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

Public Meeting – March 7, 2019
Welcome and Introduction

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

• The Institute for Clinical and Economic Review (ICER)
Sources of Funding, 2019

Funding Sources - %

- Government grants and contracts: 2%
- Non-profit foundations: 77%
- Contributions from health plans and provider groups: 13%
- Manufacturer grants and contributions: 8%

ICER Policy Summit Only
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.
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
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

- Comparative Clinical Effectiveness
- Incremental Cost-Effectiveness
- Other Benefits or Disadvantages
- Contextual Considerations

Short-Term Affordability

- Potential Budget Impact
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
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.
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
  - \textit{SMN1}: Creates fully-functional SMN protein
  - \textit{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
# SMA Types

<table>
<thead>
<tr>
<th>SMA Type</th>
<th>% of SMA cases</th>
<th>Age of Onset</th>
<th>Highest Achieved Motor Function</th>
<th>Natural Age of Death</th>
<th>Typical Number of SMN2 Copies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>60%</td>
<td>&lt;6 months</td>
<td>Sit with support only</td>
<td>&lt;2 years</td>
<td>1-3</td>
</tr>
<tr>
<td>II</td>
<td>20-30%</td>
<td>6–18 months</td>
<td>Sit independently</td>
<td>&gt;2 years</td>
<td>2-3</td>
</tr>
<tr>
<td>III</td>
<td>10-20%</td>
<td>&gt;18 months</td>
<td>Walk independently</td>
<td>Adulthood</td>
<td>3-4</td>
</tr>
</tbody>
</table>
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
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
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]
Spinraza: Infantile-Onset (Type I) Survival and Permanent Ventilatory Support

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

- Median (range) days on study
  - Spinraza: 280 (6-442)
  - Sham control: 187 (20-423)
Spinraza: Infantile-Onset (Type I) Motor Milestone Results

<table>
<thead>
<tr>
<th></th>
<th>Spinraza N=73</th>
<th>Sham Control N=37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head Control</td>
<td>16 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Roll Over</td>
<td>7 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Sitting Unassisted</td>
<td>6 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Standing with Assistance</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

- 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 range 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

<table>
<thead>
<tr>
<th></th>
<th>2 SMN2 (n=15)</th>
<th>3 SMN2 (n=10)</th>
<th>All N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alive</strong></td>
<td>15 (100)</td>
<td>10 (100)</td>
<td>25 (100)</td>
</tr>
<tr>
<td><strong>Required Respiratory Intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6 Hours/Day for ≥7 Days</td>
<td>4 (24)</td>
<td>0</td>
<td>4 (16)</td>
</tr>
<tr>
<td>≥16 Hours/Day for &gt;21 Days (Permanent Ventilation)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Motor Milestones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent Sitting</td>
<td>15 (100)</td>
<td>10 (100)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Walking with Assistance</td>
<td>12 (80)</td>
<td>10 (100)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Walking Alone</td>
<td>8 (53)</td>
<td>9 (90)</td>
<td>17 (68)</td>
</tr>
</tbody>
</table>
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)
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
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
## ICER Evidence Ratings for Spinraza and Zolgensma

<table>
<thead>
<tr>
<th>SMA Population</th>
<th>Spinraza</th>
<th>Zolgensma</th>
<th>Ability to Distinguish?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile-Onset (Type I)</td>
<td>A</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Later-Onset (Type II and III)</td>
<td>B+</td>
<td>I*</td>
<td>I†</td>
</tr>
<tr>
<td>Presymptomatic</td>
<td>B+</td>
<td>I*</td>
<td>I†</td>
</tr>
</tbody>
</table>

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

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

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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).
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
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

<table>
<thead>
<tr>
<th></th>
<th>SMA Type 1</th>
<th>Later Onset (SMA Type 2/3)</th>
<th>Presymptomatic SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spinraza</strong></td>
<td>ENDEAR (Finkel 2017); SHINE (Castro 2018)</td>
<td>CHERISH (Mercuri 2018)</td>
<td>NURTURE (De Vivo 2017)</td>
</tr>
<tr>
<td><strong>BSC</strong></td>
<td>ENDEAR (Finkel 2017)</td>
<td>CHERISH (Mercuri 2018)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Zolgensma</strong></td>
<td>Mendell 2017; Mendell 2018; Shell 2018</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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
Survival Curves

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

**Legend:**
- VFS_not sitting_BSC
- OS_not sitting_BSC
- Survival on permanent ventilation*
- Survival in "sitting" state
- Survival in "walking" state
Utilities and Costs
### Patient Utilities

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

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Estimated Real World Price Per Package</th>
<th>Source</th>
<th>Other Treatment-Related Costs†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinraza</td>
<td>$127,500*</td>
<td>Redbook 2018; Magellan 2016</td>
<td>$1,209 (per injection)</td>
</tr>
<tr>
<td>Zolgensma</td>
<td>$2 million (placeholder price)</td>
<td>Market analyst estimate</td>
<td>$137 (one-time cost)</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Monthly Costs</th>
<th>Permanent Ventilation</th>
<th>Not Sitting</th>
<th>Sitting</th>
<th>Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient Hospitalization</td>
<td>$21,863</td>
<td>$21,863</td>
<td>$3,401</td>
<td>$1,116</td>
</tr>
<tr>
<td>Outpatient Services</td>
<td>$3,341</td>
<td>$3,341</td>
<td>$2,631</td>
<td>$984</td>
</tr>
<tr>
<td>Emergency Services</td>
<td>$313</td>
<td>$313</td>
<td>$325</td>
<td>$399</td>
</tr>
<tr>
<td>Costs Specific to Permanent Ventilation</td>
<td>$2,701</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Total Monthly Cost</td>
<td>$28,218</td>
<td>$25,517</td>
<td>$6,357</td>
<td>$2,499</td>
</tr>
</tbody>
</table>
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.
## Infantile-Onset (Type I) SMA Model

<table>
<thead>
<tr>
<th>Drug Treatment Costs</th>
<th>Non-Treatment Health Care Costs</th>
<th>Total Costs</th>
<th>QALYs</th>
<th>LYs</th>
<th>Incremental Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost/QALY Gained</td>
</tr>
<tr>
<td><strong>Spinraza</strong></td>
<td>$2,231,000</td>
<td>$1,653,000</td>
<td>$3,884,000</td>
<td>3.24</td>
<td>7.64</td>
</tr>
<tr>
<td><strong>BSC</strong></td>
<td>$0</td>
<td>$789,000</td>
<td>$789,000</td>
<td>0.46</td>
<td>2.40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Treatment Costs</th>
<th>Non-Treatment Health Care Costs</th>
<th>Total Costs</th>
<th>QALYs</th>
<th>LYs</th>
<th>Incremental Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost/QALY Gained</td>
</tr>
<tr>
<td><strong>Zolgensma</strong></td>
<td>$2,000,000*</td>
<td>$1,657,000</td>
<td>$3,657,000</td>
<td>12.23</td>
<td>18.17</td>
</tr>
<tr>
<td><strong>BSC</strong></td>
<td>$0</td>
<td>$789,000</td>
<td>$789,000</td>
<td>0.46</td>
<td>2.40</td>
</tr>
</tbody>
</table>

*Placeholder price.

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### Scenario Analyses – Spinraza vs. BSC

<table>
<thead>
<tr>
<th>Scenario Description</th>
<th>Cost per QALY</th>
<th>Cost per LYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Case Results</td>
<td>$1,112,000</td>
<td>$590,000</td>
</tr>
<tr>
<td>Assuming No Utility Benefits for Interim Milestones</td>
<td>$1,303,000</td>
<td>$590,000</td>
</tr>
<tr>
<td>Assuming Lower Health State Costs for “Not Sitting” and “Permanent Ventilation” Health States</td>
<td>$990,000</td>
<td>$525,000</td>
</tr>
<tr>
<td>Assuming Lower Utilities for “Sitting” and “Walking” Health States</td>
<td>$1,265,000</td>
<td>$590,000</td>
</tr>
<tr>
<td>Assuming Lower Survival for “Sitting” and “Walking” Health States</td>
<td>$1,253,000</td>
<td>$624,000</td>
</tr>
<tr>
<td>Assuming Lower Utilities and Lower Survival for “Sitting” and “Walking” Health States</td>
<td>$1,407,000</td>
<td>$624,000</td>
</tr>
<tr>
<td>Assuming 30% in “Sitting” Health State Lose Milestone at End of Short-Term Model</td>
<td>$1,218,000</td>
<td>$601,000</td>
</tr>
<tr>
<td>Assuming 30% in “Sitting” Health State Lose milestone at End of Short-Term Model, Lower Utilities and Survival for “Sitting” and “Walking” Health States</td>
<td>$1,509,000</td>
<td>$630,000</td>
</tr>
<tr>
<td>Using a 10-Year Time Horizon</td>
<td>$1,460,000</td>
<td>$700,000</td>
</tr>
<tr>
<td>Excluding Health Care Costs Not Related to Spinraza</td>
<td>$810,000</td>
<td>$429,000</td>
</tr>
</tbody>
</table>

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.
## Scenario Analyses – Zolgensma vs. BSC

Type I SMA Model

<table>
<thead>
<tr>
<th>Scenario Description</th>
<th>Cost per QALY</th>
<th>Cost per LYG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base Case Results</strong></td>
<td>$243,000</td>
<td>$182,000</td>
</tr>
<tr>
<td>Assuming Lower Survival for “Sitting” and “Walking” Health States</td>
<td>$303,000</td>
<td>$233,000</td>
</tr>
<tr>
<td>Assuming Lower Utilities and Lower Survival for “Sitting” and “Walking” Health States</td>
<td>$371,000</td>
<td>$233,000</td>
</tr>
<tr>
<td>Assuming 30% in “Sitting” Health State Lose Milestone at End of Short-Term Model, Lower Utilities and Survival for “Sitting” and “Walking” Health States</td>
<td>$406,000</td>
<td>$253,000</td>
</tr>
<tr>
<td>Using a 10-Year Time Horizon</td>
<td>$525,000</td>
<td>$400,000</td>
</tr>
<tr>
<td>Excluding Health Care Costs not Related to Zolgensma</td>
<td>$170,000</td>
<td>$127,000</td>
</tr>
<tr>
<td>Assuming No Loss of Milestones in Patients who Received Spinraza after Zolgensma</td>
<td>$220,000</td>
<td>$165,000</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Probability of Being Cost-Effective at Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spinraza vs. BSC</td>
</tr>
<tr>
<td>$50,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$100,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$150,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$200,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$250,000/QALY</td>
<td>0%</td>
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<tr>
<td>$300,000/QALY</td>
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<tr>
<td>$350,000/QALY</td>
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<tr>
<td>$400,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$450,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$500,000/QALY</td>
<td>0%</td>
</tr>
</tbody>
</table>

Zolgensma price assumed to be $2,000,000.
## Later-Onset (Type II/III) SMA Model
### Base Case Results

<table>
<thead>
<tr>
<th>Drug Treatment Costs</th>
<th>Non-Treatment Health Care Costs</th>
<th>Total Costs</th>
<th>QALYs</th>
<th>LYS</th>
<th>Incremental Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spinraza</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$7,634,000</td>
<td>$1,514,000</td>
<td>$9,148,000</td>
<td>12.28</td>
<td>18.90</td>
<td>$8,156,000</td>
</tr>
<tr>
<td><strong>BSC</strong></td>
<td></td>
<td>$1,442,000</td>
<td>11.34</td>
<td>18.90</td>
<td>--</td>
</tr>
</tbody>
</table>

**Cost/QALY Gained**

**Cost/LYG**

---

*ICER*
## Presymptomatic SMA Model – Spinraza

<table>
<thead>
<tr>
<th></th>
<th>Drug Treatment Costs</th>
<th>Non-Treatment Health Care Costs</th>
<th>Total Costs</th>
<th>QALYs</th>
<th>LYs</th>
<th>Incremental Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost/QALY Gained</td>
</tr>
<tr>
<td>Spinraza</td>
<td>$10,565,000</td>
<td>$1,364,000</td>
<td>$11,929,000</td>
<td>21.94</td>
<td>26.58</td>
<td>$709,000</td>
</tr>
<tr>
<td>BSC</td>
<td>$0</td>
<td>$801,000</td>
<td>$801,000</td>
<td>6.25</td>
<td>9.51</td>
<td>--</td>
</tr>
</tbody>
</table>
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.
## Scenario Analyses – Spinraza vs. BSC
### Presymptomatic SMA Model

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cost per QALY</th>
<th>Cost per LYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-Case Results</td>
<td>$709,000</td>
<td>$652,000</td>
</tr>
<tr>
<td>Assuming Lower Utilities for “Sitting” and “Walking” Health States</td>
<td>$904,000</td>
<td>$652,000</td>
</tr>
<tr>
<td>Assuming Lower Utilities and Lower Survival for “Sitting” and “Walking” Health States</td>
<td>$877,000</td>
<td>$628,000</td>
</tr>
<tr>
<td>Using a 10-Year Time Horizon</td>
<td>$890,000</td>
<td>$870,000</td>
</tr>
<tr>
<td>Using 1.5% Discount Rate for both Costs and QALYs</td>
<td>$679,000</td>
<td>$612,000</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Probability that Spinraza is Cost-Effective vs. BSC at Each Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>$50,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$100,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$150,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$200,000/QALY</td>
<td>0%</td>
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</tr>
<tr>
<td>$300,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$350,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$400,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$450,000/QALY</td>
<td>0%</td>
</tr>
<tr>
<td>$500,000/QALY</td>
<td>0%</td>
</tr>
</tbody>
</table>
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.
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.
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.
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.
Questions
Manufacturer Public Comment and Discussion
## Speakers

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douglas Sproule, MD, MSc</td>
<td>Vice President, Spinal Muscular Atrophy Therapeutic Area Head</td>
<td>AveXis</td>
</tr>
<tr>
<td>Jonathan Yong, MD</td>
<td>Head of Neuromuscular Therapy Area, Global Medical Affairs</td>
<td>Biogen</td>
</tr>
</tbody>
</table>
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
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
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
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
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
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: _____________
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: ________________________________.
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: 

______________.
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
Break
Meeting will resume at 2:15 pm
Policy Roundtable
<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Organization</th>
<th>COI Declaration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandi Akins</td>
<td>Patient Advocate</td>
<td>Served as a paid moderator (&lt;$5,000) for a focus group of caregivers of children with Type I SMA for AveXis.</td>
</tr>
<tr>
<td>Emma Ciafaloni, MD, FAAN</td>
<td>Professor of Neurology, University of Rochester</td>
<td>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.</td>
</tr>
<tr>
<td>Chris Leibman, PharmD, MS</td>
<td>Senior Vice President, Value and Access, Biogen</td>
<td>Full-time employee of Biogen.</td>
</tr>
<tr>
<td>David Michelson, MD</td>
<td>Pediatric Neurologist, Loma Linda University Health</td>
<td>None declared.</td>
</tr>
<tr>
<td>Erik Schindler</td>
<td>Clinical Pharmacy Manager, UnitedHealthcare</td>
<td>Full-time employee of UnitedHealthcare.</td>
</tr>
<tr>
<td>Mary Schroth, MD</td>
<td>Chief Medical Officer, Cure SMA</td>
<td>Cure SMA receives more than 25% of its funding from health care companies.</td>
</tr>
<tr>
<td>Douglas Sproule, MD, MSc</td>
<td>Vice President, Spinal Muscular Atrophy Therapeutic Area Head, AveXis</td>
<td>Full-time employee of AveXis.</td>
</tr>
<tr>
<td>Danyelle Sun</td>
<td>Patient Advocate</td>
<td>Board member for Cure SMA, an organization that receives more than 25% of its funding from health care companies.</td>
</tr>
<tr>
<td>BCPS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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/
Adjourn