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

Public Meeting – March 7, 2019

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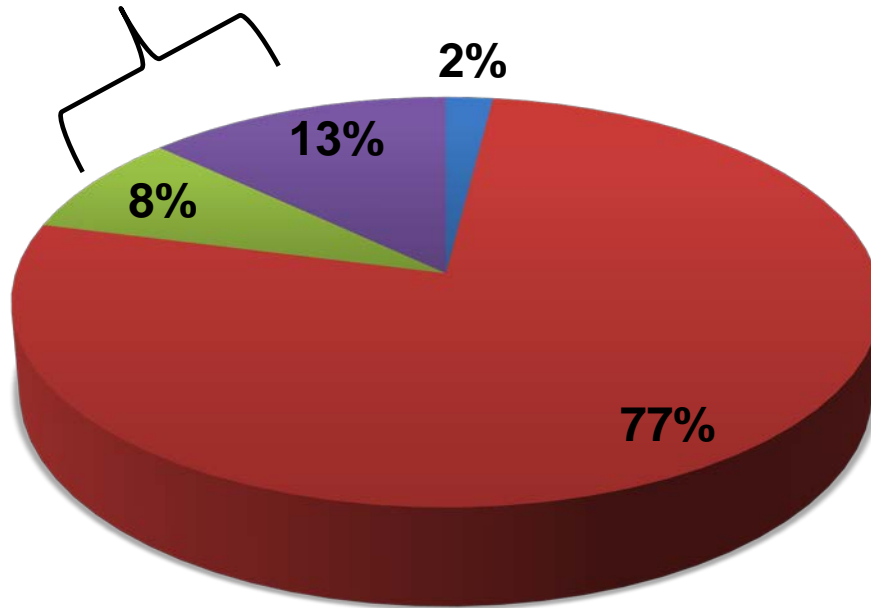INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Welcome and Introduction

- New England Comparative Effectiveness Public Advisory Council (New England CEPAC)

- The Institute for Clinical and Economic Review (ICER)

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Sources of Funding, 2019

Funding Sources - %

ICER Policy Summit Only

2%

13%

8%

77%

- Government grants and contracts
- Non-profit foundations
- Contributions from health plans and provider groups
- Manufacturer grants and contributions

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Welcome and Introduction

- **Why are we here today?**

- *The first year of [my son's] life was full of tears, 911 calls and constant fear of losing him....SMA would rob [our son] of many things, including his ability to swallow, breathe on his own, move and smile. [He] had surgery at 3 months old for a g-tube as he could no longer safely eat orally. At 7 months old [he] had a tracheostomy as he could no longer breath on his own and we had nearly lost him more times than any person should ever encounter.*

- *I know that, realistically, I'll probably never walk. Regardless, having a treatment that could give me more strength opens up so many possibilities that would drastically improve my quality of life. If I could go to the bathroom by myself, roll over in bed, unbuckle my own seat belt, or hold a baby then I could travel anywhere I want, never have to wake up anyone at night for assistance, drive to work by myself, and change my (future) child's diaper. These may sound like menial tasks to some, but to me it would be a dream come true.*

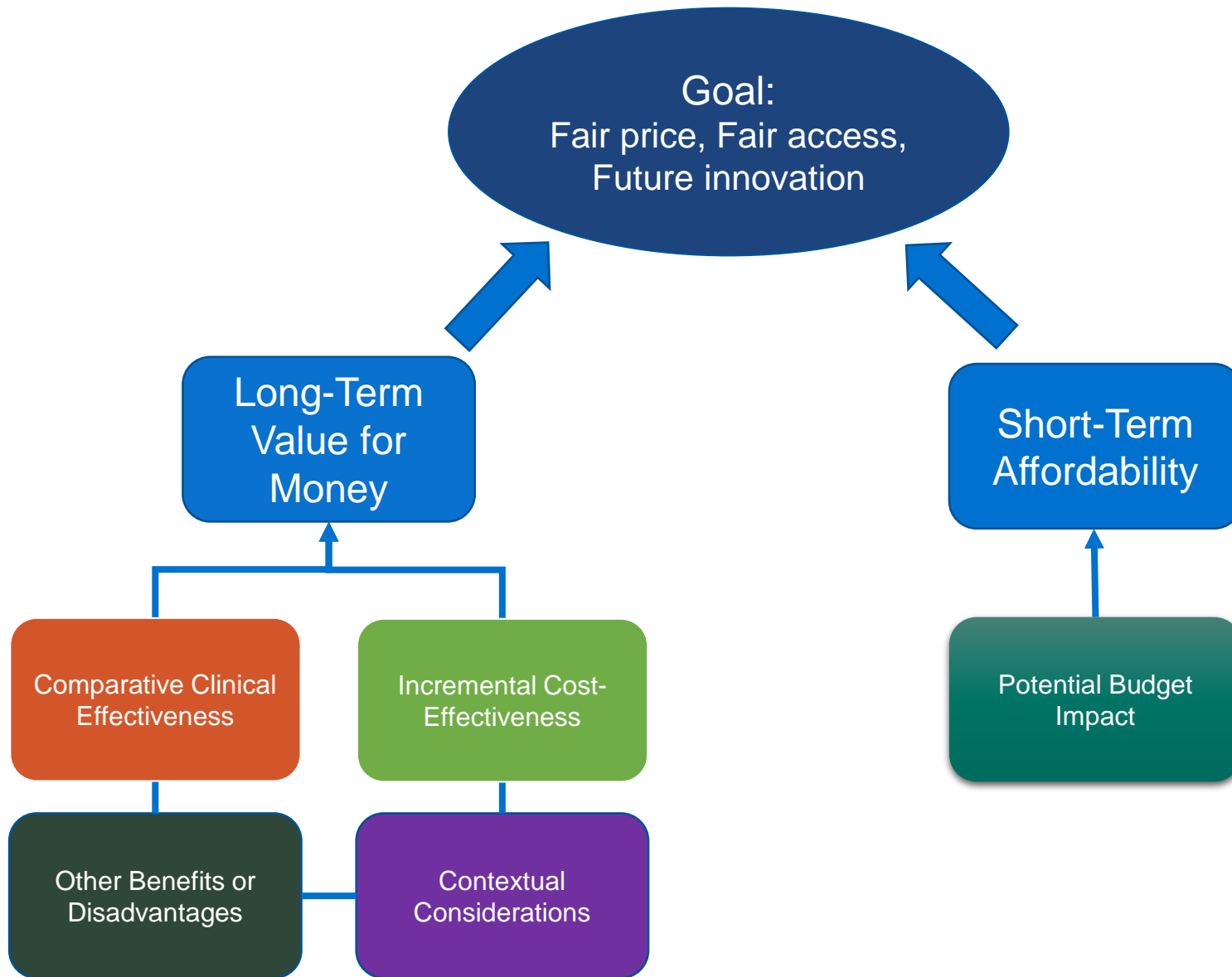**ICER**

Welcome and Introduction

- **Why are we here today?**
  - What happens the day these treatments are approved by the FDA?
  - The historical context and the challenge we all face today
  - The goals for today's meeting

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Welcome and Introduction

How was the ICER report on Spinraza and Zolgensma for spinal muscular atrophy (SMA) developed?

- Scoping with guidance from patients, clinical experts, manufacturers, and other stakeholders
- ICER evidence analysis
- University of Sheffield cost-effectiveness modeling
- Public comment and revision
- Expert report reviewers
  - Katherine Kundrat, PT, DPT, Physical Therapist
- How is the evidence report structured to support CEPAC voting and policy discussion?

Goal:
Fair price, Fair access,
Future innovation

Long-Term Value for Money

Short-Term Affordability

Comparative Clinical Effectiveness

Incremental Cost-Effectiveness

Potential Budget Impact

Other Benefits or Disadvantages

Contextual Considerations

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Agenda

9:30 am: Welcome and Opening Remarks

9:45 am: Presentation of the Evidence
Evidence Review: Alexandra G. Ellis, PhD, ICER
Cost Effectiveness: Matt Stevenson, PhD, BSc, University of Sheffield

10:55 am: Manufacturer Public Comment and Discussion

11:10 am: Public Comment and Discussion

11:30 pm: Lunch

12:30 pm: New England CEPAC Deliberation and Votes

2:00 pm: Break

2:15 pm: Policy Roundtable

3:30 pm: Reflections from New England CEPAC

4:00 pm: Meeting Adjourned

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Clinical Experts

- **Emma Ciafaloni, MD, FAAN**, Professor of Neurology, Pediatrics and Obstetrics and Gynecology; Director Pediatric Neuromuscular Medicine, University of Rochester
  - Disclosures:
    - Consulting fees >$5,000: Biogen, AveXis, Sarepta, PTC, Santhera
    - Member of DSMB for AveXis SMA gene therapy trials
    - Chair of Sarepta Duchenne muscular dystrophy gene therapy trials
- **David Michelson, MD**, Pediatric Neurologist, Loma Linda University Health
  - No conflicts of interest to disclose.

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Patient Experts

- **Brandi Akins**, Patient Advocate
  - Disclosures:
    - Served as a paid moderator (<$5,000) for a focus group of caregivers of children with Type I SMA for AveXis

- **Danyelle Sun**, Patient Advocate
  - Disclosures:
    - Board member for Cure SMA, an organization that receives more than 25% of its funding from health care companies

Evidence Review

Alexandra G. Ellis, PhD

Senior Scientist, HTA and Economic Evaluation

Institute for Clinical and Economic Review

Key Review Team Members:

Kristin Mickle, MPH, Research Associate, Evidera (formerly Research Lead, Evidence Synthesis, ICER)

Serina Herron-Smith, BA, Research Assistant, ICER

Disclosures:

We have no conflicts of interest relevant to this report.

Spinal Muscular Atrophy (SMA)

- Rare, genetic neuromuscular disease
- Caused by mutations in the survival motor neuron (SMN) gene that encodes SMN protein
  - *SMN1*: Creates fully-functional SMN protein
  - *SMN2*: 10% of SMN protein is fully-functional
- Manifests as progressive muscle weakness, causing difficulty with moving, swallowing, or breathing
  - Diagnosis prompted by clinical signs
  - Confirmed by genetic test

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SMA Types

SMA Type	% of SMA cases	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of *SMN2* Copies
I	60%	<6 months	Sit with support only	<2 years	1-3
II	20-30%	6–18 months	Sit independently	>2 years	2-3
III	10-20%	>18 months	Walk independently	Adulthood	3-4

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Disease-Modifying Treatments

- Spinraza® (nusinersen, Biogen Idec)
  - FDA approved in December 2016
  - Create more functional SMN protein from *SMN2*
  - Intrathecal injection
  - Four loading doses, every four months thereafter
- Zolgensma® (onasemnogene abeparvovec, Novartis/AveXis)
  - Investigational, FDA decision by May 2019
  - Replace defective *SMN1* with a copy
  - One-time, intravenous administration

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What We Heard from Patients and Caregivers

- Feel helpless and fearful

- Difficult to watch the disease progress in a child

- Importance of early diagnosis and treatment

- Want treatments that improve or retain strength and the ability to live independently

- Need for more studies and evidence in adults

Scope of the Review

- Population: Infants, children, and adults with SMA (any type)

- Interventions: Spinraza, Zolgensma

- Comparator: Supportive care

- Key outcomes:
  - Survival
  - Permanent ventilatory support
  - Motor functioning and milestones
  - Harms

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Spinraza: Key Trials

- **Infantile-onset (Type I) SMA**
  - 1 sham-controlled, randomized controlled trial (RCT) [ENDEAR]

- **Later-onset (Type II/III) SMA**
  - 1 sham-controlled, RCT [CHERISH]

- **Presymptomatic SMA**
  - 1 open-label, single-arm trial [NURTURE]

Spinraza: Infantile-Onset (Type I) Trial Overview

- 121 infants enrolled (80 Spinraza; 41 sham)
  - 2 *SMN2* copies
  - Mean age at treatment: 5 months
- Trial terminated early after positive results from an interim analysis
  - 78 (64%) had 6 months follow-up
- Patients could enroll in a long-term follow-up study [SHINE]

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Spinraza: Infantile-Onset (Type I) Survival and Permanent Ventilatory Support

	Spinraza N=80	Sham Control N=41	Hazard Ratio (95% CI)
Alive and No Use of Permanent Ventilation, n (%)	49 (61)	13 (32)	0.53 (0.32-0.89)
Alive, n (%)	67 (84)	25 (61)	0.37 (0.18-0.77)
No Use of Permanent Ventilation, n (%)	62 (78)	28 (68)	0.66 (0.32-1.37)

- Median (range) days on study
  - Spinraza: 280 (6-442)
  - Sham control: 187 (20-423)

Spinraza: Infantile-Onset (Type I) Motor Milestone Results

	Spinraza N=73	Sham Control N=37
Head Control	16 (22)	0
Roll Over	7 (10)	0
Sitting Unassisted	6 (8)	0
Standing with Assistance	1 (1)	0

- 45% of infants continuing with Spinraza achieved full head control and 29% achieved sitting independently after 576 days of follow-up

Spinraza: Later-Onset (Type II/III) Trial Overview

- 126 children enrolled (84 Spinraza; 42 sham)
  - Age rage at treatment: 2-9 years
  - At baseline, all children could sit without support but could not walk independently

- Trial terminated early after positive results from an interim analysis
  - All children had 6 months follow-up
  - 54 (43%) completed 15-month assessment

Spinraza: Later-Onset (Type II/III) Key Results

- Survival and permanent ventilatory support
  - No deaths in either group
  - Permanent ventilation not reported

- Motor milestones
  - 20% of children on Spinraza vs. 6% of children on sham achieved ≥1 new milestone
  - Differences not statistically significant

- Motor functioning measured by HFMSE
  - Average score improved among those on Spinraza and declined among those on sham
  - 57% of children on Spinraza vs. 25% of children on sham increased score by ≥3 points

Spinraza: Presymptomatic SMA Trial Overview

- 25 infants enrolled
    - 15 with 2 *SMN2* copies; 10 with 3 *SMN2* copies
    - Age rage at treatment: 3-42 days
- Ongoing trial; at most recent interim analysis:
    - Median (range) age: 26.0 (14.0-34.3) months
    - Median (range) time on study: 27.1 (15.1-35.5) months

Spinraza: Presymptomatic SMA Key Results

	2 *SMN2* (n=15)	3 *SMN2* n=10	All N=25
Alive	15 (100)	10 (100)	25 (100)
Required Respiratory Intervention			
≥ 6 Hours/Day for ≥7 Days	4 (24)	0	4 (16)
≥16 Hours/Day for >21 Days (Permanent Ventilation)	0	0	0
Motor Milestones			
Independent Sitting	15 (100)	10 (100)	25 (100)
Walking with Assistance	12 (80)	10 (100)	25 (100)
Walking Alone	8 (53)	9 (90)	17 (68)

Spinraza: All Populations, Harms

- Discontinuations rare
  - 16% Spinraza and 39% sham control infants in ENDEAR discontinued study due to adverse events (all with fatal outcomes)

- Lumbar puncture generally well tolerated
  - Specific AEs related to lumbar puncture (e.g., fever, headache, vomiting, back pain) reported in later-onset SMA (CHERISH)

- Spinraza prescribing information notes risk of thrombocytopenia and potential for kidney damage (renal toxicity)

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Zolgensma: Evidence Base

- **Infantile-onset (Type I) SMA**
  - 1 two-cohort trial (CL-101)

Zolgensma: Infantile-Onset (Type I) Trial Overview

- 12 infants enrolled and received high-dose
  - 2 *SMN2* copies
  - Mean age at treatment: 3.4 months
  - Note: these infants were diagnosed and treated younger than those in Spinraza trial
- Infants followed-up for 24 months

Zolgensma: Infantile-Onset (Type I) Key Results

- All 12 infants are alive and none are on permanent ventilation after 24 months

- Motor milestones achieved
  - 11 full head control, 9 roll over, 10 sit, 2 standing and walking

Zolgensma: Harms

- No discontinuations
- Serum aminotransferase elevations (liver inflammation)
  - Protocol amendment in which patients received oral prednisolone for 30 days
  - 3 patients (25%) in high-dose cohort experienced elevated aminotransferase levels

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Controversies and Uncertainties

- Generalizability of results
  - Narrow eligibility criteria of trials and small sample size (especially for Zolgensma)
  - Limited data on presymptomatic SMA

- Long-term safety and efficacy
  - Studies are ongoing
  - No waning of effect observed to date

- Comparative effectiveness of Spinraza and Zolgensma

- Combination or sequential therapy

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ICER Evidence Ratings for Spinraza and Zolgensma

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

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

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Potential Other Benefits and Contextual Considerations

- Spinraza is the first FDA-approved treatment that modifies disease progression; Zolgensma, a novel gene therapy, may follow

- Reduce burden with one-time intravenous injection of Zolgensma

- Improvements in motor functioning can allow patients greater ability for self-care and independence

- Return to school (children) or work (caregivers)

- Reduce other resources used (e.g., at school) and encourage more interaction in communities

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Public Comments Received

- Questions regarding evidence ratings and if the amount of evidence was adequately reflected in the ratings

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Summary

- Spinraza
  - Type I: Improvements in survival, reduced need for permanent ventilatory support, improvements in motor functioning
  - Type II/III: Improvements in motor functioning
  - Presymptomatic: Benefits in survival, need for permanent ventilatory support, motor functioning

- Zolgensma
  - Type I: Benefits in survival, need for permanent ventilatory support, motor functioning

- Both interventions had few harms

- Longer-term follow-up studies are ongoing

Questions

Cost Effectiveness

Matt Stevenson, PhD, BSc

Professor

University of Sheffield

Contributors:

Praveen Thokala, MASc, PhD, Senior Research Fellow, University of Sheffield

Varun Kumar, MBBS, MPH, MSc, Health Economist, ICER

Disclosures:

We have no conflicts of interest relevant to this report.

Objective

To evaluate the lifetime cost-effectiveness of nusinersen (Spinraza) and onasemnogene abeparvovec (Zolgensma), each compared to best supportive care (BSC) for the treatment of spinal muscular atrophy (SMA).

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Methods in Brief

Methods Overview

- **Model**: A new model with two phases: Short term (trial/study duration) + long-term (extrapolation)

- **Setting**: United States

- **Perspective**: Health care sector (direct medical care and drug costs)

- **Time Horizon**: Lifetime

- **Discount Rate**: 3% per year (costs and outcomes)

- **Primary Outcomes**: Cost per quality-adjusted life year (QALY) gained; cost per life year (LY) gained

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Model Overview

- Model based on:
  - Broad motor function milestones
  - Mortality
  - Permanent ventilation

- As Zolgensma was a single arm study we had to use BSC data from the ENDEAR study of Spinraza

Model Schematic for Infantile-Onset (Type I) SMA and Presymptomatic SMA Patients
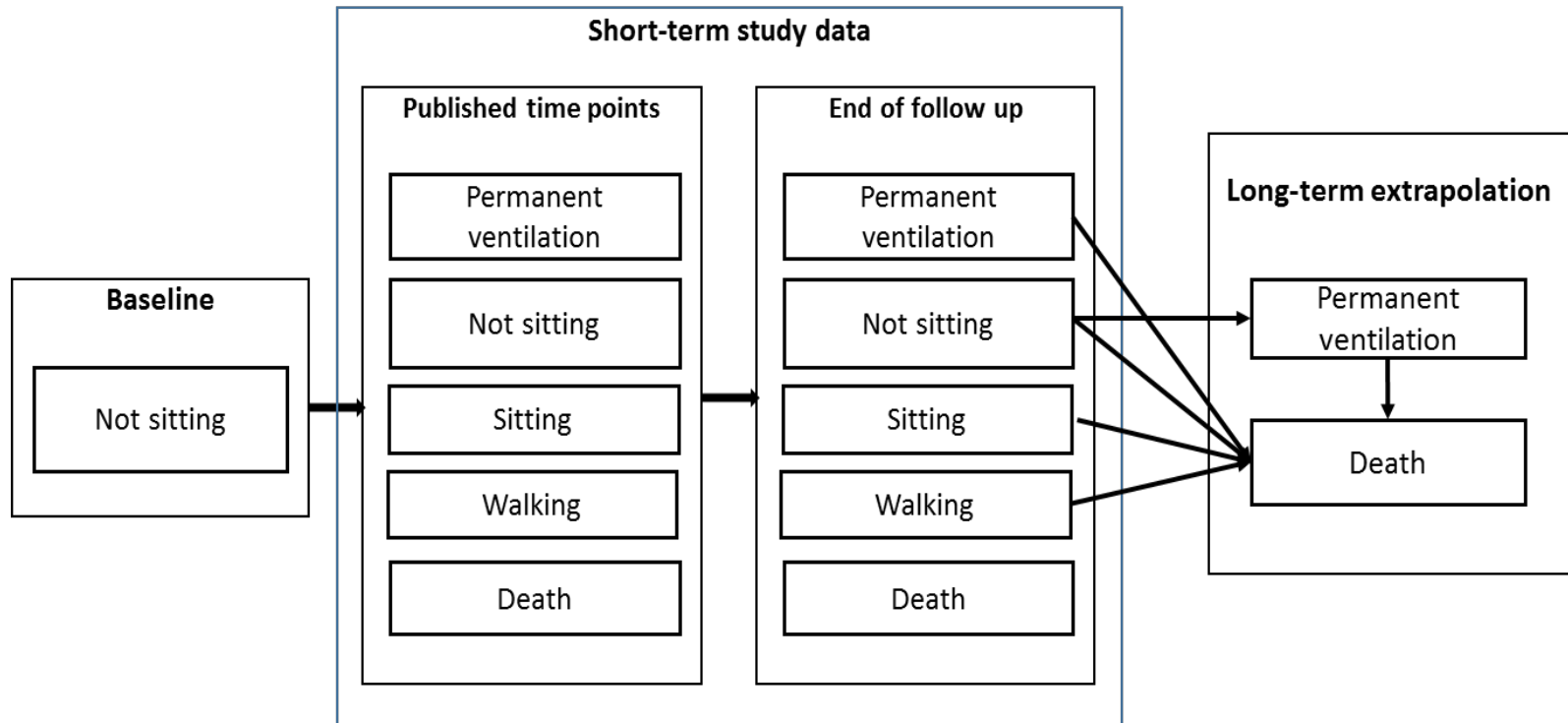
Model Schematic for Later-Onset (Type II/III) SMA Patients
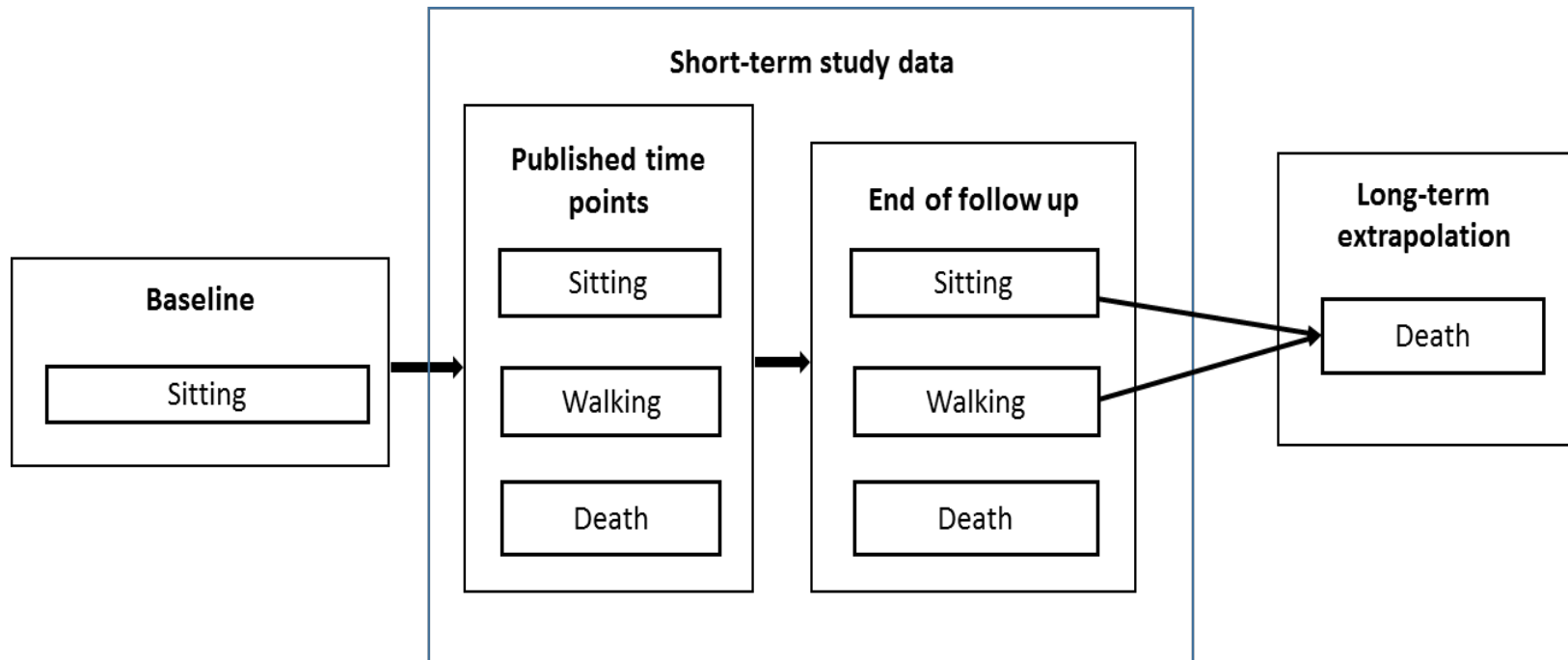
Short-Term Model Data

|	SMA Type 1	Later Onset (SMA Type 2/3)	Presymptomatic SMA
Spinraza	ENDEAR (Finkel 2017); SHINE (Castro 2018)	CHERISH (Mercuri 2018)	NURTURE (De Vivo 2017)
BSC	ENDEAR (Finkel 2017)	CHERISH (Mercuri 2018)	N/A
Zolgensma	Mendell 2017; Mendell 2018; Shell 2018	N/A	N/A

Studies in red indicate non-comparative evidence.

Potential Confounding of Zolgensma Data Due to the Use of Spinraza

- 5/12 patients who received Zolgensma started on Spinraza treatment, of whom 2 discontinued

- It is unknown whether initiation of Spinraza was due to:
  - Patient health deteriorating
  - The improvement seen in the patient was not as much as desired

- We assumed that the 3 patients continuing Spinraza were from the 9 in the sitting state

- We assumed that 1/6 of modelled patients who received Zolgensma would transit from the 'sitting' state to the 'not sitting' state (3/9 * 50%) at the end of the short-term model as a consequence of not receiving Spinraza

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Survival Curves
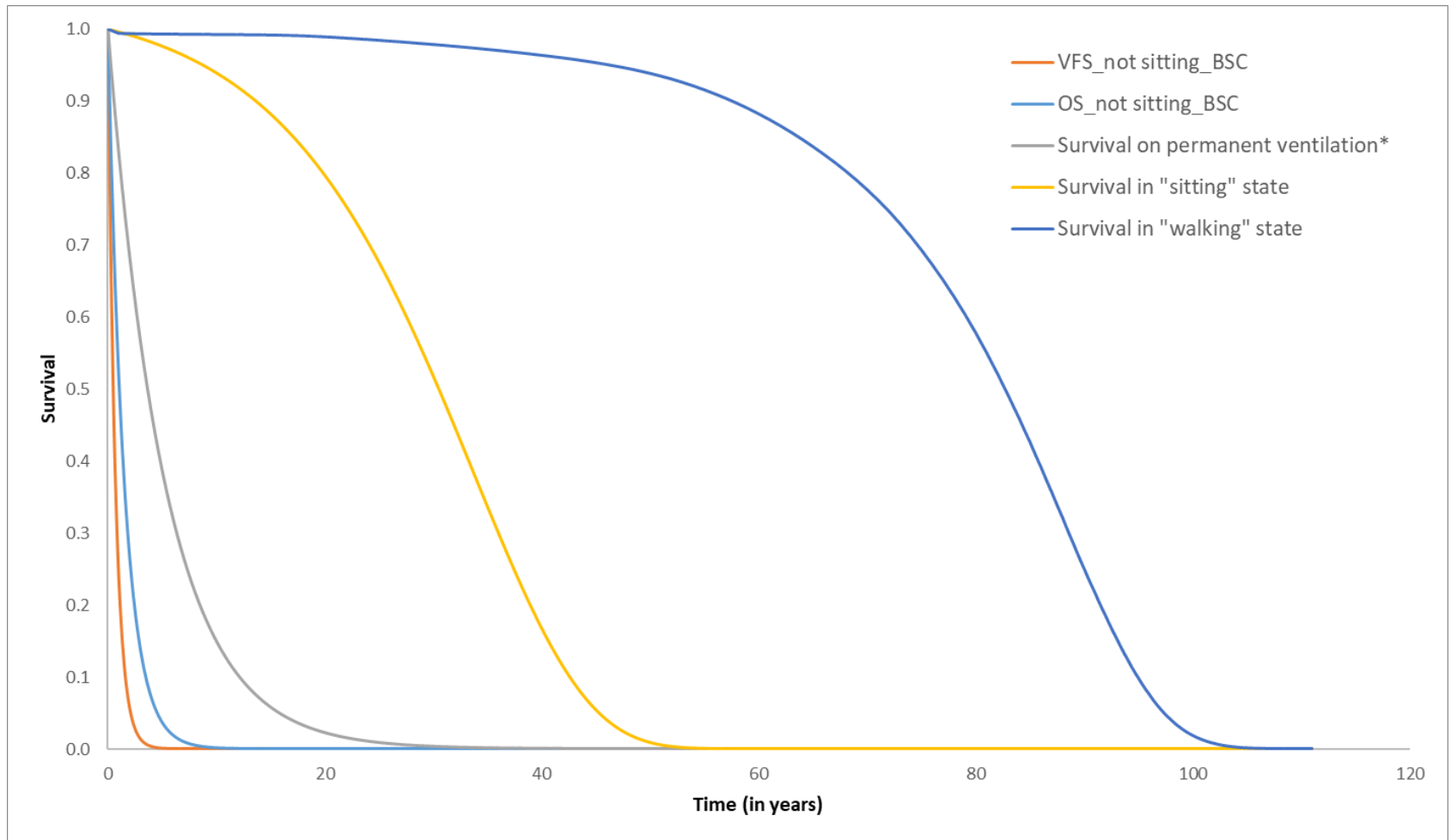
*Survival in "not sitting" health state for Spinraza and Zolgensma set equal to the survival on permanent ventilation.

Utilities and Costs

Patient Utilities

Health State	Utility in BSC Patients	Utility in Spinraza / Zolgensma Patients	Source for BSC Values (Derivation)
Permanent Ventilation	0.19	0.19	Thompson et al. (caregivers)
Not Sitting	0.19	0.29	
Sitting	0.60	0.65	Tappenden et al. (clinicians)
Walking	--		Age-matched general population utility

The increase in utility associated with Spinraza and Zolgensma patients was included to capture benefits that would not be captured within the broad health states.

Treatment-Related Costs

Intervention	Estimated Real World Price Per Package	Source	Other Treatment-Related Costs[†]
Spinraza	$127,500*	Redbook 2018; Magellan 2016	$1,209 (per injection)
Zolgensma	$2 million (placeholder price)	Market analyst estimate	$137 (one-time cost)

*Average Wholesale Price (AWP) – 15%, where AWP is $150,000 per package including hospital mark-up.
[†]Including items such as: infusion costs; monitoring costs; concomitant medications; imaging costs; and anesthesia costs. See report Tables 4.18 and 4.19 for further information.

Monthly Health State Costs

Monthly Costs	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

Results

Results Overview

- Results are presented in terms of:
  - Cost per quality-adjusted life-year (QALY) gained
  - Cost per life year gained (LYG)
  - Selected scenario analyses

- Results provided use a health care sector perspective. The modified societal perspective results were similar.

- Caregiver burden was not included as inclusion may lead to counter-intuitive results.

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Infantile-Onset (Type I) SMA Model

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LYG
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	--	--

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LYG
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	--	--

*Placeholder price.

Scenario Analyses – Spinraza vs. BSC

	Cost per QALY	Cost per LYG
Base Case Results	$1,112,000	$590,000
Assuming No Utility Benefits for Interim Milestones	$1,303,000	$590,000
Assuming Lower Health State Costs for "Not Sitting" and "Permanent Ventilation" Health States	$990,000	$525,000
Assuming Lower Utilities for "Sitting" and "Walking" Health States	$1,265,000	$590,000
Assuming Lower Survival for "Sitting" and "Walking" Health States	$1,253,000	$624,000
Assuming Lower Utilities and Lower Survival for "Sitting" and "Walking" Health States	$1,407,000	$624,000
Assuming 30% in "Sitting" Health State Lose Milestone at End of Short-Term Model	$1,218,000	$601,000
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
Using a 10-Year Time Horizon	$1,460,000	$700,000
Excluding Health Care Costs Not Related to Spinraza	$810,000	$429,000

Scenario analyses are shown which effect the cost per QALY gained and/or cost per LYG by >$100,000

The cost per QALY did not fall below $800,000 in all scenarios undertaken. The cost per LYG did not fall below $400,000 in all scenarios undertaken.

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Scenario Analyses – Zolgensma vs. BSC Type I SMA Model

	Cost per QALY	Cost per LYG
Base Case Results	$243,000	$182,000
Assuming Lower Survival for "Sitting" and "Walking" Health States	$303,000	$233,000
Assuming Lower Utilities and Lower Survival for "Sitting" and "Walking" Health States	$371,000	$233,000
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
Using a 10-Year Time Horizon	$525,000	$400,000
Excluding Health Care Costs not Related to Zolgensma	$170,000	$127,000
Assuming No Loss of Milestones in Patients who Received Spinraza after Zolgensma	$220,000	$165,000

Scenario analyses are shown which effect the cost per QALY gained and/or cost per LYG by >$50,000. More scenarios are provided in Table 4.22

Zolgensma price assumed to be $2,000,000

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Probabilistic Sensitivity Analyses Results in Infantile-Onset (Type I) SMA

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

Zolgensma price assumed to be $2,000,000.

Later-Onset (Type II/III) SMA Model Base Case Results

| | Drug Treatment Costs | Non-Treatment Health Care Costs | Total Costs | QALYs | LYs | Incremental Results | |
						Cost/QALY Gained	Cost/LYG
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	--	--

Presymptomatic SMA Model – Spinraza

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LYG
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	--	--

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Presymptomatic SMA Model – 'Drug X'

A hypothetical drug, 'Drug X' was evaluated that had the efficacy of Spinraza and an assumed one-time cost of $2,000,000.

This could inform thinking about the cost-effectiveness of Zolgensma if used presymptomatically

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

Scenario Analyses – Spinraza vs. BSC Presymptomatic SMA Model

	Cost per QALY	Cost per LYG
Base-Case Results	$709,000	$652,000
Assuming Lower Utilities for "Sitting" and "Walking" Health States	$904,000	$652,000
Assuming Lower Utilities and Lower Survival for "Sitting" and "Walking" Health States	$877,000	$628,000
Using a 10-Year Time Horizon	$890,000	$870,000
Using 1.5% Discount Rate for both Costs and QALYs	$679,000	$612,000

Scenario analyses are shown which effect the cost per QALY and/or cost per LYG by >$100,000

The cost per QALY gained and cost per LYG never fell below $600,000.

Probabilistic Sensitivity Analyses Results in Presymptomatic SMA

Threshold	Probability that Spinraza is Cost-Effective vs. BSC at Each Threshold
$50,000/QALY	0%
$100,000/QALY	0%
$150,000/QALY	0%
$200,000/QALY	0%
$250,000/QALY	0%
$300,000/QALY	0%
$350,000/QALY	0%
$400,000/QALY	0%
$450,000/QALY	0%
$500,000/QALY	0%

Summary

Model Limitations

- The lack of long-term data means there is uncertainty in future outcomes.
- The broad health states could miss benefits that are associated with Spinraza and Zolgensma treatment. As such, increased utility in the non-sitting and sitting states were modelled for Spinraza and Zolgensma
- Sensitivity and scenario analyses were undertaken to explore different assumptions related to uncertain parameters.

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Public Comments Received

- Belief that there would not be an increase in survival when entering permanent ventilation for people receiving Spinraza or Zolgensma
  - The survival in the non-sitting, non-permanent ventilation group was increased for Zolgensma and Spinraza to remove this inconsistency.

- Belief that the health states in the model were too granular to detect important benefits to the patients
  - A utility benefit for Zolgensma and Spinraza in the non-sitting and sitting states was included in the base case rather than scenario analyses.

Public Comments Received

- That we had used an inappropriate method for calculating the proportion of patients sitting for Spinraza
  - This was acknowledged. An alternative, method was employed that increased the proportion of patients sitting after receiving Spinraza.

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Summary

- 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. In the presymptomatic population, where Spinraza is believed to be most cost-effective the estimated cost per QALY gained was >$700,000; the estimated cost per LYG was >$650,000.

- For Zolgensma, used for patients with Type I SMA, the estimated cost per QALY gained was >$240,000; the estimated cost per LYG was >$180,000 when assuming a placeholder price of $2,000,000.

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Comparisons with Published Models (Zuluaga-Sanchez et al.)

- For Type I SMA the cost per QALY gained >€550,000. This was >€310,000 for Type II/III SMA.

- This model appears to be very similar to that initially submitted to the National Institute of Health and Care Excellence (NICE) with different utilities used.

- The NICE committee commented 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.*"

- It is noted that patients receiving Spinraza could not worsen, whilst a proportion improved each cycle.

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Questions

Manufacturer Public Comment and Discussion

Speakers

Name	Title	Company
Douglas Sproule, MD, MSc	Vice President, Spinal Muscular Atrophy Therapeutic Area Head	AveXis
Jonathan Yong, MD	Head of Neuromuscular Therapy Area, Global Medical Affairs	Biogen

Public Comment and Discussion

Khrystal K. Davis

Texas Rare Alliance Founder & Member of Families for Access to Spinal Muscular Atrophy Treatments

Conflict of Interest:

- None declared.

Mary Schroth, MD

Chief Medical Officer, Cure SMA

Conflict of Interest:

- Cure SMA receives more than 25% of its funding from health care companies.

Kristin Stephenson, MHA, JD

Senior Vice President, Chief Policy & Community Engagement Officer, Muscular Dystrophy Association

Conflict of Interest:

- None declared.

Lunch
Meeting will resume at 12:30 pm

Voting Questions

Which historical figure did not work at the Omni Parker House?

A. Malcolm X

B. Emeril Lagasse

C. Ho Chi Minh

D. Ralph Waldo Emerson

0   0   0   0

A.   B.   C.   D.

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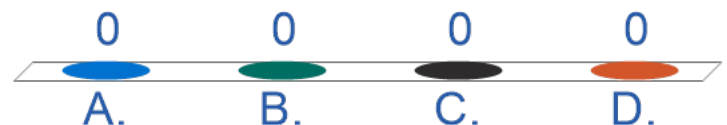
Patient Population for questions 1-3: Patients with infantile-onset (Type I) spinal muscular atrophy (SMA).

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?

A. Yes

B. No

0   0

Yes   No

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?

A. Yes

B. No

0

0

Yes

No
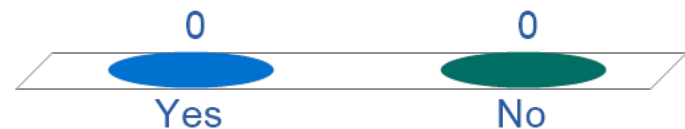
3. Is the evidence adequate to distinguish the net health benefit between Spinraza and Zolgensma?

A. Yes

B. No

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?

A. Yes

B. No

0   0

Yes   No
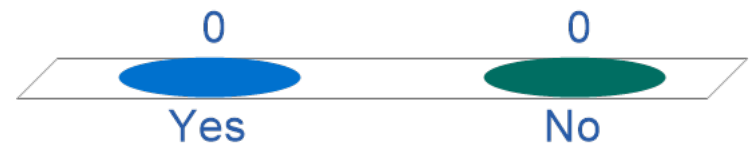
Patient Population for questions 5-6: Patients with presymptomatic SMA.

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?

A. Yes

B. No
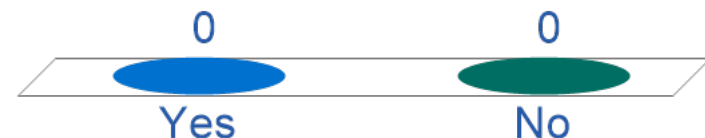
6. Is the evidence adequate to demonstrate the net health benefit of administering Zolgensma prior to development of symptoms is superior to that of supportive care alone?

A. Yes

B. No

0   0

Yes   No

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? (select all that apply)

A. Spinraza offers reduced complexity compared to other treatment options that will improve patient outcomes in the real world.

B. Spinraza has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.

C. Spinraza will significantly reduce caregiver or broader family burden.

D. Spinraza will have a significant impact on improving patients'/caregivers' ability to return to work and/or their overall productivity.

E. 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.

F. There are other important benefits—or disadvantages—that should have an important role in judgments of the value of Spinraza: _____

| 0	0	0	0	0	0
A.	B.	C.	D.	E.	F.
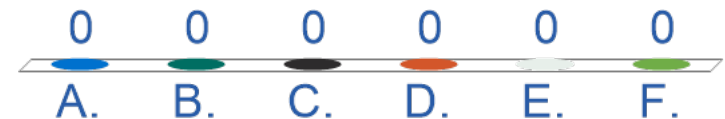
8. Are any of the following contextual considerations important in assessing Spinraza's long-term value for money? (select all that apply)
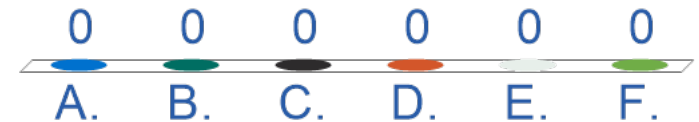
A. Spinraza is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.

B. Spinraza is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

C. Spinraza was the first to offer any improvement for patients with this condition.

D. Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of Spinraza.

E. Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of Spinraza.

F. There are additional contextual considerations that should have an important role in judgments of the value of Spinraza: _____.

0	0	0	0	0	0
A.	B.	C.	D.	E.	F.

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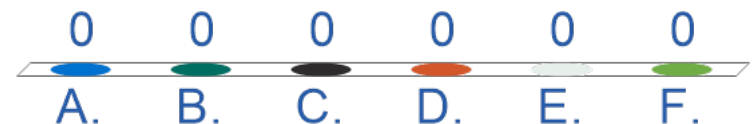
9. Is it likely that treatment with Zolgensma offers one or more of the following potential "other benefits" that are not adequately captured in the base case cost-effectiveness model? (select all that apply)

A. Zolgensma offers reduced complexity compared to other treatment options that will improve patient outcomes in the real world.

B. Zolgensma will significantly reduce caregiver or broader family burden.

C. Zolgensma has a different mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.

D. Zolgensma will have a significant impact on improving patients'/caregivers' ability to return to work and/or their overall productivity.

E. 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.

F. There are other important benefits—or disadvantages—that should have an important role in judgments of the value of **Zolgensma**: _____

10. Are any of the following contextual considerations important in assessing Zolgensma's long-term value for money? (select all that apply)

A. 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.

B. Zolgensma is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

C. Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of Zolgensma.

D. Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of Zolgensma.

E. There are additional contextual considerations that should have an important role in judgments of the value of Zolgensma: _____.

0	0	0	0	0
A.	B.	C.	D.	E.
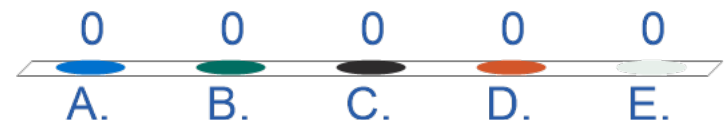
11. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Spinraza versus supportive care alone in patients with infantile-onset (Type I) SMA?
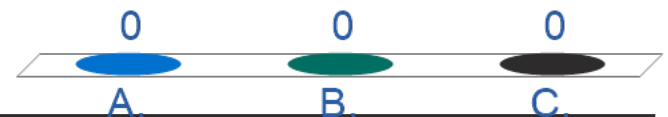
A.   Low long-term value for money

B.   Intermediate long-term value for money

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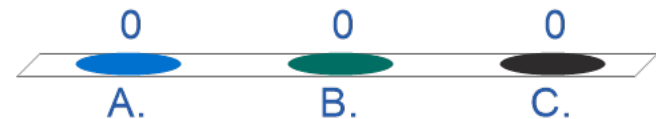
12. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Zolgensma versus supportive care alone in patients with infantile-onset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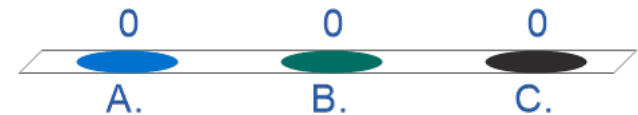
A. Low long-term value for money

B. Intermediate long-term value for money

C. High long-term value for money

13. 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 Zolgensma versus Spinraza in patients with infantile-onset (Type I) SMA?1
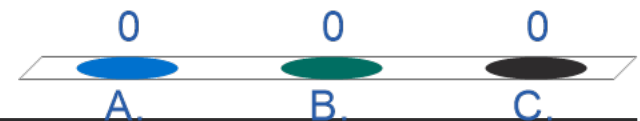
A.   Low long-term value for money

B.   Intermediate long-term value for money

C.   High long-term value for money

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?

A. Low long-term value for money

B. Intermediate long-term value for money

C. High long-term value for money

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 treating patients with Spinraza before symptoms develop versus best supportive care?

A. Low long-term value for money

B. Intermediate long-term value for money

C. High long-term value for money

0   0   0

A.   B.   C.

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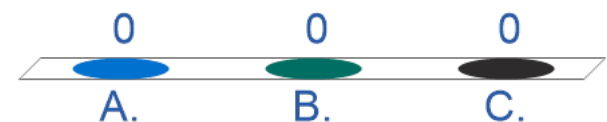
Break
Meeting will resume at 2:15 pm

Policy Roundtable

Policy Roundtable Participants

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	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.

New England CEPAC Reflections

Next Steps

- Meeting recording posted to ICER website next week

- Final Report published on/about March 28
  - Includes description of New England CEPAC votes, deliberation; policy roundtable discussion

- Materials available at

  https://icer-review.org/topic/sma/

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Adjourn