, 2 SMN2 copies, treated before 6 months | **Intervention:** Onasemnogene abeparvovec  **Comparator:** BSC  **Outcomes**: QALY  **Study perspective:** Societal perspective  **Location (Setting):** Netherlands | **One Markov model**  **Health states:**  five health states including: ‘not sitting and ‘PAV free’, ‘PAV’, ‘sitting independently’, ‘walking independently’, and ‘dead’. | **Time horizon:**  36 months for short-term and 99 years for long-term  **Cycle length:**  monthly  **Discount rate**:  4% for costs and 1.5% for benefits | Literatures (mainly ZIN report of nusinersen and the comments provided in the ZIN report of Onasemnogene abeparvovec) | **Sources of costs:**  Literature (study conducted by Klug et al. in Germany in 2016)233, 236, 237  **Currency and conversion:**  € and adjusted for 2022 |
| Broekhoff et al., 2021205 | Infants born with SMA I- Mean age (months) = 3.4 | **Intervention:** OA  **Comparator:** BSC and nusinersen  **Outcomes**: QALYs  **Study perspective:** societal perspective  **Location (Setting):** Netherlands | **One** Markov model  **Health states:**  five health states: three states corresponding to SMA types (SMA I-III), one for PV, and one for death. | **Time horizon: 100 years**  **Cycle length: one month.**  **Discount rate**: 4% for Costs and 1.5% for benefits | The base-case model utilized health state utilities sourced from the Dutch National Health Care Institute (ZIN) model, while a scenario analysis incorporated utilities from the Institute for Clinical and Economic Review (CER Institute). | **Sources of costs:**  published literature (the ZIN report, which uses cost calculations by Klug et al.)233  **Currency and conversion:**  Euro € and were inﬂated to 2019 |
| SMC Nusinersen, 2018210 | patients with symptomatic type 1 SMA | **Intervention:** Nusinersen with BSC  **Comparator:** BSC  **Outcomes**: QALY, YLG  **Study perspective:** NHS Scotland and social work  **Location (Setting):** Scotland | **Two Markov models (**type I SMA and type II or III SMA )  **Health states:**  A 10-state Markov model tracks infant patients' health progression through worsening, stabilizing, improving states, and functional milestones like 'sitting without support' or 'standing without assistance.' The model for later-onset SMA patients mirrors the infant model but includes state adjustments tailored to type II and III SMA. | **Time horizon: 80 years**  **Cycle length: Unclear**  **Discount rate**: Unclear- it seems %3 for cost and outcome | Health state utilities in the later-onset model were derived by converting PedsQL data from the CHERISH study to EQ-5D. Infantile model values were adjusted from later-onset utilities to reflect infant-specific characteristics. | **Sources of costs:**  Unclear  **Currency and conversion: £2018** |
| SMC -OA , 2021215 | patients with SMA with a bi-allelic mutation in the SMN1 gene (or up to 3 copies of the SMN2 gene) and a clinical diagnosis of SMA type 1. | **Intervention:** Onasemnogene abeparvovec  **Comparator:** Nusinersen  **Outcomes**: QALY, LYG  **Study perspective:** health and social care  **Location (Setting):** Scotland | **One Markov models**  **Health states:**  Six states including ‘normal development’ , ‘unassisted walking’ , ‘unassisted sitting’ , ‘inability to sit’ , ‘reliance on assisted ventilation’ , and ‘death’ | **Time horizon:** lifetime  **Cycle length:** six months for the first three years and annually thereafter  **Discount rate**: Unclear- it seems %3 for cost and outcome | utility values were sourced from the literature using proxy parental or carer values and/or clinical advice. | **Sources of costs:**  Scottish Health Service Costs where available  **Currency and conversion:**  pound and for 2020 |
| SMC risdiplam, 2022202 | Infants with symptomatic type 1 SMA aged 2–7 months were used in the type 1 model, while the type 2/3 model included ambulant and non-ambulant patients aged 2–25 years. | **Intervention:** Risdiplam with BSC  **Comparator:** Nusinersen with BSC  **Outcomes**: QALY  **Study perspective:** Unclear (maybe payer and social perspective)  **Setting:** Unclear  **Location:** Scotland | **Two Markov models:**  (type I SMA and type II or III SMA)  **Health states:**  Both models utilized a six-state Markov model with common motor milestone states: not sitting, sitting, standing, and walking. The type 2/3 model distinguished the 'sitting' state into 'with' and 'without support'. Type 1 model included a 'permanent ventilation (PV)' state. Death was the absorbing state in both models. | **Time horizon:** lifetime  **Cycle length:** one month  **Discount rate**: Unclear | Patient and caregiver utility data for motor milestone health states in Type 1 and Type 2/3 models were sourced from literature or NICE submission TA588. | **Sources of costs:**  Costs for drug acquisition, administration, and resource use of risdiplam and nusinersen were factored in from real-world studies by their respective companies. |
| Connock et al., 2020212 | Patients with SMA Type 1 | **Intervention:** Onasemnogene abeparvovec  **Comparator:** BSC and nusinersen  **Outcomes**: QALY  **Study perspective:** UK NHS perspective  **Location (Setting):** UK | **One Markov model**  **Health states:**  Unclear | **Time horizon:**  Lifetime  **Cycle length:**  Unclear  **Discount rate**:  Maybe 3.5% for both costs and benefits | Total lifetime QALYs for nusinersen, onasemnogene abeparvovec come from Table 8 Malone et al. 2019214  Total lifetime QALYs for BSC and nusinersen come from Biogen submission to NICE (2018)41 | **Sources of costs:**  Total lifetime costs for nusinersen and onasemnogene abeparvovec come from Malone et al. 2019214  Total lifetime costs for BSC and nusinersen come from Biogen submission to NICE (2018)41  **Currency and conversion:**  £UK using 2018 PP exchange rate |
| Dean et al. , 2021213 | Symptomatic SMA type 1 patients | **Intervention:** Onasemnogene abeparvovec  **Comparator:** Nusinersen, BSC  **Outcomes**: QALY  **Study perspective:** Commercial payer OF USA  **Location (Setting):** USA | **ONE Markov model**  **Health states:**  The states of the model are like the “ICER - nusinersen & OA 2019” study216 Markov model for Type I SMA. | **Time horizon:**  Lifetime  **Cycle length:**  6-monthly for first 3 years then annually  **Discount rate**: 3% for both costs and benefits | Equivalent to weightings used in the ICER analysis216 | **Sources of costs:**  Price of onasemnogene abeparvovec $2.125 M one-time dose, other costs were equal to costs used in the ICER analysis (2019),216 cost of ventilator estimated from a UK study(Noyes et al. 2006)238  **Currency and conversion:**  $US inflated to 2017 |
| Malone et al. , 2019214 | Paediatric with genetically confirmed SMA1 and two copies of SMN2, diagnosed before six months of age, and receiving either the recommended therapeutic amount of onasemnogene abeparvovec or nusinersen, along with BSC | **Intervention:** Onasemnogene abeparvovec  **Comparator:** Nusinersen  **Outcomes**: QALY, LYG  **Study perspective:** Commercial insurer in the U.S.  **Location (Setting):** USA | **ONE Markov model**  **Health States:**  ‘Within a broad range of normal development’, ‘Walking functionally equivalent to SMA TypeIII’ , ‘Sitting functionally equivalent to SMA TypeII’ , ‘Not sitting and living ventilation-free’ , ‘Not sitting and requiring permanent assisted ventilation’ , and ‘Death’ | **Time horizon:**  100 years  **Cycle length:**  six months for the first three years, and then 12 months for all cycles thereafter  **Discount rate**:  3% for both costs and benefits | The model incorporated utility values derived from the CHERISH (PedsQL data) clinical trial of nusinersen for later-onset SMA (NCT02292537), which were transformed to the EQ-5D youth version through a documented algorithm.227 | **Sources of costs:**  SMA patient costs in USA: commercial plans by age at first claim.239  Nusinersen product cost: based on manufacturer240  nusinersen administration cost: Micro-costed.  Hospital mark-up component and Durable medical equipment: expert opinion  Hospital stays for anesthesia-related complications: Graham et al.241  **Currency and conversion:**  $US, price year is unclear |
| Wang et al. , 2022206 | infants born with SMA Type I as the recruited patients in the clinical trials of nusinersen and onasemnogene abeparvovec | **Intervention:** Onasemnogene abeparvovec  **Comparator:** SOC and nusinersen  **Outcomes**: QALY  **Study perspective:** healthcare system in the Australian context  **Location (Setting):** Australian | **ONE** Markov model  **Health states:**  Five health states in including: ‘not sitting and PAV free’, ‘sitting independently’, and ‘walking independently’ and ‘dead’ | **Time horizon:** 100 years  **Cycle length:** Monthly  **Discount rate**: 5% annually for both costs and benefits | Utility values come from Chambers et al.2020242 | **Sources of costs:**  Treatment costs of nusinersen: PBS243Treatment costs of onasemnogene abeparvovec: Market price  Administration and monitoring costs of nusinersen and onasemnogene abeparvovec: PBS,243 MBS,244 NHCDC245  Health state costs: Recently published study in Australia242 AND ICER216  **Currency and conversion: $** Australian were converted to 2020 |
| Zuluaga et al., 2019203 | Patients with infantile-onset and later-onset SMA | **Intervention:** Nusinersen and SoC  **Comparator:** SoC  **Outcomes**: QALY  **Study perspective:** societal  **Location (Setting):** Sweden | **Two Markov model** (infantile-onset SMA and later-onset SMA)  Health states:  infantile-onset: ten states including: ‘baseline’ , ‘Worsened’, ‘stabilisation of baseline’ and ‘Improved’ , ‘Stands/walks Unaided’ , ‘Sits Unaided’ , ‘Stands aided’ , ‘Walks aided’ , ‘Loss of later-onset motor function’ , ‘Death’  Later‑Onset: ‘baseline’ , ‘Worsened’ , ‘Stabilised’ , ‘Mildly improved’ , ‘Moderately improved’ , ‘Stands unaided’ , ‘Walks unaided’ , ‘Stands/walks with assistance’ , ‘Loss of ambulation with/without assistance’ , ‘Death’ | **Time horizon:** 40 years for infantile-onset and 80 years for later-onset  **Cycle length: In** trial follow-ups for ENDEAR: days 1, 64, 183, 302 and 394; CHERISH: days 1, 92, 169, 274, 365 and 456; after follow-ups: four months  **Discount rate**: 3.0% for both costs and benefits | Health-state utility values come from Lloyd et al. 2017246  The EQ-5D (youth version) was scored using the EQ-5D-3L UK preference weights. | **Sources of costs:**  German study (Klug et al. 2016)233 and a Spanish study (López-Bastida et al. 2017)226  Country-specific unit costs were mainly collected from hospital price lists.  **Currency and conversion:**  SEK (Swedish krona)- inflated to the year 2018 |
| Thokala et al., 2020211 | patients with infantile-onset SMA (type 1) | **Intervention:** Nusinersen  **Comparator:** BSC  **Outcomes**: LYG, QALY  **Study perspective:** US health care sector  **Location (Setting):** US | **One Markov model**  The model contained two parts: (1) a short term phase concordant with clinical study data, and (2) a long-term extrapolation model.  **Health states:**  ‘permanent ventilation’, ‘not sitting’, ‘sitting’, ‘walking’, and ‘death’. | **Time horizon:** lifetime  **Cycle length:** monthly  **Discount rate**: 3% per annum for both costs and benefits | Permanent ventilation for both arms: Thomson et al., 2017227 (EQ-5D)  Not sitting in BSC arm Same as “permanent ventilation” and for Nusinersen based on assumption  Sitting for BSC based on Tappenden et al., 2018228 and for Nusinersen based on assumption | **Sources of costs:**  Nusinersen treatment cost: Magellan 2016,230 Redbook 2018229  Administration cost: Physician fee schedule 2018;232 Nationwide Children’s Hospital  The health care utilization costs: Shieh et al. 2017239  **Currency and conversion:**  $US- inflated to 2017 |
| NCPE-2017207 | infantile and later onset SMA | **Intervention:** Nusinersen  **Comparator:** SOC  **Outcomes**: QALY, LYG  **Study perspective:** Health Service Executive  **Location (Setting):** Ireland | **Two Markov models** (infantile and later onset SMA)  **Health states:**  Unclear | **Time horizon:** Lifetime  **Cycle length:** determined by motor assessments timing and maintenance dose administration.  **Discount rate**: % for costs and benefits | PedsQL data from CHERISH trial determined later-onset SMA utilities, impacting infantile SMA model. Data mapped to EQ5D scale for utility derivation. | **Sources of costs:**  Unclear  **Currency and conversion:** Euro(€) |
| BSC, best supportive care; LYG, life-year gained; PSS, personal social service; QALY, quality adjusted life-year; RWE, real-world evidence; SMA, spinal muscular atrophy; OA, Onasemnogene abeparvovec; PCA, pharmacological therapy resources; permanent assisted ventilation, PAV; purchasing power parity, PPP; United States, US; Standard Of Care, SOC; Pharmaceutical Benefits Scheme , PBS; Medicare Benefits Schedule, MBS; National Hospital Cost Data Collection, NHCDC; | | | | | | |

Appendix Table 8: Individual study results and conclusion from studies included in this systematic review

| **Study, year** | **Costs (intervention and comparator(s))** | **QALYs (intervention and comparator(s))** | **Base-case ICER** | **Sensitivity analysis** | **Conclusion** |
| --- | --- | --- | --- | --- | --- |
| NICE-Nusinersen TA588, 2019 | **Early onset (patient, and patient and caregiver):**  • Nusinersen: £2,260,700  • BSC: £71,500  **Later-onset (patient, and patient and caregiver):**  • Nusinersen: £3,153,300  • BSC: £184,300 | **Early onset (patient):**  • Nusinersen: 7.83  • BSC: 2.49  **Later-onset (patient):**  • Nusinersen: 16.76  • BSC: 14.52  **Early onset (patient and caregiver):**  • Nusinersen: 7.58  • BSC: 2.17  **Later-onset (patient and caregiver):**  • Nusinersen: 15.50  • BSC: 12.36 | **Early onset (patient):**  Nusinersen vs BSC: £410,000  **Later-onset (patients):**  Nusinersen vs BSC: £404,700  **Early onset (patient and carer):**  Nusinersen vs BSC: £1,325,800  **Later-onset (patient and carer):**  Nusinersen vs BSC: £945,700 | **Key drivers of economic model:**  Early onset: drug price, patient utility (Stands/ Walks unaided), Factor to adjust later onset mortality risk, Patient Utility (No milestone achieved), HR death SMA Infantile onset vs general population  Later-onset: Patient utility (Walks Unaided and Sits without Support but does not Roll), drug price, Factor to adjust later onset (type III) mortality risk, Patient utility (Stands Unaided)  **PSA results:** It seems that the probability of ICER (Nusinersen vs BSC) being ≤ £100,000 is zero. | The cost-effectiveness estimates presented for early onset and later onset SMA are above the range normally considered cost-effective by NICE.  Nusinersen is recommended as an option for treating 5q spinal muscular atrophy (SMA) only if:  • people have pre-symptomatic SMA, or SMA types 1, 2 or 3 and  • the conditions in the managed access agreement are followed. |
| NICE-Risdiplam TA755, 2021 | commercial in confidence | **Type 1 SMA(patient):**  • Risdiplam: 8.55  • BSC: -1.86  **Type 1 SMA (carers):**  • Risdiplam: 25.34  • BSC:5.44  **Type 2/3 SMA(patient):**  • Risdiplam: 14.11  • BSC: 1.19  **Type 1 SMA (carers):**  • Risdiplam: 42.42  • BSC: 33.25 | commercial in confidence | **Key drivers of economic model:**  Type 2/3: drug cost, the discount rate for costs, the adult patient costs of the ‘not sitting’ state, the relative dose intensity of Risdiplam and the HR for type 2 mortality  Type 1: drug cost, the discount rate for costs, the OS HR (vs Risdiplam) for the ‘not sitting’ state, the costs for PV and the EFS HR (vs Risdiplam)  **PSA results:** At list price, for type 1 model, risdiplam has only a 0.26 chance of being cost-effective at £50,000 WTP threshold. | The cost-effectiveness analysis of risdiplam for treating SMA showed higher costs than usual for NHS. Yet, it was recommended for SMA treatment under a managed access agreement. More data gathering is needed for long-term benefits assessment. |
| NICE-OA HST15-type1, 2021 | BSC: 381,131  OA: 2,640,022 | BSC: 0.210  OA: 10.007 | OA versus BSC: 230,568 | **Key drivers of economic model:** drug cost, sits unassisted utility value, Cost of hospitalisations for the sits unassisted and permanent ventilation states, Survival limit for the permanent ventilation state.  **PSA results** (Company’s revised submission): with a 95% credible range of between £203,330 and £280,686. | OA is recommended for treating type 1 SMA in 5q with specified age criteria and medical conditions, subject to certain approvals and conditions. |
| NICE-OA HST24-pre-symptomatic, 2023 | BSC: 882,564  OA: commercial in confidence | commercial in confidence | commercial in confidence | **Key drivers of economic model:** drug costs, prevalence of SMN2 gene copies, and care costs for SMA patients in different health states like non-sitter (HS1) and sitter (HS2)  **PSA results:**  commercial in confidence | OA is likely to provide value for money in the context of a highly specialised service if used in babies aged 12 months or under. So, onasemnogene abeparvovec is recommended as an option for presymptomatic SMA in this age group. |
| ICER- Nusinersen & OA, 2019 | Infantile-onset:  **•** Nusinersen: $3,884,000  • BSC: $789,000  **Infantile-onset:**  **•** Zolgensma: $3,657,000  • BSC: $789,000  **Later-onset:**  • Nusinersen:$9,148,000  • BSC: $1,442,000  **Pre-symptomatic:**  **•** Nusinersen:$11,929,000  • BSC: $801,000 | **Infantile-onset:**  • Nusinersen: 3.24  • BSC: 0.46  **Infantile-onset:**  • Zolgensma: 12.23  • BSC: 0.46  **Later-onset:**  **•** Nusinersen: 12.28  • BSC: 11.34  **Pre-symptomatic:**  **•** Nusinersen: 21.94  **•** BSC: 6.25 | **Infantile onset:**  **•** Nusinersen vs BSC: $1,112,000  **Infantile onset:**  • OA vs BSC: $243,000  **Later-onset:**  **•** Nusinersen vs BSC: $8,156,000  **Pre- symptomatic:**  **•** Nusinersen vs BSC: $709,000 | **Key drivers of economic model:**  For the Nusinersen vs BSC: monthly costs and utility values for the ‘sitting’ and ‘not sitting’ health state.  For OA vs BSC: monthly costs in the ‘sitting’ and ‘walking’ and the utility in the ‘sitting’ states.  **PSA results**: Nusinersen did not achieve a greater than zero likelihood of meeting the $500,000/QALY. OA achieved a 0.1% chance of meeting the $150,000/QALY threshold | Nusinersenis cost-effective for presymptomatic SMA at $709,000 per QALY gained from a healthcare perspective, exceeding thresholds. **OA**, at $2 million, offers promise for symptomatic Type I SMA with $243,000 per QALY gained. Both show similar results from a societal perspective. |
| CADTH- Nusinersen, 2019 | **SMA type I:**  • Nusinersen: $3,534,854  • RWC: $339,683  **SMA type II:**  • Nusinersen: $8,336.271  • RWC: $708,620  **SMA type III:**  • Nusinersen: $5,554,707  • RWC: $1,091,307 | **SMA type I:**  • Nusinersen: 3.919  • RWC: -0.881  **SMA type II:**  • Nusinersen: 23.278  • RWC: 19.602  **SMA type III:**  • Nusinersen: 12.053  • RWC: 10.490 | • **SMA type I:** Nusinersen vs RWC: $665,570  • **SMA type II:** Nusinersen vs RWC: $2,075,435  **• SMA type III:** Nusinersen vs RWC: $2,855,818 | **Key drivers of economic model:**  Unclear  **PSA results**:  For all three SMA types, the probability that nusinersen was cost-effective assuming that the threshold value for a QALY was $300,000 was 0%. | In alignment with the manufacturer’s results of its pharmacoeconomic submission, CDR found that nusinersen was not a cost-effective treatment for patients with 5q SMA types I, II, or III.  This finding has not been affected by the clinical information provided within the manufacturer’s resubmission |
| CADTH-Risdiplam , 2021 | **Type I:**  • BSC: 68,293  • Risdiplam : 961,580  • Nusinersen: 1,865,665  **Type II/III:**  • BSC: 825,656  • Risdiplam: 11,454,583  • Nusinersen: 11,892,866 | **Type I:**  • BSC: 3.53  • Risdiplam: 10.19  • Nusinersen: 10.17  **Type II/III:**  • BSC: 70.11  • Risdiplam: 71.04  • Nusinersen: 70.91 | **Type I:**  Risdiplam vs BSC: 134,229  Risdiplam vs Nusinersen: Dominant  **Type II/III:**  Risdiplam vs BSC: 1,203,108  Risdiplam vs Nusinersen: Dominant | **Key drivers of economic model:**  assumption around caregiver utilities, health state utilities, survival benefits for risdiplam versus BSC, price of nusinersen  **PSA results**:  The probability of risdiplam being cost-effective at a willingness-to-pay threshold of $50,000 per QALY is 0% for either subgroup. | CADTH's review noted limited evidence comparing risdiplam to nusinersen and best supportive care, impacting economic evaluations. Long-term efficacy data absence suggests caution. risdiplam was cost-ineffective in SMA types I, II, and III, mainly due to lower acquisition costs. However, uncertainties persist regarding its cost-effectiveness. |
| CADTH-OA, 2021 | BSC: 132,600  OA: 3,266,544  Nusinersen: 3,938,147 | BSC: 0.21  OA: 10.89  Nusinersen: 4.54 | OA vs BSC: 293,521  OA vs BSC: Dominant  Nusinersen vs BSC: Dominated | **Key drivers of economic model:** time horizon, altering the utility values, Price reductions for Nusinersen  **PSA results**: the probability of OA being cast-effective at a WTP threshold of $50,000 per QALY is 0% | The analysis faced limitations like lacking comparative long-term data for OA and uncertainty in cost implications, aligning with CADTH's findings showing an ICER of $334,090 per QALY compared to BSC. |
| Broekhoff et al., 2021 | **BSC:** 922130  **OA:** 4024879  **Nusinersen:** 3002379 | **BSC:** 4.415  **OA:** 26.757  **Nusinersen:** 7.625 | **OA vs BSC:** 138,875  **Nusinersen vs BSC:** 647,850  **OA vs Nusinersen:** 53,477 | **Key drivers of economic model:**  survival in health state 1(SMA I), Price of treatment  **PSA results:**  At a WTP of €80k/QALY, OA had a <0.0002% chance of being cost-effective vs BSC. | Treating SMA Type I with OA is not cost-effective compared to BSC under Dutch WTP thresholds. Additionally, if happen within 10 years post-treatment, ICER increase by 1.5-6x. |
| SMC Nusinersen, 2018 | **Infantile model:**  • incremental cost: £2,151,509  **Later-onset model:**  • incremental cost: £3,728,246 | **Infantile model:**  • Incremental QALYs: 5.02  **Later-onset model:**  • Incremental QALYs: 2.29 | **Infantile model:** 428,964  **Infantile model:** 1,624,951 | **Key drivers of economic model:** mortality risk factor, discounting rate, the price of Nusinersen vials  **PSA results:** Not reported | The Committee approved nusinersen for restricted use in NHS Scotland for type 1 SMA patients. The SMC was willing to tolerate more economic uncertainty. |
| SMC -OA, 2021 | **OA:** 2,704,737  **Nusinersen:** 2,800,590 | **OA:** 7.50  **Nusinersen:** 3.77 | **OA vs Nusinersen** (£/QALY)**:** -25,740 | **Key drivers of economic model:** costs of hospital stays and social services and utilities in unassisted sitting state.  **PSA results:** Not reported | The Committee accepted onasemnogene abeparvovec for restricted use in NHS Scotland. |
| SMC Risdiplam, 2022 | **Not reported** | **Not reported** | Risdiplam is estimated to be more effective and less costly than nusinersen at list prices. | **Key drivers of economic model: Unclear**  **PSA results:** Not reported | The Committee accepted risdiplam for use in NHSScotland. |
| Connock et al., 2020 | **Nusinersen:**  • Malone et al: 4,352,213  • Biogen submission to NICE: 2,258,852  **OA:**  • Malone et al (for a 2.5 USD million acquisition price): 2,903,706  • Malone et al (for a 5 USD million acquisition price): 4,576,047  **BSC:**  • Biogen submission to NICE: 26,637 | **Nusinersen:**  • Malone et al: 5.29  • Biogen submission to NICE: 7.86  **OA:**  • Malone et al (for a 2.5 USD million acquisition price): 15.65  • Malone et al (for a 5 USD million acquisition price): 15.65  **BSC:**  • Biogen submission to NICE: 2.58 | **ICER vs BSC:**  **OA drug cost US$5 m:**  • Nusinersen (Malone et al. data): Nusinersen (dominated), OA (£343, 209)  • Nusinersen (Biogen data): Nusinersen (dominated), OA (£343,209)  **OA drug cost US$2.5m:**  • Nusinersen (Malone et al. data): Nusinersen (dominated), OA (£215,257)  • Nusinersen (Biogen data): Nusinersen (dominated), OA (£215,257) | **Key drivers of economic model:** treatment cost andQALY yield  **PSA results:** Not reported | Commercial secrecy and data ambiguity complicate oversight of orphan drug reimbursements. Increasing costly therapies necessitate transparent, fair decision-making enhancements for sustainability. |
| Dean et al. , 2021 | **BSC: $1,961,710**  **Nusinersen: $4,602,692**  **Oa: $3,930,879** | **BSC: 1.15**  **Nusinersen: 2.88**  **OA: 13.33** | **OA vs BSC**: $161,648  **OA vs Nusinersen:** dominant | **Key drivers of economic model:** waning of effect of OA after 25, 15 and 10 years, remove two walker from OA arm, 95% overall survival for OA arm, improved survival for gene therapy patients who sit  **PSA results:** Not reported | New CUA model shows OA ($2.125M) cost-effective over Nusinersen for treating SMA1 patients under 2 years old. |
| Malone et al., 2019 | • **OA $2.5M:** $4,214,379  • **OA $3M:** $4,699,816  • **OA $4M:** $5,670,690  • **OA $5M:** $6,641,564  **Nusinersen:** $6,316,711 | **• OA:** 15.65  • **Nusinersen:** 5.29 | **• OA $2.5M vs Nusinersen:** Dominant  **• OA $3M vs Nusinersen:** Dominant  **• OA $4M vs Nusinersen:** Dominant  **• OA $5M vs Nusinersen:** $31,379 | **Key drivers of economic model: drug cost,** the threshold of CHOP INTEND utilized and the threshold of CHOP INTEND utilized for estimating new Nusinersen recipients  **PSA results**: minimal shifts due to high cost of drugs | OA gene therapy for SMA type I patients can provide substantial survival benefits at costs comparable to or lower than chronic nusinersen treatment, making it a cost-effective option. |
| Meijer et al., 2023 | **Base-case:**  • BSC: €350,878  • OA: €4,386,381  **pre-symptomatic**  • BSC: €350,878  • OA: €3,951,500 | **Base-case:**  • BSC: 0.37  • OA: 16.03  **pre-symptomatic**  • BSC: 0.37  • OA: 28.70 | **Base-case:**  • OA vs BSC: € 257,717  **pre-symptomatic**  • OA vs BSC: € 127,107 | **Key drivers of economic model:** discount rates, cost and utility values associated with sitting and the cost of the drug (OA)  **PSA results**: At a WTP threshold of €80,000 per QALY, OA vs BSC has a zero probability of being cost-effective. | The cost-effectiveness analysis indicates limited cost-effectiveness at a €80,000 threshold. Scenario analysis supports pre-symptomatic treatment. Limited trial evidence highlights challenges in establishing appropriate reimbursement thresholds for rare diseases. |
| Wang et al., 2022 | **SOC:** $923,335  **Nusinersen:** $2,592,526  **OA:** $5,034,806 | **SOC:** 0.301  **Nusinersen:** 0.602  **OA:** 2.574 | **• Nusinersen vs SOC:** $2,772,798  **• OA vs SOC:** $1,808,471  **• OA vs Nusinersen:** $1,238,288 | **Key drivers of economic model:** cost of drugs,Utility values in sitting and walking independently  **PSA results**: Given a WTP threshold of $50,000 per QALY, the probability that OA was cost-effective vs SOC was 1.2%. | Nusinersen and OA didn't meet cost-effectiveness at a $50,000 per QALY threshold. High-quality clinical data development and exploring suitable WTP thresholds are vital for reimbursement decision-making in rare disease treatments. |
| Zuluaga‑Sanchez et al. 2019 | **\*Total cost (SEK) -Societal perspective:**  **Infantile-onset:**  **• Nusinersen + SoC :** 23,920,567  **• SoC:** 2,066,516  **Later-onset:**  **• Nusinersen + SoC :** 66,053,350  **• SoC:** 28,029,941  **Total cost (SEK)-Payer perspective**  **Infantile-onset:**  **• Nusinersen + SoC:** 22,970,891  **• SoC:** 1,513,607  **Later-onset:**  **• Nusinersen + SoC:** 64,095,327  **• SoC:** 25,175,193  \*The total costs for 'patients' and 'patients + caregivers' are the same | **\*QALYs (patients)**  **Infantile-onset**  Nusinersen + SoC: 3.65  SoC: − 0.20  **Later-onset**  Nusinersen + SoC: 9.25  SoC: − 0.29  **QALYs (caregivers):**  **Infantile-onset**  Nusinersen + SoC: − 0.10  SoC: − 0.12  **Later-onset**  Nusinersen + SoC: − 1.37  SoC: − 3.76  \*QALYs for patient and QALYs for caregivers are the same as the ones reported for the societal perspective | **ICER (SEK/QALYs for Nusinersen + SoC vs SoC)**  **Societal perspective:**  **Patients:**  **• Infantile-onset:** 5,664,875  **• Later-onset:** 3,985,640  **patients + caregivers:**  **• Infantile-onset:** 5,635,978  **• Later-onset:** 3,187,222  **Payer perspective**  **Patients:**  **• Infantile-onset:** 5,562,027  **• Later-onset:** 4,079,635  **patients + caregivers:**  **• Infantile-onset:** 5,533,655  **• Later-onset:** 3,262,388 | **Key drivers of economic model:** utility of stands/walks unaided state and Nusinersen prices  **PSA results**: The chance of being cost-effective exceeds 0% at 4.2 million SEK/QALY for infants and 2.2 million for later-onset. | Study shows nusinersen treatment's variable QALYs and costs for different SMA onset models. Despite Swedish reimbursement, it's not cost-effective at threshold; international model adaptation recommended. |
| Thokala et al., 2020 | Nusinersen: $3,884,000  BSC: $789,000 | Nusinersen: 3.24  BSC: 0.46 | Nusinersen vs BSC (Cost/QALY gained): $1,112,000 | **Key drivers of economic model:** length of survival, utilities in both the “sitting” and “not sitting” health states  **PSA results**: Nusinersen had a zero likelihood of achieving a cost-effective ratio of less than $500,000 per QALY | Nusinersen shows potential health benefits in infantile-onset SMA, but at its current price, it does not align with standard cost-effectiveness thresholds in the US. Long-term data collection through a registry is recommended for accurate assessment. |
| NCPE, 2017 | Not reported | Not reported | Infantile onset SMA: Nusinersen vs SOC: €501,069  later onset SMA: €2,163,798 | **Key drivers of economic model:** discount rate, mortality risk factor, Nusinersen vial price, and patient utility  **PSA results**: probability for specific WTP not reported | Nusinersen is deemed not cost-effective at the current submitted price for treating 5q spinal muscular atrophy. |
| BSC, best supportive care; CDR, Common drug review; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; OA, onasemnogene abeparvovec; PSA, probabilistic sensitivity analysis; PV, permanent ventilation; RWC, Real World Care; SMA, spinal muscular atrophy; SOC, standard of care; WTP, willingness-to-pay | | | | | |

Appendix 6: Changes made to economic model

EAG’s individual parameter changes to the Roche’s base-case analysis.

Appendix Table 9: Summary of EAG changes made to Roche presymptomatic model

|  |  |
| --- | --- |
| **Description of EAG change to economic model** | **Implementation of the change in the model** |
| Time horizon | Incorporate the new value: Worksheet: [Inputs], Cell: F12 |
| Utility decrements - disease impacts and treatment related events (scoliosis respiratory, support, and bulbar dysfunction) | Incorporate the new values: Worksheet: [Inputs], Range: F491: F493 |
| Severity modifier | Calculations of Incremental 'QULYs due to incorporate the Severity Modifier: Worksheet: [Results], Range: K62: O69  Amendments of formula: Worksheet: [Results], Range: G16: I16 and M16: O16 and Cell:I67  New table for Fully incremental analysis: Worksheet: [Results], Range: C83: M87 |
| Number of caregivers | Definition of new variable: Worksheet: [Inputs], Cell: F435 and Cell: D436  Incorporate the new formula: Worksheet: [risdiplam], Columns: BI and BJ  Incorporate the new formula: Worksheet: [nusinersen], Columns: BJ and BK  Incorporate the new formula: Worksheet: [onasemnogene], Columns: BJ and BK  Incorporate the new formula: Worksheet: [BSC], Columns: BJ and BK |
| Patient: Incremental benefit for risdiplam, nusinersen, and onasemnogene abeparvovec | Incorporate the new values: Worksheet: [Inputs], Range: F444:F460 |
| Caregiver: Incremental benefit for risdiplam, nusinersen, and onasemnogene abeparvovec | Incorporate the new values: Worksheet: [Inputs], Range: F469:F485 |
| Disease impact costs | Incorporate the new values: Worksheet: [Inputs], Range: F421:F426 |
| Overall survival source for risdiplam, nusinersen, and onasemnogene abeparvovec | Incorporate the new values: Worksheet: [Survival], Columns: U, W, Y, AC, AE, and AG  Incorporate the new formula: Worksheet: [risdiplam], Columns: CC, CG, and CM  Incorporate the new formula: Worksheet: [nusinersen], Columns: CT, and CY  Incorporate the new formula: Worksheet: [onasemnogene], Columns: CT, and CY |
| Overall survival for BSC | Incorporate the new values: Worksheet: [Survival], Columns: AN, AP, and AR |

Appendix Table 10: Summary of EAG changes made to Roche type 1 SMA model

|  |  |
| --- | --- |
| **Description of EAG change to economic model** | **Implementation of the change in the model** |
| Time horizon | Incorporate the new value: Worksheet: [Inputs], Cell: F12 |
| Utility decrements - disease impacts and treatment related events (scoliosis respiratory, support, and bulbar dysfunction) | Incorporate the new values: Worksheet: [Inputs], Range: F485: F487 |
| Severity modifier | Calculations of Incremental 'QULYs due to incorporate the Severity Modifier: Worksheet: [Results], Range: K62: O69  Amendments of formula: Worksheet: [Results], Range: G16: I16 and M16: O16 and Cell:I67  New table for Fully incremental analysis: Worksheet: [Results], Range: C84: L88 |
| Number of caregivers | Definition of new variable: Worksheet: [Inputs], Cell: F429 and Cell: D430  Incorporate the new formula: Worksheet: [risdiplam], Columns: BI and BJ  Incorporate the new formula: Worksheet: [nusinersen], Columns: BJ and BK  Incorporate the new formula: Worksheet: [onasemnogene], Columns: BJ and BK  Incorporate the new formula: Worksheet: [BSC], Columns: BJ and BK |
| Patient: Incremental benefit for risdiplam, nusinersen, and onasemnogene abeparvovec | Incorporate the new values: Worksheet: [Inputs], Range: F438:F454 |
| Caregiver: Incremental benefit for risdiplam, nusinersen, and onasemnogene abeparvovec | Incorporate the new values: Worksheet: [Inputs], Range: F463:F479 |
| Disease impact costs | Incorporate the new values: Worksheet: [Inputs], Range: F415:F420 |
| Overall survival and event free survival, source for nusinersen, and onasemnogene abeparvovec | Select the new option: Worksheet: [Survival], Cell: AE8, AS8, CF8, and CO8 |

Appendix Table 11: Summary of EAG changes made to Roche type 2/3 SMA model

|  |  |
| --- | --- |
| **Description of EAG change to economic model** | **Implementation of the change in the model** |
| Utility decrements- disease impacts and treatment related events | Incorporate the new values: Worksheet: [Inputs], Range: F251: F253 |
| Severity modifier | Calculations of Incremental 'QULYs due to incorporate the Severity Modifier: Worksheet: [Results], Range: J65: N69  Amendments of formula: Worksheet: [Results], Range: G17: H17and M17: N17and Cell: H69  New table for Fully incremental analysis: Worksheet: [Results], Range: C89: N92 |
| Patient: incremental benefit for risdiplam and nusinersen | Incorporate the new values: Worksheet: [Inputs], Range: F217:F227 |
| Number of caregivers | Definition of new variable: Worksheet: [Inputs], Cell: F205 and Cell: F206  Incorporate the new formula: Worksheet: [risdiplam], Columns: BG and BH  Incorporate the new formula: Worksheet: [nusinersen], Columns: BH and BI  Incorporate the new formula: Worksheet: [BSC], Columns: BG and BH |
| Caregiver: Incremental benefit for risdiplam and nusinersen | Incorporate the new values: Worksheet: [Inputs], Range: F236:F246 |