ISIS-SMN_{Rx} Background and Current Status

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Sr. VP, Research
Isis Pharmaceuticals
**ISIS-SMN_Rx**: Modulating Splicing of SMN2 to Increase Normal SMN Protein

- Uniformly 2’-O-methoxyethyl modified (MOE) antisense drug
- Corrects the splicing disorder in SMN2, resulting in the production of fully functional SMN protein in model systems
- In mild and severe mouse models of SMA provides a phenotypic and pathological benefit when delivered centrally*
- Distributes broadly to spinal cord motor neurons after intrathecal delivery in monkeys*
- Has a long half life in CNS tissue (>6 months in animal models)

### Phase 2 Study

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Total Dose</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg</td>
<td>9 mg</td>
<td>8</td>
</tr>
<tr>
<td>6 mg</td>
<td>18 mg</td>
<td>8</td>
</tr>
<tr>
<td>9 mg</td>
<td>18 mg</td>
<td>9</td>
</tr>
<tr>
<td>12 mg</td>
<td>36 mg</td>
<td>8</td>
</tr>
</tbody>
</table>

**Screening (≤28 days)** → **Day 1 Dose** → **Day 29 Dose** → **Day 85 Dose** → **6 months Post-Treatment f/u Period**

**Interval between studies:**
- 3 mg: ~13 months
- 6 mg: ~10 months
- 9 mg: ~10 months
- 12 mg: ~7 months

### OLE Study

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Total Dose</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mg</td>
<td>48 mg</td>
<td>30</td>
</tr>
</tbody>
</table>

**Screening (≤28 days)** → **D1 Dose** → **D169 Dose** → **D351 Dose** → **D533 Dose** → **6 months Post-Treatment f/u Period**
## Baseline Demographics at Start of ISIS-SMN\textsubscript{Rx} Phase 2 Study

<table>
<thead>
<tr>
<th></th>
<th>3 mg (N = 7)</th>
<th>6 mg (N = 6)</th>
<th>9 mg (N = 9)</th>
<th>12 mg (N = 8)</th>
<th>Total (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (57.1)</td>
<td>4 (66.7)</td>
<td>5 (55.6)</td>
<td>6 (75.0)</td>
<td>19 (63.3)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.0 (6.0)</td>
<td>9.0 (6.0)</td>
<td>6.0 (4.0)</td>
<td>7.0 (4.0)</td>
<td>8.0 (5.0)</td>
</tr>
<tr>
<td><strong>SMA, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>4 (57.1)</td>
<td>2 (33.3)</td>
<td>3 (33.3)</td>
<td>3 (37.5)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>Type III</td>
<td>3 (42.9)</td>
<td>4 (66.7)</td>
<td>6 (66.7)</td>
<td>5 (62.5)</td>
<td>18 (60.0)</td>
</tr>
<tr>
<td><strong>SMN2 Copy Number</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMN2 Copy #3</td>
<td>5 (71.4)</td>
<td>4 (66.7)</td>
<td>9 (100)</td>
<td>5 (62.5)</td>
<td>23 (76.7)</td>
</tr>
<tr>
<td>SMN2 Copy #4</td>
<td>2 (28.6)</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>3 (37.5)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td><strong>Ambulation Status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulant</td>
<td>3 (42.9)</td>
<td>2 (33.3)</td>
<td>4 (44.4)</td>
<td>5 (62.5)</td>
<td>14 (46.7)</td>
</tr>
<tr>
<td>Non-Ambulant</td>
<td>4 (57.1)</td>
<td>4 (66.7)</td>
<td>5 (55.6)</td>
<td>3 (37.5)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td><strong>HFMSE BL Scores, all (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>32.1 (22.4)</td>
<td>35.2 (12.6)</td>
<td>40.0 (16.4)</td>
<td>44.5 (18.0)</td>
<td>38.4 (17.5)</td>
</tr>
<tr>
<td>HFMSE BL Scores, Subjects with BL ≤10, ≤54, (n)</td>
<td>3</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>16.7 (4.6)</td>
<td>35.2 (12.6)</td>
<td>37.8 (15.9)</td>
<td>34.4 (15.0)</td>
<td>33.4 (14.7)</td>
</tr>
<tr>
<td>6-Minute Walk Test, n</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>226.3 (162.8)</td>
<td>203.0 (32.5)</td>
<td>165.3 (138.6)</td>
<td>320.2 (264.8)</td>
<td>229.9 (175.3)</td>
</tr>
<tr>
<td>Upper Limb Module, n</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Subjects w/ BL ≤14, Mean (SD)</td>
<td>7.3 (1.5)</td>
<td>14.0</td>
<td>10.7 (2.1)</td>
<td>11.7 (1.2)</td>
<td>10.3 (2.6)</td>
</tr>
</tbody>
</table>
# Dose Range Study in Children With SMA (Phase 2): Change in HFMSE from Phase 2 Baseline to baseline for OLE

<table>
<thead>
<tr>
<th>Dose</th>
<th>Total Dose (Phase 2)</th>
<th>Mean HFMSE Change All Patients</th>
<th>Mean HFMSE Change HFMSE Baseline Score ≥ 10 and ≤ 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg</td>
<td>9 mg (3 x 3 mg)</td>
<td>0.1</td>
<td>-0.7</td>
</tr>
<tr>
<td>6 mg</td>
<td>18 mg (3 x 6 mg)</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>9 mg</td>
<td>18 mg (2 x 9 mg)</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>12 mg</td>
<td>36 mg (3 x 12 mg)</td>
<td>2.6</td>
<td>4.4</td>
</tr>
</tbody>
</table>
OLE Study: Mean Change from Baseline in Hammersmith Functional Motor Scale Expanded (HFMSE)

Mean Change (SEM) in HFMSE Points

All Subjects on 12 mg ISIS-SMN$_{Rx}$
OLE Study: Mean Change from Baseline in HFMSE
Children with SMA with baseline score $\geq 10$ and $\leq 54$ (CHERISH Phase 3 study criteria)
Mean Change from Baseline in 6-minute Walk Test (6MWT): All Ambulant Subjects

Phase 2 Study  |  OLE Study

Mean 6MWT distance increased by 55 meters at Day 260
Mean Change in Upper Limb Module (ULM) Test: Subjects with BL ≤ 14 (ULM Test is on an 18 point scale)
Safety profile of ISIS-\textsubscript{SMN\textsubscript{Rx}} in children with SMA supports continued development

- Intrathecal administration has been well tolerated with no drug-related serious adverse events in either the Phase 2 or the open-label extension studies.
- Most adverse events reported as mild or moderate in severity.
- There were no changes in the safety profile with repeated doses of ISIS-\textsubscript{SMN\textsubscript{Rx}}

- The most frequently (>20%) observed TEAEs in Phase 2/OLE study were post LP syndrome, back pain, puncture site pain and headache (attributed to LP procedure); and nasopharyngitis.

- There were no clinically significant adverse changes related to ISIS-\textsubscript{SMN\textsubscript{Rx}} in neurological examinations, laboratory parameters, vital signs or ECGs.
Phase 2/OLE Studies Summary

- Safety profile of ISIS-SMN\textsubscript{Rx} in children with SMA supports continued development

- Continued and durable increases in measures of muscle function with 57% of children achieving a 3 point or greater change in HFMSE scores

- Increases in multiple measures of muscle function at Day 260
  - Mean increase of 3.8 points in HFMSE score (n=22)
    - In a subgroup analysis of children who had incoming HFMSE scores that met the inclusion criteria for the ongoing Phase 3 CHERISH study (≥10 and ≤54; n=17) mean increase in HFMSE score was 4.4 points
  - Mean 6MWT distance increased by 55 meters (n=11)
  - Mean ULM scores increased by 2.0 points (n=12)
Phase 2 Open-Label Study of ISIS-SMN$_{Rx}$ in Patients with Infantile-onset (Type 1) Spinal Muscular Atrophy

- Multiple doses given intrathecally as LP bolus injections in male and female infants with SMA <7 months of age
  - Study conducted at 4 sites in North America

- Clinical efficacy endpoints
  - Survival and time to permanent ventilation\(^1\)
  - CHOP INTEND
  - Motor milestones

- Study designed primarily to assess safety and tolerability

<table>
<thead>
<tr>
<th>Dose Cohort</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg equivalent</td>
<td>4</td>
</tr>
<tr>
<td>12 mg equivalent</td>
<td>16</td>
</tr>
</tbody>
</table>

Subject demographics

<table>
<thead>
<tr>
<th></th>
<th>6 mg Cohort (n=4)</th>
<th>12 mg Cohort (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Female</td>
<td>3:1</td>
<td>9:7</td>
</tr>
<tr>
<td>Mean age at symptom onset (range)</td>
<td>7 weeks (4 to 10)</td>
<td>9 weeks (3 to 22)</td>
</tr>
<tr>
<td>Mean age at enrollment (range)</td>
<td>21 weeks (10 to 30)</td>
<td>20 weeks (5 to 30)</td>
</tr>
<tr>
<td>SMN2 gene #</td>
<td>2 SMN2 genes = 4</td>
<td>2 genes = 13; 3 genes = 2; unknown = 1</td>
</tr>
</tbody>
</table>

\(^1\) \(\geq16\) hours/day of ventilation continuously for \(\geq2\) weeks, in the absence of an acute reversible illness
*SMN2 copy number of 3; **SMN2 copy number not known; all other infants have SMN2 copy number of 2
Increased Muscle Function (CHOP INTEND) Scores Observed in SMA Infants Treated with ISIS-SMN$_{Rx}$ as of Sept 2, 2014 and as of April 17, 2015
Increased Muscle Function (CHOP INTEND) Scores Observed in SMA Infants Treated with ISIS-SMN$_{Rx}$ as of Sept 2, 2014 and as of April 17, 2015

12 mg Cohort (PPEP-4)

Mean change (at 15 mo.)

12 of 15 infants achieved increases in CHOP INTEND

17.0
Increased Muscle Function (CHOP INTEND) Scores Observed in SMA Infants Treated with ISIS-SMN$_{Rx}$

A Substantial Number of SMA Infants Treated with ISIS-SMN$_{Rx}$ Achieved a CHOP INTEND Score of 40 or Greater

12 mg Cohort (n=15)

<table>
<thead>
<tr>
<th>Date of Analysis</th>
<th>Median Baseline CHOP INTEND score*</th>
<th>Infants with CHOP INTEND score ≥ 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 17, 2015</td>
<td>26.0</td>
<td>8 (53%)*</td>
</tr>
</tbody>
</table>

*CHOP INTEND scores can range on a scale from 0-64

**Two infants with 3 copies of the SMN2 gene had baseline CHOP INTEND scores ≥ 40
## Achievement of New Motor Milestones Observed in Some ISIS-SMN<sub>Rx</sub>-treated SMA Infants

### Baseline

<table>
<thead>
<tr>
<th>Voluntary Grasp</th>
<th>No Grasp</th>
<th>Uses Whole Hand</th>
<th>Index finger and thumb but immature grasp</th>
<th>Pincer grasp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to Kick (in supine)</td>
<td>No Kicking</td>
<td>Kick horizontal, legs do not lift</td>
<td>Upward (vertical)</td>
<td>Touches leg</td>
</tr>
<tr>
<td>Head Control</td>
<td>Unable to maintain upright</td>
<td>Wobbles</td>
<td>All the time upright</td>
<td></td>
</tr>
<tr>
<td>Rolling</td>
<td>No rolling</td>
<td>Rolling to side</td>
<td>Prone to supine</td>
<td>Supine to prone</td>
</tr>
<tr>
<td>Sitting</td>
<td>Cannot sit</td>
<td>Sit with support at hips</td>
<td>Props</td>
<td>Stable sit</td>
</tr>
<tr>
<td>Crawling</td>
<td>Does not lift head</td>
<td>On elbow</td>
<td>On outstretched hand</td>
<td>Crawling flat on abdomen</td>
</tr>
<tr>
<td>Standing</td>
<td>Does not support weight</td>
<td>Supports weight</td>
<td>Stands with support</td>
<td>Stands unaided</td>
</tr>
<tr>
<td>Walking</td>
<td>No walking</td>
<td>Bouncing</td>
<td>Cruising (holding on)</td>
<td>Walking independently</td>
</tr>
</tbody>
</table>
Achievement of New Motor Milestones Observed in Some ISIS-SMN$_{Rx}$-treated SMA Infants

April 17, 2015  
Blue—6 mg, Red—12 mg

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</table>
Example of ISIS-SMN$_{Rx}$ Distribution Throughout the CNS and in Neurons of ISIS-SMN$_{Rx}$-treated SMA infants

- Tissue samples shown here are from treated SMA infant #3 (tissue samples from other two treated SMA infants showed similar results)

- Immunohistochemical staining confirms drug in all levels of spinal cord and in brain

- Immunohistochemical staining confirms drug in neurons*

*ISIS-SMN$_{Rx}$ in neurons indicated by red arrows; brown staining indicates ISIS-SMN$_{Rx}$ in cells
Greater Amount of Full Length SMN2 mRNA is Observed in Thoracic Spinal Cord in ISIS-SMN$_{Rx}$-treated SMA Infants Compared to Untreated SMA Infants

**Semi-Quantitative RT-PCR Analysis**

<table>
<thead>
<tr>
<th>Non SMA</th>
<th>UnTx SMA</th>
<th>ISIS-SMN$_{Rx}$ Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>W</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>X</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>Y</td>
<td>3</td>
</tr>
</tbody>
</table>

- **FL SMN2**
  - Non SMA = 6
  - Untreated SMA = 8
  - ISIS SMN$_{Rx}$ Tx = 6

- **Δ7 SMN2**
  - Non SMA = 8
  - Untreated SMA = 6
  - ISIS SMN$_{Rx}$ Tx = 8

% Full Length by Group (Mean ± SD)

- Non SMA = 21.7 ± 3.8
- Untreated SMA = 20.8 ± 5.6
- ISIS SMN$_{Rx}$ Tx = 57 ± 10.4
Localization of ISIS-SMN$_{Rx}$ in Brain Tissues

Hippocampus

Medulla

Thalamus
Greater Amount of Full Length SMN2 mRNA Observed in Tissues Analyzed from Different Spinal Cord and Brain Regions in ISIS-SMN$_{Rx}$-treated SMA Infants Compared to Untreated SMA Infants

L = Lumbar SC  
T = Thoracic SC  
C = Cervical SC  
MC = Motor Cortex  
Th = Thalamus

% Full Length SMN2 RNA

ISIS-SMN$_{Rx}$ Tx SMA Infants

FL SMN2

Δ7 SMN2

Lumbar SC  
Thoracic SC  
Cervical SC  
Motor Cortex  
Thalamus
Greater SMN Protein Observed in Thoracic Spinal Cord of ISIS-SMN\textsubscript{Rx}-Treated SMA Infants Compared to Untreated SMA Infants

**Immunofluorescence Staining for SMN Protein**

Non-SMA Subject  \hspace{1cm} UnTx SMA  \hspace{1cm} ISIS-SMN\textsubscript{Rx} Tx SMA

Subject D  \hspace{1cm} Infant X  \hspace{1cm} Infant 1

*SMN Protein = Red*

*DAPI stain (for cell nuclei) = Blue*
ISIS-SMNRx Safety and Tolerability Profile in SMA Infants Supportive of Continued Development

- 20 infants dosed with a total of 94 intrathecal injections; up to 23 months of treatment as of April 17, 2015

- ISIS-SMNRx has been well tolerated with no safety concerns to date
  - No drug-related SAEs; majority of SAEs were related to respiratory infections
  - Adverse Events (non-SAEs) mostly mild or moderate in severity
  - No potential Dose Limiting Toxicities reported
  - No drug-related changes on neurological exams
  - No clinically significant changes in CSF safety labs
  - No change in safety profile with repeated injections

- The LP injection procedure in SMA infants has been well tolerated and has been shown to be feasible without sedation
Summary of ISIS-SMN$_{Rx}$ Phase 2 Study in Infants with SMA

- Totality and consistency of clinical data give us encouragement about the performance of ISIS-SMN$_{Rx}$

- The median event-free age in infants treated with ISIS-SMN$_{Rx}$ continues to increase
  - In the 6 mg cohort, 50% of the infants (2 of 4) are event free and both infants are older than 27 months
  - In the 12 mg cohort, 73% of the infants (11 of 15) remain event-free and all of them are older than 15 months

- ISIS-SMN$_{Rx}$-treated SMA infants continue to demonstrate increases in motor function scores
  - CHOP INTEND: mean increase in the 12 mg cohort of 17 points at 15 months; 53% achieved score of 40 or greater
  - Motor milestones: nearly all ISIS-SMN$_{Rx}$-treated SMA infants achieved new motor milestones; five now sitting
Summary of ISIS-SMN$_{Rx}$ Phase 2 Study in Infants with SMA

- Clinical data are consistent with the mechanism by which ISIS-SMN$_{Rx}$ was designed to work
  - ISIS-SMN$_{Rx}$ distributes broadly throughout the CNS; ISIS-SMN$_{Rx}$ concentration in spinal cord of treated SMA infants is greater than the concentration that produced biological activity in animal studies
  - Greater amount of full length SMN2 mRNA observed in different spinal cord and brain tissues analyzed from ISIS-SMN$_{Rx}$-treated SMA infants compared to untreated SMA infants
- Safety and tolerability profile supportive of continued development
ISIS-SMN_{Rx} Phase 3 Program

- **ENDEAR (Isis study): Infant Onset SMA Registration Trial**
  - First patient dosed in August 2014
  - Eligible patients may continue in open label extension
  - Data planned 2016/2017

- **CHERISH (Isis study): Childhood Onset SMA Registration Trial**
  - First patient dosed in November 2014
  - Eligible patients may continue in open label extension study
  - Data planned 2016/2017

- **NURTURE (Biogen study): Phase 2 study in pre-symptomatic newborns that are genetically predisposed to the disease**
  - Study is designed to enhance our understanding of early diagnosis and treatment and support initiatives that will allow patients to be identified and begin treatment sooner

- **EMBRACE (Biogen study): Phase 2 study in patients with infantile or childhood-onset SMA**
  - Study is designed to bridge the gap in a small subset of patients that do not meet the age and inclusion criteria of ENDEAR and CHERISH studies
Thank You to Our Partners in this Endeavor

SMA Patients & Families
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Russell Butterfield
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Donata Trussell
Nicole Rausch

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Matt Buck
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Laury Mignon
Kristina Bowyer
Ron Baldwin
Shannon Fine

**University of Utah**
Frank Rigo
Michaela Norrbom
Dan Norris
John Matson
Gene Hung
Scott Henry
Margaret Whiteley
Viola Kam

**Johns Hopkins**
Charlotte Sumner
David Valdivia
Tom Crawford

**Boston Childrens**
Dawn McGuire
Steve Bradley