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

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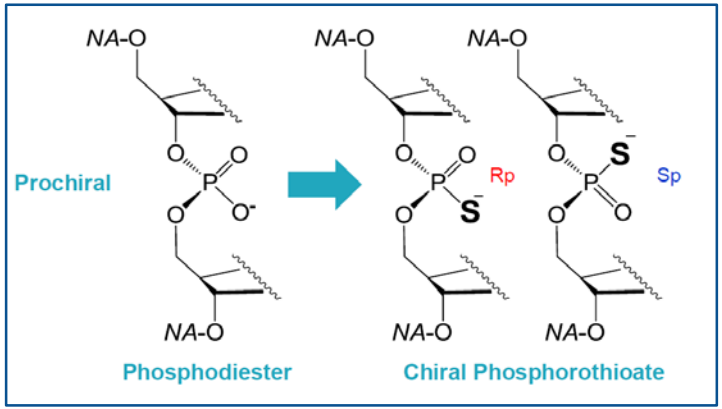
Wave chemistry controls nucleic acid backbone chirality



Traditional backbone chemistry

Nucleotide

Rp or *Sp* Linker

Uncontrolled

Stereorandom

>500,000 permutations in every dose

Wave backbone chemistry

Rp

Sp

Nucleotide

Controlled

Stereopure

One defined and consistent profile

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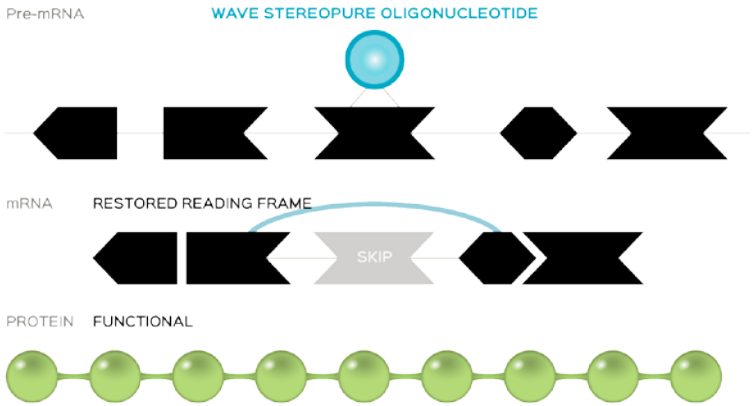
DMD: a progressive, fatal childhood disorder

- 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



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

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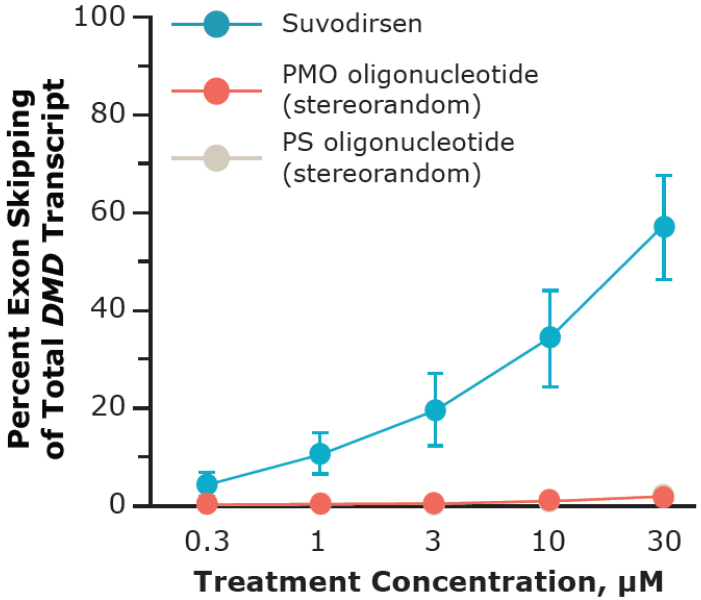
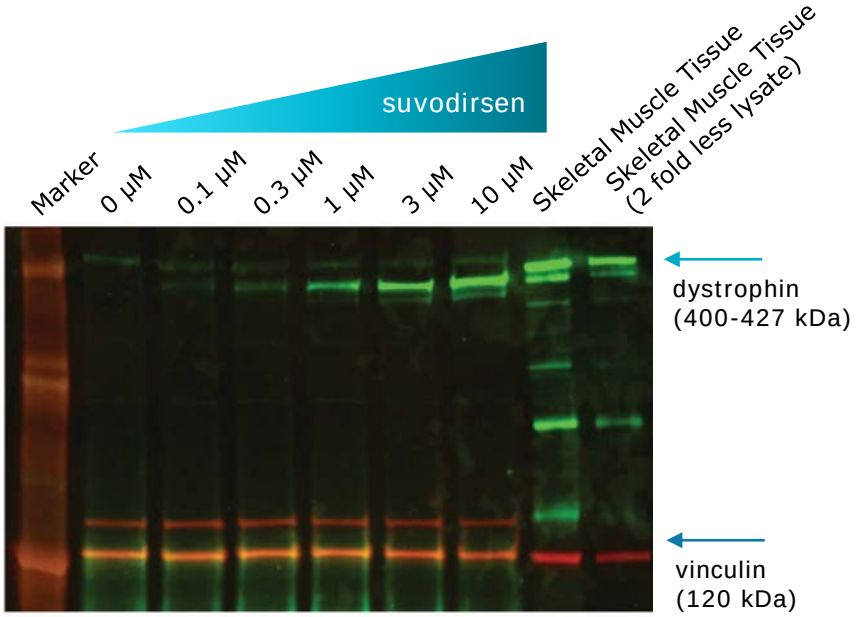
Source: Parent Project Muscular Dystrophy. About Duchenne & Becker muscular dystrophy. Available at: https://www.parentprojectmd.org/care/for-healthcare-providers/. Accessed: November 2, 2018.

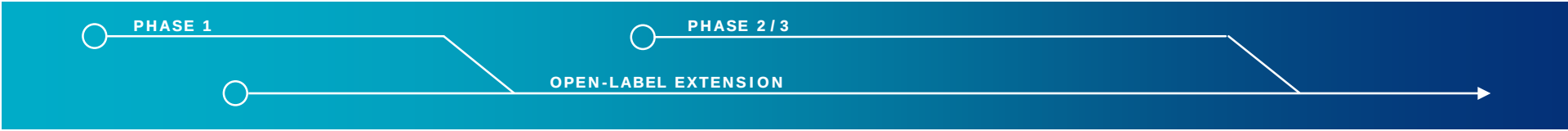
Exon 51: Suvodirsen induces dose-dependent exon skipping and dystrophin restoration *in vitro*





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

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

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

Dystrophin readout expected H2 2019

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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

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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

Goals	
Dystrophin analysis	• Bayesian repeated measures model • Trial adaptations based on interim dystrophin analyses
NSAA analysis	• Bayesian disease progression model • Inclusion of historical control data • Use of the predicted probability of success to potentially adjust enrollment

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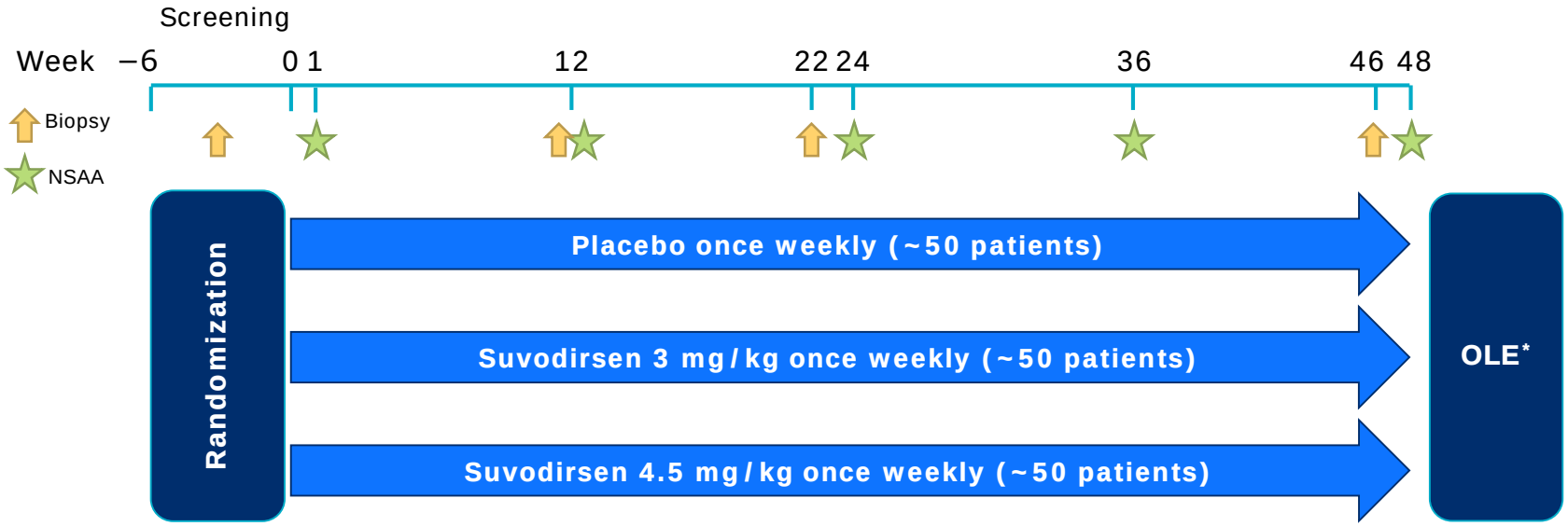
DYSTANCE 51 Phase 2/3 Trial Study Design



*OLE=Open-Label Extension

Potential Sources for Historical Control Data

Type of Study	Study Name or Sponsor	Investigated Therapy	Data Manager or PI*	Number of Untreated Patients	Status
Clinical Trial	Tadalafil DMD (NCT01865084)	Tadalafil	C-Path D-RSC^ (Eli Lilly)	116	Available
	ACT-DMD (NCT01826487)	Ataluren	C-Path D-RSC (PTC Therapeutics)	115	Available
	PhaseOut DMD (NCT02858362	Etruzomid	C-Path D-RSC (Summit Therapeutics)	39&	Available
	B5161002 (NCT02310763)	Domagrozumab	Pfizer	40*	Discussions underway
	DEMAND II (NCT01153932)	Drisapersen	Biomarin	18	Unavailable
	DEMAND III (NCT01254019)	Drisapersen	Biomarin	61	Unavailable
	DEMAND V (NCT01462292)	Drisapersen	Biomarin	16	Unavailable
Natural History Study	NorthStar Clinical Network	NA	Prof. Francesco Muntoni	533	Discussions underway
	Cooperative International Neuromuscular Research Group	NA	Therapeutic Research in Neuromuscular Disorders Solutions (TRiNDS)	>400	Discussion underway
	Universitaire Ziekenhuizen	NA	Dr. Nathalie Goemans	65	Discussions underway
	PRO-DMD-01	NA	CureDuchenne (Biomarin)	269	Unavailable

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 etruzomid but negative study

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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

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