Suvodirsen, an investigational therapy for exon 51 skipping in DMD

Parent Project Muscular Dystrophy Annual Conference
June 29, 2019
Forward-looking statements

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25 Years of Progress

PPMD Founded

Over $500M invested in DMD by the federal government

Average lifespan of people with Duchenne increased from late teens to early 30s

Over 40 pharmaceutical companies in the DMD space

Expanding list of therapies in clinical trial

- Dystrophin restoration: exon skipping, gene therapy
- Disease pathways: fibrosis, inflammation, muscle growth, cardiomyopathy

PPMD 25th Annual Congress

1994

Passage of 5 federal bills

2019

2 therapies approved in Duchenne since 2016
History of oligonucleotide therapeutics

- **Backbone modifications**
  - Introduce chiral centers
  - Generate mixtures

- **Sugar modifications**

- **Drug approvals (FDA)**
  - Chiral Phosphorothioate
  - Chiral Phosphorodiamidite Morpholino (PMO)
  - Mixtures of $2^n$ molecules ($n=$No. of chiral centers) 
    ~500,000 different molecules per dose

- **2000**
  - Fortiversen
  - Pegaptanib
  - Mipomersen
  - Eteplirsen
  - Nusinersen

- **1975**
  - Oka N, Wada T, Saigo K. JACS. 2002

- **2019**
  - WAVE Stereopure ASOs enter clinic
Potential benefits of stereopure oligonucleotide approach to treating Duchenne muscular dystrophy

**Delivery**
- Entry into cells (including progenitor cells) via free-uptake
- Nuclear entry

**Repeat administration**
- Repeat administration to address muscle cell turnover and need for broad distribution

**Exon skipping**
- Production of meaningful levels of functional dystrophin protein

**Functional dystrophin**
- Established manufacturing process for oligonucleotides

**Scalable manufacturing**
- Established manufacturing process for oligonucleotides

Uptake in the muscle cell nucleus improves with stereopure oligonucleotides vs. stereorandom *in vitro*

Data derived from preclinical research with muscle cells in a dish (*in vitro*).

Methods: Free uptake of ASOs in 18 hour differentiating human DMD myoblasts (Δ48-50).
Suvodirsen increased dystrophin restoration *in vitro*

Data derived from preclinical research with muscle cells in a dish (*in vitro*).


PMO ASO = morpholino antisense oligonucleotide; PS ASO = phosphorothioate antisense oligonucleotide.
## Suvodirsen: Comprehensive clinical program

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 1 Open-Label Extension (OLE)</th>
<th>Phase 2/3 (DYSTANCE 51)</th>
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</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Determine safety and tolerability profile and select dose(s) for OLE and Phase 2/3</td>
<td>Investigate long-term efficacy and safety</td>
</tr>
<tr>
<td>Study Description</td>
<td>Phase 1 single ascending dose clinical trial</td>
<td>Multi-dose, open-label study open to patients from Phase 1</td>
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<tr>
<td>Key Milestones</td>
<td>• Safety and tolerability profile supports Phase 2/3 initiation • Two doses selected for Phase 2/3 trial • <strong>Study complete</strong>: Results presented at MDA and PPMD*</td>
<td>• Initiated in August 2018 • On track to deliver <strong>interim analysis of dystrophin expression in 2H 2019</strong></td>
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**Dystrophin readout expected 2H 2019**

*Presented at PPMD 2019, Poster #8*
Suvodirsen single dose results support initiation of a Phase 2/3 trial

• Suvodirsen was generally safe and well tolerated at doses up to and including 5 mg/kg
  – Most common adverse events were associated with infusions (happening within 24 hours), mild to moderate in intensity, and resolved with symptomatic treatment
    • Fever, headache, vomiting, and rapid heart rate
  – Similar symptoms with increased severity at doses above 5 mg/kg

• Predictive modeling based on preclinical data and these Phase 1 data supported selection of doses for the Phase 2/3 trial
Patients continue to successfully transition to OLE study of suvodirsen at Phase 2/3 dose levels

Phase 1 open-label extension

Baseline muscle biopsies

Patients receive weekly doses at Phase 1 dose levels

Phase 2/3 dose level selected

Begin transitioning patients to weekly doses at Phase 2/3 dose levels

Follow-up muscle biopsies

As of June 18, 2019 at Phase 2/3 dose levels:
- **25 patients** dosed
- **148 total doses** administered

~**37 patients** expected to transition from Phase 1 into OLE

Interim analysis of dystrophin expression from muscle biopsies expected in 2H 2019
As of June 18, 2019:

- First 25 patients dosed at Phase 2/3 dose levels in ongoing OLE
  - No discontinuations
- 148 total doses administered
- Weekly dosing and transition from Phase 1 continues
- On track for interim dystrophin expression data 2H 2019

**Patients receiving Phase 2/3 dose levels**

**As of June 18, 2019:**

- First 25 patients dosed at Phase 2/3 dose levels in ongoing OLE
  - No discontinuations
- 148 total doses administered
- Weekly dosing and transition from Phase 1 continues
- On track for interim dystrophin expression data 2H 2019
A randomized, double-blind, placebo-controlled, efficacy and safety study of suvodirsen in ambulatory patients with DMD
DYSTANCE 51 Phase 2/3 study initiated

- Global study with enrollment anticipated in the US, Canada, Europe, Australia, Japan
- ~150 boys, aged 5-12 years inclusive, genetically confirmed diagnosis of DMD with mutations amenable to exon 51 skipping
- Weekly intravenous dose of suvodosiren or placebo for 48 weeks
- Patients to enter open-label extension phase of the study to receive ongoing treatment with suvodosiren after completion of 48 week the placebo-controlled portion
DYSTANCE 51 designed to measure functional outcomes

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<th>Objectives</th>
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<td><strong>Primary</strong></td>
<td>• Change from baseline in dystrophin protein levels (western blot, shoulder muscle) through 46 weeks (US/other regions as applicable)</td>
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<td>• Change from baseline in NSAA through 48 weeks (EU/Japan)</td>
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<td><strong>Secondary</strong></td>
<td>• Change from baseline in NSAA through 48 weeks (US/other regions)</td>
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<td></td>
<td>• Change from baseline in dystrophin protein levels (western blot, shoulder muscle) through 46 weeks (US/other regions as applicable)</td>
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<td>• Change from baseline through 48 weeks in</td>
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<td>• Upper limb proximal strength assessed by handheld myometry</td>
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<td>• Time to walk/run 10 meters</td>
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<td></td>
<td>• Time to perform 4-stair climb</td>
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<td>• Forced vital capacity</td>
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<td>• 95th percentile of stride velocity measured using the ActiMyo wearable device</td>
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<tr>
<td><strong>Exploratory</strong></td>
<td>• Change from baseline through 48 weeks in</td>
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<td></td>
<td>• PedsQL</td>
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<td></td>
<td>• Upper limb function assessed by PUL 2.0</td>
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NSAA=North Star Ambulatory Assessment; PedsQL=Pediatric Quality of Life Inventory; PUL=Performance of the Upper Limb.
DYSTANCE 51 accepted into FDA Complex Innovative Trial Design (CID) Pilot Program

CID Objective
• Modernize clinical trial design
• Streamline and advance drug development
• Inform regulatory decision-making

CID Criteria
• Innovative features of the trial design
• Therapeutic need (disease areas with limited or no treatment options)

Wave’s application
Includes plan to use:
• DMD historical control data
• Innovative statistical methods

Our Goal
Reduce the number of patients required to deliver conclusive clinical efficacy results, potentially minimizing the number of placebo patients and accelerating study completion
## Trial design by and for the Duchenne community

<table>
<thead>
<tr>
<th>Community Advice</th>
<th>Wave Action</th>
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| **Limit** exposure to placebo when possible | • Applied for and accepted into US FDA CID Pilot Program  
• Use historical control data to potentially reduce number of patients required for conclusive clinical efficacy results |
| **Minimize** the number of biopsies | • Each patient will have two biopsies: one at baseline, and one at follow-up visit |
| Provide access to open-label treatment | • Patients in DYSTANCE 51 will enter an open-label phase of the study to receive treatment with suvodirsen |
| **Listen and communicate** appropriately around the clinical trial and its results | • Phase 1 results communicated shortly after study completion at meetings and in an open letter  
• Proactively sharing trial design and placebo data from DYSTANCE 51 to enable future innovative trials  
• Working with global advocacy groups on study awareness & participant support |
**Committed to the Duchenne Community**

<table>
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<tr>
<th>THERAPEUTIC AREA/MODALITY</th>
<th>TARGET</th>
<th>DISCOVERY</th>
<th>CANDIDATE</th>
<th>CLINICAL</th>
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<tbody>
<tr>
<td>MUSCLE</td>
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<tr>
<td>Duchenne muscular dystrophy</td>
<td>Exon-skipping</td>
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<td><strong>Suvodirsen</strong></td>
<td>Exon 51</td>
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<td>OLE and Phase 2/3</td>
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<tr>
<td><strong>WVE-N531</strong></td>
<td>Exon 53</td>
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<td>exons 44, 45, 52, 54, 55</td>
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On behalf of Wave, **thank you** to all the patients, families, advocacy organizations, healthcare providers, and regulators with whom we have collaborated, particularly the families participating in our clinical trials.