# Therapies for Spinal Muscular Atrophy: Effectiveness and Value

**Draft Evidence Report**

**May 27, 2025**

**Prepared for**

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Jeffery A. Tice served as the lead author for the report. Dmitriy Nikitin led the systematic review and authorship of the comparative clinical effectiveness section of this report with assistance from Sol Sanchez. Josh Carlson, Linda Luu and Hui Hsuan Chan developed the cost-effectiveness model and authored the corresponding sections of the report. Woojung Lee and Marie Phillips conducted analyses for the budget impact model. David Rind provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Temiwunmi Shobanke, Kelsey Gosselin, Grace, Ham, and Anna Geiger for their contributions to this report.

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*In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:*

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*None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.*

*To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.*

*For a list of stakeholders from whom we requested input from, or who have submitted public comments so far, please visit:*
https://icer.org/wp-content/uploads/2025/01/ICER_SMA_Stakeholder-List_For-Publication_052725.pdf

# Conflict of Interest Disclosures for the Report

**Table 1. ICER Staff and External Collaborators Conflict of Interest Disclosures**

| ICER Staff and External Collaborators | Conflict of Interest |
|---|---|
| **Josh J. Carlson, PhD** | Josh Carlson has received consulting fees from Genentech, which are not related to SMA. |
| **Hui-Hsuan Chan, MHS** | No conflicts to disclose. |
| **Anna Geiger, BS** | No conflicts to disclose. |
| **Kelsey Gosselin, MA** | No conflicts to disclose. |
| **Grace Ham, MSc** | No conflicts to disclose. |
| **Woojung Lee, PharmD, PhD** | No conflicts to disclose. |
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| **Marie Philips, BA** | No conflicts to disclose. |
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| **Sol Sanchez, BA** | No conflicts to disclose. |
| **Temiwunmi Shobanke, MS** | No conflicts to disclose. |
| **Jeffrey A. Tice, MD** | No conflicts to disclose. |

SMA: spinal muscular atrophy

**Table 2. Expert Reviewers of the Draft Evidence Report Conflict of Interest Disclosures**

| Expert Reviewer | Conflict of Interest |
|---|---|
| **John Brandsema, MD** | Dr. Brandsema has received consulting fees from Biogen, Novartis, Genentech and Scholar Rock as well as clinical trial funding from Biogen, Novartis, Genentech and Scholar Rock. |
| **Jenna Klotz, MD** | Dr. Klotz has no conflicts to disclose. |
| **Praveen Thokala, PhD** | Dr. Praveen Thokala is involved in several advisory/consultancy projects with Novartis unrelated to SMA. Dr. Thokala participated in an Advisory board for Roche Evrysdi® (Risdiplam) to discuss potential modeling approaches and address feedback from the NICE committee as part of the managed access agreement (MAA). Praveen's role as an advisor was to participate in discussions around the appropriateness of the suggested modelling approaches. |
| **Portia Thorman** | Portia Thorman is the Head of Advocacy and Community at SMA UK. In 2024/2025, SMA UK received 15.6% of its annual funding from healthcare companies including Biogen, Genentech, Novartis, and Scholar Rock. |

SMA: spinal muscular atrophy, UK: United Kingdom

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## List of Acronyms and Abbreviations Used in this Report

| | |
|---|---|
| AAN | American Academy of Neurology |
| AAV9 | Adeno-associated virus serotype 9 |
| AE | Adverse event |
| AHRQ | Agency for Healthcare Research and Quality |
| AIAN | American Indian or Alaskan Native |
| APC | Ambulatory payment classification |
| API | Apitegromab |
| BSID-III | Bayley Scales of Infant and Toddler Development - Third Edition |
| CDA-AMC | Canada's Drug Agency (L'Agence des Médicaments du Canada) |
| CDR | Clinical trial Diversity Rating tool |
| CE | Cost-effectiveness |
| CFB | Change from baseline |
| CHOP-INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| CI | Confidence interval |
| CMAP | Compound muscle action potential |
| CMS | Centers for Medicare and Medicaid Services |
| CPT | Current procedural terminology |
| DNA | Deoxyribonucleic acid |
| DRF | Diagnosis Related Group |
| EAP | Expanded access program |
| EQ-5D | EuroQol-5 Dimensions |
| evLY | Equal value life year |
| FDA | Food and Drug Administration |
| GDP | Gross domestic product |
| GMFM | Gross Motor Function Measure |
| HCPCS | Healthcare Common Procedure Coding System |
| HIDI | Health Improvement Distribution Index |
| HINE | Hammersmith Infant Neurological Examination |
| HINE-2 | Hammersmith Infant Neurological Examination – Section 2 |
| HFMSE | Hammersmith Functional Motor Scale-Expanded |
| HUI3 | Health Utilities Index Mark 3 |
| ICER | Incremental Cost Effectiveness Ratio |
| IT | Intrathecal |
| IV | Intravenous |
| kg | Kilograms |
| LCD | Local Coverage Determination |
| LS | Least Squares |
| LY | Life year |
| MAIC | Matching-adjusted indirect treatment comparisons |
| MCID | Minimal Clinically Important Difference |
| mg | milligrams |
| Mv | Millivolt |
| N | Number |
| NA | Not applicable |
| NC | Not calculated |
| NCD | National Coverage Determination |
| NfL | Neurofilament light protein |
| NHPI | Native Hawaiian or Pacific Island |
| NICE | National Institute for Health and Care Excellence |
| NIV | Non-invasive ventilation |

| | |
|---|---|
| NR | Not reported |
| OPPS | Outpatient Prospective Payment System |
| PDRR | Participant to Disease-prevalence Representation Ratio |
| PDUFA | Prescription Drug User Fee Act |
| PNCR | Pediatric Neuromuscular Clinical Research |
| PSA | Probabilistic sensitivity analysis |
| PICOTS | Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| QALY | Quality-adjusted life year |
| RCT | Randomized controlled trial |
| RHS | Revised Hammersmith Scale |
| RULM | Revised Upper Limb Module |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SE | Standard error |
| SMA | Spinal muscular atrophy |
| SMN | Survival motor neuron |
| SoC | Standard of care |
| TAEs | Treatment emergent adverse events |
| TBD | To be determined |
| UHC | UnitedHealthcare |
| US | United States |
| USPSTF | United States Preventive Services Task Force |
| Vg | vector genomes |
| WAC | Wholesale acquisition cost |
| WHO | World Health Organization |
| WTP | Willingness-to-pay |
| Yo | Years old |
| 6MWT | 6-minute walk test |

# Executive Summary

Spinal muscular atrophy (SMA) is a rare genetic neuromuscular disease.[1,2] SMA incidence is approximately one in 15,000 live births or about 500 new SMA cases per year in the United States (US).[3] The most common cause of SMA is the homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q.[4-6] *SMN1* creates survival motor neuron (SMN) protein, a protein essential for motor neuron development. Although the survival motor neuron 2 (*SMN2*) gene also produces SMN protein, only a small amount of the protein it creates is functional. SMN protein deficiency causes the irreversible degeneration of motor neurons, which leads to progressive muscle weakness and prevents patients from reaching motor milestones or retaining motor function.[1]

The natural history of SMA has been dramatically altered by the availability of disease-modifying therapies. In the US, neonatal screening for SMA is now performed in all 50 states and allows for treatment prior to symptomatic diagnosis of the disease.[7] The mortality rate for patients with SMA has dropped by 77% from 2014 to 2024, likely due to the combination of newborn screening and the availability of SMN-targeted therapy.[8]

The first two disease modifying therapies, nusinersen and onasemnogene abeparvovec, were reviewed in a 2019 ICER report.[9] Nusinersen (Spinraza®, Biogen), approved by the Food and Drug Administration (FDA) in 2016, is an antisense oligonucleotide administered via intrathecal injection that targets *SMN2* so that it creates more functional SMN protein. Onasemnogene abeparvovec (Zolgensma®, Novartis), approved by the FDA in 2019, is a gene therapy that uses an adeno-associated virus vector to deliver a functional copy of the *SMN1* gene.[10]

Risdiplam (Evrysdi®, Genentech), approved by the FDA in 2020, is a splicing modifier that, like nusinersen, targets *SMN2* to increase the production of SMN protein. Unlike nusinersen, it is an oral medication taken once daily.

Despite improvements for patients with SMA with the above treatments, there are many individuals with SMA who have significant muscle weakness. Apitegromab (Scholar Rock) is a selective inhibitor of a myostatin precursor. Myostatin inhibits muscle growth and strength; inhibiting myostatin may increase muscle size and strength. Apitegromab is being studied in patients with Type 2 and Type 3 SMA and is given by IV infusion every four weeks.

*Apitegromab*

Among patients ages 2 to 12 years old with Type 2 or 3 SMA already receiving treatment with risdiplam or nusinersen, the added benefit of apitegromab was small: a gain of 0.6 points on the Hammersmith Functional Motor Scale-Expanded (HFMSE) (from 25.5 to 26.1) after one year,

compared with a drop of 1.2 points in patients who received placebo (p=0.019). This difference was less than the Minimal Clinically Important Difference (MCID) of three points, but more patients in the apitegromab group had an increase of at least three points at one year (30.4% versus 12.5%, p=0.016). Extended follow-up of patients participating in the Phase II trial suggests that the benefits remain steady through four years of follow-up. There were almost twice as many serious adverse events in patients treated with apitegromab (19.8% versus 10.0%). These were primarily pneumonia (6.6%) and dehydration (2.8%), neither of which occurred among patients who received the placebo. The net health benefit is based on one small, unpublished study and there were more serious adverse events in the apitegromab arm, so the level of certainty around net health benefit is modest at best. For this population, we judge that treatment with apitegromab likely provides comparable or incremental benefits compared with no additional therapy, but that there is some possibility of substantial benefit with long-term use as well as some possibility of net harm ("promising but inconclusive"; **P/I**). There are insufficient data to estimate the net health benefits of apitegromab in other populations (**I**).

*SMN-Targeted Therapies After Gene Therapy (Onasemnogene Abeparvovec)*

There is one unpublished, single-arm study of nusinersen in 29 patients with suboptimal response to onasemnogene abeparvovec. The addition of nusinersen was associated with an increase of about five points on the Hammersmith Infant Neurological Examination – Section 2 (HINE-2) score at six months and seven points at 10 months. No new harms were identified, but repeated intrathecal procedures are burdensome and have rare but serious potential adverse events. Given the substantial uncertainty, we judge that there is moderate certainty of comparable to substantial net benefit, with a small, but possible net harm from repeated intrathecal injections compared with no additional therapy (**P/I**).

Finally, there is an unpublished, single-arm study of risdiplam in patients previously treated with onasemnogene abeparvovec; nine of 14 patients had about a four-point increase in the HFSME at one year and a six-point increase at two years. In a case series of 19 children treated with risdiplam, there were some improvements in swallowing and breathing function, but no summary data were reported. The safety profile was consistent with risdiplam's known adverse events (e.g., rash, constipation). The gains are potentially substantial and there do not appear to be important harms, but there is substantial uncertainty about the magnitude of the net benefits. We judge that there is moderate certainty of a comparable, small, or substantial net health benefit compared with no additional therapy ("comparable or better"; **C++**).

*Comparative Effectiveness of SMN Therapies for SMA*

There are no head-to-head trials comparing risdiplam, nusinersen, and onasemnogene abeparvovec to each other as first-line therapy in patients with SMA of any type, *SMN2* copy number, or age. We qualitatively assessed the available clinical evidence of presymptomatic treatment with these three therapies and found all had strong evidence of benefits including increased survival, avoidance of permanent ventilation, and achievement of motor milestones. Given the lack of comparative data, we conclude that there is insufficient data to estimate the net health benefits of risdiplam, nusinersen, and onasemnogene abeparvovec compared to one another in patients with SMA of any type or age (**I**).

*Cost-Effectiveness Results for Apitegromab*

At a placeholder price of $350,000 per year, adding apitegromab to standard of care (nusinersen and risdiplam), resulted in higher incremental costs ($6,600,000) and incremental gains of approximately 0.20 QALYs (Quality Adjusted Life Years), resulting in incremental cost-effectiveness ratios of more than $32 million per evLY (equal value life years) or QALY. At the placeholder price, the incremental cost-effectiveness ratios remained above traditional willingness-to-pay thresholds in all sensitivity and scenario analyses.

# 1. Background

Spinal muscular atrophy (SMA) is a rare genetic neuromuscular disease.[1,2] The most severe cases affecting infants and young children.[1,2] SMA incidence is approximately one in 15,000 live births or about 500 new SMA cases per year in the United States (US).[3] The most common cause of SMA is the homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q.[4-6] *SMN1* creates survival motor neuron (SMN) protein, a protein essential for motor neuron development. Although the survival motor neuron 2 (*SMN2*) gene also produces SMN protein, only a small amount of the protein it creates is functional. The number of *SMN2* copies modulates the severity of SMA, however patients without *SMN1* almost never have a sufficient level of SMN protein regardless of the number of *SMN2* copies.[11] This deficiency causes the irreversible degeneration of motor neurons, which leads to progressive muscle weakness and prevents patients from reaching motor milestones or retaining motor functions.[1]

SMA subtypes are related to age of onset and highest gross motor milestones achieved (see Table 1.1 below).[2,12,13]

**Table 1.1. Clinical Classification of SMA**

| SMA Type | SMN2 Copy Number* | Age of Onset | Highest Achieved Motor Function | Natural Age of Death |
|---|---|---|---|---|
| **0** | 0-1 | Prenatal/ Fetal | None | <6 months |
| **1** | 1-3 | <6 months | Sit with support only | <2 years |
| **2** | 2-4 | 6–18 months | Sit independently | >2 years |
| **3** | 3-4 | >18 months | Walk independently | Adulthood |
| **4** | 4 – 8 | Adult (2nd or 3rd decade) | Walk during adulthood | Adult |

Adapted from Table 1 of Verhaart, IEC, Robertson, A, Wilson, IJ, et al. 2017,[2] and Figure 1 of Schorling, DC, Pechmann, A, Kirschner, J, 2020.[13]

SMA: spinal muscular atrophy, SMN2: survival motor neuron 2

*There is overlap in SMN2 copy number among the SMA subtypes.

The natural history of SMA has been dramatically altered by the availability of disease modifying therapies. In the US, neonatal screening for SMA is now performed in all 50 states and allows for treatment prior to symptomatic diagnosis of the disease.[7] The mortality rate for patients with SMA has dropped by 77% from 2014 to 2024, likely due to the combination of newborn screening and the availability of SMN-targeted therapy.[8] In the era of prenatal testing, patients with SMA are treated based on the number of *SMN2* copies before symptoms would be clinically recognized. Patients with one to four copies of *SMN2* are treated as soon as possible following diagnosis.

The first two disease modifying therapies, nusinersen and onasemnogene abeparvovec, were reviewed in a 2019 ICER report.[9] Nusinersen (Spinraza®, Biogen), approved by the Food and Drug Administration (FDA) in 2016, is an antisense oligonucleotide that targets *SMN2* so that it creates more functional SMN protein. It is administered via intrathecal injection with four loading doses (day 0, day 14, day 28, and day 63) and every four months thereafter.[14]

Onasemnogene abeparvovec (Zolgensma®, Novartis), approved by the FDA in 2019, is a gene therapy that uses the adeno-associated virus serotype 9 (AAV-9) vector to deliver a functional copy of the *SMN1* gene.[10] Onasemnogene abeparvovec is given as a one-time intravenous (IV) injection.

Risdiplam (Evrysdi®, Genentech), approved by the FDA in 2020, is a splicing modifier that, like nusinersen, targets *SMN2* to increase the production of SMN. Unlike nusinersen, it is an oral medication taken once daily. ICER did not review risdiplam in 2019.

During ICER's review in 2019, questions arose about whether patients who received onasemnogene abeparvovec were likely to also be treated with nusinersen and whether such treatment would be beneficial. During this review, we heard about the use of nusinersen or risdiplam in patients who were previously treated with onasemnogene abeparvovec, and that questions remain as to whether these drugs provide additional benefit.

Despite improvements for patients with SMA with the above treatments, there are many individuals with Type 2 and Type 3 SMA who developed the disease prior to newborn screening. While it is likely that the above therapies improve outcomes for these patients, lost nerve function is not regained. Apitegromab (Scholar Rock) is a new therapy that is being evaluated to improve muscle function in patients with symptomatic SMA with a Prescription Drug User Fee Act (PDUFA) date of September 22, 2025.[15] It is a selective inhibitor of a myostatin precursor. Myostatin inhibits muscle growth and strength; inhibiting myostatin may increase muscle size and strength. It is being studied in patients with Type 2 and Type 3 SMA and is given by intravenous (IV) infusion every four weeks.

**Table 1.2. Interventions of Interest**

| Intervention | Mechanism of Action | Delivery Route | Prescribing Information |
|---|---|---|---|
| **Apitegromab** | Myostatin inhibitor | Intravenous infusion | TBD |
| **Spinraza (nusinersen)** | Survival motor neuron-2 (SMN2)-directed antisense oligonucleotide | Intrathecal injection | 12 mg; four loading doses (50 mg), first three doses at 14-day intervals and the fourth at 30 days after the third loading dose. Maintenance dose (12 mg) every four months thereafter. |
| **Zolgensma (onasemnogene abeparvovec)** | Adeno-associated virus (AAV) vector-based gene therapy | One-time intravenous infusion | $1.10x10^{14}$ vg/kg |
| **Evrysdi (risdiplam)** | Survival motor neuron-2 (SMN2) splicing modifier | Oral solution or tablet once daily | 60 mg for the oral solution, 5 mg for the tablet.<br><br>Recommended daily dosage per age and weight:<br>Oral: 0.15 mg/kg for ages <2 months; 0.2 mg/kg for ages 2 months to ≤2 years; 0.25 mg/kg for ages ≥2 years, and weight <20 kg.<br>Oral or tablet: 5 mg for ages ≥2 years and weight ≥20 kg. |

kg: kilograms, mg: milligrams, mg/kg: milligrams per kilograms, TBD: to be determined, vg: vector genomes

# 2. Patient Community Insights

Patients and caregivers reported the desire for treatments that improve strength and the ability to live more independently. We also heard extensively about the importance of early identification of and treatment for SMA and how this has become more common since our prior report.

To supplement our discussions and open input comments, we also reviewed the "Voice of the Patient" report, which summarizes a Patient-Focused Drug Development meeting hosted by Cure SMA in April 2017.[16] The meeting gathered patients' and families' perspectives on living with SMA and on current and future therapies. Many of the key themes from the meeting echoed those we heard from our conversations with caregivers and patient advocates. Additional themes related to the burden of disease included communication challenges as children with SMA grow, the concern of developing scoliosis (particularly for patients with Type 2), and the constant worry about further loss of functional ability. Additional themes related to treatment options included optimism about disease-modifying treatments, an expectation that some symptoms will exist even with treatment, and a desire for treatments that improve strength and functional ability while also valuing treatments that stabilize the disease. It was also highlighted that relatively small improvements on one of the scales may have an enormous impact on individuals. For instance, a small gain in finger strength that allows an individual to drive a power wheelchair can be transformative for that individual patient. Or a small increase in jaw strength that allows an individual to chew more effectively may markedly improve their ability to eat.

Based on patient input, we included efficacy outcomes related to bulbar function (e.g., swallowing, speaking) to better reflect what is important to patients with SMA and their families. Comments about families' experiences with SMA provided patient-centered context for interpreting clinical trial outcomes by communicating the importance of independent functioning for older children and adults with SMA, and the delay of disease progression for infants and younger children with SMA. These comments particularly underscored the importance of not only improved mobility but also slowed progression and stabilization of current motor functions, including smiling and independent sitting, eating or feeding, toileting, and transferring from wheelchairs.

The impact of disease-modifying therapy on respiratory function is lifesaving and can prevent the need for respiratory support. However, the impact of therapies on other improvements in respiratory function are rarely captured or studied. Older patients commonly complain of fatigue, but this has rarely been reported in clinical trials. Other areas in need of further research include nutrition (for weight gain, weight loss, and optimizing strength), therapies for managing fatigue, and therapies to prevent and treat scoliosis.

We heard about the challenges with intrathecal therapy, often requiring general anesthesia with intubation to safely perform the lumbar puncture. This is traumatic for the affected child and the

parents. This can become nearly impossible if the patient requires spinal fusion with hardware to treat scoliosis.

We also reviewed Cure SMA's "2024 Annual State of SMA" report, which was released on March 31, 2025.[8] Among adult patients, 89% reported that gaining muscle strength was their greatest unmet need. Mental health challenges were common, including 45% of adults reporting that they needed mental health services but did not know how to access them. In addition to themes like those reported above, the report highlighted financial toxicity in many forms. About one in 10 adults with SMA reported that they had to skip buying medications or going to doctors' appointments to save money and reported worrying that their food would run out before they received money to buy more. Adults reported working part-time to stay below an income threshold for services, and half of caregivers reported financial issues due to travel expenses. Insurance denials for SMA treatments were reported by more than half of the individuals. When choosing SMA treatment, caregivers reported that efficacy and safety were far more important than route of administration, dosing schedule, or cost coverage. The top five unmet needs of caregivers were support for fatigue, mental health care, financial assistance, flexible work arrangements, and nursing support for their child.

# 3. Comparative Clinical Effectiveness

## 3.1. Methods Overview

Procedures for the systematic literature review are described in Supplement Section D1. A research protocol is published on Open Science Framework and registered with PROSPERO (CRD420250652453).

### Scope of Review

This review includes three components:

1. An assessment of the comparative clinical effectiveness and economic value of apitegromab as an add-on therapy to background disease-modifying therapy (nusinersen or risdiplam).

2. An evaluation of the net health benefit of risdiplam or nusinersen as add-on therapy in patients previously treated with onasemnogene abeparvovec.

3. A clinical effectiveness assessment of whether there was a comparative advantage as a first-line therapy among nusinersen, onasemnogene abeparvovec, and risdiplam.

For each component, the population includes infants, children, and adults across the entire spectrum of SMA disease (presymptomatic and Types 0-4 SMA). We sought evidence on patient-important outcomes, including increased survival, improvements in functional mobility and activities of daily living, avoidance of permanent invasive ventilation, health-related quality of life, and adverse events. The full scope of the review is described in Supplement Section D1.

## 3.2 Assessment of Apitegromab

### Evidence Base

The evidence base for apitegromab includes one uncontrolled dose-finding Phase II study (TOPAZ), a pivotal Phase III trial (SAPPHIRE), and the long-term follow-up of participants in those two trials (ONYX).

SAPPHIRE was a Phase III pivotal trial that evaluated apitegromab in non-ambulatory patients ages two to 12 with Types 2 and 3 SMA.[17] Trial enrollees were randomized to one of three study arms: intravenous infusion of apitegromab at either 10 or 20 mg/kg every four weeks, or placebo. All enrolled patients were receiving either nusinersen or risdiplam at baseline and continued their therapy throughout the trial. An exploratory subgroup of trial participants ages 13 to 21 were

randomized 2:1 to apitegromab 20 mg/kg or placebo. Prior treatment with onasemnogene abeparvovec was an exclusion criterion. See Supplement Table D3.1 for additional study details.

The primary trial population, consisting of 156 participants aged two to 12 years, was 53% male with a mean age of 7.8 years. Most participants had received nusinersen therapy prior to enrollment, typically for approximately five years. Participants predominantly had Type 2 SMA and possessed two copies of the *SMN2* gene. Furthermore, over 70% had a history of scoliosis. See Supplement Table D3.2 for additional baseline characteristics.

Study results from the SAPPHIRE trial have not yet been published in a peer-reviewed article and were most recently presented at the Muscular Dystrophy Association's Clinical & Scientific Conference in March 2025.[17] A preliminary assessment found the trial to be at low risk of bias. However, we have low certainty on this assessment because peer-reviewed results, the study protocol and the full analysis plan have not been published (Supplement Table D1.3).

The SAPPHIRE trial had two co-primary endpoints comparing the change from baseline to 12 months in the Hammersmith Functional Motor Scale Expanded (HFMSE) total score in two intervention groups compared to the change in the placebo group. The first co-primary outcome compared the change in the two apitegromab treatment groups combined (10 mg/kg and 20 mg/kg groups) to the change in the placebo group. The second co-primary outcome compared the change in the apitegromab group receiving the 20 mg/kg dose alone to the placebo group. Other measures included changes from baseline in the Revised Upper Limb Module (RULM) and World Health Organization's (WHO) motor development milestones. See Supplement A1 for an overview of study outcome measurements.

The Phase II TOPAZ study evaluated apitegromab in an open-label study of 58 participants.[18] The primary objective of the TOPAZ trial was to evaluate the safety and tolerability of the drug. As such, our main interest lies in the long-term follow-up of the drug. Patients who finished 12 months of follow-up were continued on treatment at the 20 mg/kg dose for an additional 36 months.[19]

ONYX is the long-term extension study of participants in TOPAZ or SAPPHIRE.[20] At the time of this review, no data are available from this study. OPAL is an ongoing Phase II trial that is studying apitegromab in SMA patients younger than two years old who with prior ongoing treatment of the three SMN therapies.[21] See Supplement Table D4.1 for additional details of ongoing studies.

### *Evaluation of Clinical Trial Diversity*

We rated the demographic diversity (race/ethnicity, sex) of the participants in the two trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[22] We did not assess older adult representation in clinical trials, as the SMA population is predominantly young (49% aged 17 or younger, average age 22.4).[8] (See Supplement D1 for full details of CDR methods and results).

**Table 3.1. Diversity Ratings on Race and Ethnicity, and Sex**

| Trial | Race and Ethnicity | Sex |
|---|---|---|
| **SAPPHIRE** | Poor | Good |
| **TOPAZ** | Fair | Good |

Race and Ethnicity: The SAPPHIRE trial received a "poor" rating due to underrepresentation of participants with SMA who identify as Hispanic/Latino and lack of reported data for race. The TOPAZ trial received a "fair" rating due to underrepresentation of Black/African American and Hispanic/Latino participants with SMA.

Sex: Both trials achieved a "good" rating on the representation of male and female participants.

## Clinical Benefits of Apitegromab

### *Measures of Functional Mobility*

In the SAPPHIRE trial,[17] (Table 3.2) mean HFMSE total scores increased by 0.6 points from baseline (from 25.5 to 26.1) in the combined apitegromab groups (10 and 20 mg/kg) and declined by 1.2 points in the placebo group. The between group difference was statistically significant (1.8 points, p=0.02). The difference in HFMSE scores between the 20 mg/kg group and the placebo group was not statistically significant (1.4 points, p=0.11).

An increase of three points on the HFMSE is considered clinically meaningful.[23] The proportion of patients with an increase of at least three points was greater in the combined apitegromab groups than the placebo group (30.4% vs. 12.5%, odds ratio 3.0, p=0.03).

Between group differences using RULM and WHO motor development milestones were not statistically significant.

**Table 3.2. SAPPHIRE Trial Results[17]**

| Arms | | Apitegromab + SOC (N=106) | Placebo + SOC (N=50) |
|---|---|---|---|
| HFMSE at Week 52 | LS Mean Change from Baseline (SE) | 0.6 (0.48) | -1.2 (0.66) |
| | LS Mean Change from Baseline (95% CI) vs. Placebo; p-Value | 1.8 (0.30, 3.32); p=0.02 | |
| | ≥3 Point Improvement, n/N (%) | 31/102 (30.4) | 6/48 (12.5) |
| | ≥3 Point Improvement, Odds Ratio (p-Value) | 3.0 (0.03) | |
| RULM LS Mean Change from Baseline (SE) at Week 52 | | 0.8 (0.29) | 0.1 (0.40) |
| WHO Motor Development Milestone LS Mean Change from Baseline (SE) at Week 52 | | 0.09 (0.07) | -0.03 (0.10) |

CI: confidence interval, HFMSE: Hammersmith Motor Function Scale Expanded, LS: least squares, n/N: number, RULM: Revised Upper Limb Module, SE: standard error, SOC: standard of care with treatment of either nusinersen or risdiplam, WHO: World Health Organization

*Durability of Clinical Benefit*

Evidence from the SAPPHIRE trial is limited to one year of follow-up. In the TOPAZ trial, non-ambulatory trial participants aged 2 to 19 received one year of treatment with apitegromab (2 or 20 mg/kg infusion every four weeks) added to nusinersen, followed by 20 mg/kg dose for an additional 36 months.[19] On average, participants had an improvement or maintenance of benefit in their HFMSE and RULM total scores. A high proportion of participants (83%) also saw improvement or maintenance of their WHO motor milestones at the end of follow-up.

*Other Outcomes*

The SAPPHIRE study did not measure or report other important patient-important factors, including mortality, avoidance of permanent invasive ventilation, bulbar function (e.g., swallowing and speaking), health-related quality of life, impact on activities of daily living, or caregiver burden.

### *Subgroup Analyses and Heterogeneity for Apitegromab Added to SMN Targeted Disease Modifying Therapy*

Subgroup analyses for apitegromab (10 and 20 mg/kg combined) were performed for the change from baseline HFMSE score at 12 months.[17] There was no evidence of effect modification by baseline SMN therapy (nusinersen or risdiplam), age at SMN therapy initiation (<5 or ≥5 years), or region (Europe or North America), although the small sample size precludes firm conclusions. See Supplement Section D6 for details.

There were no available data to evaluate treatment effect modification by subpopulations defined by sociodemographic factors (e.g., sex, race/ethnicity), SMA subtype, or prior treatment with onasemnogene abeparvovec.

## Harms of Apitegromab

In the SAPPHIRE trial, there were no reported adverse events that led to treatment discontinuation, study withdrawal, or death.[17] There were no notable differences in safety outcomes between study doses (10 vs. 20 mg/kg).

The most frequent adverse events observed in the trial were pyrexia, nasopharyngitis, and cough.[17] These appear to be evenly distributed between the pooled apitegromab and placebo arms; no statistical tests were reported. A greater percentage of patients experienced a serious adverse event in the pooled apitegromab study arm (19.8%) than placebo (10%). Among these, pneumonia and dehydration were only observed in patients taking apitegromab.

Evidence from the earlier Phase II TOPAZ trial demonstrated a similar safety profile. The most common adverse events across 48 months of follow-up were COVID-19, pyrexia, upper respiratory tract infection, headache, cough, and nasopharyngitis, with only one participant (1.7%) discontinuing apitegromab due to an adverse event.[19]

**Table 3.3. SAPPHIRE Safety Outcomes[17]**

| Arms | | Apitegromab (10 and 20 mg/kg) + SOC | Placebo + SOC |
|---|---|---|---|
| **N** | | 106 | 50 |
| **AE, n (%)** | | 97 (91.5) | 43 (86.0) |
| **SAE, n (%)** | | 21 (19.8) | 5 (10.0) |
| **AE Grade ≥3, n (%)** | | 20 (18.9) | 5 (10.0) |
| **AE Leading to Treatment Discontinuation, n (%)** | | 0 | 0 |
| **AE Leading to Study Withdrawal, n (%)** | | 0 | 0 |
| **AE with Highest Incidence, n (%)** | **Pyrexia** | 31 (29.2) | 16 (32.0) |
| | **Nasopharyngitis** | 26 (24.5) | 10 (20.0) |
| | **Cough** | 26 (24.5) | 11 (22.0) |
| **SAE with Highest Incidence, n (%)** | **Pneumonia** | 7 (6.6) | 0 |
| | **Dehydration** | 3 (2.8) | 0 |

AE: adverse events, kg: kilograms, mg: milligrams, n, N: number, SAE: serious adverse events, SOC: standard of care with treatment of either nusinersen or risdiplam

### Uncertainty and Controversies

It is unclear what dose of apitegromab is optimal. In the Phase II TOPAZ trial, 20 mg/kg appeared to be superior to 2 mg/kg. However, in the Phase III SAPPHIRE trial, patients receiving the 10 mg/kg dose had significantly better outcomes than the placebo group, while patients receiving the 20 mg/kg dose did not. In addition, the increase in latent myostatin levels was essentially identical in the 10 and 20 mg/kg arms at all timepoints.[24]

Given the short duration of the SAPPHIRE trial, there are uncertainties about the duration of the benefits and whether they may increase or decrease with time. Similarly, there may be unknown harms that are only identified when larger numbers of patients are treated for longer periods of time.[25]

Both pneumonia and dehydration were serious adverse events that occurred in the apitegromab-treated group and not in the placebo group, but the trial was small, so these could be by chance rather than caused by apitegromab.

There are no data on the efficacy of apitegromab in patients with Type 1 or Type 4 SMA and no data in patients younger than two years of age. The exploratory data on outcomes for patients older than 12 years in the SAPPHIRE have not been fully presented, nor is there a peer-reviewed publication for overall study results. This limits our ability to assess the risk of bias.

## 3.3 Assessment of SMN-Targeted Therapies After Gene Therapy (Onasemnogene Abeparvovec)

### Evidence Base

We identified one single-arm study of nusinersen and two studies of risdiplam in SMA patients previously treated with gene therapy.

#### *Nusinersen*

RESPOND is a single-arm open-label trial that evaluated nusinersen in infants less than 36 months old with unmet clinical needs previously treated with onasemnogene abeparvovec.[26,27] 46 participants received nusinersen, and were divided into three cohorts. Cohort 1 (n=21) included participants with two *SMN2* copies who were ≤9 months of age at first nusinersen dose; cohort 2 (n=13) participants also had two *SMN2* copies and received their first dose after 9 months of age. The third cohort (three *SMN2* copies, >9 months at treatment, n=3) had too few participants to report on outcomes of interest.

Cohort 1 participants received an SMA diagnosis at a median of 0.9 months, gene therapy at 1.7 months (median) and subsequently their first nusinersen dose at 7.7 months (median).[27] Patients in the second cohort had a later diagnosis (median age of 2.1 months), and greater time to gene therapy (median 2.7 months) and nusinersen initiation (median 16.3 months).

Interim results on motor function, biomarkers, and safety outcomes were presented at conferences following evaluations on days 183 and 302.[26,27] Full study results are expected to report on outcomes with up to 778 days of follow-up.

***Risdiplam***

JEWELFISH was an open-label exploratory study evaluating the safety and tolerability of risdiplam in 174 patients ages six months and above, 14 of whom had previously been treated with onasemnogene abeparvovec at least 12 months prior to screening.[28] At baseline, this subset of patients had a median age of two years (range of one to five) and received gene therapy at a median of 29 months (range 20 to 59) after initial SMA symptom onset.[29] The cohort consisted predominantly of Type 2 SMA patients (71%) with the remainder being Type 1 (29%). With regards to SMN2 copy number, 71% had three copies, 21% had one copy and 7% had two copies. Three out of 14 (27%) patients had a baseline HFMSE total score of less than 10 out of 66. A post hoc analysis assessed patients on changes from baseline in three motor function scales: the 32-item Motor Function Measure (MFM32), RULM, and HFMSE.

Findings from the JEWELFISH study prompted two ongoing Phase IV studies, HINALEA 1 and 2, that are evaluating the effectiveness and safety of risdiplam after onasemnogene abeparvovec treatment pre- and post-development of symptoms. Study details are provided in Supplement Table D4.1.

Additionally, we reviewed conference poster findings from a US-based multicenter case series of 19 children who had received risdiplam after initial treatment with onasemnogene abeparvovec.[30] Patients experienced onset of symptoms at a median age of 2.6 months (range of 1 week to 6.5 months) and a diagnosis at 4.9 months (range 0 to 17 months). These children predominantly had two copies of *SMN2* (79%) and were Type 1 SMA (84%). At baseline, the children had a mean CHOP-INTEND score of 26.2 (range 20 to 39) out of 64. In this population, the median time between diagnosis and administration of gene therapy was approximately one month (range 0.5 to 22), with six of the 19 children having received nusinersen treatment in between diagnosis and gene therapy. Consequently, patients received their first dose of risdiplam at approximately 14 months (range 7 to 25) after treatment with onasemnogene abeparvovec.

## Clinical Benefits of SMN-Targeted Therapies After Gene Therapy (Onasemnogene Abeparvovec)

### *Nusinersen*

Interim results of the RESPOND trial at day 302 of follow-up have been presented for two cohorts.[26] Participants in Cohort 1, children with two *SMN2* copies and first nusinersen dose at ≤9 months of age (n=21), had a mean increase of 8.7 points on the Hammersmith Infant Neurological Examination – Section 2 (HINE-2) scale. Participants in Cohort 2, children with two *SMN2* copies with first dose after 9 months of age, had a mean increase of 6.9 points (n=13). By day 302, children in Cohort 1 and 2 achieved a mean total score of 11.6 and 15.2 on the HINE-2, respectively, out of a maximum of 26 points. Additionally, 14 of 27 children (52%) achieved a new ability to sit without support.

Participants in both cohorts also showed reduced plasma neurofilament light protein (NfL) concentrations, a potential biomarker of treatment response.[31] By day 302, patients saw a decline of 77% in NfL from a mean baseline of 132.0 pg/mL in Cohort 1, and a decline of 82% from a baseline of 121.0 pg/mL in Cohort 2.

### *Other Outcomes*

The RESPOND trial is scheduled for completion in October 2025 (See Supplement Table D4.1-Ongoing Studies) and we await additional results up to 778 days of follow-up, including on outcomes of time to death/permanent ventilation, RULM, HFMSE, and WHO milestones.

### *Risdiplam*

After 104 weeks of treatment with risdiplam, nine participants in JEWELFISH had an increase of approximately 6 points on the motor function scales of MFM32, RULM, and HFMSE.[28] These results were estimated from a bar graph in the conference poster. Baseline and values at end of follow-up for the three scales were not reported.

In the case series of 19 children treated with risdiplam, there were some improvements in swallowing and breathing function.[30] Three severely affected children progressed from gastrostomy tube dependence to some oral feeding, while two with milder issues achieved complete independence from the feeding tube. Respiratory improvements included three children reducing non-invasive ventilation (NIV) from 24-hours a day to sleep-only use, and one eliminating non-invasive ventilation entirely. Two patients showed more modest respiratory gains and one started nighttime NIV, likely due to disease progression. Eleven out of twelve patients (92%) experienced either an improvement or stability in their CHOP-INTEND and HFMSE scores. No summary results were presented. Notably, one child experienced an increase of 12 points on the HFMSE (18 to 30)

after starting risdiplam at approximately 39 months of age, having first had previous treatment with nusinersen for 19 months, and receiving gene therapy at 24 months of age.

## Harms of Nusinersen

Many of the frequently reported AEs reported following treatment with nusinersen were related to the lumbar puncture procedure (e.g., fever, headache, vomiting, and back pain).[32] Additional side effects include lower respiratory infections and constipation in patients with infant-onset SMA, and pyrexia, headache, vomiting, and back pain in patients with later-onset SMA. More serious adverse events include increased risk of bleeding (due to low platelet count or coagulation issues) and renal toxicity (elevated urine protein). Ongoing monitoring for these risks is recommended at start of therapy and prior to each subsequent treatment.

## Harms of Risdiplam

Patients with SMA treated with risdiplam were more likely to experience fever, diarrhea, rash, mouth and aphthous ulcers, arthralgia, and urinary tract infection than control patients.[33] Risdiplam can be administered as an oral solution or in tablet form.

## Harms of Onasemnogene Abeparvovec

The viral vector used to deliver onasemnogene abeparvovec is associated with increased risk of serious liver injury and acute liver failure, including fatal cases, necessitating careful monitoring of liver function and the administration of systemic corticosteroids before and after infusion.[34] Patients with pre-existing liver impairment may be at increased risk of these hepatic complications. Patients are also at increased risk and require proactive monitoring for thrombocytopenia, thrombotic microangiopathy, and cardiac injury. There is also a theoretical risk of oncogenesis due to the insertion of the gene into the host deoxyribonucleic acid (DNA).

Onasemnogene abeparvovec can have infusion-related reactions including rash, urticaria, vomiting, dyspnea, respiratory symptoms and/or alterations in heart rate and blood pressure.[34]

## Uncertainty and Controversies

The majority of the data on additional treatments of patients with SMA following gene therapy are small studies that have been presented at conferences and are not peer-reviewed. In addition, all of the studies are uncontrolled. While this is generally not a problem in trials comparing disease-modifying SMA therapies to no treatment, because of the severity of the outcomes in untreated children, uncontrolled studies limit our ability to assess the benefits and harms of therapies added after gene therapy. As normal children grow, they reach additional developmental milestones due to improving strength and coordination. Children with SMA who receive SMN-target therapies may

also reach new milestones as they grow. However, children with severe forms of SMA have significant neurologic impairments at birth.[35] Even with early initiation of disease-modifying therapy, these children may never reach some milestones. However, in children who achieve milestones, with further growth there may be competing factors of improvements in strength and coordination as well as inadequate strength to manage size and weight increases. As such, changes in function, including some loss of function, may not necessarily be due to insufficient effects of gene therapy. This is necessarily difficult to assess fully without randomized trials.

## 3.4 Assessment of Comparative Effectiveness of SMN Therapies for SMA

### Evidence Base

There are no head-to-head trials between nusinersen, onasemnogene abeparvovec, and risdiplam as first-line therapy for patients with SMA.

In this section, we provide a qualitative synthesis of the known clinical benefits and harms of the three therapies. Universal newborn screening for SMA in the US has allowed for earlier diagnosis and treatment. According to the 2024 Cure SMA annual report, the average age at first treatment in 2024 was 23 days, with an estimated 74% of diagnosed infants that year receiving treatment by 30 days old [8]. Our primary interest in this report involves examining the clinical benefits and harms in patients with genetically confirmed SMA who have not yet manifested clinical symptoms. Thus, we organized our analysis into two sections: 1) evidence for patients with presymptomatic SMA (detailed below) and 2) evidence for patients with symptomatic SMA (see Supplement Section D2).

### Presymptomatic SMA

We identified three relevant single-arm interventional studies, all of which included cohorts of participants with two and three copies of *SMN2*, who are likely to develop Types 1 or 2 SMA, respectively (Table 3.4).

**Table 3.4. Interventional Studies of Presymptomatic Treatment for SMA: Baseline Characteristics**

| Trial | | NURTURE[36,37] | | SPR1NT[38,39] | | | RAINBOWFISH[40]* | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Historical Untreated Cohort (PNCR) | Treated Cohorts | | | | |
| ***SMN2* Copy Number** | | 2 | 3 | 2 | 2 | 3 | 2 | 3 | ≥4 |
| **Intervention** | | Nusinersen | | Onasemnogene abeparvovec | | | Risdiplam | | |
| **Follow-Up Period** | | 5 years, up to 8 years | | 18 months | | 24 months | 12 months, up to 7 years | | |
| **N** | | 15 | 10 | 23 | 14 | 15 | 8 | 13 | 5 |
| **Age at Diagnosis, Days, Median (Range)** | | N/A | N/A | N/A | 8.0 (1 – 14) | 8.0 (2 – 26) | NR | NR | NR |
| **Age at First Dose, Median (range)** | | 19.0 (8 – 41) | 23.0 (3 – 42) | N/A | 21.0 (8 – 34) | 32.0 (9 – 43) | 23.5 (16 – 35) | 28.0 (20 – 41) | 32.0 (24 – 40) |
| **Gender, n (%)** | **Female** | 7 (47) | 6 (60) | NR | 10 (71) | 9 (60) | 4 (50) | 9 (69) | 3 (60) |
| | **Male** | 8 (53) | 4 (40) | NR | 4 (29) | 6 (40) | 4 (50) | 4 (31) | 2 (40) |
| **SMA Identification Method, n (%)** | **Newborn Screening** | NR | NR | NR | 9 (64) | 13 (87) | 4 (50) | 11 (85) | 5 (100) |
| | **Family History** | NR | NR | NR | NR | NR | 4 (50) | 2 (15) | 0 (0) |
| | **Prenatal Testing** | NR | NR | NR | 5 (36) | 1 (7) | NR | NR | NR |
| **Baseline CHOP-INTEND Score, Median (Range)** | | 45.0 (25.0 – 60.0) | 53.5 (40.0 – 60.0) | 32.5 (31 – 33)‡ | 48.5 (28 – 57) | N/A | 46.5 (35.0 – 52.0) | 55.0 (44.0 – 62.0) | 50.0 (44.0 – 52.0) |
| **Baseline HINE-2 Score, Median (Range)** | | 3.0 (0 – 5.0) | 3.0 (0 – 7.0) | NR | NR | NR | 2.0 (0.0 – 4.0) | 3.0 (1.0 – 6.0) | 1.0 (1.0 – 4.0) |
| **CMAP Amplitude, mV†** | **Median (Range)** | 3.2 (1.1 – 9.7) | 4.00 (0.2 – 7.0) | 0.3 (0.04 – 1.1) | 3.9 (2.1 – 6.1) | 4.1 (2.7 – 7.0) | 2.0 (0.5 – 3.8) | 4.6 (2.1 – 6.7) | 3.7 (3.4 – 6.6) |
| | **Value <1.5 mV, n (%)** | NR | NR | NR | NR | NR | 3 (38) | 0 (0) | 0 (0) |
| | **Value ≥1.5 mV, n (%)** | NR | NR | NR | NR | NR | 5 (63) | 13 (100) | 5 (100) |

CMAP: compound muscle action potential, CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HINE-2: Hammersmith Infant Neurological Examination– Module 2, mV: millivolt, n:

number, N/A: not applicable, NR: not reported, PNCR: Pediatric Neuromuscular Clinical Research, SMA: spinal muscular atrophy, *SMN2*: gene coding for survival motor neuron 2
*The primary efficacy population includes five infants with two copies of the *SMN2* gene and CMAP amplitudes ≥1.5 mV at baseline. Data cut-off: 20 February 2023.
†Ulnar CMAP amplitude recorded from the abductor digiti minimi muscle at baseline for the PNCR and NURTURE studies and peroneal CMAP amplitude recorded from the tibialis anterior muscle for SPR1NT.
‡Value obtained for patients with symptom onset <3 months of age, including seven patients with two *SMN2* copies and one patient with three *SMN2* copies.

### *NURTURE (nusinersen)*

NURTURE is an ongoing Phase II study that investigated nusinersen in presymptomatic infants at risk for Type 2 SMA. The study enrolled 25 participants who were treated within 6 weeks of birth, who had either 2 copies (n=15) or 3 copies (n=10) of *SMN2*.

At baseline, infants with two copies received their first nusinersen dose at a median age of 19 days (range 8 to 41) and had a median CHOP-INTEND score of 45 out of 64. Three-copy participants received first treatment at a median of 23 days (range 3 to 42) with a median CHOP-INTEND score of 53.5.

The primary study endpoint of NURTURE was the time to death or respiratory intervention, which was defined as invasive or non-invasive ventilation for ≥6 h per day continuously for ≥7 days or tracheostomy. Secondary endpoints of the study included overall survival, achievement of WHO motor milestones (sitting without support, standing alone, walking alone), and changes in motor function (CHOP-INTEND).

### *SPR1NT (onasemnogene abeparvovec)*

SPR1NT was a Phase III trial that evaluated the efficacy and safety of a one-time intravenous infusion of onasemnogene abeparvovec against an external untreated control group in presymptomatic infants at risk of SMA Types 1, 2, or 3.[38,39] Infants were enrolled within 42 days of birth. The study was broken out into two cohorts, patients with two (n=14) or three (n=15) copies of the *SMN2* gene.

Infants with two copies of *SMN2* were diagnosed at a mean age of 7.2 days, either through newborn screening (64%) or prenatal testing (36%), and were treated with gene therapy at a mean age of 20.6 days (Table 3.4). At baseline, participants had a median CHOP-INTEND score of 49 out of 64. The primary endpoint of the study within this cohort was the ability to sit independently for at least 30 seconds at any visit by 18 months of age. Other relevant outcomes included survival without permanent ventilation, change in motor function (CHOP-INTEND), and ability to walk without assistance for at least 5 steps.

Infants with three copies of *SMN2* were diagnosed at a mean age of 9.9 days, mostly through newborn screening (87%) or prenatal testing (7%), and were treated with gene therapy at a mean age of 28.7 days (Table 3.4). The primary endpoint for this cohort was the ability to stand independently for at least 3 seconds at any visit by 24 months of age. Other secondary outcomes included survival without permanent ventilation, walking without assistance, and the ability to feed without support.

The primary and secondary outcomes from both cohorts were compared against an external control group. This group consisted of population-matched patients with two or three copies of *SMN2* from the Pediatric Neuromuscular Clinical Research (PNCR) natural history data set. Participants in the SPR1NT study were eligible for long-term follow-up via participation in the LT-002 study. Results from LT-002 were last reported at the 2023 MDA Clinical & Scientific Conference. [41]

***RAINBOWFISH (risdiplam)***

RAINBOWFISH is an ongoing single-arm Phase II trial investigating the use of risdiplam in 26 infants within 6 weeks of birth who have presymptomatic SMA. Trial participants were categorized into three cohorts: those with two, three, or four or more copies of *SMN2*.

At baseline, infants with two copies of *SMN2* (n=8) had a CHOP-INTEND median total score of 46.5 (range 35 to 52), were diagnosed with SMA via newborn screening (50%) or family history (50%), and received their first dose of risdiplam a median of 23.5 days (range 16 to 35) after birth. The three-copy cohort (n=13) had a CHOP-INTEND median total score of 55 (range 44 to 62), were primarily diagnosed via newborn screening (85%), and received their first dose at a median of 28 days (range 16 to 35).

The primary endpoint of the study was the proportion of infants with two copies of *SMN2* whose muscle response signals measured at least 1.5 millivolts at baseline, who were able to sit without support for ≥5 seconds after 12 months of treatment. Secondary endpoints included achievement of motor milestones (e.g., ability to stand or walk alone), survival and avoidance of permanent ventilation, and change in motor function. These outcomes were reported by copy number cohorts and the overall study population.

## Comparative Clinical Benefit of SMN Therapies for SMA (Presymptomatic SMA)

**Table 3.5. Interventional Studies of Presymptomatic Treatment for SMA: Primary Outcomes**

| Trial | | NURTURE[37] | | SPR1NT[38,42] | | | RAINBOWFISH[40] | |
|---|---|---|---|---|---|---|---|---|
| | | | | PNCR | Treated Cohorts | | | |
| ***SMN2* Copy Number** | | 2 | 3 | 2 | 2 | 3 | 2 | ≥3 |
| **Study Duration** | | 5 years | | 24 months | 18 months | 24 months | 12 months | |
| **Cohort Size, n** | | 15 | 10 | 23 | 14 | 15 | 8# | 18§ |
| **Survival, n/N (%)** | | 15/15 (100) | 10/10 (100) | NR | 14/14 (100)† | 15/15 (100)† | 8/8 (100) | 18/18 (100) |
| **Ventilation-Free Survival, n/N (%)** | | 15/15 (100) | 10/10 (100) | 6/23 (26)† | 14/14 (100)† | 15/15 (100)† | 8/8 (100) | 18/18 (100) |
| **BSID-III** | **Sit Without Support for ≥5 seconds, n/N (%)** | NR | NR | NR | NR | NR | 4/5¤ (80) | NR |
| | **Sit Without Support for 30 seconds, n/N (%)** | NR | NR | NR | NR | NR | 7/8 (87.5) | NR |
| **HINE-2** | **Independent Sitting, n/N (%)** | 15/15 (100) | 10/10 (100) | 0/0 (0) | 14/14 (100) | 14/15 (93) | 6/8 (75)** | 17/18 (94.4)** |
| | **Independent Standing, n/N (%)** | 13/15 (87) | 10/10 (100) | 0/0 (0) | 11/14 (79) | 15/15 (100) | 1/8 (12.5) | 12/18 (66.7) |
| | **Independent Walking, n/N (%)** | 13/15 (87) | 10/10 (100) | NR | 9/14 (64) | 14/15 (93)‡ | 1/8 (12.5) | 11/8 (61.1) |
| **Achieved Maximum CHOP-INTEND Score, n/N (%)*** | | 12/15 (80) | 10/10 (100) | NR | NR | NR | 4/5(80) | 18/18 (100) |

BSID-III: Bayley Scales of Infant and Toddler Development–Third Edition, CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HINE-2: Hammersmith Infant Neurological Examination–Module 2, n: number, NR: not reported, PNCR: Pediatric Neuromuscular Clinical Research, SMN2: survival motor neuron 2

*Achieved a CHOP-INTEND total score of ≥60 at the same two consecutive visits.

†Alive at age 14 months.

‡One additional individual walked independently by 24 months but was not captured on video.

§One infant was not tested for HINE-2 at the one-year visit in the RAINBOWFISH trial.

#One infant with ≥4 *SMN2* copies was not assessed for HINE-2 at the one-year visit in the RAINBOWFISH trial due to lack of cooperation.

¤Primary efficacy population (n=5) consisted of infants with two *SMN2* copies with a compound muscle action potential (CMAP) amplitude ≥1.5 millivolts at baseline.

**Sitting defined as 'pivots' per HINE-2 criteria.

**Table 3.6. Interventional Studies of Presymptomatic Treatment for SMA: Longest Follow-Up Data**

| | NURTURE | | SPR1NT[43] | | RAINBOWFISH[44] | |
|---|---|---|---|---|---|---|
| ***SMN2* Copy Number** | 2 | 3 | 2 | 3 | 2 | 3 |
| **Longest Follow-Up Period** | 8 years | | Mean 3.5 years (range 2.9 to 4.1) | Mean 3.2 years (range 2.8 to 3.7) | 24 months | |
| **Cohort Size, n** | NR | NR | 12 | 13 | 5 | 1 |
| **Survival, n/N (%)** | NR | NR | 12/12 (100%) | 13/13 (100%) | 5/5 (100) | 13/13 (100) |
| **Ventilation-Free Survival, n/N (%)** | NR | NR | 12/12 (100%) | 13/13 (100%) | 5/5 (100) | 13/13 (100) |
| **Independent Sitting, n/N (%)** | NR | NR | NR | NR | 5/5 (100) | 13/13 (100) |
| **Independent Standing, n/N (%)** | NR | NR | NR | NR | 3/5 (60) | 13/13 (100) |
| **Independent Walking, n/N (%)** | NR | NR | 12/12 (100%) | 13/13 (100%) | 2/5 (40) | 13/13 (100) |
| **Achieved Maximum CHOP-INTEND Score, n/N (%)** | NR | NR | NR | NR | 4/5(80) | 13/13 (100) |

CHOP-intend: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, PNCR: Pediatric Neuromuscular Clinical Research, n: number, NR: not reported, SMN2: survival motor neuron 2

### *NURTURE (nusinersen)*

A planned analysis of NURTURE assessed 25 infants at a median follow-up of 4.9 years (range 3.9 to 5.7).[37] All participants, including those with two or three copies of *SMN2*, were alive and none required permanent ventilation.

Among the two-copy cohort, all 15 (100%) participants were able to sit without support, and 13 of 15 (87%) were able to stand alone, and 13 of 15 (87%) were able to walk alone.[37] A maximum CHOP-INTEND score of 64 was achieved by 12 of 15 (80%) infants in this group.

All 10 patients (100%) in the three-copy cohort were able to sit without support, stand, and walk alone. Likewise, all 10 patients achieved the maximum CHOP-INTEND score.

*Durability of Treatment Effect*

The NURTURE study has been extended for a total follow-up period of 8 years.[45] Results at this timepoint are not yet available.

***SPR1NT (onasemnogene abeparvovec)***

Among the 14 infants with two copies of *SMN2*, all 14 (100%) were able to sit independently for at least 30 seconds at any visit up to 18 months of age. In contrast, none of the 23(0%) untreated participants in the historical control cohort achieved this milestone (p<0.0001). A greater proportion of the two-copy cohort was also able to achieve the motor milestones of standing and walking without assistance, both 10 out of 14 (71%) compared with 0% of the untreated infants (p<0.001). At 14 months of age, all 14 (100%) infants were alive and free of permanent ventilation compared with 6 of 23 (26%) in the untreated cohort (p<0.0001). By 18 months of age, all infants in this cohort had achieved a minimum CHOP-INTEND score of 58 at any visit and 13 of 14 (94%) reached a score of ≥60 points.

In the three-copy SMN2 cohort, all 15 (100%) were able to stand independently for at least three seconds at any visit up to 24 months of age compared with 19 of 81 (24%) untreated participants in the historical control cohort (p < 0.0001). Fourteen of the 15 (93%) participants were able to walk for at least 5 steps without assistance compared with 17 of 81 (21%) in the historical control cohort (p < 0.0001). All 15 (100%) participants in the cohort survived 14 months and none required permanent ventilation.

*Durability of Treatment Effect*

Long-term follow-up results from the LT-002 study reported that all SPR1NT participants were alive and none required permanent ventilation at a mean follow-up time of 3.5 (range 2.9-4.1) years and 3.2 (range 2.8-3.7) years for patients with two and three copies of *SMN2*, respectively (Table 3.6).[43]

Among the four patients who did not achieve the milestone of walking alone during the initial study timeframe, all four achieved it by May 2022. However, one of these participants did so after receiving treatment with another disease-modifying therapy.

***RAINBOWFISH (risdiplam)***

At the 12-month follow-up , four of the five (80%) infants with two copies of *SMN2* and compound muscle action potential (CMAP) amplitude of ≥1.5 mV (greater values indicate greater motor neuron function) were able to sit without support for at least five seconds, and seven of the eight (88%) infants with two copies were able to sit without support for at last 30 seconds.[40]

At the 12-month follow-up of the three or more copy cohort, 17 of 18 infants (94%) achieved independent sitting, 12 of 18 (67%) attained independent standing, and 11 of 18 (61%) were able to walk independently.

Across the entire study cohort (n=26), all infants were alive after 12 months of treatment and none required permanent ventilation. Similarly, all assessed infants were able to swallow and eat exclusively by mouth.

*Durability of Treatment Effect*

23 of the 26 original trial participants completed two years of follow-up (Table 3.6).[44] Among the five infants with two copies, 100% were able to sit without support for a minimum of both five and 30 seconds, 60% were able to stand alone, and 60% walked alone.

Among the 13 infants with three copies, all achieved the milestone of independent sitting for at least five seconds (92% were able to do so for at least 30 seconds), and 100% were able to stand and walk alone.

After two years of follow-up, there were no deaths or requirements for permanent ventilation among the two or three copy cohorts. Likewise, all participants were able to swallow and feed by mouth.

## Uncertainty and Controversies

There are no head-to-head trials comparing the potential first-line therapies for patients with SMA. Although several quantitative indirect treatment comparisons have been published, they are limited by differences in participant selection, variations in baseline characteristics, inconsistent outcome definitions, and inadequate balancing of confounding factors.[46,47]

Our qualitative overview of the evidence confirms the uncertainty in making any firm judgements between the three pivotal trial results. All three trials had small cohort sizes, variations in enrollment criteria, and different follow-up times.

The trials used varying CMAP amplitude thresholds, with higher values indicative of more functional motor neurons and healthier overall neuromuscular function. The NURTURE trial enrolled patients

with 1 mV ulnar CMAP whereas RAINBOWFISH required 1.5 mV and SPR1NT required at least 2 mV personal CMAP. These differences, along with the varying baseline total CHOP-INTEND scores shown in Table 3.4, suggest that the trials had patients with different levels of motor function and disease severity.

The NURTURE trial has the longest reported mean follow-up results of its participants of five years, compared to shorter durations of SPR1NT (mean of 3.5 years) and RAINBOWFISH (two years). Longer follow-up from each trial has shown that an increasing proportion of patients have achieved milestones not previously reached in earlier data cuts, suggesting that longer follow-up is likely to reveal better outcomes.

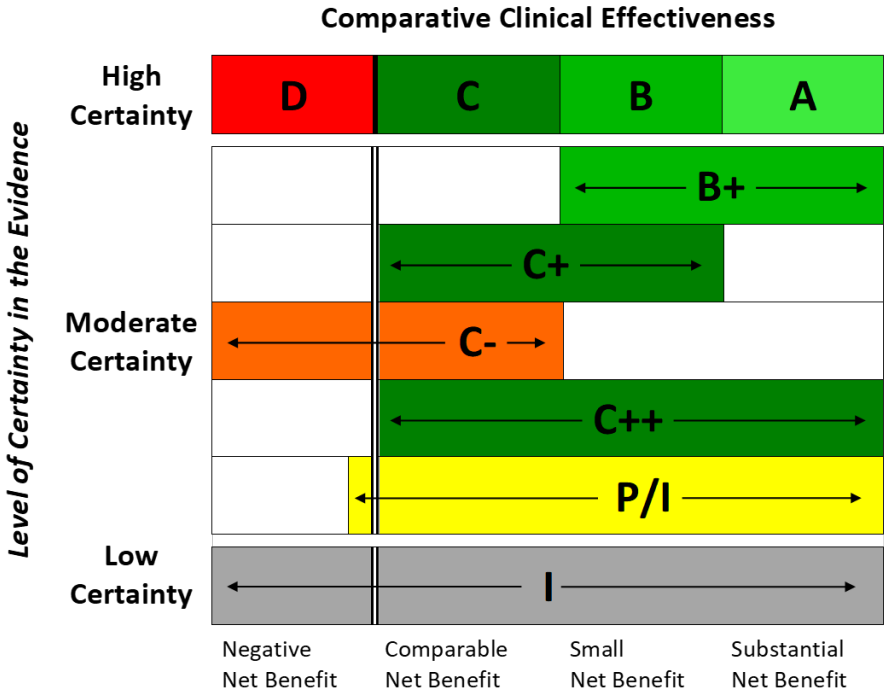
The reporting of the RAINBOWFISH results from its three-copy cohort at 12 months included participants with four or more copies, a copy number associated with a milder phenotype and slower disease progression. This comingling of copy numbers may have inadvertently inflated observed positive outcomes.

Finally, there are new formulations of the existing drugs with limited data on comparative efficacy. These include higher dose nusinersen, intrathecal delivery of onasemnogene abeparvovec, and a tablet formulation of risdiplam. It is currently unclear how these new formulations will fit into the treatment landscape.

## 3.5. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

**Figure 3.1. ICER Evidence Rating Matrix**




***A = "Superior" -*** *High certainty of a substantial (moderate-large) net health benefit*
***B = "Incremental" -*** *High certainty of a small net health benefit*
***C = "Comparable"-*** *High certainty of a comparable net health benefit*
***D= "Negative"-*** *High certainty of an inferior net health benefit*
***B+= "Incremental or Better" –*** *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
***C+ = "Comparable or Incremental" -*** *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
***C- = "Comparable or Inferior" –*** *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
***C++ = "Comparable or Better" -*** *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
***P/I = "Promising but Inconclusive"*** *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
***I = "Insufficient" –*** *Any situation in which the level of certainty in the evidence is low*

Because so few patients are living with SMA, the ICER ultra-rare disease framework applies to this report. We want to acknowledge the challenges of generating evidence for ultra-rare treatments, including challenges recruiting participants for randomized controlled trials (RCTs), validating surrogate outcome measures, and obtaining long-term data on safety and on the durability of clinical benefit. We appreciate the hard work done by the manufacturers and the patient community to generate the evidence needed to assess the value of treatments for patients with SMA.

Additionally, we want to be clear that we are not comparing disease-modifying therapy with no disease modifying therapy in this report as we continue to believe that, for most patients with SMA, we have high certainty that disease-modifying therapy provides a substantial net health benefit.

## Apitegromab

Among patients ages two to 12 years old with Type 2 or 3 SMA already receiving treatment with risdiplam or nusinersen, the added benefit of apitegromab was small: a gain of 0.6 points on the HFMSE (from 25.5 to 26.1) after one year, compared with a drop of 1.2 points in patients who received placebo (p=0.019). This difference was less than the MCID of three points, but more patients in the apitegromab group had an increase of at least three points at one year (30.4% vs. 12.5%, p=0.016). Interestingly, there was no dose response in the pivotal trial: patients receiving the 10 mg/kg dose had a greater increase in the HFSME score (2.2 points difference from placebo) than patients receiving the 20 mg/kg dose (1.4 points). Extended follow-up of patients participating in the Phase II trial suggests that the benefits remain steady through four years of follow-up. There were almost twice as many serious adverse events in patients treated with apitegromab (19.8% vs. 10.0%). These were primarily pneumonia (6.6%) and dehydration (2.8%), neither of which occurred among patients who received the placebo. It is difficult to be certain whether these serious adverse events were caused by treatment with apitegromab and no patients dropped out of the study due to AEs. Given that the net health benefit is based on one small, unpublished study, and that there were more serious adverse events in the apitegromab arm, the level of certainty around net health benefit is modest at best. We judge that treatment with apitegromab likely provides comparable or incremental benefits compared with no additional therapy in patients ages two to 12 years old with Type 2 or 3 SMA already receiving treatment with risdiplam or nusinersen, but that there is some possibility of substantial benefit with long-term use as well as some possibility of net harm. As such, we rate apitegromab “promising but inconclusive” (P/I). There are insufficient data to estimate the net health benefits of apitegromab in other populations (I).

## SMN-Targeted Therapies After Gene Therapy (Onasemnogene Abeparvovec)

There is one unpublished, single-arm study of nusinersen in 29 patients with suboptimal response to onasemnogene abeparvovec. The addition of nusinersen was associated with an increase of about five points on the HINE-2 score at six months and about seven points at 10 months. No new harms were identified, but repeated intrathecal procedures are burdensome and have rare but serious potential adverse events. Given the substantial uncertainty, we judge that there is moderate certainty of comparable to substantial net benefit, with a small, but possible net harm compared with no additional therapy (P/I).

Finally, there is an unpublished, single-arm study of risdiplam in patients previously treated with onasemnogene abeparvovec; nine of 14 patients had about a four-point increase in the HFSME at one year and a six-point increase at two years. In a case series of 19 children treated with risdiplam,

there were some improvements in swallowing and breathing function, but no summary data were reported. The safety profile was consistent with risdiplam's known adverse events (e.g., rash, constipation). The data come from two small, uncontrolled studies, making it impossible to assess whether the gains are from risdiplam or late benefits of gene therapy. The gains are potentially substantial and there do not appear to be important harms, but there is substantial uncertainty about the magnitude of the net benefits. The ongoing HINALEA 1 and 2 studies will provide additional information. We judge that there is moderate certainty of a comparable, small, or substantial net health benefit compared with no additional therapy (C++).

## Comparative Effectiveness of SMN Therapies for SMA

There are no head-to-head trials comparing risdiplam, nusinersen, and onasemnogene abeparvovec to each other as first-line therapy in patients with SMA of any type, *SMN2* copy number, or age.

We qualitatively assessed the available clinical evidence of presymptomatic treatment with three therapies and found all had strong evidence of benefit regarding survival, avoidance of permanent ventilation, achievement of motor milestones, many within the normal development times, particularly in those with three copies of *SMN2*. Historical data of untreated patients show that very few infants with two copies of *SMN2* live beyond two years.

Attempts at quantitative indirect comparisons have been made by manufacturers, but the level of evidence remains low because the included studies differ in patient selection criteria, baseline characteristics, and outcome definitions. Without individual patient-level data from all the trials, it is not possible to balance potential confounding factors, and even with such data it is not clear that adequate adjustment could be performed.

Thus, we conclude that there is insufficient data to estimate the net health benefits of risdiplam, nusinersen, and onasemnogene abeparvovec compared to one another in patients with SMA of any type or age (I).

**Table 3.7. Evidence Ratings**

| Treatment | Comparator | Evidence Rating |
|---|---|---|
| **Apitegromab as an add-on to risdiplam or nusinersen** | Risdiplam or nusinersen alone | P/I: Promising but Inconclusive in Type 2/3 SMA patients ages two to 12 years |
| | | Insufficient in all other populations |
| **Nusinersen in patients previously treated with onasemnogene abeparvovec** | No additional treatment | P/I: Promising but Inconclusive |
| **Risdiplam in patients previously treated with onasemnogene abeparvovec** | No additional treatment | C++: Comparable or Better |
| **Risdiplam** | Nusinersen | All SMA types: Insufficient |
| **Risdiplam** | Onasemnogene abeparvovec | All SMA types: Insufficient |
| **Nusinersen** | Onasemnogene abeparvovec | All SMA types: Insufficient |

SMA: Spinal muscular atrophy

# 4. Long-Term Cost Effectiveness

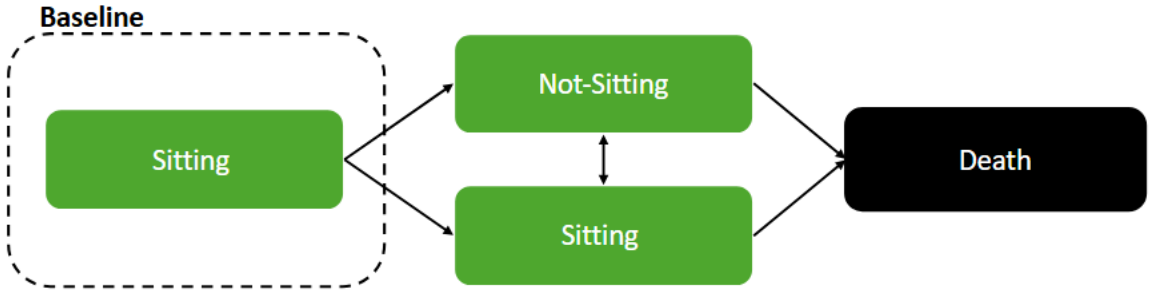
## 4.1 Overview and Model Structure

We developed a *de novo* decision analytic model examining the cost effectiveness of apitegromab versus standard or care with either nusinersen or risdiplam for this evaluation, informed by key clinical trials and prior relevant economic models. Costs and outcomes were discounted at 3% per year. We did not model the other interventions reviewed in the clinical section above.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with non-ambulatory SMA Type 2 or 3 being treated with apitegromab + SoC (Standard of Care), or SoC alone. Model cycle length was one month, based on prior published economic models and clinical data.[48] [49] In our model, patients begin in the baseline state of "sitting." Although Type 3 patients are usually able to achieve walking, this assumption was based on the inclusion criteria in SAPPHIRE requiring patients to be non-ambulatory. Additionally, mean baseline Hammersmith Functional Motor Scale – Expanded (HFMSE) scores for the population fell within the range of the sitter classification group from publicly available literature.[50,51,52] We implemented a simple model structure that does not include states for higher mobility milestones above sitting as the SAPPHIRE trial for apitegromab did not provide enough information to model patients achieving new mobility milestones.[50] Similarly, due to lack of available data, we assumed no worsening in our base case and all patients remained in the "sitting" state while alive. We explored having a proportion of patients regress into the worsened "not-sitting" state in scenario analyses.

Patients remained in the model until they died, and all patients could transition to "death" due to all causes from any of the alive health states.

**Figure 4.1. Model Schematic**



## 4.2 Key Model Choices and Assumptions

Below is a list of key model choices:

- Simple model structure with no states for higher mobility milestones above sitting due to insufficient clinical evidence.
- Monthly cycle length and lifetime time horizon.
- Treatment effect for apitegromab was calculated based on the difference in proportion of patients who achieved an HFMSE increase of ≥3 in SAPPHIRE and incorporated through treatment-specific utilities for the "sitting" health state.[50]
- Patients who achieved the treatment effect maintained it throughout the modeled time horizon.
- No disease progression into the "not-sitting" state in the base case due to insufficient data.

Our model includes several assumptions stated below.

**Table 4.1. Model Assumptions**

| Assumption | Rationale |
|---|---|
| **All patients begin in the "sitting" state.** | This assumption is based on SAPPHIRE trial inclusion criteria limiting the population to non-ambulatory Type 2/3 SMA patients.[53] Additionally, the mean baseline HFMSE scores reported in the study population (26.2) fall within the range of the sitter classification group from publicly available literature and previous clinical trials of nusinersen.[51 52] |
| **In the base case, we assumed no disease progression; all patients remained in "sitting" throughout the model's time horizon while alive. There were no transitions to either improved mobility states or worsened states.** | Available data lack sufficient detail to model progression of patients to higher WHO motor milestones than "sitting." While recent trial results from CHERISH and SHINE for nusinersen show potential continued disease progression and worsening mobility over the long-term in later-onset SMA patients on disease modifying treatments, the declines were relatively small and are from long term follow-up data with substantial patients lost to follow-up.[54] Thus, there are insufficient data to reliably model the rate patients transition to lower mobility states. In addition, most previous economic analyses of standard-of-care treatments included similar assumptions about stabilization within health states over the long term.[48-52] This limitation was addressed through scenario analyses |

| Assumption | Rationale |
|---|---|
| | exploring different assumptions about disease progression while on treatment. |
| **Patients achieving ≥3-point increase in HFMSE at the end of follow-up maintained the improvement through their lifetime in the model.** | Limited long-term data on treatment effect durability were addressed through scenario analyses that explored alternative assumptions.<br><br>The treatment effect was modeled through a utility difference for the "sitting" health state between the two arms, based on the proportion of patients observed to achieve ≥3-point increase in HFMSE in each arm. |
| **No discontinuation for apitegromab nor standard of care treatments (nusinersen and risdiplam).** | No discontinuation was observed due to adverse events in the SAPPHIRE trial and no additional discontinuation data were reported for the 12-month study.[50] Additionally, Type 2/3 SMA patients in the CHERISH trial for nusinersen had no discontinuations over the 15-month study. [55] All discontinuations in SUNFISH over the 12-month study switched to another treatment.[56]<br><br>We did not assume patients would discontinue if they did not achieve the treatment effect of a ≥3-point increase in HFMSE. Available clinical evidence shows the treatment may help maintain motor function and slow the regression seen when solely on SoC. |
| **All patients entering the model weigh over 20 kg.** | Risdiplam doses are weight dependent for patients under 20 kg but capped at a 5 mg dose for patients at or over 20 kg. We followed the assumption seen in CDA-AMC's review of risdiplam where all SMA Type 2 and Type 3 patients were 20 kg or more at model entry. [49] All patients received the flat dosing of 5 mg of risdiplam daily. |

CDA-AMC: Canada's Drug Agency, HFMSE: Hammersmith Functional Motor Scale – Expanded, kg: kilograms, mg: milligram, SMA: spinal muscular atrophy, SoC: standard of care, WHO: World Health Organization

## Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The interventions included apitegromab (Scholar Rock) with standard of care treatment nusinersen (Spinraza®, Biogen) or risdiplam (Evrysdi®, Genentech). The comparators included standard of care alone.

## Clinical Inputs

Patients in SAPPHIRE treated with apitegromab combined dose + SoC were more likely to achieve a ≥3-point improvement in HFMSE from baseline compared to those receiving placebo + SoC (30.4% versus 12.5%, OR=3.0, p=0.03) at 12 months in the 2-12 age group.[50]
A ≥3-point improvement in HFMSE is considered a moderate and clinically meaningful increase in score with meaningful gains in quality of life.[57,58] Although data have hinted that the effect may vary based on SoC treatment as well as SMA type, age of treatment initiation, and other factors,[59] our model utilized the trial population average based on the proportions observed in the study. This treatment effect was applied to the model through an additional health utility for the apitegromab treatment.

## Transition Probabilities

Due to insufficient data, there were no transitions to higher World Health Organization motor development milestones such as crawling, standing, or walking with/without support. All patients stayed in the "sitting" state through the model in our base-case analysis. We applied a transition to "not sitting" in a scenario analysis to model disease progression. Details on mortality and transitions to "not sitting" in the scenario analysis can be found in Supplement Sections E2 and E5.

### *Discontinuation*

No discontinuations due to adverse events were observed in the SAPPHIRE trial, and no additional discontinuation information was reported for the 12-month study.[50]
Based on clinical expert opinion, we assumed there is no discontinuation for apitegromab or for the SoC treatments nusinersen/risdiplam. This assumption is supported by data from the CHERISH trial for nusinersen,[55] which reported zero discontinuations in 15 months, and the SUNFISH trial for risdiplam,[56] which reported only three discontinuations in 12 months, with all discontinued patients moving to a different treatment.

### *Adverse Events*

Serious adverse events observed in the SAPPHIRE trial that occurred with a frequency greater than 5% were included in our analysis.[50] Based on this threshold, only pneumonia met the criteria for inclusion (Table 4.2). Additionally, a disutility of -0.098 (SD 0.092) was applied to patients with pneumonia for a one month duration.[60]

**Table 4.2. Adverse Events**

| Parameter | Apitegromab + SoC | Placebo + SoC | Source |
|---|---|---|---|
| **Pneumonia** | 6.6% | 0% | SAPPHIRE Trial[50] |

SoC: standard of care

### *Heterogeneity and Subgroups*

No subgroups were modeled due to insufficient data.

## Health State Utilities

Health state utilities were derived from publicly available literature, as there are currently no publicly available utility values from SAPPHIRE. The treatment effect of apitegromab was incorporated by adding an additional utility of 0.01. This additional utility is a weighted estimate based on the 17.9% difference in patients achieving a ≥3-point increase in HFMSE at 12-months in the apitegromab arm compared to the placebo arm in SAPPHIRE,[50] multiplied by the utility gain of 0.06 for achieving a ≥3-point increase in HFMSE based on EQ-5D utility values by Lloyd et al. (difference in utility between 0.10 for ≥3-point increase from baseline and 0.04 for baseline HFMSE) and was applied over the lifetime.[58] Utilities used in the model can be found in Table 4.3, with additional details in the Supplement Section E2.

**Table 4.3. Health State Utilities**

| State | Utility | | Source |
|---|---|---|---|
| | SoC | Apitegromab + SoC | |
| **Sitting** | 0.26 | 0.27 | Belter et al.[61] + Assumption for additional utility in apitegromab group[50,58] |
| **Not-Sitting** | 0.12 | 0.13 | |

SoC: standard of care

## Drug Utilization

The following inputs were used to model drug utilization (Table 4.4) and their associated costs (Table 4.5). We assumed there was no wastage for either nusinersen or risdiplam. We assumed all patients entering the model have already received the initial three doses of nusinersen and received 12 mg every four months. Additionally, we assumed all patients entering our model are at or over 20 kg and had a flat dose of risdiplam at 5 mg/day.

**Table 4.4. Treatment Regimen Recommended Dosage**

| Generic Name | Apitegromab | Nusinersen | Risdiplam |
|---|---|---|---|
| **Brand Name** | - | Spinraza® | Evrysdi® |
| **Manufacturer** | Scholar Rock | Biogen | Genentech |
| **Route of Administration** | Intravenous infusion | Intrathecal injection | Oral (liquid or tablet) |
| **Dosing** | 10 mg/kg or 20 mg/kg every four weeks | 12 mg (5 ml) every four months after an initial three doses | Daily dose for 2 years of age and older<br><20 kg: 0.25 mg/kg<br>≥20 kg: 5 mg |

kg: kilogram, mg: milligram, ml: milliliter

## Cost Inputs

All costs used in the model were updated to 2025 US dollars.

### *Drug Acquisition Costs*

Based on estimates from IPD Analytics, we used a $350,000 annual placeholder price for apitegromab,[62] as neither list price nor net prices were available. For nusinersen, we used the ambulatory payment classification (APC) price of $1,246.99 per 0.1 mg from the Centers for Medicare & Medicaid Services (CMS) outpatient prospective payment system (OPPS) addendum B and calculated an annual price for a 12 mg dose every four months.[63] For risdiplam, we used the wholesale acquisition price from RED BOOK with a discount of 12.5% obtained from IPD analytics.[62,64] Annual prices for risdiplam were calculated for a five mg dose under the assumption that all patients entering our model are ≥20 kg.

**Table 4.5. Drug Costs**

| Drug | Annual WAC/ Placeholder Price | Discount From WAC | Annual Net Price/ Placeholder Price |
|---|---|---|---|
| **Apitegromab** | $350,000* | NA | $350,000* |
| **Nusinersen (Spinraza®)** | $448,916† | NA | $448,916† |
| **Risdiplam (Evrysdi®)** | $409,445 | 12.5%[62] | $358,265 |

NA: not applicable, WAC: wholesale acquisition cost

*Apitegromab placeholder price and risdiplam discount from WAC obtained from IPD analytics

†Calculated from APC cost from CMS - includes a 6% markup

***Drug Administration Costs***

Costs for two hours of intravenous infusion were applied to the first two doses of apitegromab, with costs reduced to one hour of intravenous infusion for all subsequent doses.[65] We assumed physician visits would be done during visits for nusinersen administration or accounted for in background health care costs. Administration costs for apitegromab are detailed in Table 4.6., additional administration costs related to standard of care treatments can be found in the Supplemental Section E2.

**Table 4.6. Administration Costs for Apitegromab**

| | Value ($) | Description | Source |
|---|---|---|---|
| **Intravenous Infusion (First Hour)** | 57.90 | HCPCS 96365 | CMS Physician Fee Schedule 2025 [66] |
| **Intravenous Infusion (Additional Hour)** | 19.41 | HCPCS 96366 | |

CMS: Centers for Medicare and Medicaid Services, HCPCS: Healthcare Common Procedure Coding System

Additional costs such as those associated with adverse events and health care utilization are detailed in Supplement Section E2.

# 4.6. Results

## Base-Case Results

Discounted intervention acquisition costs, intervention-related costs, total costs, quality-adjusted life years (QALYs), equal value of life years (evLYs), and life years (LYs) are detailed in Table 4.7 below. Total costs consist of intervention acquisition costs for apitegromab and SoC treatments nusinersen and risdiplam, other intervention-related costs such as those related to markup, administration and testing, and non-intervention costs such as background health care costs. Over the lifetime, apitegromab added on to standard of care resulted in higher total costs of approximately $6,600,000 at the placeholder price, and incremental gains in QALYs of approximately 0.20 compared to standard of care alone. Incremental cost-effectiveness ratios (incremental CE ratios) representing costs for each QALY, evLY, LY, and ≥3-point increase in HFMSE gained are detailed in Table 4.8.

**Table 4.7. Results for the Base Case for Apitegromab + SoC Compared to SoC**

| Treatment | Intervention Acquisition Costs | Intervention -Related Costs† | Total Costs | QALYs | evLYs | Life Years |
|---|---|---|---|---|---|---|
| **Apitegromab* + SoC** | $14,311,000 | $442,000 | $16,507,000 | 5.04 | 5.04 | 18.86 |
| **SoC** | $7,711,000 | $428,700 | $9,892,000 | 4.84 | 4.84 | 18.86 |

evLYs: equal value of life years gained, QALYs: quality-adjusted life years, SoC: standard of care
*Based on placeholder price of $350,000 per year
†Intervention-related costs include markup costs, administration costs, and costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label

**Table 4.8. Incremental Cost-Effectiveness Ratios for the Base Case**

| Treatment | Comparator | Cost per QALY Gained | Cost per evLY Gained | Cost per Life Year Gained | Cost per ≥3-Point Increase in HFMSE |
|---|---|---|---|---|---|
| **Apitegromab* + SoC** | SoC | $32,744,000 | $32,744,000 | No Difference in Life Years | $36,951,000 |

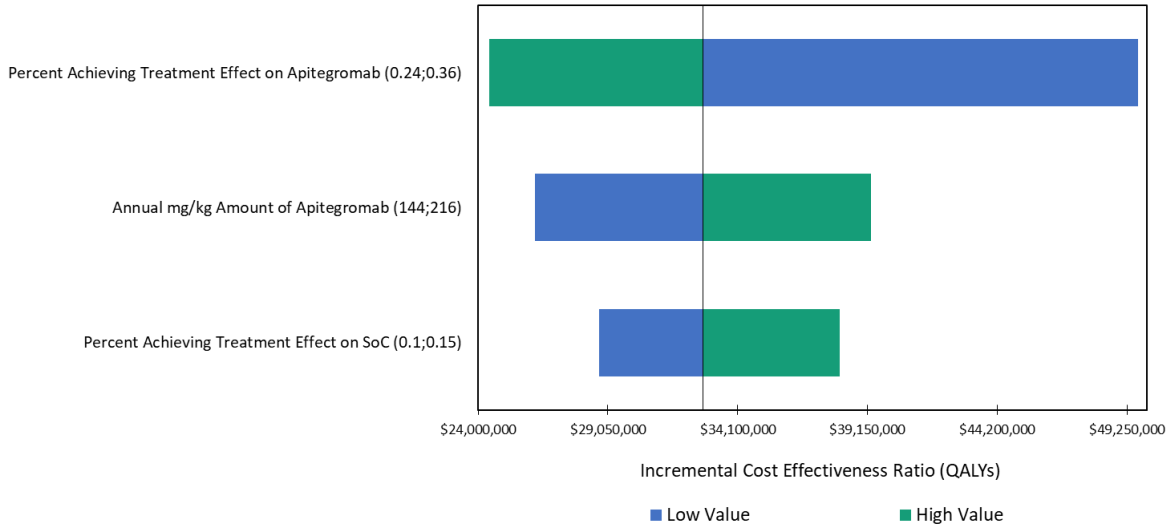
evLYs: equal value of life years, HFMSE: Hammersmith Functional Motor Scale – Expanded, QALY: quality-adjusted life year, SoC: standard of care
*Based on placeholder price of $350,000 per year

## Sensitivity Analyses

One-way sensitivity analyses were conducted to identify the impact of parameter uncertainty and the key drivers of model outcomes. Figure 4.2 presents how the incremental cost effectiveness ratio for cost per QALY gained varies for apitegromab + SoC compared to SoC alone as parameters change from the health care sector perspective. The parameters with the largest impact on the ICER were the percentage of patients achieving a ≥3-point increase in HFMSE on apitegromab, the dosage of apitegromab, and the percentage achieving a ≥3-point increase in HFMSE on SoC treatment. All other parameters exhibited minimal influence on the ICER.

Probabilistic sensitivity analyses were conducted by varying all parameters over 1,000 simulations to calculate the proportion of simulations in which apitegromab + SoC was cost-effective compared to SoC alone. Results indicated that apitegromab had a 0% probability of being cost-effective across all evaluated thresholds, as detailed in Table 4.9. Additional information on sensitivity analyses can be found in Supplement Section E4.

**Figure 4.2. Tornado Diagram for Apitegromab + SoC Compared to SoC**




kg: kilogram, mg: milligram, SoC: standard of care

**Table 4.9. Probabilistic Sensitivity Analysis Cost per QALY/evLY Gained Results: Apitegromab + SoC versus SoC**

| | Cost Effective at $50,000 per QALY/evLY Gained | Cost Effective at $100,000 per QALY/evLY Gained | Cost Effective at $150,000 per QALY/evLY Gained | Cost Effective at $200,000 per QALY/evLY Gained |
|---|---|---|---|---|
| **Apitegromab* + SoC** | 0% | 0% | 0% | 0% |

evLYs: equal value of life years, QALY: quality-adjusted life year, SoC: standard of care
*Based on placeholder price of $350,000 per year

## Scenario Analyses

We conducted scenario analyses to examine the uncertainty and potential variations in the findings. The scenarios are presented below, and the results are presented in Table 4.10:

1. Disease progression incorporating transitions to worsened mobility states for both arms (e.g., from "sitting" to "not-sitting") with and without caregiver utilities (additive approach).
2. Disease progression incorporating transitions to worsened mobility states for the SoC arm (e.g., from "sitting" to "not-sitting") with and without caregiver utilities (additive approach).

The following scenarios were also explored and found to have minimal impact on the incremental cost-effectiveness ratios:

3. Modified Societal Perspective that includes caregiver utilities
4. Exclusion of unrelated (non-drug) health care costs that are not related to the disease *per se*
5. Removing pneumonia adverse events for apitegromab
6. Health state utilities from NICE TA588 ERG Clinical Advisors[67]
7. Health state utilities from Lloyd et al.[58]

Additional details on each analysis can be found in the Supplement Section E5.

**Table 4.10. Scenario Analysis Results – Incremental Cost-Effectiveness Ratios ($/QALY)**

| Treatment | Base-Case Results | Scenario Analysis 1: Disease Progression | | Scenario Analysis 2: Disease Progression in SoC Only | |
|---|---|---|---|---|---|
| | | Without Caregiver Utility | With Caregiver Utility | Without Caregiver Disutility | With Caregiver Utility |
| **Apitegromab* + SoC** | $32,744,000 | $19,490,000 | $10,279,000 | $3,761,000 | $1,304,000 |

SoC: standard of care

*Based on placeholder price of $350,000 per year

## Threshold Analyses

Threshold analyses were conducted for apitegromab to determine the price that would meet commonly accepted cost-effective thresholds for QALYs and evLYs with results detailed in Table 4.11. Due to the minimal gains observed in quality of life, apitegromab cannot achieve cost effectiveness at the $50,000 per QALY threshold at any positive price. The costs of administration alone exceed the monetary value of health benefits at this threshold (i.e., the monetary value of the incremental QALYs or evLYs—valued at $50,000 per QALY or evLY—is lower than the incremental cost of drug administration).

**Table 4.11. QALY/evLY-Based Threshold Analysis Results**

| | Annual Price to Achieve $50,000 per QALY/evLY Gained | Annual Price to Achieve $100,000 per QALY/evLY Gained | Annual Price to Achieve $150,000 per QALY/evLY Gained | Annual Price to Achieve $200,000 per QALY/evLY Gained |
|---|---|---|---|---|
| **Apitegromab** | -$205 | $330 | $866 | $1,401 |

evLYs: equal value of life years, QALY: quality-adjusted life year

## Model Validation

See Supplement Section E7 for details on model validation.

## Uncertainty and Controversies

Our model has several key limitations based on insufficient data on treatment effects, their durability, disease progression, and the translation of changes in functional scores to changes in quality-of-life measures.

- Outcomes in SAPPHIRE were primarily measured using changes in the Hammersmith Function Motor Scale Expanded (HFMSE), an instrument with several limitations that affects its interpretation and use in modeling. Notably, there is substantial overlap of HFMSE scores between different WHO motor development milestones, making it difficult to confidently interpret an individual's overall function based on HFMSE alone. For example, in Stimpson et al.,[51] individuals with SMA Types 2 and 3 classified as non-sitters had HFMSE values ranging from 0 to 12, while sitters spanned a broader range from 2 to 40, illustrating the considerable uncertainty and variability in how HFMSE scores map onto commonly used functional milestones. Additionally, the HFMSE scale has inherent "fuzziness" in clinical interpretation. A one-point change may reflect a substantial functional improvement that meaningfully enhances daily life, or conversely, a minor change with negligible impact on quality of life. Musculoskeletal complications common in SMA patients, such as joint contractures and scoliosis, can constrain potential improvements in HFMSE scores regardless of treatment efficacy.[23] Furthermore, HFMSE scoring does not capture other important aspects of patient experience like fatigue, and psychosocial impacts. Despite these complexities, our model currently translates HFMSE changes directly into quality-of-life improvements while treating all point changes equally, potentially oversimplifying the relationship between changes in HFMSE score and quality of life improvements.

- Conventional utility measures such as the Health Utilities Index Mark 3 (HUI3) and EQ-5D may inadequately capture key aspects of SMA-related quality of life; however, these were the best available estimates for our analysis. Our approach required combining heterogeneous utility sources – specifically mixing HUI3 and EQ-5D measures to obtain baseline quality of life estimates for different WHO functional groups and assigning additional utility gains for patients achieving clinically significant motor improvements (defined as ≥3-point increases in HFMSE score). This approach may introduce measurement inconsistencies given differences in what each instrument captures and how they are valued.

- Most utility estimates we identified were reported by functional classification (e.g., sitter, walker) rather than by changes in functional measure scores relative to baseline.[61,68] Only

one source provided utilities based on changes in functional status, and in that study, baseline utilities were identical to those with mild increases in HFMSE of <3 points.[58] Utility gains were only observed for patients who achieved at least a ≥3-point increase in HFMSE. Although most clinical sources consider a ≥3-point increase in HFMSE to be clinically meaningful, there is evidence to suggest that smaller changes, such as a 1.5-point increase, may also represent meaningful functional gains.[69,70] Additionally, patients and caregivers often perceive even a one-point improvement as meaningful in daily life. However, due to the inherent fuzziness around what constitutes a clinically meaningful change, and the lack of quality of life measures that reflect differences from baseline in small HFMSE improvements, we were unable to translate such changes into meaningful gains in quality of life within our model. To reduce these uncertainties, we requested trial data on WHO motor development classifications and quality of life outcomes, but did not receive it.

- The durability of treatment effects, variability of effects in subgroups, and long-term disease progression on SMN-targeted therapies and apitegromab + SoC remain highly uncertain. Clinical evidence is limited to 12-month follow-up data from the pivotal SAPPHIRE trial, with longer-term outcomes reported only in a small, single-arm Phase II study lacking a comparator group and representing a limited patient population.[59,65] As a result, there is insufficient evidence to confidently extrapolate treatment benefits beyond the observed period. Although evidence from the TOPAZ trial show that the benefits of apitegromab are maintained for up to four years,[19] this evidence has limitations including its open-label Phase II design without placebo control, and small sample size. Data from SAPPHIRE also suggests that apitegromab's treatment effect may vary based on SoC treatment, SMA type, age of treatment initiation, and other factors.[59] We did not have sufficient data to explore any of these subgroups. Additionally, there is substantial uncertainty around long-term disease progression of patients on SMN-targeted therapies. CHERISH and SHINE trials produced patient HFMSE trajectories on nusinersen that only extend about 1.5 years beyond SAPPHIRE's time period for early-dosed patients, and data for delayed-dose patients ended within SAPPHIRE's window.[50,54,59] The extrapolation in our scenario analyses assumes a linear decline in HFMSE at a constant rate obtained from SAPPHIRE's results. This assumption was based on clinical expert opinion, but whether the decline stays linear or changes over longer time horizons remains uncertain, especially for patients on risdiplam and apitegromab where long-term progression data is even more limited.

## 4.4 Summary and Comment

Our analysis showed that apitegromab added onto standard of care treatments was able to provide small gains in QALYs. However, it is expected to exceed standard cost-effectiveness thresholds at its current placeholder price of $350,000 annually. Due to the small utility gains observed, the administration costs alone exceeded the threshold of $50,000 per QALY. We have found that the

dose of apitegromab, and percentage of patients achieving the ≥3 point improvement improvements on apitegromab + SoC or SoC alone had the largest impact on the incremental cost-effectiveness ratio in our one-way sensitivity analysis. Additionally, assumptions around disease progression (i.e., patients decline to "not sitting" over time on SoC or both SoC and apitegromab + SoC) were also observed to have large impacts on the incremental cost-effectiveness ratio. In all scenarios apitegromab is still expected to exceed standard cost-effectiveness thresholds at the current placeholder price.

# 5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the interventions in this review.

**Table 5.1. Benefits Beyond Health and Special Ethical Priorities**

| Benefits Beyond Health and Special Ethical Priorities | Relevant Information |
|---|---|
| **There is substantial unmet need despite currently available treatments.** | Current therapies either slow or stop deterioration of muscle function, but even at birth, severely affected patients have lost motor neurons and hence motor function. There is substantial unmet need to improve strength, function, and to reduce fatigue.<br><br>To inform unmet need as a benefit beyond health, the results for the absolute and proportional shortfalls have been reported below. The shortfalls were the same, regardless of whether QALY or evLY was used.<br><br>QALY and evLY shortfalls:<br>Absolute shortfall: 54.0<br>Proportional shortfall: 87.8%<br><br>The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews. |
| **This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.** | No evidence. |
| **The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.** | The net health benefits of apitegromab are at best small, which will have some impact on caregiver's quality of life, but it is unlikely to be substantial. There may be an increase in burden due to the need for travel to an infusion center for treatment every four weeks, though home infusion may mitigate this challenge. |
| **The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.** | Apitegromab requires an IV infusion every four weeks, which requires travel to an infusion center or coordination with a home infusion program, which will be a burden for many patients. |

IV: intravenous

The Health Improvement Distribution Index (HIDI) did not find evidence of a subpopulation that has a higher prevalence of SMA than the general US population.

# 6. Health Benefit Price Benchmark

ICER does not provide a health benefit price benchmark as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmark that will be presented in the next version of this Report.

# 7. Potential Budget Impact

## 7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of apitegromab for patients with SMA. Potential budget impact is defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. We used a placeholder price of $350,000 and the three threshold prices (at $50,000, $100,000, and $150,000 per evLYG) for apitegromab in our estimates of budget impact. Further details on ICER's approach to the budget impact analysis are available in Section F of the Supplement.

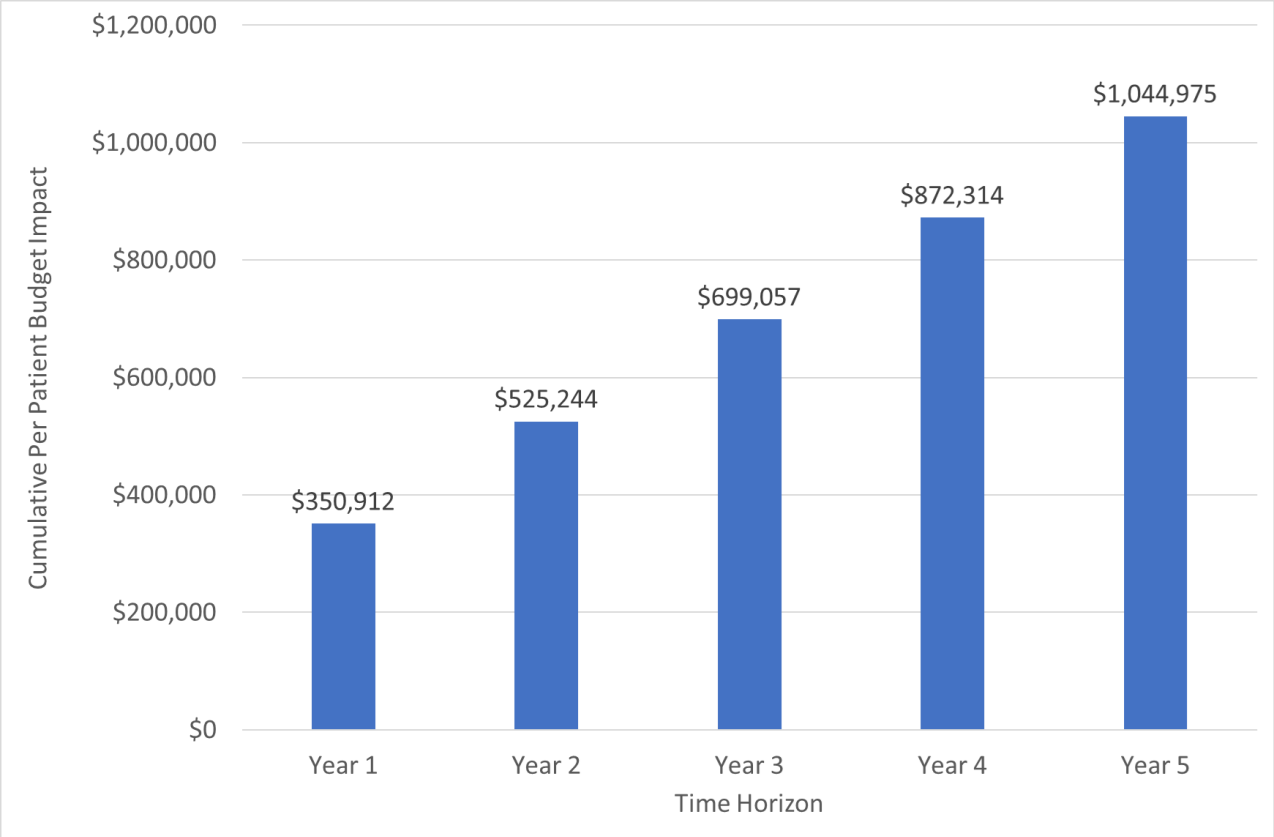
This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment, which includes Type 1, 2, or 3 SMA patients who have been treated with nusinersen or risdiplam. While the cost-effectiveness analyses primarily focused on Types 2 and 3 SMA, Type 1 SMA patients are included in this analysis to account for the possibility that apitegromab may be approved for or used in a broader indication than the trial eligibility criteria. To estimate the size of the potential candidate population, we used inputs for the overall prevalence of SMA in the Unites States (0.0028%),[8] the percentage of patients with SMA that have either Type 1, 2, or 3 SMA (96.63%),[8] and the percentage of Type 1, 2, or 3 SMA patients that have been treated with either nusinersen or risdiplam (71.24%). The overall SMA prevalence estimate of 0.0028% was calculated using the estimated number of SMA patients in the US in 2023 (9,419)[8] divided by the total US population in 2023 (334,906,305).[71] The prevalence by type were estimated to be 26.97% for Type 1, 41.57% for Type 2, and 28.09% for Type 3.[8] The proportion of patients who have been treated with nusinersen or risdiplam were estimated to be 76%, 66%, and 81%, for Types 1, 2, and 3 respectively (based on data on file provided by manufacturer). Applying these percentages to the prevalence rates for Type 1, 2, and 3 SMA results in a weighted average of 71.24% of patients who have been on either nusinersen or risdiplam among patients with Type 1, 2, or 3 SMA. This estimate is in line with the Cure SMA 2023 Report, which states that approximately 60-70% of SMA patients have been treated with an FDA-approved treatment.[8] Applying these sources to the average total US population projected over the next five years (340,927,674) results in 6,600 eligible patients in the US. For the purposes of this analysis, we assume that 20% of these patients would initiate treatment in each of the five years, or 1,320 patients per year.

## 7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated population budget impact for apitegromab compared to standard of care. The cumulative per patient annual budget impact represents the incremental costs of apitegromab compared to standard of care per patient across all patients treated within a time horizon (including those who initiated apitegromab in previous years), assuming apitegromab is used with 20% uptake each year over five years.

At the placeholder price of $350,000 for apitegromab, the average annual budget impact per patient was $350,912 in year one and increased to $1,044,975 by year five.

**Figure 7.1. Cumulative Per Patient Annual Budget Impact for Apitegromab Compared to Standard of Care**




Assuming a 20% uptake of apitegromab each year, 64% of eligible patients could be treated over five years at the placeholder price of $350,000 before reaching the ICER potential budget impact threshold of $880,000,000. All eligible patients could be treated at the $50,000, $100,000, and $150,000 per evLY threshold prices (-$203, $332, and $868) before reaching the ICER potential budget impact threshold.

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# Supplemental Materials

# A. Background: Supplemental Information

## A1. Definitions

**Table A1.1. Age Groups[8]**

| Term | Age Range (Years) |
|---|---|
| **Children** | 0-12 |
| **Teens** | 13-17 |
| **Pediatric** | 0-17 |
| **Adults** | 18+ |

Note: Classification of age groups that are commonly applied in SMA assessment tools.

**The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND):** A 16-item measure that assesses motor function in infants with neuromuscular disease using a 0-4 scale, with zero meaning no response and four meaning complete level of response. The maximum score is 64, and the MCID is a 3.4- to 4-point improvement.[72]

**Hammersmith Functional Motor Scale Expanded (HFMSE):** A 33-item measure that assesses the motor functional abilities of children and adults with Type 2 or 3 SMA using a 0-2 scale, with zero meaning the patient "is unable to perform the activity" and two meaning "can perform the activity without any modifications". The maximum score is 66. The minimal clinically important difference (MCID) is often considered as a three-point improvement, though controversy remains of assigning an MCID for all SMA types. HFMSE is considered as the gold standard for assessing motor ability and disease progression in SMA.[23,70,73]

**Hammersmith Infant Neurological Examination – Section 2 (HINE-2)**: The second section of the HINE. HINE-2 consists of eight items that assesses motor skills in infants with SMA. The maximum score is 26, with one point being awarded for each transition to a successive level of ability.[74]

**Neurofilament Light Protein (NfL):** A protein that is released into the peripheral blood and cerebrospinal fluid (CSF) in response to acute axonal damage, making it a promising biomarker of neuroaxonal damage in SMA and disease progression in children with SMA undergoing treatment. A lower NfL concentration in the CSF and blood (plasma/serum) may indicate a reduction in the rate of motor neuron loss, and a concentration of zero would indicate no further neuronal loss or damage.[31]

**Revised Hammersmith Scale (RHS):** A 36-item measure that assesses motor functional abilities of patients with Type 2 or 3 SMA. 33 items are scored using a 0-2 scale, where zero representing "least physical ability or function achieves, and two the highest". The remaining three items are scored using a 0-1 scale, with a score of zero or one indicating the inability or ability to achieve,

respectively. The maximum score is 69, and the MCID is typically between a 2-3 point improvement.[75]

**Revised Upper Limb Module (RULM):** A 20-item measure that assesses the function of upper limbs in children with Type 2 or 3 SMA scored on a 0-2 scale, with zero meaning "the task was not completed" and two meaning "the task was completed correctly". The maximum score is 37, with the MCID defined as an increase of at least two points.[76]

**Spinal Muscular Atrophy (SMA):** An autosomal recessive neuromuscular disorder characterized by progressive loss of motor neurons that presents as weakness caused by extensive skeletal muscle denervation and atrophy.[65]

**Survival Motor Neuron (SMN):** Deletions or mutations of the spinal motor neuron 1 (*SMN1*) gene cause SMA, and the number of copies of a similar gene, *SMN2*, which is one of the primary predictors of clinical severity of the disease.[77]

**World Health Organization (WHO) Motor Milestones Assessment:** A sequence of six universal gross motor milestones including "sitting without support," "hands-and-knees crawling," "standing with assistance," "walking with assistance," "standing alone," and "walking alone".[78]

### *Other Relevant Definitions*

**Absolute and Proportional Shortfalls:** Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[79] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[80,81] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

**Health Improvement Distribution Index (HIDI)**: The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above one suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

As of 2024, an estimated 9000 to 9,500 individuals live with SMA in the United States. Using most recent US Census population estimates, the disease prevalence of SMA among all Americans is an 0.00003 percent, highlighting its status as an ultra-rare disease. One race/ethnicity category had a calculated HIDI of greater than 1: Non-Hispanic White (1.15).

## A2. Potential Cost-Saving Measures in Spinal Muscular Atrophy

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for SMA (e.g., need for an assistive device), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of SMA beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with SMA that could be reduced, eliminated, or made more efficient. No suggestions have been received.

## A3. Research, Development, and Manufacturing Costs

Manufacturers of ultra-rare disease (SMA) treatments were invited to submit information on research, development, and manufacturing costs relevant to value assessment and fair pricing. No responses were received.

## A4. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients. ICER did not receive any feedback on this inquiry.

# B. Patient Community Insights: Supplemental Information

## B1. Methods

For this report, we reached out to SMA-focused groups in the US, Canada, and UK. We spoke with representatives from one patient advocacy organization.

# C. Clinical Guidelines

We reviewed guidelines on SMA issued by major US clinical societies and working groups.

### Spinal Muscular Atrophy Update in Best Practices (2024)[82]

This was an update to the 2018 consensus statement. The international committee concluded that there was sufficient data on short-term safety and efficacy to recommend treatment with nusinersen, onasemnogene abeparvovec, or risdiplam. However, they concluded that there was insufficient data on long-term safety and efficacy, the safety and efficacy of combined or sequential therapy, and the comparative efficacy of each of the individual treatments. They recommend that treatment decisions be made with patients and their caregivers, with careful consideration of the safety and harms of treatment. Age and SMN copy number should be essential considerations in decision-making. Treatment should be monitored for six to twelve months before considering changes unless there are significant side effects, medication intolerance, intolerance to the treatment administration route, or significant progression of disease.

### 2024 Update: European Consensus Statement on Gene Therapy for Spinal Muscular Atrophy[83]

This was an update to the 2020 European consensus statement. The key recommendation relevant to this review is that combination therapy is not yet recommended as there is no convincing evidence of benefit versus single therapy alone. Otherwise, the recommendations are for newborn screening and use of gene therapy in older, heavier patients only under research protocols to ensure that the balance of benefits and harms is evaluated and communicated to patients, caregivers, and physicians involved in decision-making about treatment that is appropriate to individual patients with their unique circumstances.

# D. Comparative Clinical Effectiveness: Supplemental Information

## D1. Detailed Methods

### PICOTS 1

***Population***

Individuals with SMA Type 2 or 3 on background disease modifying therapy (nusinersen or risdiplam). Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, race/ethnicity)
- Background therapy (nusinersen versus risdiplam)
- SMA subtype
- Age at start of treatment
- Prior treatment with onasemnogene abeparvovec

***Interventions***

Apitegromab (10 or 20 mg/kg IV every four weeks) as an add on to nusinersen or risdiplam.

***Comparators***

Nusinersen or risdiplam alone.

### *Outcomes*

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Mortality
    - Avoidance of permanent invasive ventilation
    - Measures of functional mobility
    - Bulbar function (e.g., swallowing, speaking)
    - Health-related quality of life
    - Impact on activities of daily living
    - Caregiver burden
    - Adverse events including
        - Any serious adverse event
        - Adverse events leading to discontinuation
        - Treatment-related adverse events
        - Injection and infusion site reactions

### *Timing*

Evidence on intervention effectiveness will be derived from studies of at least 12 months duration.

### *Settings*

All relevant settings will be considered.

## PICOTS 2

### *Population*

Infants, children, and adults with SMA. Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, race/ethnicity)
- SMA subtype
- Presymptomatic or symptomatic at start of treatment
- Age at start of treatment

### *Interventions*

The full list of interventions is as follows:

- Nusinersen (Spinraza®)
- Onasemnogene abeparvovec (Zolgensma®)
- Risdiplam (Evrysdi®)

### *Comparators*

We intend to compare the interventions to each other and, for patients who previously received onasemnogene abeparvovec, to no additional disease-modifying treatment.

### *Outcomes*

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Mortality
    - Avoidance of permanent invasive ventilation
    - Measures of functional mobility
    - Bulbar function (e.g., swallowing, speaking)
    - Health-related quality of life
    - Impact on activities of daily living
    - Caregiver burden
    - Adverse events including
        - Any serious adverse event
        - Adverse events leading to discontinuation
        - Treatment-related adverse events
        - Injection and infusion site reactions

### *Timing*

Evidence on intervention effectiveness will be derived from studies of any duration.

### *Settings*

All relevant settings will be considered.

**Table D1.1 PRISMA 2020 Checklist**

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **TITLE** | | |
| **Title** | 1 | Identify the report as a systematic review. |
| **ABSTRACT** | | |
| **Abstract** | 2 | See the PRISMA 2020 for Abstracts checklist. |
| **INTRODUCTION** | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of existing knowledge. |
| **Objectives** | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. |
| **METHODS** | | |
| **Eligibility Criteria** | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. |
| **Information Sources** | 6 | Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. |
| **Search Strategy** | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. |
| **Selection Process** | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. |
| **Data Collection Process** | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. |
| **Data Items** | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect. |
| | 10b | List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. |
| **Study Risk of Bias Assessment** | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. |
| **Effect Measures** | 12 | Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results. |

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **Synthesis Methods** | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression). |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. |
| **Reporting Bias Assessment** | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). |
| **Certainty Assessment** | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. |
| **RESULTS** | | |
| **Study Selection** | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. |
| **Study Characteristics** | 17 | Cite each included study and present its characteristics. |
| **Risk of Bias in Studies** | 18 | Present assessments of risk of bias for each included study. |
| **Results of Individual Studies** | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots. |
| **Results of Syntheses** | 20a | For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies. |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. |
| **Reporting Biases** | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. |
| **Certainty of Evidence** | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. |

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **DISCUSSION** | | |
| **Discussion** | 23a | Provide a general interpretation of the results in the context of other evidence. |
| | 23b | Discuss any limitations of the evidence included in the review. |
| | 23c | Discuss any limitations of the review processes used. |
| | 23d | Discuss implications of the results for practice, policy, and future research. |
| **OTHER INFORMATION** | | |
| **Registration and Protocol** | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. |
| **Support** | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. |
| **Competing Interests** | 26 | Declare any competing interests of review authors. |
| **Availability of Data, Code, and Other Materials** | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. |

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

## Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for SMA followed established best research methods.[84,85] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[86] The PRISMA guidelines include a checklist of 27 items (see Supplement Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

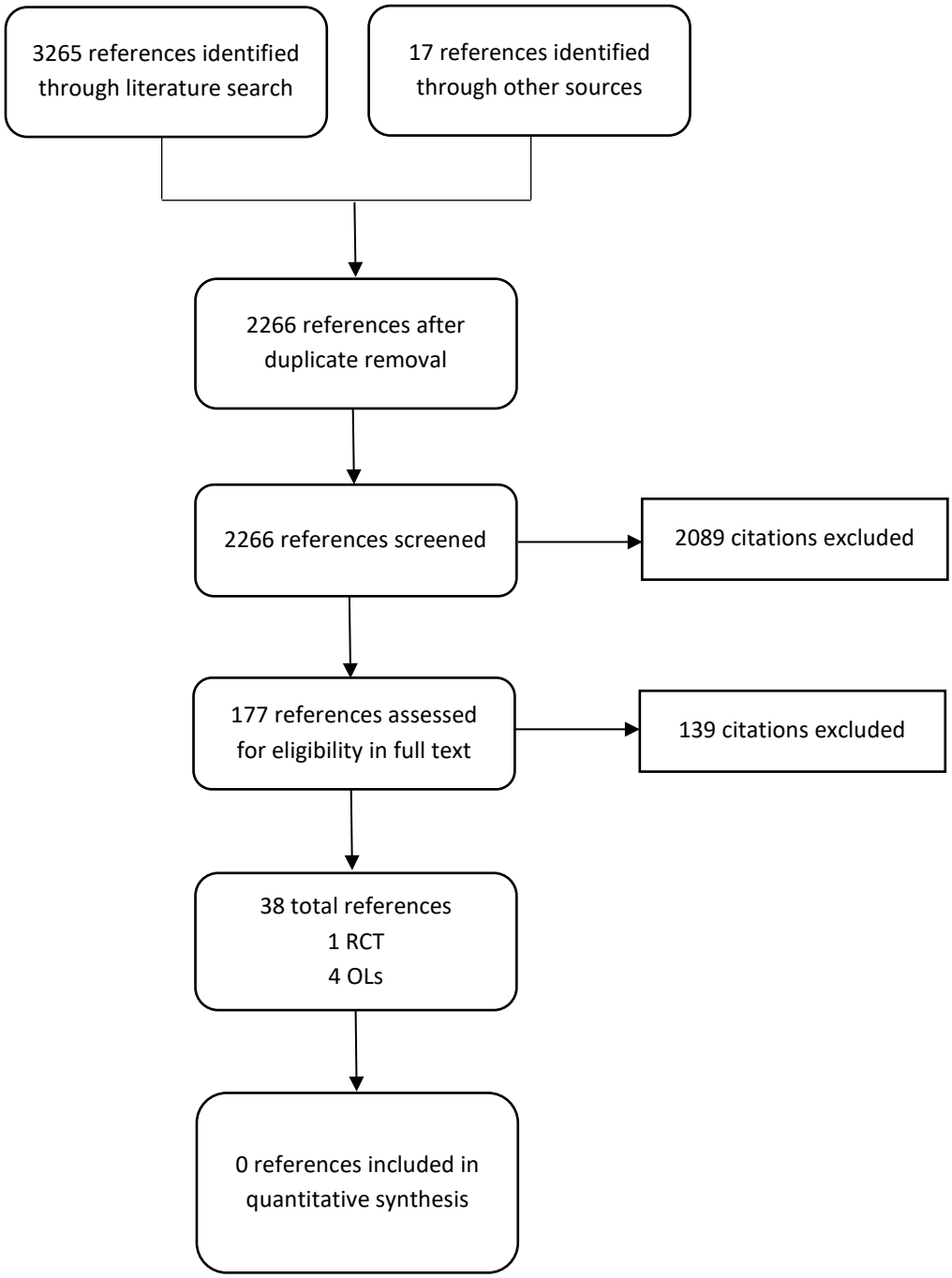
**Table D1.2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews Search Strategy for Therapies for SMA**

| | |
|---|---|
| **1** | ('Apitegromab' or 'SRK-015').ti,ab. |
| **2** | ('Zolgensma' or 'onasemnogene abeparvovec-xioi' or 'onasemnogene abeparvovec').ti,ab. |
| **3** | ('Risdiplam').ti,ab. |
| **4** | ('ISIS 396443' or 'SPINRAZA' or 'Nusinersen').ti,ab. |
| **5** | 1 or 2 or 3 or 4 |
| **6** | (animals not (humans and animals)).sh. |
| **7** | 5 NOT 6 |
| **8** | (addresses OR autobiography OR bibliography OR biography OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR interactive tutorial).pt |
| **9** | 7 NOT 8 |
| **10** | Limit 9 to English language |

**Table D1.3. EMBASE Search Strategy for Therapies for SMA**

| | |
|---|---|
| **1** | ('srk 015' OR 'srk015' OR 'apitegromab'):ti,ab |
| **2** | ('avxs 101' OR 'avxs101' OR 'charisma (drug)' OR 'oav 101' OR 'oav101' OR 'onasemnogene abeparvovec xioi' OR 'onasemnogene abeparvovec-xioi' OR 'scAAV9.CB.SMN' OR 'zolgensma' OR 'onasemnogene abeparvovec'):ti,ab |
| **3** | ('evrysdi' OR 'ro 7034067' OR 'ro7034067' OR 'risdiplam'):ti,ab |
| **4** | ('biib 058' OR 'biib058' OR 'ionis smnrx' OR 'ionis-smnrx' OR 'isis 396443' OR 'isis smnrx' OR 'isis-smnrx' OR 'isis396443' OR 'nusinersen sodium' OR 'spinraza' OR 'nusinersen'):ti,ab |
| **5** | #1 OR #2 OR #3 OR #4 |
| **6** | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp |
| **7** | #5 NOT #6 |
| **8** | ('addresses' OR 'autobiography' OR 'bibliography' OR 'biography' OR 'case report' OR 'comment' OR 'congresses' OR 'consensus development conference' OR 'duplicate publication' OR 'editorial' OR 'guideline' OR 'in vitro' OR 'interview' OR 'lecture' OR 'legal cases' OR 'legislation' OR 'letter' OR 'news' OR 'newspaper article' OR 'note' OR 'patient education handout' OR 'periodical index' OR 'personal narratives' OR 'portraits' OR 'practice guideline' OR 'short survey' OR 'video audio media')/it |
| **9** | #7 NOT #8 |
| **10** | #9 AND [English]/lim |

**Figure D1.1. PRISMA flow Chart Showing Results of Literature Search for Therapies for SMA**



## Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, Minnesota); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to nusinersen, risdiplam, and onasemnogene abeparvovec. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

## Data Extraction

Data were extracted into Microsoft Word and Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

## Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[85,87] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer.

To assess the risk of bias in trials, we rated the categories as: "low risk of bias," "some concerns," or "high risk of bias". Guidance for risk of bias ratings using these criteria is presented below:

***Low risk of bias****: The study is judged to be at low risk of bias for all domains for this result.*

***Some concerns****: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

***High risk of bias****: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the outcome of change from baseline in the HFMSE total score at 52 weeks. See Table D1.3.

**Table D1.4. Risk of Bias Assessment for HFMSE Outcome**

| Studies (Author, Year) | Randomization Process | Deviation from the Intended Interventions | Missing Outcome Data | Measurement of the Outcome | Selection of the Reported Result | Overall Risk of Bias | Comment |
|---|---|---|---|---|---|---|---|
| **Apitegromab** | | | | | | | |
| **SAPPHIRE**[50,53] | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | A preliminary risk of bias assessment was conducted using publicly available conference materials. This assessment is incomplete pending the publication of the full peer-reviewed publication and study protocol. |
| **TOPAZ**[65,88] | Low Risk | High Risk | Some Concern | Low Risk | Low Risk | High Risk | The lack of blinding in cohorts 1 and 2 introduces a high risk of bias. Participants in cohort 3 both received open-label treatment (2 or 20 mg/kg). |

HFMSE: Hammersmith Functional Motor Scale Expanded, kg: kilograms, mg: milligrams

## Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[22] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence estimates, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between zero to three was assigned based on the PDRR estimate (See Table D1.6 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.7.

**Table D1.5. Demographic Characteristics and Categories**

| Demographic Characteristics | Categories |
|---|---|
| **1. Race and Ethnicity*** | Racial categories:<br>• White<br>• Black or African American<br>• Asian<br>• American Indian and Alaskan Native<br>• Native Hawaiian and Other Pacific Islanders<br>Ethnic Category:<br>• Hispanic or Latino |
| **2. Sex** | • Female<br>• Male |
| **3. Age** | • Older adults (≥65 years) |

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

**Table D1.6. Representation Score**

| PDRR | Score |
|---|---|
| **0** | 0 |
| **>0 and Less Than 0.5** | 1 |
| **0.5 to 0.8** | 2 |
| **≥0.8** | 3 |

PDRR: Participant to Disease-prevalence Representation Ratio

Lifetime prevalence estimates for sex and racial/ethnic populations were derived from Cure SMA's State of SMA 2024 Report.[8] National prevalence estimates were reported across all SMA types. Statistics specific to Types 2 and 3 SMA (enrollment criteria of SAPPHIRE trial) are unknown. Additionally, SMA is a condition that predominantly affects younger populations, thus a prevalence estimate of adults ≥65 years living with SMA was not available.

**Table D1.7. Rating Categories**

| Demographic Characteristics | Demographic Categories | Maximum Score | Rating Categories (Total Score) |
|---|---|---|---|
| **Race and Ethnicity*** | Asian, Black or African American, White, and Hispanic or Latino | 12 | Good (11-12)<br>Fair (7-10)<br>Poor (≤6) |
| **Sex** | Male and Female | 6 | Good (6)<br>Fair (5)<br>Poor (≤4) |
| **Age** | Older adults (≥65 years) | 3 | Good (3)<br>Fair (2)<br>Poor (≤1) |

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

## Results: SMA Population

**Table D1.8. Race and Ethnicity**

| | White | Black/African American | Asian & NHPI | Hispanic/ Latino | Total Score | Diversity Rating | AIAN |
|---|---|---|---|---|---|---|---|
| **Prevalence[8]** | 67.00% | 8.00% | 5.00% | 16.00% | - | - | 0.60% |
| **SAPPHIRE[89]** | NR | NR | NR | 6.91% | - | - | NR |
| **PDRR** | NC | NC | NC | 0.43 | - | - | NC |
| **Score** | NC | NC | NC | 1 | | | NC |
| **TOPAZ[90]** | 81.00% | 3.40% | 15.50%* | 8.60% | - | - | 0.00% |
| **PDRR** | 1.21 | 0.43 | 3.10 | 0.54 | - | - | NC |
| **Score** | 3 | 1 | 3 | 2 | 9 | Fair | NC |

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

*Possible undercount of the Asian and NHPI prevalence rate as TOPAZ only reported percentage of Asian-identifying individuals in the trial.

**Table D1.9. Sex and Age**

| | Sex | | | | Age | | |
|---|---|---|---|---|---|---|---|
| | Male | Female | Score | Rating | Older Adults (≥65 Years) | Score | Rating |
| **Prevalence**[91] | 49.00 % | 51.00% | - | - | NA | - | - |
| **SAPPHIRE** | 50.00 % | 50.00% | - | - | NA | - | - |
| **PDRR** | 1.02 | 0.98 | - | - | NC | - | - |
| **Score** | 3 | 3 | 6 | Good | NC | | |
| **TOPAZ**[90] | 46.60 % | 53.40% | - | - | NA | - | - |
| **PDRR** | 0.95 | 1.05 | - | - | NC | - | - |
| **Score** | 3 | 3 | 6 | Good | NC | NC | NC |

NA: Not Applicable, NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

## Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Supplement Section D).[92,93]

## Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for apitegromab and other therapies in our scope using ClinicalTrials.gov. Search terms included "apitegromab", "SRK-015", "zolgensma", "onasemnogene abeparvovec", "evrysdi, "risdiplam", "spinraza", and "nusinersen".

We did not identify any studies that would have met our inclusion criteria, and for which no findings have been published.

## Data Synthesis and Statistical Analyses

We presented a narrative summary of relevant data on key outcomes in the main body of the review, as well as in Supplement Sections D2 and D3.

## Feasibility of Conducting Indirect Comparison/Network Meta-Analysis (NMA)

A quantitative indirect treatment comparison or NMA of nusinersen, risdiplam, and onasemnogene abeparvovec were not feasible due to notable differences in population (e.g., age, motor function at baseline), study design, outcomes definitions and measurements.

# D2. Additional Clinical Evidence

## Evidence Base

### *Assessment of SMN-Targeted Therapies After Gene Therapy (Onasemnogene Abeparvovec)*

*Harms*

Nusinersen does not appear to have any new risks when used as a subsequent treatment. In the RESPOND study, 46 children received nusinersen after initial treatment with onasemnogene abeparvovec.[26] Three children (7%) experienced a mild adverse event (proteinuria) related to treatment. No serious adverse events were considered related to nusinersen, and all children continued treatment with no discontinuations.

Among the 19 children treated with risdiplam after initial treatment with onasemnogene abeparvovec, there were three adverse events that were suspected to be risdiplam-related: rash, constipation, and minor spitting/vomiting.[30]

A higher-dose nusinersen regimen (two 50 mg loading doses separated by 14 days, then 28 mg every four months) was evaluated in the DEVOTE study against the approved regimen (four 12 mg loading doses within two months, then 12 mg every four months). Interim findings show comparable rates of adverse events leading to withdrawal and death for the higher dose (20%) compared to the approved dose (24%).[94]

Onasemnogene abeparvovec is being investigated as a one-time intrathecal injection in three trials, STEER, STRONG and STRENGTH. In the STEER trial, the gene therapy had higher rates of serious adverse events of pneumonia and vomiting than in the sham treatment.[95] In the STRENGTH trial, the most frequent treatment-emergent adverse events were nasopharyngitis, pyrexia, and vomiting.[96] Several patients in the STRONG trial experienced several of the adverse of interest noted above, including hepatoxicity, thrombocytopenia, and cardiac events.[97]

### *Assessment of Comparative Effectiveness of SMN Therapies for SMA*

#### Symptomatic SMA

Evidence Base

Symptomatic SMA has historically been categorized through the five subtypes of SMA: Type 0, 1, 2, 3, and 4. Much of the published clinical evidence is reported through this lens.

**Type 0 SMA** is a rare subtype that typically involves one copy of the *SMN2* gene and has the most severe clinical manifestation of disease (e.g., need for respiratory support at birth and death within weeks of birth). Clinical evidence on treatment for this type is limited to several case studies and

registry findings.[98-101] Considering the very limited available evidence, we found no conclusive proof of one treatment being superior to others.

**Type 4 SMA**, is also a rare subtype associated with four or more copies of *SMN2* with an adult onset of clinical symptoms that are milder than preceding SMA types. There are too few case studies of symptomatic Type 4 SMA to draw any firm conclusions from.[102]10.1016/j.jns.2020.116901[103]

**Type 1 SMA** is the most common phenotype and is characterized by an early infantile onset of symptoms within the first 6 months of birth, with severe functional impairment and high rates of mortality within the first two years of life. All three therapies have interventional studies in this population, including SHINE/ ENDEAR (nusinersen), START/STR1VE-US (onasemnogene abeparvovec), and FIREFISH (risdiplam). We will not be reporting in detail on baseline characteristics of these pivotal trials as they have been extensively covered in three matching-adjusted indirect treatment comparisons (MAIC).[46,47,104,105] Each comparison utilized individual patient data (IPD) from the manufacturer affiliated with the index treatment.

Liao et al 2020 was a Biogen-funded conference poster that compared nusinersen against onasemnogene abeparvovec on the outcomes of event-free survival (no death or permanent ventilation), overall survival, and permanent ventilation.[47] ENDEAR/SHINE patients had older age, decreased motor function, and greater needs for respiratory and nutritional support than STR1VE. A sub-group of 48 participants from ENDEAR/SHINE was created to match the STR1VE US trial's baseline characteristics (age at treatment, symptom onset, weight, sex, CHOP-INTEND score) using multiple adjustment weights. The analysis was not weighted on the characteristics of disease duration at baseline, or ventilatory and nutritional support.[46] The analysis used an unanchored MAIC because the trials lacked a common comparator (e.g. sham control or placebo).

Bischof et al 2021 was a Novartis-funded peer-reviewed study that conducted an unanchored MAIC of onasemnogene abeparvovec against nusinersen using data from START/STR1VE-US and ENDEAR/SHINE trials, respectively. The trials differed on baseline characteristics of age at first dose and CHOP-INTEND score. Patient data was weighted on CHOP-INTEND score and nutritional support (feeding tube) but not on age at first dose or age at symptom onset.[46] Comparisons were made across the outcomes of event-free survival (no death or permanent ventilation), overall survival, and achievement of motor milestones (i.e., independent sitting and walking), with up to 24 months of follow-up. Data from the STR1VE-US study were 18 months in follow-up and were carried forward and imputed through 24 months to match the follow-up duration of the START trial.

Ribero et al 2022 was a F. Hoffmann-La Roche-funded peer-reviewed study that evaluated risdiplam using FIREFISH IPD data in two separate comparisons against nusinersen (ENDEAR trial) and onasemnogene abeparvovec (STR1VE-US trial) data. Outcomes of interest included event-free survival (no death or permanent ventilation), overall survival, achievement of motor milestones, motor function, and serious adverse events, with up to 12 months of follow-up. The risdiplam

versus nusinersen comparison involved an unanchored MAIC; there were similarities in baseline characteristics between FIREFISH and ENDEAR on age and disease duration, but FIREFISH patients had lower CHOP-INTEND scores. The trials were not matched for sex, weight, length, ventilatory and nutritional support.[46] Two additional analyses have been published that updated the follow-up times of the comparison to 24 and 36 months, respectively.[106,107]

The trials in the risdiplam versus onasemnogene abeparvovec comparison had notable differences, including age at first dose, baseline CHOP-INTEND scores, and percentage of participants needing pulmonary/ventilatory support. These differences in baseline characteristics required a different type of indirect treatment comparison called the simulated treatment comparison (STC), which uses outcome regression models to adjust for patient population differences.

**Type 2 and 3 SMA** are later onset disease types. SMA Type 2 begins before 18 months with patients able to sit but not walk independently, having shortened lifespans, while Type 3 manifests after 18 months with initial walking ability that may decline over time but normal life expectancy. Interventional studies in this population include CHERISH (nusinersen) and SUNFISH (risdiplam). Onasemnogene abeparvovec evaluated an intrathecal formulation in two trials, STEER (ages two to <18 and SMA Type 2) and STRONG (sitting, nonambulatory SMA patients with 3 SMN2 copies). However, this gene therapy formulation was outside of our scope.

The aforementioned Riberto et al 2022 analysis also conducted a comparison of risdiplam versus nusinersen using trial data from the SUNFISH Part 2 and CHERISH studies, respectively. Both trials were randomized double-blind and included a placebo (SUNFISH) and sham control (CHERISH). This was an anchored MAIC due to assumptions of equivalency between the placebo and sham control arms. The outcomes assessed in this MAIC included motor function and serious adverse events. Compared to the CHERISH trial, SUNFISH Part 2 patients were older at screening, had a longer disease duration, and greater prevalence of severe scoliosis. Patient data was weighted on the characteristics of age at screening, baseline motor function (HFMSE/RULM), and SMN2 copy number. This analysis did not weigh for the effect modifiers of age at symptom onset or disease duration at baseline.[46]

Clinical Benefits

*Infantile-Onset SMA (Type 1)*

Liao 2020 reported that there were no significant differences between nusinersen and onasemnogene abeparvovec on the weighted outcomes of event-free survival (no death or permanent ventilation; p = 0.45), overall survival (p = 0.83), and permanent ventilation (p = 0.41) through 18 months of follow-up.[47]

In the Bischof 2021 MAIC, onasemnogene abeparvovec had a longer event-free survival than nusinersen (hazard ratio: 0.19; 95% CI: 0.07–0.54).[104] The difference in overall survival was not

statistically significant. At 24 months, patients receiving onasemnogene abeparvovec were significantly more likely than those treated with nusinersen to achieve unassisted sitting for ≥30 seconds (relative risk: 2.60; 95% CI: 1.05−6.49). No significant difference was observed at 6 to 18 months.

The Ribero 2022 MAIC reported a longer event-free survival for risdiplam against nusinersen (hazard ratio 0.20 [95% CI: 0.06–0.42]), as well overall survival (hazard ratio 0.26 [95% CI: 0.03-0.67]).[105] Risdiplam treatment also significantly increased the likelihood of achieving a total CHOP-INTEND score of ≥40 points (odds ratio 2.86 [95% CI: 1.43 – 6.09]) and demonstrated a reduced risk of serious adverse events (odds ratio 0.38 [0.15 – 0.97]). An updated MAIC analysis using trial data of at least 36-months of follow-up found similar results; children treated with risdiplam had a reduced rate of death or permanent ventilation (hazard ratio 0.19 [95% CI: 0.07 – 0.35] and overall survival (hazard ratio 0.22 [95% CI: 0.04 – 0.47]) compared with nusinersen.[107]

The Ribero 2022 STC reported a hazard ratio of 0.94 (95% CI: 0.03 – 4.06) for event-free survival with risdiplam compared to onasemnogene abeparvovec.[105] At 14 months, the survival probability was 93% for risdiplam and 91% for onasemnogene abeparvovec. Risdiplam also failed to produce a statistically significant difference in the likelihood of achieving a total CHOP-INTEND score of ≥40 points (odds ratio 2.30 [95% CI: 0.23 – 54.09]) or experiencing a serious adverse event (odds ratio 1.02 [95% CI: 0.22 – 5.08]).

*Later-Onset SMA (Type 2 and 3)*

In the Ribero 2022 MAIC, the difference between risdiplam and nusinersen on the RULM change from baseline was not significant (mean difference -0.49 [95% CI: -3.33 to 2.53]).[105] Analysis of the HFMSE endpoint was not performed due to notable differences between the SUNFISH placebo arm and the CHERISH sham control arm; anchored MAIC analyses require comparability of control arms. The likelihood of experiencing a serious adverse event between risdiplam and nusinersen was uncertain with a very high upper confidence interval limit (odds ratio 4.32 [95% CI: 0.88 - 37,615,888.28]).

# D3. Evidence Tables

**Table D3.1. Study Design**

| Trial (NCT) | Study Design | Arms & Dosing Regimen | Inclusion / Exclusion Criteria | Primary Outcomes |
|---|---|---|---|---|
| **SAPPHIRE (NCT05156320)** | Phase III, randomized, double-blind, placebo-controlled study.<br><br>N=188<br><br>Main population: ages 2-12, non-ambulatory, Type 2 or 3 SMA (n=156).<br>Exploratory population: ages 13-21, non-ambulatory, Type 2 or 3 SMA (n=32). | All arms were administered by an IV infusion once every four weeks:<br>• apitegromab (10 mg/kg) + SOC*<br>• apitegromab (20 mg/kg) + SOC*<br>• placebo + SOC*<br><br>*SOC: nusinersen (12 mg) or risdiplam (5 mg). | **Inclusion**<br>• 2-21 years of age.<br>• Diagnosed with later-onset SMA (Type 2 or 3) before receiving SMN therapy.<br>• Non-ambulatory at screening.<br>• Receiving nusinersen or risdiplam for the specified time and throughout the trial: ≥10 months of dosing for nusinersen, ≥6 months for risdiplam.<br>• HFMSE score between 10-45 at screening.<br>• Adherence to contraception requirement if patients have reached reproductive maturity.<br>**Exclusion**<br>• Previous treatment with onasemnogene abeparvovec or apitegromab.<br>• Use of invasive ventilation and tracheostomy.<br>• Use of chronic daytime non-invasive ventilatory support for >16 hours daily two weeks before dosing or anticipated daytime | Change from baseline in HFMSE total score at 52 weeks. |

| | | | | |
|---|---|---|---|---|
| | | | ventilator support throughout the trial.<br>• Severe scoliosis and/or contractures at screening.<br>• Major orthopedic or other intervention procedure within six months before screening. | |
| **TOPAZ (NCT03921528)** | Phase III, active treatment, three-cohort study. Randomized and double-blind for Cohort 3.<br><br>N=58<br><br>**Cohort 1:** ages 5-21, ambulatory Type 2 SMA (n=20).<br>**Cohort 2**: ages 5-21, Type 2 or non-ambulatory Type 3 SMA. (n=15).<br>**Cohort 3**: ages ≥2 years, Type 2 SMA (n=20). | All arms were administered by an IV infusion once every four weeks:<br>• apitegromab (20 mg/kg)<br>• apitegromab (20 mg/kg) + nusinersen (12 mg)<br>• apitegromab (2 mg/kg) + nusinersen (12 mg); only for Cohort 3 | **Inclusion**<br>• 5-21 years of age for Cohorts 1 and 2; Age ≥2 for Cohort 3.<br>• Diagnosed with later-onset SMA (Type 2 or 3) before receiving any therapy.<br>• Non-ambulatory patients must be able to sit independently per WHO milestone definition.<br>• Ambulatory patients must independently ambulate without aids or orthotics over 10 meters in <30 seconds at screening.<br>• Receiving the same background SMA therapy (or not on any) for ≥6 months before and throughout the study; if receiving nusinersen, completed loading regimen and initiated maintenance dosing with ≥4 weeks after first maintenance dose.<br>• Adherence to contraception requirement if patients have reached reproductive maturity. | **Cohort 1**: change from baseline in RHS total score at 52 weeks.<br>**Cohorts 2 and 3:** change from baseline in HFMSE total score at 52 weeks. |

| | | | | |
|---|---|---|---|---|
| | | | **Exclusion**<br>• Use of tracheostomy with positive pressure.<br>• Use of chronic daytime non-invasive ventilatory support for >16 hours daily two weeks before dosing, or anticipated daytime ventilator support throughout the trial.<br>• Severe scoliosis and/or contractures at screening.<br>• Major orthopedic or other intervention procedure within 6 months before screening. | |

HFMSE: Hammersmith Functional Motor Scale Expanded, IV: intravenous, mg/kg: milligrams per kilograms, RHS: Revised Hammersmith Scale, SOC: standard of care, WHO: World Health Organization

**Table D3.2. SAPPHIRE Baseline Characteristics[17]**

| Trial Population | | Main Population (Ages 2-12) | | | | Exploratory Population (Ages 13-21) | | |
|---|---|---|---|---|---|---|---|---|
| Arm | | Placebo + SOC | API 10 mg/kg + SOC | API 20 mg/kg + SOC | API combined + SOC | Placebo + SOC | API 20 mg/kg + SOC | Pooled Arms |
| N | | 50 | 53 | 53 | 106 | 10 | 22 | 32 |
| Female, Sex n (%) | | 25 (50.0) | 23 (43.4) | 26 (49.1) | 49 (46.2) | 5 (50.0) | 15 (68.2) | 20 (62.5) |
| Mean Age at Screening, Years (Range) | | 8.1 (3, 12) | 7.4 (2, 12) | 7.9 (2, 12) | 7.6 (2, 12) | 15.2 (13, 18) | 16.1 (13, 21) | 15.8 (13, 21) |
| SMN Therapy at Randomization | Nusinersen/Risdiplam (%) | 80 / 20 | 75.5 / 24.5 | 77.4 / 22.6 | 76.4 / 23.6 | 60 / 40 | 54.5 / 45.5 | 56.3 / 43.8 |
| | Nusinersen/Risdiplam Duration, Mean Years | 5.5 / 2.7 | 4.4 / 3.0 | 5.3 / 3.5 | 4.8 / 3.2 | 6.7 / 3.3 | 5.9 / 3.8 | 6.13 / 3.64 |
| SMN Therapy Age at Start, <5 / ≥5 Years (%) | | 88 / 12 | 86.8 / 13.2 | 84.9 / 15.1 | 85.8 / 14.2 | NA | NA | NA* |
| Number of SMN Therapies, 1 / 2 (%) | | 86 / 14 | 86.8 / 13.2 | 84.9 / 15.1 | 85.8 / 14.2 | 80 / 20 | 90.9 / 9.1 | NR |
| SMA Type, Type 2 /3 (%) | | 94 / 6 | 83 / 17 | 90.6 / 9.4 | 86.8 / 13.2 | 60 / 40 | 40.9 / 59.1 | 46.9 / 53.1 |
| SMN2 Copy Number, 2 / 3 / 4 (%) | | 4 / 90 / 2 | 11.3 / 77.4 / 7.5 | 7.5 / 86.8 / 5.7 | 9.4 / 82.1 / 6.6 | 0 / 80 / 10 | 4.5 / 59.1 / 18.2 | 3.1 / 65.6 / 12.5 |
| Baseline HFMSE Score, Mean (Range) | | 27.8 (9, 46) | 25.5 (9, 48) | 25.5 (10, 43) | 25.5 (9, 48) | 22.8 (10, 45) | 20.6 (8, 43) | 21.3 (*10.3*) |
| Baseline RULM Score, Mean (SD) | | NR | NR | NR | NR | NR | NR | 26.3 (5.8) |
| Baseline WHO Motor Milestones, Mean (SD) | | NR | NR | NR | NR | NR | NR | 1.3 (*0.7*) |
| History of Scoliosis (%) | | 70 | 71.7 | 71.7 | 71.7 | 90 | 86.4 | 87.5 |

API: apitegromab, HFMSE: Hammersmith Functional Motor Scale Expanded, mg/kg: milligrams per kilograms, N: number, NA: not applicable, NR: not reported, SD: standard deviation, SMA: spinal muscle atrophy, SMN: survival motor neuron, SOC: standard of care, RULM: Revised Upper Limb Module, WHO: World Health Organization

*Percentage not reported. Mean (SD) is 10.95 (3.841).[89]

Notes: Italicized data indicates digitized. "SOC" represents treatment with either nusinersen or risdiplam.

**Table D3.3. TOPAZ Baseline Characteristics[18]**

| Trial Cohort | | Cohort 1 Ambulatory, Ages 5-21, RHS Scores ≤63 | | Cohort 2 Non-Ambulatory, Ages 5-21, HFMSE Scores ≥10 | Cohort 3 Non-Ambulatory, Ages ≥2, HFMSE Scores ≥10 | | | Pooled: Cohort 2 & 3 |
|---|---|---|---|---|---|---|---|---|
| Arm | | API 20 mg/kg | API 20 mg/kg + Nusinersen | API 20 mg/kg + Nusinersen | API 2 mg/kg + Nusinersen | API 20 mg/kg + Nusinersen | Treated Cohort 3 | Pooled |
| N | | 11 | 12 | 15 | 10 | 10 | 20 | 35 |
| Female (%) | | 73 | 58 | 53.3 | 30 | 50 | 40 | 45.7 |
| Mean Age, Years (Range) | | 12.1 (7, 19) | 13.1 (7, 21) | 11.7 (8, 19) | 4.1 (2, 6) | 3.8 (2,6) | 4.0 (2, 6) | 7.3 (2, 19) |
| Mean Age at Diagnosis, Years (Range) | | 5.9 (2, 15) | 4.5 (2, 15) | 3.1 (1, 16) | 1.2 (1, 2) | 1.2 (1, 3) | NR | NR |
| Mean Age at Symptom Onset, Years (Range) | | 3.7 (0.8, 11) | 3.0 (0.7, 14) | 1.4 (0.5, 2) | 0.9 (0.5, 1.2) | 1.0 (0.5, 3.5) | 0.95 (0.5, 3.5) | 1.12 (0.5, 3.5) |
| Race, n (%) | Asian | NR | NR | 2 (13.3) | NR | NR | 1 (5.0) | 3 (8.6) |
| | Black or African American | NR | NR | 1 (6.7) | NR | NR | 1 (5.0) | 2 (5.7) |
| | White or Other | NR | NR | 12 (80.0) | NR | NR | 18 (90.0) | 30 (85.7) |
| SMA History | Contractures | NR | NR | 13 (86.7) | NR | NR | 12 (60.0) | 25 (71.4) |
| | Scoliosis | NR | NR | 11 (73.3) | NR | NR | 18 (51.4) | 18 (51.4) |
| SMN2 Gene Copies, n(%)* | 2 | 1 (9) | 0 | 0 | 1 (10) | 1 (10) | 2 (10.0) | 2 (5.7) |
| | 3 | 4 (36) | 9 (75) | 11 (73.3) | 8 (80) | 8 (80) | 16 (80.0) | 27 (77.1) |
| | 4 | 4 (36) | 1 (8) | 2 (13.3) | 1 (10) | 0 | 1 (5.0) | 3 (8.6) |
| Mean Nusinersen Maintenance Doses at Baseline (Range)[†] | | NA | 3.9 (2, 6) | 4.8 (2, 9) | 4.8 (1, 7) | NR | NR | NR |
| SMN Therapy Duration, Mean Months (Range) | | NA | 19.9 (12, 28) | 24.2 (11.8, 39.3) | 24.0 (10, 34) | NR | 24.0 (9.7, 34.2) | 24.1 (9.7, 39.3) |
| Discontinued, n | | 0 | 1[‡] | 0 | 0 | 0 | NR | NR |
| No Response | | NR | NR | 2 (13.3) | NR | NR | 1 (5.0) | 3 (8.6) |
| Baseline RHS Score, Mean (Range) | | 47.6 (26, 63) | 51.3 (43, 62) | NA | NA | NA | NR | NR |
| Baseline HFMSE Score, Mean (Range) | | NA | NA | 22.7 (13, 39) | 26.1 (12, 44) | 23.5 (14, 42) | 24.8 (12, 44) | 23.9 (12, 44) |

| Trial Cohort | Cohort 1 Ambulatory, Ages 5-21, RHS Scores ≤63 | | Cohort 2 Non-Ambulatory, Ages 5-21, HFMSE Scores ≥10 | Cohort 3 Non-Ambulatory, Ages ≥2, HFMSE Scores ≥10 | | | Pooled: Cohort 2 & 3 |
|---|---|---|---|---|---|---|---|
| **Arm** | **API 20 mg/kg** | **API 20 mg/kg + Nusinersen** | **API 20 mg/kg + Nusinersen** | **API 2 mg/kg + Nusinersen** | **API 20 mg/kg + Nusinersen** | **Treated Cohort 3** | **Pooled** |
| **Baseline RULM Score, Mean (Range)** | NA | NA | 26.6 (19, 34) | 25.0 (18, 34) | 22.6 (15, 33) | 23.8 (15, 34)[§] | 25.1 (15, 34) |

API: apitegromab, HFMSE: Hammersmith Functional Motor Scale Expanded, mg/kg: milligrams per kilograms, NA: not applicable, NR: not reported, N: number, RHS: Revised Hammersmith Scale, RULM: Revised Upper Limb Module, SMA: spinal muscle atrophy, SMN: survival motor neuron

*Data not available for all participants.

†Maintenance dose was used as a surrogate for duration of nusinersen exposure at screening.

‡Participant discontinued the trial for reasons unrelated to study drug.

§Data for n=19.

# D4. Ongoing Studies

**Table D4.1. Ongoing Studies**

| Title, NCT, & Trial Sponsor | Study Design | Arms | Inclusion Criteria & Patient Population | Primary Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **ONYX**<br>**NCT05626855**<br>**Scholar Rock** | Phase III, open-label, multicenter, extension study to evaluate the long-term safety and efficacy of apitegromab.<br><br>N=238 | Apitegromab (20 mg/kg) once every four weeks by IV infusion. | • Patients ≥2 years of age with Type 2 or 3 SMA.<br>• Completed TOPAZ or SAPPHIRE trial.<br>• Estimated life expectancy >2 years from baseline. | Incidence of TEAEs and SAEs by severity for up to six years. | May 2029 |
| **OPAL**<br>**Scholar Rock** | Phase II study to evaluate the safety and efficacy of apitegromab in patients younger than 2 who have been or continuing to be treated with any SMN therapy, including onasemnogene abeparvovec.<br><br>N=Unknown | Unknown | • Patients under 2 years of age with SMA.<br>• Current or continuation of treatment with any SMN therapy, including onasemnogene abeparvovec. | Unknown | Unknown |

| Title, NCT, & Trial Sponsor | Study Design | Arms | Inclusion Criteria & Patient Population | Primary Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **RESPOND**<br>**NCT04488133**<br>**Biogen** | Phase IV interventional study to evaluate treatment with nusinersen after onasemnogene abeparvovec.<br><br>N=46 | Nusinersen (12 mg) by IT injection; 4 loading doses (50 mg) on days 1, 15, 29, and 64, followed by maintenance dose (12 mg) every 4 months. | • Patients with SMA aged 2 to 36 months.<br>• SMN2 copy number of ≥1.<br>• ≤36 months of age at the time of first Nusinersen dose.<br>• Treated with onasemnogene abeparvovec ≥2 months prior to first Nusinersen dose. | Total HINE Section 2 Motor Milestones Score up to day 778. | October 2025 |
| **HINALEA-1**<br>**NCT05861986**<br>**Hoffman-La Roche** | Phase IV, open-label, single-arm study to evaluate the safety and efficacy of risdiplam in pediatric participants with SMA after onasemnogene abeparvovec.<br><br>N=28 | Oral risdiplam (60 mg) once daily for 120 weeks. | • Patients with SMA aged <2 years with two SMN2 gene copies.<br>• Treated with onasemnogene abeparvovec pre- or post-symptomatically no less than 3 months, but not more than 7 months, prior to enrollment.<br>• Per the investigator, no clinically significant decline in function after onasemnogene abeparvovec. | Change from baseline in the raw gross motor score on the BSID-III at 72 weeks. | March 2028 |
| **Title, NCT, & Trial Sponsor** | **Study Design** | **Arms** | **Inclusion Criteria & Patient Population** | **Primary Outcomes** | **Estimated Completion Date** |

| | | | | | |
|---|---|---|---|---|---|
| **HINALEA-2**<br>**NCT05861999**<br>**Hoffman-La Roche** | Phase IV, open-label, single-arm study to evaluate the safety and efficacy of risdiplam in pediatric participants with SMA who experienced a functional plateau or decline after onasemnogene abeparvovec.<br><br>N=28 | Oral risdiplam (60 mg) once daily for 120 weeks. | • Patients with SMA aged <2 years with two SMN2 gene copies.<br>• Treated with onasemnogene abeparvovec pre- or post-symptomatically no less than 3 months prior to enrollment.<br>• Per the investigator, has demonstrated a functional plateau or decline post-onasemnogene abeparvovec (duration ≤6 months) in swallowing AND one additional function (respiratory, motor function, other). | Change from baseline in the raw gross motor score on the BSID-III at 72 weeks. | March 2028 |
| **PUPFISH**<br>**NCT05808764**<br>**Hoffman-La Roche** | Phase II, open-label study to evaluate the pharmacokinetics and safety of risdiplam in infants with SMA.<br><br>N=10 | Oral risdiplam (0.15 mg/kg) once daily for 28 days. | • Patients aged <20 days, either diagnosed with SMA or positive identification for SMA via newborn screening or prenatal testing.<br>• Gestational age ≥37 weeks. | • Plasma concentrations, area the plasma concentration-time curve (AUC), and steady-state concentration (CSS) of risdiplam.<br>• Risdiplam free fraction.<br>• Percentage of participants with AEs, SAEs, and treatment discontinuation due to AEs. | October 2025 |

| Title, NCT, & Trial Sponsor | Study Design | Arms | Inclusion Criteria & Patient Population | Primary Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **WeSMA**<br>**NCT05232929**<br>**Genentech** | Phase IV, prospective, multi-center follow-up study to evaluate the long-term safety and efficacy of risdiplam.<br><br>N=500 | Oral risdiplam (60 mg) once daily for 120 weeks. | • Children, adults or older adults with SMA.<br>• Prescribed or continued use of risdiplam. | Number of participants with AEs, SAEs, or AESI for up to 4 ½ years. | December 2026 |
| **RESTORE**<br>**NCT04174157**<br>**Novartis** | Prospective, multinational, non-interventional, long-term safety and effectiveness registry of onasemnogene abeparvovec.<br><br>N=700 | Onasemnogene abeparvovec | • Children, adults or older adults with SMA.<br>• Treated with onasemnogene abeparvovec. | • Change in probability of survival.<br>• Change from baseline (CFB) on the CHOP-INTEND in infants with pre-symptomatic or Type 1 SMA.<br>• CFB on the HINE in infants with pre-symptomatic, Type 1 or 2 SMA.<br>• CFB on the HFMSE in patients with Type 2 or 3 SMA.<br>• Incidence of TEAEs related and unrelated to therapy, and adverse events of special interest (AESI*) for up to 15 years. | June 2038 |

| Title, NCT, & Trial Sponsor | Study Design | Arms | Inclusion Criteria & Patient Population | Primary Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **SPECTRUM**<br>**NCT05335876**<br>**Novartis** | Phase III, prospective, multi-center study to evaluate the long-term safety and efficacy of onasemnogene abeparvovec.<br><br>N=175 | Onasemnogene abeparvovec by IV infusion or IT injection. | • Children, adults, and older adults (ages 0-100 years) who participated in a onasemnogene abeparvovec clinical trial (COAV101A12306, COAV101B12301 or COAV101B12302). | Incidence of serious TEAEs and AESI* for up to 5 years. | June 2030 |
| **ASCEND**<br>**NCT05067790**<br>**Biogen** | Phase IIIb, interventional study to evaluate the higher dose regimen of nusinersen in patients previously treated with risdiplam.<br><br>N=45 | Higher-dose nusinersen (28 mg) by IT injection; two loading doses (50 mg) 2 weeks apart, followed by maintenance dose (28 mg) every 4 months for up to 2 years. | • Patients aged ≥15 to ≤50 years, with a body weight >20 kg, and diagnosed with non-ambulatory, later-onset SMA.<br>• Symptom onset >6 months of age.<br>• Prior treatment with risdiplam for ≥6 months in nusinersen -naïve participants; nusinersen -experienced participants to have been on risdiplam for ≥12 months after stopping nusinersen ≥16 months before enrollment.<br>• RULM entry item A score ≥3; RULM total score ≥5 and ≤30. | Change in total score on the RULM. | June 2027 |

| Title, NCT, & Trial Sponsor | Study Design | Arms | Inclusion Criteria & Patient Population | Primary Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **STEER**<br>**NCT05089656**<br>**Novartis** | Phase III, randomized, sham-controlled, double-blind study to evaluate the efficacy and safety of intrathecal onasemnogene abeparvovec.<br><br>N=127 | • Onasemnogene abeparvovec ($1.2 \times 10^{14}$ vg) once by IT injection.<br><br>• Sham control (skin prick in the lumbar region without any medication). | • Patients with SMA aged ≥ 2 to < 18 years.<br>• Patients are treatment-naive (historical or current use) for all SMN-targeting therapies (e.g., risdiplam and nusinersen).<br>• Symptom onset ≥6 months of age.<br>• Able to sit independently at screening, but has never had the ability to walk independently. | Change from baseline in HFMSE total score at 52 weeks. | February 2025, awaiting results |

AEs: adverse events, BSID-III: Bayley Scales of Infant and Toddler Development - Third Edition, CFB: change from baseline, CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HINE: Hammersmith Infant Neurological Examination, HFMSE: Hammersmith Functional Motor Scale Expanded, IT: intrathecal, IV: intravenous, mg: milligrams, RULM: Revised Upper Limb Manual , SAEs: serious adverse events, TEAEs: treatment emergent adverse events, vg: vector genomes

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Note: adverse events of special interested (AESI) associated with onasemnogene abeparvovec include hepatotoxicity, transient thrombocytopenia, cardiac adverse events, sensory abnormalities suggestive of ganglionopathy, and thrombotic microangiopathy.

## D5. Previous Systematic Reviews and Technology Assessments

To date, there have been no health technology assessments or systematic literature reviews of apitegromab and SMA.

The three disease modifying therapies have been assessed by Canada's Drug Agency.

### Review of Onasemnogene Abeparvovec (Zolgensma by Canada's Drug Agency (2021)[108]

The Canadian Drug Expert Committee recommended that onasemnogene abeparvovec be reimbursed for treating pediatric patients with 5q SMA with biallelic mutations in the SMN1 gene, provided specific conditions are met. These conditions include genetic documentation of the condition, and that patients are symptomatic or pre-symptomatic with one to three copies of the SMN2 gene, 180 days of age or younger, and not currently requiring permanent feeding or ventilatory support.

The recommendation was supported by two Phase III trials showing that treated patients had significantly better outcomes, with 59% able to sit independently by 18 months in STR1VE-US and all pre-symptomatic infants under six weeks alive without permanent ventilation in SPR1NT.

### Review of Risdiplam (Evrysdi) by Canada's Drug Agency (2021)[49]

The Canadian Drug Expert Committee recommended that risdiplam should be reimbursed for treatment of SMA in patients with genetic documentation of 5q SMA homozygous gene deletion or compound heterozygote status, who are symptomatic and either aged between two months and seven months with two or three copies of the SMN2 gene, or aged 8 months to 25 years, non-ambulatory, with the same genetic documentation. Additionally, patients must not require permanent invasive ventilation, and the maximum duration of initial authorization is 12 months, allowing for flexibility in assessing treatment benefits as observed in the FIREFISH and SUNFISH trials.

The FIREFISH Part 2 study showed that 29.3% of infants with SMA could sit without support after 12 months of risdiplam treatment, while 85.4% were alive without needing permanent ventilation, and the SUNFISH Part 2 study reported a mean improvement of 1.55 points in the MFM32 score for non-ambulatory patients.

The Expert Committee recommended against using risdiplam in combination with nusinersen or onasemnogene abeparvovec due to lack of evidence supporting combination therapy.

## Review of Nusinersen (Spinraza) by Canada's Drug Agency (2017, 2019, 2022)[109]

In its initial review in 2017, the Expert Committee recommended nusinersen for reimbursement for patients with SMA who had two copies of the SMN2 gene and a disease duration of less than 26 weeks. This recommendation was based on the results of the ENDEAR study (N=121), a phase III clinical trial.

In a 2019 resubmission, a conditional positive recommendation was granted for nusinersen to include patients with 5q SMA who had either two or three copies of the SMN2 gene. The criteria specified that these patients should have a disease duration of less than 6 months, symptom onset after the first week of life, and be seven months of age or younger. Additionally, the recommendation extended to patients aged 12 years or younger who experienced symptom onset after 6 months of age and had never achieved the ability to walk independently.

In a 2021 reassessment, the sponsor sought to expand the reimbursement criteria for nusinersen to include adult patients over 18 years of age with Type 2 and Type 3 SMA, regardless of their ambulatory status. However, the Committee recommended against reimbursing nusinersen for these adult patients. The rationale was based on the absence of randomized clinical trials evaluating the efficacy or safety of nusinersen in treatment-naïve adults with Type 2 or Type 3 SMA. Although evidence from four observational studies suggested potential benefits in maintaining or improving physical abilities, the limitations of these studies prevented definitive conclusions about the drug's effectiveness. Furthermore, the reviewed evidence did not demonstrate that nusinersen could adequately address the critical needs of adult patients, such as stabilizing disease progression and improving health-related quality of life.

# D6. Heterogeneity and Subgroups

**Table D6.1 SAPPHIRE Subgroup Data[17]**

| Arms | | | | Apitegromab + SOC (2-21 Years Old) | Placebo + SOC |
|---|---|---|---|---|---|
| Change in Baseline in HFMSE at Month 12 | Apitegromab vs. Placebo | N | | 128 | 60 |
| | | LSMD (95% CI) | | 1.8 (0.46, 3.16) | |
| | SMN-Targeted Therapy Type | Nusinersen | n | 93 | 46 |
| | | | LSMD (95% CI) | 2.2 (0.67, 3.77) | |
| | | Risdiplam | n | 35 | 14 |
| | | | LSMD (95% CI) | 0.5 (-2.30, 3.33) | |
| | Age of SMN-Targeted Therapy Initiation | <5 Years | n | 93 | 46 |
| | | | LSMD (95% CI) | 1.7 (0.09, 3.36) | |
| | | ≥5 Years | n | 35 | 14 |
| | | | LSMD (95% CI) | 2.4 (-0.43, 5.14) | |
| | Region | Europe | n | 84 | 33 |
| | | | LSMD (95% CI) | 2.5 (0.43, 4.62) | |
| | | North America | n | 44 | 27 |
| | | | LSMD (95% CI) | 1.0 (-0.42, 2.33) | |

CI: confidence interval, HFMSE: Hammersmith Functional Motor Scale – Expanded, LSMD: least squares mean difference, n: number, SMN: survival motor neuron, SOC: standard of care, y.o.: years old
"SOC" represents treatment with either nusinersen or risdiplam.

# E. Long-Term Cost-Effectiveness: Supplemental Information

## E1. Detailed Methods

**Table E1.1. Impact Inventory**

| Sector | Type of Impact (Add Additional Domains, as Relevant) | Included in This Analysis from […] Perspective? | | Notes on Sources (If Quantified), Likely Magnitude & Impact (If Not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Formal Health Care Sector** | | | | |
| **Health Outcomes** | Longevity effects | X | X | |
| | Health-related quality of life effects | X | X | On patients in health care sector & patients + caregivers in societal |
| | Adverse events | X | X | |
| **Medical Costs** | Paid by third-party payers | X | X | |
| | Paid by patients out-of-pocket | ☐ | ☐ | |
| | Future related medical costs | ☐ | ☐ | |
| | Future unrelated medical costs | ☐ | ☐ | |
| **Informal Health Care Sector** | | | | |
| **Health-Related Costs** | Patient time costs | NA | ☐ | |
| | Unpaid caregiver-time costs | NA | ☐ | |
| | Transportation costs | NA | ☐ | |
| **Non-Health Care Sector** | | | | |
| **Productivity** | Labor market earnings lost | NA | ☐ | |
| | Cost of unpaid lost productivity due to illness | NA | ☐ | |
| | Cost of uncompensated household production | NA | ☐ | |
| **Consumption** | Future consumption unrelated to health | NA | ☐ | |
| **Social Services** | Cost of social services as part of intervention | NA | ☐ | |
| **Legal/Criminal Justice** | Number of crimes related to intervention | NA | ☐ | |
| | Cost of crimes related to intervention | NA | ☐ | |
| **Education** | Impact of intervention on educational achievement of population | NA | ☐ | |
| **Housing** | Cost of home improvements, remediation | NA | ☐ | |
| **Environment** | Production of toxic waste pollution by intervention | NA | ☐ | |
| **Other** | Other impacts (if relevant) | NA | ☐ | |

NA: not applicable

Adapted from Sanders et al[110]

## Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[111]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

## Target Population

The population of focus for the economic evaluation included non-ambulatory Type 2 and 3 SMA patients between the ages of 2-12 who were being treated with nusinersen or risdiplam. The modeled population was a weighted average of all the treatment groups in the SAPPHIRE trial.

**Table E1.2. Base-Case Model Cohort Characteristics**

| | **Ages 2-12** |
|---|---|
| **Mean Age in Years (Range)** | 7.8 (2, 12) |
| **Percent Female (%)** | 47.4 |
| **Nusinersen/Risdiplam (%)** | 77.6/22.4 |
| **Mean Duration of Nusinersen/Risdiplam (Years)** | 5.0/3.0 |
| **SMA Type 2/3 (%)** | 89.1/10.9 |
| **Scoliosis (%)** | 71.2 |
| **Mean Baseline HFMSE Score (Range)** | 26.2 (9, 48) |

SMA: spinal muscular atrophy, HFMSE: Hammersmith Functional Motor Scale – Expanded

## Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The full list of interventions is as follows:

- Apitegromab (Scholar Rock) 10 mg/kg or 20 mg/kg with standard of care nusinersen (SPINRAZA®, Biogen) or risdiplam (Evrysdi®, Genentech)

The Comparator(s) for these interventions will be:

- Standard of care nusinersen (SPINRAZA®, Biogen) or risdiplam (Evrysdi®, Genentech)

# E2. Model Inputs and Assumptions

## Model Inputs

### *Clinical Probabilities/Response to Treatment*

Patients started in the "sitting" state and remained there throughout the duration of the model.

### *Mortality*

Following the mortality data approach from the previous ICER model,[9] our analysis used pooled data from German and Polish SMA Type 2 patients in Zerres et al.[112] for individuals in the "sitting" state and data from Gregoretti et al. for patients in the "not-sitting" state.[113]

**Table E2.1. Mortality Inputs**

| Parameter | Value | Source |
|---|---|---|
| **Mortality From Sitting** | Gompertz<br>α=0.0964<br>β=0.0037 | Zerres et al.[112] |
| **Mortality From Not-Sitting** | Exponential<br>λ=0.0158 | Gregoretti et al.[113] |

### *Utilities*

We obtained health state utilities for each health state ("not-sitting" & "sitting") stratified by SMA Type (2 and 3) displayed in Table E2.2. from a study by Belter et al.[61]
These values were combined into weighted averages for each state based on the SMA type distribution observed in the SAPPHIRE trial (Table E1.2).[53] The study obtained Health Utilities Index Mark 3 (HUI3) values using 2019 Cure SMA Community Update Survey Data that collected responses from patients/caregivers with SMA. The HUI3 measures eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain, with scores ranging from -0.36 (worst possible health state) to 1.00 (perfect health). The study stratified results by functional status

(permanent ventilation, non-sitters, sitters, etc.). Table E2.2. also presents the utilities applied to calculate the additional utility for apitegromab.

**Table E2.2. Utility Values for Health States**

| State | Utility Value | Source |
|---|---|---|
| **Sitting SMA2** | 0.26 | Belter et al.[61] |
| **Sitting SMA3** | 0.23 | |
| **Not Sitting SMA2** | 0.12 | |
| **Not Sitting SMA3** | 0.14 | |
| **Baseline HFMSE** | 0.04 | Llyod et al.[58] |
| **≥3-point Increase in HFMSE** | 0.10 | |

SMA: spinal muscular atrophy, HFMSE: Hammersmith Functional Motor Scale – Expanded

***Caregiver Utilities***

We did not expect differential mortality in this model, and as a result did not expect to observe incremental differences in the outcomes due to bereavement. Although we were aware of additional disutilities related to bereavement, we included only patient state-specific caregiver utilities in a modified societal perspective scenario analysis. The value for the utility of the caregiver (0.484) of a patient in the "not sitting" health state was taken from the NICE technology appraisal for nusinersen,[52] the estimates for which were derived from an analysis by Bastida et al. in the Spanish caregiver's subgroup.[114] This value was for the "sits without support but does not roll" (late onset) health state. This was the lowest utility reported and was therefore used for worse health states including "not sitting." The value for the utility of the caregiver (0.592) of a patient in the "sitting" health state was derived as the average of the three sitting states from the same NICE report.

***Economic Inputs***

*Administration and Monitoring Costs*

***Non-Drug Costs***

Non-drug costs associated with nusinersen administration and monitoring are displayed in Table E2.3. Risdiplam had no additional monitoring or administration costs.

**Table E2.3. Non-Drug Costs**

| | Value ($) | Description | Source |
|---|---|---|---|
| **Nusinersen Non-Drug Costs** | | | |
| **Administration Into Central Nervous System** | 74.07 | HCPCS 96450 | CMS Physician Fee Schedule 2025 [66] |
| | 331.69 | | CMS OPPS Addendum B [63] |
| **Intrathecal Injection (Drain Cerebrospinal Fluid)** | 90.89 | HCPCS 62272 | CMS Physician Fee Schedule 2025 [66] |
| | 692.52 | | CMS OPPS Addendum B [63] |
| **Fluoroguide** | 27.17 | HCPCS 77003 | CMS Physician Fee Schedule 2025[66] |
| **Complete Blood Count** | 7.77 | HCPCS 85025 | CMS Laboratory Fee Schedule 2025[115] |
| **Coagulation Testing** | 4.29 | HCPCS 85610 | |
| **Urine Protein Levels** | 3.67 | HCPCS 84156 | |
| **MD/Specialist** | 63.72 | HCPCS 99213 | CMS Physician Fee Schedule 2025 [66] |

APC: Ambulatory Payment Classification, CMS: Centers for Medicare & Medicaid Services, CPT: Current Procedural Terminology, HCPCS: Healthcare Common Procedure Coding System, OPPS: Outpatient Prospective Payment System, SD: standard Deviation

*Health Care Utilization Costs*

We assumed background health care costs obtained for childhood onset SMA applied to individuals in the "sitting" state of $7,746 (SD $10,890) per month, and early onset SMA apply to individuals in "not-sitting" of $31,092 (SD $36,285) per month.[116]

*Adverse Event Costs*

Costs associated with pneumonia were obtained from the Centers for Medicare & Medicaid Services (CMS) Medicare Severity Diagnosis Related Group (DRF) 177 for respiratory infections and inflammations with major complication or comorbidity.[117] The cost of $12,106 was applied once to the proportion of patients observed to experience the adverse event in SAPPHIRE.

*Productivity Costs*

We did not include productivity costs in the model due to limitations in available data.

# E3. Results

Base case results are described in Section 4.6 of the main report.

# E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. One way sensitivity results are displayed in Table E4.1. and mean probabilistic sensitivity analysis results with 95% intervals for qualities are detailed in table E4.2.

**Table E4.1. Tornado Diagram Inputs and Results for Apitegromab versus SoC**

| | Lower Incremental CE Ratio* | Upper Incremental CE Ratio* | Lower Input† | Upper Input† |
|---|---|---|---|---|
| **Percent Achieving Treatment Effect on Apitegromab (0.24;0.36)** | $49,656,000 | $24,426,000 | 0.24 | 0.36 |
| **Annual mg/kg Amount of Apitegromab (144;216)** | $26,209,000 | $39,280,000 | 144 | 216 |
| **Percent Achieving Treatment Effect on SoC (0.1;0.15)** | $28,722,000 | $38,077,000 | 0.10 | 0.15 |

CE: cost-effectiveness, mg: milligram, kg: kilogram, SoC: standard of care

*Based on placeholder price of $350,000 per year

†Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

**Table E4.2. Results of Probabilistic Sensitivity Analysis for Apitegromab versus SoC**

| | Apitegromab* + SoC Mean | SoC Mean | Incremental |
|---|---|---|---|
| **Costs** | $14,175,000 | $8,480,000 | $5,695,000 |
| **QALYs** | 4.28 (0.34, 8.81) | 4.11 (0.33, 8.50) | 0.17 (0.01, 0.31) |
| **evLYs** | 4.28 (0.34, 8.81) | 4.11 (0.33, 8.50) | 0.17 (0.01, 0.31) |
| **Incremental CE Ratio** | | | $33,122,000 |

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

*Based on placeholder price of $350,000 per year

Note: 0% of simulations hit key WTP thresholds

# E5. Scenario Analyses

## Scenario Analysis 1

### *Disease Progression – All Treatments*

Following clinical expert opinion, we assume patients on both treatments will experience disease progression at a parallel rate. We obtained the slope of decline in HFMSE from the placebo arm in SAPPHIRE and applied this decline to both treatments to calculate the average time for HFMSE scores to reach the upper IQR of non-sitters.[50,51] We assumed both treatments experience the same rate of decline, but that the apitegromab arm started declining from a higher HFMSE score based

on the average change from baseline at 52 weeks – resulting in a longer average time to "not-sitting" (115 months versus SoC and 125 months for apitegromab + SoC). Additionally, we assumed patients on both treatments remained in "sitting" for the first year.

The addition of caregiver utilities followed an additive approach where one caregiver and one patient create a total family QALY estimate. Caregiver utilities were obtained from the NICE technology appraisal for nusinersen[52] with estimates derived from Bastida et al. in the Spanish caregiver's subgroup.[114] The utility value for caregivers of patients in the "not sitting" health state was 0.484, obtained from the "sits without support but does not roll" (late onset) health state. This was the lowest utility reported and was equivalent to early onset patients who achieved no milestones. The utility value for caregivers of patients in the "sitting" health state was 0.592 and derived as the average of the three sitting states from the same NICE report.

This scenario reduced the difference in total costs from approximately $6,600,000 in the base case to around $4,100,000 and increased incremental QALYs by 0.01. It also created a differential in the life years of approximately 0.30. Results are further detailed in Table E5.1.

**Table E5.1. Results for Disease Progression – All Treatments**

| Treatment | Intervention Acquisition Costs | Intervention-Related Costs† | Total Costs | QALYs | QALYs + Caregiver QALYs | Life Years |
|---|---|---|---|---|---|---|
| **Apitegromab* + SoC** | $8,565,000 | $264,000 | $8,991,000 | 2.60 | 8.94 | 11.29 |
| **SoC** | $4,491,000 | $250,000 | $4,902,000 | 2.39 | 8.54 | 10.98 |

QALY: quality-adjusted life year, SoC: standard of care

*Based on placeholder price of $350,000 per year

†Intervention-related costs include markup costs, administration costs, and costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label

## Scenario Analysis 2

### *Disease Progression – SoC Only*

In this scenario we followed the same approach as scenario one. However, we assumed that apitegromab maintains patients function and prevents any disease progression through their lifetime. This resulted in a large difference in life years between the two arms of 7.87 years, a QALY difference of 2.66, and a difference in family QALY of 7.67. The incremental difference in total costs increased to almost $10,000,000 between the two arms compared to $6,600,000 in the base case due to the differences in survival.

**Table E5.2. Results for Disease Progression – SoC Only**

| Treatment | Intervention Acquisition Costs | Intervention-Related Costs† | Total Costs | QALYs | QALYs + Caregiver QALYs | Life Years |
|---|---|---|---|---|---|---|
| **Apitegromab* + SoC** | $14,311,000 | $442,000 | $14,900,000 | 5.04 | 16.21 | 18.86 |
| **SoC** | $4,491,000 | $250,000 | $4,902,000 | 2.39 | 8.54 | 10.98 |

QALY: quality-adjusted life year, SoC: standard of care

*Based on placeholder price of $350,000 per year

†Intervention-related costs include markup costs, administration costs, and costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label

## Scenario Analysis 3

### *Modified Societal Perspective*

Inputs used for the modified societal perspective analysis include caregiver QALYs following the same approach in scenario analysis 1 and 2. Lifetime QALYs of patients plus caregivers were 22.43 and 22.23 for patients on apitegromab + SoC, and SoC alone, respectively.

## Scenario Analysis 4

### *Exclusion of Unrelated Health Care Costs*

In this analysis we excluded unrelated (non-drug) health care costs that were not related to the disease *per se*. Unrelated health care costs were obtained from Tan et al.[116] who calculated the health care costs of a matched cohort without SMA to be $230 per month for patients in the "sitting" state, and $498 per month for patients in the "not-sitting" state. This scenario reduced total costs by approximately $50,000 in both treatments compared to the base case. There were no changes to other outcomes nor any increment between the two treatments.

**Table E5.3. Results for Exclusion of Unrelated Health Care Costs**

| Treatment | Intervention Acquisition Costs | Intervention-Related Costs† | Total Costs | QALYs | Life Years |
|---|---|---|---|---|---|
| **Apitegromab* + SoC** | $14,311,000 | $442,000 | $16,454,000 | 5.04 | 18.86 |
| **SoC** | $7,710,832 | $428,700 | $9,840,000 | 4.84 | 18.86 |

QALY: quality-adjusted life year, SoC: standard of care

*Based on placeholder price of $350,000 per year

†Intervention-related costs include markup costs, administration costs, and costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label

## Scenario Analysis 5

### *Removing Pneumonia as an Adverse Event*

In this analysis, we assume the difference in pneumonia observed in SAPPHIRE were due to chance and set the rate of pneumonia in the apitegromab treatment arm equal to the SoC treatment arm of 0% - removing associated costs and disutilities. This resulted in a reduction of approximately $1,000 over the lifetime on apitegromab + SoC, and no meaningful changes in QALYs over the lifetime compared to the base case.

**Table E5.4. Results for Removing Pneumonia**

| Treatment | Intervention Acquisition Costs | Intervention-Related Costs† | Total Costs | QALYs | Life Years |
|---|---|---|---|---|---|
| **Apitegromab* + SoC** | $14,311,000 | $442,000 | $16,506,000 | 5.04 | 18.86 |
| **SoC** | $7,710,832 | $428,700 | $9,892,000 | 4.84 | 18.86 |

QALY: quality-adjusted life year, SoC: standard of care

*Based on placeholder price of $350,000 per year

†Intervention-related costs include markup costs, administration costs, and costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label

## Scenario Analysis 6

### *Health State Utilities from NICE TA588 ERG Clinical Advisors*

Base utility values from Belter et al.[61] in the base case were replaced with utilities presented in the NICE TA588, estimated from clinical advisors in their evidence review group (ERG).[52] These were the highest utility values we were able to find for later-onset SMA patients. Utility values in this analysis for "sitting" were 0.60, and 0.61 for SoC and apitegromab + SoC, respectively. This resulted in much higher QALYs over the lifetime for both treatments compared to the base case, but no difference in incremental QALYs between treatments. .

**Table E5.5. Results for Utilities from NICE TA588 Clinical Advisors**

| Treatment | Intervention Acquisition Costs | Intervention-Related Costs† | Total Costs | QALYs | Life Years |
|---|---|---|---|---|---|
| **Apitegromab* + SoC** | $14,311,000 | $442,000 | $16,507,000 | 11.50 | 18.86 |
| **SoC** | $7,710,832 | $428,700 | $9,892,000 | 11.31 | 18.86 |

QALY: quality-adjusted life year, SoC: standard of care

*Based on placeholder price of $350,000 per year

†Intervention-related costs include markup costs, administration costs, and costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label

### Scenario Analysis 7

***Health State Utilities from Lloyd et al.***

Base utility values from Belter et al.[61] in the base case were replaced with EQ-5D utilities presented in Lloyd et al.[58] Utility values were derived in this study by developing case vignettes to represent various health states associated with different SMA types, informed by literature review and expect interviews. They described physical function, interventions such as ventilation and feeding tubes, and disease progression and were provided to five UK-based clinical experts to review and assess HRQoL values. These were the lowest utility values we were able to find for later-onset SMA patients. Utility values in this analysis for "sitting" were 0.04, and 0.05 for SoC and apitegromab + SoC, respectively. This resulted in much lower QALYs over the lifetime for both treatments, but no difference in the incremental between the treatments.

**Table E5.6. Results for Utilities from Lloyd et al.[58]**

| Treatment | Intervention Acquisition Costs | Intervention-Related Costs† | Total Costs | QALYs | Life Years |
|---|---|---|---|---|---|
| **Apitegromab*† SoC** | $14,311,000 | $442,000 | $16,507,000 | 0.94 | 18.86 |
| **SoC** | $7,711,000 | $428,700 | $9,892,000 | 0.75 | 18.86 |

QALY: quality-adjusted life year, SoC: standard of care

*Based on placeholder price of $350,000 per year

†Intervention-related costs include markup costs, administration costs, and costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label

## E6. Heterogeneity and Subgroups

Subgroups of interest are Type 2 versus Type 3 SMA, age group 2-12 compared to 13-21, SMN2 copy number (2/3/4), age of SMN-targeted therapy initiation, and type of SMN-targeted therapy. However, no subgroups were modeled due to insufficient data.

## E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

## Prior Economic Models

Our model is the first to evaluate apitegromab as an add-on to standard of care SMN-therapies. While there are no previous economic evaluations of apitegromab to compare our results to, we can compare our model structure and estimates from our standard of care arm to prior economic models. There, however, might be slight differences due to our SoC arm incorporating a mix of nusinersen and risdiplam treated patients whereas prior models examined a single treatment at a time. Nonetheless, the two treatments have been shown to have similar health outcomes and costs.

Our model maintains a similar structure to the previous ICER model from 2019.[48] Both models assume later-onset patients remain in the "sitting" health state throughout their lifetime in the base case. However, with more long-term data now available, our model incorporates a lower mobility state of "not sitting" in scenario analyses to reflect recent evidence that disease progression may continue even with current SMN-targeted therapies.[50,54,59] As we used the same mortality assumptions from the previous ICER model, we achieved nearly identical life years of 18.86 in our model versus 18.90 in theirs, confirming alignment in survival projections.

Despite this alignment in survival estimates, our total quality-adjusted life years (QALYs) are substantially lower at 4.84 on standard of care treatment compared to 12.28 on nusinersen in the previous report, attributable to different QALY sources (0.65 for "sitting" in 2019 model versus 0.26 in our model). The utilities sourced in the previous model were obtained from clinical advisor estimates due to the absence of directly assessed utilities.[67] We chose to use HUI3-derived estimates sourced directly from those living with or providing daily care for individuals with SMA.[61] While clinical advisors have valuable expertise from seeing many patients, HUI3 captures the continuous lived experience rather than periodic clinical snapshots and allows for standardized measurements across multiple relevant health dimensions. Comparison of costs to the previous model aligns fairly well despite our treatments comprising a mix of nusinersen and risdiplam, with $10,574,000 total costs in 2025 dollars in the previous report compared to $9,915,000 for SoC in our current model.

When benchmarking against other published analyses, our life years (18.86), quality-adjusted life years (4.84), and combined QALYs for patients and caregivers (22.23) on standard of care were comparable to those reported by NICE in their review for nusinersen, which found 19.61 LYs, 5.83 QALYs, and 20.99 QALYs for patients and caregivers.[52] The differences were more pronounced when comparing against CDA-AMC's review of a sponsor-submitted model for nusinersen that reported 7.09 QALYs [118]. This disparity widened further when examining CDA-AMC's more recent review of

risdiplam, which reported 15.34 QALYs for risdiplam and 15.20 for nusinersen [49]. These differences can be attributed to the more complex model structures employed in other analyses, with total life years in the CDA-AMC review for nusinersen at 28.53 in Type 2 and 44.16 in Type 3 [118]. Most notably, these models incorporated distributions of patients achieving higher mobility milestones beyond "sitting," resulting in differences in both survival projections and utility values.

# F. Potential Budget Impact: Supplemental Information

## Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment, which includes Type 1, 2, or 3 SMA patients who have been treated with nusinersen or risdiplam. While the cost-effectiveness analyses primarily focused on Types 2 and 3 SMA, Type 1 SMA patients are included in this analysis to account for the possibility that apitegromab may be approved for or used in a broader indication than the trial eligibility criteria. To estimate the size of the potential candidate population, we used inputs for the overall prevalence of SMA in the Unites States (0.0028%),[8] the percentage of patients with SMA that have either Type 1, 2, or 3 SMA (96.63%),[8] and the percentage of Type 1, 2, or 3 SMA patients that have been treated with either nusinersen or risdiplam (71.24%). The overall SMA prevalence estimate of 0.0028% was calculated using the estimated number of SMA patients in the US in 2023 (9,419)[8] divided by the total US population in 2023 (334,906,305).[71] The prevalence by type were estimated to be 26.97% for Type 1, 41.57% for Type 2, and 28.09% for Type 3.[8] The proportion of patients who have been treated with nusinersen or risdiplam were estimated to be 76%, 66%, and 81%, for Types 1, 2, and 3 respectively (based on data on file provided by manufacturer). Applying these percentages to the prevalence rates for Type 1, 2, and 3 SMA results in a weighted average of 71.24% of patients who have been on either nusinersen or risdiplam among patients with Type 1, 2, or 3 SMA. This estimate is in line with the Cure SMA 2023 Report, which states that approximately 60-70% of SMA patients have been treated with an FDA-approved treatment.[8] Applying these sources to the average total US population projected over the next five years (340,927,674) results in 6,600 eligible patients in the US. For the purposes of this analysis, we assume that 20% of these patients would initiate treatment in each of the five years, or 1,320 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[119,120] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2024-2025, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $880 million per year for new drugs.