DYSTANCE 51: A Phase 2/3 Clinical Trial of Investigational Suvodirsen in Patients with Duchenne Muscular Dystrophy

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Overview

• Wave approach to development of genetic medicines
• Review clinical program in DMD targeting exon 51 skipping (Suvodirsen and DYSTANCE51)
• Considerations to running this rare disease clinical trial
• Selection of suvodirsen’s Phase 2/3 study into the FDA Complex Innovative Design (CID) Pilot Program and how it is helping to address certain considerations
Wave chemistry controls nucleic acid backbone chirality

Traditional backbone chemistry

- Stereorandom
  - >500,000 permutations in every dose

Wave backbone chemistry

- Stereopure
  - One defined and consistent profile
DMD: a progressive, fatal childhood disorder

• Fatal, X-linked genetic neuromuscular disorder characterized by progressive, irreversible loss of muscle function, including heart and lung

• Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function

• Current disease modifying treatments have demonstrated minimal dystrophin expression and clinical benefit has not been established

• Impacts 1 in every 5,000 newborn boys each year; 20,000 new cases annually worldwide

Exon skipping with stereopure oligonucleotides has the potential to enable production of meaningful levels of functional dystrophin which is expected to result in therapeutic benefit

Exon 51: Suvodirsen induces dose-dependent exon skipping and dystrophin restoration *in vitro*

**Legend:**
- Suvodirsen
- PMO oligonucleotide (stereorandom)
- PS oligonucleotide (stereorandom)

**Graph:**
- X-axis: Treatment Concentration, µM
- Y-axis: Percent Exon Skipping of Total DMD Transcript

**Image:**
- Marker
- 0 µM, 0.1 µM, 0.3 µM, 1 µM, 3 µM, 10 µM
- Skeletal Muscle Tissue (2-fold less lysate)
- Dystrophin (400-427 kDa)
- Vinculin (120 kDa)

PMO = phosphorodiamidate morpholino; PS = phosphorothioate.
Suvodirsen clinical program

**Phase 1**

**OBJECTIVE**
Determine safety and tolerability profile and select dose(s) for OLE and Phase 2/3

**STUDY DESCRIPTION**
Phase 1 single ascending dose clinical trial

**KEY MILESTONES**
- Study complete
- Safety and tolerability profile supports Phase 2/3 initiation
- Doses selected for Phase 2/3 and OLE

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**Open-Label Extension (OLE)**

**OBJECTIVE**
Investigate safety & efficacy: Provide data that will be an important component of submission for accelerated approval in US

**STUDY DESCRIPTION**
Multi-dose, open-label study open to patients from Phase 1

**KEY MILESTONES**
- Initiated in August 2018
- On track to deliver interim analysis of dystrophin expression in H2 2019

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**Phase 2/3 (DYSTANCE51)**

**OBJECTIVE**
Establish safety & efficacy: Provide data as basis of regulatory submissions globally

**STUDY DESCRIPTION**
Phase 2/3 clinical trial to assess clinical efficacy and dystrophin expression

**KEY MILESTONES**
- Selected for FDA pilot program for complex innovative trial designs
- Expect to initiate in July 2019

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Dystrophin readout expected H2 2019
Clinical trial considerations

- Selection of patient population
  - Variable disease progression
    - Spontaneous improvement
    - Slow progression
    - Sudden decline
- Recruitment in rare disease trial
- Muscle integrity/variability
  - Location/sampling
  - Tissue preparation/quality
  - Assay development
- Insensitive/variable clinical endpoints
- Possibility of accelerated approval based on biomarker results and disease-specific Guidance
- Highly engaged and educated DMD families
FDA Complex Innovative Design (CID) Pilot Program

• The FDA CID pilot program is an initiative under the 21st Century Cures Act, with an objective to modernize clinical trial design and help streamline and advance drug development and inform regulatory decision-making.

• Two key criteria for evaluating submissions:
  – Innovative features of the trial design
  – Therapeutic need (disease areas with limited or no treatment options)

• Wave’s application includes a plan to leverage DMD historical control data to augment the placebo arm of the suvodirsen Phase 2/3 clinical trial, among other innovative design elements

• Through this pilot program, Wave intends to reduce the number of patients required to deliver conclusive clinical efficacy results, thereby minimizing the number of patients required in the placebo treatment arm and potentially accelerating study completion
Wave’s participation in the CID Program

<table>
<thead>
<tr>
<th>Goals</th>
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<tbody>
<tr>
<td><strong>Dystrophin analysis</strong></td>
<td>• Bayesian repeated measures model</td>
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<td>• Trial adaptations based on interim dystrophin analyses</td>
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<td><strong>NSAA analysis</strong></td>
<td>• Bayesian disease progression model</td>
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<td>• Inclusion of historical control data</td>
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<td>• Use of the predicted probability of success to potentially adjust enrollment</td>
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DYSTANCE 51 Phase 2/3 Trial Study Design

- **Screening**
  - Week -6
  - Week 0
  - Week 1

- **Randomization**
  - Week 12
  - Week 22
  - Week 24
  - Week 36
  - Week 46
  - Week 48

- **Biopsy**
- **NSAA**

- **Placebo once weekly (~50 patients)**
- **Suvodirsen 3 mg/kg once weekly (~50 patients)**
- **Suvodirsen 4.5 mg/kg once weekly (~50 patients)**

- **OLE**

*OLE=Open-Label Extension*
# Potential Sources for Historical Control Data

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<tr>
<th>Type of Study</th>
<th>Study Name or Sponsor</th>
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<th>Data Manager or PI*</th>
<th>Number of Untreated Patients</th>
<th>Status</th>
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<td>B5161002 (NCT02310763)</td>
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<td>Cooperative International Neuromuscular Research Group</td>
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<td>CureDuchenne (Biomarin)</td>
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*C-Path D-RSC=Critical Path Institute Duchenne Regulatory Science Consortium; DMD=Duchenne muscular dystrophy; NA=not applicable; PI=principal investigator; TRiNDS=Therapeutic Research in Neuromuscular Disorders Solutions.

*: estimated
^: Critical Path Institute Duchenne Regulatory Science Consortium
&: Patients treated with etruzomide but negative study
Conclusions

- Wave Life Sciences is developing an investigational stereopure oligonucleotide, suvodirsen, as a potential disease-modifying therapy for patients with Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping

- The Phase 2/3 clinical trial, DYSTANCE 51, was selected for the US Food and Drug Administration Complex Innovative Trial Design (CID) Pilot Program and was designed with input from global regulatory authorities and the global DMD community

- The innovative design of DYSTANCE 51 leverages DMD historical control data to augment clinical trial requirements, including potentially minimizing the number of patients required to deliver conclusive results

- This approach may also inform the design of future rare disease clinical trials