Design of a Phase 2/3 Randomized Controlled Trial of Suvodirsen (WVE-210201) in Patients With Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping

Kathryn Wagner,[1] Linda Cripe,[2] Michelle Eagle,[3] Francesco Muntoni,[4] Erik Niks,[5] Han Phan,[6] Volker Straub,[7] Xiao Hu,[8] Irina Antonijevic,[8*] Scott Berry,[9] Melanie Quintana,[9] Stephen L. Lake,[8] Michael Panzara[8]

[1]Kennedy Krieger Institute, Johns Hopkins School of Medicine, Baltimore, MD, USA; [2]Nationwide Children's Hospital, Columbus, OH, USA; [3]ATOM International, Ltd., Consett, UK; [4]University College London, London, UK; [5]Leiden University Medical Center, Leiden, Netherlands; [6]Rare Disease Research, LLC, Atlanta, GA, USA; [7]Newcastle University, Newcastle-upon-Tyne, UK; [8]Wave Life Sciences Ltd., Cambridge, MA, USA; [9]Berry Consultants, Austin, TX, USA

Summary

- Wave Life Sciences is developing an investigational stereopure oligonucleotide, suvodirsen (WVE-210201), as a potential disease-modifying therapy for patients with Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping.
- Safety and tolerability data from the suvodirsen Phase 1 clinical trial (NCT03508947) support initiation of a Phase 2/3 clinical trial of suvodirsen at 3 and 4.5 mg/kg.
- The Phase 2/3 clinical trial, DYSTANCE 51, was selected for the US Food and Drug Administration Complex Innovative Trial Design Pilot Program and was designed with input from global regulatory authorities and the global DMD community.
- The primary efficacy endpoints are change in dystrophin protein level and change in North Star Ambulatory Assessment. In addition, the clinical trial will include multiple functional outcome measures as secondary efficacy endpoints.
- 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.

Introduction

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disorder in which mutations in the *dystrophin* (*DMD*) gene result in absent or defective dystrophin protein.[1]
- Oligonucleotides that induce exon skipping in DMD may enable restoration of functional dystrophin protein, which is expected to result in therapeutic benefits.[1,2] However, dystrophin protein expression levels observed to date with exon skipping therapies have been minimal, and clinical efficacy of exon skipping therapies has yet to be established.
- Suvodirsen (WVE-210201), an investigational stereopure oligonucleotide designed to target exon 51 in the *DMD* gene, was studied in a Phase 1 clinical trial as a potential disease-modifying therapy for patients with DMD amenable to exon 51 skipping (NCT03508947); an open-label extension study is ongoing.
- Safety and tolerability data from the Phase 1 clinical trial support initiation of a Phase 2/3 clinical trial in patients with DMD amenable to exon 51 skipping, the design of which is presented here.
  - The Phase 2/3 clinical trial (NCT03907072) has been selected for the US Food and Drug Administration (FDA) Complex Innovative Trial Design Pilot Program.

Methods

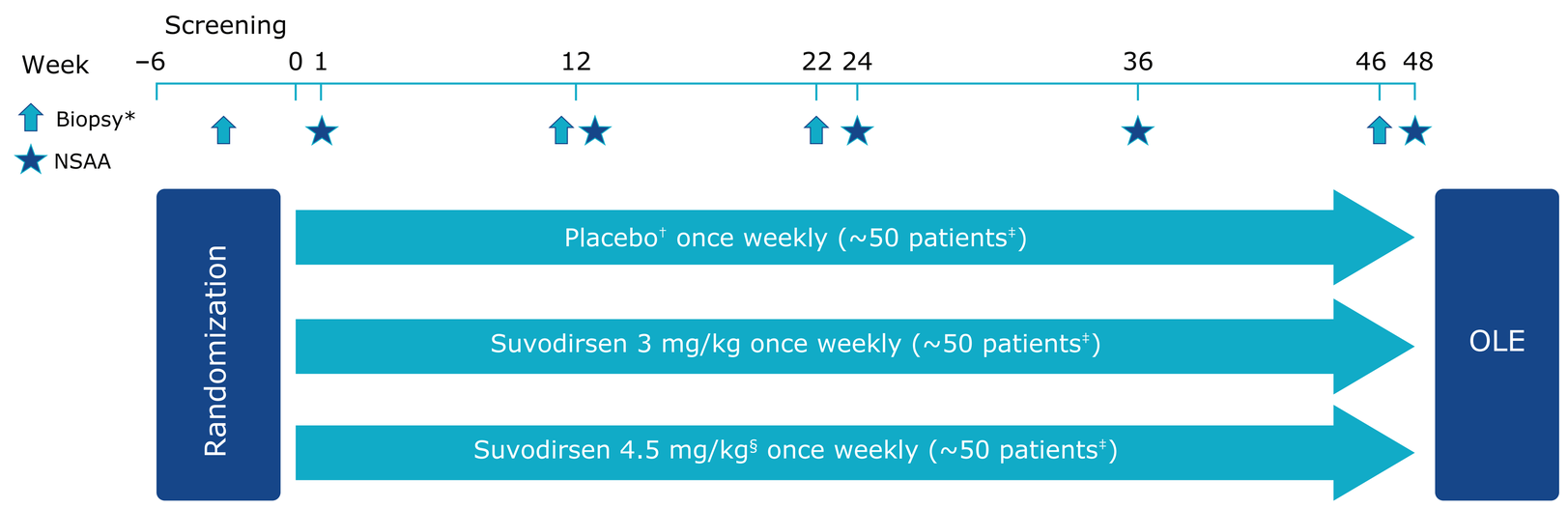
Study Design and Patients

- DYSTANCE 51 is a Phase 2/3 global, multicenter, randomized, double-blind, placebo-controlled 48-week clinical trial of the efficacy and safety of suvodirsen in ambulatory male pediatric patients with DMD amenable to exon 51 skipping. Patients who complete the Phase 2/3 clinical trial may be eligible for enrollment in an open-label extension study.
- Study design is shown in **Figure 1** and enrollment criteria in **Figure 2**.
- Patients will undergo a baseline open muscle (deltoid) biopsy ≥2 weeks before the day 1 visit and an additional biopsy at week 12, 22, or 46.
- Based on pharmacokinetic (PK) modeling incorporating preclinical data on exon skipping and the single-dose and PK safety profile from the Phase 1 clinical trial, suvodirsen doses of 3 and 4.5 mg/kg were selected for evaluation in the Phase 2/3 clinical trial.
- Patients will be randomly assigned to treatment in a 1:1:2:2 ratio to placebo 3 mg/kg, placebo 4.5 mg/kg, suvodirsen 3 mg/kg, or suvodirsen 4.5 mg/kg administered intravenously once weekly for 48 weeks.
  - The 4.5 mg/kg dose in DYSTANCE 51 provides approximately the same amount of active ingredient as the 5 mg/kg dose in the Phase 1 clinical trial.
- As part of the innovative trial design, DMD historical control data (**Table 1**) will be leveraged to help reduce the number of patients required in the study to deliver conclusive clinical efficacy results and to potentially accelerate study completion.

Study Assessments

- Efficacy assessments will include dystrophin protein levels by western blot and functional assessments.
- Functional assessments will include
  - The North Star Ambulatory Assessment (NSAA)[3,4]
  - The Performance of the Upper Limb 2.0[5]
  - Ambulation measured using the ActiMyo (Sysnav, Vernon, France) wearable device
- Safety assessments will include adverse events, physical exams, vital signs, clinical laboratory evaluations, 12-lead electrocardiogram, and echocardiogram.
- Quality of life assessments will include the Pediatric Quality of Life Inventory (PedsQL) 3.0 Neuromuscular Module[6] and the PedsQL 4.0 Generic Core Scale.[7,8]
- Pharmacodynamic assessments will include analysis of muscle biopsies for dystrophin localization using immunohistochemistry/immunofluorescence.

Figure 1. Study Design



NSAA=North Star Ambulatory Assessment; OLE=open-label extension.
*Patients will undergo 2 muscle biopsies: 1 at baseline (collected ≥2 weeks before study start) and 1 at a follow-up visit.
†Two placebo arms will be matched to their respective active-treatment arms (ie, placebo 3 mg/kg, n=25; placebo 4.5 mg/kg, n=25).
‡Final number of patients to be determined based on the predictive probability of success computed using a Bayesian disease progression model and using historical control datasets.
§The 4.5 mg/kg dose in DYSTANCE 51 provides approximately the same amount of active ingredient as the 5 mg/kg dose in the Phase 1 clinical trial.

Figure 2. Enrollment Criteria

Key Inclusion Criteria

- Diagnosis of DMD based on clinical phenotype with increased serum creatine kinase
- Documented mutation in the dystrophin gene amenable to exon 51 skipping
- Ambulatory male, able to walk independently for ≥10 meters in ≤20 seconds at the time of screening visit
- Age 5–12 years at time of randomization
- Stable pulmonary and cardiac function, as measured by
  - Reproducible percent predicted forced vital capacity ≥50%
  - Left ventricular ejection fraction >55% in patients <10 years of age and >45% in patients ≥10 years of age, as measured by echocardiogram
- On a stable systemic corticosteroid therapy regimen for ≥6 months, with no changes in dosing ≤3 months before screening visit

Key Exclusion Criteria

- Severe cardiomyopathy that cannot be managed using ACE inhibitors or beta blockers, other evidence of clinically significant structural or functional heart abnormality, or cardiac troponin I value >0.2 ng/mL
- Need or anticipated need for daytime mechanical or noninvasive ventilation
- Prior treatment with drisapersen, an investigational peptide-conjugated phosphorodiamidate morpholino oligomer, or gene therapy for DMD
- Treatment with ataluren or eteplirsen within 14 weeks before planned baseline biopsy collection
- Treatment with any investigational drug within 3 months or 5 half-lives, whichever is longer, before planned baseline biopsy collection

ACE=angiotensin-converting enzyme; DMD=Duchenne muscular dystrophy.

Table 1. 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
	PTC124-GD-007-DMD (NCT00592553)	Ataluren	C-Path D-RSC (PTC Therapeutics*)	57	Available
	ACT-DMD (NCT01826487)	Ataluren	C-Path D-RSC (PTC Therapeutics*)	115	Available
	B5161002 (NCT02310763)	Domagrozumab	Pfizer	40†	Discussions underway
	DEMAND II (NCT01153932)	Drisapersen	BioMarin	18	Not provided
	DEMAND III (NCT01254019)	Drisapersen	BioMarin	61	Not provided
	DEMAND V (NCT01462292)	Drisapersen	BioMarin	16	Not provided
Natural History Study	NorthStar Clinical Network	NA	Prof. Francesco Muntoni	533	Discussions underway
	Cooperative International Neuromuscular Research Group	NA	TRiNDS	>400	Discussions underway
	Universitaire Ziekenhuizen	NA	Dr. Nathalie Goeamans	65	Discussions underway
	PRO-DMD-01	NA	CureDuchenne (BioMarin*)	269	Not provided

C-Path D-RSC=Critical Path Institute Duchenne Regulatory Science Consortium; DMD=Duchenne muscular dystrophy; NA=not applicable; PI=principle investigator; TRiNDS=Therapeutic Research in Neuromuscular Disorders Solutions.
*Sponsor listed if different from the data manager.
†Estimated.

Efficacy Endpoints

- Efficacy endpoints are detailed in **Figure 3**. Primary efficacy endpoints differ by region in accordance with regional regulatory guidelines.

Figure 3. Efficacy Endpoints

Primary

- US (and other regions, as applicable): Change from baseline in dystrophin protein levels (western blot of deltoid muscle) through 46 weeks
- EU (and other regions, as applicable): Change from baseline in NSAA through 48 weeks

Secondary

- Change from baseline through 48 weeks in
  - Key: NSAA (at 48 weeks) or dystrophin protein levels (at 46 weeks)
  - Upper limb proximal strength assessed by handheld myometry
  - Time to walk/run 10 meters
  - Time to perform 4-stair climb
  - Forced vital capacity (% predicted)
  - 95th percentile of stride velocity measured using the ActiMyo wearable device

Key Exploratory

- Change from baseline through 48 weeks in
  - PedsQL[6-8]
  - Individual NSAA items
  - Respiratory function peak flow rate and cough peak flow
  - Upper limb function assessed by PUL 2.0[5]
- Time to loss of ambulation, loss of self-feeding, and requirement for daytime ventilation on a regular basis
- Change from baseline in daily activity as measured by ActiMyo wearable device

NSAA=North Star Ambulatory Assessment; PedsQL=Pediatric Quality of Life Inventory; PUL=Performance of the Upper Limb.

Sample Size

- A sample size of 150 patients will provide 88% power to detect a difference of 3.0 in change from baseline in NSAA at 48 weeks (2-sided significance level=5%; SD=4.5; 10% dropout).

Interim Analyses

- Two interim analyses of dystrophin protein levels using western blot of deltoid muscle open biopsies at weeks 12 and 22 will be conducted using a Bayesian repeated measures model.
- Interim analyses of the NSAA endpoint will be conducted to determine if study enrollment can stop based on the predictive probability of success computed using a Bayesian disease progression model and incorporating historical control datasets.

References: 1. Mah JK. *Neuropsychiatr Dis Treat.* 2016;12:1795-1807. 2. Nakamura A. *J Hum Genet.* 2017;62(10):871-876. 3. Mazzone ES, et al. *Neuromuscul Disord.* 2009;19(7):458-461. 4. Scott E, et al. *Physiother Res Int.* 2012;17(2):101-109. 5. Mayhew A, et al. *Dev Med Child Neurol.* 2013;55(11):1038-1045. 6. Davis SE, et al. *J Clin Neuromuscul Dis.* 2010;11(3):97-109. 7. Varni JW, et al. *Ambul Pediatr.* 2003;3(6):329-341. 8. Varni JW, et al. *Med Care.* 1999;37(2):126-139. **Acknowledgments:** Editorial support was provided by Nicole Strangman, PhD, at ICON plc (North Wales, PA, USA) and funded by Wave Life Sciences Ltd. (Cambridge, MA, USA). Wave Life Sciences Ltd. would like to thank the patients and patient groups who contributed their input to the study design along with the FDA. **Disclosures:** K Wagner: consultant for Dynacure, Lion Biotechnologies, PTC Therapeutics, Roche, Sarepta Therapeutics, and Wave Life Sciences Ltd.; Data Safety Monitoring Board for FibroGen, chair of the Wave Life Sciences Ltd. Phase 1 clinical advisory board and Dose Escalation Committee. L Cripe: nothing to disclose. M Eagle: consultant for Amicus Therapeutics, Acceleron Pharma, BioMarin, Capricor Therapeutics, Catabasis Pharmaceuticals, FibroGen, Italfarmaco, Mallinckrodt Pharmaceuticals, Pfizer, PTC Therapeutics, QED Therapeutics, ReveraGen, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics, Solid Biosciences, Therachon, and Wave Life Sciences Ltd. F Muntoni: advisory boards for AveXis, Biogen, Pfizer, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics, and Wave Life Sciences Ltd. E Niks: consultant for BioMarin, Summit Therapeutics, and Wave Life Sciences Ltd.; study investigator for BioMarin, GSK, Italfarmaco, Eli Lilly and Company, Roche, Santhera Pharmaceuticals, and Wave Life Sciences Ltd.; grants from AFM-Téléthon, Duchenne Parent Project, Spieren voor Spieren, and ZonMW. H Phan: advisory board member for Biogen, Mallinckrodt Pharmaceuticals, PTC Therapeutics, Roche, and Sarepta Therapeutics; consultant to Biogen. V Straub: chief/principal investigator for GSK, Ionis Pharmaceuticals, Italfarmaco, Pfizer, Prosensa/BioMarin, Sanofi Genzyme, Sarepta Therapeutics, and Summit Therapeutics; speaker for Sanofi Genzyme; advisory board member for Audentes Therapeutics, Biogen, Exonics Therapeutics, Italfarmaco, Roche, Sanofi Genzyme, Sarepta Therapeutics, Summit Therapeutics, UCB, and Wave Life Sciences Ltd.; research collaborations with Sanofi Genzyme and Ultragenyx Pharmaceutical. *I Antonijevic: employee of Wave Life Sciences Ltd. at the time of protocol development. S Berry: owner of Berry Consultants, which receives consulting income from Wave Life Sciences Ltd. M Quintana: employee of Berry Consultants. X Hu, SL Lake, and M Panzara: employees/stockholders of Wave Life Sciences Ltd.

Presented at the 2019 Muscular Dystrophy Association Clinical & Scientific Conference; April 13–17, 2019; Orlando, FL

Supported by Wave Life Sciences Ltd., Cambridge, MA, USA.