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Suvodirsen, an investigational therapy for exon 51 skipping in DMD

Parent Project Muscular Dystrophy Annual Conference
June 29, 2019

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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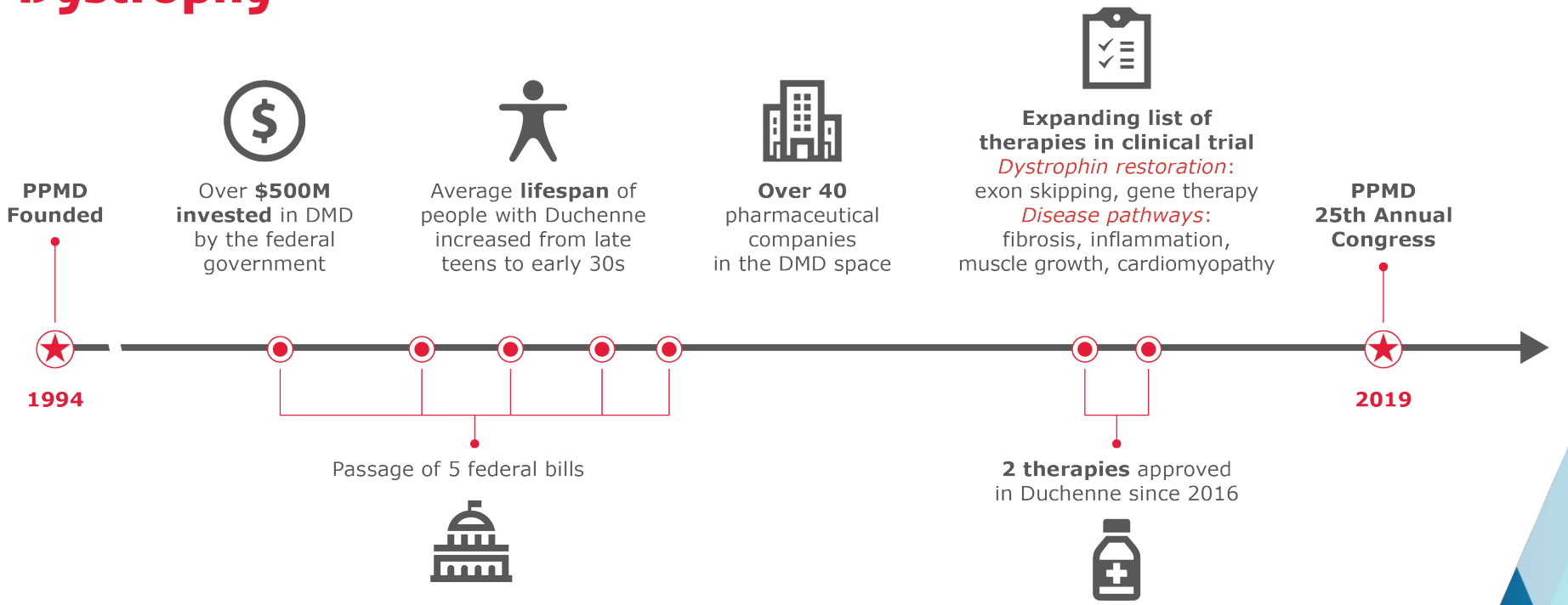
Parent Project Muscular Dystrophy

JOIN THE FIGHT. END DUCHENNE.

25 Years of Progress



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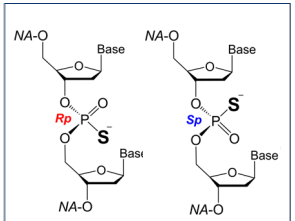
History of oligonucleotide therapeutics

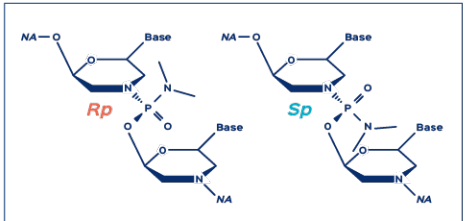
Backbone modifications
- Introduce chiral centers
- Generate mixtures

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

1975

Stec WJ, et al. J Am Chem Soc. 1989

2000

Oka N, Wada T, Saigo K. JACS. 2002

Fomiversen

Pegaptanib

Mipomersen

Nusinersen

Eteplirsen

2019

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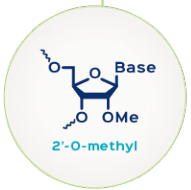
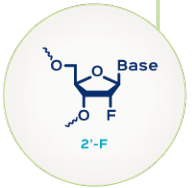
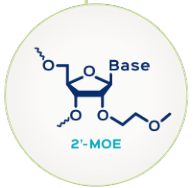
WAVE Stereopure ASOs enter clinic



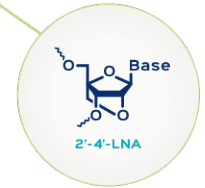
2'-O-methyl



2'-F



2'-MOE



2'-4'-LNA

2'-4'-cEt

Potential benefits of stereopure oligonucleotide approach to treating Duchenne muscular dystrophy

Delivery

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

Functional dystrophin

- Production of meaningful levels of functional dystrophin protein

Repeat administration

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

Scalable manufacturing

- Established manufacturing process for oligonucleotides

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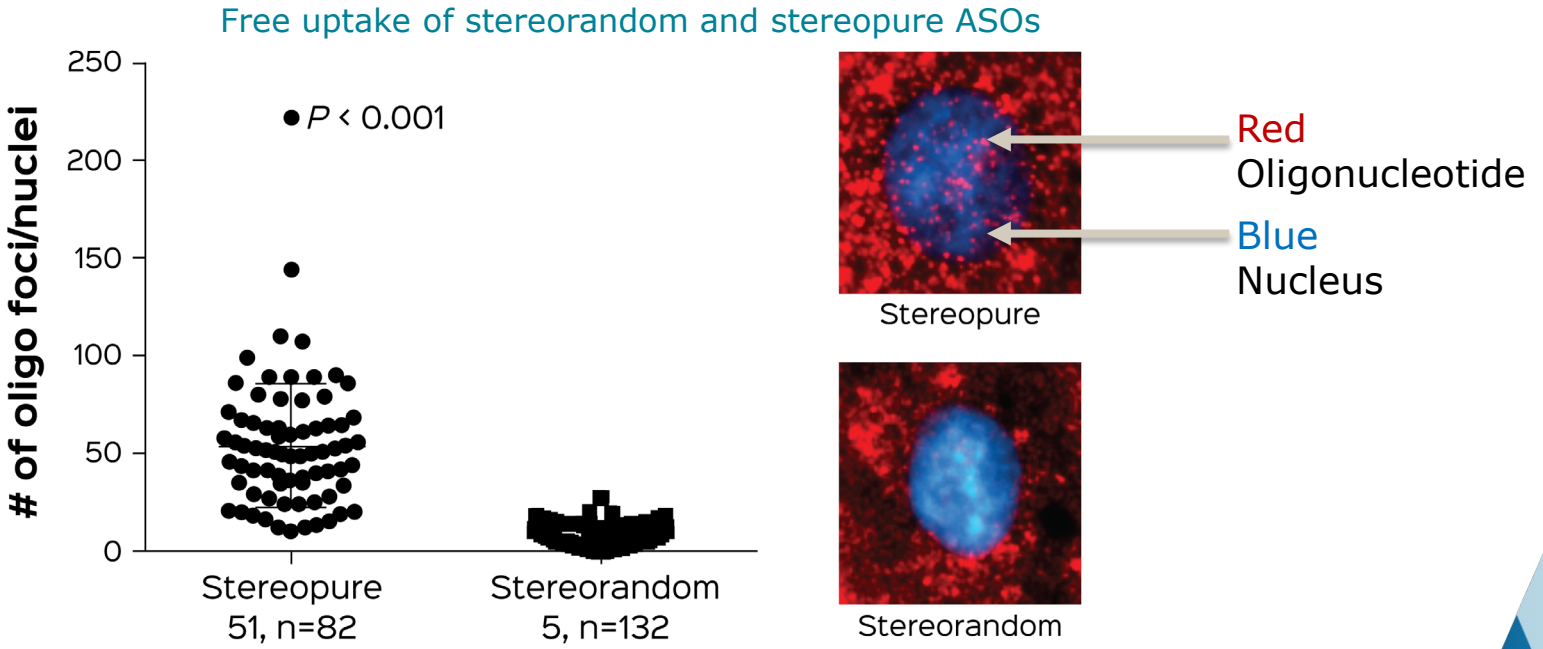
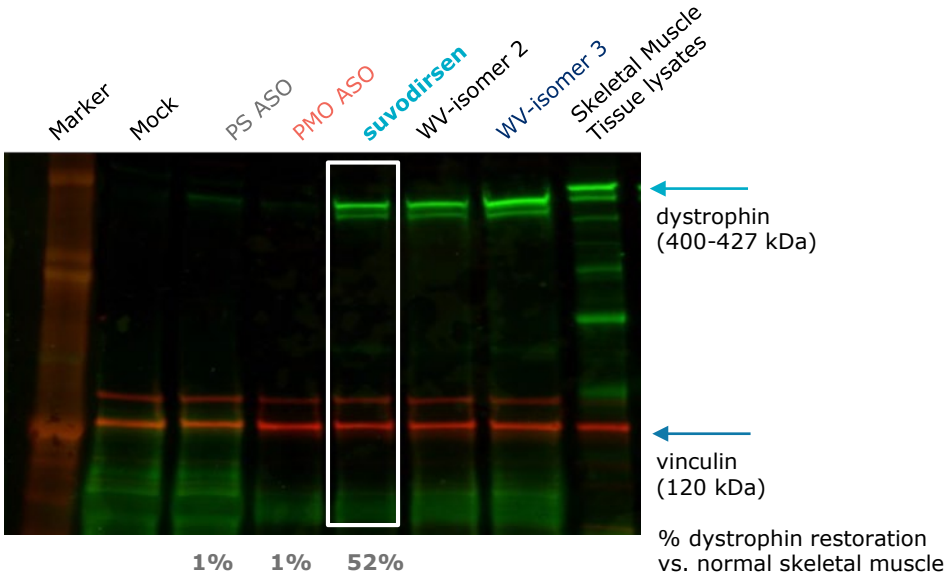
Sources: Arnett ALH, et al. *Mol Ther Methods Clin Dev.* 2014;1:14038. doi:10.1038/mtm.2014.38. Counsell JR, et al. *Sci Rep.* 2017;7:79. doi: 10.1038/s41598-017-00152-5. Duan D. *Mol Ther.* 2018;25:2337-2356. Martinsen B, Dreyer P. *Open Nurs Jrnl.* 2016;10:131-138. Stitelman DH, et al. *Mol Ther Methods Clin Dev.* 2014;1:14040. doi:10.1038/mtm.2014.40.

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*



Dystrophin protein in muscle cells *in vitro* was 52% of dystrophin protein in normal skeletal muscle, as compared with ~1% for stereorandom ASOs

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

Methods: Free uptake of ASO in human DMD myoblast cells. Dystrophin protein production determined by western blot.

PMO ASO = morpholino antisense oligonucleotide; PS ASO = phosphorothioate antisense oligonucleotide.

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Suvodirsen: Comprehensive clinical program

	Phase 1	Phase 1 Open-Label Extension (OLE)	Phase 2/3 (DYSTANCE 51)
Objective	Determine safety and tolerability profile and select dose(s) for OLE and Phase 2/3	Investigate long-term efficacy and safety	Assess efficacy and safety
Study Description	Phase 1 single ascending dose clinical trial	Multi-dose, open-label study open to patients from Phase 1	Phase 2/3 clinical trial to assess clinical efficacy and dystrophin expression
Key Milestones	• Safety and tolerability profile supports Phase 2/3 initiation • Two doses selected for Phase 2/3 trial • **Study complete**: Results presented at MDA and PPMD*	• Initiated in August 2018 • On track to deliver **interim analysis of dystrophin expression in 2H 2019**	• Selected for U.S. FDA pilot program for complex innovative trial designs • **Initiated**

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

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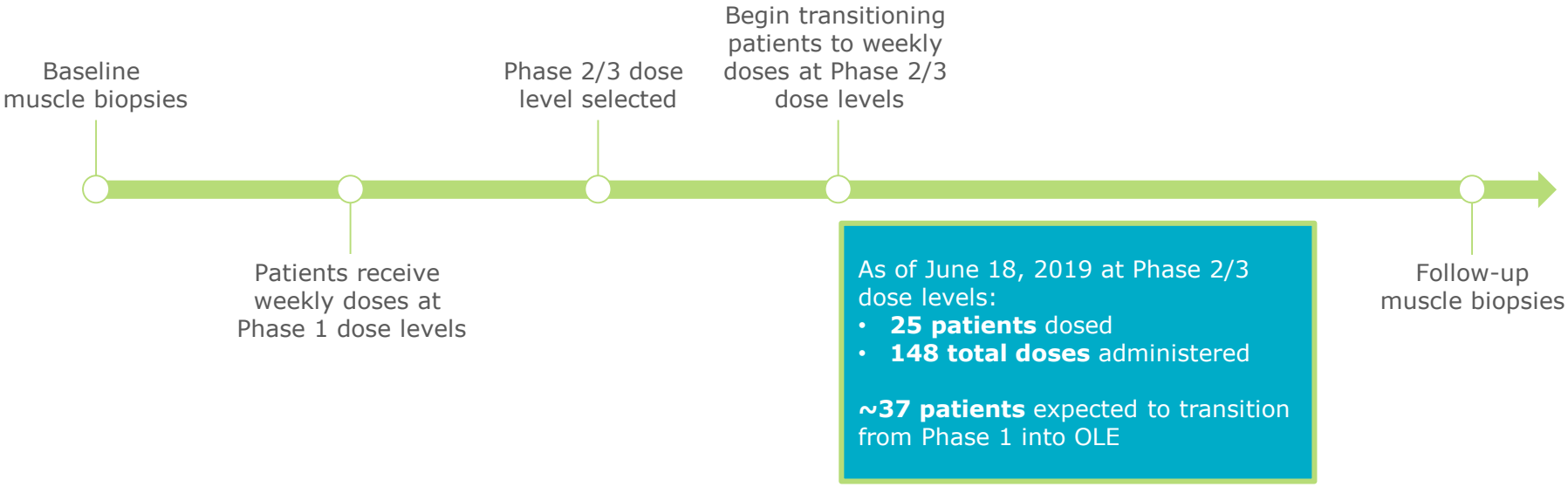
AE=adverse event; DMD=Duchenne muscular dystrophy; hsCRP=high-sensitivity C-reactive protein; IAR=infusion-associated reaction

Patients continue to successfully transition to OLE study of suvodirsen at Phase 2/3 dose levels

Phase 1 open-label extension



Interim analysis of dystrophin expression from muscle biopsies expected in 2H 2019

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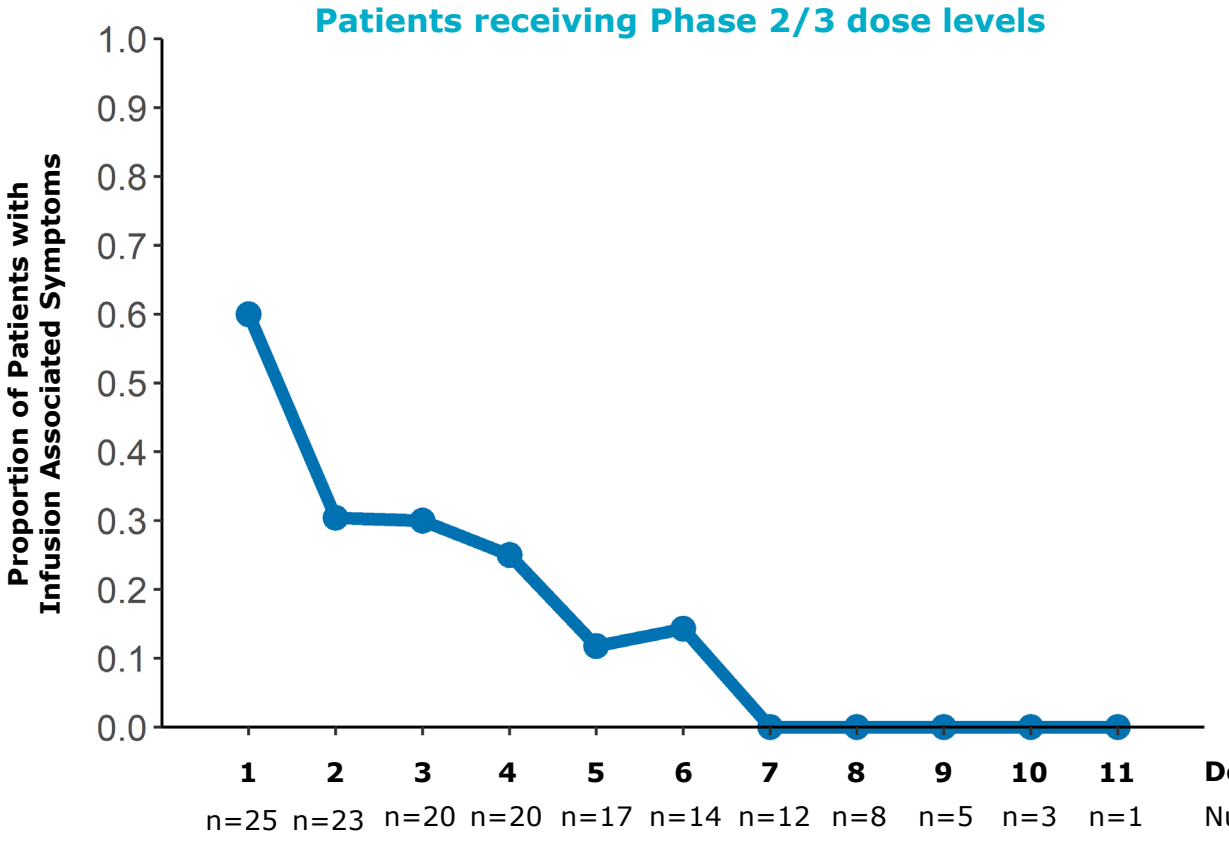
Infusion associated symptoms appear to decrease with continued dosing in OLE at Phase 2/3 dose levels



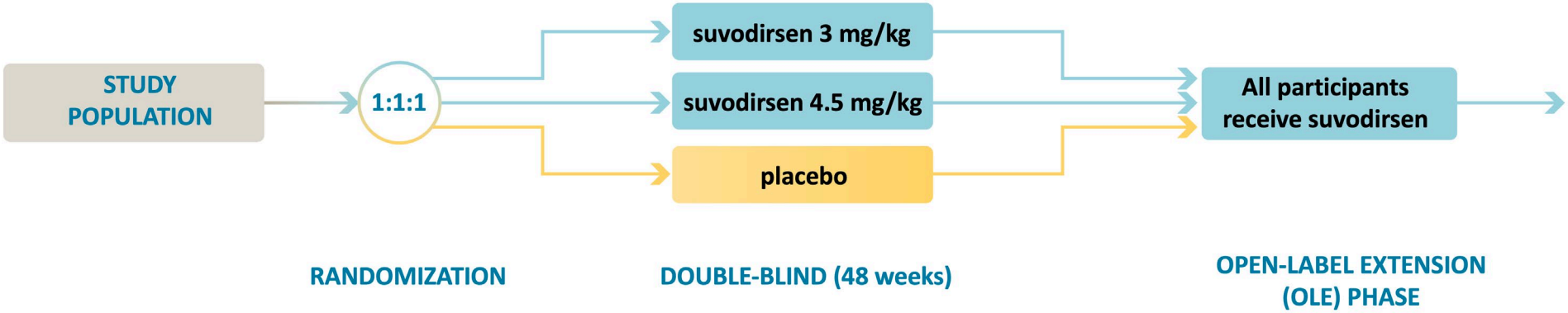
As of June 18, 2019:

- 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

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 suvodirsen or placebo for 48 weeks
- Patients to enter open-label extension phase of the study to receive ongoing treatment with suvodirsen after completion of 48 week the placebo-controlled portion

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DYSTANCE 51 designed to measure functional outcomes

Objectives	
Primary	• Change from baseline in dystrophin protein levels (western blot, shoulder muscle) through 46 weeks (US/other regions as applicable) • Change from baseline in NSAA through 48 weeks (EU/Japan)

Secondary	• Change from baseline in NSAA through 48 weeks (US/other regions)
	• Change from baseline in dystrophin protein levels (western blot, shoulder muscle) through 46 weeks (US/other regions as applicable)
	• Change from baseline through 48 weeks in
	  • Upper limb proximal strength assessed by handheld myometry
	  • Time to walk/run 10 meters
	  • Time to perform 4-stair climb
	  • Forced vital capacity
	  • 95th percentile of stride velocity measured using the ActiMyo wearable device

Exploratory	• Change from baseline through 48 weeks in
	  • PedsQL
	  • Upper limb function assessed by PUL 2.0

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

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Trial design by and for the Duchenne community

Community Advice	Wave Action
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

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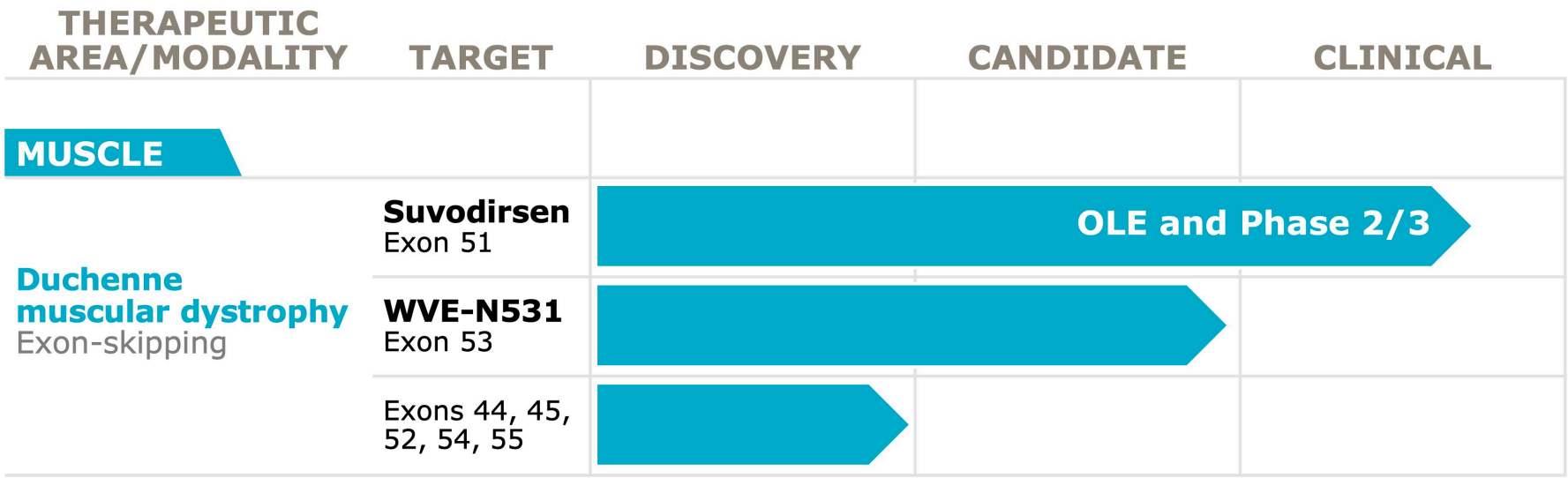
Committed to the Duchenne Community



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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

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