Therapies for Spinal Muscular Atrophy: Effectiveness and Value

Final Report

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Prepared for

MIDWEST CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

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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 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, 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 Carlson, PhD, MPH	Josh Carlson has received consulting fees from Genentech that are not related to SMA.
Hui-Hsuan Chan, MHS	No conflicts to disclose.
Sarah Emond, MPP	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.
Max Lee, PharmD	No conflicts to disclose.
Woojung Lee, PharmD, PhD	No conflicts to disclose.
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Marie Philips, BA	No conflicts to disclose.
David M. Rind, MD, MSc	No conflicts to disclose.
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 Child Neurologist, Children's Hospital of Philadelphia and Associate Professor of Clinical Neurology, Perelman School of Medicine at the University of Pennsylvania	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 Clinical Assistant Professor, Stanford University School of Medicine, Stanford Children's Health	Dr. Klotz has no conflicts to disclose.
Praveen Thokala, PhD Director, PT Health Economics Ltd, UK	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). Dr. Thokala's role as an advisor was to participate in discussions around the appropriateness of the suggested modelling approaches.

Expert Reviewer	Conflict of Interest
Portia Thorman Head of Advocacy and Community, Spinal Muscular Atrophy, UK	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.

NICE: National Institute for Health and Care Excellence, SMA: spinal muscular atrophy, UK: United Kingdom

This page includes conflict of interest disclosures for ICER staff, external collaborators, and expert reviewers of the report. For all public meeting participant disclosures, please refer to Supplement I.

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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
ml	milliliters
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 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**).

The JEWELFISH trial is an open-label study of risdiplam in patients previously treated with other spinal muscular atrophy therapies. Among the 14 patients who had previously received onasemnogene abeparvovec, nine showed a 4.7-point increase in the HFSME at one year and a 7.1 increase at two years. In a case series of 20 children treated with risdiplam, there were some improvements in swallowing and breathing function. 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 ($5.7 million) and gains of approximately 1.9 years of life and 2.0 evLYs (equal value life years) from health care system perspective, resulting in incremental cost-effectiveness ratios of more than $2.8 million per evLY gained. From the modified societal perspective—which includes family utilities—apitegromab provided a slightly higher gain of 3.30 evLYs, but the ICER remained high at $1.7 million per evLY gained. At the placeholder price, the incremental cost-effectiveness ratios remained above traditional willingness-to-pay thresholds in all sensitivity and scenario analyses, including a co-base case scenario using a modified societal perspective. After excluding non-intervention healthcare costs and standard of care costs so as to achieve positive threshold prices, the Health Benefit Price Benchmark (HBPB) for apitegromab is $4,600 to $30,200 annually.

At the placeholder price of $350,000, an estimated 64% of eligible patients could receive therapy over five years without exceeding ICER's budget impact threshold; all patients could be treated at the modified societal perspective $150,000 threshold price of $30,200. Given these numbers, and in the absence of a known price from the manufacturer, ICER is not issuing an access and affordability alert for apitegromab at this time.

Key Policy Recommendations:

Appraisal committee votes on questions of comparative effectiveness and value, along with the complete policy recommendations regarding pricing, access, and future research, are included in the main report.

- The manufacturer should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. Given the small average improvement in motor function for patients treated with

apitegromab and the uncertainty about serious adverse events, manufacturer pricing should reflect ICER's value-based price range in moderating launch pricing.

- The use of SMN-directed therapy after gene therapy or in combination should only be done in the context of research studies.
- A randomized trial should be performed of first-line therapy in asymptomatic patients identified through newborn screening to better understand the comparative advantages and disadvantages of each of the three SMN-directed therapies.

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 and newborn screening, patients with SMA are diagnosed and treated 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) infusion.

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 nationwide 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/80 mL (0.75 mg/mL) for the oral solution, 5 mg for the tablet. Recommended daily dosage per age and weight: Oral solution: 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. Oral solution or tablet: 5 mg for ages ≥2 years and weight ≥20 kg.

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

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 2019 SMA 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. The trial was found to be at low risk of bias. (Supplement Table D1.4)

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 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	Fair	Good
TOPAZ	Fair	Good

Race and Ethnicity: Both trials 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 two 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.[24] There was some evidence of effect modification by baseline SMN therapy. Patient on background risdiplam did not have a significant improvement in HFSME with the apitegromab 10 mg and 20 mg dose groups combined (0.5, 95% CI -2.30 to 3.33) and participants in the 10 mg apitegromab group did nominally worse (-0.1, 95% CI -3.52 to 3.35). However, this could be a chance finding given low numbers. There was no evidence of effect modification by 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, cough, vomiting, and upper respiratory tract infection.[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 (20%) than placebo (10%). Among these, pneumonia, dehydration, adenovirus infection, gastroenteritis, acute respiratory failure, and constipation 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[17,24]

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)
	Vomiting	27 (25.5)	8 (16.0)
	Upper respiratory tract infection	26 (24.5)	17 (34.0)
	Headache	21 (19.8)	8 (16.0)
SAE with Highest Incidence, n (%)	**Pneumonia**	7 (6.6)	0
	Dehydration	3 (2.8)	0
	Scoliosis	2 (1.9)	1 (2.0)
	Adenovirus infection	2 (1.9)	0
	Gastroenteritis	2 (1.9)	0
	Acute respiratory failure	2 (1.9)	0
	Constipation	2 (1.9)	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.[17]

As described above in the subgroup section, it is unclear whether apitegromab improves the HFSME relative to placebo in patients receiving background therapy with risdiplam. In the analysis combining the results for patients receiving either 10 mg or 20 mg/kg, the difference from the placebo group was small and non-significant. Moreover, patients on risdiplam who received the 10

mg/kg dose on average did worse than the placebo group. This is particularly surprising because overall in the trial, the 10 mg/kg group did better than the 20 mg/kg group. These results are in a small, subgroup analysis, so may be due to chance, but they represent an important uncertainty about who will benefit from apitegromab.

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]

A number of serious adverse events (e.g., pneumonia, dehydration) occurred in the apitegromab-treated group and not in the placebo group, but the trial was relatively small, so these could be by chance rather than caused by apitegromab. We would not have expected pneumonia to be more common in the apitegromab group because the drug would be expected to improve respiratory muscle function and thus reduce the risk for pneumonia.

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 are limited due to sample size (n=33).

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, 7% had two copies, and 21% had one copy. 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 in patients previously treated with onasemnogene abeparvovec treatment. Study details are provided in Supplement Table D4.1.

Additionally, we reviewed findings from a US-based multicenter case series of 20 children who had received risdiplam after initial treatment with onasemnogene abeparvovec.[30] Patients experienced onset of symptoms at a median age of 2.5 months (range of one week to 6.5 months) and a diagnosis at 4.6 months (range 0 to 17 months). These children predominantly had two copies of *SMN2* (80%) and were Type 1 SMA (85%). At baseline, the children had a mean CHOP-INTEND score of 28.7 (range 20 to 45) out of 64. Patients received their first dose of risdiplam at a mean of 15.2 months after treatment with onasemnogene abeparvovec. The most common treatment sequence among the treated children was onasemnogene abeparvovec then risdiplam, used in 13 of 20 patients. The next common sequence was nusinersen, then onasemnogene abeparvovec, and finally risdiplam, used in six of 20 patients.

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 7.1 points on the HFMSE, and approximately 6 points on the motor function scales of MFM32 and RULM.[32] Baseline and values at end of follow-up for the three scales were not reported.

In the case series of 20 children treated with risdiplam, there were some improvements in swallowing and breathing function.[30] Before risdiplam treatment, eight children had severe dysphagia. After treatment, three of these children were permitted oral taste feeds. Three children with mild dysphagia experienced complete resolution of their symptoms after treatment. Respiratory improvements included three children reducing non-invasive ventilation (NIV) from 24 hours a day to sleep-only use, and one eliminating NIV entirely. Two patients showed more modest respiratory gains and one started nighttime NIV, likely due to disease progression. Nine out of ten patients (90%) experienced either an improvement or stability in their CHOP-INTEND. Similarly, all nine patients assessed on HFMSE saw stability or improvement on their scores. No results summarizing the change in HFMSE were presented.

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).[33] 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.[34] 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.[35] 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.[35]

Uncertainty and Controversies

The data on additional treatments of patients with SMA following gene therapy are small studies that 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 children without SMA 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.[36] 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[37,38]		SPR1NT[39,40]			RAINBOWFISH[41]*		
				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)	1 (8)	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 (62)	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 six weeks of birth, who had either two copies (n=15) or three 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.[39,40] 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 five 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. [42]

RAINBOWFISH (risdiplam)

RAINBOWFISH is an ongoing single-arm Phase II trial investigating the use of risdiplam in 26 infants within six 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 20 to 41).

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[38]		SPR1NT[39,43]			RAINBOWFISH[41]	
				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	13
Ventilation-Free Survival, n/N (%)		15/15 (100)	10/10 (100)	6/23 (26)†	14/14 (100)*	15/15 (100)*	8/8 (100)	5/13 (62)
BSID-III	**Sit Without Support for ≥5 seconds, n/N (%)**	NR	NR	NR	NR	NR	7/8 (88)	13/13 (100)
	Sit Without Support for 30 seconds, n/N (%)	NR	NR	NR	NR	NR	7/8 (88)	9/13 (69)
HINE-2	**Independent Sitting, n/N (%)**	15/15 (100)	10/10 (100)	0/0 (0)	14/14 (100)	14/15 (93)	6/8 (75)‡	13/13 (100)‡
	Independent Standing, n/N (%)	13/15 (87)	10/10 (100)	0/0 (0)	11/14 (79)	15/15 (100)	1/8 (12)	10/13 (77)
	Independent Walking, n/N (%)	13/15 (87)	10/10 (100)	NR	9/14 (64)	14/15 (93)†	1/8 (12)	9/13 (69)
Achieved Maximum CHOP-INTEND Score, n/N (%)		12/15 (80)	10/10 (100)	NR	NR	NR	NR	NR

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

* Alive at age 14 months.

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

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

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

	NURTURE		SPR1NT[44]		RAINBOWFISH[41]	
***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	8	13
Ventilation-Free Survival, n/N (%)	NR	NR	12/12 (100%)	13/13 (100%)	5/8 (62)	13/13 (100)
Independent Sitting, n/N (%)	NR	NR	NR	NR	5/8 (62)	13/13 (100)
Independent Standing, n/N (%)	NR	NR	NR	NR	3/8 (38)	13/13 (100)
Independent Walking, n/N (%)	NR	NR	12/12 (100%)	13/13 (100%)	2/8 (25)	13/13 (100)
Achieved Maximum CHOP-INTEND Score, n/N (%)*	NR	NR	NR	NR	4/8(50)	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
*Achieved a CHOP-INTEND total score of ≥60 at the same two consecutive visits.

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).[38] 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.[38] 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).[44]

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, seven of the eight (88%) infants with two copies of *SMN2* 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 least 30 seconds. In this cohort, one of eight (12%) infants were able to stand or walk alone.[41]

At the 12-month follow-up of the three copy cohort, nine of 13 infants (69%) were able to sit without support for at least 30 seconds, 10 of 13 (77%) were able to stand alone, and eight of 13 (62%) were able to walk alone.[41]

Across the two cohorts (n=21), all infants were alive after 12 months of treatment and none required permanent ventilation. 20 of 21 (95%) infants were able to swallow and eat exclusively by mouth.

Durability of Treatment Effect

After 24 months of follow up (Table 3.6) and among the eight infants in the two copy cohort, 62% were able to sit without support for a minimum of both five and 30 seconds, 38% were able to stand alone, and 38% walked alone. Five of the eight infants (62%) were alive without permanent ventilation. .

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. All infants were alive without permanent ventilation.

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.

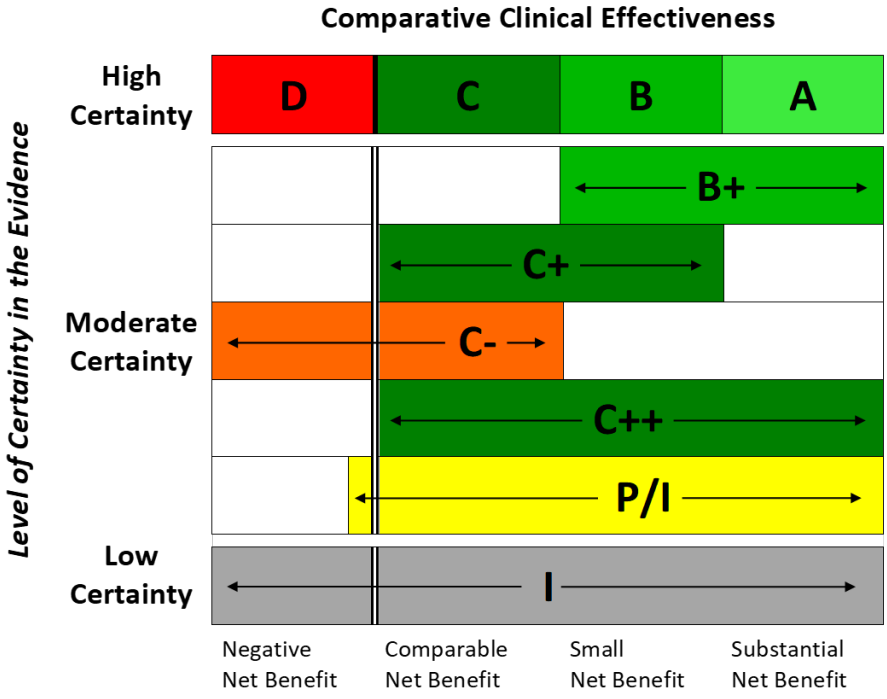
The NURTURE trial has the longest reported mean follow-up results of its participants of five years, compared to shorter durations of SPR1NT (mean of 3.5 years) and RAINBOWFISH (two years). Longer follow-up from each trial has shown that an increasing proportion of patients have achieved milestones not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

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 study, and that there were more serious adverse events in the apitegromab arm, the level of certainty for the 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 a 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 20 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 expected development times (for children without SMA), 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

Midwest CEPAC Votes

Table 3.8. Midwest CEPAC Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
For children aged 2-12 years with SMA Type 2 or 3, is the currently available evidence adequate to demonstrate that the net health benefit of apitegromab in addition to standard of care (risdiplam or nusinersen) is greater than that of standard of care alone?	5	8
For people with SMA previously treated with onasemnogene abeparvovec, is the currently available evidence adequate to demonstrate that the net health benefit of risdiplam is greater than that of no additional treatment?	1	12
For people with SMA previously treated with onasemnogene abeparvovec, is the currently available evidence adequate to demonstrate that the net health benefit of nusinersen is greater than that of no additional treatment?	1	12
For clinically presymptomatic infants with SMA, is the currently available evidence adequate to distinguish the net health benefit among nusinersen, onasemnogene abeparvovec and risdiplam as first line therapy?	0	13

Majority of the council voted that the currently available evidence is inadequate to demonstrate that the net health benefit of apitegromab in addition to standard of care is greater than that of standard of care alone in children aged 2-12 years with SMA Type 2 or 3. The council had an extended discussion on the significance of the differences in overall severe adverse effects. The council expressed their considerations of this ultra rare disease and the lack of high-quality evidence. With concerns for the magnitude of change between the lower baseline and higher baselines, the council members and clinical experts discussed about the insufficient data and the possibility of placebos and patients' varying disposition throughout the trial.

A great majority of the council voted that the currently available evidence is inadequate to demonstrate that the net health benefit of risdiplam is greater than that of no additional treatment for people with SMA previously treated with onasemnogene abeparvovec. Clinical experts and council members discussed the difficulty in differentiating the effects of the add-on therapy versus normal physiological hypertrophy of muscle fibers with growth during the first few developmental years of age. While there seems to be a small benefit, the clinical experts and council questioned the possibility of selection bias and lack of causation.

A great majority of the council voted that the currently available evidence is inadequate to demonstrate that the net health benefit of nusinersen is greater than that of no additional treatment for people with SMA previously treated with onasemnogene abeparvovec. The council came to a decision after the presentation of the additional potential harms and uncertainty of the evidence.

The council unanimously voted that the currently available evidence is inadequate to distinguish the net health benefit among nusinersen, onasemnogene abeparvovec. and risdiplam as first line therapy for clinically presymptomatic infants with SMA. The council came to a decision after hearing an overview of all the trials focused on the different therapies and how the evidence brings substantial uncertainty about any comparable differences in the outcomes.

4. Long-Term Cost Effectiveness

4.1 Overview and Model Structure

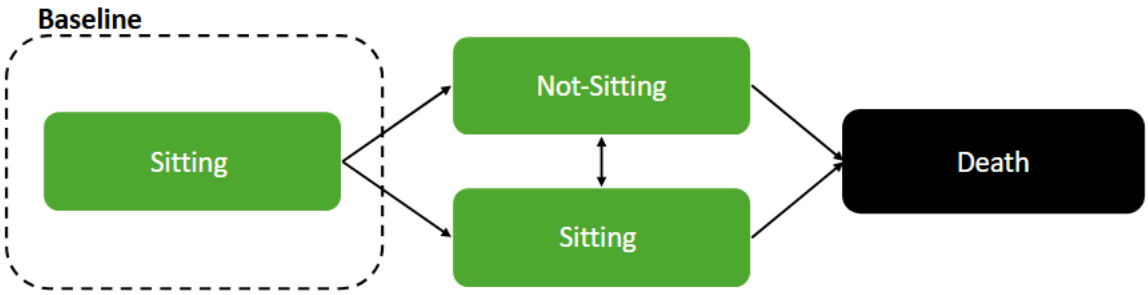
We developed a *de novo* decision analytic model examining the cost effectiveness of apitegromab versus standard of care with either nusinersen or risdiplam for this evaluation, informed by key clinical trials and prior relevant economic models. Family quality-of-life impacts were substantial relative to direct health care outcomes, and the impact of apitegromab on these outcomes were significant enough to meet criteria for including the modified societal perspective as a co-base case. Therefore, the modified societal perspective was incorporated alongside the healthcare system perspective as a co-base case. 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]

Given the limited availability of data, we implemented a simplified two-state model structure of "sitting" and "not-sitting," where "sitting" represents an aggregate of multiple motor milestones such as "sitting with support" and "sitting without support." Treatment benefits, including incremental motor function improvements that may not warrant separate health states, were captured through differential utility values applied within each health state. Patients begin in the baseline state of "sitting" based on the SAPPHIRE inclusion criteria requiring non-ambulatory patients and the mean baseline Hammersmith Functional Motor Scale – Expanded (HFMSE) scores falling within the sitter classification range from published literature.[50,51,52] This simplified model structure was necessary because current SAPPHIRE data did not provide sufficient details to model additional motor milestones as distinct health states.[50]

Disease progression to "not-sitting" was modeled based on changes in HFMSE observed during the SAPPHIRE trial period in the placebo arm, with the assumption the HFMSE declined at a constant rate over the lifetime and HFMSE scores were approximately normally distributed. We were unable to model the intermediate milestone of "sitting with support" as there were no available data on how it mapped to HFMSE scores. 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



*The sitting health state represents an aggregate of multiple motor milestones such as "sitting with support" and "sitting without support."

In response to public comments, the following changes were made to the economic evaluation between the Draft Report and the revised Evidence Report:

- We incorporated disease progression into the base case rather than solely in scenario analyses to capture a fuller picture of SMA.
- We assumed apitegromab patients were stable during the first 4 years based on HFMSE data in the TOPAZ trial.[19,53]
- We incorporated mean changes in WHO motor milestones reported in SAPPHIRE into the treatment effect. .
- We incorporated the modified societal perspective as a co-base case due to family quality-of-life values having substantial impacts on incremental cost effectiveness ratios (ICERs).

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 limited data availability.
- Monthly cycle length and lifetime time horizon.
- Treatment effect for apitegromab was incorporated through treatment-specific utilities, calculated based on the difference in proportion of patients who achieved an HFMSE increase of ≥3 and the mean change in WHO motor development milestones in SAPPHIRE.[50]
- Patients who achieved the treatment specific utility gain (increase of ≥3 and the mean change in WHO motor development milestones) maintained it throughout the modeled time horizon.

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.[54] 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.[51 52]
There were no transitions to new mobility states above "sitting".	Available data lack sufficient detail to model progression of patients to higher WHO motor milestones than "sitting." Additionally, patient motor development milestones were not reported and had to be assumed, it is unclear which states patients move to or from or whether any patients gained more than one milestone from the data available. As a result, we simply incorporated reported WHO motor milestone changes with changes in utilities.
Disease progression occurred following a normal distribution through the lifetime based on a constant decline in HFMSE.	Long-term data on disease progression in later-onset SMA patients receiving disease modifying therapies such as nusinersen or risdiplam is currently limited. Additionally, the data on how apitegromab impacts these trajectories are even more limited. To model the course of disease on these treatments, we obtained a HFMSE trajectory based on the rate of decline observed in the placebo arm at the end of SAPPHIRE[50] and mapped when each treatment group fell to the range of "not-sitting" based on published literature.[51] This provided a mean time to "not-sitting" for each treatment and we assumed the HFMSE scores followed a normal distribution.
Patients on apitegromab start progressing after 4 years.	Data from TOPAZ showed patients on apitegromab maintained function over 4 years of follow-up.[19,53] However, based on clinical expert opinion, the treatment group is still expected to experience disease progression over time. Given the uncertainty in long-term outcomes, we modeled disease progression following what was observed in TOPAZ and explored different periods of stability in scenario analyses.
Patients achieving the treatment effect at the end of trial follow-up maintained the improvement through their lifetime in the model.	Data on long-term treatment effect durability are currently limited.

Assumption	Rationale
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] 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 and were incorporated as utility increments in the model.[57,58] Smaller improvements showed no significant quality-of-life differences and were not incorporated.[58]

SAPPHIRE also reported the mean change from baseline in WHO motor development milestones observed in each treatment arm of 0.09 in apitegromab vs -0.03 in placebo at 52 weeks (p=0.33). Although this difference is not statistically significant, we incorporated these WHO milestone changes in the base case but evaluated a scenario analysis excluding them. These effects were also applied through utility increments to each treatment group.

Although data have hinted that the treatment effect may vary by 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. Applying these results to populations with different characteristics than those in SAPPHIRE would require strong assumptions about treatment effect generalizability.

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 started in the "sitting" health state and may progress to "not sitting" over time and eventually "death".

Following clinical expert opinion, we assumed patients on both treatments experience HFMSE decline at a parallel rate. We obtained the slope of decline in HFMSE from the placebo arm in SAPPHIRE[50] and applied this decline to both treatments to calculate the average time for HFMSE scores to reach a score of 4, the upper interquartile range (IQR) of non-sitters, which serves as our transition point from "sitting" to "not-sitting."[51] The average transition times for each treatment arm (125 months on apitegromab, 115 months on SoC alone) were calculated using baseline HFMSE scores from SAPPHIRE combined with average HFMSE change at 52-weeks on each treatment (+0.59 on apitegromab + SoC, -1.23 on SoC alone). These average times were used to parameterize gamma distributions (alpha = 12, beta = mean time / alpha) to model the transition to "not-sitting". The gamma distribution was selected to approximate a normal distribution of transition times, which aligns with our assumption that HFMSE scores are approximately normally distributed, while ensuring only positive transition times. These transition models were applied starting at year 4 for apitegromab + SoC and year 1 for the SoC arm as starting HFMSE scores were from 52-weeks. The models were validated by comparing expected transition times based on the HFMSE mean and ranges, to the observed transition times in our model.

Details on mortality can be found in Supplement Sections E2.

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 through two utility adjustments applied over the patient lifetime.

A utility increment of 0.06 was applied to the proportion of patients achieving a ≥3-point increase in HFMSE, who did not also gain a milestone. This was 8.9% of the treatment group based on the net difference (17.9% difference between treatment arms minus the 9% who gained milestones) achieving this threshold at 52-weeks in SAPPHIRE.[50,59] The 0.06 value was obtained from Lloyd et al. by taking the difference in utility between 0.10 for ≥3-point increase from baseline and 0.04 for baseline HFMSE.[58]

SAPPHIRE reported only aggregate mean changes in WHO motor development milestones at 52-weeks (mean change of +0.09 in apitegromab arm vs -0.03 in placebo arm), without specifying patients' baseline milestone status, which milestones were gained or lost, or whether individual patients experienced multiple milestone changes. We therefore made simplifying assumptions to convert these continuous mean changes to discrete patient-level transitions: no patients moved more than one milestone step, no patients in the apitegromab arm lost a milestone, and no patients in the placebo arm gained a milestone. Under these assumptions, 9% of apitegromab patients achieved a milestone gain and 3% of placebo patients experienced a milestone loss.

For utility gains from milestone changes, we used EQ-5D-3L values from Hu et al. derived from SMA type 2 and 3 patients under 16 in China.[61] We applied a utility increment of 0.08 (difference between "sitting unsupported" at 0.39 and "standing supported" at 0.47) to the 9% of apitegromab patients who gained a milestone. For the 3% of placebo patients who lost a milestone, we applied a utility decrement of 0.02 (difference between "sitting unsupported" at 0.39 and "sitting supported" at 0.37). Patients who achieved a milestone gain were assumed to also have a ≥3-point HFMSE increase; only the milestone utility gain was applied to avoid double-counting benefits.

The modified societal perspective incorporated caregiver quality-adjusted life years, and caregiver bereavement disutility values. An additive approach was used where one caregiver and one patient combined into a single family QALY (quality adjusted life year) and evLY (equal value life year) 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.[62] 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.

Bereavement disutility values were obtained from an unpublished paper by Tara Lavelle and submitted as academic in confidence data. Dr Lavelle derived utility values for parents of Type 1 SMA patients across time points following death. We used the utility value of [redacted] for < 5 years, [redacted] for 5-10 years, and [redacted] for 10+ years. Disutilities were calculated by subtracting the average caregiver utility of [redacted] of a parent with a child with SMA Type 1, from the utility of a bereaved parent for each time frame (Academic-in-confidence data redacted). These values were applied to our Type 2/3 SMA population, introducing uncertainty as the original data were derived from parents of Type 1 SMA patients, who typically experience different disease trajectories, age at death, and potentially different bereavement patterns. The disutilities for bereavement were applied until 20 years post patient death.

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

Patient Utility			
State	**Utility**		**Source**
	SoC	**Apitegromab + SoC**	
Sitting	0.26	0.27*	Belter et al.[63] + incremental utilities[58,61]
Not-Sitting	0.12	0.14*	
Caregiver Utility			
State	**Utility**		**Source**
Sitting	0.592		López-Bastida et al.[62]
Not-sitting	0.484		

SoC: standard of care

*Utility without treatment effects + Utility of treatment effect × Proportion of patients who achieved treatment effect

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 four 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 four doses	Daily dose for 2 years of age and older <20 kg: 0.25 mg/kg ≥20 kg: 5 mg*

kg: kilogram, mg: milligram, ml: milliliter

*All patients were assumed to be ≥20 kg

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,[64] 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.[65] For risdiplam, we used the wholesale acquisition price from RED BOOK with a discount of 12.5% obtained from IPD analytics.[64,66] 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%[64]	$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.[53] 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 [67]
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.

4.3. 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) for the health care system perspective and modified societal perspective are detailed in Table 4.7 below. The modified societal perspective included caregiver utilities following an additive approach and bereavement disutilities as a family unit with 1 caregiver. 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 $5,714,000 at the placeholder price, incremental gains in QALYs of approximately 0.74, in evLYs of 2.02, and 1.94 additional life years compared to standard of care alone in the health care system perspective. Incorporating family utilities with 1 caregiver resulted in larger differences of 2.02 QALYs and 3.30 evLYs between the two treatments. 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
Health Care System Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	3.38	4.66	13.89
SoC	$4,887,000	$271,700	$5,324,000	2.64	2.64	11.95
Incremental	$5,655,000	$54,300	$5,714,000	0.74	2.02	1.94
Modified Societal Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	10.46	11.73	13.89
SoC	$4,887,000	$271,700	$5,324,000	8.43	8.43	11.95
Incremental	$5,655,000	$54,300	$5,714,000	2.02	3.30	1.94

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†
Health Care System Perspective					
Apitegromab* + SoC	SoC	$7,702,000	$2,829,000	$2,945,000	$31,922,000
Modified Societal Perspective					
Apitegromab* + SoC	SoC	$2,823,000	$1,730,000	$2,945,000	$31,922,000

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

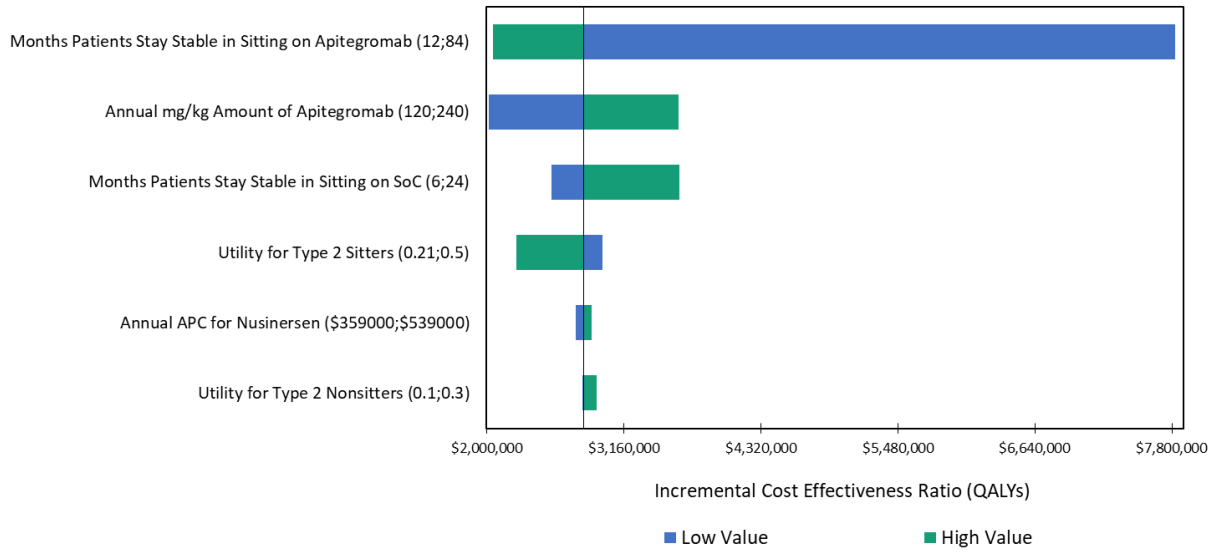
†Difference in costs/difference in proportion achieving ≥3-Point Increase in HFMSE

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 modified societal perspective. The parameters with the largest impact on the ICER were the months patients stay stable on apitegromab, the dose of apitegromab, the duration patients stay stable on SoC, and the utility for Type 2 patients in "sitting".

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, including analyses for the health care system perspective can be found in Supplement Section E4.

Figure 4.2. Tornado Diagram for Apitegromab + SoC Compared to SoC (Modified Societal Perspective)



HFMSE: Hammersmith Functional Motor Scale – Expanded, kg: kilogram, mg: milligram, SoC: standard of care, WHO: World Health Organization

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
Health Care System Perspective				
Apitegromab* + SoC	0%	0%	0%	0%
Modified Societal Perspective				
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 examined are outlined below, with results for an ICER reference case in Table 4.10. Additional details and results for other scenarios are detailed in Supplement Section E5.

1. Treatment effect excluding WHO motor development milestone changes reported in SAPPHIRE at 52 weeks
2. Exclusion of pneumonia adverse events associated with apitegromab
3. Disease progression initiates at 1-year on apitegromab
4. Disease progression initiates at 7 years on apitegromab
5. Apitegromab prevents disease progression and maintains function through the lifetime
6. Alternative health state utilities derived from NICE TA588 ERG Clinical Advisors[68] (higher utility values)
7. Alternative health state utilities derived from Lloyd et al.[58] (lower utility values)
8. Exclusion of unrelated (non-drug) health care costs that are not related to the disease *per se*
9. ICER Reference Case Scenario Analysis: When standard of care involves high-cost interventions, life-extending treatments may not achieve feasible value-based pricing under conventional cost-effectiveness methods. Following ICER's reference case guidance for these scenarios, we excluded non-intervention costs, and costs associated with standard of care treatment. This modified analysis provides additional perspective for policymaker considerations of value-based pricing.

Table 4.10. Scenario Analysis Results – Incremental Cost-Effectiveness Ratios*

Scenario	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Health Care System Perspective			
Scenario 9: ICER Reference Case – Removal of Costs Except Apitegromab Administration & Acquisition Costs	$6,567,000	$2,412,000	$2,511,000
Modified Societal Perspective			
Scenario 9: ICER Reference Case – Removal of Costs Except Apitegromab Administration & Acquisition Costs	$2,407,000	$1,475,000	$2,511,000

*Based on placeholder price for apitegromab 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 Tables 4.11 and 4.12. Due to substantial costs associated with life extension on expensive standard-of-care therapies, combined with modest gains in QALYs and evLYs, apitegromab cannot achieve cost effectiveness at the at common threshold prices ($50,000 - $200,000 per QALY or evLY) at any positive price point in either the health care system or modified societal perspective. Following ICER's reference case for such situations, we conducted threshold analyses removing all non-intervention healthcare costs and standard of care costs to achieve positive prices for all cost-effectiveness thresholds below (remaining costs include administration costs for apitegromab).

Table 4.11. QALY-Based Threshold Analysis Results with All Costs Included

	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Health Care System Perspective				
Apitegromab	No positive price	No positive price	No positive price	No positive price
Modified Societal Perspective				
Apitegromab	No positive price	No positive price	No positive price	No positive price

QALY: quality-adjusted life year

Table 4.12. evLY -Based Threshold Analysis Results with All Costs Included

	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Health Care System Perspective				
Apitegromab	No positive price	No positive price	No positive price	No positive price
Modified Societal Perspective				
Apitegromab	No positive price	No positive price	No positive price	No positive price

evLY: equal value of life year

Table 4.13. QALY-Based Threshold Analysis Results with Non-Intervention Healthcare Costs & SoC Costs Removed

	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Health Care System Perspective				
Apitegromab	$2,000	$4,600	$7,300	$10,000
Modified Societal Perspective				
Apitegromab	$5,000	$10,700	$16,400	$22,000

QALY: quality-adjusted life year

Table 4.14. evLY -Based Threshold Analysis Results with Non-Intervention Healthcare Costs & SoC Costs Removed

	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Health Care System Perspective				
Apitegromab	$6,600	$13,800	$21,100	$28,400
Modified Societal Perspective				
Apitegromab	$9,600	$19,900	$30,200	$40,400

evLY: equal value of 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 or changes in WHO motor development milestones). 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.[63,69] 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.[70,71] 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 from Scholar Rock, 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.[53,59] 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. 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.[50,59,72] Our model 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 are even more limited.

4.4 Summary and Comment

Our analysis showed that apitegromab added onto standard of care treatments was able to provide modest gains in QALYs and evLYs. However, it is expected to exceed standard cost-effectiveness thresholds at the placeholder price of $350,000 annually due to the modest utility gains observed, combined with the possible life extension requiring expensive standard-of-care treatments. When excluding non-intervention costs, adverse event costs, and standard of care costs, our analyses demonstrate that apitegromab requires steep discounts exceeding 90% from the placeholder price of $350,000 to meet standard cost-effectiveness thresholds in both health care system and modified societal perspectives.

There remains substantial uncertainty around these results given the limited long-term data available for this treatment, and the inherent challenges in modeling rare disease progression. These analyses provide initial cost-effectiveness estimates that can be refined as additional evidence becomes available.

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.

Midwest CEPAC Votes

At the public meeting, the Midwest CEPAC deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements:

Table 5.1. Midwest CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities - Condition

Benefits Beyond Health and Special Ethical Priorities	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
There is substantial unmet need despite currently available treatments.	0	0	0	5	8
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.	0	2	11	0	0

Majority of the council voted that they strongly agree that there is substantial unmet need despite currently available treatments. The council referenced the evidence including absolute shortfalls,

QALYs, and evLYs, as they appeared to be substantial and equivalent to child leukemia with minor differences.

A vast majority of the council voted that this condition is not of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system due to the evidence that showed that there are no significant differences in the prevalence of this condition across different racial and ethnic subgroups.

To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements based on the relative effects of apitegromab in addition to standard of care (risdiplam or nusinersen) versus standard of care alone:

Table 5.2. Midwest CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities – Treatment

Benefits Beyond Health and Special Ethical Priorities	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
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.	0	2	7	4	0
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	1	7	3	2	0

By a slight majority, the council voted that they remain neutral when considering how likely the treatment will produce substantial improvement in caregivers' quality of life. A patient expert shared her experience with caretaking for her son and how small gains, such as reaching for an item independently or partaking in hobbies could impact a caregiver's quality of life because it gives both caregiver and patient more independence.

By a slight majority, the council voted that they disagree this treatment offers a substantial opportunity to improve access to effective treatment. The council discussed how this treatment still requires trips to an infusion center, and there is no significant improvement in ease of access. They also considered the possibility of combining treatments of nusinersen and apitegromab into one

hospital visit, but patient experts shared that every patients' experience and needs are different and having multiple methods of treatment is necessary to significantly help with access.

Table 5.3. 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. To inform unmet need as a benefit beyond health, the results for the absolute and proportional shortfalls in the modeled population—patients aged 2 to 12 years with non-ambulatory type 2 or 3 SMA–have been reported below. The shortfalls were the same, regardless of whether QALY or evLY was used. QALY and evLY shortfalls: Absolute shortfall: 58.2 Proportional shortfall: 94.7% 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, though this may have some impact on caregiver quality of life as modeled in the modified societal perspective. However, there may also be an increase in burden due to the need for travel to an infusion center for treatment every four weeks; 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.

evLY: equal value life year, IV: intravenous, SMA: spinal muscular atrophy, QALY: quality adjusted life years

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

The Health Benefit Price Benchmark (HBPB) for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 per QALY and $150,000 per evLY gained. Table 6.1 presents the threshold prices for apitegromab from both the health care system perspective and modified societal perspective with all non-intervention, adverse event and SoC costs removed (remaining costs aside from apitegromab acquisition costs include administration costs for apitegromab). The HBPB for apitegromab is $4,600 to $30,200.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Apitegromab

Annual Prices Using…	Annual WAC*	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC* to Reach Threshold Prices
Health Care System Perspective				
QALYs Gained	$350,000*	$4,600	$7,300	(97.91%-98.69%)
evLYs Gained		$13,800	$21,100	(93.97%-96.06%)
Modified Societal Perspective				
QALYs Gained	$350,000*	$10,700	$16,400	(95.31%-96.94%)
evLYs Gained		$19,900	$30,200	(91.37%-94.31%)

evLY: equal value life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost
*Based on placeholder price of $350,000 per year

Midwest CEPAC Votes

Long-term value for money votes were not taken at the public meeting because a net price for apitegromab was not available.

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 six threshold prices (at $50,000, $100,000, and $150,000 per evLY gained from both the health care system perspective and modified societal perspective) 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.

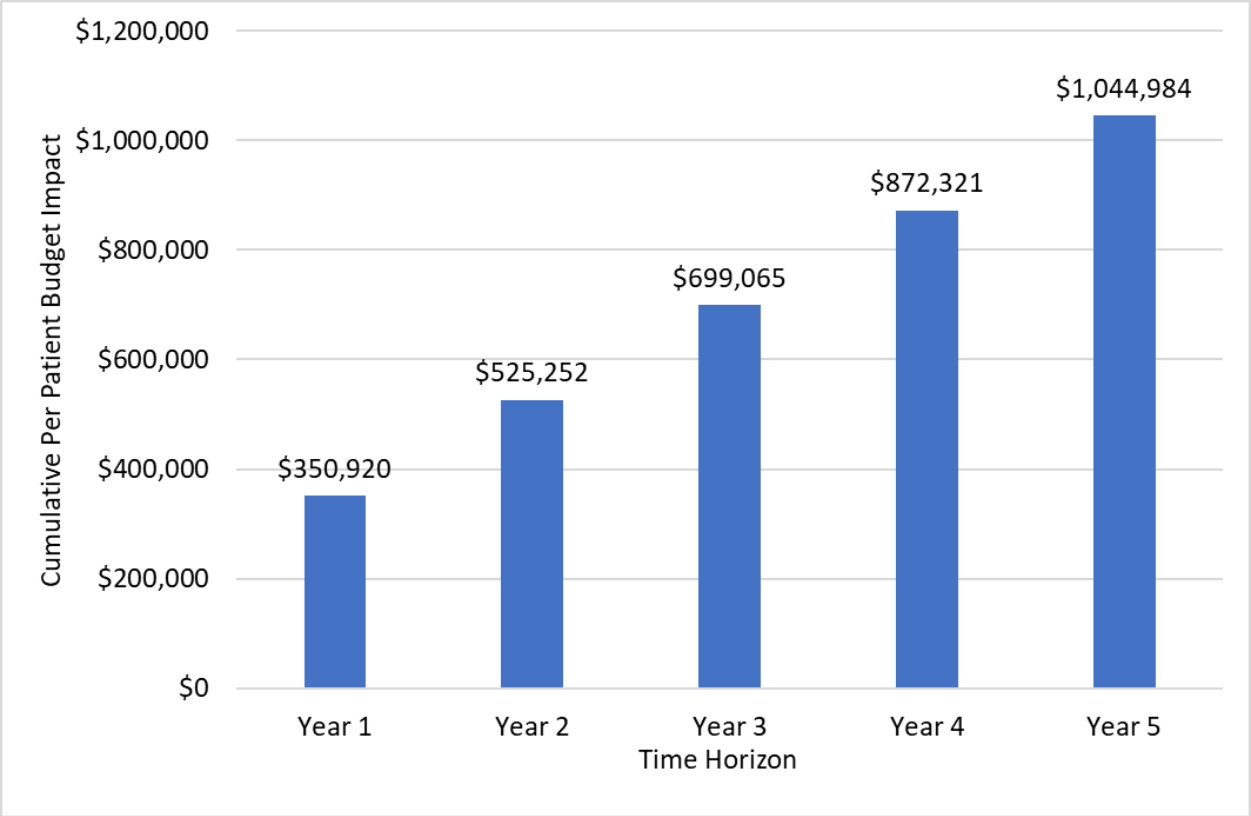
This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment, which includes Type 1, 2, or 3 SMA patients who have been treated with nusinersen or risdiplam. While the cost-effectiveness analyses primarily focused on Types 2 and 3 SMA, 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).[73] 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 $350,920 in year one and increased to $1,044,984 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 gained threshold prices ($6,600, $13,800, and $21,100 from the health care system perspective and $9,600, $19,900, and $30,200 from the modified societal perspective) before reaching the ICER potential budget impact threshold.

Access and Affordability Alert

The goal of the Access and Affordability alert is to signal that the additional health care costs introduced by a new intervention may be difficult for the health care system to absorb over the short term. In this situation, other needed services may be displaced, or health care insurance costs may rapidly rise, which would threaten sustainable access to high-value care for all patients.

At the placeholder price of $350,000, 64% of patients expected to be eligible for treatment over five years could receive therapy without exceeding the potential budget impact threshold of $880 million per year. At the $150,000 threshold prices of $21,100 from the health care system perspective and $30,200 from the modified societal perspective, 100% of eligible patients could be treated without exceeding this threshold. Given these numbers, and in the absence of a known price from the manufacturer, ICER is not issuing an access and affordability alert for apitegromab at this time.

8. Policy Recommendations

Following the Midwest CEPAC deliberation on the evidence, a policy roundtable discussion was moderated by Sarah Emond, President and CEO, ICER, around how best to apply the evidence on the use of apitegromab and other existing therapies for SMA. The policy roundtable members included two patient advocates, two clinical experts and two payers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

Health Equity

All Stakeholders

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective treatments for patients with SMA and persistent weakness are introduced in ways that will help reduce health inequities.

Muscle weakness remains a significant unmet healthcare need in patients with SMA even after SMN-directed therapy. This is particularly true for patients who were not diagnosed via newborn screening and so received treatment months to years after birth; lost motor neurons are never regained. Efforts are needed to ensure that the introduction of apitegromab does not aggravate existing health inequities. Concerns highlighted for this potentially expensive therapy, which requires IV infusion every four weeks, include the availability of specialists in SMA management, the costs of treatment, and the challenges faced by patients with limited mobility in traveling for care.

To address these concerns:

Manufacturers should take the following actions:

- **Set the price of apitegromab at launch to align with the value of added patient benefits.** The price for apitegromab has not been set, but analyst estimates are as high as $350,000 per year, which would likely lead to payers creating policies that might limit or delay patient access. ICER's analysis suggested that treatment would achieve common thresholds for cost-effectiveness if priced between $10,700 and $30,200 per year. . The manufacturer should price apitegromab so that both individual patients and the health system will view the drug as fairly priced, leading to broader access in a way that will help reduce disparities.

Payers should take the following actions:

- **Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access for vulnerable patients.**

- **Adopt standardized travel benefits or ensure access to home infusions of apitegromab for patients who have challenges traveling to an infusion center to receive therapy.**
  Patients in rural areas and those with severe muscle weakness and scoliosis often have challenges coming to medical centers for necessary services that are not available near their homes. Insurance plans variably cover the costs of travel and housing. Additionally, such coverage is commonly tied to specific diagnoses and therapies. Payers should develop standard coverage for travel for needed services to ensure equitable access to therapies like apitegromab, which requires IV infusions.

Clinicians and Clinical Specialty Societies:

- **Expand the ability of Centers of Excellence to provide consultation and support for community neurologists.**
  Because of its rarity, many neurologists may not be up to date on the latest strategies for managing SMA. Patients and their treating neurologists would benefit from collaborative care through consultation with specialists at centers of excellence. Treatment plans can be designed by specialists working with the patient and then administered by community neurologists. Centers of Excellence need to have enough clinicians to meet the demand for consultation and ongoing remote management.

- **Collaborate with patient organizations to exercise their joint power to advocate for drug prices that do not exceed a fair value for added clinical benefit.**
  Patients often have significant co-pays for drugs like apitegromab that require IV infusions, with some commercial plans requiring a high coinsurance for infused therapies. Specialty societies have an opportunity and responsibility to reach out to patient groups to form a united front and advocate for fair insurance access linked to fair prices for drugs. Drug prices that align with analyses of added benefit will often be lower than those initially set by drug makers, and lower prices will lead to fewer restrictions on access to the drugs and less financial burden on patients. In addition, this will enhance more equitable access to effective therapies.

Organizations representing patients:

- **Patient groups should seek relationships with clinical specialty societies to exercise their joint power to advocate for drug prices that do not exceed a fair value for added clinical benefit.** Patients often have significant co-pays for drugs like apitegromab that require IV infusions, with some commercial plans requiring a high coinsurance for infused therapies. Patient groups and specialty organizations have an opportunity and responsibility to advocate for fair insurance access linked to fair prices for drugs. Drug prices that align with analyses of added benefit will often be lower than those initially set by drug makers, and lower prices will lead to fewer restrictions on access to the drugs and less financial burden on patients. In addition, this will enhance more equitable access to effective therapies.

- **Patient groups should help raise international awareness about the value of newborn screening.**

  Newborn screening and immediate treatment have transformed the lives of patients living with SMA in the United States. Unfortunately, newborn screening is not universally available in other countries. Disease-modifying treatments for SMA have the highest value when started before symptoms develop clinically, and there are cost savings inside and outside the health system compared with waiting for symptoms to become clinically apparent. Many patients with SMA identified with newborn screening are expected to meet all of their developmental motor milestones and live healthy lives.

Payers

Recommendation 1

When approval of a drug that represents a first-in-class therapy for an underserved population is anticipated, payers should be evaluating the evidence and preparing policies in advance to avoid a new-to-market block on insurance coverage.

Many payers now institute "new-to-market" policies that block routine insurance coverage for new drugs 180 days or longer after Food and Drug Administration (FDA) approval. Although these blocks can be justified to allow an insurer adequate time to review the clinical evidence, consult with clinical experts, and prepare special coverage policies, in practice, many insurers place new-to-market blocks on virtually any new specialty drug. Payers should recognize their responsibility to act prior to FDA approval to ensure that their coverage policies are ready at the time of approval. This preparation is facilitated when manufacturers share data in a timely and transparent way and engage with payers prior to the approval of their products to facilitate the establishment of payment policies. Since patients with SMA often suffer from severe disabilities, prompt access to a

new therapy like apitegromab with the potential to improve motor functioning could improve their independence and reduce costs over the long term.

Recommendation 2

Payors should cover consultations between patients, their local neurologists, and Centers of Excellence.

SMA is a rare disease, and community neurologists have limited experience caring for patients with SMA. Expert consultation to establish a care plan will facilitate the use of the most up-to-date recommendations that optimize outcomes for patients.

Recommendation 3

Trial inclusion criteria are a reasonable starting point for developing coverage criteria for apitegromab, but payers should involve clinical experts and patient groups in designing flexible policies to account for the expected interest in the therapy for all SMA patients with muscle weakness.

Developing coverage policies for rare conditions can be challenging, given the evidence base. Since there are limited data from one small, randomized trial for apitegromab, and the cost is expected to be high, it would not be unreasonable for payers to use prior authorization as a component of coverage. Prior authorization criteria could be based on the inclusion and exclusion criteria from the SAPPHIRE trial, but will likely need to be sufficiently flexible to allow access for all SMA patients with muscle weakness, at least for a trial period. The process for authorization should be clear and efficient for providers and patients. Perspectives on specific elements of cost sharing and coverage criteria within insurance coverage policy are discussed below. Relevant criteria set out in ICER's previous work, Cornerstones of "Fair" Drug Coverage: Appropriate Cost-Sharing and Utilization Management Policies for Pharmaceuticals, are included.

Manufacturers

Recommendation 1

The manufacturer should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. Given the small average improvement in motor function for patients treated with apitegromab and the uncertainty about serious adverse events, manufacturer pricing should reflect ICER's value-based price range in moderating launch pricing.

Drug prices that are set well beyond the cost-effective range not only cause financial toxicity for patients and families using the treatments but also contribute to general healthcare cost growth

that pushes families out of the insurance pool and causes others to ration their own care in ways that can be harmful.

Manufacturers should, therefore, price novel treatments in accordance with the demonstrated benefits to patients. In settings of substantial uncertainty, initial pricing should err on the side of being more affordable. This would allow more patients access, generating additional data on the real-world effectiveness of novel treatments that could be used in future assessment updates. With the accumulation of evidence of substantial patient benefit, manufacturers should be allowed to increase pricing in accordance with clear evidence of significant net health benefits.

Clinicians and Clinical Societies

Recommendation 1

Update guidelines to move beyond SMA Type as the guidepost for therapy.

The use of SMA Type to describe patients and guide treatment recommendations is outdated in the era of newborn screening and early life intervention with SMN-directed therapy. Most patients in the US will appear to be asymptomatic when diagnosed as newborns. Research design and guideline development should focus instead on SMN2 copy number to characterize patients.

Patient Organizations

Recommendation 1

Cure SMA should continue to produce its annual State of SMA report.

The report was invaluable in the development of ICER's assessment. Given the rapidly evolving changes in the characteristics of patients since the advent of SMA-directed therapies and newborn screening, ongoing updates on the changing epidemiology of the community and their evolving needs are an irreplaceable service for all stakeholders.

Researchers/Regulators

Recommendation 1

Measure the impact of treatment on caregiver burden

The potential impact of effective therapy for SMA on caregiver burden was identified as an important potential benefit, but this is not explicitly measured in most clinical trials. Patient organizations have an important opportunity to partner with researchers in developing measures of

caregiver burden and encouraging pharmaceutical companies and the FDA to include them in future trials of therapies like apitegromab.

Recommendation 2

Expand research on apitegromab to populations not included in SAPPHIRE

There are currently no data on the utility of apitegromab in patients who did not meet the eligibility criteria for the study. Ambulatory patients with residual weakness may benefit, as may patients with Types 1 or 4 SMA. Finally, the drug should be studied in patients who have received gene therapy.

Recommendation 3

Expand research on measuring the clinical impact of therapies for SMA

Patients, caregivers, advocates, and clinicians agreed that changes in the HFMSE are insensitive to some meaningful benefits experienced by patients and their caregivers. Attention should be given to the development of instruments to capture the marginal gains reported by caregivers. In addition, more attention should be paid to the experience of young patients, whose voice is often not considered when assessing response to therapies. The International Consortium for Health Outcomes Measurement (ICHOM) is currently developing a new set of Patient-Centered Outcomes for patients with SMA, which may address some of these needs: https://www.ichom.org/patient-centered-outcome-measure/spinal-muscular-atrophy/

Recommendation 4

The use of SMN-directed therapy after gene therapy or in combination should only be done in the context of research studies.

Experts expressed significant skepticism about whether patients who had been treated with onasemnogene abeparvovec received any further benefit from treatment with either nusinersen or risdiplam. Adding extremely expensive therapies on top of an ideally curative therapy is not warranted without higher-quality evidence of benefit. If manufacturers will not perform such a trial, organizations like PCORI (Patient Centered Outcomes Research Institute) should consider funding a trial with regulatory requirements for medications to be provided at the cost of production. Payers could also potentially contribute to funding such a trial through a coverage with evidence development mechanism. Uncertainties also exist for combination treatment with nusinersen with risdiplam, though this is rarely covered.

Recommendation 5

A randomized trial should be performed of first-line therapy in asymptomatic patients identified through newborn screening to better understand the comparative advantages and disadvantages of each of the three SMN-directed therapies.

Experts highlighted the possibility that all three of the SMN-directed therapies (nusinersen, onasemnogene abeparvovec, and risdiplam) may maximize the protection of motor neurons. However, they have different mechanisms of action and distinct adverse events. Only randomized trials can provide an unbiased estimate of the relative benefits and harms between the three therapies. Without randomized trial data, parents making the ultimate decision in consultation with specialists must base their decision on results coming from case series with different entry criteria. If manufacturers will not collaborate to perform such a trial, organizations like PCORI should consider funding a trial with regulatory requirements for medications to be provided at the cost of production.

Recommendation 6

Remove barriers across state lines to facilitate consultations between patients, their local neurologists, and Centers of Excellence.

Eliminating barriers to expert collaboration and care coordination allows patients with SMA to access the most knowledgeable centers of excellence, regardless of geographic location.

Recommendation 7

Explore biomarkers that will help predict response to treatments for SMA

We heard preliminary evidence that neurofilament (NfL, PNF-H) levels may identify patient groups with ongoing motor neuron loss who may benefit from additional therapy. Furthermore, these markers could be used as a surrogate marker for treatment efficacy if well validated, thus improving the ability of clinicians to appropriately prescribe therapies.

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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.[74]

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) has been identified as a 1.5-point improvement and 3.2 deterioration, 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.[23,71,75]

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.[76]

32-Item Motor Function Measure (MFM32): A 32-item measure that assesses motor function abilities of individual with neuromuscular disease (NMD) using a 0-3 scale, with zero meaning no initiation of movement or no maintenance of starting position, and three meaning completion of exercise.[77] The raw score (range 0-96) is converted to a 0-100 scale, and the MCID is approximately a 5% improvement in all NMDs.

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.[78]

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.[79]

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.[53]

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.[80]

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".[81]

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.[82] 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.[83,84] 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)[85]

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[86]

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.[87,88] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[89] 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.

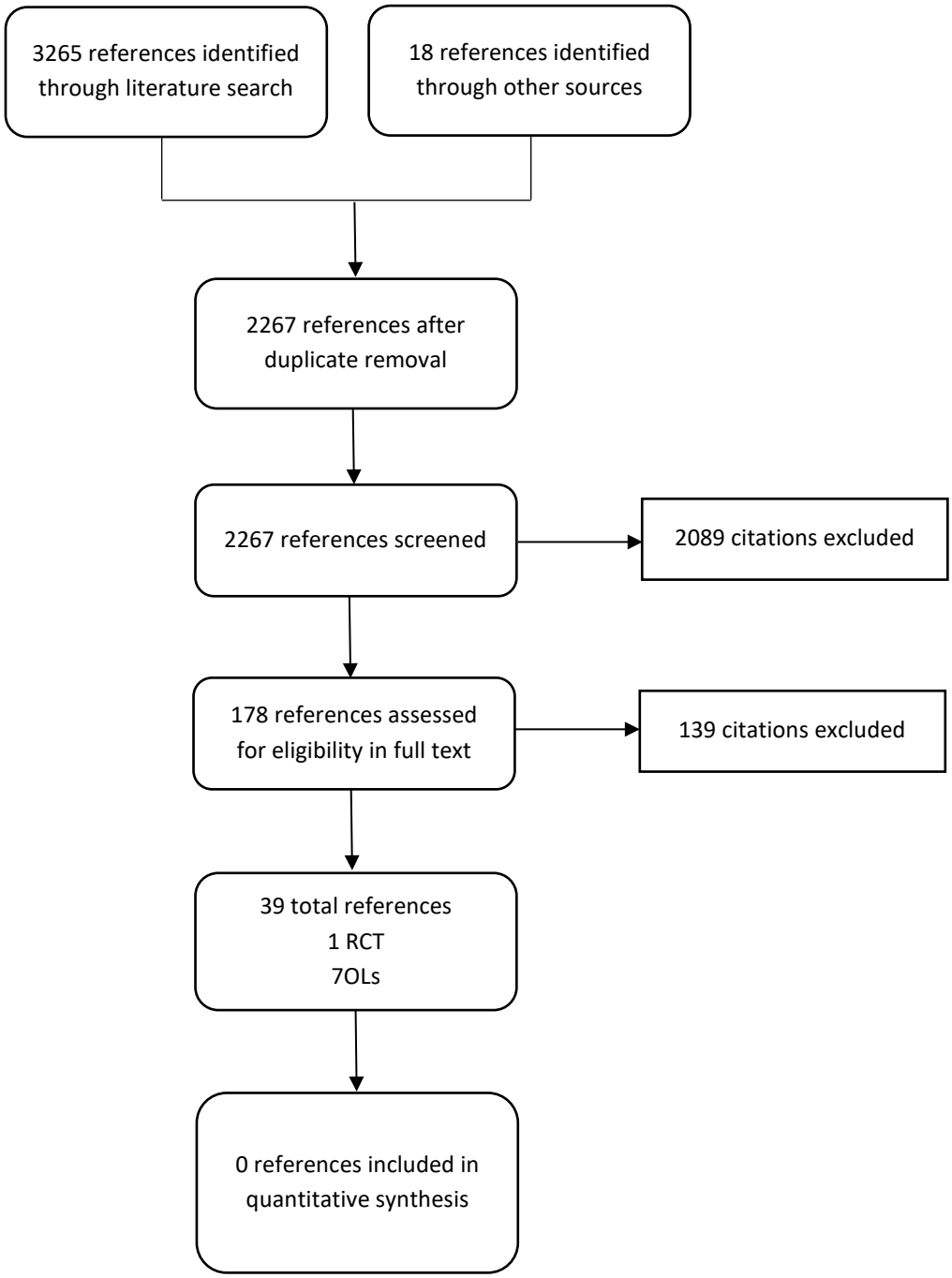
Table D1.2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews Search Strategy for Therapies for SMA

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.[88,90] 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 D1.4.

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[50,54]	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[53,91]	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: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • 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) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) 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[17]	72.34	2.13	4.26	6.91%	-	-	NR
PDRR	1.08	0.26	0.86	0.43	-	-	NC
Score	3	1	3	1	8	Fair	NC
TOPAZ[92]	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 SAPPHIRE and 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[93]	49.00%	51.00%	-	-	NA	-	-
SAPPHIRE[17]	50.00%	50.00%	-	-	NA	-	-
PDRR	1.02	0.98	-	-	NC	-	-
Score	3	3	6	Good	NC		
TOPAZ[92]	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).[94,95]

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 20 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%).[96]

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.[97] In the STRENGTH trial, the most frequent treatment-emergent adverse events were nasopharyngitis, pyrexia, and vomiting.[98] Several patients in the STRONG trial experienced several of the adverse of interest noted above, including hepatoxicity, thrombocytopenia, and cardiac events.[99]

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.[100-103] 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.[104,105]

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).[46,47,106,107] 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.[108,109]

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).[106] 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]).[107] 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.[109]

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.[107] 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]).[107] 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. N=188 **Main population**: ages 2-12, non-ambulatory, Type 2 or 3 SMA (n=156). **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: • apitegromab (10 mg/kg) + SOC* • apitegromab (20 mg/kg) + SOC* • placebo + SOC* *SOC: nusinersen (12 mg) or risdiplam (5 mg).	**Inclusion** • 2-21 years of age. • Diagnosed with later-onset SMA (Type 2 or 3) before receiving SMN therapy. • Non-ambulatory at screening. • Receiving nusinersen or risdiplam for the specified time and throughout the trial: ≥10 months of dosing for nusinersen, ≥6 months for risdiplam. • HFMSE score between 10-45 at screening. • Adherence to contraception requirement if patients have reached reproductive maturity. **Exclusion** • Previous treatment with onasemnogene abeparvovec or apitegromab. • Use of invasive ventilation and tracheostomy. • 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.

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
			ventilator support throughout the trial. • Severe scoliosis and/or contractures at screening. • 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. N=58 **Cohort 1:** ages 5-21, ambulatory Type 2 SMA (n=23). **Cohort 2**: ages 5-21, Type 2 or non-ambulatory Type 3 SMA. (n=15). **Cohort 3**: ages ≥2 years, Type 2 SMA (n=20).	All arms were administered by an IV infusion once every four weeks: • apitegromab (20 mg/kg) • apitegromab (20 mg/kg) + nusinersen (12 mg) • apitegromab (2 mg/kg) + nusinersen (12 mg); only for Cohort 3	**Inclusion** • 5-21 years of age for Cohorts 1 and 2; Age ≥2 for Cohort 3. • Diagnosed with later-onset SMA (Type 2 or 3) before receiving any therapy. • Non-ambulatory patients must be able to sit independently per WHO milestone definition. • Ambulatory patients must independently ambulate without aids or orthotics over 10 meters in <30 seconds at screening. • 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. • Adherence to contraception requirement if patients have	**Cohort 1**: change from baseline in RHS total score at 52 weeks. **Cohorts 2 and 3:** change from baseline in HFMSE total score at 52 weeks.

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
			reached reproductive maturity. **Exclusion** • Use of tracheostomy with positive pressure. • Use of chronic daytime non-invasive ventilatory support for >16 hours daily two weeks before dosing, or anticipated daytime ventilator support throughout the trial. • Severe scoliosis and/or contractures at screening. • 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[17,24]

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.	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	86.8 / 13.2	10 / 90NA	9 / 91	*9.5 / 90.5*
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	*85 / 15*
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)		27.3 (18, 37)	25.6 (9, 37)*	25.7 (13, 37)	25.6 (9, 37)*	26.3 (17 – 37)	26.3 (20-37)	26.3 (5.8)
Baseline WHO Motor Milestones Attained, Median (IQR)		1.5 (1-2)	1.0 (1-2)	1.0 (1-2)	1.0 (1-2)	1.0 (1-2)	1.0 (1-2)	1.0 (1-2)
History of Scoliosis (%)		70	71.7	71.7	71.7	90	86.4	87.5

API: apitegromab, HFMSE: Hammersmith Functional Motor Scale Expanded, IQR: interquartile range, 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

*One participant from the apitegromab 10 mg/kg group was too young at baseline to undergo the RULM.

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 **NCT05626855** **Scholar Rock**	Phase III, open-label, multicenter, extension study to evaluate the long-term safety and efficacy of apitegromab. N=238	Apitegromab (20 mg/kg) once every four weeks by IV infusion.	• Patients ≥2 years of age with Type 2 or 3 SMA. • Completed TOPAZ or SAPPHIRE trial. • Estimated life expectancy >2 years from baseline.	Incidence of TEAEs and SAEs by severity for up to six years.	May 2029
OPAL **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. N=52 (estimated)	Unknown	• Patients under 2 years of age with SMA. • 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 **NCT04488133** **Biogen**	Phase IV interventional study to evaluate treatment with nusinersen after onasemnogene abeparvovec. 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. • SMN2 copy number of ≥1. • ≤36 months of age at the time of first Nusinersen dose. • 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 **NCT05861986** **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. N=28	Oral risdiplam (60 mg) once daily for 120 weeks.	• Patients with SMA aged <2 years with two SMN2 gene copies. • Treated with onasemnogene abeparvovec pre- or post-symptomatically no less than 3 months, but not more than 7 months, prior to enrollment. • 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 **NCT05861999** **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. N=28	Oral risdiplam (60 mg) once daily for 120 weeks.	• Patients with SMA aged <2 years with two SMN2 gene copies. • Treated with onasemnogene abeparvovec pre- or post-symptomatically no less than 3 months prior to enrollment. • 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 **NCT05808764** **Hoffman-La Roche**	Phase II, open-label study to evaluate the pharmacokinetics and safety of risdiplam in infants with SMA. 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. • Gestational age ≥37 weeks.	• Plasma concentrations, area the plasma concentration-time curve (AUC), and steady-state concentration (CSS) of risdiplam. • Risdiplam free fraction. • 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 **NCT05232929** **Genentech**	Phase IV, prospective, multi-center follow-up study to evaluate the long-term safety and efficacy of risdiplam. N=500	Oral risdiplam (60 mg) once daily for 120 weeks.	• Children, adults, or older adults with SMA. • Prescribed or continued use of risdiplam.	Number of participants with AEs, SAEs, or AESI for up to 4 ½ years.	December 2026
RESTORE **NCT04174157** **Novartis**	Prospective, multinational, non-interventional, long-term safety and effectiveness registry of onasemnogene abeparvovec. N=700	Onasemnogene abeparvovec	• Children, adults or older adults with SMA. • Treated with onasemnogene abeparvovec.	• Change in probability of survival. • Change from baseline (CFB) on the CHOP-INTEND in infants with pre-symptomatic or Type 1 SMA. • CFB on the HINE in infants with pre-symptomatic, Type 1 or 2 SMA. • CFB on the HFMSE in patients with Type 2 or 3 SMA. • 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 **NCT05335876** **Novartis**	Phase III, prospective, multi-center study to evaluate the long-term safety and efficacy of onasemnogene abeparvovec. 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 **NCT05067790** **Biogen**	Phase IIIb, interventional study to evaluate the higher dose regimen of nusinersen in patients previously treated with risdiplam. 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. • Symptom onset >6 months of age. • 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. • 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 **NCT05089656** **Novartis**	Phase III, randomized, sham-controlled, double-blind study to evaluate the efficacy and safety of intrathecal onasemnogene abeparvovec. N=127	• Onasemnogene abeparvovec (1.2×10^{14} vg) once by IT injection. • Sham control (skin prick in the lumbar region without any medication).	• Patients with SMA aged ≥ 2 to < 18 years. • Patients are treatment-naive (historical or current use) for all SMN-targeting therapies (e.g., risdiplam and nusinersen). • Symptom onset ≥6 months of age. • 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)[110]

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)[111]

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[112]

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.[113]
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)

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

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.[114] for individuals in the "sitting" state and data from Gregoretti et al. for patients in the "not-sitting" state.[115]

Table E2.1. Mortality Inputs

Parameter	Value	Source
Mortality From Sitting	Gompertz α=0.0964 β=0.0037	Zerres et al.[114]
Mortality From Not-Sitting	Exponential λ=0.0158	Gregoretti et al.[115]

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.[63] These values were combined into weighted averages for each state based on the SMA type distribution observed in the SAPPHIRE trial (Table E1.2).[54] 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 increments for apitegromab and utility losses for SoC.

Table E2.2. Utility Values for Health States

State	Utility Value	Source
Sitting SMA2	0.26	Belter et al.[63]
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	
Sitting with Support	0.37	Hu et al.[61]
Sitting without Support	0.39	
Standing with Support	0.47	

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

Caregiver Utilities

We included caregiver utilities specific to patient state in a modified societal perspective scenario analysis, along with bereavement utilities. 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.[62] 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 [67]
	331.69		CMS OPPS Addendum B [65]
Intrathecal Injection (Drain Cerebrospinal Fluid)	90.89	HCPCS 62272	CMS Physician Fee Schedule 2025 [67]
	692.52		CMS OPPS Addendum B [65]
Fluoroguide	27.17	HCPCS 77003	CMS Physician Fee Schedule 2025[67]
Complete Blood Count	7.77	HCPCS 85025	CMS Laboratory Fee Schedule 2025[116]
Coagulation Testing	4.29	HCPCS 85610	
Urine Protein Levels	3.67	HCPCS 84156	
MD/Specialist	63.72	HCPCS 99213	CMS Physician Fee Schedule 2025 [67]

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.[117]

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.[118] 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 4.3 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 Figure E4.1. for the health care system perspective, and Table E4.2. for the modified societal perspective. 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 (Health Care System Perspective)

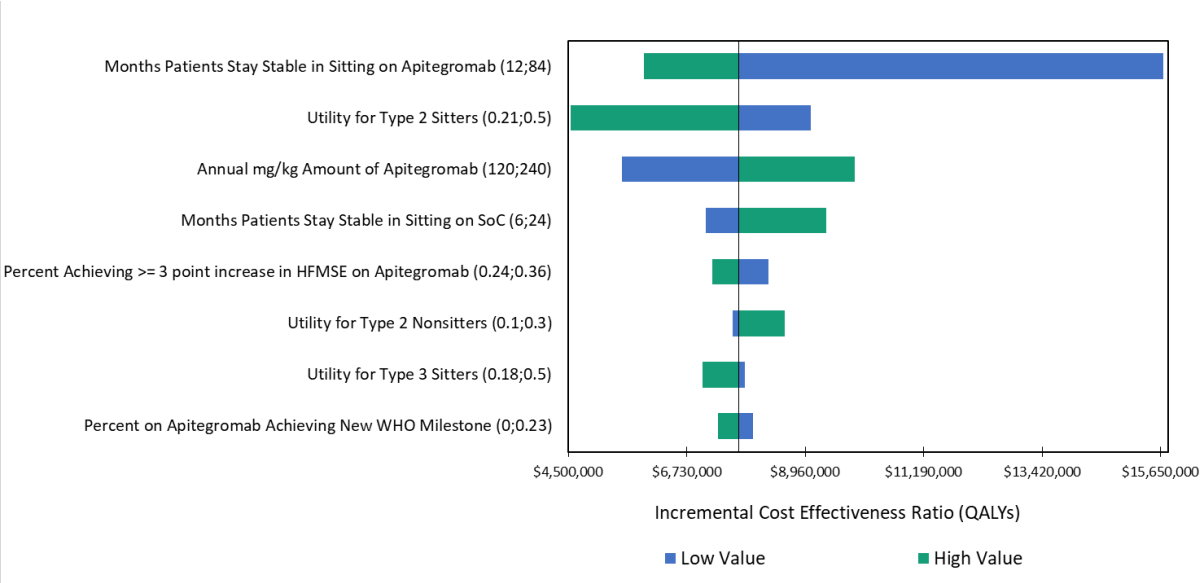
	Lower Incremental CE Ratio*	Upper Incremental CE Ratio*	Lower Input†	Upper Input†
Months Patients Stay Stable in Sitting on Apitegromab (12;84)	$15,707,000	$5,924,000	12	84
Utility for Type 2 Sitters (0.21;0.5)	$9,065,000	$4,546,000	0.21	0.5
Annual mg/kg Amount of Apitegromab (120;240)	$5,518,000	$9,887,000	120.00	240.00
Months Patients Stay Stable in Sitting on SoC (6;24)	$7,095,000	$9,357,000	6	24
Percent Achieving >= 3-point increase in HFMSE on Apitegromab (0.24;0.36)	$8,267,000	$7,210,000	0.24	0.36
Utility for Type 2 Nonsitters (0.1;0.3)	$7,600,000	$8,569,000	0.1	0.3
Utility for Type 3 Sitters (0.18;0.5)	$7,830,000	$7,031,000	0.18	0.50
Percent on Apitegromab Achieving New WHO Milestone (0;0.23)	$7,971,000	$7,326,000	0	0.23

CE: cost-effectiveness, HFMSE: Hammersmith Functional Motor Scale Expanded, kg: kilogram, mg: milligram, SoC: standard of care, WHO: World Health Organization

*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.

Figure E4.1. Tornado Diagram for Apitegromab + SoC Compared to SoC (Health Care System Perspective)



APC: ambulatory payment classification, kg: kilogram, mg: milligram, SoC: standard of care

Table E4.2. Tornado Diagram Inputs and Results for Apitegromab versus SoC (Modified Societal Perspective)

	Lower Incremental CE Ratio*	Upper Incremental CE Ratio*	Lower Input†	Upper Input†
Months Patients Stay Stable in Sitting on Apitegromab (12;84)	$7,830,000	$2,056,000	12	84
Annual mg/kg Amount of Apitegromab (120;240)	$2,022,000	$3,623,000	120	240
Months Patients Stay Stable in Sitting on SoC (6;24)	$2,547,000	$3,632,000	6.00	24.00
Utility for Type 2 Sitters (0.21;0.5)	$2,981,000	$2,250,000	0.21	0.5
Annual APC for Nusinersen ($359000;$539000)	$2,756,000	$2,889,000	$359,000	$539,000
Utility for Type 2 Nonsitters (0.1;0.3)	$2,811,000	$2,931,000	0.1	0.3

APC: ambulatory payment classification, CE: cost-effectiveness, kg: kilogram, mg: milligram, 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 E4.3. Results of Probabilistic Sensitivity Analysis for Apitegromab versus SoC

Health Care System Perspective			
	Apitegromab* + SoC Mean	**SoC Mean**	**Incremental**
Costs	$11,012,000	$5,326,000	$5,686,000
QALYs	3.35 (2.00, 5.02)	2.61 (1.56, 3.86)	0.73 (0.44, 1.17)
evLYs	4.60 (2.65, 6.62)	2.61 (1.56, 3.86)	1.98 (1.08, 2.76)
Incremental CE Ratio			$7,776,000
Modified Societal Perspective			
	Apitegromab* + SoC Mean	**SoC Mean**	**Incremental**
Costs	$11,002,000	$5,310,000	$5,692,000
QALYs	10.50 (8.10, 13.10)	8.50 (6.84, 10.27)	2.00 (1.26, 2.83)
evLYs	11.74 (8.63, 14.68)	8.50 (6.84, 10.27)	3.24 (1.79, 4.41)
Incremental CE Ratio			$2,849,000

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year, SoC: standard of care

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

Note: 0% of simulations hit key WTP thresholds

E5. Scenario Analyses

Table E5.1 presents the incremental results from several scenario analyses following a healthcare system perspective. Further details on each analysis can be found below.

Table E5.1. Results for Scenario Analyses for Apitegromab versus SoC

Health Care System Perspective			
Scenario	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per LY Gained**
Base Case	$7,702,000	$2,829,000	$2,945,000
1: Excluding Mean Change in WHO Milestones	$8,051,000	$2,870,000	$2,945,000
2: Exclusion of Pneumonia	$7,695,000	$2,828,000	$2,945,000
3: Apitegromab Disease Progression After 1 Year	$15,707,000	$7,725,000	$10,309,000
4. Apitegromab Disease Progression After 7 Years	$5,924,000	$2,095,000	$2,086,000
5. No Disease Progression on Apitegromab	$3,925,000	$1,483,000	$1,386,000
6. Higher Utility Values from NICE TA588[68]	$3,730,000	$2,343,000	$2,945,000
7. Lower Utility Values from Lloyd et al.[58]	$16,907,000	$2,753,000	$2,945,000

Health Care System Perspective			
Scenario	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per LY Gained**
8. Exclusion of Unrelated Healthcare Costs	$7,702,000	$2,829,000	$2,945,000
Modified Societal Perspective			
Scenario	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per LY Gained**
Base Case	$2,823,000	$1,730,000	$2,945,000
1: Excluding Mean Change in WHO Milestones	$2,868,000	$1,745,000	$2,945,000
2: Exclusion of Pneumonia	$2,822,000	$1,730,000	$2,945,000
3: Apitegromab Disease Progression After 1 Year	$7,830,000	$5,168,000	$10,309,000
4. Apitegromab Disease Progression After 7 Years	$2,056,000	$1,258,000	$2,086,000
5. No Disease Progression on Apitegromab	$1,337,000	$856,000	$1,386,000
6. Higher Utility Values from NICE TA588[68]	$2,030,000	$1,536,000	$2,945,000
7. Lower Utility Values from Lloyd et al.[58]	$3,526,000	$1,701,000	$2,945,000
8. Exclusion of Unrelated Healthcare Costs	$2,823,000	$1,730,000	$2,945,000

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

Scenario Analysis 1

Excluding Mean Change in WHO Milestones from Treatment Effect

This scenario removes the mean changes in WHO developmental milestones reported in SAPPHIRE at week 52 and the associated incremental utilities. Although these effects were included in the base case, there is uncertainty around them as the difference between the two arms were not statistically significant.

Table E5.2. Results for Scenario 1: Excluding Mean Change in WHO Milestones

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	QALYs	evLYs	Life Years
Health Care System Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	3.35	4.64	13.89
SoC	$4,887,000	$271,700	$5,324,000	2.65	2.65	11.95
Modified Societal Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	10.43	11.71	13.89
SoC	$4,887,000	$271,700	$5,324,000	8.44	8.44	11.95

evLYs: equal-value life year, 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

Exclusion of Pneumonia

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. Exclusion of pneumonia resulted in no noticeable difference compared to the base case due to rounding, results are detailed in Table E5.3.

Table E5.3. Results for Scenario 2: Exclusion of Pneumonia

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	QALYs	evLYs	Life Years
Health Care System Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	3.38	4.66	13.89
SoC	$4,887,000	$271,700	$5,324,000	2.64	2.64	11.95
Modified Societal Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	10.46	11.73	13.89
SoC	$4,887,000	$271,700	$5,324,000	8.43	8.43	11.95

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

Disease Progression Initiates at 1 year on Apitegromab

In this analysis we assume apitegromab maintains motor function for the first year of treatment before HFMSE scores begin to decline. After this initial maintenance period, patients receiving apitegromab experience the same rate of decline in HFMSE as SoC, but starting from higher baseline HFMSE scores observed at 52-weeks in SAPPHIRE. Since patients begin transition from a higher functional level, this results in a slightly slower rate of transitioning to "not-sitting" compared to standard of care. Results are detailed in Table E5.4. There are no positive threshold prices in this scenario.

Table E5.4. Results for Scenario 3: Disease Progression on Apitegromab after 1 Year

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	QALYs	evLYs	Life Years
Health Care System Perspective						
Apitegromab* + SoC	$9,404,000	$290,000	$9,862,000	2.93	3.23	12.39
SoC	$4,887,000	$271,700	$5,324,000	2.64	2.64	11.95
Modified Societal Perspective						
Apitegromab* + SoC	$9,404,000	$290,000	$9,862,000	9.01	9.31	12.39
SoC	$4,887,000	$271,700	$5,324,000	8.43	8.43	11.95

evLYs: equal-value life year, 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 4

Disease Progression Initiates at Year 7 on Apitegromab

In this analysis we assume apitegromab maintains motor function for 7 years before HFMSE scores begin to decline. This scenario follows the same approach as Scenario Analysis 4, and the base case except assumes a longer maintenance period. The extended 7-year maintenance period results in an even slower rate of transitioning to the "not sitting" health state compared to standard of care, despite having the same underlying rate of motor function deterioration once decline begins. Results are detailed in Table E5.5. There are no positive threshold prices in this scenario.

Table E5.5. Results for Scenario 4: Disease Progression on Apitegromab after 7 Years

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	QALYs	evLYs	Life Years
Health Care System Perspective						
Apitegromab* + SoC	$11,514,000	$356,000	$12,042,000	3.77	5.84	15.17
SoC	$4,887,000	$271,700	$5,324,000	2.64	2.64	11.95
Modified Societal Perspective						
Apitegromab* + SoC	$11,514,000	$356,000	$12,042,000	11.70	13.77	15.17
SoC	$4,887,000	$271,700	$5,324,000	8.43	8.43	11.95

evLYs: equal-value life year, 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

No Disease Progression on Apitegromab

In this analysis we assume apitegromab maintains motor function over the lifetime of the patient. Unlike the base case and previous scenarios where decline eventually occurs, patients receiving apitegromab maintain their improved HFMSE scores achieved at 52 weeks indefinitely, with no subsequent deterioration in motor function. This represents the most optimistic scenario for apitegromab's long-term efficacy, where patients avoid the natural disease progression entirely while on treatment. Results are detailed in Table E5.6. There are no positive threshold prices in this scenario.

Table E5.6. Results for Scenario 5: No Disease Progression on Apitegromab

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	QALYs	evLYs	Life Years
Health Care System Perspective						
Apitegromab* + SoC	$14,311,000	$442,000	$14,900,000	5.08	9.10	18.86
SoC	$4,887,000	$271,700	$5,324,000	2.64	2.64	11.95
Modified Societal Perspective						
Apitegromab* + SoC	$14,311,000	$442,000	$14,900,000	15.60	19.61	18.86
SoC	$4,887,000	$271,700	$5,324,000	8.43	8.43	11.95

evLYs: equal-value life year, 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.[63] 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 0.20 for "not-sitting." Since no reported utility values were available specifically for later-onset "not-sitting" patients, we applied the early-onset "no milestones achieved" value. This resulted in much higher QALYs over the lifetime for both treatments compared to the base case. Results are detailed in Table E5.7.

Table E5.7. Results for Scenario 6: Utilities from NICE TA588 Clinical Advisors

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	QALYs	evLYs	Life Years
Health Care System Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	7.44	8.34	13.89
SoC	$4,887,000	$271,700	$5,324,000	5.91	5.91	11.95
Modified Societal Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	14.51	15.42	13.89
SoC	$4,887,000	$271,700	$5,324,000	11.70	11.70	11.95

evLYs: equal-value life year, 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.[63] 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 -0.13 for "not-sitting." Results are detailed in Table E5.8.

Table E5.8. Results for Scenario 8: Utilities from Lloyd et al.[58]

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	QALYs	evLYs	Life Years
Health Care System Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	0.27	2.01	13.89
SoC	$4,887,000	$271,700	$5,324,000	-0.06	-0.06	11.95
Modified Societal Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,038,000	7.35	9.09	13.89
SoC	$4,887,000	$271,700	$5,324,000	5.73	5.73	11.95

evLYs: equal-value life year, 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 8

Exclusion of Unrelated (Non-Drug) 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.[117] 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.

Table E5.9. Results for Scenario 9: Exclusion of Unrelated Health Care Costs

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	QALYs	evLYs	Life Years
Health Care System Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,034,000	3.38	4.66	13.89
SoC	$4,887,000	$271,700	$5,321,000	2.64	2.64	11.95
Modified Societal Perspective						
Apitegromab* + SoC	$10,542,000	$326,000	$11,034,000	10.46	11.73	13.89
SoC	$4,887,000	$271,700	$5,321,000	8.43	8.43	11.95

evLYs: equal-value life year, 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 9

ICER Reference Case

This scenario analysis follows ICER's reference case guidance for situations where standard of care involves high-cost interventions that may prevent new treatments from achieving feasible value-based pricing under conventional cost-effectiveness methods. In this modified analysis, we excluded all standard of care treatment costs (including nusinersen and risdiplam acquisition and administration costs) and non-intervention costs (such as disease management, and other background healthcare costs), retaining only the incremental costs directly attributable to apitegromab (acquisition and administration costs). This approach isolates the cost-effectiveness assessment to the marginal impact of adding apitegromab to existing care, providing policymakers with an alternative perspective that may be more relevant for value-based pricing discussions when patients are already receiving expensive disease-modifying therapies. The analysis maintains the same clinical effectiveness assumptions and utility values as the base case, with only the cost structure modified to reflect this incremental cost perspective.

Table E5.10. Results for Scenario 10: ICER Reference Case – Exclusion of All Costs Except Apitegromab Administration and Acquisition Costs

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	QALYs	evLYs	Life Years
Health Care System Perspective						
Apitegromab* + SoC	$4,862,000	$10,000	$4,872,000	3.38	4.66	13.89
SoC	$0	$0	$0	2.64	2.64	11.95
Modified Societal Perspective						
Apitegromab* + SoC	$4,862,000	$10,000	$4,872,000	10.46	11.73	13.89
SoC	$0	$0	$0	8.43	8.43	11.95

evLYs: equal-value life year, 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. However, there are key differences: our SoC arm incorporating a mix of nusinersen and risdiplam treated patients (although both treatments have been shown to show comparable health outcomes and costs), with patients being on these prior treatments for approximately five years and three years, respectively, prior to model start, and our model includes disease progression.

Our model maintains a similar structure to the previous ICER model from 2019.[48] However, with more long-term data now available, our model incorporates a lower mobility state of "not sitting" to reflect recent evidence that disease progression may continue even with current SMN-targeted therapies.[50,59,72] We also used utility estimates sourced directly from those living with or providing daily care for individuals with SMA,[63] rather than estimates from clinical advisors used in the previous model.

Direct comparison between our model and previously published models is challenging due to fundamental differences in the modeling approach. Our model explicitly incorporates disease progression patterns observed in SAPPHIRE, contrasting with other models that assume patients maintain function throughout their lifetime.

When benchmarking our standard of care results – 11.95 life years, 2.63 QALYs, and 8.43 combined patient-caregiver QALYS – against published analyses, our results were substantially lower than those reported by NICE (19.61 LYs, 5.83 QALYs, 20.99 combined QALYs) and CADTH (7.09-15.34 QALYs across different reviews).[52,119] These differences reflect our incorporation of real-world disease progression as new data has shown that to be the more realistic long-term projection.

Table E7.1. Model Revisions from Draft Report

Change	Rationale
Revised base case to include data on mean changes in WHO motor development milestones at 52-weeks in SAPPHIRE.	While the observed changes did not reach statistical significance, the magnitude of effect (mainly 0.6 to 0.8 quality adjusted life year improvement in 9% of patients) may still represent clinically meaningful benefit to patients. We believe that including this data represents the best available evidence approach for rare disease modeling. We explored a scenario analysis without these effects to examine the impact on the results.
Revised base case to include disease progression, with patients on apitegromab maintaining function during the first 4 years.	Disease progression was included in scenario analyses but not the base case in the draft report due to the amount of uncertainty around disease progression on these treatments. We received comments around how a base case without progression is missing a huge aspect of the disease and agree. We assumed apitegromab maintains function for the first 4 years based on data from TOPAZ.[19]
Inclusion of bereavement disutilities in the modified societal perspective.	The addition of disease progression to the base case introduced mortality differences between the two treatments allowing us to incorporate bereavement.
Inclusion of the modified societal perspective as a co-base case.	Family quality-of-life impacts were substantial relative to direct health care outcomes, and the impact of apitegromab on these outcomes was significant.

WHO: World Health Organization

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).[73] 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.[120,121] 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.

G. Supplemental Policy Recommendations

Drug-Specific Coverage Criteria: Apitegromab

The limited data on effectiveness, combined with the potential for serious adverse effects, and the high anticipated price for apitegromab, will lead payers to develop prior authorization criteria and to consider other limits on utilization.

None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right. To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for apitegromab.

Outcome-based agreements were briefly discussed, but there was general agreement that there was no role for them with apitegromab as they would be too cumbersome to administer.

Payors should be sensitive to the cumulative effects of cost-sharing on patients and set appropriate caps on the annual out-of-pocket expenditures for patients.

In addition, payers should ensure that their review team has a deep understanding of this rare and potentially devastating illness.

Step Therapy

Given that there is no alternative therapy available that increases motor function akin to apitegromab, step therapy is not appropriate.

Clinical Coverage Criteria

- **Age:** The primary endpoint in the pivotal SAPPHIRE trial of apitegromab was assessed in children aged 2 to 12 years. However, clinical experts told us that there is no biological reason why apitegromab should not help patients with SMA of other ages; in an exploratory group of 32 patients aged 13 to 21 years, the gains in the HFSME were similar to those observed in the younger patients. Payers could consider extending the covered age to all patients with SMA who have residual weakness.

- **Clinical eligibility**: The SAPPHIRE trial studied patients with Type 2 or Type 3 SMA who are non-ambulatory and are receiving either nusinersen or risdiplam, although the majority (80%) were treated with nusinersen. Interestingly, the subgroup of patients receiving risdiplam who were treated with apitegromab saw almost no gain in the HSFME compared with placebo (change from baseline 0.5 points, 95% CI, -2.3 to +3.3).

- **Exclusion criteria**: The SAPPHIRE trial excluded patients with Hammersmith Functional Motor Scale Expanded (HFMSE) scores that were less than 10 or greater than 45. As with the age criteria, clinical experts suggested that there is no biological reason why patients with other scores could not benefit from apitegromab. It would be reasonable for payers to consider coverage for patients with a wider range of HFSME scores.

  In addition, the study excluded patients who had severe scoliosis, severe contractures, or the use of chronic daytime ventilator support.

  Finally, the study excluded patients who were previously treated with onasemnogene abeparvovec.

  Payers could consider flexible policies that require additional evidence generation (sometimes referred to as "coverage with evidence development") in the populations not studied in the SAPPHIRE trial to broaden access to other SMA patients with muscle weakness, and to further the clinical understanding of which patients would benefit from the new therapy.

- **Dose:** 10 or 20 mg/kg IV infusion every four weeks.

- **Duration of coverage and renewal criteria**: Initial coverage will likely be for a period of 4 to 6 months, which is long enough to assess response to therapy. Clinical experts and payers felt that it would be appropriate to require attestation alone for continuation of therapy.

  If payers decide to require documentation using some measure, they should recognize that there are significant challenges in assessing response with the HFMSE due to potential intercurrent illness leading to a short-term reduction in score and the small average increase in the HFMSE among treated patients. If stability or improvement in the HFMSE is required for renewal, then the trend over multiple assessments should be used rather than focusing on the most recent assessment.

- **Provider restrictions**: Clinical experts agreed that it is reasonable to restrict prescriptions for apitegromab to neurologists, ideally in consultation with an expert in the care of patients with SMA. Specialty clinicians are better suited to identify patients who are most likely to benefit, provide sufficient information for patients and families to make well-informed decisions, and monitor for response and side effects.

Site of Service Policies

Payors should establish site-of-service policies that cover home infusion or care at other low-cost sites when feasible.

Clinical experts did not suggest that there were risks of administration of apitegromab that would make it necessary to administer it in specialized clinical settings. Given the reduced cost and increased convenience for patients when infusions are delivered at home rather than at hospital-based infusion centers, payors should establish site-of-service policies that cover home infusion or care at other low-cost sites when feasible. Benefit design should enable patients to have lower cost sharing when lower-cost settings are used, and rapid, transparent procedures for exceptions should be universal.

H. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on Friday, August 1st, 2025. These summaries were prepared by those who delivered public comments at the meeting and are presented in order of delivery.

A video recording of all comments can be found here, beginning at minute 00:28. Conflict of interest disclosures for all public commenters can be found in Supplement I.

Tom Brown, PhD
Vice President, Global Medical Affairs, Scholar Rock

Good morning. I am Tom Brown, Vice President of Medical Affairs at Scholar Rock, a biopharmaceutical company committed to developing transformative treatments for children and adults living with rare, severe and debilitating neuromuscular diseases.

As we've heard today, SMA is a rare, severe neuromuscular disease resulting in irreversible loss of motor neurons and progressive muscle atrophy. While current SMN-targeted treatments have transformed the treatment landscape by addressing the motor neuron component of SMA, they do not directly address the muscle component, a key driver of long-term disability. Even with early SMN treatment, children and adults often do not reach full motor function potential and continue to battle persistent motor function decline over time, resulting in the loss of essential abilities like feeding or rolling over in bed independently, deeply impacting independence and imposing profound emotional and physical burdens on children and adults living with SMA as well as their caregivers.

The SMA community has been clear about its priorities. According to CureSMA's recent Annual Community Survey, 89% of adults living with SMA identified gaining muscle strength as a top unmet need. They also emphasized the need to gain or stabilize motor function and reduce fatigue. Scholar Rock has heard this call and is working diligently to ensure patients have access to the first and only muscle-targeted treatment option, apitegromab.

Apitegromab offers the potential to meaningfully improve the standard of care in SMA and alter the trajectory of the disease. It is the first and only investigational muscle-targeted treatment with positive and successful Phase 3 data that directly addresses the progressive muscle atrophy associated with SMA. In the Phase 3 SAPPHIRE trial, apitegromab demonstrated statistically and clinically significant improvement in motor function compared to the control group with SMN-targeted treatment alone. Further, 98% of subjects in SAPPHIRE continued onto the long-term extension study, ONYX, demonstrating the tolerability and perceived value of apitegromab. Moreover, in the Phase 2 TOPAZ trial, motor function gains were sustained over four years. Across

our studies, we have accumulated over 600 patient-years of safety data, with no serious adverse events attributed to apitegromab and no subjects discontinued due to adverse events. In short, apitegromab has demonstrated the ability to halt and reverse disease progression as measured by motor function with a well-tolerated profile.

The FDA has granted apitegromab a Priority Review designation. Priority Review is awarded to treatments that, if approved, would be significant improvements in the safety or effectiveness of the treatment of serious conditions, in this case, SMA.

By ICER's own account and reiterated by stakeholders in the public comments, ICER's model is simplistic and does not fully reflect the impact of motor function improvements that occur between major milestones. In addition, although ICER's report correctly acknowledges the threshold for clinically meaningful change for the Hammersmith scale is evolving and a recent publication has reported a 1.5-point improvement as clinically meaningful, ICER's model nevertheless utilizes a threshold of 3-points. While the SAPPHIRE trial showed impressive results at the 3 point threshold with the odds of a 3-point or greater improvement being three times more likely for apitegromab-treated patients than patients treated with SMN-targeted treatment alone, we nonetheless urge ICER to acknowledge that the threshold for meaningful change must be re-evaluated to reflect a new natural history where many patients already receive SMN-targeted treatments. As you have heard from the SMA community, a single point change on the Hammersmith scale can be the difference between being able to, for example, sit upright longer, operate a motorized wheelchair, or eat without help. For children and adults living with SMA, these differences are transformational.

ICER's evaluation of apitegromab should more fully consider the human significance of sustaining or improving motor function and recognize what is at stake for children and adults living with SMA: improvements in daily life, independence, and dignity. We urge ICER to foster meaningful dialogue regarding the threshold for meaningful change which in the current model attributes limited value to smaller changes in motor function, thereby grossly undervaluing apitegromab's potential to reduce disease burden and meaningfully improve patient and caregiver lives. Also, ICER should frame the results of this evaluation in light of the significant model limitations and avoid drawing overreaching policy conclusions.

In closing, we stand at the cusp of a promising time for patients living with SMA. Scholar Rock is working diligently to make apitegromab available to children and adults who could benefit from this innovative first and only muscle-targeted treatment, pending a favorable decision by the FDA. On behalf of Scholar Rock, thank you for listening today.

Susi Vander Wyk
Executive Director, Cure SMA Canada

Susi Vander Wyk, executive director of Cure SMA Canada for 15 years, prior board member for 10 years, also a parent of adult daughter with SMA.

Perspective of patient and patient group.

Burden of disease

- Patient mental health needs to be taken into consideration, it impacts days of work, attending school, family relationships and can result in patient physical decline, even resulting in self-harm. Patients unable to access beneficial treatments can have major impact on mental health.
- SMA impacts all members of the family, including siblings who need to assist or take a back seat to the needs of the affected sibling, resulting in anxiety, depression and anger at times.
- Parents and caregivers commonly experience post-traumatic stress disorder (PTSD) due to the stress of caring for SMA patient's high needs. They also commonly experience anxiety and depression.
- Patients and caregivers experience loss of income and experience many costs due to missed school days and cost of supporting family members due to the disease.
- Patients experience multiple hospitalizations due to illness.

Patient experiences

- Daughter has 3 copies, Type 2, power wheelchair user. Prior to access to treatment, it took three times as long as normal to achieve her undergrad due to weakness and low stamina. After access, she took an accelerated program to achieve her teaching degree and now works full time as a primary school teacher.
- I know a family where all three of their children are diagnosed with SMA. The oldest was treated later in life, uses a power chair, second child received treatment earlier, walks with impacted gait. Third child was treated presymptomatically, very ambulant, minimal disease impact.
- As an organization that has been supporting patients for over 25 years, we send out regular newly diagnosed packages and used to follow most of them up with end of life bereavement packages. Since access to treatment, we rarely send out bereavement packages.
- Many Canadian patients have experienced the negative effects of living in jurisdictions where they have been unable to access these lifesaving and life changing treatments. Due to this, they have watched others benefit with improved quality of life, and stability of their disease. Patients who are unable to access developed effective treatment that others are

accessing, is absolutely devastating, and many have stated that it is even more devastating than the diagnosis itself.

Points to Consider

- Must treat patients early for best quality of life and prevent irreversible loss of function.
- Must consider patient mental and physical need for access, providing the greatest opportunity for contributing to society.
- Important to take real world evidence and patient reported outcomes into consideration when compiling evidence to justify access as it is critical to understand the full effects of disease and treatment.
- Patients support being removed from treatment if they are not responding to it. They do need a fair period of time for it to work, they deserve a chance to experience the opportunity to improve their quality of life.
- Added beneficial treatment makes sense from a patient perspective. The three existing treatments are each effective, life changing, and offer clear disease improvement and stabilization, but they aren't a cure. Patients feel disappointment that they still experience symptoms of the disease. There are continued needs for research, improved quality of life and patient supportive care.

I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the Friday, August 1st public meeting of spinal muscular atrophy. You can find any conflicts reported by the authors of the report, or expert reviewers, on page v.

Table I1. Midwest CEPAC Panel Member Participants and Conflict of Interest Disclosures

Midwest CEPAC Member	Conflict of Interest
Bijan Borah, PhD Professor of Health Services Research, Mayo Clinic College of Medicine and Science	Dr. Borah has received a consulting fee of <$5K from Boehringer Ingelheim in 2025.
Kurt Vanden Bosch, PharmD System Formulary Lead, St. Luke's Health System	No conflicts to disclose.
Donald Casey, MD, MPH, MBA, MACP, FAHA Associate Professor of Internal Medicine, Rush Medical College	No conflicts to disclose.
Sneha Dave Executive Director, Generation Patient	No conflicts to disclose.
Stacie Dusetzina, PhD Professor of Health Policy, Vanderbilt University Medical Center	No conflicts to disclose.
Jayani Jayawardhana, PhD Associate Professor, University of Kentucky	No conflicts to disclose.
Jill Johnson, PharmD Professor, Pharmacy Practice, University of Arkansas for Medical Sciences, College of Pharmacy	Dr. Johnson receives royalties from UAMS Bioventures for intellectual property generated as part of the Evidence-based Prescription Drug program (EBRx), a service division of the UAMS College of Pharmacy. She leads a Pharmacy & Therapeutics Committee to discover the peer-reviewed, published evidence with emerging and existing drugs and to report these findings to our committee who votes on which drugs to recommend coverage for using the lowest net cost approach. Through this service arm, part of her salary is covered in addition to the IP income (about $450/month) which comes from RxResults, a private pharmacy risk management company. Additionally, she serves as a consultant to Stephens Insurance and receives $25,000 per year. However, she does not take part in the drug selection process.
David Kim, PhD Assistant Professor, University of Chicago	No conflicts to disclose.
Bradley C. Martin, PharmD, PhD Professor, University of Arkansas for Medical Sciences	Dr. Martin receives royalties of approximately $7,500/year from Trestle Tree for the commercialization of an opioid risk prediction tool. He has no other potential conflicts to disclose.
Timothy McBride, PhD Washington University in St. Louis	No conflicts to disclose.
Reem Mustafa, MD, MPH, PhD, FACP	No conflicts to disclose.

Midwest CEPAC Member	Conflict of Interest
Professor of Medicine, Division of Nephrology & Hypertension, Director of Evidence based Practice and Impact Center(EPIC), The University of Kansas Medical Center	
Rachel Sachs, JD, MPH Professor of Law, Washington University in St. Louis School of Law	No conflicts to disclose.
Stuart Winston, DO Patient Experience Consultant, Trinity Health IHA Medical Group	No conflicts to disclose.

Table I2. Clinical and Patient Experts and Conflict of Interest Disclosures

Clinical and Patient Experts	Conflict of Interest
Thomas Crawford, MD, Professor of Neurology and Pediatrics, Johns Hopkins Hospital	Dr. Crawford has served as consultant on advisory panels to Biogen, Avexis, Scholar Rock, Muscular Dystrophy Association, SMA Foundation and CureSMA. Dr Crawford has received compensation for continued conductance of clinical trials by Biogen, Novartis/Avexis, Sarepta, and Scholar Rock, as well as monetary support for participation in advisory boards by Biogen and Scholar Rock in the last 36 months.
Giles Lomax, CEO, Spinal Muscular Atrophy UK	SMA UK received 15.6% of income from pharmaceutical companies including Scholar Rock, Biogen, Novartis, and Roche in 2024/2025.
Hugh McMillan, Professor of Pediatrics/Pediatric Neurologist, University of Ottawa/Children's Hospital of Eastern Ontario	Dr. McMillan serves as a consultant for Novartis, Roche, and Biogen. He also serves as the Principal Investigator for clinical trials for Novartis, Roche, and Biogen, with funds provided to the institution.
Portia Thorman, Head of Advocacy and Community, Spinal Muscular Atrophy UK	SMA UK received 15.6% of income from pharmaceutical companies including Scholar Rock, Biogen, Novartis and Roche in 2024/2025.
Susi Vander Wyk, Executive Director, Cure SMA Canada	Susi is a full-time employee of Cure SMA Canada.

Table I3. Health Care Companies and Conflict of Interest Disclosures

Health Care Company Representatives	Conflict of Interest
Tom Brown, PhD, Vice President, Global Medical Affairs, Scholar Rock	Dr. Brown is a full-time employee of Scholar Rock.
Lindsey Samera, PharmD, Associate Director, PDL Strategy, UnitedHealthcare	Dr. Samera is a full-time employee of United Healthcare.
Emily Tsiao, PharmD, BCPS, Medical Policies Clinical Pharmacist, Premera Blue Cross	Dr. Tsiao is a full-time employee of Premera Blue Cross.