UPDATE ON
IONIS-DMPK-2.5RX

Laurence Mignon, PhD, Ionis Pharmaceuticals, Inc
Myotonic Dystrophy Foundation Annual Meeting, Sept 2016
Overview

- Background on Ionis and platform
- Preclinical Work
- Clinical Update
Improving Patient Lives by Treating Diseases...through targeting RNA

- Ionis Pharmaceuticals was founded in 1989
- Located in California; ~450 employees
- Drug discovery, early development, manufacturing
- A different approach to treating Disease—targeting the RNA

www.ionispharm.com
Three Current Drug Discovery Platforms

**Small Molecules**
- **Lipitor**

**Proteins**
- **Antibodies, e.g. Humira**

**Nucleic Acids**
- **Antisense drugs, e.g. Kynamro**
How Genetic Information Flows From DNA $\rightarrow$ Protein:
The “Central Dogma” of Molecular Biology

Gene $\rightarrow$ mRNA $\rightarrow$ Malfunctioning Protein $\rightarrow$ DISEASE
How Genetic Information Flows From DNA → Protein: The “Central Dogma” of Molecular Biology
Antisense Drugs Target RNA, Not Proteins

Gene (DNA) → Transcription → mRNA

Antisense Oligonucleotide drugs
Works at the RNA level

↓ DISEASE
The Distinctive Genetic Mechanism of DM1:
A target suited for antisense oligonucleotide drugs

- The gene responsible for DM1 is DMPK (Dystrophia Myotonica-Protein Kinase) & found on chromosome 19.
- The disease is characterized by long stretches of repeated base pairs (CTG’s) in the DNA of the DMPK gene; located at one end of the gene (3’-UTR).
  - Called a triplet repeat disease because of the repetition of these three DNA base pairs.
  - Toxic RNA clumps in the nucleus and binds to RNA splicing proteins, resulting in altered splicing events.
- People with DM1 have expanded repeats which can contain anywhere from 50 to more than 4,000 repeats of the CTG.
  - Healthy people have between 5 and 37 repeats.
- Expansion of the section of CTG repeats over each generation results in an earlier-appearing, more severe form of the disease. - This is called "anticipation."
Myotonic Dystrophy at the Molecular Level
Toxic RNA, sequestration of MBNL proteins

Muscleblind (MBNL), a family of RNA binding proteins, is sequestered by toxic RNA forming clumps in the nucleus
• leads to mis-regulation of splicing events in other genes
• results in disease symptoms
Mechanism of Action of IONIS-DMPK-2.5\textsubscript{Rx}

Degradation of toxic RNA, release of MBNL proteins
Preclinical Work with IONIS-DMPK-2.5$_\text{Rx}$

- In different mouse models of DM1, we showed
  - Good knock-down of DMPK in different tissues
  - Improvements in various splicing events
  - Improvements in myotonia
  - Long-lasting effects
In different mouse models of DM1, we showed:
- Good knock-down of DMPK in different tissues
- Improvements in various splicing events
- Improvements in myotonia
- Long-lasting effects

In monkey studies we also showed long-lasting decreases in DMPK mRNA.

DMPK mRNA in Tibialis Anterior of monkeys; 13 weeks of dosing at 40 mg/kg.
Drug Discovery
Steps in the Process

Basic Discovery

Preclinical Clinical Research

Drug Discovery Research

Toxicology/PK Studies

Phase 1 Or Phase 1/2a

Phase 2

Phase 3

Commercial

Post-marketing Research

Investigational New Drug Application (IND)

Current Study

New Drug Application (NDA)
Phase 1/2a Trial tests the safety of the drug in DM1 patients

- **Multiple-Ascending Dose Study**
  - 8 centers in the US
    - University of Rochester, Ohio State, University of Kansas, University of Florida, Kennedy Krieger Institute, University of Utah, Stanford University, Houston Methodist

---

**Screening**
- 4 weeks

**Dosing**
- 6 weeks

**Post-Treatment Evaluation Period**
- 14 weeks

**Wk1 2 3 4 5 6**

Approximately 6 Months
IONIS-DMPK-2.5<sub>Rx</sub> Phase 1/2a Clinical Trial

Inclusion/Exclusion Criteria

- **Main Inclusion Criteria**
  - Males or females; 20-55 years old
  - BMI < 35 kg.m^2
  - Genetic confirmation of DMPK CTG repeat length \( \geq 100 \)
  - Onset of disease after age 12
  - Clinically apparent myotonia equivalent to hand opening time of at least 2 seconds
  - Ambulatory

- **Main Exclusion Criteria**
  - Implanted device for the treatment of cardiac problems (pacemaker, defibrillator)
  - Clinically abnormal ECG or echocardiogram (central cardiac reader)
IONIS-DMPK-2.5\textsubscript{Rx} Phase 1/2a Clinical Trial

Study Objectives of this Safety Trial

- **Primary Objective**
  - Safety and tolerability

- **Secondary Objectives**
  - Blood and urine pharmacokinetics
  - Muscle tissue effects

- **Exploratory Objectives**
  - Biomarkers and clinical outcomes
IONIS-DMPK-2.5<sub>Rx</sub> Phase 1/2a Clinical Trial
Multiple-Ascending Dose Studies Take Time to Complete

- Cohort 1 (100mg) N=8
  - 6 active:2 PBO
- Cohort 2 (200mg) N=8
  - 6 active:2 PBO
- Cohort 3 (300mg) N=8
  - 6 active:2 PBO
- Cohort 4 (400mg) N=12
  - 10 active:2 PBO

- Post-Trt Pd

- 4 original cohorts have been enrolled and patients have completed the study
IONIS-DMPK-2.5<sub>Rx</sub> Phase 1/2a Clinical Trial

Multiple-Ascending Dose Studies Take Time to Complete

- Based on safety data we added a higher dose cohort at 600 mg
- Currently analyzing the data to determine steps forward – data anticipated end of the year
### IONIS-DMPK-2.5<sub>Rx</sub> Phase 1/2a Clinical Trial

#### Subject Demographics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>100 mg</th>
<th>200 mg</th>
<th>300 mg</th>
<th>400 mg</th>
<th>600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td><strong>Age, Median (min, max)</strong></td>
<td>38 (20, 48)</td>
<td>36 (26, 42)</td>
<td>33 (23, 47)</td>
<td>42 (33, 50)</td>
<td>39 (30, 46)</td>
<td>41 (25, 53)</td>
</tr>
<tr>
<td><strong>Gender, Female, n (%)</strong></td>
<td>5 (50%)</td>
<td>5 (83%)</td>
<td>3 (50%)</td>
<td>4 (67%)</td>
<td>8 (80%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td><strong>Race, White, n (%)</strong></td>
<td>8 (80%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>10 (100%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td><strong>Age at Symptom onset Median (min, Max)</strong></td>
<td>23 (12, 31)</td>
<td>22 (13, 33)</td>
<td>16 (13, 35)</td>
<td>23 (13, 45)</td>
<td>17 (12, 29)</td>
<td>30 (19, 44)</td>
</tr>
<tr>
<td><strong>Age at Diagnosis onset Median (min, Max)</strong></td>
<td>31 (16, 40)</td>
<td>27 (24, 35)</td>
<td>28 (10, 43)</td>
<td>26 (23, 49)</td>
<td>28 (16, 37)</td>
<td>31 (19, 45)</td>
</tr>
<tr>
<td><strong>CTG Repeats Median (min, Max)</strong></td>
<td>432 (107, 1006)</td>
<td>271 (136, 546)</td>
<td>432 (256, 670)</td>
<td>616 (210, 1000)</td>
<td>645 (156, 1026)</td>
<td>368 (153, 763)</td>
</tr>
</tbody>
</table>
Study visits are busy for everyone

- Muscle testing (Manual Muscle Test, Quantitative Muscle Testing)
- Myotonia testing (electromyography, video hand opening test, isometric handgrip myotonia)
- Functional tests (6 minute walk test, 30 foot walk/run, climb/descend 4 steps)
- Patient-reported outcomes (Myotonic Dystrophy Health Index, SF-36, CGI-I)

Goal is to standardize the tests across multiple sites, familiarize the patients with the procedures, and determine how reproducible the results are.
There was good reliability among the sites, and among the raters—there was no evidence for higher variance at different sites.
There was good reliability among the sites, and among the raters—there was no evidence for higher variance at different sites.
Summary

- Safety and exploratory data are currently being analyzed—data anticipated end of the year

- Due to the heterogeneity of DM1, individual-based analysis will be needed to better understand the relationship between the effects of the drug, splicing changes, and functional outcomes changes

- This analysis will provide important data for designing future studies in DM1
Clinical Sites and Partners

**University of Rochester**
- Liz Leubbe
- Jeanne Deckdebrun
- Kathryn Eastwood
- Lindsay Baker

**University of Utah**
- Russell Butterfield
- Winter Redd
- Melissa Dixon
- Susan Bonner
- Caren Trujillo
- Evan Pusillo
- Deanna DiBella

**Kansas University**
- Jeffrey Statland
- Mamatha Pasnoor
- Mazen Dimachkie
- Maureen Walsh
- Yunxia Wang
- April McVey
- Kelly Emmons
- Gabrielle Rico
- Nicole Jenci
- Laura Herbelin

**Ohio State University**
- Alan Sanderson
- Stanley Iyadurai
- William Arnold
- Julie Agriesti
- Filiz Muharrem
- Sharon Chelnick
- Colleen Pineda
- Wendy Koesters
- Matthew Yankie

**Stanford**
- Sarada Sakamuri
- Neelam Goyal
- Ana Carolina Tesi Rocha
- Bona Purse
- Jennifer Perez
- Tina Duong
- Richard Gee

**Kennedy Krieger**
- Kathryn Wagner
- William Reid Thompson III
- Carla Grosmann
- Genila Bibat
- Carly Stock

**University of Florida**
- S.H. Subramony
- Guangbin Xia
- Phuong Deleyrolle
- Desmond Zeng
- Aika Konn
- Alison Barnard

**Houston Methodist**
- Tetsuo Ashizawa
- Erika Simpson
- Luis Lay
- Della Brown
- Wendy Schell
- Kayla Butler

Partnered with:

[Myotonic Dystrophy Foundation Logo]

[Biogen Logo]
IONIS-DMPK-2.5<sub>Rx</sub> & Myotonic Dystrophy

Working with the Community

Working to develop a treatment for myotonic dystrophy

Committed to helping create a healthier future