IONIS-DMPK$_{Rx}$ Clinical Program in Myotonic Dystrophy
Laurence Mignon, PhD
Director, Clinical Development

Partnered with Biogen
Development of a Treatment for Myotonic Dystrophy
How Ionis got involved in Myotonic Dystrophy

• Year 2008
• Within 1 week, Frank Bennett heard from:
  – Marigold Foundation
  – Association Française contre les myopathies (AFM)
  – Charles Thornton, University of Rochester
The Search for a Treatment for Myotonic Dystrophy
Why Ionis Became Interested in Myotonic Dystrophy

Myotonic Dystrophy Type 1 (DM1) – A toxic gain-of-function RNA

- Triplet Repeat Disease – expanded CUG repeats in the DMPK gene results in the formation of long “toxic” RNAs
- Disease severity and age of onset is correlated with number of repeats (higher # repeats = more severe disease)
- Broad spectrum of symptoms, including muscle dysfunction and GI tract issues
- Juvenile and adult forms of DM1

Why IONIS became interested in DM1

- Targeting toxic RNA, uniquely possible through ASO technology
- Potential to treat multiple aspects of the disease
- This is a rare autosomal dominant genetic disease with no treatment
- No approved treatment to stop or slow the progression of DM1
How Genetic Information Flows From in DNA $\rightarrow$ Protein
The “Central Dogma” of Molecular Biology
Antisense Drugs Target RNA, Not Proteins

Gene (DNA) → mRNA → Antisense Oligonucleotide

Inhibition of RNA function

Disease-Causing Protein, e.g. huntingtin → ↓ DISEASE
IONSIS-DMPK-2.5_{Rx} is a Gen 2.5 Antisense Drug Designed to Reduce Toxic RNA Levels

- First muscle target
- IONSIS-DMPK-2.5_{Rx} targets toxic DMPK RNAs in multiple tissues
- RNase H1-mediated degradation of DMPK RNA releases sequestered proteins and restores normal cellular function

STAGE 1
IONSIS-DMPK-2.5_{Rx} targets toxic DMPK RNAs in multiple tissues

STAGE 2
RNase H1 Substrate
↑ affinity
↑ stability
↑ tolerability

RNase H1 Substrate
MOE
DNA
MOE
cET

STAGE 3
MBNL1 FREE to function in RNA splicing in the nucleus protein

Drug Discovery
Steps in the Process

Preclinical Clinical Research

Clinical Research

Post-marketing Research

Basic Research

Drug Discovery Research

Toxicology/PK Studies

Phase 1 Or Phase 1/2a

Phase 2

Phase 3

Commercial

Investigational New Drug Application (IND)

IONIS-DMPK$_{Rx}$ CS2 trial

Learnings from the trial

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
  - 5 different dose levels are tested: 100mg, 200mg, 300mg, 400mg, 600mg
  - Short 6-week treatment duration
IONIS-DMPK_{Rx}-CS2: Phase 1/2a MAD Study in Adult Patients with Myotonic Dystrophy Type 1

Study Objectives

• Primary Objective
  – safety and tolerability

• Secondary Objectives
  - blood and urine pharmacokinetics
  – muscle tissue effects

• Exploratory Objectives
  – biomarkers and clinical outcomes
IONIS-DMPK\textsubscript{Rx}-CS2: Phase 1/2a MAD Study in Adult Patients with Myotonic Dystrophy Type 1

Main Inclusion/Exclusion Criteria

- **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

- **Exclusion Criteria**
  - Implanted device for the treatment of cardiac problems (pacemaker, defibrillator)
  - Clinically abnormal ECG or echocardiogram (central cardiac reader)
• Original protocol included 4 cohorts; added the 5th cohort at 600 mg based on satisfactory safety profile

• 2 patients treated with placebo in each cohort
## Learnings from the IONIS-DMPK\textsubscript{Rx}-CS2 Trial

### Subject Baseline 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>
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<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>
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<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 Sx 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 Dx 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>
<tr>
<td><strong>Isometric Handgrip Myotonia Relaxation Time in seconds, Median (Min, Max)</strong></td>
<td>9.8 (1.4, 11.9)</td>
<td>7.6 (2.1, 11.3)</td>
<td>11.1 (2.3, 12.5)</td>
<td>5.4 (1.4, 7.6)</td>
<td>8.9 (2.8, 12.4)</td>
<td>1.3 (0.5, 10.4)</td>
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<tr>
<td><strong>6 Minute Walk Test Median (Min, Max)</strong></td>
<td>504 (285-661)</td>
<td>433 (357-545)</td>
<td>435 (260-645)</td>
<td>359 (223-640)</td>
<td>414 (283-508)</td>
<td>400 (250-637)</td>
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<td><strong>Myotonic Dystrophy Health Index, total score Median (Min, Max)</strong></td>
<td>21 (5-52)</td>
<td>36 (34-41)</td>
<td>31 (30-47)</td>
<td>22 (5-48)</td>
<td>28 (20-47)</td>
<td>32 (17-44)</td>
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</table>
Learnings from the IONIS-DMPK$_{Rx}$-CS2 Trial

Heterogeneity of Patients

• Heterogeneity of patient population within and across dosing groups
  – Not unexpected, but exemplifying the mutli-systemic nature of the disease
  – Complicates interpretation of dose response relationship for clinical and molecular outcomes
    • Inclusion/exclusion criteria to focus on a more homogenous population
    • Need to use stratification for later stage trials
• Ongoing natural history studies aimed at helping better understand the heterogeneity and the progression of the disease throughout the spectrum of the disease
Learnings from the IONIS-DMPK$_{Rx}$-CS2 Trial
Outcomes Measures

- Myotonia tests:
  - Isometric handgrip myotonia relaxation time

**1-2 day, in-person physical therapist training provided throughout the study:**
- Study start
- Yearly thereafter

Lead trainer available for 1:1 sessions in person or by phone throughout the study

- 6-minute walk test
- 4 steps climb/descend

- Patient-reported outcomes
  - MDHI

- Trial generated solid and reproducible data
  - Emphasized ability to do a multi-center trial
  - Variabilities were seen between patients
  - Natural history and network studies have laid the groundwork with respect to clinical trial readiness
Learnings from the IONIS-DMPK<sub>Rx</sub>-CS2 Trial
Reliability of Outcomes Measures Across Clinical Sites

Ankle Dorsiflexion as measured by QMT

Hand Grip as measured by QMT
Learnings from the IONIS-DMPK\textsubscript{Rx}-CS2 Trial

Biomarker Analysis

- Good quality of muscle biopsies across sites
- Good quality RNA extraction
- Initial biomarker analysis also showed variability—similar to outcomes measures
  - Changes were modest, with some trends
- More work required to better understand
  - How biomarkers are modulated
  - Impact of disease duration on biomarker changes
  - Impact of MBNL level on biomarker changes
Learnings from the IONIS-DMPK$_{Rx}$-CS2 Trial
Muscle Pharmacokinetics – The Most Important Finding

• Muscle pharmacokinetics
  – Originally we did not anticipate to do this
    • small tissue size
    • need to prioritize biomarker analysis
  – Improvements in analysis methods, especially in the ability to use very small pieces of tissue, allowed us to measure drug concentration
IONIS-DMPK$_{Rx}$ Did Not Reach Target Concentration of $\sim$10 ug/gm in the Muscle

Target tissue concentration was determined to be 10-15 ug/gm to get $\sim$50% KD in muscle.

Drug levels were based on estimated ED50 (25 mg/kg) and on muscle concentrations in mouse from GLP study.

Clinical data suggest that a 5 to 10-fold increase in drug concentration, or a 5 to 10-fold increase in potency, or combination of both may be required.
So What Now?

Antisense Oligonucleotides Designed to Human DMPK pre-mRNA
Example of a More Potent ASO Identified by Deeper Screening

Dose Dependent inhibition of human DMPK transgene in DMSXL Transgenic Mice

* TA Muscle *

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<th>Dose (mg/kg)</th>
<th>IONIS-DMPK-2.5Rx</th>
<th>DMPK ASO A</th>
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<tbody>
<tr>
<td>25 m</td>
<td>30</td>
<td>30</td>
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<tr>
<td>50 m</td>
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<td>30</td>
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<tr>
<td>100 m</td>
<td>30</td>
<td>30</td>
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* Quadriceps *

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<tr>
<td>25 m</td>
<td>60</td>
<td>20</td>
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<tr>
<td>50 m</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>100 m</td>
<td>60</td>
<td>20</td>
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Working on Better Chemistries to Improve Activity of DMPK ASO

![5'-N-Palmitoylhexylamino]

<table>
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<tr>
<th>Isis #</th>
<th>Sequence (5' to 3')</th>
<th>Conjugate (X)</th>
<th>Heart ED$_{50}$ (mg/kg/wk)</th>
<th>Quad ED$_{50}$ (mg/kg/wk)</th>
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<tr>
<td>486178</td>
<td>ACAATAAAATACCGAGG</td>
<td>none</td>
<td>21</td>
<td>11.2</td>
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<td>877864</td>
<td>XoACAATAAAATACCGAGG</td>
<td>5'-C16-hexyamino</td>
<td>5.3</td>
<td>4.8</td>
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**Heart**

- Non-LICA ED$_{50}$ 21 mg/kg
- LICA-M ED$_{50}$ 5.3 mg/kg

**Quadriceps**

- Non-LICA ED$_{50}$ 11.2 mg/kg
- LICA-M ED$_{50}$ 4.8 mg/kg
Drug Discovery
Steps in the Process

Basic Research
Drug Discovery Research
Toxicology/PK Studies
Phase 1
Or Phase 1/2a
Phase 2
Phase 3
Commercial

Post-marketing Research

Preclinical Clinical Research

Investigational New Drug Application (IND)

Identification of drug with increased potency

IONIS-DMPK<sub>Rx</sub>
CS2 trial

New Drug Application (NDA)
Conclusion

• Collaborative effort (sites, patient advocacy groups, patient community) has laid the foundation for future trials

• Due to the heterogeneity of patients with myotonic dystrophy it is important to have robust longitudinal data across the entire population for the measures used in a trial

• Our current research efforts focus on optimization of a drug with better potency

• Extracting all the data we can from the CS2 trial

• Ionis is committed to the development of a therapy for myotonic dystrophy
# Acknowledgments

THANKS TO ALL THE PATIENTS AND THEIR FAMILIES TO ALL OF YOU FOR YOUR SUPPORT AND HARD WORK

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<tr>
<th>University of Rochester</th>
<th>University of Utah</th>
<th>Kansas University</th>
<th>Ohio State University</th>
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<tr>
<td>Richard Moxley III</td>
<td>Nicolas Johnson</td>
<td>Richard Bahron</td>
<td>John Kissel</td>
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<td>Charles Thornton</td>
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<td>Matthew Yankie</td>
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<th>Stanford</th>
<th>Kennedy Krieger</th>
<th>University of Florida</th>
<th>Houston Methodist Neurological Institute</th>
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<tr>
<td>John Day</td>
<td>Doris Leung</td>
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<td>Erika Simpson</td>
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<td>Sarada Sakamuri</td>
<td>Kathryn Wagner</td>
<td>S.H. Subramony</td>
<td>Luis Lay</td>
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<td>Bona Purse</td>
<td>William Reid Thompson III</td>
<td>Guangbin Xia</td>
<td>Della Brown</td>
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<td>Jennifer Perez</td>
<td>Genila Bibat</td>
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<td>Wendy Brown</td>
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<td>Nikia Stinson</td>
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<td>Wendy Schell</td>
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Partnered with:

[Logo of the Myotonic Dystrophy Foundation: Care and a Cure]

[Logo of Biogen]