Panel II: SMA Drugs in Development

- Jinsy Andrews MD, Director of Clinical Research and Development, Cytokinetics
- Thomas Blaettler MD, Global Clinical Development Team Leader, F. Hoffmann-La Roche
- Jerry R. Mendell MD, Director, Center for Gene Therapy, Research Institute, Nationwide Children's Hospital
- Irene Gerlach PhD, Project Team Leader Rare Diseases, F. Hoffmann-La Roche
- Wildon Farwell MD, MPH, Medical Director, Neurology Early Clinical Development, Biogen
- Eugene Schneider MD, Executive Director, Clinical Development, Isis Pharmaceuticals
- Emilie Voltz PhD, Clinical Trials Leader, Neurosciences, Novartis Institutes for Biomedical Research
Jinsy Andrews MD on CK-2127107, a fast skeletal troponin activator, for the potential treatment of Spinal Muscular Atrophy (SMA)

- Five Phase I healthy volunteer studies completed
- Well-tolerated in healthy volunteers at single doses up to 4000 mg
- Exposures were generally dose proportional up to 4000 mg
- Increased the response of muscle to neuronal input with increasing dose and plasma concentration
- By directly increasing skeletal muscle function, CK-2127107 may enhance physical performance in patients with neuromuscular diseases including spinal muscular atrophy (SMA); this possibility warrants a Phase 2 study in patients with SMA.
Olesoxime Update from Roche: Thomas Blaettler, MD
WE ARE COMMITTED TO PEOPLE LIVING WITH SMA

1. What Is Olesoxime?
   - An investigational medicine
   - Studied in a double-blind, clinical trial in type II and non-walking type III SMA patients aged 3-25
   - Given orally as a liquid

2. Where Are We Today?
   - Advancing regulatory and development process needs

3. We Have A Path Forward
   Since acquiring olesoxime in March 2015, we have taken immediate actions toward:
   - Working with regulatory authorities on steps forward
   - Establishing large-scale manufacturing process

4. Our Highest Priority: Provide Olesoxime to SMA Patients
   Pending discussions with health authorities, country regulations/laws, and drug availability:
   - Open-label study in the EU, hopefully late 2015
   - 2017: Regulatory submission in the US & EU
A virus is used to deliver a functional copy of the SMN gene to patients.

- Normal SMN protein is made in motor neurons and other cells.
- Preclinical efficacy and safety studies enabled an IND.

A Phase 1/2 trial is ongoing at Nationwide Children’s Hospital.
- Preliminary results are being reviewed.
- All patients tolerated the treatment.
- A second trial using intrathecal delivery is planned.
**Irene Gerlach PhD on RG7800: WE ARE COMMITTED TO PEOPLE LIVING WITH SMA**

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<tr>
<th>1</th>
<th>RG7800</th>
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<tbody>
<tr>
<td>• An investigational molecule</td>
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<td>• Oral SMN2 splicing modifier being studied for spinal muscular atrophy</td>
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<td>• Development in collaboration with PTC Therapeutics and the SMA Foundation</td>
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<th>2</th>
<th>SMA mouse model</th>
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| SMN2 mRNA splicing modification  
(*Naryshkin et al 2014, Science*) |

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<th>3</th>
<th>Healthy volunteers – single dose study</th>
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| • Study has explored  
  - Safety & tolerability  
  - Pharmacokinetics  
  - SMN2 splicing (mechanism of action) |

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<th>First Patient Trial (Moonfish) – Type 1-3 SMA</th>
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| • Is exploring  
  - Safety & tolerability  
  - Pharmacokinetics  
  - Effects on SMN2 mRNA & SMN protein |
| • Status: First cohort dosed - clinical hold due to new animal finding |
Eugene Schneider, MD, Vice President, Clinical Development
Isis Pharmaceuticals

Wildon Farwell, MD, Neurology Medical Director
Biogen
ISIS-SMN$_{Rx}$ Studies Currently Enrolling

**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 evaluate the efficacy of the drug (whether early treatment with ISIS-SMN$_{Rx}$, before the signs of the disease are evident, could delay or prevent the development of the disease and its symptoms) and to further investigate the safety and tolerability of ISIS-SMN$_{Rx}$.
- First patient dosed in May 2015

**EMBRACE (Biogen study): Phase 2 study in patients with infantile or childhood-onset SMA**
- Study is designed to evaluate the safety and exploratory efficacy of the drug in a small subset of patients with infantile or childhood-onset SMA who do not meet the age and other criteria of the ongoing Phase 3 studies ENDEAR & CHERISH
LMI070 clinical study (NCT02268552)

Lawrence Charnas & Emilie Voltz on behalf of the SMA Team

Novartis Institutes for Biomedical Research

- **What are the objectives?** Safety and tolerability of LMI070
- **Why LMI070?** Increase the amount of functional SMN protein and prevent motor neuron loss in Type I SMA
- **How?** Oral administration of LMI070, Open label study, no Placebo arm
  - An increase in the dose of LMI070 and continuation of LMI070 treatment beyond the initial 13 week study may be possible when safety is demonstrated
- **Who can participate?** Infants diagnosed with SMA Type I between 1 and 7 months with 2 SMN2 copies
- **Where is the trial?** Currently open in Europe

**III. Expansion for Clinical Efficacy**

Design to be defined

**Part 1. Once weekly dosing**

Ascending dose cohorts
13 week duration

- Are safety and maximum tolerated dose achieved?
- Is there an increase in SMN protein in blood and muscle growth?

- Yes

**Part 2. Multiple doses per week**

12 week duration

- Are safety and tolerability maintained?
- Are there increases in SMN protein level and muscle growth/function?

- Yes

Currently recruiting

Treatment extension