Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value

Final Evidence Report

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Prepared for

ICER Staff and Consultants	The University of Sheffield Modeling Group
Alexandra G. Ellis, PhD Senior Scientist, HTA and Economic Evaluation Institute for Clinical and Economic Review **Kristin Mickle, MPH** (Former) Research Lead, Evidence Synthesis Institute for Clinical and Economic Review **Serina Herron-Smith, BA** Research Assistant Institute for Clinical and Economic Review **Varun M. Kumar, MBBS, MPH, MSc** Health Economist Institute for Clinical and Economic Review **Laura Cianciolo, BA** Program Associate Institute for Clinical and Economic Review **Matt Seidner, BS** Program Director Institute for Clinical and Economic Review **David Rind, MD, MSc** Chief Medical Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review	**Praveen Thokala, PhD, MASc** Senior Research Fellow Health Economics and Decision Science (HEDS), School of Health and Related Research (ScHARR) The University of Sheffield **Matt Stevenson, PhD, BSc** Professor of Health Technology Assessment Health Economics and Decision Science (HEDS), School of Health and Related Research (ScHARR) The University of Sheffield *The role of the University of Sheffield modeling group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the University of Sheffield.

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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The New England Comparative Effectiveness Public Advisory Council (New England CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. The New England CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. This individual should not be considered responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/sma-stakeholder-list/

Expert Reviewer

Katherine Kundrat, PT, DPT
Physical Therapist
Children's National Health System
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

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List of Acronyms 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
CADTH	Canadian Agency for Drugs and Technologies in Health
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMS	Centers for Medicare and Medicaid Services
EAP	Expanded access program
FDA	Food and Drug Administration
GDP	Gross domestic product
GMFM	Gross Motor Function Measure
HINE	Hammersmith Infant Neurological Examination
HFMSE	Hammersmith Functional Motor Scale-Expanded
LCD	Local Coverage Determination
LY	Life year
NCD	National Coverage Determination
NICE	National Institute for Health and Care Excellence
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
RULM	Revised Upper Limb Module
SAE	Serious adverse event
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
UHC	UnitedHealthcare
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost
WHO	World Health Organization
WTP	Willingness-to-pay
6MWT	6-minute walk test

Executive Summary

Update (Added May 24, 2019)

Because of heightened interest in Zolgensma in light of its FDA approval and the limited evidence base at the time of publication of ICER's Final Report, we are including this brief discussion of additional data/interim analyses from ongoing trials of Zolgensma that have been made public through conferences (Muscular Dystrophy Association Clinical and Scientific Conference April 13-17, 2019 and American Academy of Neurology Annual Meeting May 4-10, 2019)[1-3] and manufacturer press releases.[4,5] This is not a systematic review of new evidence. Note that outside of this text box, no other sections of the report have been revised.

- In a Phase III, single-arm trial (STR1VE) of infants with Type I SMA, 21 of 22 infants were alive with a median age of 14.4 months.[5] The death was deemed not related to treatment. Five months after treatment, CHOP-INTEND scores increased by an average of 14.3 points, which was similar to the results from the START trial.
- In another Phase III, single-arm trial (STR1VE EU) of infants with Type I SMA, 1 death was reported by the manufacturer (Novartis/AveXis).[6] The death was attributed to severe respiratory infection with neurological complications and may be treatment-related. An autopsy has been performed but results are not known publicly. No other results from this trial are available as of May 24, 2019.
- In a Phase I dose comparison trial (STRONG) of intrathecal administration of Zolgensma in patients with Type II SMA, treatment was well tolerated with two serious adverse events of transaminase elevation.[5] A number of the patients achieved new motor milestones.
- A Phase III single-arm trial (SPR1NT) evaluated intravenous Zolgensma in presymptomatic patients with SMA and two or three copies of *SMN2*.[5] The patients were six weeks of age or less at the time of treatment. After a median follow-up of 5.4 months (median age 6.1 months), all 18 children were alive and "event free." Among 8 patients with two copies of *SMN2*, all reportedly achieved age-appropriate motor milestones including 4 who could sit without support and 1 who could stand with assistance.

The new data from STR1VE are largely consistent with previously available findings. While the additional death in STR1VE EU is concerning, this additional information does not change the overall conclusions reached in our report regarding treatment in Type I SMA.

No data were available on Zolgensma in patients with Type II SMA at the time of publication of the Final Report and we rated the evidence as insufficient. If further reports from STRONG

confirm the initial findings, a revised evidence rating may include more certainty of at least a small benefit in this patient population.

Similarly, at the time the Final Report was published no data were available on Zolgensma in patients with presymptomatic SMA, and we rated the data as insufficient in the Final Report, in part because of concerns about safety in young infants; some efficacy in patients with presymptomatic SMA and two copies of *SMN2* would have been likely given efficacy in symptomatic Type I SMA. As with Spinraza in presymptomatic SMA, the early results of SPR1NT are encouraging. If further follow-up confirms these initial findings, a revised evidence rating may include more certainty of a substantial benefit in this patient population.

The economic analyses in the Final Report included an analysis of a hypothetical "Drug X" for presymptomatic SMA, assumed to have the one-time administration and pricing structure of Zolgensma and the efficacy of Spinraza. Given the early results of SPR1NT and the FDA approval including presymptomatic SMA patients, some stakeholders may wish to consider the analyses of Drug X in thinking about the value of Zolgensma. A value-based price benchmark for Drug X at $100,000-150,000 per quality-adjusted life year (QALY) gained would be approximately $1.1 million to $1.9 million, and at $100,000-$150,000 per life-year gained (LYG) would be approximately $1.2 million to $2.1 million. These value-based price benchmarks, and the report's existing benchmarks for Spinraza, assume that the US widely and rapidly adopts the recommendation to add screening for SMA to routine newborn screening.[7]

Once additional data (particularly from SPR1NT) are available, ICER may choose to perform a New Evidence Update for Zolgensma. Such an update would likely also review additional data on Spinraza.

Background

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease with the most severe cases affecting infants and young children.[8,9] In the United States (US), SMA incidence is approximately one in 10,000 live births or about 500 new SMA cases per year.[10] 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.[11-13] *SMN1* creates 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. Hence, while the number of *SMN2* copies modulates the severity of SMA, patients without *SMN1* have an insufficient level of SMN protein regardless of the number of *SMN2* copies.[14] 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.[8]

SMA subtypes are related to age of onset and number of motor milestones achieved (see Table ES1 below).[9,15] Type 0 SMA, the most severe subtype, affects individuals before birth and is very rare. Type I SMA (infantile-onset SMA) represents approximately 60% of all diagnosed SMA cases.[10] Approximately 20-30% of patients diagnosed with SMA have Type II and approximately 10-20% have Type III.[9,10] Type IV SMA, a very rare and the least severe subtype, presents in adults.

Table ES1. Clinical Classification of SMA

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of *SMN2* Copies
0	Prenatal/fetal	None	<6 months	1
I	<6 months	Sit with support only	<2 years	1-3
II	6–18 months	Sit independently	>2 years	2-3
III	>18 months	Walk independently	Adulthood	3-4
IV	Adult (20s-30s)	Walk through adulthood	Adult	≥4

Adapted from Table 1 of Verhaart et al. 2017.[9]
Number of *SMN2* copies based on Calucho et al. 2018.[16]

Historically, life expectancy in the most common and severe form of SMA (Type I) was less than two years. Survival depends on respiratory function, and many infants and children eventually require permanent ventilation. SMA does not affect cognitive function, and there is often a contrast between a patient's alertness and ability to move. To maintain mobility and function as long as possible, multidisciplinary, supportive care including respiratory, nutritional, gastrointestinal, orthopedic, and other support is needed.[17-19] Nevertheless, supportive care does not modify disease progression and patients may be entirely dependent on family members and caregivers. The intense care and physical effort involved with caring for a patient with SMA may cause loss of sleep, stress, anxiety, and emotional distress for caregivers.[20,21] Hence, SMA may affect the health-related quality of life of patients as well as their families and caregivers.

Diagnosis of SMA is typically prompted by the clinical symptoms of muscle weakness, and because of SMA's rapid progression, early treatment to preserve motor functioning is important. Currently, only one disease-modifying therapy (nusinersen, Spinraza®, Biogen Idec) has been approved to treat SMA.[22] Spinraza, an antisense oligonucleotide, targets *SMN2* so that it creates more functional SMN protein. It is administered via intrathecal injection (into the fluid surrounding the spinal cord) with four loading doses (day 0, day 14, day 28, and day 63) and maintenance doses every four months thereafter. Spinraza has been studied in patients with or likely to develop SMA Types I-III,[23-25] with several studies ongoing.[26-28] In December 2016, the Food and Drug Administration (FDA) approved Spinraza for the treatment of SMA (any subtype).[22]

A new gene therapy, Zolgensma® (onasemnogene abeparvovec, Novartis/AveXis), is currently in development to treat patients with SMA. Zolgensma, formerly known as AVXS-101, uses the adeno-associated virus serotype 9 vector to deliver a copy of *SMN* to supplement the defective *SMN1*.[29]

Zolgensma is being studied as a one-time, intravenous administration. The FDA granted Zolgensma a Breakthrough Therapy Designation and Fast Track Designation, with an FDA decision expected by mid-2019.[30]

In this report, we review the clinical evidence on both drugs and estimate their long-term cost-effectiveness and potential budget impact.

Insights Gained from Discussions with Patients and Patient Groups

Throughout the conceptualization of this review, we heard from patient advocates and caregivers how devastating the diagnosis of Type I SMA can be and how difficult it is to watch the disease progress in a child. Parents and caregivers feel helpless and fearful while also needing to be vigilant and constantly providing care. Care entails approaches to preserve respiratory and muscle function, including physical therapy, nutritional support, and extensive medical equipment. We heard from adults with SMA how frustrating it is that new interventions have not been commonly studied in adults and that more data are needed in this population, including data on appropriate dosages. Patients and caregivers reported wanting 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. In addition, six families submitted public comments on our Draft Scope, which provided additional context on the experience of children with SMA and their parents. These comments described the devastating urgency of treatment and severity of SMA symptoms, and many described the positive impact of treatment.

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.[31] 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 burden of disease included communication challenges as children with SMA grow, the concern of developing scoliosis (particularly for patients with Type II), 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.

Following our scoping discussions and public comment periods, we updated our draft scope to include efficacy outcomes related to bulbar function (e.g., swallowing, speaking) to better reflect what is important to patients with SMA and their families. These families' experiences provided patient-centered context for interpreting clinical trial outcomes by communicating the importance of independent functioning for older children and adults with SMA, and 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.

ICER also received public comments on its Draft Evidence Report from a mix of patients, patient advocacy organizations, manufacturers, and providers. All three families who provided public comments described children with SMA who are receiving Spinraza; these families all reported a positive outlook on treatment with Spinraza. We also heard from three patient advocacy organizations who provided context about the patient experience living with SMA as well as feedback on key decisions made in the cost-effectiveness evaluation. We also heard from patients at different time points in this review about the spillover effects of this disorder on patients' caregivers, mainly parents, and we explored approaches to incorporate this caregiver burden into our model accordingly. However, due to the methodological uncertainty in estimating caregiver quality of life over a long-term horizon, we did not include this in our analyses. Further details are provided in Section 4.

Potential Cost-Saving Measures in SMA

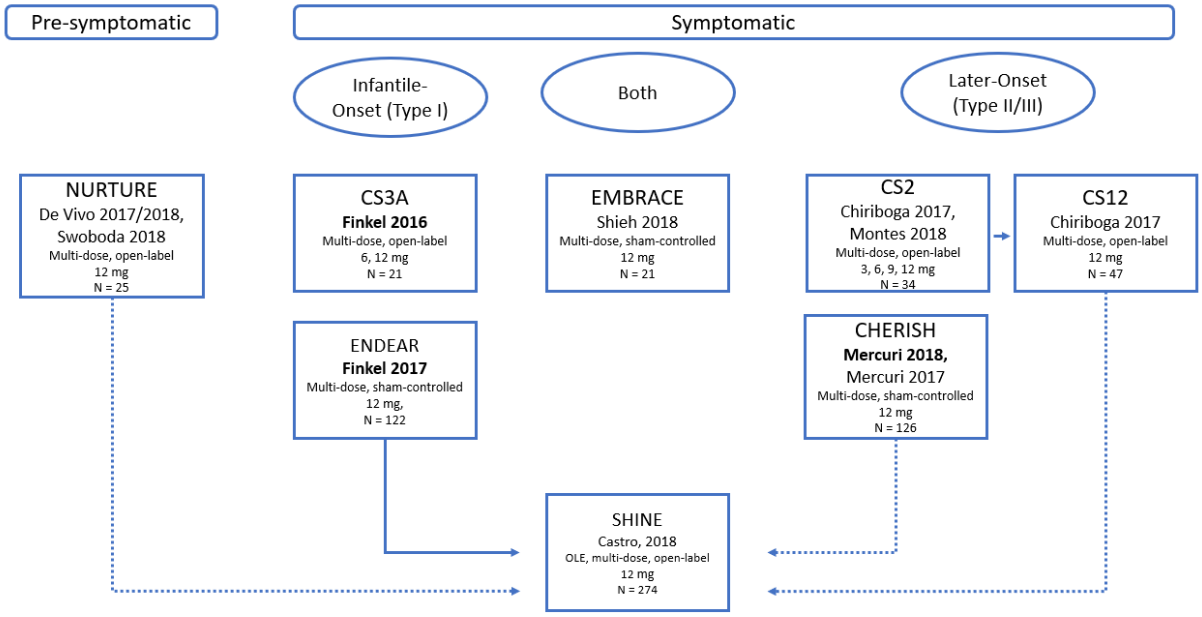
Stakeholders did not identify any opportunities to reduce unnecessary care or other cost-saving measures in the care of SMA that could help provide resources for new treatments.

Comparative Clinical Effectiveness

This review focused on efficacy, safety, and effectiveness of Spinraza and Zolgensma in comparison to supportive care (with or without sham administration) in SMA patients of all ages and types. Below, we summarize the evidence on the following key outcomes: mortality, permanent ventilation, motor function and milestones, and safety.

Spinraza clinical trials include: one randomized controlled trial (RCT) with a sham control (ENDEAR) and one open-label, dose-escalation study (CS3A) in Type I SMA; one RCT with a sham control (CHERISH) and one open-label, multiple dose study (CS2/CS12) in Type II/III SMA; one open-label, single-arm study (NURTURE) in presymptomatic SMA; and one RCT with a sham control (EMBRACE) in patients with Type I, II, or III SMA ineligible for the other trials (Figure ES1). Patients who completed the above trials were eligible to enroll in a single-arm, open-label extension (OLE) study (SHINE). Note that for SHINE, results are currently available for only the patients with Type I SMA who had been enrolled in ENDEAR.

Figure ES1. Clinical Trials of Spinraza



Results are not yet available for the individuals who enrolled in SHINE from the trials indicated with dashed lines.

In addition, we identified three cohort studies of patients with Type I SMA receiving Spinraza through extended access programs and two cohort studies in patients with Type II SMA receiving Spinraza. Details of these studies are described in Section 3 of this report.

The evidence base for Zolgensma consists of one open-label, two-cohort clinical trial (CL-101) in patients with infantile-onset (Type I) SMA and its extension study (START).[29] Note that in CL-101, three infants received a low-dose of Zolgensma and 12 infants received a high-dose of Zolgensma. This Executive Summary focuses on the high-dose cohort only; results from the low-dose cohort are described in Section 3.

We did not identify any studies of patients with Type 0 or Type IV SMA. Below, we summarize the evidence on clinical benefits by type of SMA (infantile-onset, later-onset, presymptomatic). Harms are summarized together for all populations.

Infantile-Onset (Type I) SMA: Clinical Benefits

Evidence Base for Spinraza

We included three clinical trials of Spinraza in infantile-onset (Type I) SMA, including two RCTs with sham control (ENDEAR and EMBRACE)[24,32] and one open-label, dose-escalation study (CS3A).[23] Longer-term results are also available for infants in ENDEAR who enrolled in the single-arm OLE (SHINE).[33]

Note that for ENDEAR, an interim analysis comparing the proportion of Hammersmith Infant Neurological Examination-Section 2 (HINE-2) responders was completed when 78 patients were followed for at least six months ("interim efficacy set": 27 sham control and 51 Spinraza patients; 43 patients were not yet followed for six months).[24] This analysis showed statistical superiority of HINE-2 responders favoring Spinraza and the study was subsequently terminated prior to the planned 13-month follow up. Because of the early termination, there are differences in the number of infants included in the outcomes assessed as noted in the results below.

EMBRACE enrolled infants and children with Type I, II, or III SMA who were ineligible for other Spinraza trials. In this section, we only report on the subgroup of infants with Type I SMA. Results for the subgroup of children with Type II/III SMA are presented in the subsequent section.

Evidence Base for Zolgensma

We included one open-label, two-cohort clinical trial of Zolgensma (CL-101) and its extension study (START) in infantile-onset (Type I) SMA.[29] Below, we present results from the 12 infants in the high-dose cohort.

Baseline Characteristics of Key Trials

Key baseline characteristics of the two key trials (ENDEAR for Spinraza and CL-101 for Zolgensma) are shown in Table ES2. Infants in both trials had two copies of *SMN2*. Note that infants in ENDEAR were diagnosed and treated later, on average, than those in CL-101. Given these differences, direct comparisons between the trials' results should not be made.

Table ES2. Key Baseline Characteristics of ENDEAR and CL-101

	ENDEAR[24]		CL-101[29]
Key Characteristics	**Spinraza**	**Sham Control**	**Zolgensma**
No. of Participants	80	41	12
Age at Onset, months	1.8 (0.5-4.2)*	2.2 (0.2-4.6)*	1.4 (0-3.0)
Age at Diagnosis, weeks	12.6 (0-29)	17.5 (2-30)	8.6 (0-19.4)†
Disease Duration, weeks	13.2 (0-25.9)	13.9 (0-23.1)	NR
Age at Treatment Initiation, months	5.4 (1.7-8.0)‡	6.0 (1.0-8.6)‡	3.4 (0.9-7.9)
Ventilatory Support, n (%)	21 (26)	6 (15)	2 (17)
Nutritional Support, n (%)	7 (9)	5 (12)	5 (42)
Mean HINE-2 Score	1.29 ± 1.07	1.54 ± 1.29	ND
Mean CHOP-INTEND Score	26.63 ± 8.13	28.43 ± 7.56	28 (12-50)

Data are mean (range) or ±SD.
CHOP-INTEND: Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders, HINE-2: Hammersmith Infant Neurological Examination-Section 2, ND: no data, NR: not reported
*Converted from weeks to months by multiplying by 12 months and dividing by 52 weeks.
†Converted from days to weeks by dividing value by 7.
‡Converted from days to months by multiplying by 12 months and dividing by 365 days.

Clinical Benefits: Survival and Permanent Ventilatory Support

In ENDEAR, permanent ventilatory support was defined as ventilatory support or tracheostomy for at least 16 hours per day for 21 days without an acute, reversible event. Spinraza demonstrated a statistically-significant 47% decrease in the risk of death or permanent assisted ventilation compared with sham (HR [95% CI]: 0.53 [0.32, 0.89], p=0.005); 31/80 (39%) of Spinraza and 28/41 (68%) of sham control recipients died or needed permanent ventilatory support.[24] In the sham control group, the median time to death or permanent assisted ventilation was 22.6 weeks, whereas the Spinraza group had not reached this endpoint by the end of the trial. Interim long-term follow-up data from SHINE show the median time to death or permanent ventilation for infants who received Spinraza in ENDEAR and SHINE was 73.0 weeks (95% CI: 36.3, NA).[33]

Seven infants receiving Spinraza in the CS3A study died or required permanent ventilation; because most infants in CS3A were alive and without permanent ventilation, the median age of event-free survival was not reached.[23]

In CL-101, permanent ventilatory support was defined as ventilatory assistance for at least 16 hours per day for at least 14 days without an acute, reversible illness. All infants treated with Zolgensma in CL-101 were alive and event-free through 24 months of follow-up.[29,34] One patient in the low-dose cohort met criteria for permanent ventilatory support but later improved; this patient was considered event-free.

Clinical Benefits: Hammersmith Infant Neurological Examination-Section 2 (HINE-2)

HINE-2 scores or response were reported in three trials of Spinraza (ENDEAR, EMBRACE, CS3A), but this outcome was not measured in the Zolgensma study. HINE-2 consists of eight items to assess infants' changes in head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. Partial attainment of a skill can be captured in subscores. Each milestone is measured on a 3- to 5-point scale with higher scores indicating better functioning. To meet responder criteria, infants had to improve in one or more milestones and show more milestones with improvement than worsening. In ENDEAR, the mean HINE-2 score in infants receiving Spinraza improved over the course of treatment whereas the mean HINE-2 score in infants receiving sham did not improve. In ENDEAR and EMBRACE, high proportions of HINE-2 responders were reported among patients with Type I SMA receiving Spinraza; no one who received sham met responder criteria (Table ES3). In addition, 13 of 15 (87%) children with Type I SMA receiving Spinraza in the CS3A study met identical criteria as HINE-2 responders.[23]

Table ES3. HINE-2 Results for Spinraza in Infantile-Onset (Type I) SMA

	ENDEAR[24]		EMBRACE[35]	
Treatment	Spinraza	Sham Control	Spinraza	Sham Control
Assessment Timepoint	Day 183*		14 months	
No. of Participants	59	23	9	4
Mean Baseline Score, Points	1.29 ± 1.07	1.54 ± 1.29	NR	NR
Mean Change from Baseline, Points	2.4 (2.8, 3.1)	0 (-0.3, 0.3)	NR	NR
Responder†‡, n (%)	21 (41)‡	0‡	7 (78)	0

Data are mean (min, max) or ±SD.

HINE-2: Hammersmith Infant Neurological Examination-Section 2, NR: not reported

*Data estimated from publication by ICER.

†Responder defined as meeting two criteria: score improvement in one or more categories and improvement in more motor milestone categories than worsening.

‡Based on interim data analysis. Denominators were 51 for Spinraza and 27 for sham control.

Clinical Benefits: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)

CHOP-INTEND results were reported in two trials of Spinraza (ENDEAR, CS3A) and in the CL-101 study of Zolgensma. CHOP-INTEND assesses 16 motor skills, and each motor skill is scored from 0 (no response) to 4 (complete response). On average, healthy infants aged three months have a CHOP-INTEND score (range) of 50.1 (32-62) while similarly-aged infants with SMA have an average score of 20.2 (10-33) points.[36] The literature typically cites a 40-point threshold as indicating clinically-meaningful function; it is rare for infants with Type I SMA to ever achieve a score of 40 or more points on the CHOP-INTEND.[37,38] A 4-point change is generally considered an important change in CHOP-INTEND response. Overall, improvements in CHOP-INTEND scores were observed among infants receiving Spinraza or Zolgensma (Table ES4).

Table ES4. CHOP-INTEND Results for Spinraza and Zolgensma in Infantile-Onset (Type I) SMA

	ENDEAR[24]		CS3A[23]	CL-101[29]
Follow-Up	Final analysis*		18 months	Interim analysis†
Treatment	Spinraza	Sham control	Spinraza	Zolgensma
No. of Participants	73	37	14	12
Mean Baseline Score, Points	26.63 ± 8.13	28.43 ± 7.56	30 (17-64)	28.2 (12-50)
Mean Change from Baseline, Points	NR	NR	15.2	24.6
Responder‡, n (%)	52 (71)	1 (3)	12 (86)	NR

Data are mean (range) or ±SD. Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table ES3.

CHOP-INTEND: Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders, NR: not reported

*The final efficacy set included infants with assessments at day 183, 302, or 394 and had at least 190 days or more between their first dose of Spinraza and cut-off date of the interim analysis.

†Data cut-off at August 7, 2017. 7/12 patients had 24 months of follow-up.

‡Responder defined as achieving ≥4-point increase in CHOP-INTEND score.

Clinical Benefits: Specific Motor Milestones

Motor milestones achieved among infants treated with Spinraza (ENDEAR) and Zolgensma (CL-101) are shown below in Table ES5. Among infants with at least six months of follow-up in ENDEAR, no infant who received sham achieved any milestone, whereas 22% of patients who received Spinraza achieved head control and 1% achieved standing with assistance. Long-term follow-up data shows additional motor milestone achievements for infants receiving Spinraza who transitioned from ENDEAR to SHINE. Data from the interim analysis (June 15, 2017) are presented in Table ES6.[33] After 576 days, approximately 45% of infants achieved full head control and 29% achieved sitting independently.

Table ES5. Motor Milestone Results for Spinraza and Zolgensma in Infantile-Onset (Type I) SMA

	ENDEAR[24]*		CL-101[29]†
Other Motor Milestones	Spinraza N=73	Sham Control N=37	Zolgensma N=12
Head Control	16 (22)	0	11 (92)
Roll Over	7 (10)	0	9 (75)
Sitting Unassisted	6 (8)‡	0‡	10 (83)§
Standing with Assistance	1 (1)	0	2 (17)
Standing Independently	NR	NR	2 (17)
Walking Independently	NR	NR	2 (17)

All data are n (%). Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table ES3.
HINE-2: Hammersmith Infant Neurological Examination-Section 2, NR: not reported
*The HINE-2 motor milestone achievements of infants at the later of days 183, 302, and 394. Infants with opportunity for at least a 6-month assessment were included.
†24 month follow-up.
‡Includes "stable sit" and "pivots" from HINE-2.
§Sitting unassisted for at least 10 seconds is in accordance with WHO Motor Milestones criteria.

Table ES6. ENDEAR to SHINE Motor Milestone Achievements in Infantile-Onset (Type I) SMA[33]

	Baseline	Day 64	Day 183	Day 302	Day 394	Day 578	Day 689
No. with Available Data	81	70	65	51	48	31	17
% Achieved Full Head Control	0	7	17	25	33	45	35
% Achieved Independent Sitting	0	1	5	10	15	29	24

Data are from children who received Spinraza in ENDEAR and SHINE.

After 24 months since Zolgensma treatment, 92% of patients achieved head control and 17% could walk independently (Table ES5). Two more children achieved standing with support during additional follow-up in START.[39]

Later-Onset (Type II/III) SMA: Clinical Benefits

Evidence Base for Spinraza

One RCT with sham control (CHERISH) reported on outcomes of Spinraza in children ages two to 12 years with later-onset SMA (Types II or III), and one Phase Ib/IIa open-label, multiple dose study (CS2/CS12) reported on outcomes in children ages two through 15 with later-onset SMA.[25,35] In addition, the sham-controlled EMBRACE trial, which included children with Type I, II, or III, presented results on the subgroup of eight children diagnosed with later-onset (Type II/III) SMA, with broader inclusion criteria than that of CHERISH.

Note that for CHERISH, the sponsor conducted a prespecified interim analysis of the primary outcome (Hammersmith Functional Motor Scale-Expanded; HFMSE) when all children had been enrolled for a minimum of six months **and** 39 or more children had completed 15-month evaluations.[24] Results of the interim analysis showed a statistically-significant benefit on HFMSE score favoring Spinraza, and CHERISH was terminated early.

Evidence Base for Zolgensma

We did not identify any trials assessing Zolgensma in this population.

Clinical Benefits: Survival and Permanent Ventilatory Support

There were no deaths during CHERISH or CS2/CS12, and no data on permanent ventilation were available.

Clinical Benefits: Hammersmith Functional Motor Scale-Expanded (HFMSE)

HFMSE was reported in CHERISH and CS2/CS12.[25,35] The HFMSE is a clinician-rated, 33-item scale developed to assess the motor ability of children with SMA with limited ambulation. Each item in the HFMSE is measured on a 3-point scale with higher scores indicating better functioning. Untreated patients with SMA Type II or III are unlikely to improve by more than 2 points; patients and caregivers consider a 1-point increase to be meaningful.[40,41]

The interim analysis of CHERISH included 15-month data from 39 Spinraza and 19 sham control recipients, which is 43% of the enrolled population; authors imputed data for the remaining 45 Spinraza and 23 sham control recipients. At the interim analysis, Spinraza demonstrated a statistically-superior least-squares mean increase from baseline HFMSE score compared to the sham control (Table ES7), leading to early study termination.[25] For the final analysis, HFMSE data from 18 Spinraza and eight sham control recipients were imputed, as these children still had not yet completed the 15-month assessment. With fewer data imputed, results from the final analysis of mean increase from baseline HFMSE showed a smaller treatment difference than from the interim analysis, although the results remained favorable to Spinraza (mean difference [95% CI]: 4.9 [3.1, 6.7], Table ES7).[25] A greater proportion of children who received Spinraza showed a response of ≥3-point increase in HFMSE score versus the sham control, and the calculated odds ratio favored Spinraza treatment over sham control (odds ratio [OR] [95% CI]: 6 [2-15]).

At study day 253 in CS2/CS12, 9/11 (82%) and 3/16 (19%) SMA Type II and III children improved by ≥3 points from baseline HFMSE.[35]

Table ES7. HFMSE Results from CHERISH in Later-Onset (Type II/III) SMA

CHERISH[25]			
	Spinraza* N=84	Sham Control* N=42	Treatment Difference†
Interim Analysis			
n (%) with 15-Month Data	35 (42)	19 (45)	--
n (%) with HMFSE Data Imputed	49 (58)	23 (55)	--
HFMSE‡ Change from Baseline	4.0 (2.9-5.1)	-1.9 (-3.8-0)	5.9 (3.7, 8.1)
Final Analysis			
n (%) with 15-Month Data	66 (79)	34 (81)	--
n (%) with HFMSE Data Imputed	18 (21)	8 (19)	--
HFMSE‡ Change from Baseline	3.9 (3.0-4.9)	-1.0 (-2.5-5.0)	4.9 (3.1, 6.7)
% of HFMSE Responders§	57 (46-68)	26 (12-40)	OR: 6 (2, 15)

HFMSE: Hammersmith Functional Motor Scale-Expanded, OR: odds ratio

*Data are mean (min-max) or n (%).

†Data are the difference in treatment with Spinraza vs. sham (95% CI).

‡Least-squares mean change from baseline.

§Defined as change from baseline of ≥3 points.

Clinical Benefits: Upper Limb Function

Revised Upper Limb Module (RULM) is an assessment of 19 tasks designed to assess upper limb function in non-ambulatory patients with SMA. Each item is measured on a 3-point scale with higher scores indicating better functioning.[42] In CHERISH, upper limb motor function measured via RULM improved with Spinraza treatment (least-squares mean score [95% CI]: 4.2 [3.4, 5.0]) and remained stable in the sham control group (0.5 [-0.6, 1.6]). The treatment difference for RULM score (3.7 [2.3, 5.0]) was not formally tested for statistical significance.

In CS2/CS12, four of six (67%) children with Type II SMA followed through day 1,050 demonstrated clinically-meaningful improvement (≥2 points) in upper limb motor function, as assessed by ULM. Motor function of all children (n=6) with Type III improved, based on the clinically-meaningful threshold for the 6-minute walk test (6MWT; gain of ≥30 meters).

Clinical Benefits: Specific Motor Milestones

New achievements in walking with assistance, standing alone, and any World Health Organization (WHO) motor milestone in children with later-onset SMA were reported by similar proportions of Spinraza and sham control groups in CHERISH (Table ES8). Note these data were analyzed only among the children who had completed the 15-month assessment (i.e., no data were imputed). One child in each group gained the ability to stand alone, and one child in the Spinraza group achieved walking with assistance.[25] Of the eight children in EMBRACE with later-onset SMA, 2/5

(40%) of those who received Spinraza and 2/3 (66%) of those who received sham achieved standing (Table ES8).

Table ES8. Motor Milestone Results for Spinraza in Later-Onset (Type II/III) SMA

	CHERISH[25]		EMBRACE[43]	
	Spinraza* N=84	Sham Control* N=42	Spinraza N=5	Sham Control N=3
Assessment Timepoint	Final Analysis		Final Analysis†	
N (%) Analyzed	66 (79)	34 (81)	5 (100)	3 (100)
% Who Achieved New WHO Motor Milestone	20 (11-31)	6 (1-20)	NR	NR
Sitting, n (%)	NR	NR	4 (80)	1 (33)
Crawling, n (%)	NR	NR	3 (60)	1 (33)
Standing, n (%)	1 (2)‡	1 (3)‡	2 (40)§	2 (67)§
Walking, n (%)	1 (2)‡	0 (0)‡	1 (20)§	0§

NR: not reported, WHO: World Health Organization
*Data are mean (min-max) or n (%).
†Individuals with 6 month (day 183), 10 month (day 304), and 14 month (day 422) visit included. The last assessment available was used for this analysis.
‡Per WHO motor development milestones definition.
§Per HINE-2 definition.

Presymptomatic SMA: Clinical Benefits

Evidence Base for Spinraza

One ongoing, single-arm study (NURTURE) reported on Spinraza treatment in 25 presymptomatic infants with two or three copies of *SMN2*. Number of copies of *SMN2* is predictive of SMA type, with infants with two copies more likely to have Type I SMA and those with three copies more likely to have Type II/III SMA. In NURTURE, the most recent interim analysis was completed in May 2018, at which time the median age was 26.0 months (range: 14.3-34.3), and median time on treatment was 27.1 months (15.1-35.5).

Evidence Base for Zolgensma

Trials of Zolgensma are ongoing and no data have been presented to date.

Clinical Benefits: Survival and Permanent Ventilatory Support

As of May 2018, all 25 children were alive and no children required permanent ventilatory support. Four (16%) children met the primary outcome of required respiratory intervention (defined as requiring six or more hours per day for seven consecutive days or tracheostomy); all four children

had two *SMN2* copies. All of these children received respiratory intervention during an acute, reversible illness, and none required permanent ventilation or tracheostomy.

Clinical Benefits: CHOP-INTEND

With a median (range) time on treatment of 27.1 months (15.1-35.5), the mean (range) CHOP-INTEND scores for children with two and three *SMN2* copies were similar and reflected near-maximal motor function (two copies: 61.0 [46-64]; three copies: 62.6 [8-64]).

Clinical Benefits: Specific Motor Milestones

By May 2018, caregivers reported all 25 (100%) children had achieved sitting without support, 22/25 (88%) of children had achieved walking with assistance, and 17/25 (68%) had achieved walking alone (Table ES9).

Table ES9. WHO Motor Milestone Achievements for Spinraza in Presymptomatic SMA

WHO Motor Milestone	Expected Age Range of Attainment*	July 2017†‡		May 2018†§	
		2 *SMN2* Copies	3 *SMN2* Copies	2 *SMN2* Copies	3 *SMN2* Copies
Independent Sitting	3.8 – 9.2	14 (93)	8 (80)	15 (100)	10 (100)
Walking with Assistance	5.9 – 13.7	5 (33)	7 (70)	12 (80)	10 (100)
Walking Alone	8.2 -17.6	3 (20)	5 (50)	8 (53)	9 (90)

*Data reported in months. Range defined by 1st-99th percentile for the windows of milestone achievement.
†Data reported as N (%).
‡The median age at the most recent visit was 14.7 months (range: 2.8-23.3).
§The median age at the most recent visit was 26.0 months (range: 14.3-34.3).

All Populations: Harms

Safety data were collected in four clinical trials of Spinraza (ENDEAR, CHERISH, EMBRACE, and SHINE) and in the trial of Zolgensma (CL-101).

Harms with Spinraza

Sixteen percent of infants who received Spinraza and 39% of sham control infants in ENDEAR discontinued study participation due to adverse events (AEs).[24] No children in CHERISH or NURTURE discontinued due to AEs.[25,44]

Treatment-related AEs were rare in all Spinraza trials. Serious AEs were more frequently reported by sham control than Spinraza recipients in ENDEAR (95% vs. 76%, respectively) and CHERISH (29% vs. 17%, respectively).[24,25] Many of the frequently-reported AEs reported following treatment with Spinraza were related to the lumbar puncture procedure (e.g., fever, headache, vomiting, and back pain). Lumbar-puncture-associated AEs were reported only by children in CHERISH; however, this is

likely due in part to the difficulty of collecting this information from infants. Additional common AEs associated with Spinraza include lower respiratory tract infection and constipation. Fever was more common among infants (ENDEAR) than older children (CHERISH) compared to the sham control.

Based on clinical trial data and known side-effects related to oligonucleotides with a phosphorothioate backbones,[45] two safety concerns are highlighted in the Spinraza prescribing information: risk of thrombocytopenia and potential for kidney damage (renal toxicity).[22] FDA-required monitoring to assess patient safety includes coagulation and quantitative spot urine testing prior to each dose.

Harms with Zolgensma

In CL-101, two infants had elevated serum aminotransferase levels after Zolgensma infusion; both were considered treatment related and met criteria for grade 4 AEs.[29] A protocol amendment requiring oral prednisolone treatment (1 mg/kg) for 30 days starting 24 hours prior to Zolgensma infusion was added following the first infant's dosing and subsequent serum aminotransferase elevation. Two infants also experienced asymptomatic elevations in serum aminotransferase levels which were deemed nonserious, treatment-related AEs.

Controversies and Uncertainties

The currently available trials of Spinraza (SMA Types I-III) and Zolgensma (SMA Type I) show prolonged survival and improved motor function compared with historical controls or sham injections. However, there remain several important uncertainties. First, for both interventions, the narrow eligibility criteria of trials and the limited sample size (especially for Zolgensma) raises concerns about generalizability of results to the wider population of patients with SMA. The ineligible or otherwise unselected patients are likely more severely ill, experience different or additional comorbidities (e.g., scoliosis), or have a different genetic profile than those selected for the clinical trials.

In addition, there is a lack of data on the long-term safety and efficacy of both interventions. The currently-available data do not indicate diminishing benefit, which is promising. Nevertheless, because SMA is a rare disease and the trials have short-term follow-up, understanding the long-term effects of Spinraza or Zolgensma will take time. For Spinraza, there is uncertainty in the long-term effects of the repeated lumbar punctures in patients, particularly as they age or progress along the disease course. In terms of other safety concerns, the Spinraza prescribing information notes the risks of thrombocytopenia and renal toxicity. For Zolgensma, there is uncertainty in the duration of expression of the novel gene therapy which may provide life-long benefit to patients. On the other hand, if the expression wanes over time, the subsequent treatment pathway is unclear. If antibodies to AAV form, the patient would be unable to receive another dose of

Zolgensma. In terms of safety, liver toxicity was mitigated by amending the protocol to include an administration of prednisolone before and after Zolgensma infusion. It will be important to monitor liver functioning in patients treated with Zolgensma. Long-term extension studies may provide additional data, and these studies are ongoing.

For Zolgensma, an additional concern is the single-arm design and the small sample size. Comparisons with historical controls can exaggerate perceived treatment effects, particularly when standards of care improve over time or when there is a variable natural history,[46] which are both true of SMA. For example, in older natural history studies, approximately 68% of patients with Type I SMA died by two years of age. In part due to the improvements in and increased utilization of nutritional and respiratory support, more recent estimates of mortality are approximately 30% at two years of age with approximately half of survivors reliant on noninvasive ventilation. In the trial of Zolgensma, although all 12 patients in the high-dose cohort remained alive and not using permanent ventilation at two years, the outcomes that would have been observed had a concurrent control group been included are unknowable.

Given the differences in baseline characteristics between the trials of infantile-onset (Type I) SMA, comparisons between Zolgensma and Spinraza should be avoided. For example, there are differences in age at treatment initiation and duration of disease, which are known to be modifiers of treatment effect. In addition, the time point of analysis (median of approximately nine months in ENDEAR and 24 months in START) and approach for assessing motor milestones (HINE-2 vs. WHO) differs between the studies. There is also an open question regarding the use of combination or sequential therapy with Zolgensma and Spinraza. Some patients who received Zolgensma in START went on to take Spinraza after the trial, but the effects of combination or sequential therapies have not been well studied.

Finally, for presymptomatic patients, the current evidence base is limited. As newborn screening for SMA becomes more common, it is likely that patients will be treated soon, perhaps before developing symptoms. A single-arm, uncontrolled study of Spinraza is ongoing with preliminary results presented only in conference form. A single-arm study of Zolgensma has started, but no results have been presented to date. Presymptomatic treatment may provide more benefit to patients, although there remains uncertainties in the current evidence base.

Summary and Comment

SMA is a rare, genetic neuromuscular disease that causes irreversible motor neuron damage that prevents patients from gaining or retaining motor functions. Survival depends on respiratory function, and many infants and children become permanently ventilated. Considering that SMA is a rare disease, the existing evidence base contains many of the common limitations pervasive in rare disease areas, including a small patient population, clinical trial design challenges, and lack of long-term safety and efficacy data. Overall, where data were available, Spinraza and Zolgensma

demonstrated improvements in motor function, survival, and need for permanent ventilatory support. The current limitations of the clinical evidence for Spinraza and Zolgensma include study populations that limit the generalizability of clinical outcomes to SMA patients who differ from those included in the trials, limited long-term safety (e.g., repeated lumbar puncture procedures) and efficacy data (e.g., durability of novel gene therapy), and the uncontrolled, open-label design of the CL-101 trial of Zolgensma. Should additional data regarding treatment safety and efficacy become available, the conclusions of this report may require updating.

A comprehensive summary of evidence ratings for Spinraza and Zolgensma for each population defined are shown in Table ES10. Additional details are provided in Section 3.5.

Table ES10. Evidence Ratings for Spinraza and Zolgensma for SMA

Population	Spinraza	Zolgensma	Ability to Distinguish?
Type 0 SMA	I*	I*	I†
Infantile-Onset (Type I) SMA	A	A	I
Later-Onset (Type II and III) SMA	B+	I*	I†
Type IV SMA	I*	I*	I*
Presymptomatic SMA	B+	I*	I†

*No studies (e.g., RCTs, observational, etc.) identified.
†Comparison is based on lack of available evidence for Zolgensma.

Spinraza for Infantile-Onset SMA

Based on the evidence, Spinraza demonstrated statistically-significant reductions in the need for ventilatory support and improvements in survival. Spinraza was also superior to standard care in improving motor function and milestone achievement, as measured by the HINE-2 and CHOP-INTEND assessments.

We noted some differences between the Spinraza and sham control groups at baseline which suggests more severe symptoms in the Spinraza group. We also noted potentially limited generalizability, as Type I SMA patients with more severe disease were underrepresented in the trials and may not adequately reflect the "real-world" patient population.

Despite these limitations, we have high certainty that Spinraza provides a substantial net health benefit compared to standard care and rate the evidence as "superior" to standard care (A).

Zolgensma for Infantile-Onset SMA

All infants in the Phase I CL-101 trial were alive following at least 24 months of follow-up. Infants also showed gains in CHOP-INTEND motor milestones and most infants who received the proposed therapeutic dose (cohort two) achieved full head control and rolling over motor milestones.

Despite the limitations of the single-arm, open-label design in which 12 infants received the proposed therapeutic dose, we have high certainty that Zolgensma provides a substantial net health benefit, and rate the evidence base as "superior" to standard care (A).

Zolgensma versus Spinraza for Infantile-Onset SMA

Differences in trial populations related to age at treatment initiation and disease duration limit our ability to adequately distinguish the net health benefit of Zolgensma versus Spinraza for infantile-onset SMA. We therefore rate the evidence to be insufficient (I).

Spinraza for Later-Onset SMA

Based on the single randomized controlled trial of Spinraza in later-onset SMA patients (CHERISH), Spinraza demonstrated statistically-superior improvements in changes from baseline HFMSE, and in the proportion of HFMSE responders, versus the sham control.

Spinraza's superiority in improving HFMSE was evident at the interim analysis, and the study was subsequently terminated early. The interim analysis imputed data from approximately 57% of the enrolled population that had not yet been observed for the full 15-month period. Nevertheless, the final analysis, with 79% (100/126) of patients having been observed for 15-months, continued to show superior benefits of Spinraza on HFMSE scores. Among the 100 patients with observed 15-month data, Spinraza was not superior, however, in improving WHO motor milestone achievements such as unassisted sitting, standing, or walking compared to the sham control.

Similar to ENDEAR, we noted potentially limited generalizability, in that the trial population may not reflect the all patients eligible for treatment. Another limitation is that survival, ventilation, and event-free survival were not evaluated in CHERISH. Finally, we did not find any data regarding long-term safety and durability of clinical benefit.

Overall, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit and rate the evidence as "incremental or better" (B+).

Spinraza for Presymptomatic SMA

Evidence from the NURTURE trial shows all 25 infants enrolled were alive and four (16%) children met the primary outcome of required respiratory intervention, all of whom had two *SMN2* copies. CHOP-INTEND scores for children with two and three copies were similar and reflected near-maximal motor function. Many children with one year of follow-up, however, had developed one or more clinical symptoms of SMA; the severity of these symptoms are not reported. Furthermore, we found only grey literature (i.e., conference presentations), which have not been peer-reviewed.

Overall, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit and rate the evidence as "incremental or better" (B+).

Comparison of Evidence Ratings for Spinraza and Zolgensma

With respect to the comparison of Spinraza and Zolgensma in infantile-onset (Type I) SMA, the evidence base for Spinraza includes multiple randomized placebo-controlled trials, while the evidence base for Zolgensma is primarily an uncontrolled study in 12 patients. Despite the clear differences in evidence bases, in the ICER rating system, we have rated both therapies as "superior" to standard care (A) for patients with infantile-onset SMA. This judgment reflects that while we have far greater uncertainties about the exact net benefits of Zolgensma than Spinraza, the magnitude of effect in these 12 patients was large enough to have high certainty that Zolgensma provides a substantial net health benefit compared with standard care. Additionally, for both therapies, even if efficacy were maintained only for the duration already observed in the studies evaluating them, we would still assign an "A" rating to the therapies. As stated in ICER Evidence Rating Matrix: A User's Guide, "We find it useful to consider that conceptual confidence intervals around a point estimate that do not extend beyond a single box of comparative net health benefit represent a 'high' level of certainty." The ratings of "A" for both therapies should not be interpreted to mean that we are able to state that they have similar net benefits, or that we believe the studies within the evidence bases to be of equal quality. It should also not be interpreted to mean that we have similar "conceptual confidence intervals" around net benefits – we do not. Such conceptual confidence intervals are much wider around the net benefit of Zolgensma than Spinraza. However, in each case we judge that the conceptual confidence intervals do not extend below "substantial" net benefit compared with standard care.

Long-Term Cost Effectiveness

We developed three *de novo* economic models that evaluated the cost-effectiveness of Spinraza and Zolgensma, each compared to best supportive care (BSC), from a US health care sector perspective for patients with SMA, in alignment with ICER's Value Assessment Framework for Ultra Rare Diseases. The models included 1) one for symptomatic patients with infantile-onset (Type I) SMA; 2) one for symptomatic patients with later-onset (Type II/III) SMA; and 3) one for presymptomatic SMA patients. For each population, we estimated the lifetime costs, life years gained, and quality adjusted life years (QALYs) gained, discounted at 3% per annum, for Spinraza and BSC. We used these results to generate incremental cost per QALY gained and incremental cost per life-year gained, comparing Spinraza to BSC. We also estimated these outcomes for Zolgensma among patients with Type I SMA and compared the results of Zolgensma versus BSC. Several scenario analyses evaluated the impact of a different perspective including a modified societal perspective, alternative survival, cost, and utility assumptions. Although we present a scenario analysis that compares Zolgensma to Spinraza, we do not consider this a suitable base case for the purposes of determining long-term value for money or as the basis of a value-based price recommendation as Spinraza is relatively new and our analyses suggest it is not cost effective at usual thresholds.

Performing an analysis on the incremental cost per "equal value of life years gained" (evLYG) was explored for this report. ICER committed to complement its cost per QALY calculations with a cost per evLYG result in order to provide policymakers with a broader view of cost-effectiveness. This new outcome measure was introduced too late in the course of this current review to be able to work out the technical aspects adequately, and therefore the cost per LYG is used as a surrogate result. As with the cost per evLYG, the cost per LYG considers any extension of life at the same "weight" no matter what treatment is being evaluated.

The models were dependent on three constructs: the motor function milestones achieved, need for permanent ventilation, and the time to death. The motor function milestones included sitting and walking. Other interim motor function milestones such as head control, rolling, crawling, and standing were not modelled as explicit health states, but health benefits associated with such improvements were included at utility benefit with interventions. All three models used the same model structure, and contained two main components: 1) a short-term model concordant with clinical study data, and 2) a long-term extrapolation model (Figures ES2 and ES3). Data inputs for the short-term model for each intervention was derived from their respective clinical trials and used directly to elicit patient proportions in each health state at different time points in this model. There is no trial of Zolgensma versus BSC, so data from the BSC arm in ENDEAR was used to inform this comparison.[22]

Figure ES2. Model Schematic for Patients with Infantile-Onset (Type I) SMA and Presymptomatic SMA Patients

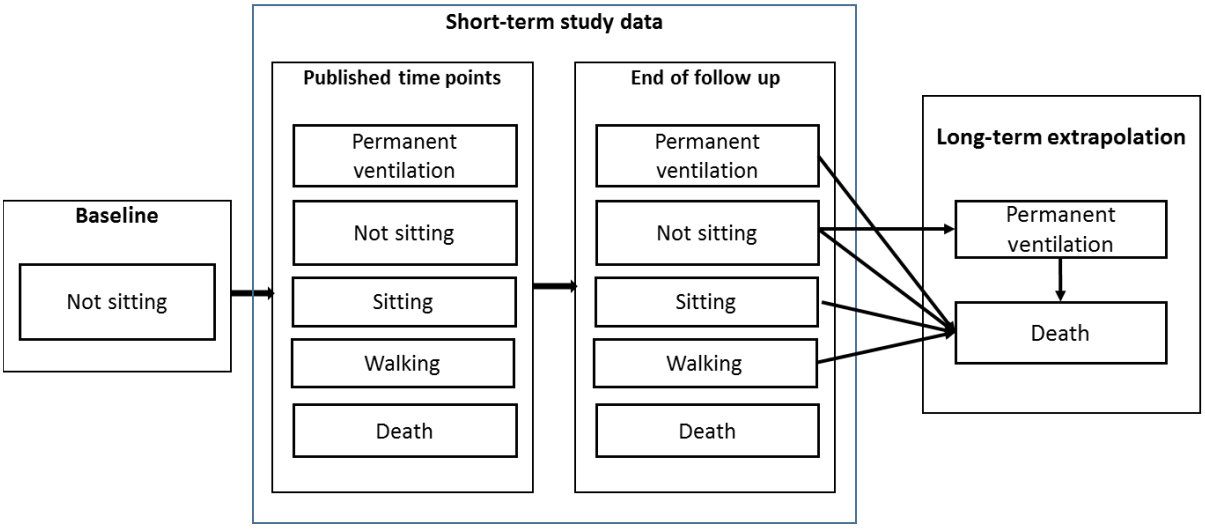
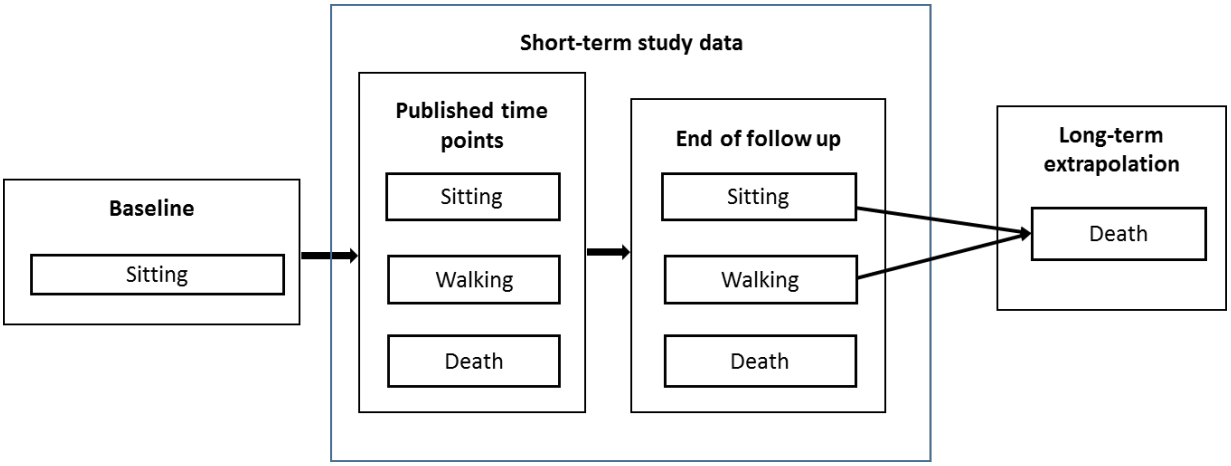


Figure ES3. Model Schematic for Patients with Later-Onset (Type II/III) SMA



The long-term model involved the extrapolation of motor function milestones, permanent ventilation, and mortality, the latter of which was assumed to be conditional on health states, over a lifetime horizon, using monthly (30.44 days) cycles. In the base-case analysis, we assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death (i.e., patients stayed in the same motor function milestone-based health state until death). In addition, we also modeled more conservative scenarios (only for Type I SMA patients) for the interventions where a proportion of patients lost milestones.

Our model was informed by several key assumptions listed below. A comprehensive list of assumptions and accompanying rationales for each assumption is available in Section 4 of the report.

- Our analyses used a naïve comparison between Zolgensma and BSC, and Spinraza and BSC due to non-availability of any published head-to-head trials comparing the two interventions to each other, or Zolgensma to any intervention.
- Data from the trials were used directly in the short-term model.
- In the short-term model for Spinraza, we assumed that the proportion of patients sitting among those alive who are not followed up is the same as the observed proportion of patients sitting among who attended the follow-up visits.
- Motor-function milestone achieved at the end of follow up were sustained until death.
- We assumed a utility benefit in the intervention arms for patients achieving interim motor function milestones such as head control, rolling, crawling, and standing. This was attributed to those patients in the "not sitting" and "sitting" health states.
- Only patients in the "not sitting" health state can transition to "permanent ventilation" state.

- Patients in the "not sitting" health state at the end of the short-term model had the same survival as those on "permanent ventilation." This assumption is favorable to the drugs given that observational data suggest lower mortality for patients on permanent ventilation compared to those who were unable to sit.
- In the BSC arm, we used a partitioned survival approach to model at the end of the short-term model to estimate transitions to death and permanent ventilation from the "not sitting" health state. In the intervention arms we assumed the same mortality for those in the "not sitting" state as those in the "permanent ventilation" state.
- We assumed a treatment stopping rule at 24 months for patients on Spinraza who did not achieve motor function milestones with the treatment.

Model inputs pertaining to proportions in each health state vary by intervention and target population. As mentioned earlier, trial-specific inputs informed the short-term model directly, while the long-term model extrapolation was dependent on the health state patients were in at the end of the short-term model for each intervention. In the SMA Type I model, for Spinraza, data for the short-term model was derived from the ENDEAR and SHINE trials.[22,33] The true proportion of patients on Spinraza who achieved motor-function milestones was derived using a multi-stage process which is described in more detail in Appendix Table E2. No patient in the BSC arm achieved any motor function milestones according to trial data. For Zolgensma, the short-term model data was shared by the manufacturer. All patients achieved motor function milestones. Based on the observed data, we assumed that a third of patients in the "sitting" health state in this arm also received Spinraza at the end of the short-term model, with an additional assumption that 50% of those who received the additional Spinraza treatment dropped a milestone (to "not sitting").

Mortality for patients on Spinraza and BSC were derived from the ENDEAR and SHINE, and ENDEAR trials, respectively.[22,33] No patient on Zolgensma died,[29] and while we modeled this as per trial data, we acknowledge the uncertainty around this due to the small sample size in the Zolgensma trial. Inputs on permanent ventilation were derived from the ENDEAR and SHINE, and SHINE trial for Spinraza and BSC, respectively.[22,33] As per Zolgensma's trial data, we modeled no transition to permanent ventilation for patients in this treatment arm.[29]

In the later onset SMA (Type II/III) population, based on trial data, all patients on Spinraza and BSC remained in the sitting health state in the short-term model. No data exists for Zolgensma in this population. For the pre-symptomatic SMA population, data on Spinraza's effectiveness in achieving motor function milestones was derived from the NURTURE trial,[28] and assumed that 60%, 30% and 10% of all patients in this group had SMA Types I, II and II, respectively, based on real-world evidence on *SMN2* copies predicting SMA type.[9,10]

For the long-term model, patient proportions in different health states ("permanent ventilation," "not sitting," "sitting," or "walking") based on motor function milestones at the end of the short-term model were assumed to remain unchanged until death. In a more conservative scenario

analysis, we assumed deterioration of milestones, specifically from the "sitting" health state. We modeled transition to "permanent ventilation" or "death" from the "not sitting" health state in the BSC arm alone. For those "not sitting" who transition to death, we included the cost of permanent ventilation in the three months leading to death. Patients in the "not sitting" and "permanent ventilation" health state were assumed to have the same mortality, to account for the survival benefit gained from achieving interim milestones for those on the interventions when in the "not sitting" health state. This is an assumption favorable to the drug given that observational data suggest lower mortality for patients on permanent ventilation compared to those who were unable to sit. Mortality from all health states were modeled using best fitting parametric curves that were derived from digitized published Kaplan Meier (KM) curves.[24,47,48] Details on this can be found in Section 4 and Appendix Tables E3-E6 of the report.

Utility estimates for patients in the different health states were derived from several sources.[49,50,51] Patients in the walking state were attributed general population age-dependent utilities. We assumed additional utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. This was implemented in the model as an additional utility of 0.1 compared to BSC for the "not sitting" health state and an additional utility of 0.05 compared to BSC for the "sitting" health state. Costs in the models included those of the interventions, their associated administration and monitoring costs, and costs of health care resources used, as well as non-medical costs associated with professional caregiving. A detailed sub-section of costs used in the model can be found in Section 4 of the report. For Spinraza, due to the nature of its administration in a hospital setting, we included a hospital mark-up. For Zolgensma, we used a placeholder one-time cost of $2 million for the base-case analysis. For a scenario analysis using a modified societal perspective, we also included societal costs in the form of patient productivity gains costs.

In addition to the base-case analyses, we conducted one-way and probabilistic analyses, threshold analyses (for price) as well as specific scenario analyses. Separate scenario analyses were conducted based on input and evidence provided by stakeholders, manufacturers, and informed by internal discussions. Some of the key scenarios include 1) a modified societal perspective, 2) excluding health care costs directly related to treatment, 3) a comparison of Zolgensma to Spinraza, 4) using different utility or cost estimates, 5) not accounting for the utility benefit gained from achieving interim milestones, 6) shorter time horizon, and 7) alternative discount rate. A full list of scenario analyses conducted is available in Section 4 of the report.

Model Validation

Several approaches were undertaken to validate the model. First, preliminary methods and results were presented to manufacturers, patient groups, and clinical experts, with data inputs changed as needed and scenario analyses defined. Second, model input parameters were varied to evaluate the face validity of changes in results. As part of ICER's initiative for modeling transparency, we

shared the model with AveXis for external verification shortly after publishing the draft report for this review. Biogen chose not to receive the model. The outputs from the model were validated against the trial and study data of the interventions as well as any relevant observational datasets. Finally, the results were compared to other cost-effectiveness models in this therapy area.

Results

Infantile-Onset (Type I) SMA Model

Results from the health care sector perspective for both interventions are presented below in Tables ES11 and ES12. Results for Zolgensma were derived using a placeholder price of $2,000,000. Both interventions resulted in more QALYs and life years gained relative to BSC, resulting in incremental cost effectiveness ratios of approximately $1.1 million per QALY for Spinraza and approximately $243,000 per QALY for Zolgensma. The cost per life year (LY) gained for Spinraza and Zolgensma were approximately $590,000 and $182,000, respectively.

Table ES11. Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,231,000	$1,653,000	$3,884,000	3.24	7.64	$1,112,000	$590,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table ES12. Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,657,000	$3,657,000	12.23	18.17	$243,000	$182,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

We found from the one-way sensitivity analyses that the utility when in the "sitting" health state and the health care costs in the "not sitting" health state influenced model results the most for Spinraza, and for Zolgensma the factors that most affected the results were the cost and utility associated with the "sitting" health state. Probabilistic analyses showed that for Spinraza, none of the simulations produced incremental results that were cost-effective up to a threshold of $500,000

per QALY. For Zolgensma, all simulations produced results that were cost-effective at and above a threshold of $300,000 per QALY.

The modified societal perspective scenario analyses produced results very similar to those seen using the health care sector perspective. The results of the modified societal perspective analysis are presented in the main report in Tables 4.17 and 4.18. In the scenario analysis excluding intervention background health care costs, results were more favorable to both interventions with incremental cost effectiveness ratios versus BSC at approximately $810,000 per QALY for Spinraza and approximately $170,000 per QALY for Zolgensma.

Table ES13 presents the results for a scenario analysis comparing Zolgensma with Spinraza from the health care sector perspective. Instead of a naïve comparison that used the costs, QALYs, and LYs for Zolgensma and Spinraza from their respective comparisons with BSC, we performed a separate analysis incorporating the add-on costs of Spinraza in the Zolgensma arm (as opposed to assuming that a proportion of the patients lose a milestone in the base-case analysis). This analysis assumed that 33% of the patients in the "sitting" state of the Zolgensma arm (i.e., 25% of overall patients) receive Spinraza according to the standard dosing regimen after the end of the short-term model.

The total costs in the Zolgensma arm were approximately $5.3 million with 13.46 QALYs and 19.76 LYs gained. The costs are higher than in the base case for Zolgensma versus BSC due to the additional costs associated with Spinraza treatment. However, the QALYs and LYs are also higher than in the base case, as this analysis does not assume any loss of milestones. The total costs in the Spinraza arm were around $3.9 million with 3.24 QALYs and 7.64 LYs gained. This resulted in an incremental cost per QALY gained of approximately $139,000 and an incremental cost per LY gained of $117,000 for Zolgensma compared to Spinraza.

Table ES13. Results for Zolgensma versus Spinraza in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$3,630,000*	$1,671,000	$5,301,000	13.46	19.76	$139,000	$117,000
Spinraza	$2,231,000	$1,653,000	$3,884,000	3.24	7.64	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Includes the Zolgensma costs (placeholder price of $2 million) and additional Spinraza costs.

Results of all other included scenario analyses produced results similar to the base-case analyses for both interventions. These results can be found in Tables 4.20 and 4.21 of the report for Spinraza and Zolgensma, respectively.

Later Onset (Type II/III) SMA Model

Results for this population are specific to Spinraza alone since no published data on Zolgensma's effectiveness in this population exists. Since none of the patients were able to walk as per trial data in this population, QALY differences were minimal between Spinraza and BSC, with Spinraza resulting in marginally more QALYs due to utility benefit associated with achieving interim milestones.

Table ES14. Results for Spinraza versus BSC in Later Onset SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$7,634,000	$1,514,000	$9,148,000	12.28	18.90	$8,156,000	Dominated
BSC	$0	$1,442,000	$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

One-way sensitivity analyses were not performed for this model as parameters were the same in both arms, except for drug cost and the utility benefit for achieving interim milestones in the Spinraza arm, which was considered in scenario analyses. Probabilistic analyses showed that Spinraza did not achieve a greater than zero likelihood of meeting the $500,000/QALY or lower threshold across the range of values tested. Results from the societal perspective scenario analysis were similar to those from the health sector perspective. Other scenario analyses results pertaining to this population are presented in Table 4.3 and Appendix Tables E32 to E34 of the report. Threshold analyses indicated that no annual price of Spinraza was attainable at the $50,000 per QALY threshold due to the additional fixed administration costs coupled with a marginal utility benefit in the Spinraza arm for achieving interim milestones. At other thresholds between $100,000 per QALY and $500,000 per QALY its annual price ranged from approximately $1,100 to approximately $20,000 in this target population.

Presymptomatic SMA Model

Results for the presymptomatic SMA population are specific to Spinraza alone since no published data on Zolgensma's effectiveness in this population exists. It must be noted that these results are based on the proportion of Type I, II, and III SMA patients derived primarily from natural history data and these results may not be generalizable to a population with different proportions. From the health care sector perspective, the cost per QALY and cost per LY gained were approximately $709,000 and $652,000 respectively (Table ES15).

Table ES15. Results for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$10,565,000	$1,364,000	$11,929,000	21.94	26.58	$709,000	$652,000
BSC	$0	$801,000	$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

The key drivers of uncertainty included monthly costs in the "walking" health state and the utility in the "sitting" health state. Spinraza did not achieve a greater than zero likelihood of meeting $500,000/QALY or lower thresholds across the range of values tested.

In a scenario analysis taking a modified societal perspective, the cost per QALY and cost per LY gained were approximately $687,000 and $632,000, respectively. A list of additional scenario analyses results specific to this population are listed in Table 4.34 and Appendix Tables E39 to E43 of the report.

We received comments suggesting that Zolgensma could be approved by the FDA with an indication encompassing use among presymptomatic patients. Since there are no data on the effectiveness of Zolgensma in this population, we decided to conduct a scenario analyses for a hypothetical drug ("Drug X") treatment which had the one-time costs of Zolgensma with the unrelated health care costs, QALYs, and LYs associated with Spinraza in presymptomatic SMA patients. This analysis which was conducted from a health care sector perspective resulted in Drug X having a cost per QALY and cost per LY gained at approximately $157,000 and $144,000, respectively (Table ES16).

Table ES16. Hypothetical Drug X for Presymptomatic SMA: Health Care Sector Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Drug X	$3,264,000	21.94	26.58	$157,000	$144,000
BSC	$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Threshold analyses indicated that Spinraza's annual price to achieve thresholds of $50,000 to $500,000 per QALY ranged from approximately $8,000 to approximately $264,000 in this target population.

Limitations

Our analyses have several limitations that are fully addressed in the main report. Despite remaining uncertainty, we believe that the additional scenario analyses and sensitivity analyses allowed us to have confidence that our base-case results represent the best estimate of the clinical and economic effects of treatment.

Summary and Comment

For Spinraza, our base-case results found that, at its current price, it does not meet traditional cost-effectiveness thresholds in any population of use. Its cost-effectiveness is best in the presymptomatic population, but even there its price would need to be reduced below $65,000 per year to meet a $150,000 per QALY threshold. For later-onset SMA the incremental cost-effectiveness of Spinraza was over $8 million per QALY gained, as current evidence did not demonstrate life extension and the benefits of treatment translate to small improvements in quality of life compared to best supportive care.

For Zolgensma at a placeholder price of $2 million, our base-case results found that it too does not meet traditional cost-effectiveness benchmarks for use for patients with Type I SMA and would have to have its price reduced to under $900,000 for the one-time administration to meet a $150,000 per QALY threshold. However, using a cost per LYG threshold, the price for Zolgensma could be set near $1.5 million to meet a $150,000 per LYG threshold.

In order to provide policymakers with a broad view of cost-effectiveness, we have sought to enhance the visibility of the cost per LY gained results in conjunction with those arising from cost per QALY calculations. The cost per LYG approach values any life extension, even at a very low quality of life, as equal to life extension at full health. Cost per LYG does not capture improvements in quality of life as intended by ICER's stated goal of highlighting an "equal value for life-year gained" (evLYG) measure, but for this review it was not possible to construct a feasible technical approach to create an evLYG for this model. Therefore, viewing results of both the cost per LY gained and the cost per QALY gained will ensure that policymakers can feel confident that they are considering information that poses no risk of discrimination against this patient group.

Our economic evaluation included multiple analyses targeting different SMA sub-populations. We also conducted numerous scenario analyses to explore questions about the best way to model the connection between motor skill improvements and quality of life, the impact of different time horizons and of a societal perspective on modeling results, and the relevance of substantial non-drug health care costs that continue to accrue when a treatment extends life. Except for one scenario analysis, we assumed in all other analyses that the short-term benefits of both treatments persist for a lifetime. Although there remains substantial uncertainty about whether this will prove true, input from clinical experts and judgments based on the mechanism of action of the two

treatments leads us to believe that our base-case assumption of lifetime durability of benefit, while it may be viewed as optimistic by some, is the best starting point for a judgment of the value of these treatments at this time.

Among the most challenging aspects of this cost-effectiveness analysis has been uncertainty about the future clinical use of these treatments. Will they be used primarily for presymptomatic patients? With data demonstrating effectiveness of Spinraza in this population, this evolution seems quite likely, a judgment confirmed by input from clinical experts. For Zolgensma the future is less clear due to the fact that it has not yet been studied in presymptomatic patients. But with the possibility of its use in this population we decided to create a hybrid "Drug X" that had the placeholder cost of Zolgensma and the effectiveness of Spinraza in this population. Given that Drug X is administered as a one-time infusion, we found its cost-effectiveness very near traditional ranges assuming a placeholder price of $2 million. There is obviously substantial uncertainty in the potential effectiveness of Zolgensma in the presymptomatic population, but our hypothetical Drug X results may serve as a starting point for policy debates should the FDA approval language suggest that Zolgensma may be used in this population even without supporting clinical data.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits

Table ES17. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	Zolgensma is a one-time, intravenous administration which may reduce complexity and reduce caregiver burden compared with repeated lumbar punctures with Spinraza. As a one-time administration, there may also be reduced complexity for patients and caregivers navigating insurance policies.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	No impact identified.
This intervention will significantly reduce caregiver or broader family burden.	Effective treatment with Spinraza or Zolgensma may reduce anxiety and stress among caregivers and wider communities. As a one-time, intravenous injections, Zolgensma may also reduce reduced burden for patients and caregivers. Furthermore, effective treatment with

	Spinraza or Zolgensma may lead to incremental improvements in motor abilities, which can allow patients greater ability for self-care and independence.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	Spinraza has a novel mechanism of action and is the first FDA approved treatment that modifies disease progression. Zolgensma is a novel gene therapy which also modifies disease progression.
This intervention will have a significant impact on improving return to work and/or overall productivity.	For both interventions, if treatment improves or retains children's mobility, children may attend school and caregivers may return to work.
This intervention will have a significant positive impact outside the family, including communities.	Effective treatment with Spinraza or Zolgensma may reduce other resources used (e.g., in schools) and promote more interaction between children with SMA and others in the community.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	Spinraza is the first FDA approved treatment that modifies disease progression. The availability of a disease-modifying treatment has paved the way for newborn screening, which may help to identify and subsequently treat infants with SMA sooner.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	No impact identified.

Contextual Considerations

Table ES18. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	SMA is a condition of particularly high severity and rapid progression, with the most severe cases affecting infants and young children. In the most common and severe form of SMA, estimates of the median age at death range from 10.4 months up to four years.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	SMA is a genetic condition that affects patients and caregivers throughout their lives. Supportive care does not modify disease progression, and patients may be entirely dependent on family members who expend intense emotional and physical effort when constantly caring for a patient.
This intervention is the first to offer any improvement for patients with this condition.	Spinraza is the first FDA approved treatment that modifies disease progression.
There is significant uncertainty about the long-term risk of serious side effects of these interventions.	Uncertainties remain regarding the long-term use of Spinraza with respect to repeated lumbar punctures. The

	long-term safety of a gene therapy like Zolgensma has not been established.
There is significant uncertainty about the magnitude or durability of the long-term benefits of these interventions.	The long-term effects of Spinraza or Zolgensma will take time to emerge as SMA is a rare disease and the trials have short-term follow-up.
There are additional contextual considerations that should have an important role in judgments of the value of these interventions.	No impact identified.

Value-Based Benchmark Prices

Our value-based price benchmarks for Spinraza and Zolgensma are presented in Table ES19. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. Value based prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]) and as one-time cost for Zolgensma. We did not use the modified societal analysis results as a dual base case for this review because we did not feel these drugs met the criterion that "the impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial and these costs are large in relation to health care costs" as described in the Value Assessment Framework for Ultra Rare Diseases.

We note that for treatments of ultra-rare disorders, decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than those applied to decisions about other treatments. We there include below full threshold price analyses for both drugs, ranging from $50,000-$500,000 per QALY and per LYG.

For Spinraza, we believed that the most relevant population on which to base a value-based price benchmark is the presymptomatic SMA population. This decision is based upon our judgment that Spinraza is most likely to be used in this population now that there are data supporting its effectiveness. SMA has been added to the Recommended Uniform Screening Panel for newborns in the US,[52] making it likely that many patients will be identified and treated before symptoms develop. Given the greater magnitude of clinical benefit seen in this group, our results suggest that the cost-effectiveness of Spinraza is best when used before symptoms appear.

For Zolgensma, the value-based benchmark price was estimated in the SMA Type I population as this is the only population in which it has been evaluated, and although its use in presymptomatic infants will be considered by clinicians and families, data are not yet available from its use in this population.

Table ES19. Value-Based Benchmark Prices of Spinraza and Zolgensma

	List Price + Estimated Mark-Up	Population	VBP at $100,000 per QALY Threshold	VBP at $150,000 per QALY Threshold	Discount Required to Achieve Threshold Prices
Spinraza	$382,500	Presymptomatic SMA	$36,400*	$64,800*	83% to 90%
Zolgensma	$2,000,000†	Infantile-Onset (Type I) SMA	$310,000	$899,000	N/A as real-world price is unknown

QALY: quality-adjusted life year, VBP: value-based benchmark price

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+. Year one value-based benchmark prices are $72,800 to $129,400 due to the required loading doses.

†Placeholder price.

As described earlier, we are increasing reference to the cost per LYG figures to ensure that policymakers are aware of the complementary information these results can provide to the cost per QALY findings. The annual price at which Spinraza meets the $100,000 to $150,000 per LYG range for use in presymptomatic patients is $41,400 to $72,300. This range is quite similar to the cost/QALY range. For Zolgensma, however, there is notable difference. The relevant cost per LYG price range for Zolgensma when used for Type I SMA is $710,000 to $1,498,000 for the $100,000 to $150,000 per LYG thresholds.

Broader Threshold Price Analyses

Table ES20 presents the threshold price results for Spinraza compared to BSC for presymptomatic individuals at thresholds from $50,000 to $500,000 per QALY gained and per LY gained. Threshold prices are reported as annual costs for Spinraza, including administration fees.

Table ES20. Threshold Prices for Spinraza in Presymptomatic SMA

	Per QALY*	Per LY Gained*
Threshold Price at $50,000/QALY	$8,000	$10,500
Threshold Price at $100,000/QALY	$36,400	$41,400
Threshold Price at $150,000/QALY	$64,800	$72,300
Threshold Price at $200,000/QALY	$93,200	$103,000
Threshold Price at $300,000/QALY	$150,000	$165,000
Threshold Price at $500,000/QALY	$264,000	$289,000

LY: life-year, QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Table ES21 presents the threshold price results for Zolgensma compared to BSC in Type I SMA at thresholds from $50,000 to $500,000 per QALY gained and per LY gained. Threshold prices are reported for the one-time cost for Zolgensma.

Table ES21. Threshold Prices for Zolgensma in Type I SMA

	Per QALY*	Per LY Gained*
Threshold Price at $50,000	--	--
Threshold Price at $100,000	$310,000	$710,000
Threshold Price at $150,000	$899,000	$1,498,000
Threshold Price at $200,000	$1,488,000	$2,287,000
Threshold Price at $300,000	$2,666,000	$3,865,000
Threshold Price at $500,000	$5,021,000	$7,020,000

LY: life-year, QALY: quality-adjusted life year

*Threshold prices are based on a one-time cost for Zolgensma.

Potential Budget Impact

We used the cost-effectiveness model to estimate the potential budgetary impact of Zolgensma in the SMA Type I population relative to BSC. Given that Spinraza is currently available, we conducted a scenario analysis in which we measured the potential budgetary impact of Zolgensma relative to a 75:25 Spinraza:BSC mix in the same patient population. Our analyses were conducted using the placeholder price ($2 million), price to reach $150,000 per QALY ($898,976) and $100,000 per QALY ($310,097) thresholds for Zolgensma, and the scenario analysis used the net price for Spinraza. Because of high background health care costs in SMA, there was no price of Zolgensma that achieved an incremental cost effectiveness ratio of $50,000 per QALY. Based on published estimates, we calculated the incident SMA Type I population at 215 patients each year.

Table ES22 and ES23 illustrate the results of our budget impact analyses. Compared to BSC alone, the annual per-patient potential budgetary impact for Zolgensma ranged from approximately $174,500 at the price to reach the $100,000 per QALY threshold to approximately $946,300 at its placeholder price. At Zolgensma's placeholder price, treating the entire target population would reach approximately 45% of the ICER annual potential budget impact threshold of $991 million. Compared to the Spinraza:BSC mix, Zolgensma's annual per-patient potential budgetary impact ranged from cost-savings of approximately $198,700 at the price to reach the $100,000 per QALY threshold to approximately $573,100 in additional costs at its placeholder price. In this scenario, treating the entire target population would reach 24% of the $991 million threshold using the placeholder price for Zolgensma.

Table ES22. Per-Patient Budget Impact Calculations for Zolgensma Compared to BSC, Over a Five-Year Time Horizon

	Average Annual per Patient Budget Impact		
	Assumed Placeholder	$150,000/QALY	$100,000/QALY
Zolgensma*	$1,113,600	$610,800	$341,900
BSC	$167,400		
Difference	$946,300	$443,500	$174,500

QALY: quality-adjusted life year, WAC: wholesale acquisition cost
All costs rounded to the nearest $100.
*Based on a placeholder price of $2,000,000.

Table ES23. Per-Patient Budget Impact Calculations for Zolgensma Compared to Spinraza/BSC (75%/25%), Over a Five-Year Time Horizon

	Average Annual per Patient Budget Impact		
	Assumed Placeholder	$150,000/QALY	$100,000/QALY
Zolgensma*	$1,113,600	$610,800	$341,900
Spinraza/BSC (75%/25%)	$540,600		
Difference	$573,100	$70,300	-$198,700†

QALY: quality-adjusted life year, WAC: wholesale acquisition cost
All costs rounded to the nearest $100.
*Based on a placeholder price of $2,000,000.
†Cost-saving.

With the recent FDA recommendation on newborn screening for SMA and its increasing adoption in many states,[52,53] we felt it pertinent to include a scenario comparing Spinraza to BSC in the presymptomatic SMA population. Due to a lack of published data on the efficacy of Zolgensma in this particular population, we could not undertake a similar budget impact analysis for the gene therapy. At Spinraza's net price, the per patient annual potential budgetary impact versus BSC was estimated to be approximately $573,900. When treating the entire eligible population (approximately 370 patients annually), potential budget impact reached 58% of the $991 million threshold.

New England CEPAC Votes

The New England Comparative Effectiveness Public Advisory Council (CEPAC) deliberated on key questions raised by ICER's report at a public meeting on March 7, 2019 in Boston, Massachusetts. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

Patient Population for questions 1-3: Patients with infantile-onset (Type I) spinal muscular atrophy (SMA).

1) Is the evidence adequate to demonstrate that the net health benefit of nusinersen (Spinraza, Biogen Inc.) added to supportive care is superior to that provided by supportive care alone?

Yes: 12 Votes	No: 0 Votes

2) Is the evidence adequate to demonstrate that the net health benefit of onasemnogene abeparvovec (Zolgensma, AveXis/Novartis AG) added to supportive care is superior to that provided by supportive care alone?

Yes: 12 Votes	No: 0 Votes

3) Is the evidence adequate to distinguish the net health benefit between Spinraza and Zolgensma?

Yes: 0 Votes	**No: 12 Votes**

Patient Population for question 4: Patients with later-onset (Type II/III) SMA.

4) Is the evidence adequate to demonstrate the net health benefit of Spinraza plus supportive care is superior to that provided by supportive care alone?

Yes: 12 Votes	No: 0 Votes

Patient Population for questions 5-6: Patients with presymptomatic SMA.

5) Is the evidence adequate to demonstrate the net health benefit of administering Spinraza prior to development of symptoms is superior to that of supportive care alone?

Yes: 10 Votes	No: 2 Votes

6) Is the evidence adequate to demonstrate the net health benefit of administering Zolgensma prior to development of symptoms is superior to that of supportive care alone?

Yes: 0 Votes	**No: 12 Votes**

7) Is it likely that treatment with Spinraza offers one or more of the following potential "other benefits" that are not adequately captured in the base case cost-effectiveness model?

Spinraza offers reduced complexity compared to other treatment options that will improve patient outcomes in the real world.	N/A
Spinraza has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	N/A
Spinraza will significantly reduce caregiver or broader family burden.	12/12
Spinraza will have a significant impact on improving patients'/caregivers' ability to return to work and/or their overall productivity.	10/12
Spinraza will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	12/12
There are other important benefits – or disadvantages – that should have an important role in judgments of the value of Spinraza.	N/A

8) Are any of the following contextual considerations important in assessing Spinraza's long-term value for money?

Spinraza is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	11/12
Spinraza is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	11/12
Spinraza was the first to offer any improvement for patients with this condition.	12/12
Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of Spinraza.	7/12
Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of Spinraza.	7/12
There are additional contextual considerations that should have an important role in judgments of the value of Spinraza.	NA

9) Is it likely that treatment with Zolgensma offers one or more of the following potential "other benefits" that are not adequately captured in the base case cost-effectiveness model?

Zolgensma offers reduced complexity compared to other treatment options that will improve patient outcomes in the real world.	12/12
Zolgensma will significantly reduce caregiver or broader family burden.	11/12
Zolgensma has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	N/A
Zolgensma will have a significant impact on improving patients'/caregivers' ability to return to work and/or their overall productivity.	10/12
Zolgensma will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	11/12
There are other important benefits – or disadvantages – that should have an important role in judgments of the value of Zolgensma.	N/A

10) Are any of the following contextual considerations important in assessing Zolgensma's long-term value for money?

Zolgensma is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	10/12
Zolgensma is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	10/12
Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of Zolgensma.	6/12
Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of Zolgensma.	7/12
There are additional contextual considerations that should have an important role in judgments of the value of Zolgensma.	N/A

11) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Spinraza versus supportive care alone in patients with infantile-onset (Type I) SMA?

Low Long-Term Value for Money: 12 Votes	Intermediate Long-Term Value for Money: 0 Votes	High Long-Term Value for Money: 0 Votes

12) No vote was taken, as Zolgensma did not have a publicly-known price at the time of the meeting.

13) No vote was taken, as Zolgensma did not have a publicly-known price at the time of the meeting.

14) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Spinraza versus supportive care in patients with later-onset (Type II/III) SMA?

Low Long-Term Value for Money: 12 Votes	Intermediate Long-Term Value for Money: 0 Votes	High Long-Term Value for Money: 0 Votes

15) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Spinraza before symptoms develop versus best supportive care?

Low Long-Term Value for Money: 12 Votes	Intermediate Long-Term Value for Money: 0 Votes	High Long-Term Value for Money: 0 Votes

Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Council engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on Spinraza and Zolgensma for SMA to policy and practice. The policy roundtable members included a three patients/patient advocates, two clinical experts, two insurers, and representatives from AveXis and Biogen. 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 in the full report.

Payers

- Given the substantial remaining uncertainty regarding the benefits of these treatments in certain subpopulations and their high cost, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use. Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed in Section 8.3.
- Payers should provide responses to prior authorization requests within 48 hours.
- Given that Spinraza and Zolgensma have new mechanisms of action, lack long-term safety and efficacy data, and are very expensive, it is reasonable for insurers and other payers to negotiate outcomes-based contracts with manufacturers. Outcomes-based contracts should be scaled so that a substantial portion of the cost of these treatments is at risk should patients not receive adequate and sustained clinical benefit.

- Providers, payers, and manufacturers need to collaborate to determine meaningful clinical outcome measures that can serve as the basis for outcome-based contracts for patients with different types of SMA. Options for specific elements are discussed in Section 8.3.

Manufactures

- To align reasonably with the benefits for patients and families, the price for Spinraza should be far lower, and that for Zolgensma should be lower than the hypothetical $4-5 million price the manufacturer has suggested could be justified. To achieve the needed balance between incentives for innovation and health system affordability, all manufacturers should exercise their monopoly pricing power responsibly, setting prices that do not exceed a reasonable cost-effectiveness threshold.
- Given the substantial remaining uncertainty regarding the benefits of initiating disease-modifying treatments in certain subpopulations, manufactures should provide treatment at no cost where evidence is lacking.
- Although the evidence base for Zolgensma was judged adequate to demonstrate benefit versus standard supportive care, the number of patients treated is very small, and only a single uncontrolled trial was performed. Manufacturers should not view this as a generalizable roadmap for generating adequate evidence for patients, clinicians, and payers. As shown by the evidence for Spinraza, even for ultra-rare conditions, manufacturers can and should seek to conduct larger, randomized trials with long follow-up.

Patient Advocacy Organizations

- Patient organizations should view their longer-term mission in support of patients to include active engagement with manufacturers to demand reasonable value-based pricing of the therapies that patients and their families helped bring to the market.

Clinicians and Clinical Specialty Societies

- Individual clinicians and clinical specialty societies should assume a broad leadership role in advocating for patients by taking four actions: 1) highlight and work to address insurance barriers to appropriate care; 2) be vocal witnesses to the negative effects of excessive prices on patients and families; 3) integrate considerations of value into clinical guidelines; and 4) embody a broad model of professionalism that calls upon clinicians to work towards a health system that improves access and provides a sustainable model for future innovation through fair pricing.

Future Research

- Better measures of motor functioning are needed.
- Registries such as those maintained by CureSMA should be utilized to help answer remaining uncertainties in the evidence base.

1. Introduction

Update (Added May 24, 2019)

Because of heightened interest in Zolgensma in light of its FDA approval and the limited evidence base at the time of publication of ICER's Final Report, we are including this brief discussion of additional data/interim analyses from ongoing trials of Zolgensma that have been made public through conferences (Muscular Dystrophy Association Clinical and Scientific Conference April 13-17, 2019 and American Academy of Neurology Annual Meeting May 4-10, 2019)[1-3] and manufacturer press releases.[4,5] This is not a systematic review of new evidence. Note that outside of this text box, no other sections of the report have been revised.

- In a Phase III, single-arm trial (STR1VE) of infants with Type I SMA, 21 of 22 infants were alive with a median age of 14.4 months.[5] The death was deemed not related to treatment. Five months after treatment, CHOP-INTEND scores increased by an average of 14.3 points, which was similar to the results from the START trial.
- In another Phase III, single-arm trial (STR1VE EU) of infants with Type I SMA, 1 death was reported by the manufacturer (Novartis/AveXis).[6] The death was attributed to severe respiratory infection with neurological complications and may be treatment-related. An autopsy has been performed but results are not known publicly. No other results from this trial are available as of May 24, 2019.
- In a Phase I dose comparison trial (STRONG) of intrathecal administration of Zolgensma in patients with Type II SMA, treatment was well tolerated with two serious adverse events of transaminase elevation.[5] A number of the patients achieved new motor milestones.
- A Phase III single-arm trial (SPR1NT) evaluated intravenous Zolgensma in presymptomatic patients with SMA and two or three copies of *SMN2*.[5] The patients were six weeks of age or less at the time of treatment. After a median follow-up of 5.4 months (median age 6.1 months), all 18 children were alive and "event free." Among 8 patients with two copies of *SMN2*, all reportedly achieved age-appropriate motor milestones including 4 who could sit without support and 1 who could stand with assistance.

The new data from STR1VE are largely consistent with previously available findings. While the additional death in STR1VE EU is concerning, this additional information does not change the overall conclusions reached in our report regarding treatment in Type I SMA.

No data were available on Zolgensma in patients with Type II SMA at the time of publication of the Final Report and we rated the evidence as insufficient. If further reports from STRONG

confirm the initial findings, a revised evidence rating may include more certainty of at least a small benefit in this patient population.

Similarly, at the time the Final Report was published no data were available on Zolgensma in patients with presymptomatic SMA, and we rated the data as insufficient in the Final Report, in part because of concerns about safety in young infants; some efficacy in patients with presymptomatic SMA and two copies of *SMN2* would have been likely given efficacy in symptomatic Type I SMA. As with Spinraza in presymptomatic SMA, the early results of SPR1NT are encouraging. If further follow-up confirms these initial findings, a revised evidence rating may include more certainty of a substantial benefit in this patient population.

The economic analyses in the Final Report included an analysis of a hypothetical "Drug X" for presymptomatic SMA, assumed to have the one-time administration and pricing structure of Zolgensma and the efficacy of Spinraza. Given the early results of SPR1NT and the FDA approval including presymptomatic SMA patients, some stakeholders may wish to consider the analyses of Drug X in thinking about the value of Zolgensma. A value-based price benchmark for Drug X at $100,000-150,000 per quality-adjusted life year (QALY) gained would be approximately $1.1 million to $1.9 million, and at $100,000-$150,000 per life-year gained (LYG) would be approximately $1.2 million to $2.1 million. These value-based price benchmarks, and the report's existing benchmarks for Spinraza, assume that the US widely and rapidly adopts the recommendation to add screening for SMA to routine newborn screening.[7]

Once additional data (particularly from SPR1NT) are available, ICER may choose to perform a New Evidence Update for Zolgensma. Such an update would likely also review additional data on Spinraza.

1.1 Background

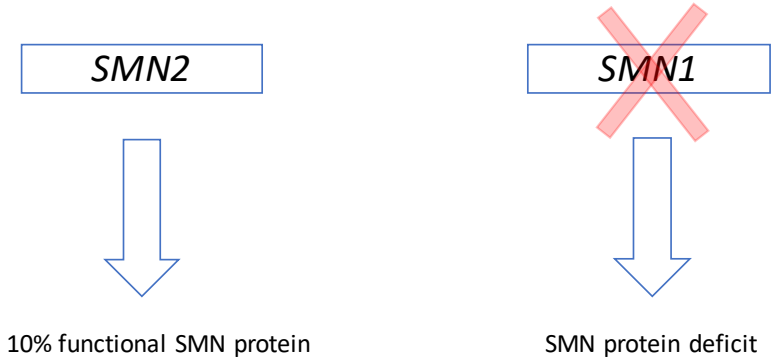
Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease caused by mutations in the survival motor neuron (*SMN*) gene that encodes the SMN protein. The SMN protein is essential for the development and maintenance of motor neurons, which control muscle movement. A deficiency in SMN protein causes irreversible degeneration of motor neurons, which clinically manifests as progressive muscle weakness such that patients may have difficulty moving, swallowing, or breathing.[8]

The most common form of SMA has been mapped to chromosome 5q, which contains two *SMN* genes.[12] The telomeric copy of the gene (*SMN1*) and the centromeric copy of the gene (*SMN2*) are nearly identical and both encode the SMN protein. A difference in the genes at a single nucleotide

produces an alternative splicing of exon 7, which affects the structure of the resulting SMN protein.[54] Using the information from *SMN1*, a full-length and fully functional SMN protein is created. In contrast, 80-90% of the SMN protein generated from each *SMN2* is nonfunctional (Figure 1.1), although individuals typically have two to four copies of *SMN2*. Hence, most of the functional SMN protein is created by *SMN1*, and mutations in *SMN1* are associated with development of SMA.[54] Although the number of *SMN2* copies modulates the severity of SMA, patients without a functional copy of *SMN1* have an insufficient level of SMN protein regardless of the number of *SMN2* copies.[14,54]

Figure 1.1. Genetics of SMA



SMA is commonly caused by homozygous deletion or deletion and point mutation of the alleles in the survival motor neuron 1 (*SMN1*) gene that mainly produces full-length SMN protein (right). The *SMN2* gene differs from *SMN1* by a few nucleotides, such that only 10% of the SMN protein it generates is fully-functional (left).

In the United States (US), SMA incidence is approximately one in 10,000 live births or about 500 new SMA cases per year.[10] The most severe cases of SMA affect infants and young children, and the disease rapidly progresses once symptoms present.[8,9] Muscle weakness commonly presents as weakness of the limbs, especially in the muscles of the torso, upper legs, and upper arms, and patients may have difficulty swallowing or breathing. Historically, life expectancy in the most common and severe form of SMA (Type I) was less than two years. In part due to improvements in standard of care, more recent estimates of the median age at death in this type of SMA range from ten months up to four years.[37,55,56] Survival depends on respiratory function, and many infants and children eventually require permanent ventilation. SMA does not affect cognitive function, and there is often a contrast between a patient's alertness and ability to move.

SMA subtypes are classified into clinical groups based on age of onset and maximum motor function achieved (Table 1.1).[9,15] Clinical severity also depends on the level of SMN protein, which is related to the number of *SMN2* copies as noted above.

Table 1.1. Clinical Classification of SMA

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of *SMN2* Copies
0	Prenatal/fetal	None	<6 months	1
I	<6 months	Sit with support only	<2 years	1-3
II	6–18 months	Sit independently	>2 years	2-3
III	>18 months	Walk independently	Adulthood	3-4
IV	Adult (20s-30s)	Walk through adulthood	Adult	≥4

Adapted from Table 1 of Verhaart et al. 2017.[9]
Number of *SMN2* copies based on Calucho et al. 2018.[16]

Type 0 SMA, the most severe subtype, affects individuals before birth and is very rare. Newborns with Type 0 have severe hypotonia (low muscle tone), need respiratory support, and have a life expectancy of minutes to weeks after birth. Type I SMA (infantile-onset SMA) represents approximately 60% of all diagnosed SMA cases.[10] These patients typically have one to three copies of *SMN2*,[16] present with symptoms before six months of age, do not achieve key motor milestones (e.g., sitting without support), and lose motor functioning over time. Muscles in the respiratory and digestive tracts are also affected, which can cause breathing complications, difficulty swallowing, and constipation. Patients may die or need permanent respiratory support within two years of life.[10] Approximately 20-30% of patients diagnosed with SMA have Type II.[9,10] Type II SMA presents between six to 18 months of age with patients typically having three copies of *SMN2*, although some have two or four copies.[16] These patients cannot walk independently, and most patients survive to adulthood with aggressive supportive care.[10] Approximately 10-20% of patients diagnosed with SMA have Type III.[9,10] Type III SMA presents in patients aged 18 months to 18 years, and patients typically have three or four copies of *SMN2*.[16] Patients have a normal life expectancy and can walk independently, although they may lose this ability over time. Type IV SMA, a very rare and the least severe subtype, presents in adults. Adults with Type IV SMA typically retain the ability to walk independently, do not suffer from respiratory issues, and have a normal life expectancy.[9,15]

Diagnosis and Care

Diagnosis of SMA is typically prompted by the clinical symptoms of muscle weakness described above. In part because of SMA's rapid progression and the importance of early treatment to preserve motor functioning, the disease was recently added as a recommended condition for which to screen all newborns in the US.[52] Diagnosis is based on a genetic molecular test. SMA is autosomal recessive, meaning that two copies of *SMN1* must have mutations in order for SMA to develop in an individual. In most patients with SMA, the disease is caused by homozygous deletion or deletion and point mutation of the alleles of *SMN1*.[11-13] Although the number of *SMN2* copies does not confirm the diagnosis of SMA, it is strongly correlated with the severity of disease and may be an important aspect when considering treatment options.

Patients with SMA may need intensive care and support, especially those with SMA Type I. To maintain mobility and function as long as possible, multidisciplinary supportive care including respiratory, nutritional, gastrointestinal, orthopedic, and other support is needed.[17-19] Nevertheless, supportive care does not modify disease progression, and patients may be entirely dependent on family members and caregivers. The intense emotional and physical effort involved with caring for a patient with SMA may cause loss of sleep, stress, anxiety, and emotional distress for caregivers.[20,21] Hence, SMA may affect the health-related quality of life of patients as well as their families and caregivers.

Disease-Modifying Therapies

Currently, only one disease-modifying therapy (nusinersen, Spinraza®, Biogen Idec) has been approved to treat SMA.[22] Spinraza, an antisense oligonucleotide, targets the messenger RNA from *SMN2* so that it creates more functional SMN protein (Figure 1.2a). It is administered via intrathecal injection (i.e., into the cerebrospinal fluid that surrounds the spinal cord and brain) with four loading doses (day 0, day 14, day 28, and day 63) and every four months thereafter. Spinraza has been studied in patients with or likely to develop SMA Types I-III,[23-25] with several studies ongoing.[26-28] In December 2016, the US Food and Drug Administration (FDA) approved Spinraza for the treatment of SMA (any subtype).[22]

A new gene therapy, Zolgensma® (onasemnogene abeparvovec, Novartis/AveXis), is currently in development to treat patients with SMA. Zolgensma, formerly known as AVXS-101, uses the adeno-associated virus serotype 9 vector (AAV9) to deliver a copy of the *SMN* gene to replace the defective *SMN1* gene (Figure 1.2b).[29] Zolgensma is being studied as a one-time, intravenous administration in patients with Type I SMA. The FDA granted Zolgensma a Breakthrough Therapy Designation and Fast Track Designation, with an FDA decision expected by mid-2019.[30]

Figure 1.2. Disease-Modifying Interventions for SMA

(a) Spinraza (b) Zolgensma

The availability of a disease-modifying therapy has altered the landscape of SMA management. Nevertheless, important uncertainties remain regarding the effectiveness of Spinraza in certain patient subgroups (e.g., type of SMA and duration of symptoms) and its duration of benefit. There are additional uncertainties around Zolgensma and its comparative effectiveness with Spinraza. With both agents, it is uncertain how well the cost of therapy is aligned with benefits. All stakeholders will benefit from a comprehensive review of the clinical evidence on both drugs and an analysis of their long-term cost-effectiveness and potential budget impact.

1.2 Scope of the Assessment

Overview

This report assesses the comparative clinical effectiveness and economic impacts of Spinraza and Zolgensma versus supportive care for patients with SMA. The assessment aims to systematically evaluate the existing evidence, taking uncertainty and patient-centered considerations into account. To that aim, the assessment is informed by two research components (a systematic review of the existing evidence and an economic evaluation) developed with input from a diverse group of stakeholders, including patients and their families, clinicians, researchers, representatives from SMA patient advocacy groups, and manufacturers of the agents of focus in this review. Below, we present the review's scope in terms of the research questions, PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design) elements, and an analytic framework diagram.

Research Questions

The following research questions were developed with input from clinical experts, patients, and patient groups:

1) By type of SMA (Types 0-IV), what is the comparative efficacy, safety, and effectiveness, in terms of mortality, permanent invasive ventilatory support, motor function and mobility, respiratory and nutritional support, quality of life, adverse events, and other key outcomes of:
    - Spinraza versus supportive care?
    - Zolgensma versus supportive care?
    - Spinraza versus Zolgensma?

2) In presymptomatic patients with SMA, what is the comparative efficacy, safety, and effectiveness, in terms of mortality, permanent invasive ventilatory support, motor function and mobility, respiratory and nutritional support, quality of life, adverse events, and other key outcomes of:
    - Spinraza versus supportive care?
    - Zolgensma versus supportive care?
    - Spinraza versus Zolgensma?

PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS elements.

Populations

The population of focus for the review is infants, children, and adults with SMA. Where data are available, we will look at subpopulations defined by age of onset (including presymptomatic, infant-onset, later-onset), SMA subtype (0-IV), or number of *SMN2* copies.

Interventions

Our review will seek information on Spinraza and Zolgensma.

Comparators

Where data permit, we intend to compare the agents to each other and to supportive care (with or without sham administration).

Outcomes

The outcomes of interest are listed below.

Efficacy

- Mortality
- Permanent invasive ventilatory support
- Motor function, including:
    - Hammersmith Functional Motor Scale-Expanded (HFMSE)
    - Hammersmith Infant Neurological Examination-Section 2 (HINE-2)
    - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)
    - Revised Upper Limb Module (RULM)
    - World Health Organization motor development milestones (sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing along, walking alone)
- Mobility (e.g., 6-Minute Walk Test)
- Bulbar function (e.g., swallowing, speaking)
- Use of respiratory or gastrointestinal support (e.g., gastrointestinal tube)
- Other complications of SMA (e.g., scoliosis)
- Quality of Life (e.g., PedsQoL)

Safety

- Treatment-related adverse events (AEs)
    - Injection or infusion site reactions
    - Thrombocytopenia and low platelets
    - Renal toxicity
    - Liver function (e.g., elevated aminotransferase)
    - Complications of lumbar puncture (e.g., back pain, vomiting, headache)
- Serious adverse events (SAEs)
- Adverse events leading to discontinuation

Timing

Evidence on intervention efficacy, safety, and effectiveness will be collected from studies of any duration.

Settings

Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

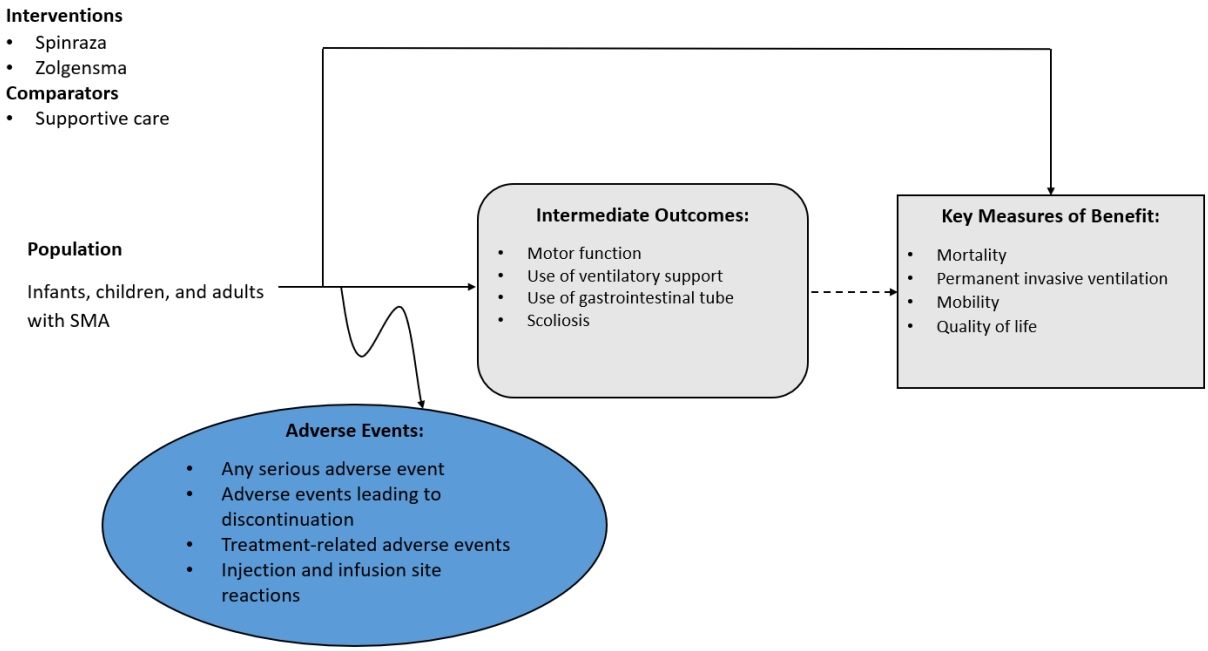
Study Design

Randomized controlled trials, non-randomized comparative studies, and single arm-studies with any sample size will be included.

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.3.

Figure 1.3. Analytic Framework



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., use of ventilatory support), and those within the squared-off boxes are key measures of clinical benefit (e.g., quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.[57]

Value Framework Considerations

ICER is assessing Spinraza and Zolgensma under an adaptation of the ICER value framework focused on treatments for serious, ultra-rare conditions because the assessment meets the following criteria:

- The eligible patient populations for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

1.3 Definitions

Genes

SMN1: The telomeric copy of the *SMN* gene responsible for generating most of the functional SMN protein. Homozygous deletion or deletion and point mutation of the alleles of *SMN1* causes SMA.[11-13]

SMN2: The centromeric copy of the *SMN* gene, also referred to as the "SMN back-up gene," which generates only a limited amount of functional SMN protein. A higher number of *SMN2* copies can modulate the severity of SMA.

SMA Types

Type 0: Affects individuals before birth and is very rare. Newborns with Type 0 have severe hypotonia (low muscle tone), need respiratory support, and have a life expectancy of minutes to weeks after birth.

Type I: Also called infant-onset SMA, patients present with symptoms before six months of age, do not reach key motor milestones (e.g., sitting without support), and lose motor functions over time. Patients may die or need permanent respiratory support within two years of life, although survival has increased in recent years due to advancements in supportive care.[10,37,55,56]

Type II: This type of SMA together with Type III is also referred to as later-onset SMA. Patients with Type II SMA present between six to 18 months of age, cannot walk independently, and survive to adulthood with aggressive supportive care.[10]

Type III: This type of SMA together with Type II is also referred to as later-onset SMA. Patients with Type III present between 18 months to 18 years of age, and have a normal life expectancy, and can walk independently, although they may lose this ability over time.[10]

Type IV: A very rare and the least severe subtype, presents in adults. Adults with Type IV SMA typically retain the ability to walk independently, do not suffer from respiratory issues, and have a normal life expectancy.[9,15]

Outcomes

Hammersmith Functional Motor Scale-Expanded (HFMSE): An expanded version of the Hammersmith Functional Motor Scale (HFMS) to evaluate ambulatory SMA patients (i.e., Type II or III SMA). The HFMS is a clinician-rated, 20-item scale developed to assess the motor ability of children with SMA with limited ambulation. The HFMSE extends the HFMS by adding 13 items from the Gross Motor Function Measure (GMFM), a measure developed for assessing change in motor function in children with cerebral palsy. Each item in the HFMSE is measured on a 3-point scale with higher scores indicating better functioning. Untreated patients with SMA Type II or Type III are unlikely to improve by more than 2 points; patients and caregivers consider a 1-point increase to be meaningful.[40,41]

Hammersmith Infant Neurological Examination-Section 2 (HINE-2): HINE assesses development of neurological function in healthy infants. Section 2 in HINE focuses on motor milestone achievement, which is an area typically not attained by infants with SMA. HINE-2 consists of eight items to assess infants' changes in head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. Partial attainment of a skill can be captured in subscores. Each milestone is measured on a 3- to 5-point scale with higher scores indicating better functioning. Untreated patients with SMA Type I are unlikely to attain a score of >1 in any milestone.[58,59]

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND): A validated 16-item scale designed to capture motor function in SMA infants with Type I. Each item is measured on a 5-point scale (total 0–64 points) with higher scores indicating better functioning.[60,61]

Revised Upper Limb Module (RULM): An assessment of 19 tasks designed to assess upper limb function in non-ambulatory patients with SMA. Each item is measured on a 3-point scale with higher scores indicating better functioning.[42]

World Health Organization (WHO) Motor Development Milestones: Captures six dichotomous yes/no motor skills (sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone, walking alone).[62] Age windows of achievement for healthy infants are in Table 1.2. Note that the six windows overlap, and the sequence of achievement varies. Most infants follow the order below with hands-and-knees crawling shifting between earlier or later milestones.

Table 1.2. Age Windows of Achieving Motor Development Milestones

	Sitting without Support	Standing with Assistance	Hands-and-Knees Crawling	Walking with Assistance	Standing Alone	Walking Alone
Age in Months, 1st-99th Percentiles	3.8-9.2	4.8-11.4	5.2-13.5	5.9-13.7	6.9-16.9	8.2-17.6

Adopted from the WHO Multicenter Growth Reference Study Group.

6-Minute Walk Test (6MWT): A measure of ambulatory function, specifically how far an individual can walk within six minutes.[63]

1.4 Insights Gained from Discussions with Patients and Patient Groups

Throughout the conceptualization of this review, we heard from patient advocates and caregivers how devastating the diagnosis of Type I SMA can be and how difficult it is to watch the disease progress in a child. Parents and caregivers feel helpless and fearful while also needing to be vigilant and constantly providing care. Care entails approaches to preserve respiratory and muscle function, including physical therapy, nutritional support, and extensive medical equipment. We heard from adults with SMA how frustrating it is that new interventions have not been commonly studied in adults and that more data are needed in this population, including data on appropriate dosages. Patients and caregivers reported wanting 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. In addition, six families submitted public comments on our Draft Scope, which provided additional context on the experience of children with SMA and their parents. These comments described the devastating urgency of treatment and severity of SMA symptoms, and many described the positive impact of treatment.

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.[31] 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 burden of disease included communication challenges as children with SMA grow, the concern of developing scoliosis (particularly for patients with Type II), 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.

Following our scoping discussions and public comment periods, we updated our draft scope to include 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 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.

ICER also received public comments on its on its Draft Evidence Report from a mix of patients, patient advocacy organizations, manufacturers, and providers. All three families who provided public comments described children with SMA who are receiving Spinraza; these families all reported a positive outlook on treatment with Spinraza. We also heard from three patient advocacy organizations who provided context about the patient experience living with SMA as well as feedback on key decisions made in the cost-effectiveness evaluation. We also heard from patients at different time points in this review about the spillover effects of this disorder on patients' caregivers, mainly parents, and we explored approaches to incorporate this caregiver burden into our model accordingly. However, due to the methodological uncertainty in estimating caregiver quality of life over a long-term horizon, we did not include this in our analyses. Further details are provided in Section 4.

1.5 Research, Development, and Manufacturing Costs

As described in ICER's modified framework for assessing value of treatments for ultra-rare diseases, ICER invited manufacturers to submit relevant information on research, development, and manufacturing costs that may impact pricing of a drug. For this report, no manufacturer submitted information on development or production costs that would be an important factor in justifying the price of their products.

1.6. Potential Cost-Saving Measures in SMA

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include 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-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by Spinraza or Zolgensma (e.g., respiratory support), 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. Currently, we have not identified any potential cost-saving areas.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for Spinraza, we reviewed publicly-available coverage policies from the Centers for Medicare and Medicaid Services (CMS), MassHealth, Husky Health Connecticut, Vermont Medicaid, and from regional and national commercial insurers (Aetna, Blue Cross Blue Shield of Massachusetts [BCBSMA], Cigna, Harvard Pilgrim Health Care, Humana, and UnitedHealthcare [UHC]). At the time the evidence report was published, we were unable to survey policies pertaining to Zolgensma because the medication is not yet approved by the FDA. We were unable to locate any National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs) for Spinraza.

To obtain coverage for Spinraza, all commercial payers require prior authorization. These requirements vary somewhat across payers but are largely consistent. All six commercial payers require a confirmed diagnosis of SMA Type I, II, or III. Aetna, BCBSMA, Harvard Pilgrim, and UHC specify that the diagnosis of SMA must be made by a neurologist. Aetna, Cigna, Humana, and UHC require the submission of medical records to document either 1) homozygous gene deletion or mutation, or 2) compound heterozygous mutation. Harvard Pilgrim and UHC specify that the patient seeking coverage must have at least two copies of the *SMN2* gene; Humana states that patients may have no more than two copies. To obtain coverage under Cigna and UHC, patients must not be dependent on invasive ventilation or tracheostomy, and must not require non-invasive ventilation except during sleep. In addition to results from genetic testing, several payers, including BCBSMA, Cigna, and UHC require results from one of the following exams to establish baseline motor ability: CHOP-INTEND, HINE-2, HFMSE, ULM, RULM, or 6MWT. Humana specifies that if approved, initial authorization is granted for three months, Cigna and Harvard Pilgrim grant authorization for six months, and BCBSMA grants authorization for up to one year.[64-68]

Table 2.1. Private and Public Payer Coverage for Spinraza Based on Subtype and Genetic Criteria

Coverage Authorized Based on Subtype and Genetic Criteria									
	Subtype					Number of Copies of *SMN2*			
	Type 0	Type I	Type II	Type III	Type IV	1	2	3	4
Aetna	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
BCBSMA	NS	Yes	Yes	Yes	NS	NS	NS	NS	NS
Cigna	No	Yes	Yes	Yes	No	NS	NS	NS	NS
Harvard Pilgrim	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Humana	Yes	Yes	NS	NS	No	Yes	Yes	No	No
UHC	No	Yes	Yes	Yes	NS	No	Yes	Yes	Yes
MassHealth	No	Yes	Yes	Yes	No	NS	NS	NS	NS
Husky Health CT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
VT Medicaid	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes

BCBSMA: Blue Cross Blue Shield of Massachusetts, NS: not specified, *SMN2*: survival motor neuron 2, UHC: UnitedHealthcare

All payers list similar requirements for continued use of Spinraza. Each of the six commercial payers require a positive clinical response or improvement in motor milestones from the pretreatment baseline as demonstrated by results from one of the following tests: CHOP-INTEND, HINE-2, HFMSE, ULM, RULM, or 6MWT. If reapproved, Harvard Pilgrim grants authorization for an additional six months, Humana for an additional four months, and UHC for twelve months.[64-68]

MassHealth, Husky Health Connecticut, and Vermont Medicaid require prior authorization in order to obtain Spinraza. Similar to the commercial payers surveyed, MassHealth requires a genetic test that confirms a diagnosis of SMA Type I, II, or III. Documentation from a neurologist must be provided, as well as results from a baseline motor function test.[69]

The policy of Husky Health Connecticut is nearly identical to MassHealth, but the coverage guidelines are categorized by SMA type. For patients with Type I, both the diagnosis and the request for Spinraza must be made by a neurologist. Genetic testing must confirm the mutation/deletion in chromosome 5q (homozygous gene deletion, homozygous gene mutation, or compound heterozygous mutation) and that the patient has at least two copies of *SMN2*. The patient cannot be dependent on ventilation or tracheostomy or need non-invasive ventilation beyond use for sleep. Lastly, a baseline motor exam must be completed to determine motor ability. For any other SMA type, the policy lists the same requirements, but includes an additional note that the attending neurologist must include documentation as to why the patient should be treated with Spinraza. Continuation of therapy may be approved if the patient exhibits an improvement in motor ability as defined by a specified increase in a HINE, HFSME, ULM, or CHOP-INTEND score.[70]

The policy of Vermont Medicaid is similarly comprehensive.[71] It specifies that the patient must have at least two copies of *SMN2* and must not be dependent on invasive or noninvasive ventilation for more than six hours per day. The policy requires the following four laboratory tests to be

conducted prior to each dose: platelet count, prothrombin time, activated partial thromboplastin time, and quantitative spot urine protein. For continuation of therapy, patients with Vermont Medicaid must submit documentation that supports an improvement or maintenance, or a slowed progression of disease.[71]

2.2 Clinical Guidelines

We reviewed guidelines on SMA and Spinraza issued by major US clinical societies and working groups, as well as guidance from the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence (NICE). Guidelines pertaining to supportive care may be found in Appendix F.

American Academy of Neurology (AAN)

Evidence in Focus: Spinraza Use in Spinal Muscular Atrophy (2018)[72]

The AAN states that Spinraza is beneficial to SMA patients with Types I or II in early or middle symptomatic stages, as these patients have the highest potential for improvement in motor function. There exists less evidence concerning the use of Spinraza in patients with milder forms of SMA, or those with advanced disease and disability. Moreover, as the AAN notes, the cost-benefit profile is less favorable in older patients with less severe disease or with very advanced disease, even though these populations may respond to treatment. The AAN states that future research on Spinraza should not only include studies with patients with more advanced disease and adults with Types III and IV, but should also include cost-benefit analyses for these different groups.

Additional comments and recommendations for treatment with Spinraza include the importance of early diagnosis (including screening tools to assess infants), psychological counseling, periodic evaluations by physicians and physical therapists, and the need for a joint approach to care among doctors, therapists, and families.

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH Canadian Drug Expert Committee Recommendation (Final) – Spinraza (Spinraza – Biogen Canada Inc.) (2017)[73]

The CADTH Canadian Drug Expert Committee (CDEC) recommends Spinraza for patients with pre-symptomatic and infantile-onset (Type I) SMA. Patients with later-onset SMA must be under the age of 12 and non-ambulatory to receive Spinraza. To obtain Spinraza, patients must also complete a baseline assessment, such as CHOP-INTEND, HINE-3, or HFMSE. Lastly, patients with SMA must receive care from a specialist with experience in SMA. In its guidance, CDEC lists a pricing condition recommending a reduction in the price of Spinraza, as the committee determined that the

treatment was unlikely to be cost-effective at the manufacturer-submitted price. Given the high cost of treatment, CDEC states that Spinraza should be administered to patients who are most likely to benefit from treatment.

National Institute for Health and Care Excellence (NICE)

Appraisal Consultation Document: Spinraza for Treating Spinal Muscular Atrophy (2018)[74]

In August 2018, NICE issued a provisional recommendation against treatment for SMA with Spinraza due to the lack of long-term evidence, and the subsequent uncertainty surrounding long-term benefits. In the document, NICE also cites uncertainties in the economic evidence, emphasizing the drug's considerably high list price. The appraisal committee does acknowledge that Spinraza shows substantial benefit compared to a sham procedure in clinical trials — especially for patients with early-onset SMA — but concludes that because the size and nature of long-term benefits is uncertain, it cannot recommend Spinraza as a cost-effective use of NHS resources. As of November 12, 2018, negotiations around pricing and coverage were still ongoing, and once complete, NICE will offer its final guidance on Spinraza.

3. Comparative Clinical Effectiveness

3.1 Overview

This review of clinical effectiveness of Spinraza and Zolgensma for SMA in comparison to supportive care was informed by the evidence from available clinical studies meeting the inclusion criteria (i.e., PICOTS), whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents). The scope of this review is detailed in Section 1.2. In brief, this review focused on efficacy, safety, and effectiveness of Spinraza and Zolgensma in comparison to supportive care (with or without sham administration) in SMA patients of all ages and types. We sought evidence on the following key clinical outcomes: mortality, permanent ventilation, event-free survival, motor function and milestones, and safety (e.g., AEs, discontinuations due to AEs, SAEs). Other outcomes described in Section 1.2 were sparsely reported and are detailed in Appendix D, where available. None of the studies included in our review reported outcomes related to quality of life or scoliosis.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for SMA followed established best research methods.[75,76] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[77] The PRISMA guidelines include a checklist of 27 items, which are listed in Appendix Table A1. This review was prospectively registered with PROSPERO (CRD42018112419) and the full research protocol is available online (https://osf.io/ra46v/).

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, and Study Design elements described above. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms. The full search strategy is available in Appendix Tables A2 and A3. The date of the most recent search is January 7, 2019.

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 relevant 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 http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Study Selection

Studies meeting the PICOTS criteria described in Section 1.2 were eligible for our review. To be included, studies were required to assess Spinraza or Zolgensma (any dose or regimen) in infants, children, or adults with SMA with any number of *SMN2* copies. For any study that also assessed supportive care, we accepted and used the study's definition of supportive care. We excluded studies only assessing supportive care (e.g., comparative studies of different support care options or single-arm supportive care studies), studies comparing different lumbar puncture approaches using Spinraza, and studies where participants received a single dose of Spinraza because these studies do not reflect how Spinraza is used in practice. Case-control studies were also excluded.

Data Extraction and Quality Assessment

Data from included studies were extracted directly into Microsoft Excel. Data elements extracted include a description of patient populations (type of SMA, presymptomatic SMA, ventilation use at baseline, motor function at baseline, age at diagnosis and treatment initiation), sample size, duration of follow-up, funding source, study design features (randomization, location, frequency of visits), interventions (agent, dosage, frequency, schedules, and routes of administration), supportive therapy allowed and used (e.g., any pharmacologic or non-pharmacologic agent along with frequency and schedules), outcome assessments, results, and study quality assessment for each study.

We assessed the quality of randomized controlled trials and non-randomized comparative studies according to the criteria published by the US Preventive Services Task Force (USPSTF), using the categories "good," "fair," or "poor."[78] A study quality rating was not assigned to grey literature (conference abstracts/posters) because they lack granular details. The USPSTF criteria are summarized below.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important

outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

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 Appendix D).[79]

Assessment of Publication Bias

We assessed publication bias for Spinraza and Zolgensma using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. We consider the presence of any such studies indicative of publication bias. We did not find any such studies in our review of ongoing trials. See Appendix C for an overview of the ongoing trials we identified.

Data Synthesis and Statistical Analyses

For each outcome of interest, the results of the studies are presented in the text or tables. When reviewing clinical evidence in ultra-rare populations, ICER acknowledges the challenges of study design, recruitment, and availability of data on long-term outcomes. We recognize the difficulty in validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. As such, we aim to add specific context to our findings regarding potential challenges in study design, when possible.

Analyses are descriptive only due to differences in entry criteria, patient populations, outcome assessments, lack of available patient-level data, and other factors that precluded formal quantitative direct or indirect assessments of Zolgensma and Spinraza versus each other or supportive care.

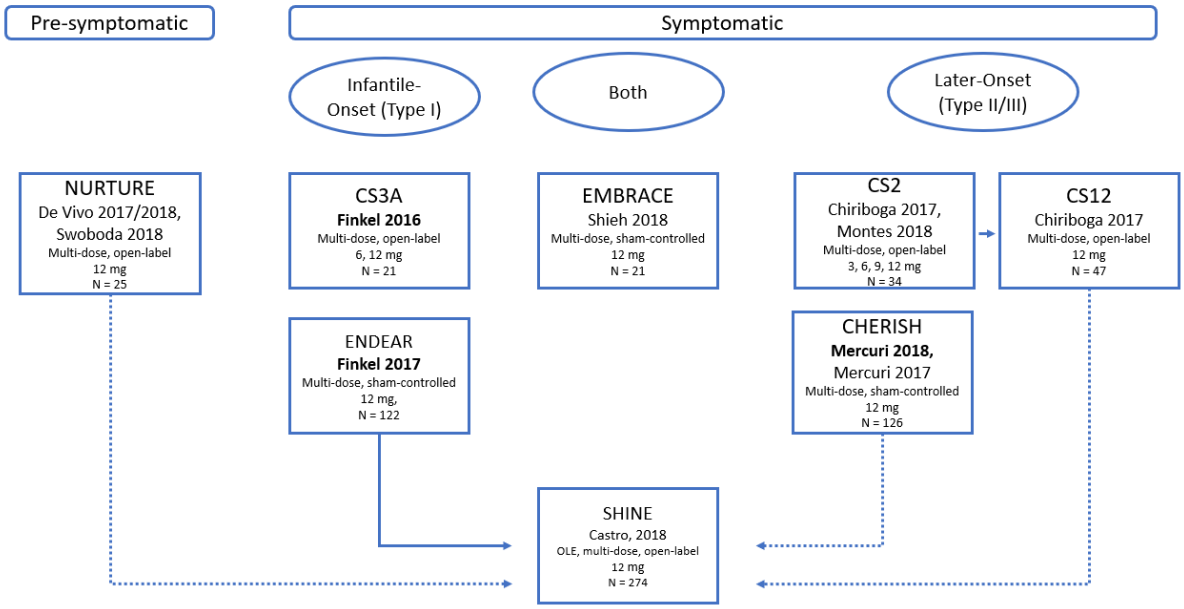
3.3 Results

Study Selection

Twenty-two references met the full PICOTS criteria (Appendix A, Figure A1). Primary reasons for exclusion were reporting of outcomes not relevant to this review and conference abstracts or posters reporting data subsequently published in peer-reviewed literature.

Overall, the 22 references correspond to six unique trials of Spinraza, one open-label extension (OLE) of Spinraza, five cohort studies of patients receiving Spinraza, and one trial of Zolgensma. Specifically, the Spinraza clinical trials include: one RCT with sham control (ENDEAR, one publication and two conference abstracts), and one open-label, dose-escalation study (CS3A; one publication and two conference abstracts) in Type I SMA; one RCT with sham control (CHERISH, one publication and one conference abstract) and one open-label, multiple dose study (CS2/12; one conference abstract and one conference poster) in Types II and III; one single-arm study (NURTURE, three conference abstracts) in presymptomatic SMA; and one RCT with sham control (EMBRACE, one publication and one conference abstract) in patients with Types I, II, or III SMA ineligible for the other trials (Figure 3.1). Patients who completed the above trials were eligible to enroll in an OLE (SHINE, one conference abstract), although results are currently available for only the patients with Type I SMA who had been enrolled in ENDEAR. In addition, we identified three cohort studies (three publications) of patients with Type I SMA receiving Spinraza through extended access programs (EAPs) and two cohort studies (two publications) in patients with Type II SMA.

Figure 3.1. Clinical Trials of Spinraza



Results are not yet available for the individuals who enrolled in SHINE from the trials indicated with dashed lines.

Finally, one publication and one conference presentation reported on the Zolgensma Phase I, two-cohort study, CL-101, and one publication on its long-term follow-up study, START, in patients with Type I SMA.

We found no trials or data on any treatment for newborns with SMA Type 0 or adults with Type IV.

Full details of all studies included in our systematic literature review are provided in Appendix D. Key trial details including participant characteristics and clinical benefits are presented below in the corresponding section by type of SMA (e.g., infantile-onset, later-onset, and presymptomatic). Harms are summarized together for all populations.

Quality of Individual Studies

We rated the quality of three sham-controlled RCTs: ENDEAR, CHERISH, and EMBRACE. As noted in the methods (Section 3.2), we did not rate the quality of non-comparative studies (e.g., NURTURE, CS3A, CS2/CS12, CL-101) or OLEs (SHINE, START).

We rated all three RCTs to be of good quality based on the USPSTF criteria. Additional details for each trial regarding the comparability of groups, participant blinding, validity of outcome assessments, intervention definitions, and key outcome reporting can be found in Appendix D. Overall, we noted some differences in baseline characteristics between the Spinraza and sham control arms of both ENDEAR and CHERISH that suggest more severe SMA symptoms in the Spinraza arms compared to the placebo arms. The direction of potential bias in the results is unclear. The differences in baseline characteristics are highlighted in the sections that follow.

Infantile-Onset (Type I) SMA

In infantile-onset (Type I) SMA, we included three clinical trials of Spinraza, including two sham-controlled RCTs (ENDEAR and EMBRACE)[24,32] and one open-label, dose-escalation study (CS3A).[23] We also included longer-term results for infants in ENDEAR who enrolled in the single-arm OLE (SHINE).[33] In addition, we included three cohort studies of patients receiving Spinraza through EAPs.[80-82] Finally, we included a two-cohort clinical trial of Zolgensma (CL-101) and its extension study (START).[29]

Overview of Trials

ENDEAR

ENDEAR included infants likely to be diagnosed with SMA Type I.[24] Infants ≤7 months of age with two copies of *SMN2* who also showed clinical symptoms consistent with SMA at or before the age of six months were eligible for screening. Eligible infants were randomized 2:1 to receive either intrathecal Spinraza or sham injection. Randomization was stratified by disease duration (before or

after 12 weeks of disease); duration was determined by subtracting the age at symptom onset from the age at screening. Following randomization, participants received loading doses on study days 1, 15, 29, 64, and maintenance doses on study days 183 and 302. Spinraza was administered by lumbar puncture at a dosage adjusted to a dose equivalent to 12 mg in a child ≥2 years of age. Note this dosing differs slightly from the approved 12 mg dose for all patients.[22] The sham injection was a small needle prick in the skin over the lumbar spine, covered with a bandage to resemble the Spinraza lumbar puncture. Parents of infants and trial personnel performing outcome assessments were blinded to treatment assignment, while trial personnel administering Spinraza and sham injections were aware of treatment assignment. As noted in Spinraza's label, more infants in the Spinraza group showed SMA symptoms before 12 weeks of age (88% vs. 77%), but the two treatment groups were otherwise balanced in baseline characteristics.[22]

ENDEAR's primary clinical outcomes were the proportion of HINE-2 [a] responders and event-free survival.[24] HINE-2 responders were defined by meeting two criteria: score improvement in one or more categories **and** improvement in more motor milestone categories than worsening. Deaths and withdrawals were considered non-responses. Event-free survival was defined as death or permanent assisted ventilation, including tracheostomy or ventilation for ≥16 hours per day for 21 continuous days in the absence of an acute, reversible illness. Permanent assisted ventilation was adjudicated by an independent committee unaware of treatment assignments. Secondary outcomes relevant to our review included the proportion of CHOP-INTEND [b] responders, defined by a ≥4-point change from baseline, overall survival, and event-free survival by disease duration sub-groups (≤12 vs. >12 weeks).

An interim analysis comparing the proportion of HINE-2 responders was completed when 78 patients were followed for at least six months ("interim efficacy set": 27 sham control and 51 Spinraza patients; 43 patients were not yet followed for six months).[24] This analysis showed statistical superiority of HINE-2 responders favoring Spinraza and the study was subsequently terminated prior to the planned 13-month follow up. All other endpoints were analyzed in the final analysis. Following early termination, participants could complete their end-of-trial (i.e., outcome assessment planned for day 394) visit at least two weeks after their most recent Spinraza dose or sham injection. The final efficacy set included 37 sham control and 73 Spinraza patients; 11 patients did not yet have the required visit at day 183 by the cut-off date for the final analysis. Safety analyses included all patients who were randomized and received at least one dose of their assigned treatment ("safety set," Spinraza: 80, sham: 41). Participants completing ENDEAR were eligible to enroll in the open-label extension trial, SHINE.

[a]HINE-2 consists of eight items that assess incremental changes in head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. Higher scores indicate better functioning.
[b]A validated 16-item scale (0–64 points) designed specifically to capture motor function in SMA infants with Type I. Higher scores indicate better functioning.

SHINE

SHINE is an ongoing Phase III OLE study that includes infants and children who completed ENDEAR and CHERISH, among other studies.[33] All participants receive Spinraza. Prior to FDA approval, Spinraza dosing followed the dosing used in ENDEAR and CHERISH (i.e., dosing scaled to a 12-mg equivalent for children under two and 12 mg for all other children); following FDA approval in 2016, all participants began to receive the 12-mg dose.[33] The key outcome of SHINE is to assess long-term safety including the incidence of AEs and SAEs. Of the infants from ENDEAR, 24/41 previously randomized to sham and 65/84 to Spinraza enrolled in SHINE and are now receiving Spinraza. Currently, results are only available for this subpopulation that were a part of the ENDEAR trial.

CS3A

CS3A is a Phase II, open-label, dose-escalation study. This study enrolled participants who showed symptoms consistent with SMA Type I between three weeks and six months of life.[23] Eligible infants between three weeks and seven months of age were enrolled and received either 6 or 12 mg-equivalent doses (based on enrollment order) on study days 1, 15, 85, 253, and every four months thereafter. We report only data from the 16 participants who received 12 mg doses from study day 1 onward, as this regimen more closely aligns with the FDA label. Key outcomes relevant to this report included safety, HINE-2 scores and individual motor milestones of this tool, and CHOP-INTEND.

EMBRACE

EMBRACE was a two-part, randomized, sham-controlled, Phase II trial evaluating Spinraza in infants and children meeting any one of three criteria:[32]

- Onset of clinical symptoms before six months of age and three *SMN2* copies
- Onset of clinical symptoms before six months of age, older than seven months of age, and have two *SMN2* copies
- Onset of clinical symptoms after six months of age, are 18 months of age or younger, and have two or three *SMN2* copies

Thirteen children in EMBRACE were diagnosed with infantile-onset SMA; data from these children are reported in the following section. Eight children were diagnosed with later-onset SMA; data pertaining to these children are reported in a later section (see "Later-Onset SMA"). Study enrollment, randomization, and the Spinraza dosing regimen were similar to ENDEAR and CHERISH. The primary outcome of part one was to assess Spinraza safety and tolerability in children ineligible to enroll (i.e., a more diverse population) in ENDEAR and CHERISH. Part one was terminated early following the ENDEAR interim analysis that demonstrated a statistically-significant benefit on HINE-2 response favoring Spinraza over standard care. Participants were subsequently able to enroll in

the EMBRACE open-label part two, in which all children received Spinraza. Data from this part of the study have not yet been reported.

Expanded Access Programs

We identified and included three prospective open-label cohort studies that evaluated clinical outcomes of patients receiving Spinraza prior to regulatory approval through EAPs.[80-82] All patients were diagnosed with infantile-onset SMA and received age-adjusted doses of Spinraza through an EAP in Germany, Italy, or Australia. The Spinraza regimen was similar to the Spinraza label, with four loading doses on days 1, 15, 30, and 60 followed by maintenance doses every four months thereafter. Study eligibility was not restricted by *SMN2* copy number and the trial populations were generally more heterogenous than the ENDEAR trial population (e.g., age at treatment initiation up to 35 years of age with 20 Italian patients older than 10 years). Key outcomes included changes in CHOP-INTEND, HINE-2, and ventilatory and nutritional support following six months of treatment.

CL-101 and START

CL-101 was a two-cohort Phase I study of Zolgensma in 15 symptomatic infants likely to develop Type I SMA.[29] Infants with genetically-confirmed double-deletion of *SMN1* exon 7 and two copies of *SMN2* were eligible for inclusion. Infants were also screened for antibodies against the viral vector, AAV9, which would interfere with gene therapy using this vector; those with anti-AAV9 antibody titers >1:50 were excluded (n=1). Following screening, the first three patients received a single intravenous "low dose" of 6.7×10^{13} vector genomes (vg) per kilogram (kg); the next 12 patients received a single intravenous "high dose" of 2.0×10^{14} vg per kg. Due to elevated serum aminotransferase levels following dosing in the first patient, a protocol amendment added a prednisolone regimen of 1 mg/kg starting 24 hours before dosing through 30 days post-gene therapy administration. Concomitant treatment with Spinraza was not allowed during the 24 months of follow-up.

Treatment-related AEs of grade three or higher through the first two years following administration were CL-101's primary outcome, and the time until death or permanent ventilatory support was the secondary outcome.[29] Permanent ventilation was defined as 16 or more hours per day of ventilatory assistance for 14 or more days in the absence of an acute, reversible illness or perioperative state. Motor milestone achievements and CHOP-INTEND score changes through 13.6 months of age were measured as exploratory outcomes. Sitting unassisted was evaluated under three existing definitions: sitting unassisted for at least 5, 10, and 30 seconds. CHOP-INTEND scores were analyzed by a mixed-effects model for repeated measures, with the cohort and visit as a fixed effect and baseline CHOP-INTEND as a covariate. The use of nutritional and ventilatory support was also reported over time.

Infants were followed for two years, and data were reported by patient. One peer-reviewed publication included in our literature search reported data as of August 7, 2017, at which time all infants were 20 months of age or older.[29] At this time, all three low-dose recipients and 7/12 high-dose recipients had the full 24 months of follow-up. Infants completing CL-101 were eligible for a long-term follow-up study (START), during which some patients received Spinraza treatment. A second publication included in our review reported early data from START.[39]

Patient Characteristics

Key baseline characteristics of the populations enrolled in the two key trials, ENDEAR and CL-101, are shown in Table 3.1. We noted key differences at baseline with respect to age at diagnosis and age at treatment initiation which compromises the comparability of the two trial populations. Infants in ENDEAR were diagnosed later, on average, than those in CL-101 (Table 3.1).

Table 3.1. Key Baseline Characteristics of ENDEAR and CL-101

	ENDEAR[24]		CL-101[29]	
Key Characteristics	Spinraza	Sham Control	Zolgensma Cohort 1	Zolgensma Cohort 2
No. of Participants	80	41	3	12
Age at Onset, mo	1.8 (0.5-4.2)*	2.2 (0.2-4.6)*	1.7 (1.0-3.0)	1.4 (0-3.0)
Age at Diagnosis, wks	12.6 (0-29)	17.5 (2-30)	4.7 (0.6-12.1)†	8.6 (0-19.4)†
Disease Duration, wks	13.2 (0-25.9)	13.9 (0-23.1)	NR	NR
Age at Treatment Initiation, mo	5.4 (1.7-8.0)‡	6.0 (1.0-8.6)‡	6.3 (5.9-7.2)	3.4 (0.9-7.9)
Ventilatory Support, n (%)	21 (26)	6 (15)	3 (100)	2 (17)
Nutritional Support, n (%)	7 (9)	5 (12)	3 (100)	5 (42)
Mean HINE-2 Score	1.29 ± 1.07	1.54 ± 1.29	ND	ND
Mean CHOP-INTEND Score	26.63 ± 8.13	28.43 ± 7.56	16 (6-27)	28 (12-50)

Data are mean (range) or ±SD.
CHOP-INTEND: Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders, HINE-2: Hammersmith Infant Neurological Examination-Section 2, mo: months, ND: no data, NR: not reported, wks: weeks
*Converted from weeks to months by multiplying by 12 months and dividing by 52 weeks.
†Converted from days to weeks by dividing value by 7.
‡Converted from days to months by multiplying by 12 months and dividing by 365 days.

We also noted differences in baseline characteristics between the Spinraza and sham control arms of the ENDEAR trial (Table 3.1). In particular, there was a 4.8-week difference in mean age at diagnosis between the Spinraza and sham control arms and nearly 3-week difference in mean age at treatment initiation (163 days vs. 181 days for Spinraza and sham control, respectively).[24] Compared to the sham control, infants randomized to Spinraza had a higher incidence of paradoxical breathing (where breathing movements occur in reverse of the normal chest wall movement, 89% vs. 66%), pneumonia and respiratory illness (35% vs. 22%), swallowing or feeding

difficulties (51% vs. 29%), and more commonly required ventilatory support (26% vs. 15%), suggesting more severe disease in the Spinraza arm.[24] None of these differences were tested for statistical significance.

Most infants in the 12 mg Spinraza group in the CS3A study carried two copies of *SMN2* (n=13, 81%).[23] Mean age at Spinraza initiation was considerably younger (mean age: 77 days, range: 15-130), and mean motor function was higher (mean HINE-2: 2 [1-12], mean CHOP-INTEND: 30 (17-74]) compared to infants enrolled in ENDEAR and START.

Three of four (75%) infants randomized to receive the sham control in EMBRACE and 3/9 (33%) randomized to Spinraza had two copies of *SMN2*. On average, children in the sham control group were older than those in the Spinraza arm (median age [range] at first dose: 25.6 [16-53] vs. 15.3 [7-49] months), however, the sample size was small.

In the German EAP, the 61 participants enrolled had either two *SMN2* copies (n=38, 62.3%) or three or more *SMN2* copies (n=20, 32.8%; missing data n=3) and were generally older than those enrolled in ENDEAR (mean age ± SD at treatment initiation: 21.08 ± 20.23). The mean (range) baseline CHOP-INTEND score was 22.3 (0-50), mean baseline HINE-2 score was 0.8 (0-8), and 55.8% of all children enrolled required nutritional support (i.e., feeding tube or gastrostomy). The primary outcome was mean change from baseline CHOP-INTEND at 60 and 180 days after initiating Spinraza treatment. CHOP-INTEND was assessed as the primary outcome; secondary outcomes included HINE-2 response and nutritional and ventilatory support. Drug dosing was the same as in SHINE (e.g., age-adjusted dosing for children under two years of age prior to approval and 12 mg for all children post-approval).

The Australian and Italian EAPs included similar participants, eligibility criteria, and outcomes as the German EAP.[81,82] The 16 Australian participants started Spinraza treatment at a median (range) age of 20.0 months (2.5–35 years). The 104 Italian participants ranged in age from 0 to 19 years old.

Survival

In ENDEAR, the Spinraza group showed a 63% lower risk of death versus the sham control (hazard ratio [HR] [95% CI]: 0.37 [0.18, 0.77], p=0.004).[24] Overall, mortality was lower in infants in the Spinraza group versus the sham control group (16% vs. 39%). In a prespecified subgroup analysis, Spinraza demonstrated a statistically-significant survival benefit over the sham control (standard care) for children who initiated treatment within 12 weeks of disease onset (HR: 0.22 [NR], p=0.03).[83] A statistically significant benefit was not demonstrated for children initiating Spinraza treatment more than 12 weeks after symptom onset (HR: 0.45 [NR], p=0.09]).

Three of 16 (19%) infants in the CS3A 12-mg group died during study follow-up: one due to SMA disease progression and two due to recent pulmonary infection.[23]

All infants treated with Zolgensma in CL-101 were alive at 20 months of age, per results reported at a data cut-off of August 7, 2017.[29] All 12 patients followed in START (mean post-treatment age: 39 months) were alive.[30]

Permanent Ventilatory Support

In ENDEAR, there was no statistically-significant difference between the Spinraza and sham control groups in avoiding permanent ventilatory support: at the end of the trial, 62/80 (78%) and 28/41 (68%) of infants did not require permanent assisted ventilation (HR [95% CI]: 0.66 [0.32, 1.37]).[24] Compared to baseline, a smaller proportion of Spinraza recipients required ventilatory support at the final analysis while more sham control infants required ventilation versus baseline (Table 3.2).

Prespecified subgroup analysis showed statistically-significant benefits on ventilation-free survival favoring Spinraza over standard care for infants initiating treatment within 12 weeks of disease onset (HR [95% CI]: 0.158 [NR], p<0.004). Analyses of patients with disease duration less than or equal to the group median (13.1 weeks) showed similar results. A statistically significant benefits on ventilation-free survival were not demonstrated for children who initiated Spinraza more than 12 weeks after symptom onset (HR [95% CI]: 0.816 [NR], p=0.5).

Table 3.2. Ventilatory Support in ENDEAR and START

	ENDEAR[24]*		CL-101[29]†	
	Spinraza	Sham Control	Zolgensma Cohort 1	Zolgensma Cohort 2
Follow-Up	Final analysis		Interim analysis	
No. of Participants	80	41	3	12
Baseline Ventilation Support	21 (26)	6 (15)	3 (100)	2 (17)
Post-Treatment Ventilation Support	18 (22.5)	13 (32)	NR	5 (42)

All data are n (%). Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table 3.1.
NR: not reported
*The final efficacy set included infants with assessments at day 183, 302, or 394 and had at least 190 days or more between their first dose of Spinraza and cut-off date of the interim analysis.
†24 month follow-up.

None of the infants in the 12 mg group in the CS3A study required permanent ventilation during study follow-up.[23]

Nineteen (31%) of German EAP participants were ventilator-free after six months of Spinraza treatment and four (7%) children reported decreased use of ventilatory support.[80] Six (10%) participants began noninvasive ventilation for less than 16 hours per day, four (7%) children

required noninvasive ventilation for more than 16 hours per day, and three (5%) children underwent tracheostomy.

One patient in the CL-101 cohort 1 qualified as needing permanent ventilatory support per the protocol definition but later required only 15 hours per day of ventilatory support following a salivary gland ligation operation.[29] This event was not included in the analysis of event-free survival.

Event-Free Survival

Spinraza demonstrated a statistically-significant 47% decrease in the risk of death or permanent assisted ventilation (HR [95% CI]: 0.53 [0.32, 0.89], p=0.005); 49/80 (61%) of Spinraza and 13/41 (32%) of sham control recipients avoided death and permanent ventilatory support.[24] In the sham control group, the median time to death or permanent assisted ventilation was 22.6 weeks, whereas the Spinraza group had not reached this endpoint by the end of the trial. Interim long-term follow-up data from SHINE show the median time to death or permanent ventilation for infants who received Spinraza in ENDEAR and SHINE was 73.0 (95% CI: 36.3, NA) weeks.[33]

Seven infants in the CS3A study died or required permanent ventilation; because most infants in CS3A were alive and without permanent ventilation, the median age of event-free survival was not reached.[23]

None of the participants of the Australian EAP died or required ventilation for 16 or more hours per day after a median treatment period of 5.1 months.[82]

All infants treated with Zolgensma in CL-101 were alive and event-free through 24 months of follow-up.[29,34] As described above, one patient in the low-dose cohort met criteria for permanent ventilatory support but later improved; this patient was considered event-free.

Motor Function and Milestones

HINE-2

HINE-2 response was the primary outcome in ENDEAR (Table 3.3).[24,29] Key motor or developmental milestones evaluated in the HINE-2 included head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. To meet responder criteria, infants had to improve in one or more milestones and show more milestones with improvement than worsening. Infants who received Spinraza in ENDEAR showed statistically-significant improvements in HINE-2 response compared to sham control at the interim analysis (21/51 [41%] of Spinraza and 0/27 of sham control group; p<0.001).[24] In the final analysis, 37/73 (51%) of Spinraza and 0/37 sham control patients met criteria for HINE-2 response. On average, infants who received Spinraza through study day 394 (n=26) gained a mean 5.9 (min, max: 4.9, 6.9) milestones compared to sham control infants

(n=11), who showed minimal changes in HINE-2 motor milestones (mean [min, max]: -0.2 [-0.9, -0.4]). Nearly twice as many infants with SMA disease duration ≤12 weeks met HINE-2 responder criteria compared to infants with disease duration of more than 12 weeks (75% vs. 32%).[83]

The EMBRACE and CS3A studies show similarly high proportions of HINE-2 responders among small sample sizes. Seven of nine (78%) of infants with infantile-onset SMA in EMBRACE met criteria as HINE-2 responders based upon the last available assessment for each child (day 183, 304 or 422).[35] None of the children randomized to receive the sham control met any of the milestones assessed in the HINE-2. Thirteen of 15 (87%) children with SMA Type I in the CS3A study met identical criteria as HINE-2 responders.[23]

Table 3.3. HINE-2 Results for Spinraza in Infantile-Onset (Type I) SMA

	ENDEAR[24]		EMBRACE[35]	
Treatment	Spinraza	Sham Control	Spinraza	Sham Control
Assessment Timepoint	Day 183		14 months	
No. of Participants	59	23	9	4
Mean Baseline Score, Points	1.29 ± 1.07	1.54 ± 1.29	NR	NR
Mean Change from Baseline, Points	2.4 (2.8, 3.1) *	0 (-0.3, 0.3) *	NR	NR
Mean Score at Follow-Up, Points	NR	NR	NR	NR
Responder†, n (%)	21 (41)‡	0§	7 (78)	0

Data are mean (min, max) or ±SD.
HINE-2: Hammersmith Infant Neurological Examination-Section 2, NR: not reported
*Data estimated from publication by ICER.
†Responder defined as meeting two criteria: score improvement in one or more categories and improvement in more motor milestone categories than worsening.
‡Based on interim data analysis. Denominators were 51 for Spinraza and 27 for sham control.

Under identical HINE-2 responder criteria, 21 (34.4%) of children in the German EAP demonstrated motor response (mean change from baseline: 1.4 ± 2.1).[80] Italian patients, which included eight infants as well as patients aged 2, 5, 7, 9, 12, 14, and 35 years old, showed similar improvements in HINE-2 scores (mean change from baseline: 1.3 ± 2.2).[81] The Australian EAP did not report HINE-2 data.

CL-101 did not collect HINE-2 data, and there are no published data reporting HINE-2 scores with Zolgensma treatment.

CHOP-INTEND

CHOP-INTEND results from ENDEAR (secondary) and CL-101 (exploratory) are shown in Table 3.4. There is no minimal clinically-important difference (MCID) defined in the literature, however, a 4-point change is considered an important change in CHOP-INTEND response across trials for both

Spinraza and Zolgensma. In general, the literature cites a 40-point threshold as indicating clinically-meaningful function; it is rare for infants with Type I SMA to have a score of 40 or more points on the CHOP-INTEND.[37,38] Briefly, CHOP-INTEND assesses 16 motor skills, such as hand grip, rolling, and head control. Each motor skill is scored from 0 (no response) to 4 (complete response); a response of 4 points may reflect complete response in head control, or slight improvement across hand grip, rolling, and head control, among other motor skills. On average, healthy infants aged three months have a CHOP-INTEND score (range) of 50.1 (32-62) while similarly aged infants with SMA have an average score of 20.2 (10-33) points.[36]

In ENDEAR, 71% of infants treated with Spinraza achieved an increase of ≥4 points in CHOP-INTEND score between baseline and their end-of-trial visit (Table 3.4); only one infant in the sham control arm achieved improvement.[24] Decreases in CHOP-INTEND scores were reported in far fewer infants who received Spinraza compared to the sham control (7% vs. 49%).[24]

Infants treated with the high dose of Zolgensma (cohort 2) in the CL-101 trial showed improvement in CHOP-INTEND scores at one- and three-months post-treatment with Zolgensma (9.8 and 15.4 points, respectively).[29] CHOP-INTEND scores through the data cut-off for the preliminary analysis showed slight increases for the low-dose cohort (Table 3.4), however, all three patients remained below the threshold of ≥40 points that indicates clinically-meaningful function. Cohort 2 showed marked improvement in score (Table 3.4); 11 of 12 infants achieved and maintained a CHOP-INTEND score of ≥40 points at a median age of 20 months.

Table 3.4. CHOP-INTEND Results for Spinraza and Zolgensma in Infantile-Onset (Type I) SMA

	ENDEAR[24]		CS3A[23]	CL-101 [29]	
Follow-Up	Final analysis*		18 months	Interim analysis†	
Treatment	Spinraza	Sham control	Spinraza	Zolgensma, Cohort 1	Zolgensma, Cohort 2
No. of Participants	73	37	14	3	12
Mean Baseline Score, Points	26.63 ± 8.13	28.43 ± 7.56	30 (17-64)	16.3 (6-27)	28.2 (12-50)
Change from Baseline, Points	NR	NR	15.2	7.7	24.6
Responder‡, n (%)	52 (71)	1 (3)	12 (86)	NR	NR

Data are mean (range) or ±SD. Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table 3.1.
CHOP-INTEND: Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders, NR: not reported
*The final efficacy set included infants with assessments at day 183, 302, or 394 and had at least 190 days or more between their first dose of Spinraza and cut-off date of the interim analysis.
†Data cut-off at August 7, 2017. 3/3 and 7/12 patients had 24 months of follow-up.
‡Responder defined as achieving ≥4-point increase in CHOP-INTEND score.

Twelve of 14 (86%) infants in the dose-ranging CS3A study who received 12 mg doses of Spinraza

improved by an average 15.2 (p=0.0013) points from baseline in CHOP-INTEND (Table 3.4).[23] The number of infants reaching the clinical threshold of 40 points on the CHOP-INTEND increased from no children at baseline to 7/13 (54%) infants with two *SMN2* copies in the 12 mg group.

Two of the three included EAPs reported CHOP-INTEND results. Data from the German EAP showed a mean ± standard deviation CHOP-INTEND improvement of 9.0 ± 8.0 points, for a total score of 31.2 ± 16.2 after six months of treatment.[80] Thirteen percent of children achieved a CHOP-INTEND improvement of 4 or less points; 54% showed an improvement of 5 to 14 points, and 18% improved by 18 or more points. Despite having lower CHOP-INTEND scores at baseline, children with two copies of *SMN2* achieved similar motor function gains after treatment compared to children with three *SMN2* copies (8.1 ± 7.0 vs. 8.2 ± 5.3). The study observed an age-related treatment effect on change from baseline CHOP-INTEND, where children seven months and younger improved more than children older than seven months (14.4 ± 9.2 vs. 7.0 ± 6.6, respectively). Subsequent univariate analysis demonstrated that the age at treatment initiation was correlated with change in CHOP-INTEND.

Italian EAP participants improved by a mean 19.6 ± 16.4 points from baseline CHOP-INTEND ($p<0.001$ for baseline vs. six-month score). Improvements from baseline CHOP-INTEND were statistically significant ($p<0.001$) regardless of *SMN2* copy number. Twenty of the 71 patients (28%) older than two years and six of 20 patients (30%) older than 10 years demonstrated an improvement of ≥4 points from baseline CHOP-INTEND.

Motor Milestones

Motor milestones achieved in ENDEAR and CL-101 are shown in Table 3.5. A majority of infants who received Zolgensma achieved head control and rolling over and a minority of infants who received Spinraza achieved head control, rolling over, sitting assisted, or standing with assistance (Table 3.5). Data from the CL-101 trial showed 11 of 12 (92%) children in cohort 2 treated with Zolgensma were able to sit unassisted for ≥5 seconds, 10 (83%) for at least 10 seconds, and 9 (75%) for at least 30 seconds at the end of the two-year trial follow-up.[29] Two more children also achieved sitting unassisted for 30 or more seconds during additional follow-up past two years.[39] Nine (75%) children achieved rolling and 2 (17%) achieved crawling, pulling to stand, standing, and walking independently during CL-101 two-year follow-up.[29] Two more children achieved standing with support in the additional follow-up in START (4/12 [33%] in total).[39]

Table 3.5. Motor Milestone Results for Spinraza and Zolgensma in Infantile-Onset (Type I)

	ENDEAR[24]*		CL-101[29]†	
Other Motor Milestones	Spinraza N=73	Sham Control N=37	Zolgensma, Cohort 1 N=3	Zolgensma, Cohort 2 N=12
Head Control	16 (22)	0	NR	11 (92)
Roll Over	7 (10)	0	NR	9 (75)
Sitting Unassisted	6 (8)‡	0‡	NR	10 (83)§
Standing with Assistance	1 (1)	0	NR	2 (17)
Standing Independently	NR	NR	NR	2 (17)
Walking Independently	NR	NR	NR	2 (17)

All data are n (%). Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table 3.1.
HINE-2: Hammersmith Infant Neurological Examination-Section 2, NR: not reported
*The HINE-2 motor milestone achievements of infants at the later of days 183, 302, and 394. Infants with opportunity for at least a 6-month assessment were included.
†24 month follow-up.
‡Includes "stable sit" and "pivots" from HINE-2.
§Sitting unassisted for at least 10 seconds is in accordance with WHO Motor Milestones criteria.

Long-term follow-up data from SHINE shows additional motor milestone achievements for infants who transitioned from ENDEAR to SHINE. Data from the interim analysis (June 15, 2017) are presented in Table 3.6.[33]

Table 3.6. ENDEAR to SHINE Motor Milestone Achievements[33]

	Baseline	Day 64	Day 183	Day 302	Day 394	Day 578	Day 689
No. with Available Data	81	70	65	51	48	31	17
% Achieved Full Head Control	0	7	17	25	33	45	35
% Achieved Independent Sitting	0	1	5	10	15	29	24

Data are from children who received Spinraza in ENDEAR and SHINE.

In EMBRACE, none of the children who randomized to receive the sham control met any of the milestones assessed in the HINE-2; four (44%) children achieved improvements in head control, six (67%) in rolling, and five (56%) in sitting.[35] None of the children with infantile-onset in the study showed improvements in crawling, standing, or walking.

After six months of Spinraza, children in the Italian and German EAPs achieved one less motor milestone compared to infants who received Spinraza in ENDEAR.[80,81] Four German children (7%) achieved full head control, two (3%) could sit independently, however, none of the children achieved independent standing or walking.[80]

Other Outcomes

Bulbar Function and Nutritional Support

Twenty-four months after treatment with Zolgensma, 11 (92%) CL-101 patients treated in cohort 2 were able to swallow safely, enabling oral feeding (vs. four at baseline).[39] The same 11 patients were able to speak. Additional follow-up in START showed sustained swallowing which enabled oral feeding in all 10 patients followed. Two of these patients received Spinraza during this extension study.[30] Finally, we found limited data regarding post-treatment nutritional support in both the CL-101 and ENDEAR trials (e.g., gastrointestinal tubes) (Table 3.7).

Following six months of Spinraza treatment, 39% of German EAP participants were free of nutritional support via gastronomy tube; five children (8%) required nutritional support during Spinraza treatment.[80] Three Italian EAP participants required nutritional support during Spinraza treatment; all three patients had two copies of *SMN2,* disease onset before three months of age, and were diagnosed prior to the start of the EAP.[81]

Table 3.7. Nutritional Support Results for Spinraza and Zolgensma in Infantile-Onset (Type I) SMA

	ENDEAR[24]		CL-101 [29,39]	
	Spinraza	Sham Control	Zolgensma Cohort 1	Zolgensma Cohort 2
Follow-Up	Final analysis*		Final analysis†	
No. of Participants	80	41	3	12
Baseline GI Tube Use	7 (9)	5 (12)	3 (100)	5 (42)
Post-Treatment GI Tube Use	NR	NR	NR	6 (50) ‡

All data are n (%). Note that the two trial populations differ in baseline characteristics and should not be directly compared; see Table 3.1.
GI: gastrointestinal, NR: not reported
*The final efficacy set included infants with assessments at day 183, 302, or 394 and had at least 190 days or more between their first dose of Spinraza and cut-off date of the interim analysis.
†24 month follow-up.
‡Of five patients requiring tube at baseline, four were able to feed orally and 11/12 were able to swallow independently at last follow-up.

Later-Onset (Type II and III) SMA

One sham-controlled RCT (CHERISH) reported on outcomes of Spinraza in children ages two to 12 years with later-onset SMA (Types II and III), and one Phase Ib/IIa open-label, dose-ranging study (CS2/CS12) on outcomes in children ages two through 15.[25,35] EMBRACE reported on eight children diagnosed with later-onset SMA with broader inclusion criteria than that of CHERISH. Two

prospective cohort studies reported on Spinraza in ambulatory and non-ambulatory adolescents and adults. We did not identify any trials assessing Zolgensma in this population.

Overview of Trials

CHERISH

CHERISH is a sham-controlled RCT which evaluated the safety and efficacy of Spinraza in children two through 12 years old who developed SMA symptoms after six months of age.[24] Children scoring between 10 and 54 points on the Hammersmith Functional Motor Scale-Expanded (HFMSE) [c] who were able to sit unassisted but unable to walk independently were eligible for screening. Children with severe scoliosis and those requiring ventilatory support, defined as requiring invasive or non-invasive support for greater than six hours per day, or gastric tubes for nutritional support were excluded. Eligible children were randomized 2:1—stratified by age (<6 vs. ≥6 years old)—to receive either Spinraza or sham injections on study days 1, 29, 85, and 274, which differs from the approved administration schedule of loading doses on days 1, 15, 29, and 59, followed by maintenance doses every four months thereafter. Spinraza doses were 12 mg delivered by lumbar puncture. The sham injection procedure and study blinding were similar to that described above for ENDEAR, with the addition that children were sedated during their treatment procedure.

CHERISH's primary outcome was the least-squares mean change from baseline in HFMSE score after 15 months of treatment, with a threshold of three points considered clinically meaningful.[24] The proportion of children with an increase of three or more points in HFMSE between baseline and 15 months was a secondary outcome, along with the proportion of children achieving one or more new WHO motor milestones and the change from baseline in the RULM [d] score.

The sponsor conducted a prespecified interim analysis of the primary outcome when all children had been enrolled for a minimum of six months **and** 39 or more children had completed 15-month evaluations.[24] At the time of interim analysis, 54 children (43%) had completed their 15-month evaluation; for the 72 children (57%) who had not yet reached the 15-month assessment, multiple imputation was used to account for HFMSE scores for children with shorter follow-up. Results of the interim analysis showed a statistically-significant benefit on HFMSE score favoring Spinraza, and the trial was terminated early. Like the ENDEAR study, children were invited to complete the 15-month assessment at this time and were eligible to enroll in SHINE to receive Spinraza. The final analysis included all outcomes; however, the primary outcome was not tested statistically a second time. At the time of final analysis, 100 children (79%) had completed their 15-month evaluation; for

[c] A clinician-rated, 20-item scale developed to assess the motor ability of children with SMA with limited ambulation. Higher scores indicate better functioning. Patients and caregivers consider a 1-point increase meaningful.

[d] An assessment designed for upper limb function in patients with SMA. Higher scores indicate better functioning.

the 26 children (21%) who had not yet reached the 15-month assessment, multiple imputation was used for three outcomes (change from baseline in the HFMSE score, percentage of children with a change in HFMSE score of at least 3 points, and change from baseline in the RULM score).

CS2/CS12

CS2 was a multiple-dose, open-label study followed by its open-label extension study, CS12. CS2 included four cohorts of children which received one of four doses – 3, 6, 9, or 12 mg – on the same regimen as CHERISH (study days 1, 29, and 85).[35] The first two cohorts each included eight children and the second two cohorts each included nine children (n=34). Children were followed for six months after the last day of treatment (day 85). The subsequent CS12 study enrolled children from CS2 as well as other eligible children. The enrolled children could receive four doses of Spinraza on CS12 study days 1, 169, 351, and 533; participants rolling over from CS2 received a total of eight doses through day 533 of CS12. Children were followed for six months following the day 533 dose. The primary outcome of these two studies was safety and tolerability of Spinraza lumbar punctures. Exploratory outcomes included the HFMSE, ULM in non-ambulatory children, and 6MWT [e] for ambulatory children.

EMBRACE

As described in the infantile-onset section, EMBRACE was a two-part Phase II trial evaluating Spinraza in a broader population of infants and children compared to ENDEAR.[32] Eight children were diagnosed with later-onset SMA; relevant data are summarized below. Study enrollment, randomization, and the Spinraza dosing regimen were similar to ENDEAR and CHERISH. The primary outcome of part one was to assess Spinraza safety and tolerability in children ineligible to enroll (i.e., a more diverse population) in ENDEAR and CHERISH.

Prospective Cohort Studies

Ambulatory and non-ambulatory patients with later-onset SMA received Spinraza in two prospective cohort studies.[84,85] Stolte et al., treated 28 adults (nine with Type II and 19 with Type III) ages 18-61 with nusinersen, and Wurster et al., treated 20 adolescents and adults (nine with Type II and 11 with Type III). Inclusion criteria for both studies were less restrictive compared to CHERISH and EMBRACE (e.g., did not exclude participants with scoliosis or spine fusion surgeries[85] or nonambulatory participants.[84])

Patient Characteristics and Follow-up

Baseline characteristics of children who participated in CHERISH are presented in Table 3.8. The Spinraza and sham control groups were well-balanced regarding the age at diagnosis and overall

[e] A measure of ambulatory function, specifically how far an individual can walk within six minutes.

motor function and milestones. Children in the Spinraza group appeared to be older with a longer duration of SMA symptoms compared to the sham control group (Table 3.8). There were also fewer children able to walk in the Spinraza group than in the sham control.[25]

Table 3.8. Key Baseline Characteristics of CHERISH

	CHERISH[25]	
Baseline Characteristic	**Spinraza**	**Sham Control**
No. of Participants	84	42
Age at Onset, mo	10.0 (6-20)	11 (6-20)
Age at Diagnosis, mo	18.0 (0-48)	18 (0-46)
Disease Duration, mo	39.3 (8-94)	30.2 (10-80)
Age at Screening, yr	4.0 (2-9)	3.0 (2-7)
Mean HFMSE Score	22.4 ±8.3	19.9 ±7.2
RULM Score	19.4 ±6.2	18.4 ±5.7
Ability to Sit Without Support*	84 (100)	42 (100)
Ability to Walk Without Support*	20 (24)	14 (33)
Ability to Walk Independently*, ≥15m	0	0

Data are mean (range) or ±SD.
HFMSE: Hammersmith Functional Motor Scale-Expanded, mo: months, NR: not reported, RULM: Revised Upper Limb Module, yr: years
*Motor milestone ever achieved. Data are n (%).

Similar proportions of patients in the two treatment groups completed the end-of-study visit (79% vs. 81%) or were followed through the study termination (21% and 19%).[25] Discontinuation of study participation was also similar between groups, with only one child in the Spinraza group discontinuing participation due to early study termination.

Children enrolled in the CS2 study were generally older than children in CHERISH (mean age [SD]: 7.0 years [4.0]).[35] These children were, on average, diagnosed later in life compared to those in CHERISH, however, there was a large difference in age at diagnosis in CS2 where children with Type II were diagnosed much younger than those with Type III (15.4 [6.3] vs. 43.6 [32.4]). Most children (75%) in the study had two copies of *SMN2*, and approximately half were able to walk. All children could sit without assistance, 61% could walk with assistance, 43% could stand unassisted, and 46% could walk independently.

Children diagnosed with later-onset SMA in EMBRACE (n=8) were generally younger than children in CHERISH; the median age (range) at the first dose for the Spinraza and sham control arms were 18.1 (16-19) months and 17.0 (15-19) months, respectively. All five of the Spinraza recipients and two of three sham control recipients had three copies of *SMN2*, while the remaining sham control recipient had only two copies of *SMN2.*

The mean age for participants of the prospective cohort studies were notable older. For adults with Type II and III SMA in the Stolte et al. study, mean age at first dose of Spinraza was 31.2 years (range: 24-48) and 37.9 (range: 18-61), respectively.[84] About half of adults with Type III were able to walk, and none of those with Type II could walk at treatment initiation and baseline RULM scores reflected this split (mean ± SD: 9.9 ± 4.6 and 29.5 ± 8.5 for Types II and III, respectively). HFMSE scores similarly reflected differences in functional motor abilities between Types II and III (mean ± SD: 3.1 ± 2.5 and 31.2 ± 18.1, respectively). Participants in the Wurster et al. study were ages 11-60. The nine participants with SMA Type II and 11 with Type III had a mean HFMSE score of 1.7 (SD: 2.2) and 30.1 (25.0).[85] Baseline RULM scores were not reported.

Survival

Survival was not a prespecified outcome of CHERISH, CS2/CS12, or the prospective cohort studies. There were no deaths during either of these studies.

Permanent Ventilatory Support

Permanent ventilation was not a prespecified outcome of CHERISH, CS2/CS12, or the prospective cohort studies, and no data on permanent ventilation were available.

Event-Free Survival

Event-free survival was not a prespecified outcome of CHERISH, CS2/CS12, or the prospective cohort studies, and no data on event-free survival were available.

Motor Function and Milestones

HFMSE

Spinraza demonstrated a statistically-superior least-squares mean increase from baseline HFMSE score after 15 months of treatment compared to the sham control at the interim analysis (Table 3.9), leading to early study termination.[25] As described previously, the CHERISH interim analysis used the multiple imputation method to account for data missing from children who had not yet completed the 15-month assessment. This analysis included 15-month data from 39 Spinraza and 19 sham control recipients, which is 43% of the enrolled population; data for the remaining 45 Spinraza and 23 sham control recipients were imputed.

For the final analysis, HFMSE data from 18 Spinraza and eight sham control recipients were imputed, as these children still had not yet completed the 15-month assessment. With fewer data imputed, results from the final analysis of mean increase from baseline HFMSE showed a smaller treatment difference than in the interim analysis, although the results remained favorable to Spinraza (mean difference [95% CI]: 4.9 [3.1, 6.7], Table 3.9).[25] A greater proportion of children

who received Spinraza showed a response of ≥3-point increase in HFMSE score versus the sham control, and the calculated odds ratio favored Spinraza treatment over sham control (odds ratio [OR] [95% CI]: 6 [2-15]).

Participants in the Stolte et al. study with Types II and III showed stable HFMSE scores after four doses of Spinraza compared to baseline scores (Type II: 2.0 ± 2.5 vs. 9.9 ± 4.6, p=0.6; Type III: 30.8 ± 24.8 vs. 31.2 ± 18.1, p=0.3). EMBRACE and Wurster et al. did not report post-treatment HFMSE data.

Table 3.9. HFMSE Results from CHERISH in Later-Onset (Type II/III) SMA

CHERISH[25]			
	Spinraza* N=84	Sham Control* N=42	Treatment Difference†
Interim Analysis			
n (%) with 15-Month Data	35 (42)	19 (45)	--
n (%) with HMFSE Data Imputed	49 (58)	23 (55)	--
HFMSE‡ Change from Baseline	4.0 (2.9-5.1)	-1.9 (-3.8-0)	5.9 (3.7, 8.1)
Final Analysis			
n (%) with 15-Month Data	66 (79)	34 (81)	--
n (%) with HFMSE Data Imputed	18 (21)	8 (19)	--
HFMSE‡ Change from Baseline	3.9 (3.0-4.9)	-1.0 (-2.5-5.0)	4.9 (3.1, 6.7)
% of HFMSE Responders§	57 (46-68)	26 (12-40)	OR: 6 (2, 15)

HFMSE: Hammersmith Functional Motor Scale-Expanded, OR: odds ratio
*Data are mean (min-max) or n (%).
†Data are the difference in treatment with Spinraza vs. sham (95% CI).
‡Least-squares mean change from baseline.
§Defined as change from baseline of ≥3 points.

Upper Limb Function

In CHERISH, upper limb motor function, as measured with RULM, improved with Spinraza treatment (least-squares mean score [95% CI]: 4.2 [3.4, 5.0]) and remained stable in the sham control group (0.5 [-0.6, 1.6]).[25] The treatment difference for RULM score (3.7 [2.3, 5.0]) was not formally tested for statistical significance.

In CS2/CS12, at study day 253, 9/11 (82%) and 3/16 (19%) SMA Type II and III children improved by ≥3 points from baseline HFMSE.[35] All six Type III children followed through day 1,050 showed the same improvement; however, only 2/7 (29%) Type II children met the same clinical threshold. Four of six (67%) children with Type II SMA followed through day 1,050 demonstrated clinically-meaningful improvement (≥2 points) in upper limb motor function, as assessed by ULM. Motor function of all children (n=6) with Type III improved, based on the clinically-meaningful threshold for the 6MWT (gain of ≥30 meters).

Motor Milestones

New achievements in walking with assistance, standing alone, and any WHO motor milestone were reported by similar proportions of Spinraza and sham control groups (Table 3.10). Note these data were analyzed only among the children who had completed the 15-month assessment (i.e., no data were imputed). One child in each group gained the ability to stand alone, and one child in the Spinraza group achieved walking with assistance.[25]

Table 3.10. Motor Milestone Results for Spinraza in Later-Onset (Type II/III) SMA

	CHERISH[25]		EMBRACE[43]	
	Spinraza* N=84	Sham Control* N=42	Spinraza N=5	Sham Control N=3
Assessment Timepoint	Final Analysis		Final Analysis†	
N (%) Analyzed	66 (79)	34 (81)	5 (100)	3 (100)
% Who Achieved New WHO Motor Milestone	20 (11-31)	6 (1-20)	NR	NR
Sitting, n (%)	NR	NR	4 (80)	1 (33)
Crawling, n (%)	NR	NR	3 (60)	1 (33)
Standing, n (%)	1 (2) ‡	1 (3) ‡	2 (40) §	2 (67) §
Walking, n (%)	1 (2) ‡	0 (0) ‡	1 (20) §	0 §

NR: not reported, WHO: World Health Organization
*Data are mean (min-max) or n (%).
†Individuals with 6 month (day 183), 10 month (day 304), and 14 month (day 422) visit included. The last assessment available was used for this analysis.
‡Per WHO motor development milestones definition.
§Per HINE-2 definition.

Presymptomatic SMA

One single-arm trial included in our systematic literature review, NURTURE, reported on Spinraza treatment in presymptomatic infants. Trials of Zolgensma are ongoing and no data have been presented to date.

Overview of Trial

NURTURE

NURTURE is a Phase II, single-arm, open-label, multi-center trial of presymptomatic infants. To be eligible for NURTURE, infants were required to be six weeks of age or less, have a documented genetic diagnosis of SMA, and have two or three copies of *SMN2* (i.e., infants most likely to develop SMA Type I or II).[86] Infants showing any signs or symptoms suggestive of SMA onset were excluded. Twenty-five infants were enrolled and will be followed through January 2022 to evaluate the

primary outcome of time to death or respiratory intervention. Respiratory intervention is defined as invasive or non-invasive ventilation for six or more hours a day for seven days or longer or tracheostomy. Secondary outcomes include: the proportion of infants manifesting SMA symptoms, survival, HINE and WHO motor milestones, CHOP-INTEND, HFMSE, and AEs.

Patient Characteristics and Follow-up

Data are reported by *SMN2* subgroup; having two copies of *SMN2* is predictive of later developing SMA Type I, and three copies is predictive of SMA Type II. Most infants received their first dose within the first 28 days of life (Table 3.11). Baseline CHOP-INTEND scores were slightly lower in infants with two *SMN2* copies than those with three *SMN2* copies. The most recent interim analysis was completed in May 2018, at which time the median age at the most recent visit was 26.0 months (range: 14.0-34.3), and median time on treatment was 27.1 months (15.1-35.5).

Table 3.11. Key Baseline Characteristics from NURTURE

Baseline Characteristics		2 *SMN2* Copies	3 *SMN2* Copies	All Participants
No. of Participants		15	10	25
Age at First Dose, Days	≤14	6 (40)	3 (30)	9 (36)
	>14 and ≤28	7 (47)	5 (50)	12 (48)
	>28	2 (13)	2 (20)	4 (16)
	Median	19.0 (8-41)	23.0 (3-42)	22.0 (3-42)
Females		7 (47)	6 (60)	13 (52)
CHOP-INTEND Score		45.0 (25.0-60.0)	53.5 (40.0-60.0)	50.0 (25.0-60.0)
HINE Total Milestones		3.0 (0-5.0)	3.0 (0-7)	3.0 (0-7)

Data are n (%) or median (range).

Survival and Permanent Ventilatory Support

In NURTURE, all 25 children treated with Spinraza were alive at the May 2018 interim analysis. Four (16%) children met the primary outcome of required respiratory intervention (defined as requiring six or more hours per day for seven consecutive days or tracheostomy); all four children had two *SMN2* copies. All of these infants received respiratory intervention during an acute, reversible illness, and none required permanent ventilation or tracheostomy.

Motor Function and Milestones

Interim data from July 2017 evaluated whether children participating in NURTURE showed any protocol-defined symptoms of SMA by 13 months of age. A total of 17 children had analyzable data from the Day 365 study visit, of whom 8/12 (67%) and 1/5 (20%) children with two and three *SMN2* copies, respectively, had developed one or more SMA symptoms. None of these nine children achieved hands and knees crawling (average age of attainment: 8.5 months). Five of 12 (42%) children with two *SMN2* copies were unable to stand with assistance (average age of attainment:

9.2 months; Table 3.12). It is equally common for infants to achieve hands-and-knees crawling before standing with assistance as it is to achieve standing with assistance before hands-and-knees crawling.[62]

By the May 2018 interim analysis, caregivers reported all 25 (100%) children had achieved sitting without support, 22/25 (88%) of children had achieved walking with assistance, and 17/25 (68%) had achieved walking alone (Table 3.12). Four children each achieved sitting unsupported and walking alone later than expected in healthy children, and seven children were able to walk with assistance later than expected. At the most recent study visit, the mean (range) CHOP-INTEND scores for children with two and three *SMN2* copies were similar and reflected near-maximal motor function (two copies: 61.0 [46-64]; three copies: 62.6 [8-64]).

Table 3.12. WHO Motor Milestone Achievements for Spinraza in Presymptomatic SMA

WHO Motor Milestone	Expected Age Range of Attainment*	July 2017†‡		May 2018†§	
		2 *SMN2* Copies	3 *SMN2* Copies	2 *SMN2* Copies	3 *SMN2* Copies
Independent Sitting	3.8 – 9.2	14 (93)	8 (80)	15 (100)	10 (100)
Walking with Assistance	5.9 – 13.7	5 (33)	7 (70)	12 (80)	10 (100)
Walking Alone	8.2 -17.6	3 (20)	5 (50)	8 (53)	9 (90)

*Data reported in months. Range defined by 1st-99th percentile for the windows of milestone achievement.
†Data reported as N (%).
‡The median age at the most recent visit was 14.7 months (range: 2.8-23.3).
§The median age at the most recent visit was 26.0 months (range: 14.3-34.3).

All Populations: Harms

Safety data were collected in four clinical trials of Spinraza (ENDEAR, CHERISH, EMBRACE, and SHINE) and Zolgensma (CL-101/START). Integrated safety data from the Spinraza trials and CL-101/START are presented in Table 3.13.

Sixteen percent of infants who received Spinraza and 39% of sham control infants in ENDEAR discontinued study participation due to AEs (Table 3.13).[24] No children in CHERISH or NURTURE discontinued due to AEs.[25,44] Treatment-related AEs were rare in all Spinraza trials (Table 3.13). SAEs were more frequently reported by sham control than Spinraza recipients in ENDEAR (95% vs. 76%, respectively) and CHERISH (29% vs. 17%, respectively).[24,25]

We noted differences in AEs related to the route of administration. Many of the frequently-reported AEs reported following treatment with Spinraza were related to the lumbar puncture procedure (e.g., fever, headache, vomiting, and back pain). Lumbar-puncture-associated AEs were reported only by children in CHERISH; however, this is likely due to the difficulty of collecting information from infants. Additional common AEs associated with Spinraza include: lower

respiratory tract infection and constipation (Table 3.13). Fever was more common among infants (ENDEAR) than older children (CHERISH) compared to the sham control.

Based on clinical trial data and known side-effects related to oligonucleotides with a phosphorothioate backbones,[45] two safety concerns are highlighted in the Spinraza prescribing information: risk of thrombocytopenia and potential for kidney damage (renal toxicity).[22] FDA-required monitoring to assess patient safety includes coagulation and quantitative spot urine testing prior to each dose.

Table 3.13. Harms Reported in START and Spinraza Clinical Trials

	CL-101 (Zolgensma) (Cohort 2 only; n=12)	ENDEAR & CS3A (n=100)	CHERISH & CS1,2,10 &12 (n=140)	NURTURE (N=20)	ENDEAR & CHERISH (n=83)
Summary of AEs					
AEs Leading to Discontinuation	0 (0)	16 (16)	0 (0)	0 (0)	16 (19)
Treatment-Related AEs	3 (25)	0 (0)	1 (<1)	0 (0)	0 (0)
Patient Death	0 (0)	17 (17)	0 (0)	0(0)	16 (19)
Incidence of AEs	12 (100)	77 (77)	19 (14)	6 (30)	50 (60)
Common AEs, No. of Events, No. of Patients	NR	1,627 97 (97)	1,187 134 (96)	141 16 (80)	909 82 (99)
Common AEs*					
Pyrexia	6 (50)	59 (59)	49 (35)	5 (25)	39 (47)
URTI	10 (83)	36 (36)	50 (36)	8 (40)	25 (30)
Nasopharyngitis	NR	21 (21)	33 (24)	4 (20)	15 (18)
Vomiting	NR	22 (22)	33 (24)	0 (0)	8 (10)
Headache	NR	0 (0)	51 (36)	0 (0)	0 (0)
Constipation	NR	37 (37)	0 (0)	2 (10)	14 (17)
Back Pain	NR	0 (0)	44 (31)	0 (0)	0 (0)
Cough	NR	15 (15)	26 (19)	3 (15)	17 (20)
Pneumonia	2 (17)	30 (30)	0 (0)	2 (10)	14 (17)
Respiratory Distress	NR	28 (28)	0 (0)	0 (0)	12 (14)
Scoliosis	NR	11 (11)	18 (13)	0 (0)	0 (0)
Diarrhea	NR	16 (16)	0 (0)	0 (0)	7 (8)
Respiratory Failure	3 (25)	26 (26)	0 (0)	0 (0)	16 (19)
Atelectasis	4 (33)	NR	NR	NR	NR
Post-Lumbar Puncture Syndrome	NR	0 (0)	26 (19)	0 (0)	0 (0)

All data are n (%).

AE: adverse event, SAE: serious adverse events, URI: upper respiratory tract infection

*Reported by >10% of participants.

In CL-101, two infants had elevated serum aminotransferase levels after Zolgensma infusion; both were considered treatment related and met criteria for grade 4 AEs (patient 1, cohort 1: 31 times upper limit of normal [ULN] for alanine aminotransferase [ALT] and 14 times ULN for aspartate aminotransferase [AST]; patient 2, cohort 2: 35 times ULN ALT and 37 times ULN AST).[29] A protocol amendment requiring oral prednisolone treatment (1 mg/kg) for 30 days starting 24 hours prior to

Zolgensma infusion was added following the first infant's dosing and subsequent serum aminotransferase elevation. Two infants also experienced asymptomatic elevations in serum aminotransferase levels which were deemed nonserious, treatment-related AEs.

3.4 Controversies and Uncertainties

The currently available trials of Spinraza (SMA Types I-III) and Zolgensma (SMA Type I) show prolonged survival and improved motor function compared with historical controls or sham injections. However, there remains considerable uncertainty in the generalizability of the results and in the long-term durability and tolerability of treatment. In particular, for both interventions, the narrow eligibility criteria of trials and the limited sample size (especially for Zolgensma) raises concerns about generalizability of results to the wider population of patients with SMA. The ineligible or otherwise unselected patients are likely more severely ill, experience different or additional comorbidities (e.g., scoliosis), or have a different genetic profile than those selected for the clinical trials. For example, the EAP studies enrolled more heterogeneous patients than in the clinical trials for Spinraza, and treatment with Spinraza had a smaller magnitude of benefit in terms of motor functioning compared with the benefits observed in the clinical trials.

In addition, there is a lack of data on the long-term safety and efficacy of both interventions. The currently-available data do not indicate diminishing benefit, which is promising. Nevertheless, because SMA is a rare disease and the trials have short-term follow-up, understanding the long-term effects of Spinraza or Zolgensma will take time.

For the evidence on Zolgensma, an additional concern is the single-arm design which presents challenges in identifying an appropriate comparison group or "counterfactual." In other words, we do not know how the 15 patients would have progressed if they had not been treated with Zolgensma. Comparisons with historical controls can exaggerate perceived treatment effects, particularly when standards of care improve over time or when there is a variable natural history,[46] which are both true of SMA. For example, in older natural history studies, approximately 68% of patients with Type I SMA died by two years of age. In part due to the improvements in and increased utilization of nutritional and respiratory support, more recent estimates of mortality are approximately 30% at two years of age with approximately half of survivors reliant on noninvasive ventilation. In the trial of Zolgensma, although all 12 patients in the high-dose cohort remained alive and not using permanent ventilation at two years, the outcomes that would have been observed had a concurrent control group been included are unknowable.

Another uncertainty pertinent to Zolgensma relates to the unknown duration of expression of the gene therapy. Gene therapy may provide life-long benefit to patients. On the other hand, if the expression wanes over time, the subsequent treatment pathway is unclear. If antibodies to AAV form, the patient would be unable to receive another dose of Zolgensma. Some patients who received Zolgensma in START went on to take Spinraza after the trial, but the effects of combination

or sequential therapies have not been well studied. In terms of safety, liver toxicity was mitigated by amending the protocol to include an administration of prednisolone before and after Zolgensma infusion. It will be important to monitor liver functioning in patients treated with Zolgensma. Finally, Zolgensma has currently been studied in 15 patients with symptomatic Type I SMA. Early, presymptomatic treatment may provide more benefits to patients, but no data from presymptomatic patients are currently available. Single-arms trials of patients with presymptomatic SMA and other trials with symptomatic SMA Types II-III (other route of administration) are forthcoming (see Appendix C).

For the evidence on Spinraza, an additional source of uncertainty relates to the repeated lumbar punctures in patients, particularly as they age or progress along the disease course. While repeated lumbar punctures were generally tolerated in the clinical trials, some patients required sedation to limit movements during the procedure. The procedure can be further complicated in patients with scoliosis or respiratory complications. In terms of other safety concerns, the Spinraza prescribing information notes the risks of thrombocytopenia and renal toxicity. Finally, although Spinraza has only been studied in patients with SMA Types I-III, it is indicated for patients with SMA of any type. To our knowledge, there are no planned studies to assess the benefits of Spinraza in patients with Type 0 or Type IV. As newborn screening for SMA becomes more common, it is likely that patients will be treated soon, perhaps before developing symptoms. Single-arm trials of patients with presymptomatic SMA are ongoing (see Appendix C).

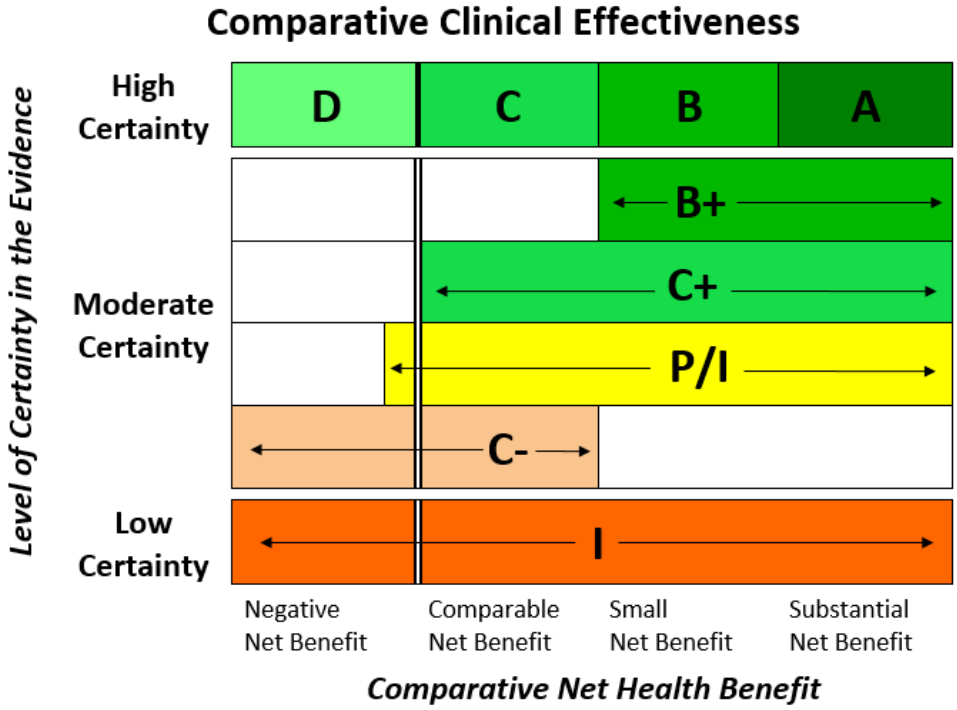
Although it can be tempting to compare the effectiveness of Spinraza and Zolgensma by looking at the results from the ENDEAR and START trials, such comparisons should be avoided. The enrolled populations differed between the trials. For example, there are differences in age at treatment initiation and duration of disease, which are known to be modifiers of treatment effect. In addition, the time point of analysis (median of approximately nine months in ENDEAR and 24 months in START) and approach for assessing motor milestones (HINE-2 vs. WHO) differs between the studies.

3.5 Summary and Comment

SMA is a rare, genetic neuromuscular disease that causes irreversible motor neuron damage that prevents patients from gaining or retaining motor functions. Survival depends on respiratory function, and many infants and children become permanently ventilated. Considering that SMA is a rare disease, the existing evidence base contains many of the common limitations pervasive in rare disease areas, including a small patient population, clinical trial design challenges, and lack of long-term safety and efficacy data. The current limitations of the clinical evidence for Spinraza and Zolgensma include study populations that limit the generalizability of clinical outcomes to SMA patients who differ from those included in the trials, limited long-term safety (e.g., repeated lumbar puncture procedures) and efficacy data (e.g., durability of novel gene therapy), and the uncontrolled, open-label design of the CL-101 trial of Zolgensma. Should additional data regarding

treatment safety and efficacy become available, the conclusions of this report may require updating.

Figure 3.2. 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 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 comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

We identified several gaps in evidence relevant to our review. Based on the lack of relevant data, we've rated the following evidence in the following populations as "insufficient" (I).

- Type 0 SMA
  - Spinraza
  - Zolgensma
- Later-onset (Types II and III) SMA
  - Zolgensma
- Type IV SMA
  - Spinraza
  - Zolgensma

- Presymptomatic
    - Zolgensma

A comprehensive summary of evidence ratings for Spinraza and Zolgensma for each population defined in Section 1.2 are shown in Table 3.14. Additional details are provided below.

Table 3.14. Evidence Ratings for Spinraza and Zolgensma for SMA

Population	Spinraza	Zolgensma	Ability to Distinguish?
Type 0 SMA	I*	I*	I†
Infantile-Onset (Type I) SMA	A	A	I
Later-Onset (Type II and III) SMA	B+	I*	I†
Type IV SMA	I*	I*	I*
Presymptomatic SMA	B+	I*	I†

*No studies (e.g., RCTs, observational, etc.) identified.

†Comparison is based on lack of available evidence for Zolgensma.

Spinraza for Infantile-Onset SMA

Based on the evidence, Spinraza demonstrated statistically-significant reductions in the need for ventilatory support and improvements in survival. Spinraza was also superior to standard care in improving motor function and milestone achievement, as measured by the HINE-2 and CHOP-INTEND assessments.

We noted some differences between the Spinraza and sham control groups at baseline which suggests more severe symptoms in the Spinraza group. We also noted potentially limited generalizability, as Type I SMA patients with more severe disease were underrepresented in the trials and may not adequately reflect the "real-world" patient population.

Despite these limitations, we have high certainty that Spinraza provides a substantial net health benefit compared to standard care and rate the evidence as "superior" to standard care (A).

Zolgensma for Infantile-Onset SMA

All infants in the Phase I CL-101 trial were alive following at least 24 months of follow-up. Infants also showed gains in CHOP-INTEND motor milestones and most infants who received the proposed therapeutic dose (cohort two) achieved full head control and rolling over motor milestones. Despite the limitations of the single-arm, open-label design in which 12 infants received the proposed therapeutic dose, we have high certainty that Zolgensma provides a substantial net health benefit, and rate the evidence base as "superior" to standard care (A).

Zolgensma versus Spinraza for Infantile-Onset SMA

Differences in trial populations related to age at treatment initiation and disease duration limit our ability to adequately distinguish the net health benefit of Zolgensma versus Spinraza for infantile-onset SMA. We therefore rate the evidence to be insufficient (I).

Spinraza for Later-Onset SMA

Based on the single randomized controlled trial of Spinraza in later-onset SMA patients (CHERISH), Spinraza demonstrated statistically-superior improvements in changes from baseline HFMSE, and in the proportion of HFMSE responders, versus the sham control.

Spinraza's superiority in improving HFMSE was evident at the interim analysis, and the study was subsequently terminated early. The interim analysis imputed data from approximately 57% of the enrolled population that had not yet been observed for the full 15-month period. Nevertheless, the final analysis, with 79% (100/126) of patients having been observed for 15-months, continued to show superior benefits of Spinraza on HFMSE scores. Among the 100 patients with observed 15-month data, Spinraza was not superior, however, in improving WHO motor milestone achievements such as unassisted sitting, standing, or walking compared to the sham control.

Similar to ENDEAR, we noted potentially limited generalizability, in that the trial population may not reflect the all patients eligible for treatment. Another limitation is that survival, ventilation, and event-free survival were not evaluated in CHERISH. Finally, we did not find any data regarding long-term safety and durability of clinical benefit.

Overall, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit and rate the evidence as "incremental or better" (B+).

Spinraza for Presymptomatic SMA

Evidence from the NURTURE trial shows all 25 infants enrolled were alive and four (16%) children met the primary outcome of required respiratory intervention, all of whom had two *SMN2* copies. CHOP-INTEND scores for children with two and three copies were similar and reflected near-maximal motor function. Many children with one year of follow-up, however, had developed one or more clinical symptoms of SMA; the severity of these symptoms are not reported. Furthermore, we found only grey literature (i.e., conference presentations), which have not been peer-reviewed.

Overall, we have moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit and rate the evidence as "incremental or better" (B+).

Comparison of Evidence Ratings for Spinraza and Zolgensma

The evidence base for Spinraza includes multiple randomized placebo-controlled trials, while the evidence base for Zolgensma is primarily an uncontrolled study in 12 patients. Despite the clear differences in evidence bases, in the ICER rating system, we have rated both therapies as "superior" to standard care (A) for patients with infantile-onset SMA. This judgment reflects that while we have far greater uncertainties about the exact net benefits of Zolgensma than Spinraza, the magnitude of effect in these 12 patients was large enough to have high certainty that Zolgensma provides a substantial net health benefit compared with standard care. Additionally, for both therapies, even if efficacy were maintained only for the duration already observed in the studies evaluating them, we would still assign an "A" rating to the therapies. As stated in ICER Evidence Rating Matrix: A User's Guide, "We find it useful to consider that conceptual confidence intervals around a point estimate that do not extend beyond a single box of comparative net health benefit represent a 'high' level of certainty." The ratings of "A" for both therapies should not be interpreted to mean that we are able to state that they have similar net benefits, or that we believe the studies within the evidence bases to be of equal quality. It should also not be interpreted to mean that we have similar "conceptual confidence intervals" around net benefits – we do not. Such conceptual confidence intervals are much wider around the net benefit of Zolgensma than Spinraza. However, in each case we judge that the conceptual confidence intervals do not extend below "substantial" net benefit compared with standard care.

4. Long-Term Cost Effectiveness

4.1 Overview

The aim of this economic evaluation was to estimate the cost-effectiveness of Spinraza and Zolgensma, each compared to best supportive care (BSC), from the US health care sector for patients with SMA, in alignment with ICER's Value Assessment Framework for Ultra Rare Diseases. We developed three *de novo* models in Microsoft Office Excel 2016 (Redmond, WA): a model for symptomatic patients with infantile-onset (Type I) SMA; a model for symptomatic patients with later-onset (Type II/III) SMA; and a model for presymptomatic SMA patients. For each population, we estimated the half-cycle corrected lifetime costs, life years gained, and quality adjusted life years (QALYs) gained, discounted at 3% per annum, for Spinraza and BSC. We used these results to generate incremental cost per QALY gained and incremental cost per life-year gained, comparing Spinraza to BSC. We also estimated these outcomes for Zolgensma among patients with Type I SMA and compared the results of Zolgensma versus BSC. Several scenario analyses evaluated the impact of taking a modified societal perspective, alternative survival, cost, and utility assumptions. Although we present a scenario analysis that compares Zolgensma to Spinraza, we did not consider this to be a suitable base case. The rationale for this decision is discussed in Section 4.4. The structure of the models, assumptions, data, and results are described in detail below.

4.2 Methods

Model Structure

The models were dependent on three constructs: the motor function milestones achieved, need for permanent ventilation, and the time to death. The motor function milestones included sitting and walking. Other motor function milestones such as head control, rolling, crawling, and standing were not modelled as explicit health states, but health benefits associated with such improvements were explored. The models did not include scoliosis surgery. Figures 4.1 and 4.2 depict the analytic frameworks for the models. Note that the same model structure was used for patients with infantile-onset (Type I) SMA and presymptomatic SMA patients.

The models contained two parts: 1) a short-term model concordant with clinical study data, and 2) a long-term extrapolation model. A brief description of each is provided here, with detailed explanations on assumptions and data presented in subsequent sections.

Figure 4.1. Model Schematic for Patients with Infantile-Onset (Type I) SMA and Presymptomatic SMA Patients

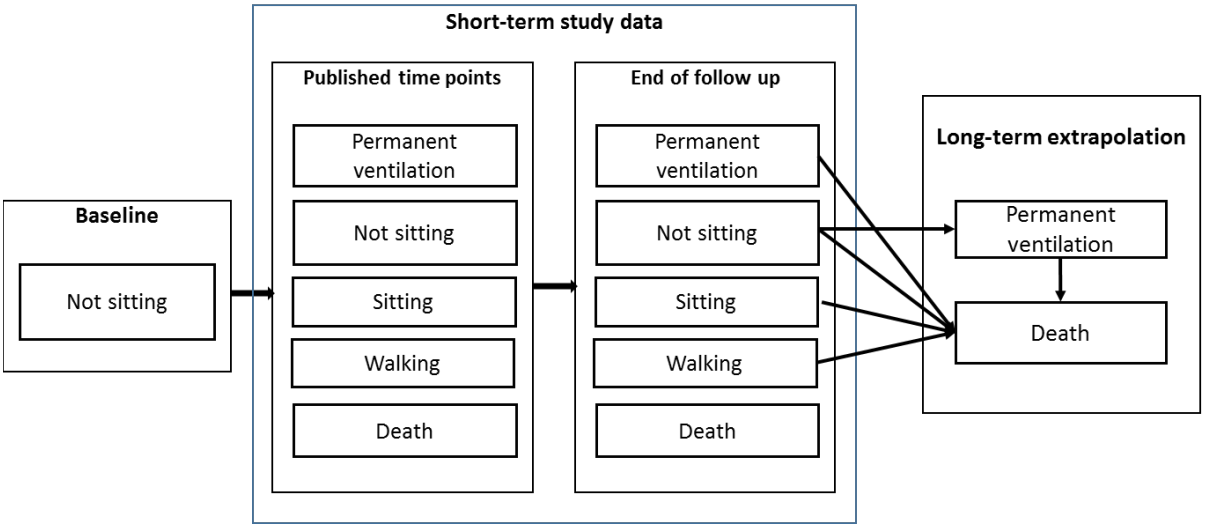
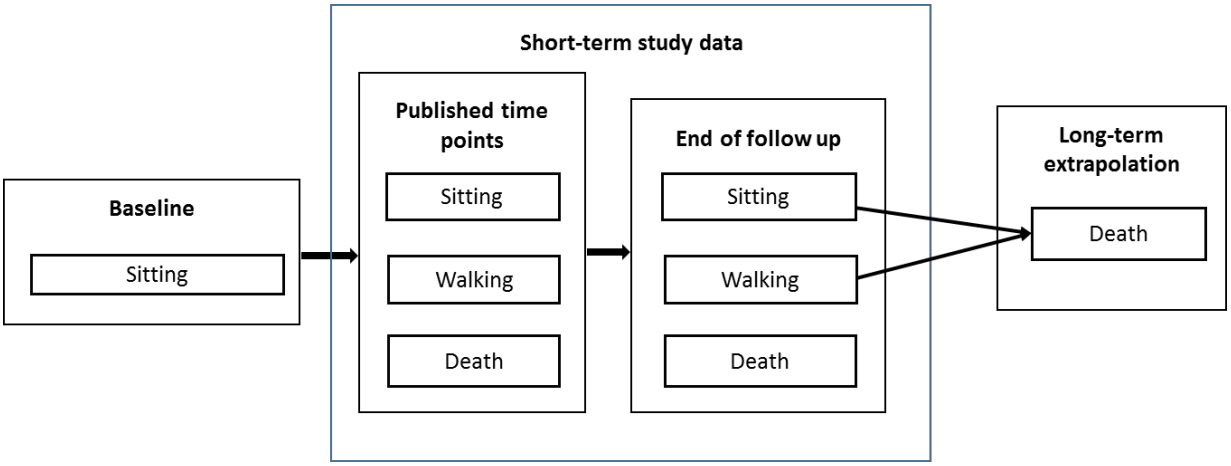


Figure 4.2. Model Schematic for Patients with Later-Onset (Type II/III) SMA



Short-Term Model

Data inputs for each intervention (Spinraza, Zolgensma) were derived from their respective clinical trials and used directly in the model to capture the proportion of the patients in the different health states at different points in time. These data allowed an estimate of the discounted costs, discounted LYs, and discounted QALYs for each of the two interventions and BSC within the study periods. There is no trial of Zolgensma versus BSC, so data from the BSC arm in ENDEAR was used to inform this comparison.

Long-Term Model

The long-term model involved the extrapolation of motor function milestones, permanent ventilation, and mortality, the latter of which was assumed to be conditional on health states. The long-term model used monthly time cycles (i.e., of 30.44 days [365.25 days/12 months]) to estimate lifetime costs and QALYs.

We modeled the extrapolation of motor function milestones over a lifetime using different scenarios. In the base-case analysis, we assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death (i.e., patients stayed in the same motor function milestone-based health state until death). In addition, we also modeled conservative scenarios (only for Type I SMA patients) for the interventions where a proportion of patients lost milestones.

Transition to the permanent ventilation health state in the model was only possible for patients who did not have any motor function milestones (i.e., those in the "not sitting" health state). For these patients, both overall survival (OS) and ventilation-free survival (VFS) were modelled. Patients who achieved motor function milestones were not considered to be at risk of transitioning to permanent ventilation.

Target Populations

The average age and gender distribution at treatment of the SMA populations considered for the model are presented in Table 4.1, which are based on average values reported in the key clinical trials.[24,27-29]

Table 4.1. Base-Case Model Cohort Characteristics

	Infantile-Onset (Type I) SMA	Later Onset (Type II/III) SMA	Presymptomatic SMA
Mean Age	4.4 months	2 years	21 days
Female	55%	50%	52%

Treatment Strategies

The interventions of interest were Spinraza and Zolgensma. Spinraza is administered per its labelled indication as four initial loading doses and once every four months thereafter using intrathecal injection. Zolgensma is a one-time therapy administered using single intravenous infusion. The interventions were compared to BSC, consisting of standard respiratory, gastrointestinal, and nutritional care for SMA patients.

Key Model Choices and Assumptions

The assumptions for the base-case model are described in Table 4.2.

Table 4.2. Key Model Assumptions

Assumption	Rationale
The analyses used a naïve comparison between Zolgensma and BSC, and Spinraza and BSC.	There are no head-to-head trials comparing Zolgensma to the other interventions, and individual patient data (IPD) would be needed to perform matched, adjusted indirect comparisons or simulated treatment comparisons. As IPD were not available, only a naïve comparison is possible. Thus, the model compared the results of Zolgensma to BSC and Spinraza to BSC without any adjustment for differences in patient characteristics between the studies.
Data from the trials and studies on motor function milestones, permanent ventilation, and mortality were used directly in the short-term model.	Robust estimation of disease progression parameters (e.g., transition probabilities) was not possible without access to IPD from the trials and studies. As such, data for the different interventions during the study period were used directly in the model to estimate short-term costs/QALYs.
In the short-term model for Spinraza, we assumed that the proportion of patients sitting among those alive who are not followed up is the same as the observed proportion of patients sitting among who attended the follow up visits.	The proportion of patients reported sitting in Castro et al.[27] are based on those attending the follow-up visits at that time point and we do not know the proportion of patients who were able to sit among those who did not attend follow up visits. As such, we assumed that they are the same.
Motor function milestones achieved at the end of the follow up are sustained until death.	There were no long-term data on the extrapolation of motor function milestones identified; the base-case analyses assume that these milestones are sustained until death. However, alternative scenario analyses were also considered.
Utility benefit was assumed in the treatment arms for patients achieving interim motor function milestones such as head control, rolling, crawling, and standing.	Although interim milestones are not modelled as explicit health states in the model, utility benefit was assumed in the treatment arms to account for achieving these interim milestones. This was implemented as additional utility benefit in treatment arms for the "not sitting" and "sitting" health states.
Only patients in the "not sitting" health state can transition to "permanent ventilation" state.	Clinical experts deemed it reasonable to assume that patients achieving motor function milestones are not at risk of permanent ventilation.
In the BSC arm, for patients in the "not sitting" health state at the end of the short-term model, a partitioned survival modelling approach was used to estimate the proportions of patients dying and moving to permanent ventilation.	The data sources only reported the OS and the VFS, so the VFS curve is subtracted from the OS curve to estimate the proportion of patients in "permanent ventilation" health state.

In the treatment arms, we assumed that patients in the "not sitting" health state at the end of the short-term model had the same survival as those on "permanent ventilation".	The data show better survival in "permanent ventilation" state than "not sitting" state. As such, we made this assumption to account for the survival benefit in the treatment arms for achieving interim milestones such as head control and rolling among patients in the "not sitting" health state. This is an assumption favorable to the drug given that observational data suggest lower mortality for patients on permanent ventilation compared to those who were unable to sit.
No explicit transitions from "not sitting" to "permanent ventilation'" were modelled in the treatment arms.	We did not know the transition between these two health states. However, additional costs for permanent ventilation were included for three months prior to death in the "not sitting" state
Patients with SMA Type I who are in "sitting" health state are assumed to have mortality similar to that of SMA Type II patients.	Clinical experts deemed it reasonable to assume that SMA Type I patients who can sit have similar prognosis as SMA Type II patients who are able to sit but not walk.
Patients with SMA Type I who are in "walking" health state are assumed to have mortality similar to that of SMA Type III patients.	Clinical experts deemed it reasonable to assume that SMA Type I patients who can walk have similar prognosis to SMA Type III patients who are able to walk.
Patients on Spinraza who did not achieve motor function milestones at 24 months discontinued the treatment. We assumed no other patients discontinue Spinraza in the model.	In the Spinraza model submitted to the National Institute for Health and Care Excellence (NICE), this was assumed to be 13 months. However, our model used 24 months to reflect the patients who continue to receive Spinraza, as observed in SHINE[27] extension study.
AE costs and disutilities were not included in the model.	Given the nature of SMA, it is difficult to disentangle the AEs due to treatment from the complications associated with SMA, which are already accounted for in the health state costs and disutilities. As such, separate costs and disutilities for adverse events are not included in the model.
The costs of BSC are not broken out beyond the health state costs in the model.	It is likely that the health state costs included in the model already include the costs of BSC.
The transition probabilities were not adjusted for age at the start of treatment in the SMA Type I model.	The data sources used to estimate the mortality risks for SMA Type I patients have similar starting ages, so they are not explicitly adjusted for age at treatment.
None of the patients in the Zolgensma arm are assumed to die in the short-term model.	None of the 12 patients receiving Zolgensma in the single arm study[29] had died at the last follow up and as such this is reflected in the short-term model. Given the small sample size, we acknowledge that it may be misrepresentative of real-world scenarios to assume that no patients on Zolgensma will ever die in the short-term model.

Model Inputs

In the subsections below, we first present the health state inputs for each of the short-term models (i.e., infantile-onset SMA, later-onset SMA, and presymptomatic SMA). The health state inputs for long-term extrapolation are common across these models, and as such are presented together in the next subsection. In subsequent sections, health state utilities, costs, and productivity gains are presented.

Infantile-Onset (Type I) SMA Short-Term Model

Motor Function Milestones

The data on proportions of Spinraza patients achieving motor function milestones at different time points for the different interventions were based on the ENDEAR trial[24] and SHINE study.[27] For Spinraza, Castro et al.[27] reported the proportion of patients achieving sitting at different time points, which are presented in Table 4.3.

Table 4.3. Motor Function Milestones Achieved on Spinraza

	Baseline n=81	Day 64 n=70	Day 183 n=65	Day 302 n=51	Day 394 n=48	Day 578 n=31	Day 698 n=17
% Achieving Independent Sitting (But Not Walking)	0	1	5	10	15	29	24
% Achieving Walking	0	0	0	0	0	0	0

With different numbers of patients at risk at these time points, we followed a multi-stage process to estimate the true proportions of Spinraza patients achieving the milestones (i.e., proportions using n=81 at the baseline) as described in Appendix Table E2.

No patients in the BSC arm were assumed to achieve any motor function milestones at any time points since the trial reported that 0% of the patients in the sham control group achieved the ability to sit independently during assessments at days 183, 302, or 394. We could not include longer-term data on this estimate in the BSC arm as all sham control patients in ENDEAR[24] switched to Spinraza treatment in SHINE, an OLE trial.[27]

For Zolgensma, we used the data submitted in confidence by the manufacturer, which were unmasked in November 2020 per ICER's Data-in-Confidence policy and can be found in Appendix Table E50. Five of 12 patients treated with Zolgensma were started on Spinraza at the end of the study period; however, two of these patients discontinued, leaving three patients on treatment. As it was not clear whether these patients were not sitting, sitting, or walking, we assumed that they were in the sitting health state, which had the greatest proportion (75%) of patients at the end of the short-term model. So, a third of the patients in the "sitting" health state at the end of the

short-term model (i.e., three out of nine) in the Zolgensma arm received Spinraza. As we did not know whether they received Spinraza because their health state started to deteriorate or because they did not improve as much as desired, we assumed that half of the patients would lose a milestone in the absence of Spinraza. We therefore assumed that a sixth (33% * 50%) of the patients in the sitting health state at the end of the short-term model in the Zolgensma arm dropped a milestone (i.e., to not sitting) to reflect those patients who apparently required Spinraza after the study period.

Mortality

The proportions of patients alive at different time points were estimated from the OS data presented for each intervention. The OS data for Spinraza were from patients who received Spinraza in both ENDEAR[24] and SHINE.[27] The OS data for BSC were from patients who received sham control in ENDEAR, but only the data until the end of the ENDEAR trial period were used in the model, as all sham control patients switched to Spinraza in SHINE.[27]

None of the 12 patients receiving Zolgensma in the single-arm study[29] died at the last follow-up of 24 months, and this is reflected in the model. Given the small sample size, we acknowledge this may not be representative of real-world scenarios to assume 100% survival in the short-term model.

Permanent Ventilation

The VFS rates at different time points were estimated from the combined VFS data in ENDEAR[24] and SHINE,[27] and subtracted from the OS data to estimate the proportion of patients under permanent ventilation for the Spinraza arm. The VFS data for BSC were from patients who received sham control in ENDEAR[24] alone. We did not use data from SHINE[27] since patients in the sham control arm in ENDEAR[24] were switched to Spinraza in SHINE. None of the 12 patients receiving Zolgensma in the single-arm study[29] received permanent ventilation at the last follow up, and this is reflected in the model.

Not Sitting

In the short-term model, the proportion of patients in the "not sitting" health state was estimated as the complement of the sum of proportions of patients on permanent ventilation, patients achieving milestones, and patients that died. That is, patients not in any of the above health states remained in the "not sitting" health state.

When estimating these proportions, patients were assigned to the highest milestone. That is, if a patient achieved both sitting and walking, they were accounted for in the "walking" health state but not accounted for in the "sitting" health state.

Later-Onset (Type II/III) SMA Short-Term Model

Motor Function Milestones

The short-term model for patients with later onset SMA assumed that the Spinraza patients remain in the "sitting" health state until the end of the short-term model based on trial data,[25] where none of the patients achieved the ability to walk independently and only one patient (out of 84) was able to walk with assistance.

Trial results showed that none of the patients in the sham control arm (n=42) achieved the ability to walk independently or walk with assistance.[25] As such, the model assumed that the BSC patients remain in the "sitting" health state until the end of the short-term model.

Presymptomatic SMA Short-Term Model

Effectiveness of Spinraza in achieving motor function milestones in presymptomatic patients was estimated from the NURTURE study.[28] The model for symptomatic SMA Type I patients was adapted to estimate the costs and QALYs for presymptomatic SMA patients. As the NURTURE study[28] does not report which patients would have been SMA Type I or SMA Type II/III, the proportions of these patients were estimated based on *SMN2* copies and expected proportions of different SMA types in the real world. The proportions of patients with SMA Type I, SMA Type II and SMA Type III in the presymptomatic model were 60%, 30%, and 10% respectively. These proportions were derived by assuming that the patients with two *SMN2* copies (n=15) were SMA Type I patients and the patients with three *SMN2* (n=10) copies were SMA Type II and SMA Type III patients.

Exploratory analyses were also performed to estimate the cost-effectiveness of a hypothetical drug which has the costs of Zolgensma and efficacy of Spinraza in the presymptomatic SMA population.

Long-Term Model

Extrapolation of Motor Function Milestones

Motor function milestones in the long-term model were extrapolated based on milestone status at the end of the short-term model, with a base-case assumption that milestone status remained the same until death.

As stated earlier in this section, we also modeled more conservative scenarios (for SMA Type I patients only), where we assumed that a proportion (ranging from 10% to 30%) of patients in the "sitting" health state lost their motor function milestones.

Extrapolation of Mortality and Permanent Ventilation

At the end of the short-term model, patients were in one of the following health states: "permanent ventilation," "not sitting," "sitting," or "walking." Those in the "not sitting" health state in the BSC arm could either transition to permanent ventilation or die, and we modeled both, both OS and VFS for these patients. For those in the treatment arms, we modeled transition to only death and not permanent ventilation among those in the "not sitting" health state. However, we included the costs for permanent ventilation for the three months prior to death for those transitioning to death from this health state. The patients in all other health states were not considered to be at risk of transitioning to permanent ventilation and, as such, could only transition to death.

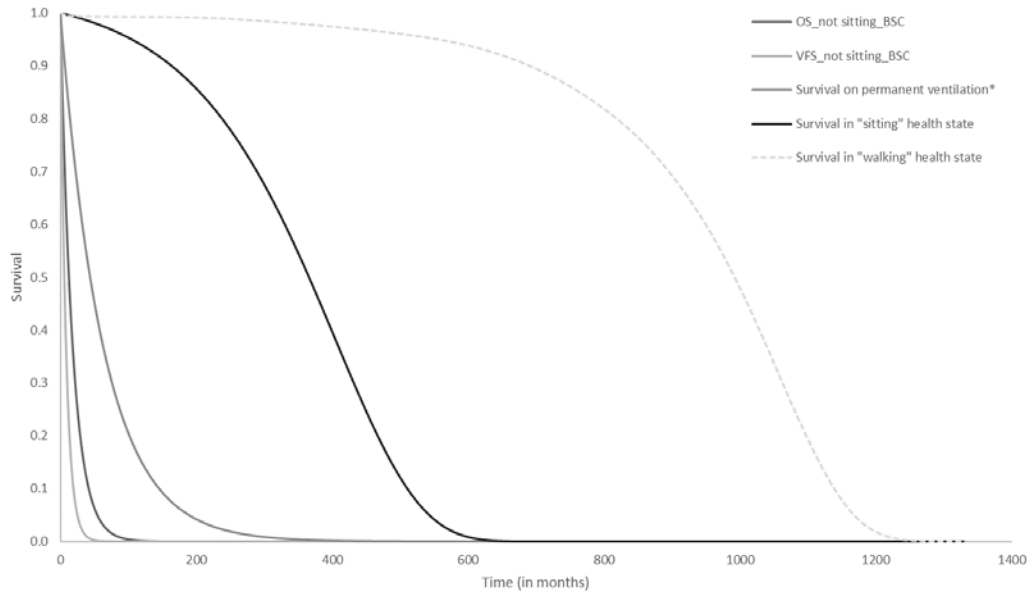
The long-term risks of mortality associated with each of the health states were modelled by fitting survival curves to digitized, published Kaplan-Meier (KM) data most relevant to each health state. We digitized the KM data and reconstructed the individual data using the methods described in Guyot et al.[87] We fitted different parametric distributions (exponential, Weibull, gamma, Gompertz, log-normal, log-logistic, and generalized gamma) to this survival data. We identified the best fitting curves based on a combination of clinical plausibility, fit statistics such as Akaike information criteria (AIC) and Bayesian information criteria (BIC), and visual inspection. For each health state, a single parametric distribution was selected to calculate the estimated probability of death in each time period (e.g., a given month).

The transitions from different health states, assumptions, data sources, and parametric distributions selected to extrapolate survival are presented in Table 4.4. The survival curves used in the base-case analysis for long-term extrapolation are presented in Figure 4.3. Appendix Tables E3-E6 presents the data on AIC and BIC, along with plots of the different parametric distributions.

Table 4.4. Summary of the Long-Term Extrapolation

	Description	Assumption	Source	Distribution Selected	Parameters
Not Sitting (BSC Arm)	OS	Assumed to be same as BSC patients	ENDEAR sham control arm[24]	Exponential	λ_{tw}=0.0127
	VFS	Assumed to be same as BSC patients	ENDEAR sham control arm[24]	Exponential	λ_{tw}=0.0276
Not Sitting (Treatment Arms)	OS	Assumed to be same as when on permanent ventilation	Gregoretti et al[47] (NRA curve)	Exponential	λ_{tm}=0.0158
	VFS	Not explicitly modelled	--	--	--
Permanent Ventilation	Mortality	Assumed to be same as patients on non-invasive respiratory muscle aid, including non-invasive ventilation, tracheostomy, or mechanically assisted cough	Gregoretti et al[47] (NRA curve)	Exponential	λ_{tm}=0.0158
Sitting	Mortality	Assumed to be same as SMA Type II patients	Zerres and Schöneborn et al.[48]	Gompertz	α=0.0964, β=0.0037
Walking	Mortality	Assumed to be same as general population	US population mortality[88]	--	--

Figure 4.3. Survival Curves Used in the Long-Term Extrapolation Model



BSC: best supportive care, OS: overall survival, VFS: ventilation-free survival
*Survival in "not sitting" health state in treatment arm is the same as survival on permanent ventilation.

In Figure 4.3, the OS and VFS curves represent the overall survival and ventilation-free survival of the patients in the "not sitting" health state in the BSC arm, which were assumed to be the same as

that of the patients in the sham control arm of ENDEAR. The OS curve represents the survival of patients in the "not sitting" health state at the end of the short-term model, with a mean survival time of 1.55 years. The VFS curve, with a mean survival of 0.74, is subtracted from the OS curve to estimate the patients in the permanent ventilation health state that moved from the "not sitting" health state in the long-term model.

The curve "survival on permanent ventilation" represents the survival of patients in the "permanent ventilation" health state at the end of the short-term model, with a mean survival of 5.3 years. The survival in the "not sitting" health state in the treatment arms is assumed to be the same as the survival on "permanent ventilation."

The "sitting" curve represents the survival of patients in the "sitting" health state at the end of the short-term model, based on the assumption that they have the same survival as SMA Type II patients, with a mean survival of 29.3 years. The "walking" curve represents the survival of patients in the "walking" health state at the end of the short-term model, based on the assumption that they have the same survival as the general population, with a mean survival of 78.7 years.

Permanent Ventilation and Mortality from the "Not Sitting" Health State in the BSC arm

Patients in the "not sitting" health state in the BSC arm can transition to either the "permanent ventilation" health state or to death. We used the BSC arm of the ENDEAR study; the OS and VFS curves were digitized from the KM data presented in the study. At each monthly cycle, the proportions of patients dying from this health state were estimated from the OS curve, and the VFS curve was subtracted from the OS curve to estimate the proportion of patients in the "permanent ventilation" health state.

Permanent Ventilation and Mortality from the "Not Sitting" Health State in the treatment arms

The patients in the "not sitting" health state in the treatment arms were assumed to have the same mortality as in the "permanent ventilation" health state. This is to account for the survival benefit of the "not sitting" patients in the treatment arms for achieving interim milestones such as head control and rolling. No explicit transitions from "not sitting" to "permanent ventilation" were modelled, however, additional costs for permanent ventilation were included for three months prior to death in the "not sitting" state.

Mortality from the "Permanent Ventilation" Health State

We used retrospective data[47] of SMA Type I patients from four Italian centers from 1992 to 2010 to model mortality in the "permanent ventilation" health state. In this study, 31 patients required continuous non-invasive respiratory muscle aid, including non-invasive ventilation and mechanically assisted cough (n=31). Of these 31 patients, seven also received tracheostomy.

Mortality from the "Sitting" Health State

Treated SMA Type I patients who can sit were assumed to have similar prognosis as SMA Type II patients who are able to sit but not walk. Pooled data from German and Polish studies on SMA Type II patients (n=240) presented in Zerres and Schöneborn et al.[48] were used to model mortality from the "sitting" health state.

Mortality from the "Walking" Health State

Treated patients with Type I SMA who can walk are assumed to have similar prognosis as patients with SMA Type III who are able to walk. A previously-conducted study[48] reported no significant reduction in lifespan among SMA Type III patients compared to the general population. As such, we use the general population mortality[88] for patients with Type I SMA who can walk.

Health State Utilities

Patient Utilities

The utilities used in the base-case analyses were derived from multiple sources and are presented in Table 4.5. The utilities reported by Thomson et al. in 2017[49] were from a cross-sectional study of individuals with SMA in Europe; investigators collected parent/proxy–assessed quality of life using the EuroQol-5 Dimensions (EQ-5D) 3-level version. The mean utility value for patients with Type I SMA in the UK was 0.19 (n=7); we assumed this value was the same for both "permanent ventilation" and "not sitting" health states.

The utility for the "sitting" health state was sourced as 0.6 from the Tappenden et al.[50] evidence review group (ERG) report evaluating the submission of Spinraza for NICE. Tappenden et al. report the utilities elicited from the clinical experts who advised the ERG, who were asked to provide plausible utility estimates for the different health states; it should be noted that these utility estimates are not preference-based.

We assumed additional utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. The proportions of patients achieving these interim milestones were not available at different time points, so the model assumed an additional utility benefit for all patients in the "not sitting" and "sitting" health states. This was implemented in the model as a utility of 0.29 for the "not sitting" health state (i.e., an additional utility of 0.1 compared to BSC) and a utility of 0.65 for the "sitting" health state (i.e., an additional utility of 0.05 compared to BSC).

The utility for the "walking" health state was sourced from general population utilities[51], as presented in in Table 4.6. A scenario analysis was also performed using a utility value of 0.878 for

patients in the "walking" health state, based on a study by Thomson et al.[49] which provided parent-proxy assessment of quality of life.

All utilities were capped at the general population utility for that age group, to ensure they did not exceed the utilities of the general population. Also, we used the utility for 18-29 age group presented in Table 4.6 as the utility for patients in the "walking" health state aged less than 18.

Table 4.5. Patient Utility Values for Health States

	Utility Value (BSC Arm)	Source	Utility Value (Treatment Arms)	Source
Permanent Ventilation	0.19	Thomson et al., 2017[49]	0.19	Thomson et al., 2017[49]
Not Sitting	0.19		0.29	Assumption
Sitting	0.60	Tappenden et al., 2018[50]	0.65	Assumption
Walking	--	General population utility[51]	--	General population utility[51]

Table 4.6. General Population Utility Values

Age Group	Mean	Std. Error
18-29	0.922	0.0019
30-39	0.901	0.0021
40-49	0.871	0.0024
50-59	0.842	0.0028
60-69	0.823	0.0034
70-79	0.790	0.0036
>=80	0.736	0.0062

Cost Inputs

The costs used in the model include treatment costs, administration/monitoring costs, and costs associated with being in each health state. All costs were inflated to 2017 values using the methods described in the ICER Reference Case.

Drug Acquisition Costs

The recommended dosage for Spinraza is four loading doses (the first three loading doses administered at 14-day intervals with the fourth loading dose administered 30 days after the third dose) and a maintenance dose administered once every four months thereafter. Since Spinraza is administered in a hospital setting, we included mark-ups associated with the treatment aligning with the ICER Reference Case. We used the average wholesale price (AWP) to which we applied a

15% discount, reflecting the weighted average mark-ups seen for treatments administered specifically in a hospital outpatient setting.[89]

Zolgensma is potentially a one-time therapy administered using a single intravenous infusion. Zolgensma currently has no publicly-known list or net price; we therefore used a placeholder price for Zolgensma, as forecast by a market analyst estimate.[90] These costs are presented in Table 4.7.

Table 4.7. Treatment Cost Inputs

Intervention	Administration	Package Size	WAC* per Package	Estimated Net Cost per Package†	Source
Spinraza	Intrathecal injection	2.4 mg/ml (5 ml)	$125,000	$127,500	Redbook 2018[91]; Magellan 2016[89]
Zolgensma	Intravenous infusion	--	--	$2,000,000‡	Market analyst estimate[90]

*Wholesale acquisition cost (WAC) as of November 2, 2018.
†AWP – 15%, where AWP is $150,000 per package as of November 2, 2018.
‡Placeholder price.

Administration and Monitoring Costs

All administration, laboratory, and monitoring costs associated with the treatments are presented in Tables 4.8 and 4.9. For Spinraza, it was assumed that 40% of the patients receive the treatment in an inpatient setting and accrue the costs of inpatient stay and anesthesia. For Zolgensma, it was assumed that the infusion will last two hours and that the costs of prednisolone are only for the first month.

Table 4.8. Costs Associated with Spinraza Treatment

	Cost	Description	Source
Intrathecal Injection (Lumbar Puncture into Central Nervous System)	$82.44	Current Procedural Terminology (CPT) code 96450	Physician fee schedule 2018;[92] facility price
Intrathecal Injection (Drain Cerebrospinal Fluid)	$86.76	CPT 62272	
MD/Specialist	$52.20	CPT 99213	
Monitor for Thrombocytopenia	$5.53	CMS laboratory fee schedule 85049	
Monitor for Renal Toxicity	$10.72	CMS laboratory fee schedule 80069	
Anesthesia for Lumbar Puncture	$133.13	HCPCS 00635	
Imaging (Ultrasound or Fluoroscopy – Average Cost)	$78.66	CPT 77003, 76942	
Inpatient Cost per Diem (Routine Surgery)	$1,316	Using a cost:charge ratio of 1:3	Nationwide Children's Hospital[93]
Inpatient Anesthesia	$583	Using a cost:charge ratio of 1:3	
Total Administration Cost	$1,209	Assuming 40% of patients receive Spinraza in inpatient settings	

Table 4.9. Costs Associated with Zolgensma Treatment

	Cost	Description	Source
Single Dose Intravenous Infusion	$74.16 $22.32 per additional hour	CPT 96365 CPT 96366	Physician fee schedule 2018;[92] facility price
Anti-AAV9 Diagnostic Test	$15.89	CPT 86603	
Laboratory Monitoring	$10	CPT 80069	
Prednisolone	$15	Oral, 1 mg/kg 30-day prescription	Redbook 2018[91]
Total Administration Cost	$137	Assuming the infusion is for two hours	

Health Care Utilization Costs

The monthly costs associated with the different health states are presented in Table 4.10. They were sourced from a claims analysis of commercial health plans comprising infantile-onset SMA (n=23), childhood-onset SMA (n=22) and later-onset SMA (n=296) patients, based on the study reported by Shieh et al.[94] The costs of infantile SMA patients were used for the "not sitting" health state. The costs of childhood-onset SMA and later-onset SMA were used for the "sitting" and "walking" health states, respectively.

The costs in the "permanent ventilation" health state were estimated as the costs associated with permanent ventilation added to the costs of the "not sitting" health state. These included the costs of equipment and disposable equipment and supplies that are associated with ventilator-dependent children living at home, estimated from a UK study by Noyes et al.[95] These costs were converted into US dollars using 2002 exchange rates[96] and then inflated to 2017 dollars. The additional costs of permanent ventilation were estimated as $32,413 per year, which translates to an additional monthly cost of $2,701. In total, the monthly costs of the permanent ventilation health state were estimated as $28,218.

Table 4.10. Background Costs in Different Health States

	Permanent Ventilation	Not Sitting	Sitting	Walking
Inpatient Hospitalization	$21,863	$21,863	$3,401	$1,116
Outpatient Services	$3,341	$3,341	$2,631	$984
Emergency Services	$313	$313	$325	$399
Costs Specific to Permanent Ventilation	$2,701	--	--	--
Total Monthly Cost	$28,218	$25,517	$6,357	$2,499

Scenario analyses were performed using cost data from Armstrong et al.[97] who reported additional total annual health care costs for patients with SMA diagnosed before and after one year of age, respectively. Scenario analyses were also performed using cost data from a report by the Lewin Group[98] that reported additional total annual health care costs broken out for patients with early onset and other types of SMA.

Non-Medical Costs

Annual non-medical costs associated with the different health states were obtained from a report by the Lewin Group,[98] and are summarized in Table 4.11. We excluded the "professional caregiving" costs from non-medical costs, as the costs in the "professional caregiving" category included some costs that we considered to medical (e.g., home health aides, skilled nurses, or nurse assistants) and others that may be incurred by health care payers (e.g., government programs, insurance, etc.). While this category also included some types of paid caregiving that would not be considered as medical (e.g., "relatives/friends who are paid by families or state programs to care for the affected persons"), the proportions of medical versus non-medical costs were not reported.

In a scenario analysis using a modified societal perspective, we used a weighted average of early onset and other SMA patients' non-medical cost for all health states (except the walking health state, which had zero non-medical costs). The costs, which included moving or modifying the home and purchasing or modifying a vehicle, were estimated as mean annual costs but the follow-up period was not clear. Given this, these costs were assumed as recurring costs in the model, rather than stopping or changing over time.

Table 4.11. Monthly Non-Medical Costs

	Permanent Ventilation	Not Sitting	Sitting	Walking
Total Costs	$964	$964	$964	$0

Patient Productivity Gains

Patient productivity gains are included in a scenario analysis using a modified societal perspective. No productivity changes were assumed for those in the "permanent ventilation" and "not sitting" health states. For other health states, data from the Lewin Group report[98] on educational attainment for SMA patients were combined with data on income by education level in the US from the Bureau of Labor Statistics[99] to estimate the productivity gains of patients. These proportions were weighted by monthly earnings to estimate the potential monthly income as $4,450, as shown in Appendix Table E7. These productivity gains are estimated from the age of 25 years until an age of 67 years.

Sensitivity Analyses

One-way sensitivity analyses were performed using plausible ranges based on published data and expert opinion to identify the key drivers of model outcomes. Probabilistic sensitivity analysis (PSA) was performed by jointly varying all model parameters, using 1,000 simulation runs. Due to the lack of data, the distributions used for costs and utilities in the PSA are on mean values ±20%. As such, the true uncertainty is likely to be more than that represented in our probabilistic analyses.

Additionally, a threshold analysis was performed by calculating the drug prices that would achieve willingness-to-pay (WTP) thresholds between $50,000 and $500,000 per QALY.

Scenario Analyses

In addition to the base-case analysis, we conducted the following scenario analyses:

- Analyses using a modified societal perspective
- Analyses excluding health care costs other than those directly related to treatment with Spinraza or Zolgensma for patients with Type I SMA
- Zolgensma compared to Spinraza for patients with Type I SMA
- Analyses using alternative utility estimates
- Analyses using alternative health state costs
- Not accounting for utility benefits of achieving interim milestones (such as head control, rolling, crawling, and standing)
- Exploratory analysis of a hypothetical drug with the costs of Zolgensma and efficacy of Spinraza in presymptomatic patients

- Conservative scenario where the patients lose milestones, and have lower survival and utility in "sitting" and "walking" health states
- Analyses using a 10-year time horizon
- Analyses using 1.5% discounting

Model Validation

Several approaches were undertaken to validate the model. First, preliminary methods and results were presented to manufacturers, patient groups, and clinical experts, with data inputs changed as needed and scenario analyses defined. Second, model input parameters were varied to evaluate the face validity of changes in results. As part of ICER's initiative for modeling transparency, we shared the model with AveXis for external verification shortly after publishing the draft report for this review. Biogen chose not to receive the model. The outputs from the model were validated against the trial and study data of the interventions as well as any relevant observational datasets. Finally, the results were compared to other cost-effectiveness models in this therapy area.

4.3. Results

For each of the three modeled SMA sub-types, base-case results are presented from the health care sector perspective. Costs and cost-effectiveness ratios are rounded to the nearest $1,000.

Infantile-Onset (Type I) SMA Model

Base-Case Results

Tables 4.12 and 4.13 present the base-case results from the health care sector perspective. Table 4.12 presents the results for the Spinraza versus BSC comparison, while Table 4.13 presents the results for the Zolgensma versus BSC comparison. The breakdown of LYs, QALYs, and costs according to health state for the different interventions are presented in Appendix Tables E10 to E13.

In the Type I SMA population, the total costs in the Spinraza arm were approximately $3.9 million, which is just under five times the total costs in the BSC arm of around $790,000. However, the Spinraza arm has higher QALYs and LYs (3.24 and 7.64, respectively) compared to the BSC arm (0.46 QALYs and 2.40 LYs, respectively). This resulted in an incremental cost per QALY gained of approximately $1,112,000 and an incremental cost per LY gained of $590,000 for Spinraza compared to BSC.

Table 4.12. Base-Case Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,231,000	$1,653,000	$3,884,000	3.24	7.64	$1,112,000	$590,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

In the Type I SMA population, the total costs in the Zolgensma arm (using a placeholder price of $2 million) were approximately $3.7 million, which is just under five times the total costs in the BSC arm of around $790,000. However, the Zolgensma arm has higher QALYs and LYs (12.23 and 18.17, respectively) compared to the BSC arm (0.46 QALYs and 2.40 LYs, respectively). This resulted in an incremental cost per QALY gained of $243,000 and an incremental cost per LY gained of $182,000 for Zolgensma compared to BSC.

Table 4.13. Base-Case Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,657,000	$3,657,000	12.23	18.17	$243,000	$182,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

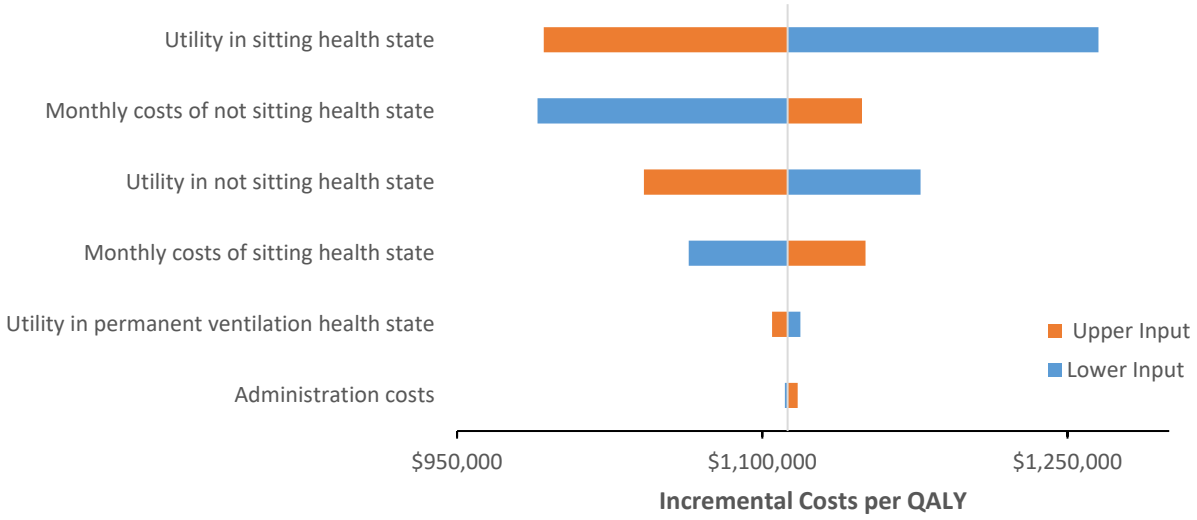
*Placeholder price.

Sensitivity Analyses Results

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.

For the Spinraza versus BSC comparison, key drivers of uncertainty included monthly costs and utility values for the "sitting" and "not sitting" health states (Figure 4.4 and Table 4.14). In probabilistic analyses, Spinraza did not achieve a greater than zero likelihood of meeting the $500,000/QALY or lower threshold across the range of values tested (Table 4.16 and Figures E5 and E6 in Appendix E).

Figure 4.4. Tornado Diagram for One-Way Sensitivity Analyses of Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective



QALY: quality-adjusted life year

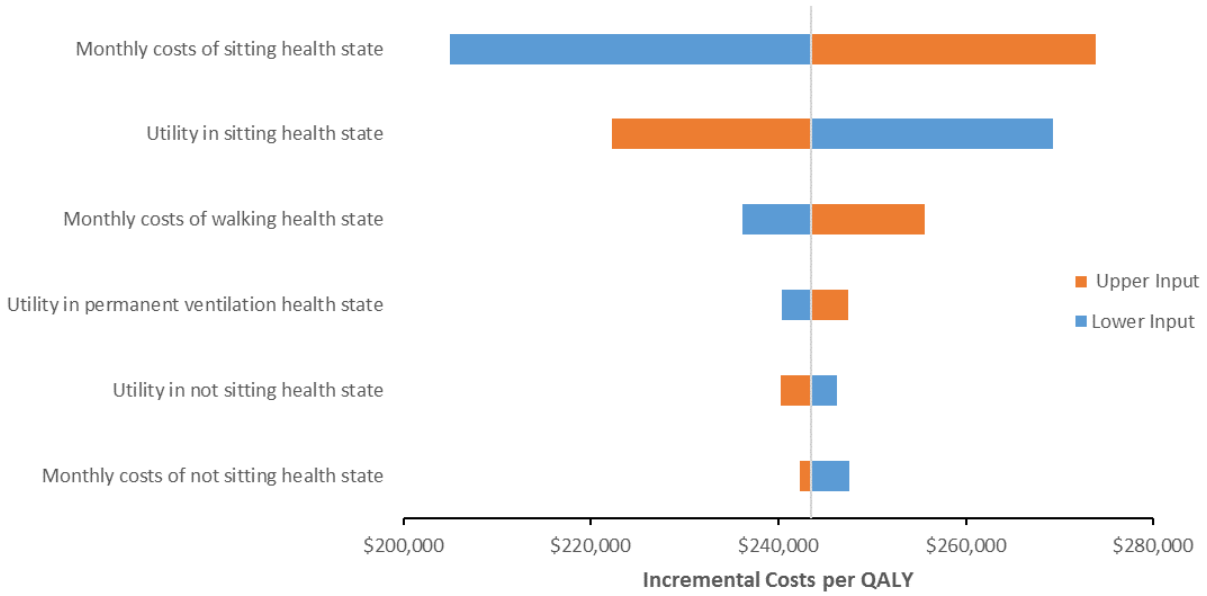
Table 4.14. Tornado Diagram Inputs and Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

Input Name	Lower Incremental Cost-Effectiveness Ratio	Upper Incremental Cost-Effectiveness Ratio	Lower Input	Upper Input
Utility in Sitting Health State*	$993,000	$1,265,000	0.5	0.7
Monthly Costs of Not Sitting Health State	$990,000	$1,149,000	$10,434	$30,000
Utility in Not Sitting Health State*	$1,042,000	$1,178,000	0.1	0.3
Monthly Costs of Sitting Health State	$1,064,000	$1,151,000	$3,000	$9,000
Utility in Permanent Ventilation Health State*	$1,105,000	$1,119,000	0.1	0.3
Administration Costs	$1,111,000	$1,117,000	$1,000	$2,000

*Lower input corresponds to higher incremental cost-effectiveness ratio and vice versa.

For the comparison of Zolgensma versus BSC, key drivers of uncertainty included monthly costs in the "sitting" and "walking" health states and the utility in the "sitting" health state (Figure 4.5, Table 4.15). In probabilistic sensitivity analyses, Zolgensma achieved a 0.1% chance of meeting the $150,000/QALY threshold (Table 4.16 and Figures E7 and E8 in Appendix E).

Figure 4.5. Tornado Diagram for One-Way Sensitivity Analyses of Zolgensma* versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective



QALY: quality-adjusted life year
*Based on a placeholder price of $2,000,000.

Table 4.15. Tornado Diagram Inputs and Results for Zolgensma* versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

Input Name	Lower Incremental Cost-Effectiveness Ratio	Upper Incremental Cost-Effectiveness Ratio	Lower Input	Upper Input
Monthly Costs of Sitting Health State	$205,000	$274,000	$3,000	$9,000
Utility in Sitting Health State†	$222,000	$269,000	0.5	0.7
Monthly Costs of Walking Health State	$236,000	$256,000	$1,000	$5,000
Monthly Costs of Not Sitting Health State†	$242,000	$248,000	$10,434	$30,000
Utility in Permanent Ventilation Health State	$240,000	$247,000	0.1	0.3
Utility in Not Sitting Health State†	$240,000	$246,000	0.1	0.3

*Based on a placeholder price of $2,000,000.
†Lower input corresponds to higher incremental cost-effectiveness ratio and vice versa.

Table 4.16. Probabilistic Sensitivity Analyses Results in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Spinraza vs. BSC	Zolgensma* vs. BSC
Cost-Effective at $50,000/QALY	0%	0%
Cost-Effective at $100,000/QALY	0%	0%
Cost-Effective at $150,000/QALY	0%	0.1%
Cost-Effective at $200,000/QALY	0%	0.7%
Cost-Effective at $250,000/QALY	0%	62.5%
Cost-Effective at $300,000/QALY	0%	100%
Cost-Effective at $350,000/QALY	0%	100%
Cost-Effective at $400,000/QALY	0%	100%
Cost-Effective at $450,000/QALY	0%	100%
Cost-Effective at $500,000/QALY	0%	100%

BSC: best supportive care, QALY: quality-adjusted life year
*Based on a placeholder price of $2,000,000.

Scenario Analyses Results

We performed a number of scenario analyses to identify the effect of alternative inputs and assumptions on the cost-effectiveness results.

Tables 4.17 and 4.18 present the results from a scenario analysis taking a modified societal perspective, which includes patient-centric societal costs (i.e., non-medical costs reported in Table 4.11) and productivity gains, along with patient QALYs, LYs, and health care costs. Table 4.17 presents the results for Spinraza versus BSC comparison, while Table 4.18 presents the results for the Zolgensma versus BSC comparison.

The incremental cost per QALY and incremental cost per LY gained for Spinraza compared to BSC in the modified societal perspective were slightly less favorable than those in the health care perspective. This was because non-medical costs (which included moving or modifying the home and purchasing or modifying a vehicle), provided in Table 4.11, accrue for all the health states (except walking) for a lifetime, while patient productivity gains are only for patients sitting or walking between ages 25 and 67 years. As such, the productivity gains did not offset the non-medical costs for Spinraza in the SMA Type I population, as only around 19% of the patients in Spinraza arm were in the "sitting" health state and none were in the "walking" health state.

Table 4.17. Scenario Analysis Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Spinraza	$3,944,000	3.24	7.64	$1,124,000	$596,000
BSC	$817,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

The incremental cost per QALY and incremental cost per LY gained for Zolgensma compared to BSC in the modified societal perspective were slightly more favorable than those in the health care perspective. In the Zolgensma arm, a majority of the patients were in the "sitting" health state and a proportion were in the "walking" health state, which resulted in the non-medical costs being offset by the productivity gains, leading to more favorable incremental cost-effectiveness ratios.

Table 4.18. Scenario Analysis Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Zolgensma	$3,619,000*	12.23	18.17	$238,000	$178,000
BSC	$817,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year
*Based on a placeholder price of $2,000,000.

Tables 4.19 and 4.20 present results from a scenario analysis from the health care sector perspective that excludes health care costs other than those directly related to treatment with Spinraza or Zolgensma (i.e., only treatment and administration costs). Table 4.19 presents the results for Spinraza versus BSC, while Table 4.20 presents the results for the Zolgensma versus BSC comparison.

The results for Spinraza compared to BSC in this scenario were more favorable than those in the base-case health care sector perspective, at $810,000 per QALY gained and $429,000 per LY gained.

Table 4.19. Scenario Analysis Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective Excluding Other Health Care Costs

	Drug Treatment Costs	Non-Treatment Health Care Costs*	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,231,000	$21,154	$2,252,000	3.24	7.64	$810,000	$429,000
BSC	$0	$0	$0	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Administration costs associated with Spinraza.

In this scenario analysis, the total costs in the Zolgensma arm were approximately $2 million, the assumed placeholder price for Zolgensma, because of one-time administration and the exclusion of background health care costs. This resulted in an incremental cost per QALY gained of $170,000 and an incremental cost per LY gained of $127,000.

Table 4.20. Scenario Analysis Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective Excluding Other Health Care Costs

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$137	$2,000,000	12.23	18.17	$170,000	$127,000
BSC	$0	$0	$0	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

We present the summary results for the other scenario analyses of Spinraza versus BSC comparison in Table 4.21, and the summary results for other scenario analyses of Zolgensma versus BSC comparison in Table 4.22. We present more detailed description of the assumptions behind each of these scenario analyses and detailed results in Appendix E (Tables E14 to E31). Note that there are no patients in the "walking" health state in the Spinraza arm, as such the assumptions about "walking" health state have no bearing on the Spinraza results, but to ensure consistency between Table 4.21 and 4.22, the scenarios describe assumptions about both "sitting" and "walking." However, when describing the Spinraza results we only mention the assumptions about "sitting" health state.

In the scenario analyses for Spinraza versus BSC in Type I SMA patients, removing utility benefit for achieving interim milestones increased the incremental cost per QALY to $1,303,000. Assuming lower health state costs resulted in more favorable incremental cost per QALY ratios. However, assuming lower survival or utilities for "sitting" health states resulted in less favorable incremental cost-effectiveness ratios. When both lower survival and utilities for the "sitting" health state are

used, the incremental cost per QALY gained was around $1.4 million. This suggests that the base-case incremental cost per QALY is an underestimate if the patients achieving "sitting" do not do as well as SMA Type II patients.

If an increased proportion of patients in the "sitting" health state were to lose their milestones, the incremental cost-effectiveness ratios become less favourable (scenarios #7a-7c in Table 4.21). The conservative scenario which assumed that 30% of the patients in the "sitting" health state lose milestones and also assumed lower survival and lower utilities for those in the "sitting" health state, resulted in an incremental cost per QALY of approximately $1.5 million and an incremental cost per LY gained of $630,000. Note that the conservative scenario still includes the utility benefit for achieving interim milestones, as in the base case.

The scenario analyses using a 10-year time horizon resulted in an incremental cost per QALY of approximately $1.5 million as the all the benefits for the patients in the "sitting" health state are not included. The scenario analyses using a discount rate of 1.5% for both costs and QALYs, resulted in an in incremental cost per QALY of approximately $1 million.

Table 4.21. Scenario Analyses for Spinraza versus BSC in Infantile-Onset (Type I) SMA

	Cost per QALY	Cost per LY
Base-Case Results	$1,112,000	$590,000
Scenario #1: Assuming No Utility Benefits for Interim Milestones	$1,303,000	$590,000
Scenario #2: Assuming Lower Health State Costs for "Not Sitting" and "Permanent Ventilation" Health States	$990,000	$525,000
Scenario #3: Assuming Lower Utilities for "Sitting" and "Walking" Health States	$1,265,000	$590,000
Scenario #4: Assuming Lower Survival for "Sitting" and "Walking" Health States	$1,253,000	$624,000
Scenario #5: Assuming Lower Utilities and Lower Survival for "Sitting" and "Walking" Health States	$1,407,000	$624,000
Scenario #7a: Assuming 10% in "Sitting" Health State Lose Milestone at End of Short-Term Model	$1,143,000	$593,000
Scenario #7b: Assuming 20% in "Sitting" Health State Lose Milestone at End of Short-Term Model	$1,178,000	$597,000
Scenario #7c: Assuming 30% in "Sitting" Health State Lose Milestone at End of Short-Term Model	$1,218,000	$601,000
Conservative Scenario: Assuming 30% in "Sitting" Health State Lose milestone at End of Short-Term Model, Lower Utilities and Survival for "Sitting" and "Walking" Health States	$1,509,000	$630,000
Scenario #8: Using a 10-Year Time Horizon	$1,460,000	$700,000
Scenario #9: Using 1.5% Discount Rate for Both Costs and QALYs	$1,052,000	$566,000

LY: life-year, QALY: quality-adjusted life year

In the scenario analyses for Zolgensma versus BSC in infantile-onset (Type I) SMA patients, removing utility benefit for achieving interim milestones increased the incremental cost per QALY results to $261,000. Assuming lower health state costs in the "not sitting" and "permanent ventilation" health states resulted in less favorable incremental cost per QALY ratios. Assuming lower survival or utilities for "sitting" and "walking" health states resulted in less favorable incremental cost-effectiveness ratios. When both lower survival and utilities for the "sitting" and "walking" health states are used, the incremental cost per QALY was $371,000. This suggests that the base-case incremental cost per QALY is an underestimate if the patients in the "sitting" and "walking" health states do not do as well as SMA Type II patients and the general population.

If an increased proportion of patients in the "sitting" health state were to lose their milestones, the incremental cost-effectiveness ratios become less favorable (scenarios #7b-7c in Table 4.22). Scenario #7a is not presented, as our base case for Zolgensma arm already included 16.7% in the "sitting" health state losing milestone (as proxy for receiving Spinraza). The conservative scenario, which assumed that 30% of the patients in the "sitting" health state lose milestones and also

assumed lower survival and lower utilities for those in the "sitting" and "walking" health states, resulted in an incremental cost per QALY ratio of over $400,000 and an incremental cost per LY gained of approximately $250,000. Note that the conservative scenario still includes the utility benefit for achieving interim milestones, as in the base case.

The scenario analyses using a 10-year time horizon resulted in an incremental cost per QALY of approximately half a million as the all the treatment costs are included but the benefits for the patients in the "sitting" and "walking" health state are only for the 10 years. The scenario analyses using a discount rate of 1.5% for both costs and QALYs, resulted in an in incremental cost per QALY of approximately $200,000.

Table 4.22. Scenario Analyses for Zolgensma* versus BSC in Infantile-Onset (Type I) SMA

	Cost per QALY	Cost per LY
Base-Case Results	$243,000	$182,000
Scenario #1: Assuming No Utility Benefits for Interim Milestones	$261,000	$182,000
Scenario #2: Assuming Lower Health State costs for "Not Sitting" and "Permanent Ventilation" Health States	$248,000	$185,000
Scenario #3: Assuming Lower Utilities for "Sitting" and "Walking" Health States	$296,000	$182,000
Scenario #4: Assuming Lower Survival for "Sitting" and "Walking" Health States	$303,000	$233,000
Scenario #5: Assuming Lower Utilities and Lower Survival for "Sitting" and "Walking" Health States	$371,000	$233,000
Scenario #6: Assuming No Loss of Milestones as a Proxy for Use of Spinraza in Zolgensma Arm	$220,000	$165,000
Scenario #7b: Assuming 20% in "Sitting" Health State Lose Milestone at End of Short-Term Model	$249,000	$186,000
Scenario #7c: Assuming 30% in "Sitting" Health State Lose Milestone at End of Short-Term Model	$266,000	$198,000
Conservative Scenario: Assuming 30% in "Sitting" Health State Lose milestone at End of Short-Term Model, Lower Utilities and Survival for "Sitting" and "Walking" Health States	$406,000	$253,000
Scenario #8: Using a 10-Year Time Horizon	$525,000	$400,000
Scenario #9: Using 1.5% Discount Rate for Both Costs and QALYs	$199,000	$149,000

LY: life-year, QALY: quality-adjusted life year
*Based on a placeholder price of $2,000,000.

Tables 4.23 and 4.24 present the results for a scenario analysis comparing Zolgensma with Spinraza from the health care sector and modified societal perspectives, respectively. Instead of a naïve

comparison that used the costs, QALYs, and LYs for Zolgensma and Spinraza from their respective comparisons with BSC, we performed a separate analysis incorporating the add on costs of Spinraza in the Zolgensma arm (as opposed to assuming that a proportion of the patients lose a milestone in the base-case analysis). This analysis assumed that 33% of the patients in the "sitting" state of the Zolgensma arm (i.e., 25% of overall patients) receive Spinraza according to the standard dosing regimen after the end of the short-term model.

From the health care sector perspective, the total costs in the Zolgensma arm were approximately $5.3 million with 13.46 QALYs and 19.76 LYs gained. The costs are higher than in the base case for Zolgensma versus BSC due to the additional costs associated with Spinraza treatment. However, the QALYs and LYs are also higher than in the base case, as this analysis does not assume any loss of milestones. The total costs in the Spinraza arm were around $3.9 million with 3.24 QALYs and 7.64 LYs gained. This resulted in an incremental cost per QALY gained of approximately $139,000 and an incremental cost per LY gained of $117,000 for Zolgensma compared to Spinraza.

Table 4.23. Scenario Analysis Results for Zolgensma versus Spinraza in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$3,630,000*	$1,671,000	$5,301,000	13.46	19.76	$139,000	$117,000
Spinraza	$2,231,000	$1,653,000	$3,884,000	3.24	7.64	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Includes the Zolgensma costs (placeholder price of $2 million) and additional Spinraza costs.

The results for the same comparison when taking a modified societal perspective are slightly lower than those in the health care perspective, with an incremental cost per QALY gained of $129,000 and an incremental cost per LY gained of $109,000. This was due to a greater proportion of patients in the "sitting" and "walking" health states for the Zolgensma arm than the Spinraza arm, resulting in more of the non-medical costs being offset by the patient productivity gains in the Zolgensma arm compared to Spinraza.

Table 4.24. Scenario Analysis Results for Zolgensma versus Spinraza in Infantile-Onset (Type I) SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Zolgensma	$5,262,000*	13.46	19.76	$129,000	$109,000
Spinraza	$3,944,000	3.24	7.64	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Includes the Zolgensma costs (placeholder price of $2 million) and the additional Spinraza costs.

Threshold Analyses Results

Table 4.25 presents the threshold results for Spinraza and Zolgensma compared to BSC at thresholds from $50,000 to $500,000 per QALY gained, while excluding health care costs that may be considered "unrelated," as described earlier.[100] While we understand that it may be controversial to treat these costs as unrelated, we thought it is important to explore the effect of excluding these costs from the analysis. As earlier, threshold prices are reported as annual costs for Spinraza and as one-time cost for Zolgensma.

Excluding these "unrelated" health care costs resulted in threshold prices at each cost per QALY threshold. For Spinraza, the annual threshold prices are $44,000 and $67,900 at thresholds of $100,000/QALY and $150,000/QALY, respectively. For Zolgensma, the one-time threshold prices are $1,178,000 and $1,767,000 at thresholds of $100,000/QALY and $150,000/QALY, respectively.

Table 4.25. QALY-Based Threshold Analyses Excluding "Unrelated" Health Care Costs in Type I SMA: Health Care Sector Perspective

	Spinraza* vs. BSC	Zolgensma† vs. BSC
Threshold Price at $50,000/QALY	$20,200	$589,000
Threshold Price at $100,000/QALY	$44,000	$1,178,000
Threshold Price at $150,000/QALY	$67,900	$1,767,000
Threshold Price at $200,000/QALY	$91,800	$2,355,000
Threshold Price at $300,000/QALY	$139,000	$3,533,000
Threshold Price at $500,000/QALY	$235,000	$5,889,000

QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

†Threshold prices are based on a one-time cost for Zolgensma.

Table 4.26 presents the threshold price results for Spinraza and Zolgensma compared to BSC at thresholds from $50,000 to $500,000 per QALY gained (including "unrelated" health care costs). Threshold prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]) and as one-time cost for Zolgensma.

Table 4.26. QALY-Based Threshold Analyses in Type I SMA: Health Care Sector Perspective

	Spinraza* vs. BSC	Zolgensma† vs. BSC
Threshold Price at $50,000/QALY	--	--
Threshold Price at $100,000/QALY	--	$310,000
Threshold Price at $150,000/QALY	--	$899,000
Threshold Price at $200,000/QALY	--	$1,488,000
Threshold Price at $300,000/QALY	--	$2,666,000
Threshold Price at $500,000/QALY	$90,000	$5,021,000

QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

†Threshold prices are based on a one-time cost for Zolgensma.

Note that there are no threshold prices for Spinraza for thresholds of $300,000/QALY and below because although more patients are alive in the Spinraza arm compared to BSC, only a proportion (around 19%) of the patients are in the "sitting" health state, with the rest in either "permanent ventilation" or "not sitting" health states; both of these health states have high costs of around $300,000 per year and a low utility value of 0.19. As such, even at zero price for Spinraza, it is not possible for the incremental cost effectiveness ratios to reach thresholds less than $300,000 per QALY. This phenomenon has been summarized in a NICE Decision Support Unit report.[100] As such, we have additionally reported the threshold prices for incremental costs per LY gained and for incremental cost per QALY gained excluding what may be considered as health state costs that are not related to the treatment *per se* (Tables 4.27 and 4.25, respectively).

Table 4.27 presents the threshold results for Spinraza and Zolgensma compared to BSC at thresholds from $50,000 to $500,000 per LY gained. Threshold prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., costs of three doses]) and as a one-time cost for Zolgensma. As explained above, due to the majority of the patients in Spinraza arm being in "not sitting" and "permanent ventilation" health states, which are associated with high health care costs and low utility values, there are no threshold prices for Spinraza below thresholds of $200,000 per LY gained.

Table 4.27. LYG-Based Threshold Analyses in Infantile-Onset (Type I) SMA: Health Care Perspective

	Spinraza* vs. BSC	Zolgensma† vs. BSC
Threshold Price at $50,000/LY	--	--
Threshold Price at $100,000/LY	--	$710,000
Threshold Price at $150,000/LY	--	$1,498,000
Threshold Price at $200,000/LY	$31,900	$2,287,000
Threshold Price at $300,000/LY	$122,000	$3,865,000
Threshold Price at $500,000/LY	$302,000	$7,020,000

LY: life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

†Threshold prices are based on a one-time cost for Zolgensma.

Later-Onset (Type II/III) SMA Model

Base-Case Results

Table 4.28 presents the base-case results from the health care sector perspective for the Spinraza versus BSC comparison. Note that no patients in either arm achieved the walking milestone (i.e., they were all in the "sitting" health state). In the CHERISH trial, one patient out of 84 in Spinraza arm managed to walk with assistance but was not considered to have achieved the "walking" health state in the base-case analysis. As such, Spinraza was dominated by BSC in cost/LY analyses, with higher costs but no increase in LYs. However, the QALYs are higher due to the inclusion of utility benefit for achieving interim milestones. This resulted in incremental cost effectiveness ratio of around $8 million per QALY.

Table 4.28. Base-Case Results for Spinraza versus BSC in Later Onset SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$7,634,000	$1,514,000	$9,148,000	12.28	18.90	$8,156,000	Dominated
BSC	$0	$1,442,000	$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Sensitivity Analyses Results

One-way sensitivity analyses were not performed as all the parameters were the same in both arms, except for drug cost and the utility benefit for achieving interim milestones in the Spinraza arm, which was considered in scenario analyses. The incremental cost-effectiveness ratio did not change with any changes to other parameters, as any shifts affected both arms equally.

We performed probabilistic sensitivity analyses to understand effects of uncertainty on both costs and health outcomes, by varying input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges (±20% of the mean). In the later onset SMA patients, Spinraza did not achieve a greater than zero likelihood of meeting the $500,000/QALY or lower threshold across the range of values tested.

Scenario Analyses Results

Table 4.29 presents results from a scenario analysis taking a modified societal perspective, which includes patient-centric societal costs (i.e., non-medical costs) and productivity gains, along with health care costs. As above, Spinraza was dominated by BSC, with higher costs but no increase in LYs. However, the QALYs are higher due to the inclusion of utility benefit for achieving interim milestones. This resulted in an incremental cost effectiveness ratio of around $8 million per QALY.

Table 4.29. Scenario Analysis for Spinraza versus BSC in Later-Onset SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Spinraza	$9,217,000	12.28	18.90	$8,156,000	Dominated
BSC	$1,510,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

We performed additional scenario analyses to identify the effect of alternative inputs and assumptions on the cost effectiveness results. We present the summary results for Spinraza versus BSC in Table 4.30. We present more detailed description of the assumptions behind each of these scenario analyses below and detailed results in Appendix E (Tables E36 to E38). Note that we do not present cost per LY results here as these scenarios have no impact on life expectancy and thus do not impact cost per LY.

In the first scenario, we assumed even greater additional utility benefits in the Spinraza arm for achieving interim milestones such as standing, walking with assistance, etc. This scenario assumed an even higher utility benefit for all patients in the "sitting" health states, implemented in the model as a utility of 0.7 for the "sitting" health state in the Spinraza arm (i.e., an additional utility of 0.1 compared to BSC).

In the second scenario, we assumed that Spinraza treatment was stopped after two years and applied a utility benefit for achieving interim milestones in the Spinraza arm (i.e., a utility of 0.65 for "sitting" health state in the Spinraza arm, an additional utility of 0.05 compared to BSC).

In the third scenario, we assumed that there is no utility benefit for achieving interim milestones which resulted in Spinraza being dominated by BSC, as it results in higher costs but same QALYs.

Table 4.30. Scenario Analyses for Spinraza versus BSC in Later Onset (Type II and III) SMA: Health Care Sector Perspective

	Cost per QALY
Base-Case Results	$8,156,000
Scenario #1: Assuming Further Utility Benefits for Interim Milestones	$4,078,000
Scenario #2: Assuming Utility Benefits for Interim Milestones and Stopping Spinraza after Two Years	$1,204,000
Scenario #3: Assuming No Utility Benefits for Interim Milestones	Dominated

Threshold Analyses Results

Threshold analyses results were produced for the base-case analysis, but note that the results were based on assumed utility benefits for achieving interim milestones. No price exists for Spinraza at the $50,000 per QALY threshold due to the marginal utility benefit and fixed administration costs of the drug. At other thresholds, Spinraza's price ranged from approximately $1,100 annually at the $100,000 per QALY threshold to approximately $20,000 annually at the $500,000 per QALY threshold, as seen Table 4.31.

Table 4.31. QALY-Based Threshold Analyses in Later-Onset SMA: Health Care Sector Perspective

	Spinraza* vs. BSC
Threshold Price at $50,000/QALY	--
Threshold Price at $100,000/QALY	$1,100
Threshold Price at $150,000/QALY	$3,400
Threshold Price at $200,000/QALY	$5,800
Threshold Price at $300,000/QALY	$10,500
Threshold Price at $500,000/QALY	$20,000

QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Presymptomatic SMA Model

Base-Case Results

Table 4.32 presents the base-case results from the health care sector perspective for the Spinraza versus BSC comparison in the presymptomatic SMA population, where we assumed that that 60% of patients had SMA Type I, 30% had SMA Type II, and 10% had SMA Type III. It should be noted that the results presented in this section relate to this specific split of SMA patients, and may not be generalizable if the proportions are different to those outlined above. The breakdown of LYs, QALYs, and costs according to health state for the different interventions are presented in Appendix Tables E39 to E42.

The total costs in the Spinraza arm were approximately $12 million, approximately fifteen times the total costs in the BSC arm of approximately $800,000. However, the Spinraza arm had more QALYs and LYs (21.94 and 26.58, respectively) compared to the BSC arm (6.25 QALYs and 9.51 LYs, respectively). This resulted in an incremental cost per QALY gained of $709,000 and an incremental cost per LY gained of $652,000 for Spinraza compared to BSC.

Table 4.32. Base-Case Results for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$10,565,000	$1,364,000	$11,929,000	21.94	26.58	$709,000	$652,000
BSC	$0	$801,000	$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Sensitivity Analyses Results

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. The key drivers of uncertainty included monthly costs in the "walking" health state and the utility in the "sitting" health state (Figure 4.6 and Table 4.33). Spinraza did not achieve a greater than zero likelihood of meeting $500,000/QALY or lower thresholds across the range of values tested (see Appendix E, Figures E9 and E10).

Figure 4.6. Tornado Diagram for Spinraza versus BSC in Presymptomatic SMA: Health Care Perspective

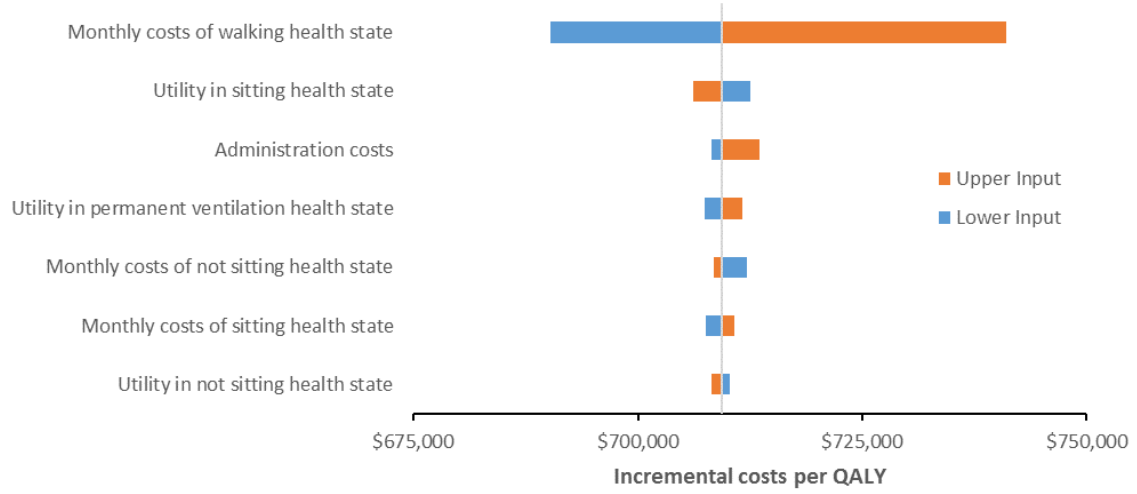


Table 4.33. Tornado Diagram Inputs and Results for Spinraza versus BSC in Presymptomatic SMA: Health Care Perspective

Input Name	Lower Incremental Cost-Effectiveness Ratio	Upper Incremental Cost-Effectiveness Ratio	Lower Input	Upper Input
Monthly Costs of Walking Health State	$690,000	$741,000	$1,000	$5,000
Utility in Sitting Health State*	$706,000	$712,000	0.5	0.7
Administration Costs	$708,000	$713,000	$1,000	$2,000
Utility in Permanent Ventilation Health State	$707,000	$712,000	0.1	0.3
Monthly Costs of Not Sitting Health State*	$708,000	$712,000	$10,434	$30,000
Monthly Costs of Sitting Health State	$707,000	$711,000	$3,000	$9,000
Utility in Not Sitting Health State*	$708,000	$710,000	0.1	0.3

*Lower input corresponds to higher ICER and vice versa.

Scenario Analyses Results

Table 4.34 presents the results from a scenario analysis taking a modified societal perspective, which included patient-centric societal costs (i.e., non-medical costs) and productivity gains, along with patient QALYs and health care costs. The incremental cost per QALY and incremental cost per LY gained for Spinraza compared to BSC in this modified societal perspective were slightly more favorable than those in the health care sector perspective. In the Spinraza arm, a majority of the patients were in the "walking" health state and a proportion in the "sitting" health state, which resulted in the non-medical costs being offset by the productivity gains, leading to lower (more favorable) incremental cost-effectiveness ratios.

Table 4.34. Scenario Analysis for Spinraza versus BSC in Presymptomatic SMA: Modified Societal Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Spinraza	$11,559,000	21.94	26.58	$687,000	$632,000
BSC	$773,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

We performed several additional scenario analyses to identify the effects of alternative inputs and assumptions on the cost-effectiveness results in presymptomatic SMA. We present the summary results for the Spinraza versus BSC comparison in Table 4.35. We present more detailed description of the assumptions behind each of these scenario analyses and detailed results in Appendix E (Tables E43 to E49).

In the scenario analyses for Spinraza versus BSC in presymptomatic SMA patients, assuming no utility benefit for achieving interim milestones increased the incremental cost per QALY to $727,000. Assuming lower health state costs resulted in lower (more favorable) incremental cost per QALY, as did assuming lower survival for the "sitting" and "walking" health states. However, assuming lower utilities for "sitting" and "walking" health states resulted in a higher incremental cost-effectiveness ratio of $904,000 per QALY. This suggests that the base-case incremental cost per QALY is an underestimate if the patients' utility in the "sitting" and "walking" health states are not as high as those in patients with SMA Type II and the general population, respectively.

Table 4.35. Scenario Analyses for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Cost per QALY	Cost per LY
Base-Case Results	$709,000	$652,000
Scenario #1: Assuming No Utility Benefits for Interim Milestones	$727,000	$652,000
Scenario #2: Assuming Lower Health State costs for "Not Sitting" and "Permanent Ventilation" Health States	$712,000	$655,000
Scenario #3: Assuming Lower Utilities for "Sitting" and "Walking" Health States	$904,000	$652,000
Scenario #4: Assuming Lower Survival for "Sitting" and "Walking" Health States	$678,000	$628,000
Scenario #5: Assuming Lower Utilities and Lower Survival for "Sitting" and "Walking" Health States	$877,000	$628,000
Scenario #6: Using a 10-Year Time Horizon	$890,000	$870,000
Scenario #7: Using 1.5% Discount Rate for Both Costs and QALYs	$679,000	$612,000

LY: life-year, QALY: quality-adjusted life year

Scenario analyses were also conducted for a hypothetical drug ("Drug X") treatment which had the one-time costs of Zolgensma with the health care costs, QALYs, and LYs associated with Spinraza in presymptomatic SMA patients.

The total costs in the Drug X arm were approximately $3.3 million, which is around four times the total costs in the BSC arm of around $800,000. However, the Drug X arm had higher QALYs and LYs (21.54 and 26.59, respectively) compared to the BSC arm (6.26 QALYs and 9.54 LYs, respectively). This resulted in an incremental cost per QALY gained of $161,000 and an incremental cost per LY gained of $145,000 for Drug X compared to BSC, as shown in Table 4.38.

Table 4.38. Hypothetical Drug X for Presymptomatic SMA: Health Care Sector Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Drug X	$3,264,000	21.94	26.58	$157,000	$144,000
BSC	$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Given the uncertainty involved with the long-term prognosis of presymptomatic population, we also performed scenario analyses for Drug X, assuming lower survival (approximately halving survival compared to estimates used in the base case) and lower utilities of 0.5 and 0.7 in "sitting" and "walking" health states, respectively. This resulted in an incremental cost per QALY gained of $242,000 and an incremental cost per LY gained of $174,000 for Drug X compared to BSC, as presented in Table 4.39.

Table 4.39. Hypothetical Drug X for Presymptomatic SMA Assuming Lower Survival and Utilities in "Sitting" and "Walking" Health States: Health Care Sector Perspective

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LY Gained
Drug X	$2,984,000	13.21	20.19	$242,000	$174,000
BSC	$615,201	3.43	6.55	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Threshold Analyses Results

Table 4.36 presents the threshold price results for Spinraza compared to BSC at thresholds from $50,000 to $500,000 per QALY. Threshold prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]). For Spinraza compared to BSC in presymptomatic SMA patients, the annual threshold-based prices are around $8,000 and $264,000 at thresholds of $50,000/QALY and $500,000/QALY, respectively.

Table 4.36. Threshold Analyses for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Spinraza* vs. BSC
Threshold Price at $50,000/QALY	$8,000
Threshold Price at $100,000/QALY	$36,400
Threshold Price at $150,000/QALY	$64,800
Threshold Price at $200,000/QALY	$93,200
Threshold Price at $300,000/QALY	$150,000
Threshold Price at $500,000/QALY	$264,000

QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Table 4.37 presents the threshold price results for Spinraza compared to BSC at thresholds from $50,000 to $500,000 per LY. Threshold prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]). For Spinraza compared to BSC in presymptomatic SMA patients, the annual threshold-based prices are $10,500 and $289,000 at thresholds of $50,000/LY and $500,000/LY, respectively.

Table 4.37. Threshold Analyses for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Spinraza* vs. BSC
Threshold Price at $50,000/LY	$10,500
Threshold Price at $100,000/LY	$41,400
Threshold Price at $150,000/LY	$72,300
Threshold Price at $200,000/LY	$103,000
Threshold Price at $300,000/LY	$165,000
Threshold Price at $500,000/LY	$289,000

LY: life-year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

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 specific input values (e.g., all set to 0, or all set to 1, etc.) 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. We shared the model with AveXis for external verification. Biogen chose not to receive the model.

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

Prior Published Evidence on Costs and Cost Effectiveness

In our review of prior economic models, we found no models comparing Zolgensma to other treatment options in patients with SMA. Key models included here are those submitted by the manufacturer of Spinraza to NICE[20] and CADTH,[101] which compared Spinraza to BSC.

Two manufacturer-developed models submitted to NICE compared Spinraza to BSC in early-onset (Type I) and later-onset (Types II/III) SMA in the UK. This model was reviewed by an evidence review group (ERG) contracted by the Department of Health.[20] Both the ICER and manufacturer-submitted models employed health states based on motor function milestones, but beyond the trial period, the ICER models assumed patients remained in the same health state as at end of trial, while the manufacturer models extrapolate the trial-derived transition probabilities (using CHOP-INTEND scores) beyond the trial period. As highlighted by the ERG and noted by the review committee, this extrapolation was favorable to Spinraza, in that patients receiving Spinraza could not worsen over time, but only improve or remain stable in each cycle, while patients in the BSC arm could not improve over time but could only worsen or stay within the same health state. Another important difference is that the manufacturer-submitted models did not include permanent ventilation as a health state, while the ICER models do. The manufacturer-submitted Type I model included Spinraza discontinuation at 13 months even if patients were able to sit, based on the ENDEAR trial, while the ICER model extends Spinraza duration for up to 24 months before discontinuation among patients who achieved no improvement in milestones, based on the SHINE extension trial. The manufacturer-submitted models included scoliosis surgery and subsequent Spinraza discontinuation, while the ICER models do not include scoliosis surgery. We are unable to compare utility values between the manufacturer-submitted and ICER models since the former models' utility inputs remain confidential. We do not compare the costs of Spinraza, BSC, and other health care costs in the different sets of models, due to the very different cost structures between the US and the UK.

Comparing outcomes in the SMA Type I model, the manufacturer-submitted models produced 7.86 and 2.49 QALYs for Spinraza and BSC, respectively, in the base case. However, NICE commented in bold that: *"The company's transition probabilities are optimistic and do not reflect clinical practice."; "The modelled long-term overall survival benefit is based on optimistic assumptions and is highly uncertain";* and that *"Utility values in the economic model are highly uncertain.*" Further details are provided in their Appraisal Consultation Document.[20] The ICER model resulted in 3.24 and 0.46 QALYs for Spinraza and BSC, respectively. The difference in QALYs gained between the manufacturer-submitted and the ICER models are being driven primarily by assumptions relating to long-term treatment outcomes, the baseline patient health state distributions, and the lack of

permanent ventilation as an outcome in the manufacturer-submitted model. Using either the manufacturer-submitted models or the ERG's modifications to the manufacturer-submitted model resulted in incremental cost-effectiveness ratios for Spinraza ranging from approximately £400,000 per QALY to approximately £630,000 per QALY.

The SMA Type II/III model submitted by the manufacturer to NICE resulted in 16.88 and 14.52 QALYs for Spinraza and BSC, respectively, in the base case subject to the limitations described by NICE. The ICER model resulted in 12.28 and 11.34 QALYs for Spinraza and BSC, respectively, in the base-case analysis. Using either the manufacturer-submitted models or the ERG's modifications to the manufacturer-submitted model resulted in incremental cost-effectiveness ratios for Spinraza ranging from being dominated to approximately £1.25 million per QALY. In the ICER model's base case and modified societal perspective analyses, Spinraza had a cost-effectiveness ratio of a little over $8 million per QALY.

Similar models for Spinraza were submitted by the manufacturer to CADTH's Common Drug Review (CDR).[101] Some of the key differences between the NICE and CADTH models were separation of the Type II/III models into separate models for Type II and Type III, a change in the modeled time horizon, and use of a 1.5% discount rate versus 3.5%. The CDR raised similar concerns with the manufacturer-submitted models as those raised by the ERG in the NICE appraisal. Key concerns included continued treatment benefit in the Spinraza arm beyond the trial duration, the use of unpublished utility estimates, initial state probabilities based on trial-specific distribution of patients by motor function milestones achieved, and uncertainty around mortality estimates for SMA Types I and II. The manufacturer-submitted model showed health outcomes (QALYs) in SMA Types I, II, and III for Spinraza versus BSC as 3.92 versus -0.88, 23.28 versus 19.60, and 12.05 versus 10.49, respectively. Incremental cost-effectiveness ratios for the SMA Type I, II, and II models were estimated at approximately $670,000 per QALY, $2.1 million per QALY and $2.8 million per QALY, respectively. The CDR reanalyzed the manufacturer-submitted model, making modifications to it such as including published utilities, assuming no continued benefit of Spinraza beyond trial duration, and changes to mortality estimates. These modifications resulted in substantially lower QALY gains for Spinraza and subsequently higher incremental cost-effectiveness ratios, at approximately $9.2 million per QALY, $24.4 million per QALY and $7.4 million per QALY for SMA Types I, II, and III, respectively.

A recently published manufacturer-funded model compared Spinraza to best-supportive care in early (Type I) and later (Types II/III) onset SMA patients in Sweden. Both cost-utility models were developed from a Swedish societal perspective, with a health care perspective analysis undertaken as a scenario.[102] The Type I and Types II/III models used a 40-year and 80-year time horizon, respectively, and used data from the key trials of Spinraza in early and later onset SMA. The models were very similar structurally and parametrically to the manufacturer-submitted models to NICE, with changes mainly to the patient utilities used and the costs to match those from a Swedish perspective. Like the NICE models, the Swedish models also assumed an optimistic scenario in the

base case that reflected continuous ongoing milestone achievement beyond trial duration for patients on Spinraza. This assumption was criticized by the NICE committee as not reflecting real-world practice.

While the manufacturer-funded model included caregiver utilities, it appears that the change in the caregiver utility was governed by the change in patient utility as they transitioned through different health states. This approach would compound the uncertainty surrounding patient health state utilities, and introduce the additional uncertainty around the potential for family utility to eventually increase over time when patients who cannot sit independently die, and the degree to which the new technologies will impact caregiver burden. These factors served as reasons for caregiver utilities to be not considered in our model either for the base case or the modified societal perspective.

Comparing patient quality-of-life outcomes alone in the early onset population, the ICER model produced 3.24 QALYs per patient while the manufacturer-funded model produced 3.65 QALYs. Life years gained were similar in both models. It must be noted however that the ICER model was over a lifetime horizon while the manufacturer-funded model for this population was 40 years. The inclusion of caregiver burden increased the QALY gain compared with best supportive care by 0.02.

In the later-onset population, patient QALYs gained in the ICER model was 12.28 for Spinraza, while those in the manufacturer-funded model was 9.25. Life years gained in the ICER model for this population was 18.9 years while it was 23.13 years in the manufacturer-funded model, which highlights the difference in utilities used, with the manufacturer model assuming that standing or walking with assistance had a utility of 0.39 compared with the ICER model of 0.65 for sitting patients. The inclusion of caregiver burden increased the QALY gain compared with best supportive care by 2.39 QALYs.

Incremental cost-effectiveness results from the payer perspective in the ICER model were approximately $1.1 million per QALY and approximately $8.2 million per QALY in the early- and later-onset SMA populations, respectively. Corresponding results were substantially more favorable in the manufacturer-funded model, at approximately SEK 5.6 million ($623,000) per QALY and approximately SEK 4.1 million ($457,000) per QALY. These differences in results between the ICER and manufacturer-funded models are primarily due to the optimistic assumption of potentially continuous improvement with Spinraza beyond the trial duration in the manufacturer-funded model, which is not consistent with clinical data observed to date.

Limitations

Our analyses have important limitations. Most of these relate to the lack of availability of robust data and the assumptions required to overcome this. There is no long-term follow-up for either treatment, resulting in considerable uncertainty related to the prognosis of patients with SMA. We

used motor function milestones to define broad health states and had to assume relationships between these motor function milestone-based health states and survival. Uncertainty in long-term survival was partially accounted for in sensitivity and scenario analyses that evaluated different assumptions. As there are no long-term data on the extrapolation of motor function milestones, the base-case analyses assume that these are sustained until death. However, we performed conservative scenario analyses assuming a proportion of the patients in the "sitting" health state lose their milestones.

Furthermore, relevant interim milestones could not be included in the model, as these data were not available for all the treatments. However, the base-case analyses included utility benefit in the treatment arms compared to BSC to make allowances for better functioning in treatment arms within these broad health states.

For Spinraza in presymptomatic SMA patients and for Zolgensma in SMA Type I patients, the evidence was based on single-arm studies. Thus, the uncertainty produced from this analysis likely underestimates the total uncertainty involved. We could not estimate disease progression parameters (e.g., transition probabilities) without access to individual patient data from the studies. As such, the data for the different interventions during the study period were used directly in the model to estimate short-term costs/QALYs. This is subject to limitations, especially towards the end of the follow up period, where survival probabilities remain constant for an extended period of time due to small numbers at risk and the censoring involved. However, this methodology does have the advantage of matching the study data, subject to the caveat related to naïve comparisons due to single-arm studies.

There were some structural assumptions in the model. While the survival of those who are in "permanent ventilation" at the end of the short-term model is included, the mortality of the patients that transition to the "permanent ventilation" state from the "not sitting" health state is not modelled explicitly in the long-term model. However, additional costs for permanent ventilation were included for three months prior to death in the "not sitting" state.

There is no explicit discontinuation of Spinraza treatment in the later onset SMA and presymptomatic SMA models. In the SMA Type I model, the patients in the Spinraza arm who were in "permanent ventilation" and "not sitting" health states were assumed to stop treatment after 24 months.

Robust utility data were lacking for these populations, with many identified studies lacking face validity. As such, we used utility data derived from several sources that were believed to be coherent. The base-case analyses were complemented with sensitivity and scenario analyses to explore the uncertainty in these values. Similarly, cost data were lacking, requiring several assumptions to be made. Importantly, the cost of Zolgensma is unknown. These uncertainties were partially addressed through altering the cost inputs in sensitivity analyses, as well as

presenting threshold-based price ranges. However, due to the lack of data, the distributions used for costs and utilities in the PSA are on mean values ±20%. As such, the true uncertainty is likely to be more than that represented in our probabilistic analyses.

Given the nature of SMA, it is difficult to disentangle the adverse events due to treatment from the complications associated with SMA itself, which are already accounted for in the health state costs and disutilities. As such, the costs and disutilities of adverse events were not included in the model.

Finally, our analyses using a modified societal perspective do not include quality of life burden associated with caregivers, as the methods for performing economic evaluations including such caregiver burden are still under development. Incorporating caregiver burden may lead to counter-intuitive results due to prolonged negative productivity effects and unknown quality of life effects on caregivers when children who need substantial care live longer. Furthermore, there is a lack of data on utilities and lost income for caregivers of patients with SMA. As such, we present our thinking on these considerations in Appendix E (Tables E8 and E9) but we do not present results of the analyses using modified societal perspective including caregiver burden.

Conclusions

Spinraza appears to be most cost effective when used in patients with presymptomatic SMA. In this population, the estimated incremental cost-effectiveness of Spinraza is $709,000 per QALY gained from a health care sector perspective and $687,000 from a modified societal perspective, far exceeding usual cost-effectiveness thresholds. The estimated cost per LY gained in this setting is $652,000 from the health care sector perspective and $632,000 from the modified societal perspective. For Zolgensma (at a placeholder price of $2 million) the estimated incremental cost-effectiveness from a health care sector perspective in patients with symptomatic Type I SMA is $243,000 per QALY gained and the estimated cost per LY gained is $182,000; the results were very similar from a modified societal perspective.

4.4 Summary and Comment

We have presented multiple analyses of Spinraza and Zolgensma to address considerations including:

- Different patient populations (symptomatic/presymptomatic; Type I, Type II/III SMA)
- Value of survival in a health state with poor quality of life
- Difficulties in finding a price to meet commonly cited willingness-to-pay thresholds when background medical treatment costs are extremely high

For Spinraza, our base-case results found that, at its current price, it does not meet traditional cost-effectiveness thresholds in any population of use. Spinraza, as used in its randomized trial in

symptomatic Type I SMA, prolonged the lives of some children who were on permanent ventilation or unable to sit. These children have very high health care costs, and so a drug with these characteristics may not appear cost-effective at any price. Using suggested guidance regarding this circumstance,[100] we performed an analysis where we excluded "unrelated" health care costs. In this analysis, the incremental cost-effectiveness of Spinraza was $810,000 per QALY and $429,000 per LY gained, still exceeding usual cost-effectiveness thresholds. Even when used in a presymptomatic population, where cost-effectiveness results were most favorable, Spinraza's price would need to be reduced below $65,000 per year to meet a $150,000 per QALY threshold. For later-onset SMA the incremental cost-effectiveness of Spinraza was over $8 million per QALY gained, as current evidence did not demonstrate life extension and the benefits of treatment translate to small improvements in quality of life compared to best supportive care.

For Zolgensma at a placeholder price of $2 million, our base-case results found that it too does not meet traditional cost-effectiveness benchmarks for use for patients with Type I SMA and would have to have its price reduced to under $900,000 for the one-time administration to meet a $150,000 per QALY threshold. Although we present a scenario analysis that allows Zolgensma to offset costs of Spinraza, we do not consider this a suitable base case for the purposes of determining long-term value for money or as the basis of a value-based price recommendation. Spinraza is relatively new and our analyses suggest it is not cost effective at commonly-cited usual thresholds. Additionally, it is important to recognize that the evidence for Zolgensma in this setting is based on 12 patients, while the evidence for Spinraza comes from a randomized trial with over 100 patients. As in prior reports, we feel it is inappropriate for a therapy to appear cost effective simply by offsetting costs of a recently introduced very expensive alternative. In this scenario, at a placeholder price of $2 million, the incremental cost-effectiveness of Zolgensma from a health care sector perspective was $139,000 per QALY and $117,000 per LY gained. Policymakers will have the results of the Zolgensma versus Spinraza modeling to support their own judgment of value.

In order to provide policymakers with a broad view of cost-effectiveness, we also examined costs per LY gained. This approach values any life extension, even at a very low quality of life, as equal to life extension at full health. Cost per LY gained does not capture improvements in quality of life as intended by ICER's stated goal of highlighting an "equal value for life-year gained" (evLYG) measure, but in this case it was not possible to construct this measure, and viewing results of both the cost per LYG and the cost per QALY gained will ensure that policymakers can feel confident that they are considering information that poses no risk of discrimination against this patient group. For Spinraza in presymptomatic SMA, we estimated the cost per LYG as $652,000 from the health care sector perspective. For Zolgensma in patients with symptomatic Type I SMA, at a placeholder price of $2 million the corresponding finding in the health care sector analysis was $182,000 per LYG. In this analysis, Zolgensma's price would need to be approximately $1.5 million to meet a $150,000 per LYG threshold. We performed multiple additional sensitivity and scenario analyses to address multiple avenues of uncertainty. We conducted numerous scenario analyses to explore questions

about the best way to model the connection between motor skill improvements and quality of life, the impact of different time horizons and of a societal perspective on modeling results, and the relevance of substantial non-drug health care costs that continue to accrue when a treatment extends life. Except for one scenario analysis, which took a 10-year time horizon, we assumed in all other analyses that the short-term benefits of both treatments persist for a lifetime. Although there remains substantial uncertainty about whether this will prove true, input from clinical experts and judgments based on the mechanism of action of the two treatments leads us to believe that our base-case assumption of lifetime durability of benefit, while it may be viewed as optimistic by some, is the best starting point for a judgment of the value of these treatments at this time.

For Spinraza, when accounting for model input uncertainty through scenario and one-way sensitivity analyses, the incremental cost effectiveness ratios did not fall below $670,000 per QALY gained. The results were most sensitive to the length of survival, the costs associated with treating people with SMA, and the utilities in both the "sitting" and "not sitting" health states. Results from the probabilistic sensitivity analyses found that Spinraza had a zero likelihood of achieving cost-effective thresholds of less than $500,000 per QALY gained.

For Zolgensma, when accounting for model input uncertainty through scenario and one-way sensitivity analyses the range in the incremental cost-effectiveness ratios was $199,000 to $406,000 per QALY gained. The results were most sensitive to the length of survival, health care costs, and utility in both the "sitting" and "walking" health states. Results from the base-case probabilistic sensitivity analysis found that Zolgensma had a 0.1% chance of being cost effective at thresholds of $150,000 per QALY but 100% chance of being cost-effective at thresholds above $300,000 per QALY gained.

Among the most challenging aspects of this cost-effectiveness analysis has been uncertainty about the future clinical use of these treatments. Will they be used primarily for presymptomatic patients? With data demonstrating effectiveness of Spinraza in this population, this evolution seems quite likely, a judgment confirmed by input from clinical experts. For Zolgensma the future is less clear due to the fact that it has not yet been studied in presymptomatic patients. But with the possibility of its use in this population we decided to create a hybrid "Drug X" that had the placeholder cost of Zolgensma and the effectiveness of Spinraza in this population. Given that Drug X is administered as a one-time infusion, we found its cost-effectiveness very near traditional ranges assuming a placeholder price of $2 million. There is obviously substantial uncertainty in the potential effectiveness of Zolgensma in the presymptomatic population, but our hypothetical Drug X results may serve as a starting point for policy debates should the FDA approval language suggest that Zolgensma may be used in this population even without supporting clinical data.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of Spinraza and Zolgensma to supportive care and compared to one another. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 5.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework and the framework adaptation for ultra-rare diseases. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
This intervention will have a significant positive impact outside the family, including communities.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
There is significant uncertainty about the long-term risk of serious side effects of this intervention.
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

As discussed in Section 1, SMA is a condition of particularly high severity and rapid progression, with the most severe cases affecting infants and young children.[8,9] In the most common and severe form of SMA, estimates of the median age at death range from 10.4 months up to four years.[37,55,56] Survival depends on respiratory function, and many infants and children become permanently ventilated. Patients with SMA may need intensive care and support, especially those with SMA Type I. To maintain mobility and function as long as possible, multidisciplinary, supportive care is needed. Supportive care does not modify disease progression, and patients may be entirely dependent on family members who expend intense emotional and physical effort when constantly caring for a patient. Hence, SMA may affect the health-related quality of life of patients as well as their families, caregivers, and wider communities.

Spinraza is the first FDA approved treatment that modifies disease progression. The availability of a disease-modifying treatment has paved the way for newborn screening. A federal recommendation to screen SMA in newborns was approved in July 2018, and several states have decided to adopt or pilot test SMA newborn screening since then.[52,53]

Zolgensma is a one-time, intravenous administration which may reduce complexity and reduce caregiver burden compared with repeated lumbar punctures. As a one-time administration, there may also be reduced complexity for patients and caregivers navigating insurance policies.

Both interventions may have benefits beyond the outcomes assessed in trials. For example, if treatment improves or retains children's mobility, children may attend school and caregivers may return to work. An effective treatment also may reduce anxiety and stress among caregivers and wider communities, reduce other resources used (e.g., in schools), and promote more interaction between children with SMA and others in the community. Furthermore, for some patients and families, retaining current function is a meaningful outcome, and small improvements in motor abilities can allow patients greater ability for self-care and independence. The potential for an effective treatment may also reduce concerns of families having another child.

Overall, the existing evidence on Spinraza (SMA Types I-III) or Zolgensma (SMA Type I) suggested that treatment prolonged survival and improved motor functioning compared with historical cohorts or sham controls. At this time, data on presymptomatic patients with SMA and on longer-term durability and tolerability in symptomatic patients are limited. Additional data from open-label extensions and other future studies will help provide insights on long-term potential benefits and harms of treatments, on which uncertainty remains.

6. Value-Based Price Benchmarks

Our value-based price benchmarks for Spinraza and Zolgensma are presented in Table 6.1. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. We note that for treatments of ultra-rare disorders, decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than those applied to decisions about other treatments.

For Spinraza, the value-based benchmark price was estimated in the presymptomatic SMA population. Spinraza showed the most benefits in this population, and SMA has been added to the Recommended Uniform Screening Panel for newborns in the US,[12] making it likely that many patients will be identified and treated before symptoms develop. For Zolgensma, the value-based benchmark price was estimated in the SMA Type I population as currently data are not available for presymptomatic treatment with Zolgensma.

Value based prices are reported as annual costs for Spinraza (assumed to be post-year one costs [i.e., cost of three doses]) and as one-time cost for Zolgensma.

Table 6.1. Value-Based Benchmark Prices of Spinraza and Zolgensma

	List Price + Estimated Mark-Up	Population	VBP at $100,000 per QALY Threshold	VBP at $150,000 per QALY Threshold	Discount Required to Achieve Threshold Prices
Spinraza	$382,500	Presymptomatic SMA	$36,400*	$64,800*	83% to 90%
Zolgensma	$2,000,000†	Infantile-Onset (Type I) SMA	$310,000	$899,000	N/A as real-world price is unknown

QALY: quality-adjusted life year, VBP: value-based benchmark price

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+. Year one value-based benchmark prices are $72,800 to $129,400 due to the required loading doses.

†Placeholder price.

We are increasing reference to the cost per LYG figures to ensure that policymakers are aware of the complementary information these results can provide to the cost per QALY findings. The annual price at which Spinraza meets the $100,000 to $150,000 per LYG range for use in presymptomatic patients is $41,400 to $72,300. This range is quite similar to the cost per QALY range. For Zolgensma, however, there is notable difference. The relevant cost per LYG price range for Zolgensma when used for Type I SMA is $710,000 to $1,498,000 for the $100,000 to $150,000 per LYG thresholds.

Broader Threshold Price Analyses

Table 6.2 presents the threshold price results for Spinraza compared to BSC for presymptomatic individuals at thresholds from $50,000 to $500,000 per QALY gained and per LY gained. Threshold prices are reported as annual costs for Spinraza, including administration fees.

Table 6.2. Threshold Prices for Spinraza in Presymptomatic SMA

	Per QALY*	Per LYG*
Threshold Price at $50,000/QALY	$8,000	$10,500
Threshold Price at $100,000/QALY	$36,400	$41,400
Threshold Price at $150,000/QALY	$64,800	$72,300
Threshold Price at $200,000/QALY	$93,200	$103,000
Threshold Price at $300,000/QALY	$150,000	$165,000
Threshold Price at $500,000/QALY	$264,000	$289,000

LYG: life-year gained, QALY: quality-adjusted life year

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Table 6.3 presents the threshold price results for Zolgensma compared to BSC in Type I SMA at thresholds from $50,000 to $500,000 per QALY gained and per LY gained. Threshold prices are reported for the one-time cost for Zolgensma.

Table 6.3. Threshold Prices for Zolgensma in Type I SMA

	Per QALY*	Per LYG*
Threshold Price at $50,000	--	--
Threshold Price at $100,000	$310,000	$710,000
Threshold Price at $150,000	$899,000	$1,498,000
Threshold Price at $200,000	$1,488,000	$2,287,000
Threshold Price at $300,000	$2,666,000	$3,865,000
Threshold Price at $500,000	$5,021,000	$7,020,000

LYG: life-year gained, QALY: quality-adjusted life year

*Threshold prices are based on a one-time cost for Zolgensma.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of Zolgensma in patients diagnosed with SMA Type I in the US. Because no published evidence exists that can inform an economic evaluation of this therapy in presymptomatic or in Type II/III SMA patients, we restricted our budget impact to only SMA Type I patients. We used the assumed placeholder price and the threshold prices calculated using our base-case QALY results for Zolgensma (Table 4.25) in our estimates of budget impact. We did not estimate the budget impact of Spinraza because it has already been in use in the US marketplace for over a year.

7.2 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 net cost of using Zolgensma compared with BSC only for the treated population, calculated as health care costs (including drug costs) minus any offsets in these costs from averted health care events. In a separate scenario, we also examined the potential budget impact of use of Zolgensma compared with a mix of Spinraza and BSC in that population. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

To estimate the eligible population, we first identified the incidence of SMA in the US. The incidence was assumed to be the US SMA birth prevalence (9.4 per 100,000 live births) as estimated by Lally et al.[10] We then applied this estimate to the most recent, published data on the number of live births in the US, to estimate the number of new cases of SMA in the US each year.[103] The distribution of type-specific birth prevalence indicates that approximately 58% of all SMA cases are Type I.[104] Applying these estimates to the projected 2019 to 2023 US population[105] resulted in an average of 215 new SMA Type I patients eligible to be treated with Zolgensma each year.

ICER's methods for estimating potential budget impact are described in detail elsewhere[106] and have been recently updated. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2018-19, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $991 million per year for new drugs.

To estimate potential budget impact, we evaluate a new therapy that would take market share from one or more existing therapies/treatments and calculate the blended budget impact

associated with displacing use of existing therapies with the new intervention. For this analysis, we evaluated the potential budget impact of using Zolgensma compared to BSC only for SMA treatment. In a separate scenario analysis for Zolgensma, we assumed that most of the incident patients would have received the treatment currently on the market (i.e., Spinraza) in the absence of Zolgensma. We therefore assumed that, in the absence of Zolgensma, 75% of patients would initiate treatment with Spinraza while 25% would receive BSC. In light of a July 2018 federal recommendation that all newborns be screened for SMA and several states subsequently deciding to adopt or pilot test SMA newborn screening,[52,53] we included an additional scenario analysis where we assumed all incident SMA patients would be treated with Spinraza in place of BSC. We used Spinraza's current net price (including hospital mark-up) for this scenario. Since current published trial evidence in the presymptomatic SMA patient group is limited to Spinraza, we did not consider Zolgensma for this scenario. We estimated this incident population size at approximately 370 patients per year.

7.3 Results

Table 7.1 illustrates the per-patient budget impact calculations of Zolgensma, based on the assumed placeholder price ($2 million per one-time treatment) and the prices to reach $150,000 and $100,000 per QALY for Zolgensma ($899,000 and $310,000, respectively), compared to BSC only. Note that because of high background costs, there was no price of Zolgensma that achieved an incremental cost effectiveness ratio of $50,000 per QALY.

Table 7.1. Per-Patient Budget Impact Calculations for Zolgensma Compared to BSC Only, Over a Five-Year Time Horizon

	Average Annual per Patient Budget Impact		
	Assumed Placeholder	$150,000/QALY	$100,000/QALY
Zolgensma*	$1,113,600	$610,800	$341,900
BSC	$167,400		
Difference	$946,300	$443,500	$174,500

QALY: quality-adjusted life year, WAC: wholesale acquisition cost
All costs rounded to the nearest $100.
*Based on a placeholder price of $2,000,000.

The average potential budgetary impact compared to BSC only when using the assumed placeholder price was an additional per-patient cost of approximately $946,300. Average potential budgetary impact at the cost-effectiveness threshold prices for the drug ranged from approximately $443,500 per patient using the annual price to achieve $150,000 per QALY to approximately $174,500 per patient using the annual price to achieve a $100,000 per QALY cost-effectiveness threshold.

The annual potential budgetary impact of treating the entire eligible population with Zolgensma rather than BSC only did not exceed the $991 million threshold across all three prices, reaching 45% of the threshold at the assumed placeholder price of $2 million (Table 7.2), largely due to the relatively small number of patients eligible for treatment. The potential budget impact would be even lower at the two threshold prices.

Table 7.2. Estimated Total Potential Budget Impact (BI) of Zolgensma* Treatment Compared to BSC Only, Using Different Prices Over a Five-Year Time Horizon, Assuming 215 Eligible Patients per Year

	Zolgensma*: Percent of Threshold
Assumed Placeholder Price	45%
$150,000 per QALY Threshold Price	21%
$100,000 per QALY Threshold Price	8%

*Based on a placeholder price of $2,000,000.

Scenario Analysis Compared to Spinraza/BSC Mix

Table 7.3 illustrates the per-patient budget impact calculations, based on the assumed placeholder price ($2 million per one-time treatment) and the prices to reach $150,000 and $100,000 per QALY for Zolgensma, compared to a 75%/25% mix of Spinraza/BSC. As before, because of high background costs, there was no price of Zolgensma that achieved an incremental cost effectiveness ratio of $50,000 per QALY.

Table 7.3. Per-Patient Budget Impact Calculations for Zolgensma Compared to Spinraza/BSC (75%/25%), Over a Five-Year Time Horizon

	Average Annual per Patient Budget Impact		
	Assumed Placeholder	$150,000/QALY	$100,000/QALY
Zolgensma*	$1,113,600	$610,800	$341,900
Spinraza/BSC (75%/25%)	$540,600		
Difference	$573,100	$70,300	-$198,700†

QALY: quality-adjusted life year, WAC: wholesale acquisition cost
All costs rounded to the nearest $100.
*Based on a placeholder price of $2,000,000.
†Cost-saving.

In this case, the average potential budgetary impact when using the assumed placeholder price was an additional per-patient cost of approximately $573,100. Average potential budgetary impact at the cost-effectiveness threshold prices for the drug ranged from approximately $70,300 per patient using the annual price to achieve $150,000 per QALY to saving approximately $198,700 per patient using the annual price to achieve a $100,000 per QALY cost-effectiveness threshold.

The annual potential budgetary impact of treating the entire eligible population with Zolgensma rather than a mix of Spinraza/BSC did not exceed the $991 million threshold across all three prices, reaching only 24% of the threshold at the assumed placeholder price of $2 million (Table 7.4), again due to the relatively small number of patients eligible for treatment. Furthermore, Zolgensma treatment was estimated to be cost-saving at the $100,000 per QALY threshold price, mainly due to the high costs associated with the comparator (75%/25% mix of Spinraza/BSC).

Table 7.4. Estimated Total Potential Budget Impact (BI) of Zolgensma* Treatment Compared to Spinraza/BSC (75%/25%), Using Different Prices Over a Five-Year Time Horizon, Assuming 215 Eligible Patients per Year

	Zolgensma*: Percent of Threshold
Assumed Placeholder Price	24%
$150,000 per QALY Threshold Price	1%
$100,000 per QALY Threshold Price	-12%†

*Based on a placeholder price of $2,000,000.
†Cost-saving.

Scenario Analysis Comparing Spinraza to BSC in Pre-symptomatic SMA Patients

In this scenario, the average annual potential budgetary impact of using Spinraza relative to BSC in the pre-symptomatic SMA patient group was approximately $573,900. The annual potential budgetary impact of treating this entire eligible population with Spinraza reached 58% of $991 million annual threshold at its current net price.

8. Summary of the Votes and Considerations for Policy

8.1 About the New England CEPAC Process

During New England CEPAC public meetings, the New England CEPAC Council deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Council members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to New England CEPAC Council members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the New England CEPAC Council during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

After the New England CEPAC Council votes, a policy roundtable discussion is held with the New England CEPAC Council, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the March 7, 2019 meeting, the New England CEPAC Council discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of Spinraza and Zolgensma for SMA. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at 1:19:14), the New England CEPAC Council voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to Spinraza and Zolgensma. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by New England CEPAC Council members during the voting process.

In its deliberations and votes related to value, the New England CEPAC Council considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

a. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The New England CEPAC Council uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

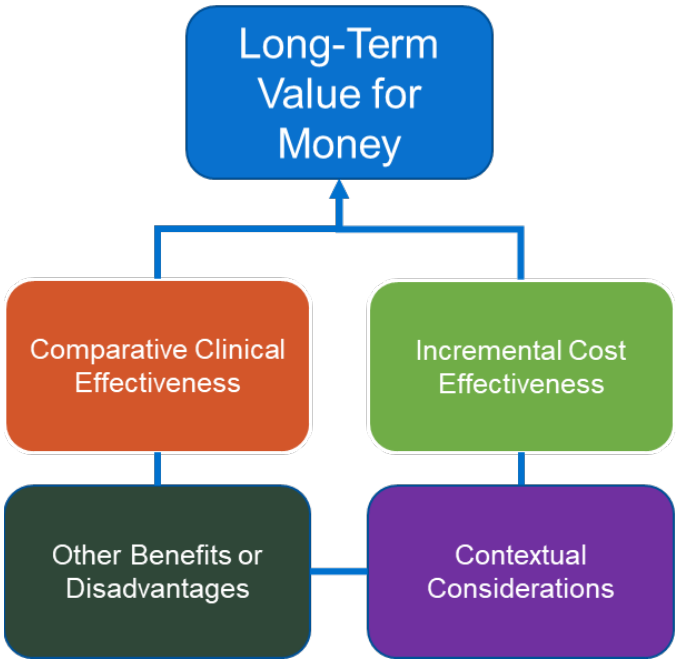
b. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the New England CEPAC voting council follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

c. Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

d. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1. Conceptual Structure of Long-Term Value for Money



8.2 Voting Results

Patient Population for questions 1-3: Patients with infantile-onset (Type I) spinal muscular atrophy (SMA).

1) Is the evidence adequate to demonstrate that the net health benefit of nusinersen (Spinraza, Biogen Inc.) added to supportive care is superior to that provided by supportive care alone?

Yes: 12 Votes	No: 0 Votes

The Council unanimously determined that the evidence was adequate to demonstrate a superior net health benefit of Spinraza compared to supportive care alone in patients with Type I SMA. Council members cited several high-quality clinical trials that established clear and convincing health benefits, such as motor milestone attainment and avoidance of permanent ventilation.

2) Is the evidence adequate to demonstrate that the net health benefit of onasemnogene abeparvovec (Zolgensma, AveXis/Novartis AG) added to supportive care is superior to that provided by supportive care alone?

Yes: 12 Votes	No: 0 Votes

The Council unanimously judged that the evidence was adequate to demonstrate a superior net health benefit of Zolgensma compared to supportive care alone in patients with Type I SMA. Although some Council members recognized the smaller evidence base of Zolgensma in comparison to that of Spinraza, overall, they argued that the magnitude of clinical benefit was persuasive. Several Council members compared the natural history of the disease, which is typically progression to permanent ventilation and/or death, with the positive outcomes seen in the trial, such as the attainment of motor milestones.

3) Is the evidence adequate to distinguish the net health benefit between Spinraza and Zolgensma?

Yes: 0 Votes	**No: 12 Votes**

The Council unanimously concluded that the evidence was inadequate to distinguish the net health benefit between Spinraza and Zolgensma. Council members noted the lack of head-to-head studies and that the existing trials were not comparable.

Patient Population for question 4: Patients with later-onset (Type II/III) SMA.

4) Is the evidence adequate to demonstrate the net health benefit of Spinraza plus supportive care is superior to that provided by supportive care alone?

Yes: 12 Votes	No: 0 Votes

The Council unanimously voted that the evidence was adequate to demonstrate a superior net health benefit of Spinraza compared to supportive care alone in patients with Type II/III SMA. The Council found the outcomes data convincing, and noted that patients are likely to receive benefits that would not be captured by current outcome measures. Several Council members cited testimony from patient advocates and caregivers, and noted that these other treatment benefits might include improvements in speech and vocalization, recovery time from illness, stamina, and range of arm movement.

Patient Population for questions 5-6: Patients with presymptomatic SMA.

5) Is the evidence adequate to demonstrate the net health benefit of administering Spinraza prior to development of symptoms is superior to that of supportive care alone?

Yes: 10 Votes	No: 2 Votes

A majority of the Council determined that the evidence was adequate to demonstrate a superior net health benefit of presymptomatic treatment with Spinraza. Although the data was derived from an interim analysis, the Council members noted that the studied patient population and trial methodology appeared to be appropriate, and several emphasized that without treatment, many of the children in the study would have eventually required permanent ventilation or would have died.

The Council members who voted in the negative expressed methodologic concerns. One Council member argued that the evidence was inadequate because it was only available as an abstract and had not been subject to peer review. This Council member further noted that although the actual results appeared to demonstrate a clinical benefit, in order to deem the overall evidence base adequate, additional peer reviewed data would be required.

6) Is the evidence adequate to demonstrate the net health benefit of administering Zolgensma prior to development of symptoms is superior to that of supportive care alone?

Yes: 0 Votes	**No: 12 Votes**

The Council unanimously judged the evidence to be inadequate to demonstrate a superior net health benefit of presymptomatic treatment with Zolgensma. The Council highlighted that Zolgensma has yet to be studied in a presymptomatic population and the potential for unique safety issues in a neonatal population, including the possibility of impaired liver function.

7) Is it likely that treatment with Spinraza offers one or more of the following potential "other benefits" that are not adequately captured in the base case cost-effectiveness model?

Spinraza offers reduced complexity compared to other treatment options that will improve patient outcomes in the real world.	N/A
Spinraza has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	N/A
Spinraza will significantly reduce caregiver or broader family burden.	12/12
Spinraza will have a significant impact on improving patients'/caregivers' ability to return to work and/or their overall productivity.	10/12
Spinraza will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	12/12
There are other important benefits – or disadvantages – that should have an important role in judgments of the value of Spinraza.	N/A

The Council unanimously determined that treatment with Spinraza is likely to reduce caregiver or broader family burden. Numerous Council members noted that SMA is a family disease that impacts all aspects of home life, including marriage and dynamics among siblings. Based on testimony from patient advocates, several Council members emphasized that caregivers have difficulty maintaining a social life and participating in recreational activities, and that effective treatment may allow them to re-engage in these aspects of their lives. A majority of the Council also noted that treatment with Spinraza will likely allow caregivers to return to work and patients to return to or participate more fully in schools and communities. A number of Council members stressed that caregivers are often required to change jobs and careers, which may mean that families have to endure periods with reduced income. This, as several Council members noted, is exceptionally difficult for caregivers of patients with SMA, as equipment and home and vehicle modifications are expensive.

The Council also universally acknowledged that Spinraza is likely to have a significant impact on the entire "infrastructure" of care. Numerous Council members noted that many aspects of care have already changed since the development of Spinraza, including the advent of neonatal screening for SMA and increased knowledge and awareness about the disease, which allows patients to be treated earlier before symptoms become particularly severe. In addition, with the advent of Spinraza, the clinical community is now able to provide effective treatment as opposed to supportive care alone.

Furthermore, the Council enumerated several other important benefits and disadvantages that were not captured in the official tally. Some Council members predicted a potential influx of neuromuscular specialists who are interested in working with these new treatments, and others emphasized that families affected by SMA may be likelier to have more children now that effective

treatments are available. On a broader scale, one Council member noted that a successful trial in the pediatric space may incentivize future studies on other diseases that affect children. Lastly, the Council highlighted a potential disadvantage of treatment: that Spinraza may create or widen socioeconomic, geographic, racial, and/or ethnic disparities as it will be offered primarily at academic medical centers, which may be more difficult for certain populations to access. Nevertheless, the Council expressed confidence that universal neonatal screening may help mitigate this issue.

8) Are any of the following contextual considerations important in assessing Spinraza's long-term value for money?

Spinraza is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	11/12
Spinraza is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	11/12
Spinraza was the first to offer any improvement for patients with this condition.	12/12
Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of Spinraza.	7/12
Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of Spinraza.	7/12
There are additional contextual considerations that should have an important role in judgments of the value of Spinraza.	NA

A majority of the Council considered SMA to represent a condition of high severity with a high lifetime burden of illness, and unanimously acknowledged that Spinraza was the first treatment to offer improvement for patients with SMA. A slight majority expressed concern regarding the uncertainty about the long-term risk of serious side effects and the durability of the long-term benefits of Spinraza due to the relatively short trial duration.

9) Is it likely that treatment with Zolgensma offers one or more of the following potential "other benefits" that are not adequately captured in the base case cost-effectiveness model?

Zolgensma offers reduced complexity compared to other treatment options that will improve patient outcomes in the real world.	12/12
Zolgensma will significantly reduce caregiver or broader family burden.	11/12
Zolgensma has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	N/A
Zolgensma will have a significant impact on improving patients'/caregivers' ability to return to work and/or their overall productivity.	10/12
Zolgensma will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	11/12
There are other important benefits—or disadvantages—that should have an important role in judgments of the value of Zolgensma.	N/A

The Council unanimously judged that Zolgensma, which is delivered as a one-time intravenous infusion and does not require an overnight hospital stay, offers reduced complexity compared to Spinraza. Council members noted that intravenous administration poses fewer risks than intrathecal injections of Spinraza, which must be delivered every four months at specialty centers. Council members reiterated that SMA is a family disease, and noted that their responses in Question 7 apply to Zolgensma as well.

10) Are any of the following contextual considerations important in assessing Zolgensma's long-term value for money?

Zolgensma is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	10/12
Zolgensma is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	10/12
Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of Zolgensma.	6/12
Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of Zolgensma.	7/12
There are additional contextual considerations that should have an important role in judgments of the value of Zolgensma.	N/A

As stated in their votes on Question 8, a majority of the Council considered SMA to represent a condition of high severity with a high lifetime burden of illness. Similar to the vote in Question 8, at least half the Council expressed concern regarding the uncertainty about the long-term risk of serious side effects and the durability of the long-term benefits of Zolgensma, a novel gene therapy. Other Council members noted these concerns, but were swayed by positive trial results, which

demonstrate an altered disease course.

11) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Spinraza versus supportive care alone in patients with infantile-onset (Type I) SMA?

Low Long-Term Value for Money: 12 Votes	Intermediate Long-Term Value for Money: 0 Votes	High Long-Term Value for Money: 0 Votes

The Council unanimously judged the long-term value for money of Spinraza to be "low" for patients with Type I SMA. Council members emphasized that their vote was driven by the considerably high cost of Spinraza. These Council members noted that at its current price, the cost-effectiveness of Spinraza far exceeds commonly-cited cost-effectiveness thresholds. Still, Council members reiterated that Spinraza demonstrates superior clinical effectiveness and dramatically alters the course of the disease. In addition, the Council enumerated many other benefits that were not captured in the model, such as a reduction in caregiver burden, important societal benefits, and a positive impact on the infrastructure of care.

12) No vote was taken, as Zolgensma did not have a publicly-known price at the time of the meeting.

13) No vote was taken, as Zolgensma did not have a publicly-known price at the time of the meeting.

14) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Spinraza versus supportive care in patients with later-onset (Type II/III) SMA?

Low Long-Term Value for Money: 12 Votes	Intermediate Long-Term Value for Money: 0 Votes	High Long-Term Value for Money: 0 Votes

The Council unanimously judged the long-term value for money of Spinraza to be "low" for patients with Type II/III SMA. Although the Council acknowledged that Spinraza demonstrates superior clinical effectiveness to supportive care, they were once again concerned by the high price. Several Council members noted that for Type II/III patients, treatment with Spinraza would be less cost-effective, as these patients typically follow a less severe disease course than Type I patients.

15) Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Spinraza before symptoms develop versus best supportive care?

Low Long-Term Value for Money: 12 Votes	Intermediate Long-Term Value for Money: 0 Votes	High Long-Term Value for Money: 0 Votes

The Council unanimously judged the long-term value for money of Spinraza to be "low" for presymptomatic patients with SMA. While the vast majority Council members agreed that Spinraza is clinically effective in patients with presymptomatic SMA, several reiterated their concerns about the lack of peer-reviewed, published studies in this population. As in their responses to other long-term value for money votes, the Council argued that Spinraza is too expensive and exceeds commonly-cited cost-effectiveness thresholds.

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Council engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on Spinraza and Zolgensma for SMA to policy and practice. The policy roundtable members included three patient advocates, two clinical experts, two payers, and two representatives from pharmaceutical manufacturers. 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 names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix Table H3.

Table 8.1. Policy Roundtable Participants

Name	Title and Affiliation
Brandi Akins	Patient Advocate
Emma Ciafaloni, MD, FAAN	Professor of Neurology, University of Rochester
Chris Leibman, PharmD, MS	Senior Vice President, Value and Access, Biogen
David Michelson, MD	Pediatric Neurologist, Loma Linda University Health
Erik Schindler, PharmD, BCPS	Clinical Pharmacy Manager, UnitedHealthcare
Mary Schroth, MD	Chief Medical Officer, Cure SMA
Douglas M. Sproule, MD, MSc	Vice President, SMA Therapeutic Area Head, AveXis
Danyelle Sun	Patient Advocate
John Watkins, PharmD, MPH, BCPS	Pharmacy Manager, Formulary Development, Premera Blue Cross

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Payers

1. Given the substantial remaining uncertainty regarding the benefits of these treatments in certain subpopulations and their high cost, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use. Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Spinraza

Patient Eligibility Criteria

a. **Diagnosis:** SMA should be confirmed by genetic testing for both symptomatic and pre-symptomatic patients. Insurers should not require repeated documentation of genetic testing results.

b. **Presymptomatic SMA:** Given that screening at birth will soon become universal, pre-symptomatic individuals with different numbers of *SMN2* copies will be identified. Although genotype is not precisely predictive of phenotype, existing research suggests that a very small number of individuals with four or more copies of *SMN2* will develop the most severe forms of SMA. A recent article authored by clinical experts from across the US, including many with research and other links to industry, found divided opinions on whether individuals found at birth to have four or more copies of *SMN2* should be treated immediately or whether it was reasonable to wait and monitor them to see if any signs of diminished muscle function emerged. The final proposal from this group supported the option of surveillance with the possibility of later treatment for this subpopulation.[107]

c. **Age:** No age restrictions. For presymptomatic individuals, treatment should be initiated as quickly as possible. For symptomatic patients, based on the lack of data on treatment among older patients, some countries have limited coverage to patients under the age of 12 or 15, but patient and clinical expert testimony suggests that there is no basis for assuming that benefits cannot be significant for patients with Type II-III at all ages.

d. **Other clinical criteria:** For presymptomatic individuals, no clinical criteria should be required for coverage. For symptomatic patients, payers may opt to have no clinical criteria related to severity or they may consider the option of requiring that clinical criteria be met that demonstrate that the patient is not too severely affected in some way to retain the possibility of benefit from treatment. For example, some payers have required that patients not be on permanent ventilation. Although there are no data on the benefits of initiating Spinraza treatment among permanently ventilated patients, family and clinical expert

testimony argued that ventilated patients can benefit from treatment even with relatively small improvements in motor function that can allow the self-direction of motorized wheelchairs or the use of tablets for communication. A related policy recommendation on manufacturer provision of treatment in such circumstances in which evidence is lacking is provided below.

Some countries have not provided coverage for Spinraza when patients have attained the ability to walk independently. Although the cost-effectiveness of treatment for symptomatic patients is worse among patients who are less severely affected, clinical experts and patient representatives argued that for some patients who can walk independently there are still important upper limb motor function benefits that are possible with treatment.

e. **Renewal criteria:** Many payers will seek to set a time threshold at which coverage must be re-assessed in light of whether there have been demonstrated benefits of treatment. Although a clear threshold is not evident from trial data, it is not unreasonable to expect results after six to 12 months of treatment. If there has been no improvement, or at least no halt to a steady decline in symptoms at that time, payers may determine that continued coverage for Spinraza is not medically necessary. Payers may require that response to treatment be documented by a clearly defined outcome chosen by the provider based on the patient's current motor function (e.g., HINE-2, HFMSE, CHOP-INTEND, 6MWT, ULM, or RULM). Of note, some countries have used achievement or maintenance of sitting as a single outcome measure by which to determine whether continued use of Spinraza is justified, but clinical expert comment suggested that for many patients sitting is not a relevant measure of clinical benefit. Alternatively, given the clinical heterogeneity of patients, and the challenge of determining which clinical outcome measure is best suited for a specific patient, payers may opt for clinician attestation as the most reasonable option for determining whether coverage should be renewed.

f. **Concomitant/sequential use with Zolgensma:** There are no data by which to make informed judgments about the risks and benefits of adding Zolgensma treatment to ongoing treatment with Spinraza. Because of the lack of evidence and the high costs, payers are likely to deny coverage for Zolgensma unless Spinraza treatment is halted completely, either due to the patient not achieving their desired level of improvement or side effects. If Spinraza therapy has not provided sustained substantial clinical benefit, payers should engage with clinicians to determine whether switching to Zolgensma therapy would offer a superior chance of clinical benefit.

Provider criteria

a. **Provider criteria:** Payers are likely to set criteria for providers to require either that the provider be a specialist in neuromuscular medicine or work in consultation with such a specialist. For patients with symptomatic SMA it is likely that patients will benefit from

treatment under the direction of a multi-disciplinary team skilled at coordinating care across neurological, pulmonary, nutritional, and other domains, and payers may consider limiting coverage to care provided at these Centers of Excellence. The downside of such coverage limitation is the risk that access will made more difficult for patients who do not live near academic health centers of other areas where these teams are available. Another consideration is that successful treatment of children with pre-symptomatic disease may not require the broader expertise offered by these teams.

Zolgensma

Patient Eligibility Criteria

a. **Diagnosis:** SMA should be confirmed by genetic testing for both symptomatic and pre-symptomatic patients. Insurers should not require repeated documentation of genetic testing results.

b. **Presymptomatic SMA*:*** At the time of this final report Zolgensma has not received FDA approval and therefore it remains unclear how broad will be its labeled indications. Even though there are no public data available on the use of Zolgensma outside of infantile-onset (Type I) SMA, it seems reasonable to assume that Zolgensma will receive broad approval that includes use as a treatment for asymptomatic individuals identified through postnatal screening. Given that screening at birth will soon become universal, presymptomatic individuals with different numbers of *SMN2* copies will be identified. Although genotype is not precisely predictive of phenotype, existing research suggests that a very small number of individuals with four or more copies of *SMN2* will develop the most severe forms of SMA. A recent article authored by clinical experts from across the US, including many with research and other links to industry, found divided opinion on whether individuals found at birth to have SMA with four or more copies of *SMN2* should be treated immediately or whether it is reasonable to wait and monitor them to see if any signs of diminished muscle function emerge before starting treatment. The final proposal from this group supported the option of surveillance with the possibility of later treatment for this subpopulation.[107]

c. **Age:** Testimony from clinical experts suggested that safety concerns about use among newborns (primarily related to liver inflammation) may lead the FDA and some clinicians to limit use until infants are age six months or older. Although the labeled indication is not known, since the only data in the public domain on Zolgensma are for treatment of symptomatic Type I patients, insurers may consider limiting coverage to this population. However, patient and clinical expert testimony suggests that benefits of treatment with Spinraza in older patients with Type II-III SMA can be clinically meaningful, and by analogy the same will be assumed of Zolgensma. Insurers may therefore wish to consider broadening coverage criteria to match the FDA label even in the absence of data at this time.

d. **Other clinical criteria:** If Zolgensma is approved for pre-symptomatic individuals, no clinical criteria should be required beyond those in the label (which could include age or weight) for coverage. For symptomatic patients, payers may opt to have no clinical criteria related to severity or they may consider the option of requiring that clinical criteria be met that demonstrate that the patient is not too severely affected in some way to retain the possibility of benefit from treatment. For example, with Spinraza, some payers have required that patients not be on permanent ventilation, and the same possibility will arise with coverage criteria for Zolgensma. Although there are no data on the use of Zolgensma among permanently ventilated patients, family and clinical expert testimony argued that ventilated patients can benefit from treatment even with relatively small improvements in motor function that can allow the self-direction of motorized wheelchairs or the use of tablets for communication. A related policy recommendation regarding manufacturer provision of free treatment in such circumstances in which evidence is lacking is provided below.

   Some countries have not extended coverage for Spinraza for patients who have attained the ability to walk independently. Similar considerations are likely to arise with Zolgensma. Although the cost-effectiveness of treatment for symptomatic patients is worse among patients who are less severely affected, clinical experts and patient representatives argued that for some patients who can walk independently there may be important upper limb motor function benefits that are still possible with treatment. Given that there are no data on treatment with Zolgensma among this patient group, many insurers will consider non-coverage.

e. **Renewal criteria:** There is no evidence or clinical expert testimony supporting the idea of repeated dosing with Zolgensma.

f. **Concomitant/sequential use with Spinraza:** There are no data by which to make informed judgments about the risks and benefits of adding Zolgensma treatment to ongoing treatment with Spinraza. Because of the lack of evidence and the high costs, payers are likely to deny coverage for Zolgensma unless Spinraza treatment is halted completely, either due to the patient not achieving their desired level of improvement or side effects. For patients treated initially with Zolgensma, however, evidence already suggests that clinicians and families will consider subsequent use of Spinraza to potentially achieve additional benefit. Given the lack of evidence on the risks and benefits of this course of treatment, payers may deny coverage, or they will develop criteria for "failure" of Zolgensma that must be met before consideration can be given for coverage of Spinraza. If this course is taken it may be possible to use specific clinical outcome measures to identify patients who either do not achieve initial improvement with Zolgensma or those for whom initial benefits fade. The single pivotal trial of Zolgensma used the CHOP-INTEND to measure results, and this outcome measure could serve well among Type I patients, but if presymptomatic treatment or treatment among Type II-III patients is included in the label for Zolgensma, the

heterogeneity of patients may lead payers to rely instead on general clinician attestation of "failure" of Zolgensma therapy should follow-on treatment with Spinraza be covered at all.

Provider Criteria

a. **Provider criteria:** Payers are likely to set criteria for providers to require either that the provider be a specialist in neuromuscular medicine or work in consultation with such a specialist. For patients with symptomatic SMA it is likely that patients will benefit from treatment under the direction of a multi-disciplinary team skilled at coordinating care across neurological, pulmonary, nutritional, and other domains, and payers may consider limiting coverage to care provided at these Centers of Excellence. The downside of such coverage limitation is the risk that access will made more difficult for patients who do not live near academic health centers of other areas where these teams are available. Another consideration is that successful treatment of children with pre-symptomatic disease may not require the broader expertise offered by these teams. But given the special handling and the extraordinary expense of the one-time Zolgensma therapy, it is very likely that payers will require that patients travel, if necessary, to receive the treatment from a limited number of providers at Centers of Excellence.

2. Payers should provide responses to prior authorization requests within 48 hours.

Diagnosis of SMA in an infant should be treated by providers and payers as an emergency requiring rapid decision-making and the delivery of treatment as soon as possible. Providers should submit prior authorization requests immediately upon diagnosis following discussion with the family. Payers should develop fail-safe mechanisms to ensure that these requests are evaluated and responded to within 48 hours. Payers should make every attempt to communicate with providers and families to resolve any prior authorization challenges as soon as possible.

3. Given that Spinraza and Zolgensma have new mechanisms of action, lack long-term safety and efficacy data, and are very expensive, it is reasonable for insurers and other payers to negotiate outcomes-based contracts with manufacturers. Outcomes-based contracts should be scaled so that a substantial portion of the cost of these treatments is at risk should patients not receive adequate and sustained clinical benefit.

4. Providers, payers, and manufacturers need to collaborate to determine meaningful clinical outcome measures that can serve as the basis for outcome-based contracts for patients with different types of SMA.

Specific options include:

a. **Death or permanent ventilation:** Although these outcomes are easiest to track in administrative databases, they might not be able to capture near-term lack of benefit

for some Type I patients and are completely inadequate outcome measures for treatment of later-onset or presymptomatic patients (many of whom will have Type II-III SMA).

b. **Existing outcome scales (e.g., CHOP-INTEND, HINE-2, HFMSE, 6MWT)**: Clinical experts affirm that these outcome measures are feasible to assess in clinical practice.[107] Given the heterogeneity of patients, it should be explored whether the treating clinician can determine which of the available measures are most appropriate to use to track outcomes for an individual patient given their unique clinical status. For ambulatory patients with Type II-III the six-minute walk test may be most relevant, whereas for pre-symptomatic patients any one of several measures of the onset of muscular dysfunction could be used to indicate the "failure" of treatment.

c. **New outcome measures:** Cure SMA is establishing a national registry through which the outcomes of all patients with SMA can be tracked.[108] Payers and manufacturers should seek to support this effort and explore whether it can be used to help develop new or combination outcome measures that will be able to be more sensitive and specific in tracking the relative benefits of treatment for patients.

d. **Switch to other treatment:** If payers implement coverage criteria that do not allow the use of Zolgensma while continuing to receive Spinraza, then switching from Spinraza to Zolgensma can be considered a sign of "inadequate" clinical response for the purposes of an outcomes-based contract. Similarly, if payers do not allow the use of Spinraza following Zolgensma unless clinical outcomes or attestation determine that there has been "inadequate" benefit with Zolgensma, then any use of Spinraza following treatment with Zolgensma is a reasonable measure of "inadequate" treatment response with Zolgensma. If payers adopt coverage policies that allow for combination therapy, then switching or adding on of treatments cannot serve as suitable outcome measures.

Manufacturers

5. To align reasonably with the benefits for patients and families, the price for Spinraza should be far lower, and that for Zolgensma should be lower than the hypothetical $4-5 million price the manufacturer has suggested could be justified. To achieve the needed balance between incentives for innovation and health system affordability, all manufacturers should exercise their monopoly pricing power responsibly, setting prices that do not exceed a reasonable cost-effectiveness threshold.

The price of innovative treatments for SMA should better align with the demonstrated benefits for patients. The New England CEPAC acknowledge the remarkable effectiveness and many additional potential benefits and contextual considerations of Spinraza and Zolgensma; nevertheless, the

panel voted 12-0 that Spinraza represented low long-term value for money due to its high price. It is possible for a high-cost treatment to demonstrate good cost-effectiveness in a life-threatening rare condition (e.g., Kymriah, a CAR-T cell therapy for B-cell acute lymphoblastic leukemia). The US health care system cannot sustain paying prices far above traditional cost-effectiveness levels for the growing tide of treatments for ultra-rare disorders.

6. Given the substantial remaining uncertainty regarding the benefits of initiating disease-modifying treatments in certain subpopulations, manufactures should provide treatment at no cost where evidence is lacking.

For both interventions, evidence on the benefits and risks of starting a disease-modifying treatment in certain subpopulations is lacking, such as among adults with any type of SMA and symptomatic individuals of any age who are on permanent ventilation. Manufactures should collect evidence about the potential benefits of these treatments in such subpopulations and provide treatment at no cost to payers or patients until sufficient evidence has been generated.

7. Although the evidence base for Zolgensma was judged adequate to demonstrate benefit versus standard supportive care, the number of patients treated is very small, and only a single uncontrolled trial was performed. Manufacturers should not view this as a generalizable roadmap for generating adequate evidence for patients, clinicians, and payers. As shown by the evidence for Spinraza, even for ultra-rare conditions, manufacturers can and should seek to conduct larger, randomized trials with long follow-up.

In SMA, an ultra-rare condition with approximately 500 new cases in the US per year, Biogen conducted multiple RCTs, many of which enrolled over 100 individuals. Their efforts to generate such high-quality evidence sets a standard of excellence which other manufacturers should follow.

Patient Advocacy Organizations

8. Patient organizations should view their longer-term mission in support of patients to include active engagement with manufacturers to demand reasonable value-based pricing of the therapies that patients and their families helped bring to the market.

Patient advocacy groups for SMA are well organized and played a leading role in funding, organizing, and promoting the research that led to effective treatments. Patient groups should feel proud of this accomplishment. They should also accept a broader mission on behalf of patients by exercising their power to influence pricing in order to improve long-term access and affordability. It is evident across the health system that when prices are viewed as fair and justifiable, access is improved in the short term without vitiating the incentives that will draw further investment and research.

Clinicians and Clinical Specialty Societies

9. Individual clinicians and clinical specialty societies should assume a broad leadership role in advocating for patients by taking four actions: 1) highlight and work to address insurance barriers to appropriate care; 2) be vocal witnesses to the negative effects of excessive prices on patients and families; 3) integrate considerations of value into clinical guidelines; and 4) embody a broad model of professionalism that calls upon clinicians to work towards a health system that improves access and provides a sustainable model for future innovation through fair pricing.

Future Research

10. Better measures of motor functioning are needed.

Important uncertainties remain regarding what measurements should be used once patients attain near-maximal function on existing scales, and how to capture interim movement milestones such as finger strength that are meaningful to patients and clinicians. Given that treatment will be shifting toward a presymptomatic population, there is a need for outcome measures other than death or permanent ventilation that are meaningful for outcomes based contracting.

11. Registries such as those maintained by Cure SMA should be utilized to help answer remaining uncertainties in the evidence base.

Registries can collect data pertaining to key uncertainties such as the potential benefits and harms of concomitant use of Spinraza and Zolgensma; the natural course of SMA among individuals treated with Spinraza or Zolgensma, which could be used to define treatment failure; to define more sensitive outcome measures; and to capture caregiver burden.

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This is the first ICER review of Spinraza and Zolgensma.

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115. Day JW, Feltner D, Ogrinc F, et al. AVXS-101 gene replacement therapy for SMA type 1: Pivotal study (STR1VE) update. *Neurology.* 2018;90(24):e2182-e2194.
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119. Lopez-Bastida J, Pena-Longobardo LM, Aranda-Reneo I, Tizzano E, Sefton M, Oliva-Moreno J. Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain. *Orphanet J Rare Dis.* 2017;12(1):141.

APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item	Section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	N/A
ABSTRACT			
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1.1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1.2
METHODS			
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3.2
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	1.2
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3.2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3.2
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3.2
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	1.2
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3.2
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3.2
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3.3
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3.3, Appendix D
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	3.3, Appendix D
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	3.3
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	3.3
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	3.5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3.4, 3.5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	3.4
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page iii

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

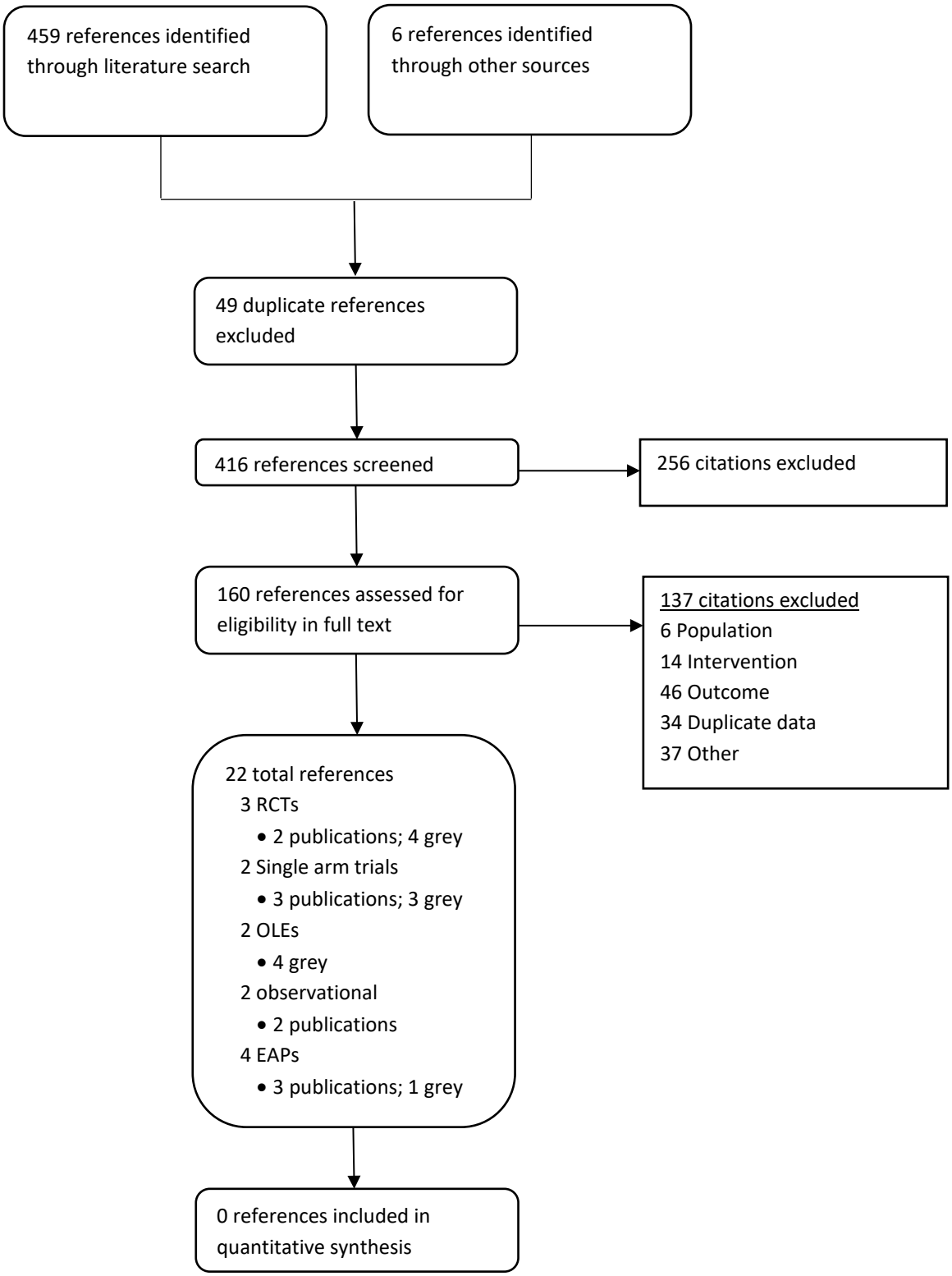
Table A2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Using OVID)

No.	Search Terms
1	exp spinal muscular atrophy
2	Werdnig Hoffman.mp.
3	Kugelberg Welander.mp.
4	Spinraza.mp.
5	ISIS$396443.mp.
6	AVXS$101.mp.
7	Zolgensma.mp.
8	OR/1-3
9	OR/4-7
10	8 AND 9
11	(animals not (humans and animals)).sh.
12	10 not 11
13	(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 patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
14	12 not 13
15	limit 14 to English language

Table A3. Search Strategy of EMBASE SEARCH

No.	Search Terms
#1	'spinal muscular atrophy'
#2	'werdnig hoffmann disease'
#3	'kugelberg welander disease'
#4	#1 or #2 or #3
#5	'Zolgensma'
#6	'avxs 101'
#7	'Spinraza'
#8	'spinraza'
#9	'ISIS 396443'
#10	'antisense oligonucleotide'
#11	'gene therapy'
#12	#5 or #6 or #7 or #8 or #9 OR #10 or #11
#13	#4 AND #12
#14	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#15	'human'/exp
#16	#14 AND #15
#17	#14 NOT #16
#18	#13 NOT #17
#19	#18 AND [english]/lim
#20	#19 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#21	#19 NOT #20

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Spinraza and Zolgensma for Spinal Muscular Atrophy



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified one systematic review of Spinraza for the treatment of SMA Types I, II, and III, summarized below.

CADTH (2018). Spinraza (Spinraza) Clinical Review Report.[109] CADTH Clinical Review Report.

CADTH conducted a systematic review to evaluate current treatments available for SMA. Only one trial met their criteria for a systematic review: the ENDEAR study (CS3B), a randomized, double-blind, sham-controlled, multi-center study. One hundred and twenty-one patients were randomized 2:1 to receive either Spinraza (n=80) or placebo (n=41). The primary outcome of this study was the Hammersmith Infant Neurological Examination (HINE). Patients received either 12 mg of Spinraza intrathecally through lumbar puncture with four loading does on days 0, 14, 28 and 63 with maintenance doses every four weeks or a matched sham injection. Interim analysis showed that patients in the Spinraza group showed improvement in motor function milestones, as measured by the HINE scale, versus that of the placebo group (difference in percentage=50.7, p-value<0.0001). As a result of the statistical significance in HINE scores, the trial was ended early.

Appendix C. Ongoing Studies

Title/Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Onasemnogene Abeparvovec					
Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type I **AveXis, Inc.** **NCT03461289**	Phase III, open-label, single-arm, single-dose trial Estimated Enrollment: 40	Intervention: AVXS-101	Inclusion Criteria Patients with SMA Type I Patients <6 months of age Swallowing evaluation Exclusion Criteria Previous, planned, expected scoliosis surgery Use of invasive ventilation support Use of requirement of 12+ hours of non-invasive ventilation support Patient with signs of aspiration Participation in recent SMA treatment clinical trial	Primary Outcomes Sitting without support up 18 months of age Secondary Outcomes Survival	November 2020

Title/Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Long-term follow up study for Patients from AVXS-101-CL-101 **AveXis, Inc.** NCT03421977	Observational Estimated Enrollment: 15	Intervention: AVXS-101	Inclusion Criteria Patient who received AVXS-101 in the AVXS-101-CL-101 Gene replacement therapy Clinical trial for SMA Type I Parent/Legal guardian willing and able to complete informed consent process Exclusion Criteria Parent/legal guardian unable or unwilling to participate in long term follow up safety procedure	Primary Outcomes Long-term safety	December 2023

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type I (STR1VE) **AveXis, Inc.** NCT03306277	Phase III, open-label, single-arm Estimated Enrollment: 20	Intervention: AVXS-101	Inclusion Criteria Patient who received avxs-101 in the AVXS-101-CL-101 Gene replacement therapy Clinical trial for SMA Type I Parent/Legal guardian willing and able to complete informed consent process Exclusion Criteria Parent/legal guardian unable or unwilling to participate in long term follow up safety procedure	Primary Outcomes Achievement of independent sitting Event-free survival Secondary Outcomes Ability to thrive Ventilatory support independence	March 31, 2020
Pre-Symptomatic Study of Intravenous AVXS-101 in Spinal Muscular Atrophy (SMA) for patients with Multiple Copies of SMN2 (SPR1NT) **AveXis, Inc.** NCT03505099	Phase III, open-label, single arm study Estimated Enrollment: 44	Intervention: AVXS-101 One-time intravenous fusion of AVXS at 1.1 X 1014 vg/kg	Inclusion Criteria Age ≤6 weeks at time of dose Compound muscle action potential (CMAP) Age ≤6 weeks (≤42 days) at time of dose Ability to tolerate thin liquids Patients with 2 copies of *SMN2* (n ≥15) Patients with presymptomatic SMA Type I Exclusion Criteria Weight at screening visit <2 kg Hypoxemia Any clinical signs or symptoms at screening or immediately prior to dosing that are	Primary Outcomes 2 copies of *SMN2* gene: functional independent sitting 3 copies of *SMN2* gene: standing with support 4 copies of *SMN2* gene: demonstrating motor improvements inconsistent with SMA natural history	April 2023

			Tracheostomy or current prophylactic use or requirement of noninvasive ventilatory support Treatment with an investigational or commercial product, including Spinraza, given for the treatment of SMA.		
Study of intrathecal Administration of AVXS-101 for Spinal Muscular Atrophy (STRONG) **AveXis, Inc.** NCT03381729	Phase I, non-randomized, parallel assignment, open-label Estimated enrollment:	Intervention: AVXS-101 Experimental: Dose A 6.0 x 10^3 vg of avxs-101 Experimental: Dose B 1.2 x 10^14 vg of avxs-101	Inclusion Criteria: Patients up to 60 months of age at time of dosing Diagnostic confirmation by genotype Negative gene testing for SMN2 gene modifier Onset of clinical signs + symptoms Able to sit independently and not standing or walking independently Exclusion Criteria: Current or historical ability to stand or walk independently Severe contractures as determined by designated physical therapist Severe scoliosis Previous, planned, or expected scoliosis procedure Use of invasive ventilatory support Medical necessity for feeding tube	Primary Outcomes Incidence of adverse events Determine optimal dose Patients <24 months: standing milestone Patients ≥24 months and <60 months: change in HFMSE score Secondary Outcomes Patients <24 months: walking milestone Patients ≥24 months and <60 months: walking milestone	September 1, 2020

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Spinraza					
A Study for Participants with Spinal Muscular Atrophy (SMA) Who Previously Participated in Spinraza Investigational Studies. (SHINE) **Biogen** NCT02594124	Phase III, non-randomized, parallel assessment, triple-masking (participant, investigator, outcomes assessor) Estimated Enrollment: 292	Experimental Group 1: Participants transitioned from ISIS 396443-CS3B (NCT02193074) Intervention: Spinraza Experimental Group 2: Participants transitioned from ISIS 396443-CS4 (NCT02292537) Intervention: Spinraza Experimental: Group 3: Participants transitioned from ISIS 396443-CS12 (NCT02052791) Intervention: Spinraza Experimental: Group 4: Participants transitioned from	Inclusion Criteria Signed informed consent Completion of index study Exclusion Criteria Have any condition or worsening condition that in investigator opinion would make the participant ineligible Clinically significant abnormalities in hematology Participant's guardian is not willing or able to meet standard of care guidelines Treatment with another investigational agent, biological agent, or device within a month of screening	Primary Outcomes Number of patients experiencing: AEs or SAEs clinically significant vital sign abnormalities weight abnormalities neurological abnormalities laboratory abnormalities coagulation abnormalities 12-lead electrocardiograms Secondary Outcomes Percentage of participants who Attained motor milestones Not required permeant ventilation Change from baseline in CHOP-INTEND motor function scale Change from baseline in Hammersmith Functional Motor Scale Change from baseline in revised upper limb module Change from baseline 6-minute walk test Change from baseline in body length, head/chest/arm circumference CMAP responders	August 1, 2023

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
		ISIS 396443-CS3A (NCT01839656) Intervention: Spinraza Experimental: Group 5: Participants transitioned from 232SM202 (NCT02462759) Intervention: Spinraza			

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of Multiple Doses of Spinraza (ISIS 396443) Delivered to Infants with Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy **Biogen** **NCT02386553**	Phase II, single group assessment, open label Estimated enrollment: 25	Intervention: Spinraza administered as an intrathecal injection	Inclusion Criteria Age <6 weeks at first dose Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation Genetic documentation of 2 or 3 copies of SMN2 Ulnar compound muscle action potential Exclusion Criteria Hypoxemia Any clinical signs of SMA Clinically significant abnormalities Treatment with investigational drug given for the treatment of SMA biological agent or device	Primary Outcomes Time to death or respirator incident Secondary Outcomes Percentage of participants developing clinically manifested SMA who attained motor milestones assessed as part of the Hammersmith Infant Neurological Examination (HINE) who attained motor milestones as assessed by World Health Organization (WHO) criteria Change from Baseline in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale Change from Baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE) Change from Baseline in weight for age/length Change from Baseline in arm/chest / head circumference ratio Incidence of adverse events (AEs) and/or serious adverse events (SAEs)	January 26, 2022

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Assess the Safety and Tolerability of Spinraza (ISIS 396443) in Participants with Spinal Muscular Atrophy (SMA) (EMBRACE) **Biogen** NCT02462759	Phase II, randomized, parallel assignment, quadruple masking Estimated enrollment:	Intervention Spinraza Intervention Sham comparator	Inclusion Criteria: Genetic documentation of 5q SMA homozygous gene deletion, mutation, or compound heterozygote Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures. Exclusion Criteria: Meets additional study criteria Any previous exposure to ISIS 396443 Clinically significant abnormalities to hematology	Primary Outcomes number of participants with adverse events and serious adverse events Change from Baseline in clinical laboratory parameters Change from Baseline in electrocardiograms (ECGs) Change from Baseline in vital signs Change from Baseline in neurological examination outcomes	April 9, 2019

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
Spinraza in Adult Spinal Muscular Atrophy (SAS) **Washington University School of Medicine** **NCT03709784**	Longitudinal, observational study Estimated enrollment: 73	Intervention Spinraza	Inclusion Males and females with SMA type II or III, aged 18 to 60 years at the time of enrollment Genetic documentation of 5Q homozygous gene deletion, mutation, or compound heterozygote. Are treatment naïve to Spinraza Estimated life expectancy at least 30 months from first dosing Revised upper limb module (RULM) score ≥4 Group 1 Be free of major orthopedic deformities that limit ambulation Group 2 Ability to walk at least 10 meters without assistance Be free of major orthopedic deformities that limit ambulation An ambulatory subject can qualify for both group 1 and group 2 if the RULM score is ≤34 Exclusion revised upper limb score ≤3 Respiratory insufficiency Hospitalization/presence of severe symptoms Previous exposure to Spinraza	Primary Outcomes Change from baseline in the 6-minute walk test (6MWT) for ambulatory patients Change from baseline in Revised upper limb module (RULM) for weak ambulatory and non-ambulatory SMA patients	January 30, 2022

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Primary Outcomes	Estimated Completion Date
European Registry of Patients with Infantile-onset Spinal Muscular Atrophy **Institut de Myologie, France** NCT03339830	Observational (patient registry)	Any	Inclusion Spinal Muscular Atrophy diagnosed in childhood and genetically confirmed For patients with SMA type I: never acquired independent sitting position (more than 30 sec. without hand support or any external support) For any patients with SMA type II or III: patients treated with a market approved treatment for SMA or with a treatment in an expanded access program Any age Patients over 18 years of age or parent(s)/legal guardian(s) of patients <18 years of age not opposed to data collection for research purposes	Primary Outcomes Change from baseline to survival in psychomotor development number in lower track infections ventilation use cough assist use forced vital capacity diurnal saturation nocturnal hypercapnia Secondary Outcomes Change from baseline in treatment of psychomotor development in the number of hospitalizations in duration of hospitalizations in scoliosis occurrence in arthrodesis occurrence in wheelchair use in feeding status in HINE-2 in CHOP-INTEND score In HFMSE In therapy sessions per week	December 1, 2022

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

Appendix D. Comparative Clinical Effectiveness Supplemental Information

Study Selection and Quality Assessment

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. 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 Spinraza. 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.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table D1).[78] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking*

outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

A study quality rating was not assigned to grey literature (conference abstracts/posters) because they lack granular details. Additionally, we did not rate the quality of non-comparative studies (NURTURE , CS3A, CS2/CS12, CL-101) or OLEs (SHINE).

Table D1. Study Quality Assessment Results

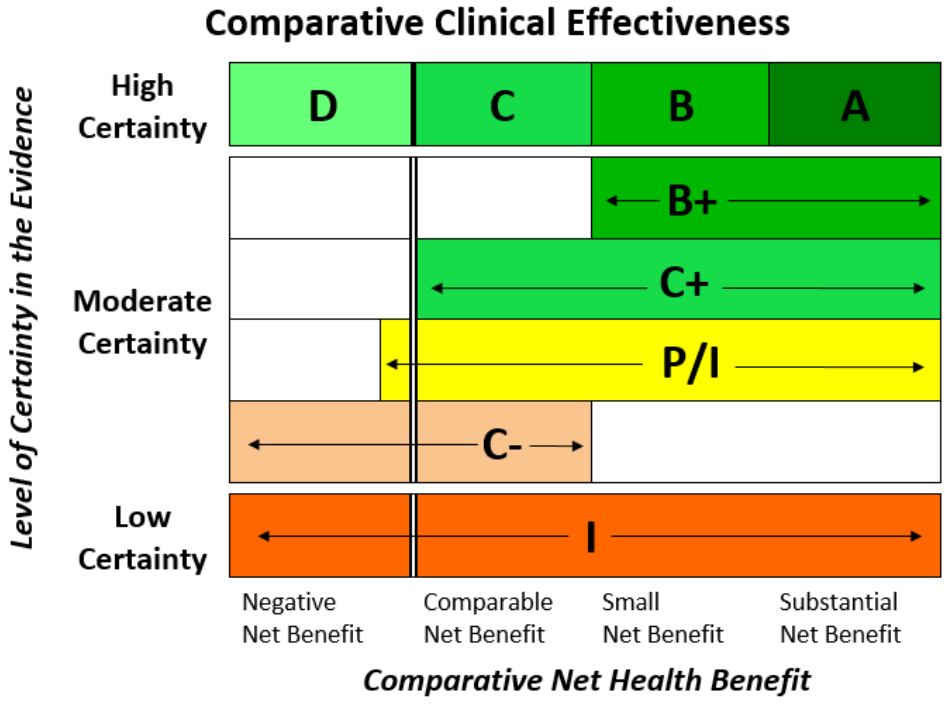
Study	Comparable Groups	Double-Blind	Measurements Equal and Valid	Clear Definition of Intervention	Key Outcomes Assessed	Quality
ENDEAR	Yes	Yes	Yes	Yes	Yes	Good
CHERISH	Yes	Yes	Yes	Yes	Yes	Good
EMBRACE	Yes	Yes	Yes	Yes	Yes	Good

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[79]

Figure D1. 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 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 comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Supplemental Data

Table D2. Baseline Study Characteristics

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
Type I										
ENDEAR										
Finkel, 2017[24]	Randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial	13 months	Spinraza	80	163 (range: 52-242) days	7.9 (2-18) weeks	12.6 (0 - 29) weeks	13.2 (0-25.9) weeks	43 (54)	NR
			Sham control	41	181 (range: 30-262) days	9.6 (2-30) weeks	17.5 (2 - 30) weeks	13.9 (0 -23.1) weeks	24 (59)	NR
Servais, 2017[83]	Subgroup analysis by median disease duration (≤12 vs. >12 weeks); final analysis set	13 months	DD ≤12 weeks; sham	18	136.0 (30–228) days	8.0 (1–20) weeks	10.5 (2–25) weeks	9.9 (0–12) weeks	7 (39)	NR
			DD ≤12 weeks; Spinraza	34	117.0 (52–235) days	6.0 (3–18) weeks	9.5 (0–22) weeks	8.7 (0–12) weeks	18 (53)	NR
			DD >12 weeks; sham	23	213.0 (143–262) days	8.0 (4–16) weeks	20.0 (12–30) weeks	18.0 (13–23) weeks	17 (74)	NR
			DD >12 weeks; Spinraza	46	196.0 (127–242) days	8.0 (2–16) weeks	12.0 (2–29) weeks	16.3 (12–26) weeks	25 (54)	NR
McNeil, 2017[110]	Phase 3, randomized, double-blind,	13 months	≤13 weeks: Spinraza	39	NR	NR	NR	NR	NR	NR
			≤13 weeks: control	21	NR	NR	NR	NR	NR	NR

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
	sham controlled procedure		≥13 weeks: Spinraza	41	NR	NR	NR	NR	NR	NR
			≥13 weeks: control	20	NR	NR	NR	NR	NR	NR
SHINE (OLE)										
Castro, 2018[33]	Open-label extension study	Up to 5 years	Spinraza → Spinraza	81	5.4 (2–15) months	1.6 (0–4) months	NR	NR	NR	NR
			Sham → Spinraza	24	17.8 (10–23) months; age at first dose	Median: 2.1 (1–5) months	NR	NR	NR	NR
CS3A / Phase II										
Darras, 2013[111]	Open-label, dose-escalating	88 days	1, 3, 6 or 9 mg of Spinraza	28	2-14 years	NR	NR	NR	NR	NR
Finkel, 2016[23]	Phase 2, open-label, dose-escalating study	32 months	6-12 mg	4	145 (67-207) days	47 (28–70) days	74 (42-105) days	NR	1 (25)	7.1 (5.2-8.9) kg
			12 mg	16	140 (36-210) days	63 (21-154) days	80 (0-154) days	NR	7 (44)	6.7 (5.1-9.3) kg
EMBRACE										
Shieh, 2018[43]	Phase 2, double-blind, sham-controlled	14 months	≥6 months (12 mg Spinraza)	5	18.1 (16-19) months	9.0 (7.6-11.0) months	13.0 (9.9-15.0) months	NR	1 (20)	NR
			≥6 months (sham)	3	17.0 (15-19) months	9.0 (7.0-11.0) months	13.0 (12.0-14.0) months	NR	2 (67)	NR
			≤6 months (12 mg Spinraza)	9	15.3 (7-79) months	4.6 (2.0-6.0) months	8.0 (6.9-11.0) months	NR	4 (44)	NR
			≤6 months (sham)	4	25.6 (16-53) months	3.85 (1.8-5.1) months	7.7 (5.5-14.0) months	NR	3 (75)	NR

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
Expanded Access Program (EAP)										
Farrar, 2018 [82]	Prospective, multicenter study (Australia)	NR	New SMA diagnosis during Spinraza EAP	8	NR	2.8 (1-5) weeks	6.4 (2.1-11) (NR)	5.0 (0.5-72) months	3 (NR)	NR
			SMA diagnosis prior to EAP start	8	NR	5.1 (3-5.9) weeks	10.5 (7-72) (NR)	5.0 (0.5-72) months	5 (NR)	NR
Scoto, 2018[112]	Observational	9 months	Spinraza	69	14 (1-9.5)	NR	NR	NR	39 (65)	NR
Pechmann, 2018[80]	Prospective, multicenter study (Germany)	6 months	Spinraza	61	21.1 (1-93)	2.78 (0-6) months	N/A	NR	30 (49)	NR
Pane, 2018[81]	Prospective, multicenter study (Italy)	6 months	Spinraza	104	3-19 (months to years)	NR	NR	NR	NR	NR
CL-101 (Zolgensma)										
Mendell, 2017[29]	Phase 1, single-arm, open-label	24 months	Low dose	3	6.3 (5.9-7.2) months	1.7 (1.0-3.0) months	33 (4-85) days	NR	2 (67)	6.6 (6.0-7.1)
			High Dose	12	3.4 (0.9-7.9) months	1.4 (0-3.0) months	60 (0-136) days	NR	7 (58)	5.7 (3.6 - 8.4)
Al-Zaidy, 2019[39]	Phase 1, single-arm, open-label	24 months	High Dose	12	3.4 (0.9 – 7.9)	NR	NR	NR	NR	NR

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
Types II and III										
CHERISH										
Mercuri, 2018[25]	Multicenter, double-blind, sham-controlled, phase 3 trial	15 months	Spinraza	84	4.0 (NR)	10 (6-20) weeks	18 (0-40) months	39.3 (8-94) months	46 (55)	NR
			Sham control	42	3.0 (NR)	11 (6 - 20) weeks	18 (0 - 46) months	30.2 (10-80) months	21 (50)	NR
Mercuri, 2017[113]	Phase 3, randomized, double-blind sham controlled	15 months	Spinraza	35	NR	NR	NR	NR	NR	NR
			Sham control	19	NR	NR	NR	NR	NR	NR
Stolte, 2018[84]	Open-label , single-arm study	NR	Spinraza, Type II	9	31.2 (24-48) years	NR	NR	NR	6 (66.7)	NR
			Spinraza, Type III	19	37.9 (18-61) years	NR	NR	NR	4 (21.1)	NR
Wurster , 2018[85]	Open-label , single-arm study	NR	Spinraza, Type II	9	27.0 (11-48)	NR	NR	NR	NR	NR
			Spinraza, Type III	11	37.6 (13-60)	NR	NR	NR	NR	NR
CS2, CS12										
Chiriboga, 2017[35]	Multicenter, open-label study	1050 days	SMA type II	11	4.4 (4.0) years	11.0 (3.4) months	15.4 (6.3) months	NR	3 (27)	NR
			SMA type III	17	8.9 (4.4) years	22.0 (13.5) months	43. 6 (32.4) months	NR	10 (59)	NR
Montes et al, 2018[114]	Multi-center, open-label clinical trial	1050 days	Spinraza (multiple doses)	14	8.6 years (age at screening)	23.9 (NR) months	NR	NR	NR	NR

STUDY	Study Overview	Planned Duration of Trial	Arm	N	Mean Age at Baseline (Range)	Mean Age Onset (Range)	Mean Age at Genetic Diagnosis	Disease Duration (Range)	Female Sex (%)	Mean Weight (Range)
STRIVE										
Day, 2018[115]	Open-label, multicenter, phase 3	baseline data update	Spinraza	22	3.7 (0.5-5.9) months	1.9 (0-4.0) weeks	62 (15-120) days	NR	12 (55)	5.8 (3.9-7.5) kg
NURTURE (Presymptomatic)										
De Vivo, 2017[116]	Phase 2 OLE in presymptomatic children	5 years	Spinraza (12 mg)	9	NR	NR	NR	NR	NR	NR
De Vivo, 2018[117] (Cure SMA)	Phase 2 OLE in presymptomatic children	5 years	Spinraza (12 mg)	25	See Swoboda 2018 for baseline	NR	NR	NR	NR	NR
Swoboda, 2018[44]	Phase 2 OLE in presymptomatic children	5 years	Spinraza (12 mg)	25	Median at age of first dose: 22.0 (3-42) days	N/A	N/A	N/A	13 (52)	NR

DD: disease duration, MDD: median disease duration, N/A: not applicable, NR: not reported

Table D3. Baseline Motor Milestones

STUDY	Planned Duration of Follow-Up	Arm	N	Mean HFMSE Score	Mean HINE-2 Score	Mean CHOP-INTEND Score	Ventilation Use (%)	Gastrointestinal Tube Use (%)	WHO Motor Milestones Achieved	RULM Score
ENDEAR (Type I)										
Finkel, 2017[24]	Interim and final (max 13 months)	Spinraza	80	NR	1.29 ± 1.07 (SD)	26.63 ± 8.13	21 (26)	7 (9)	NR	NR
		Sham control	41	NR	1.54 ± 1.29 (SD)	28.43 ± 7.56	6 (15)	5 (12)	NR	NR
Servais, 2017[83]	Subgroup analysis by median disease duration (≤12 vs. >12 weeks); final analysis set	DD ≤12 weeks; sham	18	N/A	NR	NR	2 (11)	NR	NR	NR
		DD ≤12 weeks; Spinraza	34	N/A	NR	NR	4 (12)	NR	NR	NR
		DD >12 weeks; sham	23	N/A	NR	NR	4 (17)	NR	NR	NR
		DD >12 weeks; Spinraza	46	N/A	NR	NR	17 (37)	NR	NR	NR
McNeil, 2017[110]	13 months	DD ≥13 weeks: Spinraza	39	NR	NR	NR	NR	NR	NR	NR
		DD ≥13 weeks: control	21	NR	NR	NR	NR	NR	NR	NR
		DD ≤13 weeks: Spinraza	41	NR	NR	NR	NR	NR	NR	NR
		DD ≤13 weeks: control	20	NR	NR	NR	NR	NR	NR	NR
SHINE (OLE)										
Castro, 2018[33]	Interim	Spinraza → Spinraza	81	NR	1.3 (1.08)	26.7 (8.13)	NR	NR	NR	NR
		Sham → Spinraza	24	NR	1.3 (1.08)	17.3 (9.71)	NR	NR	NR	NR

STUDY	Planned Duration of Follow-Up	Arm	N	Mean HFMSE Score	Mean HINE-2 Score	Mean CHOP-INTEND Score	Ventilation Use (%)	Gastrointestinal Tube Use (%)	WHO Motor Milestones Achieved	RULM Score
CS3A/ Phase 2										
Darras, 2013[111]	NR	1, 3, 6, or 9 mg of Spinraza	28	NR	NR	NR	NR	NR	NR	NR
Finkel, 2016[23]	32 months	6-12 mg	4	NR	2 (1-3)	27 (22-34)	0	1	NR	NR
		12 mg	16	NR	2 (1-12)	30 (17-64)	0	1	NR	NR
EMBRACE										
Shieh, 2018[43]	14 months	≥6 months (12mg Spinraza)	5	NR	NR	NR	NR	NR	NR	NR
		≥6 months (sham)	3	NR	NR	NR	NR	NR	NR	NR
		≤6 months (12 mg NSRSN)	9	NR	NR	NR	NR	NR	NR	NR
		≤6 months (sham control)	4	NR	NR	NR	NR	NR	NR	NR
Expanded Access Program (EAP)										
Farrar, 2018[82]	NR	New SMA diagnosis during Spinraza EAP	8	NR	NR	NR	NR	NR	NR	NR
		SMA diagnosis prior to EAP start	8	NR	NR	NR	NR	NR	NR	NR
Scoto, 2018[112]	9 months	Spinraza	69	NR	NR	25/64 (5-52)	36/69 required NIV	1 (needed a tracheostomy)	NR	NR
Pechmann, 2018[80]	6 months	Spinraza	61	N/A	0.8 (range: 0-8)	22.3 (range: 1-50)	18 (29.5); NIV >16 h/day + tracheostomy categories	34 (55.7); "Feeding tube or gastronomy"	NR	NR

STUDY	Planned Duration of Follow-Up	Arm	N	Mean HFMSE Score	Mean HINE-2 Score	Mean CHOP-INTEND Score	Ventilation Use (%)	Gastrointestinal Tube Use (%)	WHO Motor Milestones Achieved	RULM Score
Pane, 2018[81]	6 months	Spinraza	104	NR	NR	15.08 (13.53)	NR	NR	NR	NR
CL-101 (Zolgensma)										
Mendell, 2017[29]	24 months	Low dose	3	NR	NR	16 (6-27)	3 (100)	3 (100)	NR	NR
		High Dose	12	NR	NR	28.2 (12-50)	2 (17)	5 (42); 4 (33) ability to swallow	NR	NR
Al-Zaidy, 2019[39]	24 months	High Dose	12	NR	NR	NR	83 (did NOT require ventilation)	NR	NR	NR
Types II and III										
CHERISH										
Mercuri, 2018[25]	15 months (9 months of treatment + 6 months of follow up)	Spinraza	84	22.4 ± 8.3; scores	NR	NR	NR	NR	1.4 ± 1.0	19.4 ± 6.2
		Sham control	42	19.9 ± 7.2	NR	NR	NR	NR	1.5 ± 1.0	18.4 ± 5.7
Mercuri, 2017[113]	Interim	Spinraza	35	NR	NR	NR	NR	NR	NR	NR
		Sham control	19	NR	NR	NR	NR	NR	NR	NR
Stolte, 2018[84]	NR	Spinraza, Type II	9	3.1 ± 2.5	NR	NR	NR	NR	NR	9.9 ± 4.6
		Spinraza, Type III	19	31.2 ± 18.1	NR	NR	NR	NR	NR	29.5 ± 8.5
Wurster, 2018[85]	NR	Spinraza, Type II	9	1.7 (2.2)	NR	NR	7/9 use NIV	2/9 use PEG	NR	NR
		Spinraza, Type III	11	30.1 (25.0)	NR	NR	0/11 use NIV	0/11 use PEG	NR	NR
CS2, CS12										
Chiriboga, 2017[35]	1050 days	SMA Type II	11	21.3 (SE: 2.9)	NR	NR	NR	NR	NR	NR
		SMA Type III	17	48.9 (SE: 3.0)	NR	NR	NR	NR	NR	NR
Montes et al, 2018[114]	1050 days	Spinraza	14	NR	NR	NR	NR	NR	NR	NR

STUDY	Planned Duration of Follow-Up	Arm	N	Mean HFMSE Score	Mean HINE-2 Score	Mean CHOP-INTEND Score	Ventilation Use (%)	Gastrointestinal Tube Use (%)	WHO Motor Milestones Achieved	RULM Score
STR1VE OLE (Type I)										
Day, 2018[115]	baseline data update	Spinraza	22	NR	NR	32 (17-52)	0 (0)	0 (0)	NR	NR
NURTURE (Presymptomatic)										
De Vivo, 2017[116]	1 year (interim results)	Spinraza (12 mg)	9	NR	NR	NR	NR	NR	NR	NR
De Vivo, 2018 (Cure SMA)[117]	Interim	Spinraza (12 mg)	25	NR	NR	NR	NR	NR	NR	NR
Swoboda, 2018 [44]	Interim	Spinraza (12 mg)	25	N/A	3.0 (0-7); Total milestones	50.0 (25.0-60.0)	NR	NR	NR	NR

DD: disease duration, EAP: expanded access program, MDD: moderate disease duration, N/A: not applicable, NIV: non-invasive ventilation, NR: not reported

Table D4. Outcomes I: Survival, Event-Free Survival

					Survival			Event Free Survival			
	Timepoint	Arm	Treatment N	Placebo N	No. Alive in Treatment Arm	No. Alive in Placebo Arm	Treatment Difference?	Definition	Estimate for Treatment Arm	Estimate for Placebo Arm	Treatment Difference
ENDEAR (Type I)											
Finkel, 2017[24]	Final analysis	--	80	41	67 (84)	25 (61)	HR (95% CI): 0.37 (0.18-0.77)	NR	Not reached	22.6 weeks	HR (95% CI): 0.53 (0.32-0.89)
Servais, 2017[83]	Final analysis set	≤12 weeks	34	18	NR	NR	HR, 0.219; P=.0299	NR	NR	NR	HR: 0.158 (p=0.004, no 95% CI)
		>12 weeks	46	23	NR	NR	HR, 0.455; P=.0880	NR	NR	NR	HR: 0.816 (p=0.5325, no 95% CI)
McNeil , 2018[110]	Final analysis set	≤13.1 weeks	39	21	NR	NR	NR	Time to death or permanent ventilation	9 (11%)	14 (34)	NR
		>13.1 weeks	41	20	NR	NR	NR		22 (28%)	14 (34)	NR
SHINE (OLE)											
Castro, 2018[33]	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza : 24	NR	NR	NR	Time to death or permanent ventilation	22.6 (13.6 -31.3)	73.0 (36.3 – N/A)	NR
CS3A/ Phase 2											
Finkel, 2016[23]	32 months	--	4	16	NR	NR	NR	NR	NR	NR	NR
Expanded Access Program (EAP)											
Scoto, 2018[112]	9 months	--	69	NA	65	NA	NR	NR	NR	NR	NR

					Survival			Event Free Survival			
	Timepoint	Arm	Treatment N	Placebo N	No. Alive in Treatment Arm	No. Alive in Placebo Arm	Treatment Difference?	Definition	Estimate for Treatment Arm	Estimate for Placebo Arm	Treatment Difference
Pechmann, 2018[80]	24 months	--	61	N/A	60	N/A	N/A	NR	NR	NR	NR
CL-101 (Zolgensma)											
Mendell, 2017[29]	24 months	Low dose	3	N/A	3	N/A	N/A	NR	NR	NR	N/A
		High dose	12	N/A	12	N/A	N/A	NR	NR	NR	N/A
Al-Zaidy, 2019[39]	38 months	High dose	12	N/A	12	N/A	NR	Alive and without permanent ventilation	100% - 1 patient needs ventilation needs are below 16 hrs./day	N/A	NR
CHERISH (Type II, II)											
Mercuri, 2018[25]	Final analysis	--	84	42	84	42	Median: 4.0 (2-9)	NR	NR	18 (0-48) months	N/A
NURTURE (Presymptomatic)											
De Vivo, 2017[116]	1-year interim analysis	2 copies SMN2	6	0	6	N/A	N/A	All alive without permanent ventilation	N/A	N/A	N/A
		3 copies SMN2	3	0	3	N/A	N/A		N/A	N/A	N/A
Swoboda, 2018[44]	Interim	--	25	N/A	25 (100%)	N/A	N/A	NR	NR	N/A	N/A

N/A: not applicable, NR: not reported

Table D5. Outcomes II: Ventilation

	Timepoint	Arms	Treatment N	Placebo N	Definition	No. People Not Ventilated in Treatment Arm	No. People Not Ventilated in Placebo	Treatment Difference
ENDEAR (Type I)								
Finkel, 2017[24]	Final analysis	--	80	41	Tracheostomy or ventilatory support for at least 16 hours per day for more	62 (78)	28 (68)	HR (95% CI): 0.66 (0.32-1.37)
Servais, 2017[83]	Final Analysis	≤12 weeks	34	18	NR	NR	NR	NR
		≥12 weeks	46	23	NR	NR	NR	NR
McNeil , 2018[110]	13 months	≤13 weeks:	39	21	NR	NR	NR	NR
		≥13 weeks:	41	20	NR	NR	NR	NR
SHINE (OLE)								
Castro, 2018[33]	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza: 24	NR	NR	NR	NR
CS3A/ Phase 2								
Finkel, 2016[23]	32 months	--	4	16	21 continuous days in the absence of an acute reversible event	NR	NR	p=0.0014
Expanded Access Program (EAP)								
Scoto, 2018[112]	9 months	--	69	N/A	Additional patients who needed ventilation	7	NR	43 (total)
Pechmann, 2018[80]	NR	--	61	N/A	Non-invasive ventilator >16 hr/day + tracheostomy	19	N/A	N/A
CL-101 (Zolgensma)								
Mendell, 2017[29]	24 months	Low dose	3	N/A	≥16 hours/day of continuous respiratory support for at least 14 days in the absence of an acute, reversible illness or perioperative state	1	N/A	N/A
		High dose	12	N/A		12 (100%)	N/A	N/A
Al-Zaidy, 2019[39]	38 months	high dose cohort	12	N/A	Of 10 patients who did not require BiPAP support before	7 (70%)	N/A	N/A

	Timepoint	Arms	Treatment N	Placebo N	Definition	No. People Not Ventilated in Treatment Arm	No. People Not Ventilated in Placebo	Treatment Difference
					dosing, # of patients who continued to not require BiPAP 24 months after dosing			
CHERISH (Type II, III)								
Mercuri, 2018[25]	Final analysis	--	84	42	NR	NR	10 (6-20) months	NR
NURTURE (Presymptomatic)								
De Vivo, 2017[116]	1-year interim analysis	2 copies SMN2	6	0	Tracheostomy/ventilation for ≥6 hours/day for ≥7 days	6	N/A	N/A
		3 copies SMN2	3	0		3	N/A	N/A
Swoboda, 2018[44]	Interim	--	25	N/A	≥16 hour/day continuously for >21 days (permanent ventilation) in the absence of an acute, reversible event or tracheostomy	0	N/A	N/A

DD: disease duration, MDD: moderate disease duration, N/A: not applicable, NIV: non-invasive ventilation, NR: not reported

Table D6. Outcomes III: CHOP-INTEND

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)	Mean CFB in Tx (95% CI or SE)	Mean CFB in Placebo (95% CI or SE)
ENDEAR (Type I)										
Finkel, 2017[24]	Final analysis	--	80	41	52 / 73 (71%)	1 / 37 (3%)	P = <0.0001	NR	NR	NR
Servais, 2017[83]	Final analysis	≤12 weeks	34	18	88% (of 32)	0	NR	NR	NR	NR
		>12 weeks	46	23	59% (of 16)	5% (of 21)	NR	NR	NR	NR
SHINE (OLE)										
Castro, 2018[33]	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza: 24	51	4	NR	NR	16.9 (11.9–21.9)	3.6 (−0.9 to 8.1)
CS3A / Phase 2										
Finkel, 2016[23]	32 months	--	4	16	14	12	11.5	15.2	p = 0.0080	p = 0.0013
EMBRACE										
Shieh, 2018[43]	14 months	Onset ≤6 month	9	4	NR	NR	NR	NR	NR	NR
		Onset >6 month	5	3	NR	NR	NR	NR	NR	NR
Expanded Access Program (EAP)										
Scoto, 2018[112]	9 months	--	69	NA	1-17 points	NR	36/64	NR	NR	NR
Pechmann, 2018[80]	NR	--	61	N/A	47 (77.0%)	N/A	31.2 ± 16.2 (SD)	N/A	9.0 ± 8.0 (SD)	N/A
Pane, 2018[81]	6 months	--	104	NA	-7 to 27	NR	4.51 (5.80)	NR	P < 0.001	NR
CL-101 (Zolgensma)										

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)	Mean CFB in Tx (95% CI or SE)	Mean CFB in Placebo (95% CI or SE)
Mendell, 2017[29]	24 months	Low dose	3	N/A	NR	N/A	NR	NR	7.7 (from baseline)	N/A
		proposed therapeutic dose	12	N/A	22.5 (mean increase)	N/A	NR	NR	9.8 (month 1); 15.4 (month 3); 24.6 (at study cutoff)	N/A
NURTURE (Presymptomatic)										
De Vivo, 2017[116]	1-year interim analysis	2 copies SMN2	6	0	N/A	N/A	All pts: 62.0 (44-64)	N/A	N/A	N/A
		3 copies SMN2	3	0	N/A	N/A	All pts: 62.0 (44-64)	N/A	N/A	N/A
Swoboda, 2018[44]	Interim	--	25	N/A	NR	N/A	NR	N/A	NR	N/A

N/A: not applicable, NR: not reported

Table D7. Outcomes IV: Sitting, Walking, Standing

Study					Sitting		Standing		Walking	
	Timepoint	Arms	Treatment N	Placebo N	No. (%) of Responders in Tx	No. of Responders in Placebo	No. of Responders in Tx	No. of Responders in Placebo	No. of Responders in Tx	No. of Responders in Placebo
ENDEAR (Type I)										
Finkel, 2017[24]	Final analysis	--	80	41	8%	0	1%	0	NR	NR
Servais, 2017[83]	Final analysis	≤12 weeks	34	18	NR	NR	NR	NR	NR	NR
		≥12 weeks	46	23	NR	NR	NR	NR	NR	NR
SHINE (OLE)										
Castro, 2018[33]	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza : 24	Day 64: NR (1%) of 70; Day 183 5% of 65; Day 302: 10% of 51; Day 394: 15% of 48; Day 578: 29% of 31; Day 698: 24% of 17	NR	0	0	0	0
CS3A/ Phase 2										
Finkel, 2016[23]	32 months	--	4	16	NR	NR	NR	NR	NR	NR
EMBRACE										
Shieh, 2018[43]	14 months -	Onset ≤6 month	9	4	5 (56)	0	0	0	0	0
		Onset >6 month	5	3	4 (80)	1 (33)	2 (40)	2 (67)	1 (20)	0
Expanded Access Program (EAP)										
Pechmann, 2018[80]	NR	--	61	N/A	2 (3.3%)	N/A	0	N/A	0	N/A
CL-101 (Zolgensma)										
Mendell, 2017[29]	24 months	Low dose	3	N/A	NR	N/A	NR	N/A	NR	N/A
		High dose	12	N/A	75% (rolls over); 92% (sits with	N/A	2	N/A	2	N/A

Study					Sitting		Standing		Walking	
	Timepoint	Arms	Treatment N	Placebo N	No. (%) of Responders in Tx	No. of Responders in Placebo	No. of Responders in Tx	No. of Responders in Placebo	No. of Responders in Tx	No. of Responders in Placebo
					assistance); 92% sits unassisted ≥5 sec; 83% sits unassisted ≥10 sec; 75% sits unassisted ≥30 sec					
Al-Zaidy, 2019[39]	38 months	High Dose	12	N/A	92% (sitting with assistance) ; 92% (sitting unassisted > 5s) ; 92% (sitting unassisted > 10s) ; 92% (sitting unassisted > 30s)	N/A	33% (standing assisted)	N/A	NR	N/A
CHERISH (Types II, III)										
Mercuri, 2018[25]	Final analysis	--	84	42	NR	22.4 ± 8.3 (SD)	1(2)	1 (3)	1 (2)	0 (0)
NURTURE (Presymptomatic)										
De Vivo, 2017[116]	1-year interim analysis	2 copies SMN2	6	0	3 (50) pivots	N/A	1 (17) stands unaided	N/A	2 (33) cruising	N/A
		3 copies SMN2	3	0	3 (100) pivots	N/A	2 (67) stands unaided	N/A	3 (100) cruising	N/A
Swoboda, 2018[44]	Interim	--	25	N/A	25 (100)	N/A	NR	N/A	22 (88)/17 (77)	N/A

N/A: not applicable, NR: not reported

Table D8. Outcomes V: HFMSE

	Timepoint	Arm	Treatment N	Placebo N	Definition of Response	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)	Mean CFB in Tx (95% CI or SE)	Mean CFB in Placebo (95% CI or SE)
Phase 2											
Darras, 2013[111]	3 months	--	1 or 3 mg	6 or 9 mg	NR	NR	6/10	NR	3.1	NR	NR
Type II and III											
CHERISH											
Mercuri, 2018[25]	Interim	--	35	19	HFMSE score ≥3 points	NR	NR	NR	NR	4.0 (2.9, 5.1)	-1.9 (-3.8, 0)
Mercuri, 2018[25]	Final analysis	--	66	34	--	57 (46, 68)	26 (12, 40)	NR	NR	3.9 (3.0, 4.9)	-1.0 (-2.5, 0.5)
Wurster, 2018[85]	After 4 loading doses, per label schedule	Spinraza, Type II	9	0	N/A	N/A	N/A	2.0 (2.5)	N/A		N/A
		Spinraza, Type III	11	0	N/A	N/A	N/A	30.8 (24.8)	N/A		N/A
CS2, CS12											
Chiriboga, 2017[35]	253 days	--	Type II - 11	0	HFMSE score ≥3 points	9/11 (82)	NR	NR	NR	NR	NR
	1050 days	--	Type II - 11	0		6/6 (100)	NR	NR	NR	12.3 (SE: 2.2)	NR
	253 days	--	Type III - 17	0		3/16 (19)	N/A	NR	NR	NR	NR
	1050 days	--	Type III - 17	0		2/7 (29)	N/A	NR	NR	1.6 (SE: 1.5)	NR

N/A: not applicable, NR: not reported

Table D9. Outcomes VI: HINE-2

Study	Timepoint	Arms	Treatment N	Placebo N	Definition of Responder	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)
ENDEAR (Type I)									
Finkel, 2017[24]	Interim analysis	--	80	41	improvement in at least one category AND more categories with improvement than categories with worsening	21/51 (41)	0/27	NR	NR
	Final analysis	--	80	41		37/73 (51)	0/37	NR	NR
Servais, 2017[83]	Final analysis	≤12 weeks	34	18	(1) ≥1-point increase in head control, rolling, sitting, crawling, standing, or walking or a ≥2-point increase or achievement of maximal score in kicking ability; and (2) improvement in more HINE categories than worsening.	75% (of 32)	0	P<0.0001	NR
		>12 weeks	46	23		32% (of 41)	0	P=0.0026	NR
SHINE (OLE)									
Castro, 2018[33]	Interim analysis	--	Spinraza → Spinraza: 81	Sham → nusinersen: 24	≥2-point increase or achievement of touching toes in ability to kick, or ≥1-point increase in other 6	20/24	74/81	5.8 (4.58-7.04);	1.1 (0.20-1.90)
CS3A/ Phase 2									
Finkel, 2016[23]	32 months	--	4	16	improvement in at least one category	16	15	p=0.002	p=0.001
EMBRACE									
Shieh, 2018[43]	14 months	Onset ≤6 month	9	4	Individuals demonstrating improvement in more motor milestone categories than worsening	7 (78)	0	0.78 (0.45-0.94)	0.80 (0.38-0.96)

Study	Timepoint	Arms	Treatment N	Placebo N	Definition of Responder	No. of Responders in Tx	No. of Responders in Placebo	Mean Tx Group Score (95% CI or SE)	Mean Placebo Group Score (95% CI or SE)
		Onset ≥6 month	5	3		4 (80)	2 (67)	0 (0.00-0.60)	0.67 (0.21-0.94)
Expanded Access Program (EAP)									
Pechmann, 2018[80]	NR	--	61	N/A	improvement in at least 1 category by ≥1 point and more categories with improvement than categories with worsening	21 (34.4%)	N/A	2.5 ± 3.3 (SD)	N/A
CS2, CS12									
Montes et al, 2018[114]	253 days	--	14	0	NR	NR	N/A	NR	N/A
	1050 days	--	14	0	NR	NR	N/A	NR	N/A
Chiriboga, 2017[35]	253 days	--	Type II - 11	0	NR	NR	NR	NR	NR
	1050 days	--	Type II - 11	0	NR	NR	NR	NR	NR
	253 days	--	Type III - 17	0	NR	NR	NR	NR	NR
	1050 days	--	Type III - 17	0	NR	NR	NR	NR	NR

N/A: not applicable, NR: not reported

Table D10. Outcomes VII: 6MWT

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Mean CFB in Tx (95% CI or SE)	Mean CFB in Placebo (95% CI or SE)
ENDEAR (Type I)								
Finkel, 2017[24]	Final analysis	--	80	41	NR	NR	NR	NR
Servais, 2017[83]	≤12 weeks	End of study results	34	18	NR	NR	NR	NR
	≥12 weeks		46	23	NR	NR	NR	NR
SHINE (OLE)								
Castro, 2018[33]	Interim analysis	--	Spinraza → Spinraza: 81	Sham → Spinraza: 24	N/A	N/A	N/A	N/A
CS3A/ Phase 2								
Finkel, 2016[23]	32 months	--	4	16	NR	NR	NR	NR
EMBRACE								
Shieh, 2018[43]	14 months	Onset ≤6 month	9	4	NR	NR	NR	NR
		Onset >6 month	5	3	NR	NR	NR	NR
Expanded Access Program (EAP)								
Pechmann, 2018[80]	NR	--	61	N/A	NR	NR	NR	NR
CS2, CS12								
Montes et al, 2018[114]	253 days	--	14	0	NR	N/A	17 (-47, 99)	N/A
	1050 days	--	14	0	NR	N/A	99.0 (31, 150)	N/A
Chiriboga, 2017[35]	253 days	--	Type II - 11	0	N/A	N/A	N/A	N/A
	1050 days	--	Type II - 11	0	N/A	N/A	N/A	N/A
	253 days	--	Type III - 17	0	6/12 (50)	N/A	NR	N/A
	1050 days	--	Type III - 17	0	6/6 (100)	N/A	96.7 (17.3)	N/A

N/A: not applicable, NR: not reported

Table D11. Outcomes VIII: Other

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Ventilation Use (%) Tx	Ventilation Use (%) Placebo	Motor Milestone Response Tx	Motor Milestone Response Placebo	RULM Score in Tx Group	RULM Score in Placebo Group
ENDEAR (Type I)												
Finkel, 2017[24]	6 months, early termination	<13.1 weeks	80	41	22% Full head control	0	30/39 (77)	7/21 (33)	NR	NR	NR	NR
		>13.1 weeks					19/41 (46)	6/20 (30)	NR	NR	NR	NR
SHINE (OLE)												
Castro, 2018[33]	Interim analysis	--	Nusinersen → Spinraza: 81	Sham → Spinraza: 24	Full head control: Day 64: 7% of 70; Day 183: 17% of 65; Day 302: 25% of 51; Day 394: 33% of 48; Day 578: 45% of 31; Day 698: 35% of 17	NR	NR	NR	NR	NR	N/A	N/A
Swoboda, 2018[44]	Interim	--	25	N/A	88% (of 25); "Good suck and swallow"	N/A	NR	NR	NR	NR	N/A	N/A

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Ventilation Use (%) Tx	Ventilation Use (%) Placebo	Motor Milestone Response Tx	Motor Milestone Response Placebo	RULM Score in Tx Group	RULM Score in Placebo Group
EMBRACE												
Shieh, 2018[43]	14 months	Onset ≤6 month	9	4	4 (44) Head control, ≥1-point increase	0	1.236 (3.712)	2.123 (3.023)	NR	NR	NR	NR
		Onset ≥6 month	5	3	1 (20) Head control, ≥1-point increase	0	NR	NR	NR	NR	NR	NR
Expanded Access Program (EAP)												
Pechmann, 2018[80]	NR	--	61	N/A	4 (6.6%) Head control; 37 (60.7%) GI tube	N/A	NR	NR	NR	NR	NR	NR
CL-101 (Zolgensma)												
Mendell, 2017[29]	24 months	High dose	12	N/A	11 (swallow); 11 (speaking); 50% (GI tube)	N/A	5/12 had no support	NR	NR	NR	NR	NR
Al-Zaidy, 2019[39]	38 months	High dose	12	N/A	11/12 (92%) swallow; 11/12 (92%) speaking	N/A	NR	N/A	NR	N/A	N/A	N/A

	Timepoint	Arms	Treatment N	Placebo N	No. of Responders in Tx	No. of Responders in Placebo	Ventilation Use (%) Tx	Ventilation Use (%) Placebo	Motor Milestone Response Tx	Motor Milestone Response Placebo	RULM Score in Tx Group	RULM Score in Placebo Group
CHERISH (Types II, III)												
Mercuri, 2017[113]	INTERIM	--	35	19	NR	NR	NR	NR	17.1%	10.5%	NR	Treatment difference: 3.4 (NR)
CS2, CS12												
Chiriboga, 2017[35]	253 days	Type II	11	0	NR	NR	NR	NR	NR	NR	5/11 improved by ≥2 points	N/A
	1050 days		11	0	NR	NR	NR	NR	NR	NR	CFB: 4.6 (SE: 1.4); 4/6 improved by ≥2 points	N/A
	253 days	Type III	17	0	NR	NR	NR	NR	NR	NR	NR	N/A
	1050 days		17	0	NR	NR	NR	NR	NR	NR	NR	N/A

N/A: not applicable, NR: not reported

Table D12. Harms I (AEs, SAEs, Discontinuation, Death)

Study				Adverse Events		Serious Adverse Events (SAE)		Treatment-Related AE		AE Leading to Discontinuation		Deaths	
	Timepoint	Treatment N	Placebo N	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)
ENDEAR													
Finkel, 2017[24]	Final analysis	80	41	77 (96)	40 (98)	61 (76)	39 (95)	NR	NR	13 (16)	16 (39)	NR	NR
SHINE (OLE)													
Castro, 2018[33]	Interim analysis	65 (Spinraza → Spinraza, SHINE time only)	24 (sham → Spinraza, SHINE time only	60 (92)	23 (96)	39 (60)	13 (54)	0	0	4 (6)	2 (8)	NR	NR
CS3A / Phase 2													
Finkel, 2016[23]	32 months	4	16	4 (100)	16 (100)	3 (75)	13 (81)	NR	NR	NR	NR	1	2
EMBRACE													
Shieh, 2018[43]	14 months	14	7	14 (100)	6 (86)	5 (36)	3 (43)	0	0	0	0	0	1 (14)
Expanded Access Program (EAP)													
Pechmann, 2018[80]	6 months	61	N/A	53	NR	29 (54.7%)	NR	NR	NR	NR	NR	1	NR
CL-101 (Zolgensma)													
Mendell, 2017[29]	24 months - low dose	3	N/A	3 (100)	N/A	3 (100)	N/A	1 (33)	N/A	0	N/A	0	N/A
	24 months - proposed	12	N/A	12 (100)	N/A	10 (83)	N/A	3 (25)	N/A	0	N/A	0	N/A

Study				Adverse Events		Serious Adverse Events (SAE)		Treatment-Related AE		AE Leading to Discontinuation		Deaths	
	Timepoint	Treatment N	Placebo N	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)
	therapeutic dose												
Types II and III													
Mercuri, 2018[25]	Final analysis	84	42	78 (93)	42 (100)	4 (5)	3 (7)	NR	NR	0	0	NR	NR
Stolte, 2018[84]	After 4 loading doses	28	0	22 (81.5)	N/A	0	N/A	NR	N/A	0	N/A	0	N/A
NURTURE (presymptomatic)													
De Vivo, 2017[116]	1-year interim analysis	6	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Swoboda, 2018[44]	Interim	25	N/A	25 (100)	N/A	9 (36)	N/A	0	N/A	0	N/A	0	N/A
Other													
Mercuri, 2017[113]	247 patient-years	17 - presymptomatic	N/A	13 (76%)	N/A	5 (29%)	N/A	NR	NR	NR	NR	NR	NR
		100 - symptomatic infants	N/A	92 (92%)	N/A	72 (72%)	N/A	NR	NR	NR	NR	NR	NR

NA: not applicable, NR: not reported

Table D13. Harms II (Constipation, Fever, RSV, Respiratory Failure)

Study				URI-AE		Constipation		Pyrexia/Fever		RSV		Respiratory Failure	
	Timepoint	Treatment N	Placebo N	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%))	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)
ENDEAR													
Finkel, 2017[24]	Final analysis	80	41	24 (30)	9 (22)	28 (35)	9 (22)	NR	NR	23 (29) pneumonia; 5 (6) bronchitis viral; 6 (8) bronchitis	7 (17) pneumonia	20 (25)	16 (39)
SHINE (OLE)													
Castro, 2018[33]	Interim analysis	65 (Spinraza → Spinraza, SHINE time only)	24 (sham → Spinraza, SHINE time only	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phase 2													
Finkel, 2016[23]	32 months	4	16	3 (75)	11 (69)	1 (25)	8 (50)	3 (75)	11 (69)	1 (25) pneumonia	6 (38) pneumonia	NR	6 (38)
EMBRACE													
Shieh, 2018[43]	14 months	14	7	5 (36)	2 (29)	NR	NR	6 (43)	1 (14)	NR	NR	NR	NR
Expanded Access Program (EAP)													
Pechman n, 2018[80]	6 months	61	N/A	31 (58.5%)	NR	NR	NR	NR	NR	NR	NR	8 (15.1)	NR
CL-101 (Zolgensma)													

Study				URI-AE		Constipation		Pyrexia/Fever		RSV		Respiratory Failure	
Mendell, 2017[29]	24 months - low dose	3	NR	1 (33)	NR	1 (33)	NR	1 (33)	NR	1 (33) pneumonia; 1 (33) bronchitis	NR	1 (33)	NR
	24 months – high dose	12	NR	10 (83)	NR	7 (58)	NR	6 (50)	NR	2 (17) pneumonia; 2 (17) bronchitis	NR	3 (25)	NR
Types II and III													
Mercuri, 2018[25]	Final analysis	84	42	25 (30)	19 (45)	NR	NR	36 (43)	15 (36)	NR	NR	NR	NR
Stolte, 2018[84]	After 4 loading doses	28	0	1 (4)	N/A	2 (7)	N/A	NR	N/A	NR	N/A	NR	N/A
NURTURE (Presymptomatic)													
De Vivo, 2017[116]	1-year interim analysis	6	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Swoboda, 2018[44]	Interim	25	N/A	NR	N/A	1 (4)	N/A	NR	N/A	NR	N/A	NR	N/A
Other													
Mercuri, 2017[113]	247 patient-years	17 - presymptomatic	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	247 patient-years	100 - symptomatic infants	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

N/A: not applicable, NR: not reported

Table D14. Harms III (Respiratory Distress, Nasopharyngitis, Headache, Other)

Study				Respiratory Distress		Atelectasis		Nasopharyngitis		Headache		Other	
	Timepoint	Treatment N	Placebo N	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n group (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)	Treatment, n (%)	Placebo, n (%)
ENDEAR													
Finkel, 2017[24]	Final analysis	80	41	21 (26)	12 (29)	18 (22)	12 (29)	NR	NR	NR	NR	NR	NR
SHINE													
Castro, 2018[33]	Interim analysis	65 (Spinraza → Spinraza, SHINE time only)	24 (sham → Spinraza, SHINE time only	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phase 2													
Finkel, 2016[23]	32 months	4	16	1 (25)	6 (38)	NR	NR	NR	6 (38)	NR	NR	NR	NR
EMBRACE													
Shieh, 2018[43]	14 months	14	7	NR	NR	NR	NR	3 (21) nasal congestion	0	NR	NR	4 (26) vomiting; 7 (50) cough	1 (14) vomiting; 1 (14) placebo
Expanded Access Program (EAP)													
Pechmann, 2018[80]	6 months	61	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
CL-101 (Zolgensma)													
Mendell, 2017[29]	24 months - low dose	3	NR	NR	NR	0	NR	NR	NR	NR	NR	NR	NR
	24 months - high dose	12	NR	NR	NR	4 (33)	NR	NR	NR	NR	NR	NR	NR

Study				Respiratory Distress		Atelectasis		Nasopharyngitis		Headache		Other	
Types II and III													
Mercuri, 2018[25]	Final analysis	84	42	2 (2)	2 (5)	NR	NR	20 (24)	15 (36)	24 (29)	3 (7)	NR	NR
Stolte, 2018[84]	After 4 loading doses	28	0	NR	N/A	NR	N/A	NR	N/A	17 (63)	N/A	6 (22.2) back pain ; 4 (14.8) nausea	N/A
NURTURE													
De Vivo, 2017[116]	1-year interim analysis	6	3	NR	NR	NR	NR	NR	NR	NR	NR	1 (Weight-loss)	NR
Swoboda, 2018[44]	Interim analysis	25	N/A	NR	N/A	NR	N/A	NR	N/A	NR	N/A	NR	NR
OTHER													
Mercuri, 2017[113]	247 patient-years	17 - presymptomatic	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		100 - symptomatic infants	N/A	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

N/A: not applicable, NR: not reported

Appendix E. Comparative Value Supplemental Information

Table E1. 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	
	Adverse events	☐	☐	
Medical Costs	Paid by third-party payers	X	X	Included within cost estimates
	Paid by patients out-of-pocket	X	X	Included in modified societal perspective to the extent possible
	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 Sectors				
Productivity	Labor market earnings lost	NA	X	Patient productivity gains included in modified societal perspective
	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	X	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.[118]

Estimating Proportions of "Sitting" Patients at Different Time Points on Spinraza

Whilst we know the proportion sitting among those who attended the follow up visits, we do not know the proportion of patients sitting among those who did not. Given this, we made an assumption that all the patients alive have the same likelihood to be in the 'sitting' health state i.e. the patients who did not attend the follow up have a similar proportion sitting as those who attended the follow up visits. Note that this is an assumption favorable to Spinraza as in reality it is likely that those who are in permanent ventilation have less likelihood to move to sitting health state compared to those who are in not sitting health state. As such, we multiplied the proportions of Spinraza patients alive at each of the time points and with the proportions of patients sitting at each time point to estimate the proportion sitting in Spinraza at different time points.

For estimating the proportion of Spinraza patients alive over time, we digitized the KM curve for OS in SHINE to estimate the survival at different time points. The manufacturer (Biogen) also provided data on number of patients deceased at each of the follow up visits. These data were submitted as academic in confidence data, were unmasked in November 2020 per ICER's policy on unmasking such information, and are presented below. We used the data given by Biogen to estimate the proportion alive at the follow up visit time points and for the other time points we used the approximated survival estimates from the digitized KM curve.

Supplemental Table. Number Deceased at Each Study Visit in Castro 2018*

	Study Day						
	Baseline	Day 64	Day 183	Day 302	Day 394	Day 578	Day 698
Number deceased	0	5	11	13	14	17	17

*Castro D, et al. Longer-term Assessment of the Safety and Efficacy of Nusinersen for the Treatment of Infantile-Onset Spinal Muscular Atrophy (SMA): An Interim Analysis of the SHINE Study. Paper presented at: Presented at AAN2018; Los Angeles, CA.

As the data on proportion sitting in Castro et al poster is presented as integers, we followed a multi-stage process to estimate the true proportions of Spinraza patients sitting at the different time points. In step one, the numbers of patients sitting at each time point were estimated. In step two, these were rounded to the nearest integer. In step three, these integer values representing the number of patients sitting were divided by the number of patients at risk at each time point to estimate the true proportions of patients sitting. Also, to match with the model structure, the days at the follow up visits were converted into months and rounded to the nearest integer.

Table E2. Estimating Proportions of "Sitting" Patients at Different Time Points on Spinraza

	Baseline Month 0 n=81	Day 64 Month 2 n=70	Day 183 Month 6 n=65	Day 302 Month 10 n=51	Day 394 Month 13 n=48	Day 578 Month 19 n=31	Day 698 Month 23 n=17
% Achieving Independent Sitting (But Not Walking)	0	1	5	10	15	29	24
Step 1: Estimating Numbers of Patients at Each Period	0	0.7	3.25	5.1	7.2	8.99	4.08
Step 2: Rounding the Numbers to the Nearest Integer	0	1	3	5	7	9	4
Step 3: Proportion Sitting in Those Attending Follow Up	0.000	0.0143	0.0462	0.0980	0.1458	0.2903	0.2353
% Sitting	0.0000	0.0134	0.0399	0.0823	0.1206	0.2294	0.1859

Survival Modeling

The model used health state-specific mortality risks for the proportion of patients alive at the end of the short-term model. The long-term risk of mortality associated with each of the health states was modelled by fitting survival curves to the digitized published Kaplan-Meier (KM) data most relevant to each health state. For each health state, a single parametric distribution was selected to calculate the estimated probability of death in each time period (i.e. each month).

The KM data was digitized, and the individual data were reconstructed using the methods described in Guyot et al.[87] Different parametric distributions were fitted and the best fitting curves were identified based on a combination of: visual inspection, fit statistics such as Akaike information criteria (AIC)/Bayesian information criteria (BIC), and clinical plausibility.

The mortality risks associated with each health state are described in detail below.

Transitions from "Not Sitting" State

Patients from the "not sitting" state could transition to either the "permanent ventilation" health state or to death. At each monthly cycle, the ventilation free survival (VFS) curve was subtracted from the OS curve to estimate the proportion of patients in the "permanent ventilation" health state.

The source of data available to model these (i.e., VFS and OS) of SMA Type I patients was the sham control arm of the ENDEAR trial (n=41), with a follow-up of 52 weeks. In the model analysis plan (MAP), it was proposed to use NeuroNEXT data to estimate these transition probabilities; however,

it had a smaller sample size compared to the sample size of the sham control arm in the ENDEAR trial. As such, we used the parametric distributions fitted to the data from sham control arm of ENDEAR[24]. Exponential distributions were selected to model the VFS and OS based on clinical plausibility, visual fit, and AIC/BIC.

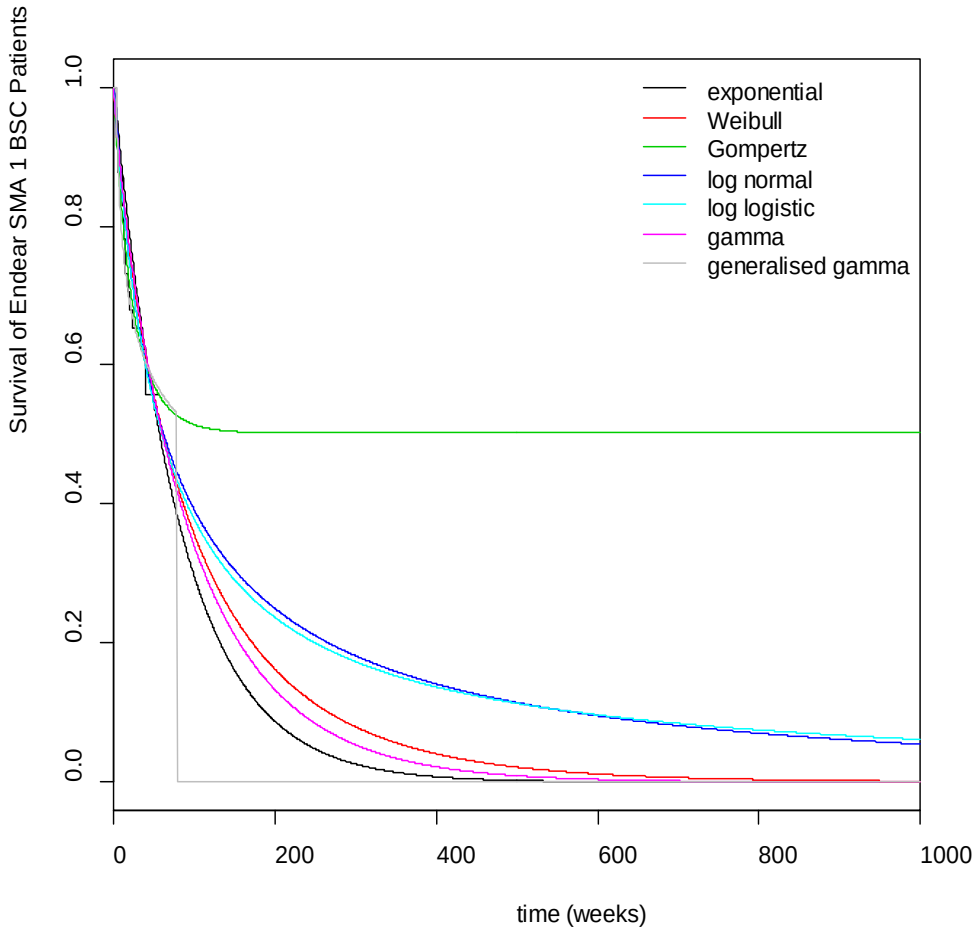
Not Sitting to Death

Table E3. Fit Statistics for Parametric Distributions Fitted to Overall Survival of Sham Control Arm in ENDEAR[24]

Distribution	AIC	BIC
Exponential	185.79	187.50
Weibull	186.86	190.28
Gompertz	183.72	187.15
Log-Normal	183.87	187.29
Log-Logistic	185.42	188.85
Gamma	187.21	190.63
Generalized Gamma	180.00	185.14

AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria

Figure E1. Parametric Distributions Fitted to Overall Survival of Sham Control Arm in ENDEAR[24].



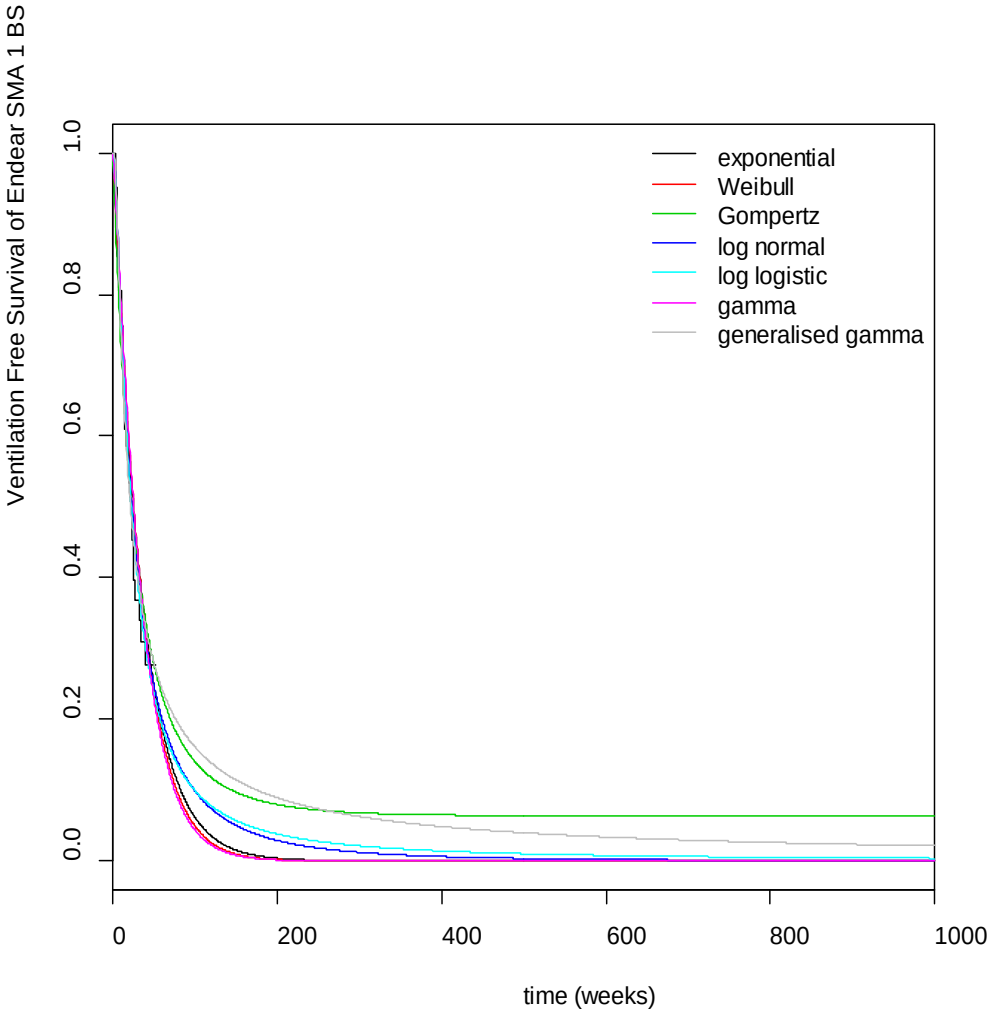
Not Sitting to Death or Permanent Ventilation

Table E4. Fit Statistics for Parametric Distributions Fitted to Ventilation Free Survival of Sham Control Arm in ENDEAR[24].

Distribution	AIC	BIC
Exponential	258.27	259.99
Weibull	260.11	263.54
Gompertz	259.48	262.91
Log-Normal	255.25	258.68
Log-Logistic	256.20	259.62
Gamma	259.69	263.12
Generalized Gamma	255.77	260.91

AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria

Figure E2. Parametric Distributions Fitted to Sham Control Arm in ENDEAR[24].



Mortality in Permanent Ventilation Health State

The Gregoretti et al. study, which was a retrospective data analysis[47] of SMA Type I patients from four Italian centers from October 1992 to December 31, 2010, presented survival data for SMA Type I patients on permanent ventilation. In the MAP, we proposed to use data from two patient cohorts reported in this retrospective study: a) patients with continuous non-invasive respiratory muscle aid, including non-invasive ventilation, and mechanically assisted cough (n=31), represented as the NRA curve in the figure below, and b) patients with tracheostomy and invasive mechanical ventilation (n=42), represented as the TV curve. The curve NT represents the no treatment arm.

However, seven patients received tracheostomy in the NRA arm and the study did not present any details about whether the data presented for the NRA arm were after censoring for these patients or including these patients. Furthermore, they also did not present the numbers at risk for either arm, so it was difficult to understand the robustness of these survival estimates. The study also did

not provide the reasons for patients receiving different treatments and it is possible that the survival estimates would be confounded (for example, if patients with less-severe disease received a specific treatment such as TV).

Given all these issues, the NRA curve alone was used to model the mortality risk from the permanent ventilation state. Different parametric curves were fitted and exponential distribution was chosen based on visual inspection, fit statistics (AIC/BIC), and clinical plausibility.

Figure E3. Parametric Distributions Fitted to NRA Arm in Gregoretti et al.[47]

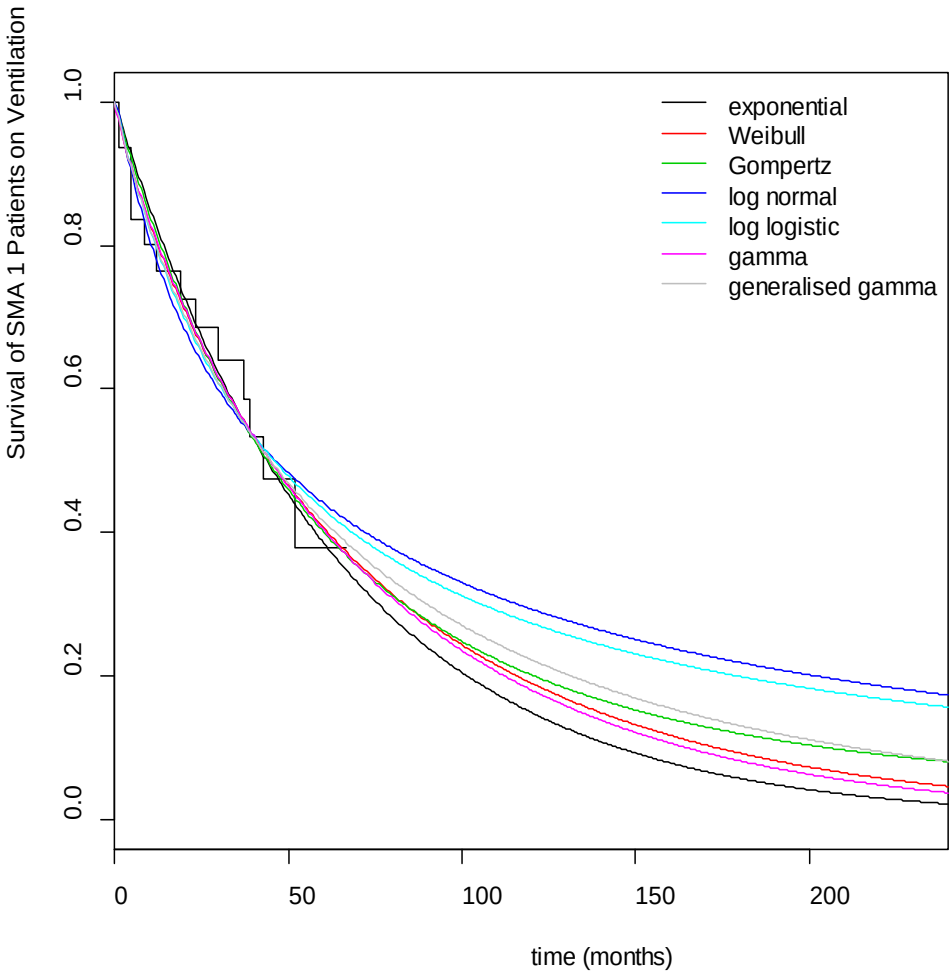


Table E5. Fit Statistics for Parametric Distributions Fitted to NRA Arm in Gregoretti et al.

Distribution	AIC	BIC
Exponential	146.07	147.50
Weibull	147.78	150.65
Gompertz	148.00	150.87
Log-Normal	147.95	150.82
Log-Logistic	148.13	151.00
Gamma	147.79	150.65
Generalized Gamma	149.78	154.08

AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria

SMA Type II (Sitting)

Treated SMA Type I patients who can sit were assumed to have similar prognosis as SMA Type II patients, who are able to sit but not walk. Pooled data from German and Polish studies on SMA Type II patients (n=240) presented in Zerres and Schöneborn et al.[48] were used to model the mortality from the "sitting" health state.

The original KM curve was digitized, and the individual data were reconstructed using the methods described in Guyot et al.[87] The KM curve has substantial censoring in the early time periods and the study did not report the numbers at risk at different time periods. In the absence of numbers at risk at different time periods, the algorithm in Guyot et al.[87] assumes that the censoring is constant over the entire time period. As such, the algorithm estimates that all the events happened within 25 years (see figure below). That is, it only outputs part of the K-M curve.

This issue can be addressed by using educated approximations of the numbers at risk at different time points. For example, when assuming the number at risk at 10 years to be 100, the algorithm estimated a bigger proportion of the KM curve. This can be extended even further by assuming that the number at risk at 10 years to be 80, where the algorithm estimated the whole of the KM curve.

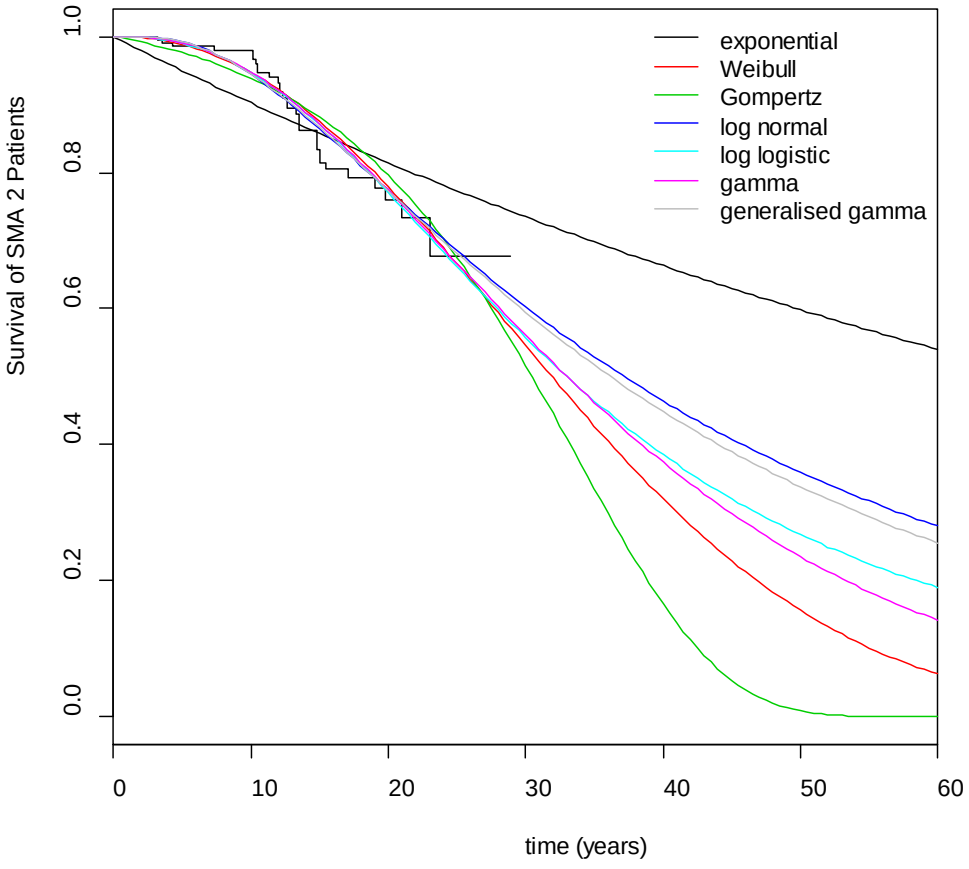
However, the numbers of patients at risk in the later parts of the curve (e.g., after 25 years) seems quite low as each event caused a large difference to the survival curve. Given these patients were outliers, after discussions with survival modelling experts, we decided to use the first analysis, only fitting to the early part of the KM curve as estimated by the algorithm in Guyot et al.[87] assuming constant censoring over the entire time period. Different parametric curves were fitted and Gompertz distribution was chosen based on visual inspection, fit statistics (AIC/BIC), and clinical plausibility.

Table E6. Fit Statistics for Parametric Distributions Fitted to Survival of SMA Type II Patients in Zerres and Schöneborn et al.[48]

Distribution	AIC	BIC
Exponential	347.86	351.34
Weibull	327.96	334.92
Gompertz	335.64	342.60
Log-normal	325.92	332.88
Log-logistic	326.50	333.46
Gamma	326.53	333.49
Generalized Gamma	327.89	338.33

AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria

Figure E4. Parametric Distributions Fitted to Survival of SMA Type II Patients in Zerres and Schöneborn et al.[48]



Patient Productivity Gains

No productivity changes were assumed for those in the "permanent ventilation" and "not sitting" health states. For other health states, data from the Lewin Group report[98] on educational attainment for SMA patients were combined with data on income by education level in the US from the Bureau of Labor Statistics[99] to estimate the productivity gains of patients. These proportions were weighted by monthly earnings to estimate the potential monthly income as $4,450, as shown in Table E7 below. These productivity gains were estimated from the age of 30 years until an age of 65 years.

Table E7. Patient Productivity Gains

Education Level	Numbers (n) (N=188)	Proportions (i.e., n/N)	Weekly Earnings*
Data Not Available	8	0.0426	$520†
Less than High School	8	0.0426	$520
High School Graduate	28	0.1489	$712
Some College/Associate Degree/Post-High School Education	56	0.2979	$836
College Graduate	51	0.2713	$1,173‡
Post-Graduate	37	0.1968	$1,660§
Potential Monthly Income	$4,450		

*https://www.bls.gov/emp/tables/unemployment-earnings-education.htm.

†Assumed to be the earnings of those who have less than high school diploma.

‡Assumed to be the earnings from bachelor's degree.

§Assumed to be average of earnings from master's degree, professional degree, and doctoral degree.

Modified Societal Perspective Including Caregiver Burden

As the methods for performing economic evaluation including caregiver burden are still under development, we present here our thoughts on considerations and methodologies for performing a modified societal perspective analysis that includes caregiver burden.

Bastida et al. in 2017[119] surveyed 81 caregivers of patients with different subtypes of SMA in Spain, and reported that the mean utility of all caregivers, estimated using the EuroQol-Five Dimension (EQ-5D) questionnaire with the time trade-off method, was 0.484. Out of 81 patients, eight had SMA Type I, 60 had SMA Type II, and 13 had SMA Type III.[119] They also reported the mean utility value for Type II patients as 0.472, as shown in Table E8.

Given the very low utility values reported, there were concerns with the face validity of this data. We thus used the baseline utility of 0.484 for caregivers of patients in the "permanent ventilation" health state and assumed that the utility for those caring for patients in the "walking" health state was 0.878 (i.e., the same as the patients themselves). The utility values for caregivers of patients in

"not sitting" and "sitting" health states were estimated by assuming a slope of increasing utility. The difference between the "walking" and "permanent ventilation" health states (i.e., 0.878-0.484) was estimated and a quarter of this difference was added to the utility of the "permanent ventilation" health state to get the utility for the "not sitting" health state; and half of this difference was added to the utility of the "permanent ventilation" health state to derive the utility for the "not sitting" health state. The utility values estimated for caregivers are presented in Table E8.

We would assume that there are two caregivers for each patient. Also, caregiver disutilities would be used instead of an added utility approach, because we do not know caregiver disutility after the death of an SMA patient or the duration of this disutility; hence, we would propose using disutilities instead of an added utility approach. In each health state, caregiver disutilities would be estimated by subtracting the utility of caregivers in the "walking" health state (i.e., 0.878) from the utility of the caregivers in that health state. Table E8 presents the caregiver disutilities in the societal perspective analyses that includes caregiver burden.

This could result in negative QALYs due to the fact that the disutility of the caregivers (-0.394) is higher than the utility for the patients (0.19 for the "not sitting" and "permanent ventilation" states).

Table E8. Caregiver Utility Values

Health State	Caregiver Utility	Description	Caregiver Disutility
Permanent Ventilation	0.484	Assumption	-0.394
Not Sitting	0.583	Assumption	-0.2955
Sitting	0.681	Assumption	-0.197
Walking	0.878	Assumption	0

Lost Household Income

The Lewin Group report[98] estimated lost household income from caring for SMA patients using regression analyses. Two different estimates for lost family income were presented: estimate one was of lost household income directly; estimate two used the difference between potential and current income as an estimate of the lost household income. Scenario analyses would be performed using both estimates in Table E9.

Table E9. Lost Household Income

	Estimate 1		Estimate 2	
	SMA Early Onset	SMA Other	SMA Early Onset	SMA Other
Predicted Loss	$19,833	$14,800	$39,783	$12,407
Standard Error	$13,633	$3,557	$2,750	$700

Breakdown of the SMA Type I Model Results

The breakdown of the LYs, QALYs, and costs according to health state for the different interventions in the SMA Type I population are presented here. Table E10 presents the breakdown for LYs. As can be observed, the majority of the LYs and QALYs gained are in the "sitting" and "walking" health states. This is because of the longer survival associated with these health states compared with the "not sitting" and "permanent ventilation" health states (Figure E3). None of the patients in BSC arm achieved milestones, and as such the LYs achieved in this arm were lower compared with the treatment arms. In the Spinraza arm, around 19% of the patients were in the sitting health state at the end of the short-term model, which provided 5.32 LYs, while in the Zolgensma arm approximately 62.5% of the patients were in the sitting health state, which provided 17.84 LYs. The Zolgensma arm also had approximately 16.7% in the walking health state at the end of the short-term model, which provided a further 12.93 LYs. This is as expected, as the model assumed that those in the walking health state have general population mortality.

Table E10. Undiscounted LYs by Health State in the SMA Type I Model

Undiscounted LYs	Ventilated	Not Sitting	Sitting	Walking	Total Undiscounted LYs
BSC	1.99	0.70	0.00	0.00	2.68
Spinraza	2.23	2.73	5.32	0.00	10.28
Zolgensma	0.00	2.36	17.84	12.93	33.13

LY: life-year

The breakdown of the discounted LYs and QALYs according to health state for the different interventions are presented in Tables E11 and E12. These results follow the same pattern as Table E10, but the absolute numbers are lower due to discounting (for discounted LYs) and the use of QoL weights (see Table 4.5) for discounted QALYs. The utility values in the "not sitting" and "permanent ventilation" health states were 0.19, resulting in quite low QALYs for BSC. For Spinraza and Zolgensma, the majority of the QALYs are from the patients in the "sitting" health state, who have a utility of 0.6. As before, Zolgensma also had a proportion of patients (16.7%) who were in the "walking" health state at the end of short-term model, but they contributed over 33% of the total QALYs. This is because the utility in the walking health state is the same as general population utilities, which are much higher than utilities in the other health states.

Table E11. Discounted LYs by Health State in the SMA Type I Model

Discounted LYs	Ventilated	Not Sitting	Sitting	Walking	Total Discounted LYs
BSC	1.71	0.68	0.00	0.00	2.40
Spinraza	1.89	2.40	3.36	0.00	7.64
Zolgensma	0.00	2.13	11.27	4.77	18.17

LY: life-year

Table E12. Discounted QALYs by Health State in the SMA Type I Model

Discounted QALYs Gained	Ventilated	Not Sitting	Sitting	Walking	Total Discounted QALYs
BSC	0.33	0.13	0.00	0.00	0.46
Spinraza	0.36	0.70	2.18	0.00	3.24
Zolgensma	0.00	0.62	7.32	4.29	12.23

QALY: quality adjusted life-year

The breakdown of the discounted costs according to health state for the different interventions are presented in Table E13. The costs are broken out into treatment costs, administration costs, and non-treatment health care costs.

For Spinraza and Zolgensma, as seen in Table E13, treatment costs made up the majority of overall costs. In the Spinraza arm, treatment costs were broadly proportional to the LYs gained in each health state; it should be noted that the model assumed that treatment is discontinued after 24 months for patients who do not achieve milestones (i.e., the patients in the "not sitting" and "permanent ventilation" states). Zolgensma was modeled as a one-time upfront cost.

For BSC, health care costs were associated only with patients in the "not sitting" and "permanent ventilation" health states. The costs of permanent ventilation were higher for BSC, reflecting the longer survival of these patients.

Regarding the non-treatment health care costs, for Spinraza and Zolgensma, most of the costs associated with the "sitting" health state were accrued in the short-term model, due to most patients starting in this state (while they achieve the milestones) and to these costs not being affected by discounting, as they are accrued at the beginning of the model. Again, the costs of permanent ventilation were higher for Spinraza, reflecting the longer survival of these patients. For Zolgensma, although none of the patients in the Zolgensma study received permanent ventilation, the long-term model included a proportion of patients in the "not sitting" health state who were simulated to move into permanent ventilation and have costs in that state. Furthermore, in the Zolgensma treatment arm, the patients in the "sitting" and "walking" health states had more LYs and accrued further costs, even though the costs associated with those health states ($6,357 and $2,499 per month, respectively) were lower than costs associated with the "not sitting" and "permanent ventilation" health states ($25,517 and $28,218 per month, respectively).

Table E13. Breakdown of the Discounted Costs by Health State

Treatment Costs	Ventilated	Not Sitting	Sitting	Walking	Total
BSC	--	--	--	--	--
Spinraza	$156,569	$794,619	$1,279,642	--	$2,230,829
Zolgensma	--	$2,000,000*	--	--	$2,000,000
Administration Costs	**Ventilated**	**Not Sitting**	**Sitting**	**Walking**	**Total**
BSC	--	--	--	--	--
Spinraza	$1,485	$7,535	$12,134	--	$21,154
Zolgensma	--	$137	--	--	$137
Health Care Costs	**Ventilated**	**Not Sitting**	**Sitting**	**Walking**	**Total**
BSC	$580,684	$208,793	--	--	$789,477
Spinraza	$641,516	$733,869	$256,173	--	$1,631,557
Zolgensma	$1,375	$653,126	$859,378	$143,123	$1,657,002

*Placeholder price.

Probabilistic Sensitivity Analyses Results for Type I SMA Model

This panel presents cost-effectiveness clouds from the probabilistic sensitivity analysis (PSA) for the Spinraza versus BSC comparison in Type I SMA model. Due to the lack of data, the distributions used for costs and utilities in the PSA are mean values ±10%. Figure E5 below presents the cost-effectiveness clouds (i.e., the scatterplot of incremental costs vs. incremental QALYs) for Spinraza versus BSC in the Type I SMA Model.

Figure E5. Cost-Effectiveness Clouds for Spinraza versus BSC in Type I SMA Model

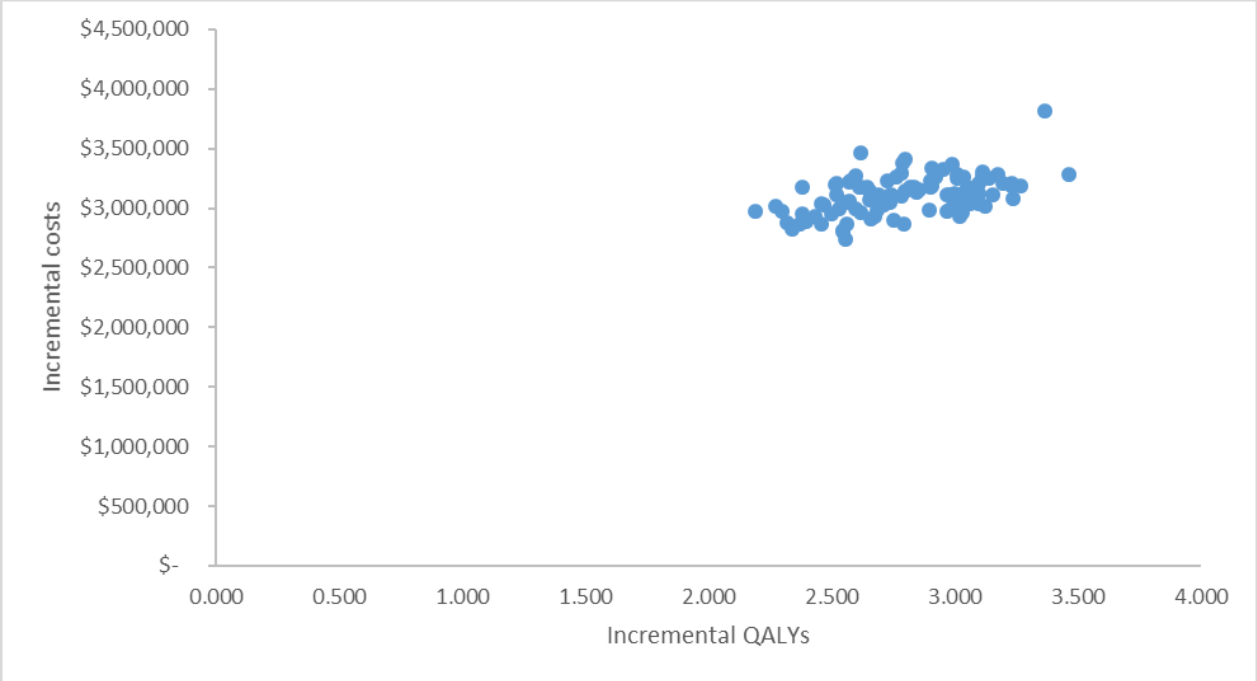


Figure E6 below presents the cost-effectiveness acceptability curve for Spinraza versus BSC in the Type I SMA Model. Spinraza had no likelihood of being cost-effective at thresholds less than $500,000 per QALY.

Figure E6. Cost-Effectiveness Acceptability Curve for Spinraza versus BSC in Type I SMA Model

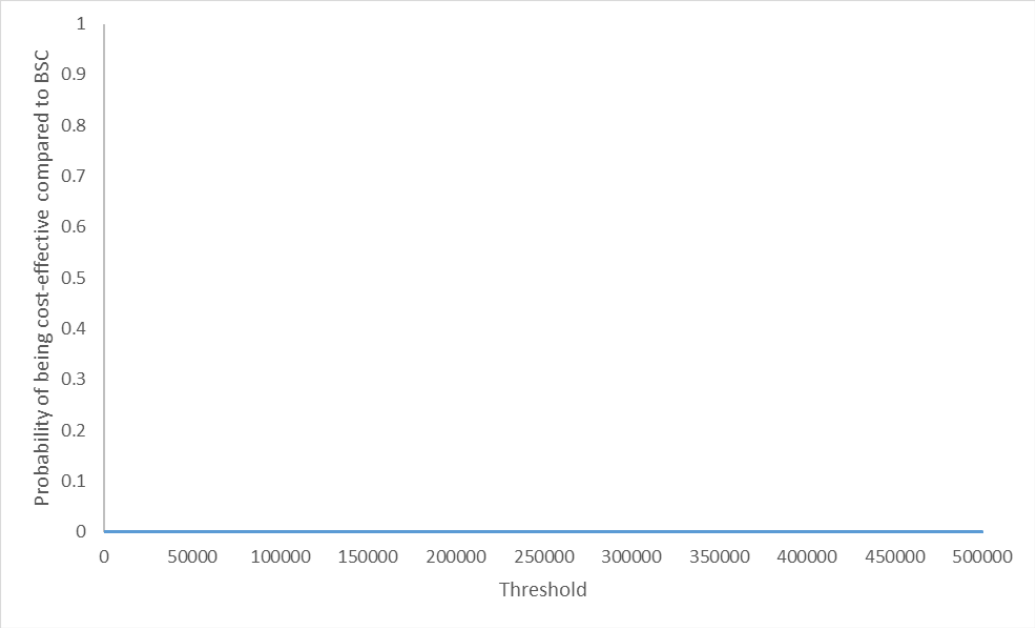


Figure E7 below presents the cost-effectiveness cloud (i.e., the scatterplot of incremental costs vs. incremental QALYs) for Zolgensma versus BSC in the Type I SMA Model.

Figure E7. Cost-Effectiveness Clouds for Zolgensma versus BSC in Type I SMA Model

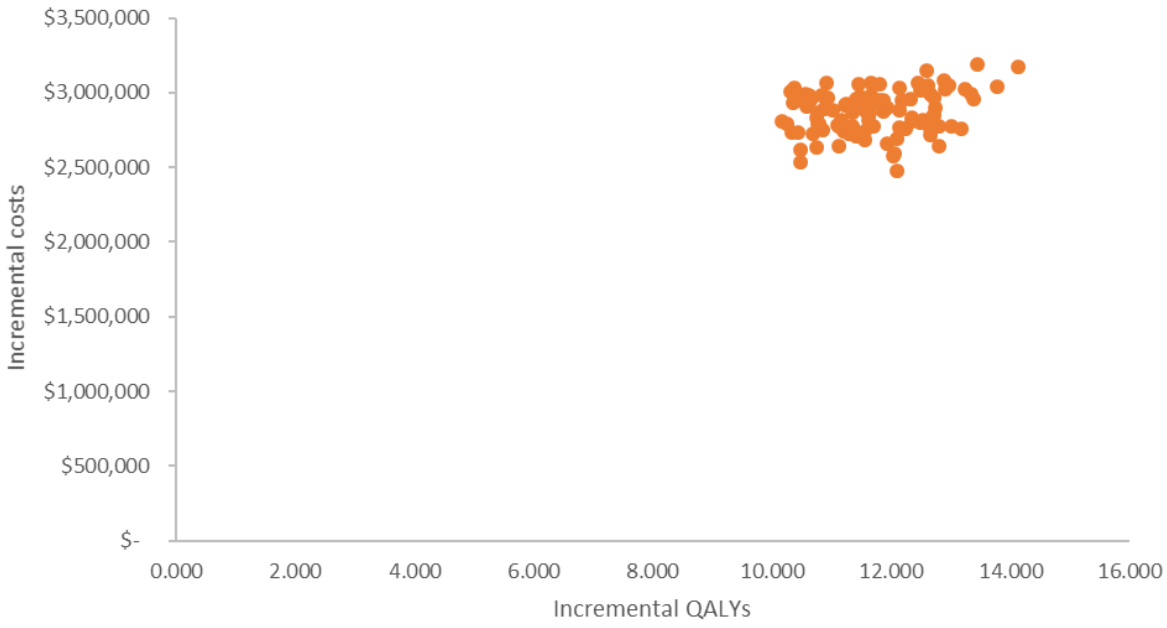
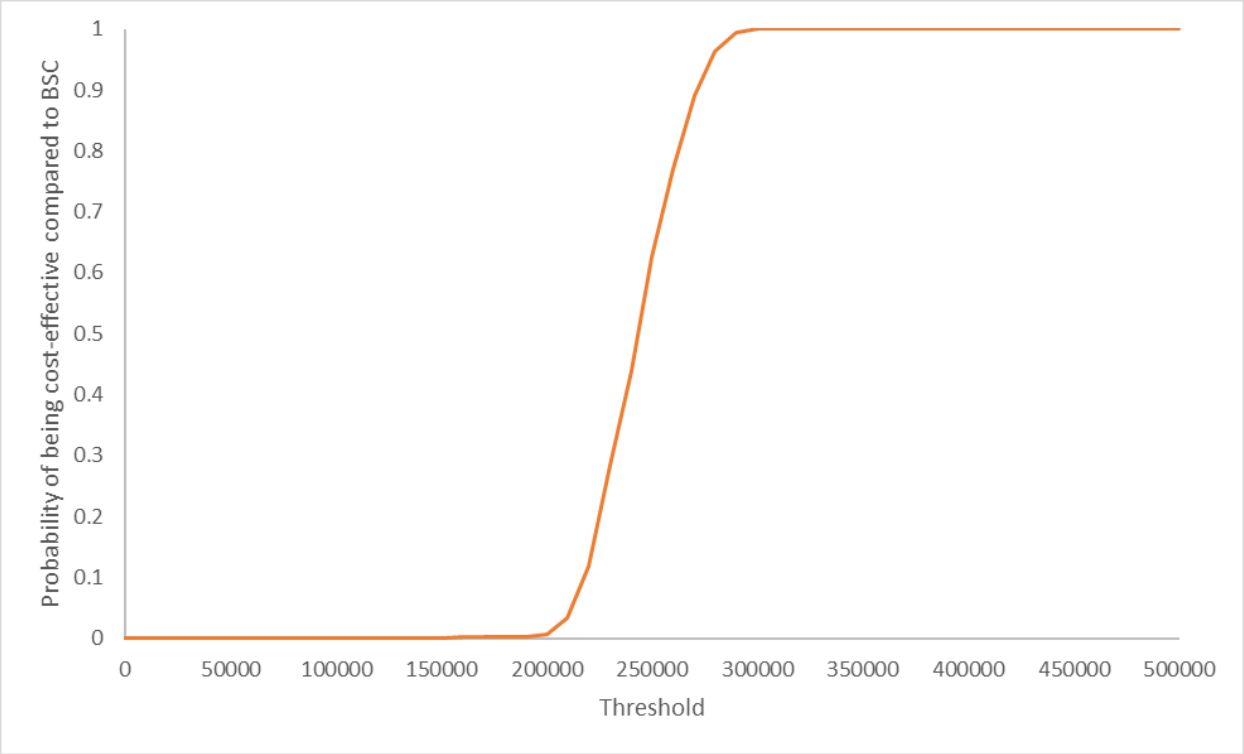


Figure E8 presents the cost-effectiveness acceptability curve for Zolgensma versus BSC in the Type I SMA Model. Zolgensma had a 0.1% chance of being cost effective at a threshold of $150,000 per QALY but 100% chance of being cost-effective at thresholds above $300,000 per QALY gained.

Figure E8. Cost-Effectiveness Acceptability Curve for Zolgensma versus BSC in Infantile-Onset (Type I) SMA Model



Scenario Analyses Results for Type I SMA Model

We performed several scenario analyses to identify the effect of alternative inputs and assumptions on the cost effectiveness results. In scenario analysis #1, we assumed no additional utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. In scenario analysis #2, we used lower health state costs of $10,434 for the "not sitting" health state and $13,135 for the "permanent ventilation" health state. In scenario analysis #3, we used lower utilities of 0.5 for the "sitting" health state and 0.7 for the "walking" health state. In scenario analysis #4, we assumed roughly half the mean survival for the "sitting" and "walking" health states. This led to a mean survival of 15.6 years and 39.65 years for the "sitting" and "walking" health states, respectively. This scenario was implemented using HRs of five and 16 to the survival curves for "sitting" and "walking" health states, respectively. Also, for face validity, we imposed a constraint that the survival in "sitting" health state cannot be greater than "walking" health state.

In scenario analysis #5, we used the assumptions in scenarios #3 and #4 together (i.e., both roughly half the mean survival and lower utilities for the "sitting" and "walking" health states).

Scenario analysis #6 was only relevant to Zolgensma versus BSC, where we assumed that none of the patients in the Zolgensma arm received Spinraza and there was no loss of milestones assumed after the short-term model, as a proxy for receiving Spinraza.

We have also conducted scenario analyses assuming a proportion of the patients in the "sitting" health state would lose their milestones (scenario analyses #7a to #7c). We tested a range of proportions from 10% to 30%. Finally, given the lack of long-term follow up and the optimistic assumptions used in the base-case analysis, we have also conducted analyses for a "pessimistic" scenario, which assumed 30% of the patients in the "sitting" health state lose milestones while also assuming lower survival and utilities for those in the "sitting" health state.

Scenario analysis #8 uses a 10-year time horizon and scenario analysis #9 uses 1.5% discount rate for both costs and QALYs.

Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Health Care Sector Perspective

Here, we assumed no utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. This was implemented in the model as a utility of 0.19 for the "not sitting" health state and a utility of 0.65 for the "sitting" health state for both BSC and treatment arms.

Tables E14 and E15 present the results for the health care sector perspective for this scenario analysis. Table E14 presents the results for Spinraza versus BSC while Table E15 presents results for Zolgensma versus BSC. As expected, the QALY gains in the Spinraza and Zolgensma arms are lower, resulting in higher incremental cost-effectiveness ratios compared to the base-case analyses.

Table E14. Results for Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

						Incremental Results	
	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,231,000	$1,653,000	$3,884,000	2.83	7.64	$1,303,000	$590,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E15. Results for Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,657,000	$3,657,000	11.46	18.17	$261,000	$182,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming Lower Health State Costs for Not Sitting and Permanent Ventilation Health States – Health Care Sector Perspective

Tables E16 and E17 present the results for the health care sector perspective for the scenario analysis assuming lower costs of $10,434 for the "not sitting" health state and $13,135 for the "permanent ventilation" health state. Table E16 presents the results for Spinraza versus BSC while Table E17 presents results for Zolgensma versus BSC.

Table E16. Results for Scenario Analysis Assuming Lower Health State Costs for Not Sitting and Permanent Ventilation – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,231,000	$877,000	$3,108,000	3.24	7.64	$990,000	$525,000
BSC	--	$356,000	$356,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E17. Results for Scenario Analysis Assuming Lower Health State Costs for Not Sitting and Permanent Ventilation – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,271,000	$3,271,000	12.23	18.17	$248,000	$185,000
BSC	--	$356,000	$356,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Health Care Sector Perspective

Tables E18 and E19 present the results for the health care sector perspective for the scenario analysis assuming lower utilities of 0.5 for the "sitting" health state and 0.7 for the "walking" health state. Table E18 presents the results for Spinraza versus BSC while Table E19 presents the results for Zolgensma versus BSC.

Table E18. Results for Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,231,000	$1,653,000	$3,884,000	2.90	7.64	$1,265,000	$590,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E19. Results for Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,657,000	$3,657,000	10.16	18.17	$296,000	$182,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Health Care Sector Perspective

Tables E20 and E21 present the results for the health care sector perspective for the scenario analysis assuming roughly halved mean survival for the "sitting" and "walking" health states, a mean survival of 15.6 years and 39.65 years for the "sitting" and "walking" health states, respectively. This scenario was implemented using HRs of 5 and 16 to the survival curves for "sitting" and "walking" health states, respectively. Also, for face validity, we imposed a constraint that the survival in "sitting" health state cannot be greater than "walking" health state. Table E20 presents the results for Spinraza versus BSC while Table E21 presents the results for Zolgensma versus BSC.

Table E20. Results for Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$1,807,000	$1,564,000	$3,371,000	2.52	6.53	$1,253,000	$624,000
BSC	--	$790,000	$790,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E21. Results for Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,340,000	$3,340,000	8.87	13.34	$303,000	$233,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming Lower Survival and Lower Utility for Sitting and Walking Health States – Health Care Sector Perspective

Tables E22 and E23 present the results for the health care sector perspective for the scenario analysis assuming roughly halved mean survival and lower utilities for the "sitting" and "walking" health states. Table E22 presents the results for Spinraza versus BSC while Table E23 presents the results for Zolgensma versus BSC.

Table E22. Results for Scenario Analysis Assuming Lower Survival and Utilities for Sitting and Walking Health States – Spinraza versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$1,807,000	$1,564,000	$3,371,000	2.29	6.53	$1,407,000	$624,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table E23. Results for Scenario Analysis Assuming Lower Survival and Utilities for Sitting and Walking Health States – Zolgensma versus BSC for Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,340,000	$3,340,000	7.34	13.34	$371,000	$233,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Using No Loss of Milestones in Zolgensma as a Proxy for Spinraza Follow-On Therapy – Health Care Sector Perspective

In this scenario, no patients in the Zolgensma arm were assumed to drop any milestones. This is to understand the effect of dropping the assumption made in the base-case analyses that 16.7% in the "sitting" health state drop a milestone, as a proxy for receiving Spinraza add-on therapy. Table E24 presents the results for the health care sector perspective for this scenario analysis.

Table E24. Results for Scenario Analysis Assuming No Loss of Milestones in Zolgensma as a Proxy for Spinraza Follow-On Therapy: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,655,000	$3,655,000	13.46	19.76	$220,000	$165,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Placeholder price.

Scenario Analysis Assuming 10% Loss of Milestones in "Sitting" Health State for Spinraza versus BSC in Type I SMA – Health Care Sector Perspective

In this scenario, 10% of the patients in the "sitting" health state of the Spinraza arm were assumed to drop a milestone. This scenario was only performed for Spinraza as the base-case analyses for Zolgensma already assumes 16.7% of the patients in the "sitting" state lose a milestone at the end of the short term model. Table E25 presents the results for the health care sector perspective for this scenario analysis comparing Spinraza to BSC.

Table E25. Assuming 10% of Patients in the "Sitting" Health State Lose Milestone at the End of the Short-Term Model for Spinraza versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,114,000	$1,652,000	$3,766,000	3.06	7.41	$1,143,000	$593,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

Scenario Analysis Assuming 20% Loss of Milestones in "Sitting" Health State for Spinraza versus BSC in Type I SMA – Health Care Sector Perspective

In this scenario, 20% of the patients in the "sitting" health state of the Spinraza arm were assumed to drop in milestones. Table E26 presents the results for the health care sector perspective for this scenario analysis.

Table E26. Assuming 20% of Patients in the "Sitting" Health State Lose Milestone at the End of the Short-Term Model for Spinraza versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$1,996,000	$1,652,000	$3,648,000	2.88	7.18	$1,178,000	$597,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

Scenario Analysis Assuming 20% Loss of Milestones in "Sitting" Health State for Zolgensma versus BSC in Type I – Health Care Sector Perspective

In this scenario, 20% of the patients in the "sitting" health state of the Zolgensma arm were assumed to drop in milestones. Table E27 presents the results for the health care sector perspective for this scenario analysis.

Table E27. Assuming 20% of Patients in the "Sitting" Health State Lose Milestone at the End of the Short-Term Model for Zolgensma versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,658,000	$3,658,000	11.99	17.85	$249,000	$186,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

*Placeholder price.

Scenario Analysis Assuming 30% Loss of Milestones in "Sitting" Health State for Spinraza versus BSC in Type I – Health Care Sector Perspective

In this scenario, 30% of the patients in the "sitting" health state of the Spinraza arm are assumed to drop in milestones. Table E28 presents the results for the health care sector perspective for this scenario analysis.

Table E28. Assuming 30% of Patients in the "Sitting" Lose Milestone at the End of the Short-Term Model for Spinraza versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$1,879,000	$1,651,000	$3,530,000	2.70	6.95	$1,218,000	$601,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

Scenario Analysis Assuming 30% Loss of Milestones in "Sitting" Health State for Zolgensma versus BSC in Type I – Health Care Sector Perspective

In this scenario, 30% of the patients in the "sitting" health state of the Zolgensma arm are assumed to drop in milestones. Table E29 presents the results for the health care sector perspective for this scenario analysis.

Table E29. Assuming 30% of Patients in the "Sitting" Lose Milestone at the End of the Short-Term Model for Zolgensma versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,659,000	$3,659,000	11.25	16.90	$266,000	$198,000
BSC	--	$790,000	$790,000	0.46	2.40	--	--

*Placeholder price.

Pessimistic Scenario Analysis Assuming 30% Loss of Milestones in "Sitting" Health State and Assuming Lower Survival and Utilities for Sitting Health States for Spinraza versus BSC in Type I SMA – Health Care Sector Perspective

Given the lack of long-term follow up and the optimistic assumptions used in the base-case analysis, we also conducted a "pessimistic scenario," which assumes 30% of patients in the "sitting" health state lose milestones as well as lower survival and utilities for those in the "sitting" health states. Although the assumptions about "walking" health state are changed to ensure consistency with the scenario analysis in Zolgensma arm, they do not affect the results as there are no patients in the "walking" health state in the Spinraza arm. Table E30 presents the results for the health care sector perspective for this scenario analysis. Note that this pessimistic scenario still includes the utility benefit in the treatment arms for achieving interim milestones.

Table E30. Pessimistic Scenario assuming 30% of Patients in the "Sitting" Health State Lose Milestone at the End of the Short-Term Model and Assuming Lower Utilities and Lower Survival for "Sitting" and "Walking" Health States for Spinraza versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$1,582,000	$1,589,000	$3,171,000	2.03	6.18	$1,509,000	$630,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

Table E31 presents the results for the health care sector perspective for this scenario analysis for Zolgensma versus BSC.

Table E31. Pessimistic Scenario assuming 30% of Patients in the "Sitting" Health State Lose Milestone at the End of the Short-Term Model and Assuming Lower Utilities and Lower Survival for "Sitting" and "Walking" Health States for Zolgensma versus BSC in Type I SMA

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,387,000	$3,387,000	6.85	12.67	$406,000	$253,000
BSC	--	$789,000	$789,000	0.46	2.40	--	--

*Placeholder price.

Scenario Analysis Using 10-Year Time Horizon – Health Care Sector Perspective

Tables E32 and E33 present the results for the health care sector perspective for the scenario analysis using a 10-year time horizon. Table E32 presents the results for Spinraza versus BSC while Table E33 presents the results for Zolgensma versus BSC.

Table E32. Using a 10-Year Time Horizon for Spinraza versus BSC in Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$1,484,000	$1,338,000	$2,822,000	1.85	5.21	$1,460,000	$700,000
BSC	--	$727,000	$727,000	0.42	2.21	--	--

Table E30 presents the results for the health care sector perspective for this scenario analysis for Zolgensma versus BSC.

Table E33. Using a 10-Year Time Horizon for Zolgensma versus BSC in Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,005,000	$3,005,000	4.76	7.91	$525,000	$400,000
BSC	--	$727,000	$727,000	0.42	2.21	--	--

*Placeholder price.

Scenario Analysis Using 1.5% Discounting for Costs and QALYs – Health Care Sector Perspective

Tables E34 and E35 present the results for the health care sector perspective for the scenario analysis using 1.5% discounting for both costs and QALYs. Table E34 presents the results for Spinraza versus BSC while Table E35 presents the results for Zolgensma versus BSC.

Table E34. Using 1.5% Discounting for Spinraza versus BSC in Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,549,000	$1,818,000	$4,368,000	3.84	8.77	$1,052,000	$566,000
BSC	--	$834,000	$834,000	0.48	2.53	--	--

Table E35 presents the results for the health care sector perspective for this scenario analysis for Zolgensma versus BSC.

Table E35. Using 1.5% Discounting for Zolgensma versus BSC in Type I SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,976,000	$3,976,000	16.29	23.62	$199,000	$149,000
BSC	--	$834,000	$834,000	0.48	2.53	--	--

*Placeholder price.

Later-Onset SMA Model

In the later-onset SMA model, based on the CHERISH trial data, all patients are assumed to be in the "sitting" health state. As such, no breakdown of the costs, LYs, and QALYs by health state is provided.

Scenario Analyses Results – Later Onset SMA Model

Scenario Analysis Assuming Further Utility Benefits for Interim Milestones – Health Care Sector Perspective

This scenario included further utility benefits in the Spinraza arm for achieving interim milestones such as standing, walking with assistance, etc. This was implemented in the model as a utility of 0.7 for the "sitting" health state for the Spinraza arm (i.e., an additional utility of 0.1 compared to BSC).

Table E36 presents the results for the health care sector perspective for this scenario analysis. As expected, the QALY gains in the Spinraza arm were higher, resulting in a more favorable cost-effectiveness ratio compared to base-case analyses.

Table E36. Results for Scenario Analysis Assuming Further Utility Benefits for Interim Milestones – Spinraza versus BSC for Later Onset SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$7,634,000	$1,514,000	$9,148,000	13.23	18.90	$4,078,000	Dominated
BSC	--	$1,442,000	$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Stopping Spinraza after Two Years – Health Care Sector Perspective

Here, we assumed that the Spinraza treatment was stopped after two years. We also assumed a utility benefit (as in the base case) for achieving interim milestones in the Spinraza arm (i.e., utility of 0.65 for the "sitting" health state in the Spinraza arm, and an additional utility of 0.05 compared to BSC). Table E37 presents the results for the health care sector perspective for this scenario analysis. As expected, the treatment costs in the Spinraza arm were lower, resulting in more favorable cost-effectiveness ratios compared to base-case analyses.

Table E37. Results for Scenario Analysis Assuming stopping Spinraza after Two Years and Utility Benefits for Interim Milestones – Spinraza versus BSC for Later Onset SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$1,127,000	$1,452,000	$2,579,000	12.28	18.90	$1,204,000	Dominated
BSC	--	$1,442,000	$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Health Care Sector Perspective

Here, we assumed no additional utility benefits in the treatment arms for achieving interim milestones such as standing, crawling, etc. This was implemented in the model as a utility of 0.65 for the "sitting" health state for the Spinraza and the BSC arms. Table E38 presents the results for the health care sector perspective for this scenario analysis. As expected, the QALYs in the Spinraza arm and BSC arm are the same, resulting in Spinraza being dominated.

Table E38. Results for Scenario Analysis Assuming Further Utility Benefits for Interim Milestones – Spinraza versus BSC for Later Onset SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$7,634,000	$1,514,000	$9,148,000	11.34	18.90	Dominated	Dominated
BSC	--	$1,442,000	$1,442,000	11.34	18.90	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Presymptomatic SMA Model

Breakdown of the Presymptomatic SMA Model Results

The breakdown of LYs according to health state for the different interventions are presented below in Table E39. As can be observed, a majority of the LYs gained were in the "sitting" and the "walking" health states. This was because of the longer survival associated with these health states compared to "not sitting" and "permanent ventilation" states (see Figure 4.3).

In the BSC arm, as the baseline population included 30% of patients who have SMA Type II (i.e., patients in the "sitting" state) and 10% of patients who have SMA Type III (i.e., patients with survival similar to general population), this was where the majority of LYs were accrued in the BSC

arm (8.79 LYs and 7.87 LYs in the "sitting" and "walking" health states, respectively). In the Spinraza arm, a majority of the patients were in the walking state at the end of the short term model, which was where the majority of LYs were accrued (52.9 LYs, as the model assumed that those in the walking state had general population mortality).

Table E39. Breakdown of the LYs by Health State in Presymptomatic SMA Model

Undiscounted LYs	Permanent Ventilation	Not Sitting	Sitting	Walking	Total Undiscounted LYs
BSC	0.49	0.42	8.78	7.87	17.55
Spinraza	0.00	0.63	9.74	52.91	63.28

BSC: best supportive care, LY: life-year

The breakdown of discounted LYs and QALYs according to health state for the different interventions are presented below in Tables E40 and E41. These results followed the same pattern as Table E39, but the absolute numbers are lower due to discounting (for discounted LYs) and the use of QoL weights (see Table 4.5) for discounted QALYs. The utilities increased as patients achieved milestones, and the majority of the QALYs for the BSC arm were accrued by the 30% of patients in the "sitting" state, while in the Spinraza arm, a majority of the QALYs were from the patients who are in the "walking" state.

Table E40. Discounted LYs by Health State in the Presymptomatic SMA Model

Discounted LYs Gained	Ventilated	Not Sitting	Sitting	Walking	Total Discounted LYs
BSC	0.46	0.41	5.64	3.00	9.51
Spinraza	0.00	0.63	6.35	19.61	26.58

LY: life-year

Table E41. Discounted QALYs by Health State in the Presymptomatic SMA Model

Discounted QALYs Gained	Ventilated	Not Sitting	Sitting	Walking	Total Discounted QALYs
BSC	0.09	0.08	3.39	2.70	6.25
Spinraza	0.00	0.18	4.12	17.63	21.94

QALY: quality adjusted life-year

The breakdown of the discounted costs according to health state for the different interventions is presented below in Table E42. The costs are presented separately for treatment, administration costs and non-treatment health care.

BSC costs are solely the health care costs associated with patients being in a given health state. The majority of the costs were accrued by patients in the "sitting" state. For Spinraza, as seen in Table E38, treatment costs made up the majority of overall costs. In the Spinraza arm, the treatment costs were broadly proportional to the LYs gained in each health state, because the model assumed that patients are on Spinraza treatment for the entire life time. The discontinuation rule did not apply here, as all patients are in "sitting" or "walking" states.

In the Spinraza arm, the patients in the "sitting" and "walking" health states had higher LYs and accrue further costs, even though the costs associated with those health states ($6,357 and $2,499 per month, respectively) were lower than costs associated with "not sitting" and "permanent ventilation" health states ($25,517 and $28,218 per month).

Table E42. Discounted Costs by Health State

Treatment Costs	Ventilated	Not Sitting	Sitting	Walking	Total
BSC	--	--	--	--	--
Spinraza	--	$665,506	$2,413,760	$7,488,868	$10,568,134
Administration Costs	**Ventilated**	**Not sitting**	**Sitting**	**Walking**	**Total**
BSC	--	--	--	--	--
Spinraza	--	$6,311	$22,889	$71,014	$100,214
Health Care Costs	**Ventilated**	**Not sitting**	**Sitting**	**Walking**	**Total**
BSC	$155,387	$125,487	$430,424	$89,843	$801,140
Spinraza	--	$191,725	$484,022	$587,986	$1,263,733

Probabilistic Sensitivity Analyses Results for Presymptomatic SMA Model

This panel presents cost-effectiveness clouds from the probabilistic sensitivity analysis (PSA) for Spinraza versus BSC in the presymptomatic SMA Model. Due to lack of data, the distributions used for costs and utilities in the PSA are mean values ±20%. As such, the true uncertainty is likely to be more than that represented in our probabilistic analyses. Figure E9 presents the cost-effectiveness clouds (i.e., the scatterplot of incremental costs vs. incremental QALYs) for Spinraza versus BSC in the presymptomatic SMA Model.

Figure E9. Cost-Effectiveness Clouds for Spinraza versus BSC in Presymptomatic SMA Model

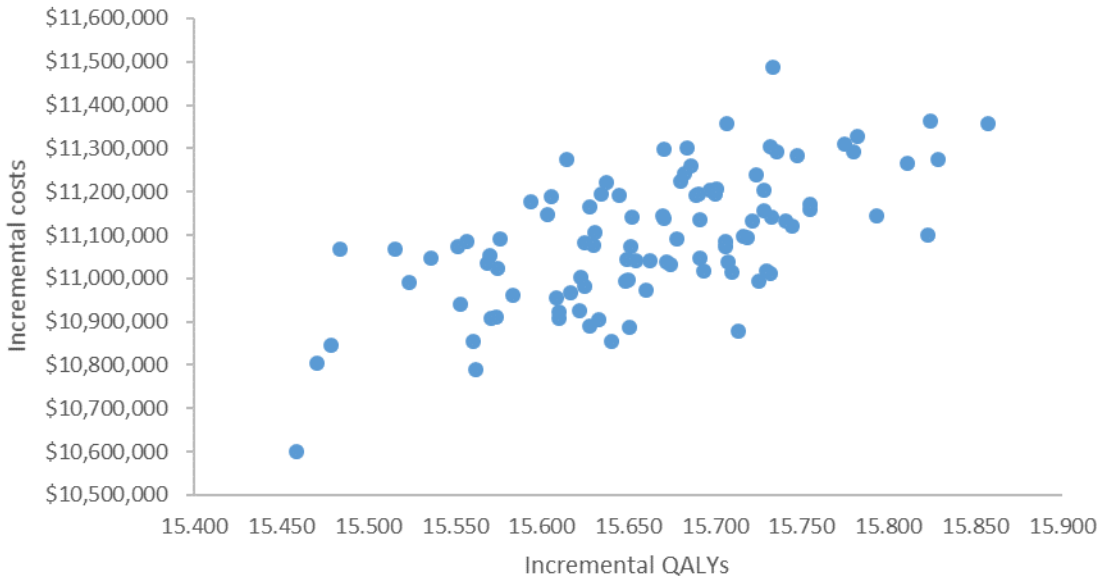
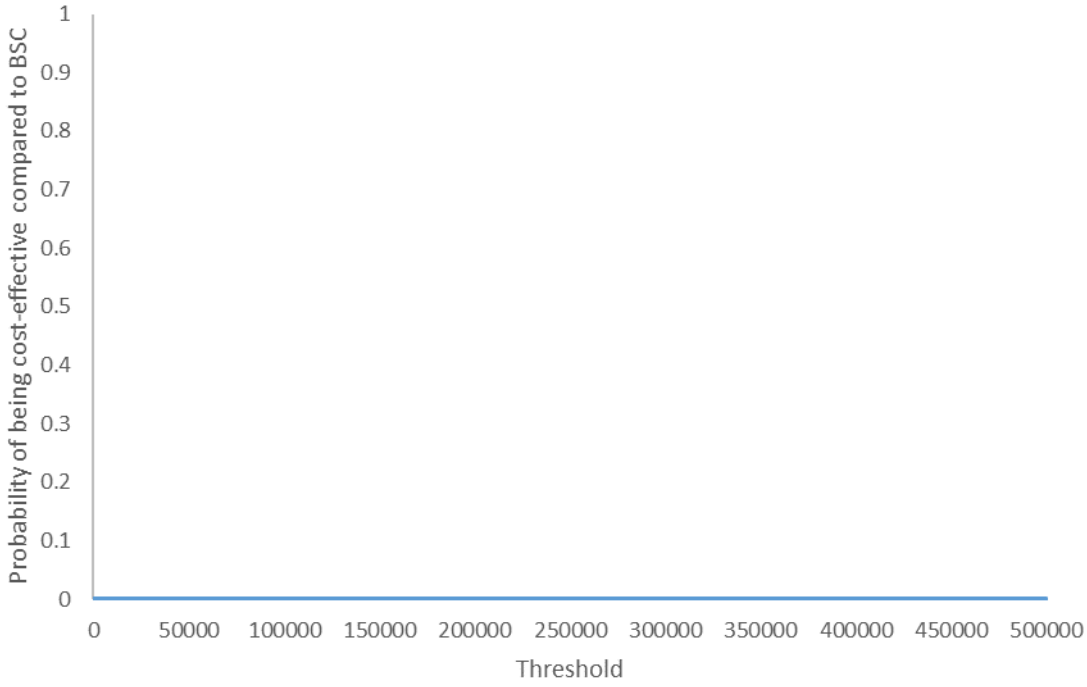


Figure E10 below presents the cost-effectiveness acceptability curve for Spinraza versus BSC in the presymptomatic SMA Model. Spinraza had zero likelihood of being cost-effective at thresholds less than $500,000 per QALY.

Figure E10. Cost-Effectiveness Acceptability Curve for Spinraza versus BSC in Presymptomatic SMA Model



Scenario Analyses Results for Presymptomatic SMA Model

We performed a number of scenario analyses to identify the effect of alternative inputs and assumptions on the cost effectiveness results.

In scenario analysis #1, we assumed no additional utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc.

In scenario analysis #2, we used lower health state costs of $10,434 for the "not sitting" health state and $13,135 for the "permanent ventilation" health state.

In scenario analysis #3, we used lower utilities of 0.5 for the "sitting" health state and 0.7 for the "walking" health state.

In scenario analysis #4, we assumed roughly half the mean survival for the "sitting" and "walking" health states. This led to a mean survival of 15.6 years and 39.65 years for the "sitting" and "walking" health states, respectively. This scenario was implemented using HRs of 5 and 16 to the

survival curves for "sitting" and "walking" health states, respectively. Also, for face validity, we imposed a constraint that the survival in "sitting" health state cannot be greater than "walking" health state.

In scenario analysis #5, we used the assumptions in scenarios #3 and #4 together (i.e., both roughly half the mean survival and lower utilities for the "sitting" and "walking" health states).

In Scenario analysis #6, we use a 10-year time horizon and in scenario analysis #7 we use 1.5% discount rate for both costs and QALYs.

Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Health Care Sector Perspective

Here, we assumed no utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. This was implemented in the model as a utility of 0.19 for the "not sitting" health state and a utility of 0.6 for the "sitting" health state in both the BSC and Spinraza arms.

Table E43 presents the results for the health care sector perspective for this scenario analysis. As expected, the QALY gains in the Spinraza arm were lower, resulting in less favorable cost effectiveness ratios compared to base-case analyses.

Table E43. Results for Scenario Analysis Assuming No Utility Benefits for Interim Milestones – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$10,568,000	$1,364,000	$11,932,000	21.56	26.58	$727,000	$652,000
BSC	--	$801,000	$801,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Lower Health State Costs for Not Sitting and Permanent Ventilation Health States – Health Care Sector Perspective

Table E44 presents the results for Spinraza versus BSC using the health care sector perspective for the scenario analysis assuming lower costs of $10,434 for the "not sitting" health state and $13,135 for the "permanent ventilation" health state.

Table E44. Results for Scenario Analysis Assuming Lower Health State Costs for Not Sitting – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$10,568,000	$1,251,000	$11,819,000	21.94	26.58	$712,000	$655,000
BSC	--	$644,000	$644,000	6.25	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Health Care Sector Perspective

Table E45 presents the results for the health care sector perspective for the scenario analysis assuming lower utilities of 0.5 for the "sitting" health state and 0.7 for the "walking" health state.

Table E45. Results for Scenario Analysis Assuming Lower Utilities for Sitting and Walking Health States – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$10,568,000	$1,364,000	$11,932,000	17.40	26.58	$904,000	$652,000
BSC	--	$801,000	$801,000	5.08	9.51	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Health Care Sector Perspective

Table E46 presents the results for the health care sector perspective for the scenario analysis assuming roughly halved mean survival for "sitting" and "walking" health states. That resulted in a mean survival of 15.6 years and 39.65 years for the "sitting" and "walking" health states, respectively. This scenario was implemented using HRs of 5 and 16 to the survival curves for "sitting" and "walking" health states, respectively. Also, for face validity, we imposed a constraint that the survival in "sitting" health state cannot be greater than "walking" health state. As such, there high mortality in the first couple of years in the "sitting" and "walking" health states in the BSC arm as it uses the survival curves directly (due to lack of short-term data on these presymptomatic patients without treatment). However, as we use short-term data from NURTURE in the Spinraza arm, there is a survival advantage biased towards Spinraza. And as such, the ICER is lower in this analysis although the absolute QALY gains are lower.

Table E46. Results for Scenario Analysis Assuming Lower Survival for Sitting and Walking Health States – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$8,126,000	$1,061,000	$9,187,000	16.89	20.19	$678,000	$628,000
BSC	--	$615,000	$615,000	4.24	6.55	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Assuming Lower Survival and Lower Utility for Sitting and Walking Health States – Health Care Sector Perspective

Table E47 presents the results for the health care sector perspective for the scenario analysis assuming roughly halved mean survival and lower utilities for the "sitting" and "walking" health states, respectively.

Table E47. Results for Scenario Analysis Assuming Lower Survival and Utilities for Sitting and Walking Health States – Spinraza versus BSC for Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$8,126,000	$1,061,000	$9,187,000	13.21	20.19	$877,000	$628,000
BSC	--	$615,000	$615,000	3.43	6.55	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Scenario Analysis Using 10-Year Time Horizon – Health Care Sector Perspective

Tables E48 presents the results for the health care sector perspective for the scenario analysis using a 10-year time horizon.

Table E48. Using a 10-Year Time Horizon for Spinraza versus BSC in Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$3,685,000	$605,000	$4,290,000	6.74	8.62	$890,000	$870,000
BSC	--	$500,000	$500,000	2.48	4.27	--	--

Scenario Analysis Using 1.5% Discounting for Costs and QALYs – Health Care Sector Perspective

Tables E49 presents the results for the health care sector perspective for the scenario analysis using 1.5% discounting for both costs and QALYs.

Table E49. Using 1.5% Discounting for Spinraza versus BSC in in Presymptomatic SMA: Health Care Sector Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$15,203,000	$1,837,000	$17,040,000	32.08	38.69	$679,000	$612,000
BSC	--	$953,000	$953,000	8.38	12.39	--	--

Supplemental Table

Table E50. Age of Motor Milestone Achievements in CL-101

Subject	Cohort	Age at Infusion (months)	Age Sit 5sec (months)	Age: Walk Alone (months)
E04	2	5.6	27.4	
E05	2	4.2	21.6	
E06	2	1.9	8.0	23.2
E07	2	3.6	22.7	
E08	2	7.9		
E09	2	4.9	17.9	
E10	2	0.9	8.2	16.3
E11	2	2.3	17.6	
E12	2	2.6	11.9	
E13	2	0.9	13.0	
E14	2	4.1	20.6	
E15	2	2.1	20.5	

Appendix F. Supportive Care Clinical Guidelines

Cure SMA Working Group

Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening (2018)[107]

In its 2018 treatment algorithm, the working group stresses the need for early intervention through newborn screening to maximize the benefit of treatment. The group recommends the development of dependable and validated screening techniques to enable treatment of presymptomatic patients who may be more responsive to treatment than those already experiencing symptoms. For patients with SMA Types II or III with three or fewer copies of the *SMN2* gene, the group recommends immediate treatment with a disease modifying therapy and referral to both a neuromuscular specialist and a geneticist; for those with only one copy of *SMN2* who are symptomatic at birth, the group states that the attending physician should determine whether the patient and family would benefit from treatment. Lastly, patients with four copies of *SMN2* should be screened periodically for symptoms and referred to a geneticist to determine the exact number of *SMN2* copies, but the working group recommends against immediate treatment with a disease modifying therapy.

The working group offers further recommendations for patients with four or more copies of *SMN2* who are not immediately treated with a disease modifying therapy. Overall, the group states that the clinical judgment of the physician, as well as the patient and family's wishes, should be the overarching factor in determining treatment. Ideally, the patient should meet every three to six months with a neuromuscular specialist to assess disease progress; once the patient reaches two years of age, visits can occur every six to twelve months. Follow-up assessments should include electromyography, compound muscular action potential monitory, and myometry.

Working Group on Behalf of SMA Care Group

Diagnosis and Management of Spinal Muscular Atrophy: Part 1: Recommendations for Diagnosis, Rehabilitation, Orthopedic and Nutritional Care (2017)[18]

The International Conference on the Standard of Care for SMA published a consensus statement in 2007; in 2017, the group issued this update to the previous statement. In the new consensus statement, the group recommends genetic testing of *SMN1* and *SMN2* as the first line of examination when SMA is suspected. Testing of *SMN2* should be conducted primarily to determine the severity of the condition. If a diagnosis is confirmed, the patient and family should be referred to a genetic counselor, and in many cases, the family should be offered psychological support. Further, the group recommends a multidisciplinary approach to care, and advises that all specialist

visits and assessments should be arranged by a neurologist familiar with the disease. A collaborative approach allows physicians and families to be proactive in patient care, which may positively influence disease trajectory. After diagnosis and every six months thereafter, the patient should undergo a physical examination to determine whether or to what degree musculoskeletal and functional impairments are present. This examination should focus primarily on motor function that may affect daily life.

The group offers separate recommendations for patients who are able to sit and for those who are not, but overall emphasizes that regular physical therapy is important to influencing the trajectory of disease. For sitters, the aim of physical therapy is to prevent contractures and scoliosis, and to maintain or restore motor function. For non-sitters, the group notes that the techniques may vary based on disease severity, but should include stretching and positioning exercises. The group recommends power wheelchairs, adapted seating systems, and assistive technology for both sitters and non-sitters. Prophylactic chest physiotherapy to promote airway clearance and ventilation is essential for both sitters and non-sitters. All patients with SMA should be assessed regularly by a nutritionist to promote growth and an appropriate diet that encourages a healthy weight and sufficient fluid, macronutrient, and micronutrient intake. Patients with SMA often experience gastrointestinal complications, and as such, should be monitored for symptoms. The group recommends swallowing studies for both sitters and non-sitters, and continued periodic nutritional evaluations.

Diagnosis and Management of Spinal Muscular Atrophy: Part 2: Pulmonary and Acute Care; Medications, Supplements and Immunizations; Other Organ Systems; and Ethics (2017)[17]

In the second half of the updated consensus statement, the working group offers further recommendations for patients with SMA. For both sitters and non-sitters, the group recommends clinic visits with physical examinations (every six months for sitters and every three months for non-sitters), airway clearance techniques (manual chest physiotherapy, mechanical insufflation-exsufflation, and oral suctioning devices), and positive pressure ventilation to prevent respiratory failure. Lastly, other preventive measures, such as immunizations against influenza, pneumococcus, and other respiratory viruses should be taken.

Appendix G. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on March 7, 2019 in Boston, MA. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. One speaker did not submit a summary of their public comments.

A video recording of all comments can be found here, beginning at 1:19:14. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Khrystal K. Davis, TX Rare
President

As the parent of a seven-year-old child with SMA Type 1, I understand access to approved therapies is essential. Absent treatment SMA is a relentless disease that continues to take until it robs the very last breath.

Before Hunter began treatments under the EAP, he had lengthy and expensive hospital stays. When Hunter was emergently intubated and admitted my husband was in India for business. My husband flew home to be with us during the medical crisis missing business opportunities and work, which impacted the company. The QUALY measure and ICER value fail to capture these significant economic impacts. Since beginning Spinraza treatments, Hunter has not been hospitalized.

We've seen little impact relating to Spinraza treatments and insurance. Our company continues to receive 80/20 rule letters and returned premiums.

The FDA approved Spinraza for all SMA patients. Insurance policies routinely deny access to the weakest patients. We cannot exclude these patients from trials and deny them access due to lack of data. We must ensure equity of access to treatments.

Medical services cost increases outpace those of pharmaceutical costs despite innovative therapies approved for rare diseases. Patients are provided access to medical services to treat acute medical situations caused by their conditions. They have a much harder time accessing treatments to avoid severe medical crises.

Presymptomatic diagnosis and treatment will allow SMA babies the opportunity to run, walk, and play freely with their friends instead of being tethered to lifesaving equipment that moves, feeds, and breathes for them.

No conflicts of interest to disclose.

Mary Schroth, MD, Cure SMA
Chief Medical Officer

At Cure SMA, we advocate for the patient voice to be included and be the primary factor in decisions about treatment and care. Each individual and family should choose for themselves the treatment that best fits their unique goals, needs, and challenges.

ICER Report response:

1. Non sitting survival
   The assumptions used for the non-sitting health status modeling incorrectly gave lesser outcomes to the treated and improved non-sitting group that were associated with a completely different natural history group. The survival rates for this treated and interim milestone attaining non-sitter group should be positioned between permanent ventilation and sitters.

2. QALY
   The ICER analysis benchmark of $150,000 per QALY does not reflect the unique challenges and opportunities associated with an ultra-rare condition like SMA, as stated by ICER previously, nor the severity of the disease and the impact of new therapies on the disease natural history. For SMA, the benchmark of $500,000 per QALY should be highlighted and shown in conclusions and all public statements.

3. Discounting Life Years
   For a fatal pediatric disease such as SMA, that now has transformative and impactful treatments which may extend life dramatically, the ICER model of financially discounting life years is flawed. Scenarios where life years are not discounted should be shown and highlighted.

4. Clinical Trials
   Although ICER frequently cited “controversies” in the clinical data, these are actually just the usual future uncertainties typical from all clinical trials. We encourage ICER to avoid creating and bringing controversies into the collaborative SMA community.

Cure SMA receives more than 25% of its funding from health care companies.

Douglas Sproule, MD, MSc, AveXis
Vice President, Spinal Muscular Atrophy Therapeutic Area Head

Introduction of one-time gene therapies require redefining the value of treatments for patients with ultra-rare diseases.

ICER found ZOLGENSMA® to be cost-effective up to $5 million at the ultra-rare disease threshold of $500,000 per QALY and up to $7 million when using life-years gained compared to best supportive care. Multiple experts—including NICE, CureSMA, and the Muscular Dystrophy Association—have recommended higher-than-standard QALY thresholds for ultra-rare diseases. We feel strongly that traditional measures do not adequately evaluate rare disease treatments, particularly those delivered in a single administration and we support ICER's ongoing work to guide value-based pricing of potential cures.

ICER's review has elevated discussion around the significant medical, economic, and societal burdens faced by families affected by SMA. We are grateful to the families and advocates who provided personal insights into the pain, fear, and frustrations of this disease to better inform ICER's analysis. We continue to focus on what matters most: delivering therapies with the potential to save the lives of babies born with SMA Type 1–the leading genetic cause of infant death.

The chronic, lifetime treatment of ultra-rare disease can cost the healthcare system tens of millions of dollars. AveXis is challenging this paradigm with the introduction of one-time gene therapies, including ZOLGENSMA. We are exploring risk-sharing and pay-over-time options with payors, and meaningful ways to enable access and affordability for families. We encourage ICER to identify better ways to recognize the value that groundbreaking gene therapies like ZOLGENSMA will provide to families impacted by SMA.

Jonathan Yong, MD, Biogen
Head of Neuromuscular Therapy Area, Global Medical Affairs

Biogen is a pioneer and world leader in the neurosciences. Through our collaborations with the SMA community we have learned critical lessons which have informed our feedback to ICER on its assessment. Biogen would like to highlight three areas of concern:

First, ICER's evaluation of SPINRAZA and ZOLGENSMA does not take into account the substantial differences between the available data for each therapy. ICER also does not make an effort to adjust for these baseline characteristics or differences in the certainty of the data supporting the respective treatments. ICER's approach for evaluating ZOLGENSMA today could unfortunately create an incentive for manufacturers to generate less robust data at the time of regulatory submission. At the same time, in assigning similar ratings to the two therapies, ICER has failed to acknowledge the robustness of SPINRAZA's credible data package.

Second, Biogen believes that ICER underestimates the long-term costs of treating patients with ZOLGENSMA, since ICER has not accounted for some patients in the CL-101 study who also received SPINRAZA in the extension study.

Finally, the ICER report contrasts sharply with the outcomes of numerous HTA assessments globally. The ICER evaluation fails to capture the real-world value experienced by SMA patients, especially in the later-onset patient population. Specifically, ICER's QALYs for SPINRAZA in later-onset patients differ drastically from many global HTA assessments, including a recent peer-reviewed, published cost-effectiveness study that found an incremental QALY gain of 9.54 for SPINRAZA, whereas the incremental QALY gain was less than 1 in the ICER report.

Appendix H. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the March 7, 2019 Public meeting of the New England CEPAC.

Table H1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Laura Cianciolo, BA	ICER	*
Alexandra Ellis, PhD, MSc, AM	ICER	*
Sarah K. Emond, MPP	ICER	*
Serina Herron-Smith, BA	ICER	*
Catherine Koola, MPH	ICER	*
Varun Kumar, MBBS, MPH, MSc	ICER	*
Steve Pearson, MD, MSc	ICER	*
David Rind, MD, MSc	ICER	*
Matt Seidner, BS	ICER	*
Matt Stevenson, PhD, BSc	University of Sheffield	*
Praveen Thokala, MASc, PhD	University of Sheffield	*
Dave Whitrap, BA, BES	ICER	*

*No conflicts of interest to disclose, defined as individual health care stock ownership in any health plan or pharmaceutical, biotechnology, or medical device manufacturers, or any health care consultant income or honoraria from health plans or manufacturers.

Table H2. New England CEPAC COI Disclosures

Name	Organization	Disclosures
Robert Aseltine, Jr., PhD	UConn Health	*
Stacey L. Brown, PhD	University of Connecticut School of Medicine	*
Austin Frakt, PhD	Boston University School of Medicine and School of Public Health	*
Marthe Gold, MD, MPH	New York Academy of Medicine	*
Claudia B. Gruss, MD, FACP, FACG	Private Practice	*
Christopher Jones, PhD	University of Vermont Health Network	*
Stephen Kogut, PhD, MBA, RPh	University of Rhode Island College of Pharmacy	*
Kimberly Lenz, PharmD (ex-officio)	MassHealth	*
Stephanie Nichols, PharmD, BCPS, BCPP, FCCP	Husson University	*
Brian O'Sullivan, MD	Geisel School of Medicine at Dartmouth College	*
Jeanne Ryer, MSc, EdD	New Hampshire Citizens Health Initiative	*
Jason Wasfy, MD, MPhil	Massachusetts General Hospital	*
Rev. Albert Whitaker, MA	American Diabetes Association	*

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table H3. Policy Roundtable Participant COI Disclosures

Name	Title and Organization	COI Declaration
Brandi Akins	Patient Advocate	Served as a paid moderator (<$5,000) for a focus group of caregivers of children with Type I SMA for AveXis.
Emma Ciafaloni, MD, FAAN	Professor of Neurology, University of Rochester	Served as paid consultant in advisory boards for AveXis, Biogen, PTC, Santhera, and Sarepta; member of DSMB for AveXis SMA gene therapy trials; chair of Sarepta Duchenne muscular dystrophy gene therapy trials.
Chris Leibman, PharmD, MS	Senior Vice President, Value and Access, Biogen	Full-time employee of Biogen.
David Michelson, MD	Pediatric Neurologist, Loma Linda University Health	None declared.
Erik Schindler, PharmD	Clinical Pharmacy Manager, UnitedHealthcare	Full-time employee of UnitedHealthcare.
Mary Schroth, MD	Chief Medical Officer, Cure SMA	Cure SMA receives more than 25% of its funding from health care companies.
Douglas Sproule, MD, MSc	Vice President, Spinal Muscular Atrophy Therapeutic Area Head, AveXis	Full-time employee of AveXis.
Danyelle Sun	Patient Advocate	Board member for Cure SMA, an organization that receives more than 25% of its funding from health care companies.
John Watkins, PharmD, MPh, BCPS	Pharmacy Manager, Formulary Development, Premera Blue Cross	Full-time employee of Premera Blue Cross.