# Forward looking statements

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Introduction to Wave
Biotechnology company developing targeted therapies for patients impacted by rare diseases

- Founded in 2009 – merger of Chiralgen and Ontorii
- Rationally designed stereopure nucleic acid therapeutics
- Utilizing multiple modalities including antisense, exon skipping and RNAi
- Expertise and core focus in neurology
- DMD Exon 51 Phase 1 trial ongoing, safety data expected Q3 2018
- DMD Exon 53 Phase 1 trial expected to initiate in Q1 2019
- Active research in additional DMD exon skipping approaches underway
- In-house manufacturing capability ranging from high throughput to large scale GMP production
Our growing pipeline is focused primarily on neuromuscular and central nervous system disorders.

<table>
<thead>
<tr>
<th>CNS diseases</th>
<th>TARGET</th>
<th>BIOMARKER</th>
<th>MECHANISM</th>
<th>TRIAL PHASE</th>
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<td>Phase 1b/2a</td>
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<table>
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<td>Dystrophin</td>
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<td>Phase 1</td>
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<td>Triglyceride</td>
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<td>Multiple (4) ‡</td>
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*S* = silencing.  
*A* = allele-specific silencing.  
**E** = exon skipping.

† During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.  
‡ Pfizer has nominated four undisclosed targets in addition to APOC3.
Building oligonucleotides

- Each oligonucleotide is made of strings of nucleotides (typically 20) held together by chemical linkages

- Linkages can be modified by phosphorothioate or morpholino chemistry

- With traditional synthesis methods, the orientation of atoms at each linkage occurs randomly, adopting either an “left” (Sp) or “right” (Rp) orientation

- This results in a mixture of >500,000 molecules \(2^{19}\)

- Random orientations have implications for drug stability, efficacy, and safety
Building optimized and stereopure oligonucleotides

STANDARD OLIGONUCLEOTIDE APPROACHES (PS, PMO, etc.)

Pharmacologic properties include >500,000 permutations in every dose

Impact:
Unreliable therapeutic effects
Unintended off-target effects

WAVE RATIONAL DESIGN

Stereochemistry enables precise control, ability to optimize critical constructs into one defined and consistent profile

Impact:
Potential for safer, more effective, targeted medicines that can address difficult-to-treat diseases
Creating a new class of potential therapies

Exon skipping therapeutic approach

- Exon skipping approaches have the goal of enabling natural production of functional dystrophin protein.
- Partial restoration of dystrophin is expected to result in therapeutic benefit.

Dysfunctional splicing

Exon skipping approach
WVE-210201
An investigational stereopure exon 51 targeted oligonucleotide
WVE-210201 induces dose-dependent exon skipping in vitro

<table>
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<th>Treatment Concentration (μM)</th>
<th>mRNA Skipping Efficiency (% Exon Skipping)</th>
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<tr>
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Data derived from in vitro preclinical research; WVE-210201 currently being evaluated in clinical studies.

Methods: Free uptake of ASO in human DMD myoblast cells. Skipping quantified by TaqMan assay.

PMO ASO = Morpholino Antisense Oligonucleotide; PS ASO = Phosphorothioate Antisense Oligonucleotide.
WVE-210201 increases natural dystrophin production \textit{in vitro}

Green bands below show level of natural dystrophin protein expression with brighter/bolder bands indicating more protein expression.

Methods: Free uptake of ASO in human DMD myoblasts ($\Delta$48-50). Protein expression determined by western blot.

PMO ASO = Morpholino Antisense Oligonucleotide; PS ASO = Phosphorothioate Antisense Oligonucleotide.

Data derived from \textit{in vitro} preclinical research; WVE-210201 currently being evaluated in clinical studies.
Wave’s chemistry improves oligonucleotide uptake in the nucleus where splicing occurs

Stereopure oligonucleotides are designed to readily enter the nuclei of cells under free-uptake conditions, which approximates natural delivery in the body.

Free uptake of stereorandom and stereopure ASOs

Data derived from *in vitro* preclinical research; WVE-210201 currently being evaluated in clinical studies.

Methods: Free uptake of ASOs in 18 hour differentiating human DMD myoblasts (Δ48-50).
WVE-210201 produces exon skipping in multiple muscle tissues including heart muscle in monkeys

**Methods:** Healthy monkeys received 5 doses of 30 mg/kg/week SC for 4 weeks. Muscle tissues were collected 2 days after the last dose.

**Nested PCR Assay**

5 doses @ 30 mg/kg/week for 4 weeks healthy NHP by subcutaneous dosing

Data derived from *in vitro* preclinical research; WVE-210201 currently being evaluated in clinical studies.
WVE-210201 supported by correlation of *in vitro* and *in vivo* data in mdx 23 mice

**Methods:**

**In vitro** - Free uptake of ASO in human DMD myoblast cells.

**In vivo** - 4 weekly IV dosing.

Necropsy 96h post last dose. RNA skipping efficiency determined by Taqman assay.

*Representative muscle tissue*
Exon skipping efficiency yields substantial natural dystrophin protein restoration in \textit{mdx} 23 mice

Surrogate stereopure oligonucleotide restored 70-90\% of natural dystrophin production \textit{in vivo}

*Numbers indicate individual animals

Methods: \textit{mdx} 23 mice received 4 weekly IV doses (150 mg/kg). Tissues collected 96 hours post final dose. Protein expression determined by western blot.
WVE-210201 clears rapidly from liver and kidney in mice

Single *in vivo* IV dose at 30 mg/kg in *mdx* 23 mice

- WVE-210201 shows faster clearance from liver and kidney compared with a drisapersen analog made by Wave
- Wave’s stereopure oligonucleotides can be optimized to allow faster clearance

Data derived from *in vivo* preclinical research; WVE-210201 currently being evaluated in clinical studies.

Methods: *mdx* 23 mice received a single dose of ASO 30 mg/kg IV.
# WVE-210201 Phase 1 clinical trial

**ClinicalTrials.gov Identifier:** NCT03508947

## Design

<table>
<thead>
<tr>
<th>Methods</th>
<th>Global, randomized, double-blind, placebo-controlled, single ascending dose Phase 1 study</th>
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</table>
| Endpoints     | **Primary** Safety and tolerability  
               | **Secondary** Pharmacokinetics                                                        |
| Study Sites   | North America, Europe                                                                   |
| Dosing        | 3:1 randomization to WVE-210201 or placebo by IV infusion                              |

## Key Enrollment Criteria

- Boys ages 5 to 18, amenable to exon 51 skipping
- Ambulatory and non-ambulatory
- Prior treatment with eteplirsen and ataluren allowed (following appropriate washout period)
- Prior treatment with drisapersen excluded
- Must be on a stable steroid regimen ≥1 month prior to enrollment

- Safety data expected in Q3 2018
- Participants eligible for planned open-label extension study with muscle biopsy
WVE-210201 Next Steps

• Next WVE-210201 study is being designed with the DMD community and regulators
  – Design: Double-blind, placebo-controlled, multi-dose study assessing dystrophin expression and clinical outcomes
  – Measurement of dystrophin via standardized Western Blot
  – Interim analysis of dystrophin expression in muscle biopsies
  – Efficacy data readout anticipated H2 2019
Wave’s Progress in DMD
Stereopure oligonucleotides for DMD

• Wave’s chemistry platform allows us to precisely design, optimize and manufacture stereopure oligonucleotides

• Stereopure molecules are intended to enhance the efficiency of exon skipping, with the goal of delivering and maintaining meaningful levels of natural dystrophin protein restoration

• Learnings from WVE-210201 and surrogate stereopure oligonucleotides are being applied to Wave’s exon 53 and future DMD programs
Data derived from \textit{in vitro} preclinical research.

Methods: Free uptake of ASOs in a DMD patient-derived \(\Delta 45-52\) cell line. Skipping determined by TaqMan assay.

Exon 53: Stereopure lead molecules demonstrate increasing exon skipping efficiency
Exon 53 targeting oligonucleotides rapidly distribute to muscle (24 hours after IV injection)

Data derived from *in vivo* preclinical research.

Methods: A single dose of stereopure ASO 30 mg/kg IV was administered to *mdx* 23 mice. Tissues collected 24 hours post dose and ASO was detected in muscles using ViewRNA.
Wave’s commitment to DMD

- Exon 51: WVE-210201 Ph1 ongoing clinical trial
- Exon 53: planned clinical trial initiation in Q1 2019
- Develop candidates for additional exons

- Deep Genomics is a world leader in artificial intelligence
- Collaboration to identify new muscle targets, and optimal regions or sequences within those targets, to be addressed by Wave’s stereopure oligonucleotides
- The goal is to help as many patients as possible

Deep Genomics muscle research collaboration

WAVE CHEMISTRY PLATFORM
As we work to advance potential therapies for boys with DMD we will continue to:

• Put patients’ and families’ best interests first

• Be good listeners and trusted community partners

• Move with a true sense of urgency