Safety and Tolerability of Suvodirsen (WVE-210201) in Patients With Duchenne Muscular Dystrophy: Results From a Phase 1 Clinical Trial

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Summary

- Wave Life Sciences is developing suvodirsen (WVE-210201), an investigational stereopure oligonucleotide, as a potential disease-modifying therapy for patients with Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping of the *dystrophin* gene.
- Suvodirsen was studied in a global, multicenter, double-blind, placebo-controlled Phase 1 clinical trial to evaluate the safety, tolerability, and plasma concentrations of single ascending doses of suvodirsen administered intravenously.
- No serious adverse events (AEs), deaths, or discontinuations due to AEs were observed in any patients treated with suvodirsen.
- Suvodirsen was generally safe and well tolerated up to and including 5 mg/kg.
- The mean (SD) maximum plasma concentration was 40.7 (21.4) µg/mL in patients receiving 5 mg/kg of suvodirsen.
- Based on *in vitro* and *in vivo* preclinical data and results from the 0.5–5 mg/kg suvodirsen cohorts, Wave selected an initial dose of 5 mg/kg for its planned Phase 2/3 clinical trial of suvodirsen, which was subsequently confirmed upon study completion.
- Results from this first-in-human clinical trial support the initiation of the global Phase 2/3 efficacy and safety trial of suvodirsen in patients with DMD amenable to exon 51 skipping (DYSTANCE 51).
  - DYSTANCE 51 has been selected for the US Food and Drug Administration Complex Innovative Trial Design Pilot Program.

Introduction

Duchenne Muscular Dystrophy

- Duchenne muscular dystrophy (DMD) is a rare, X-linked, progressive neuromuscular disorder caused by mutations in the gene coding for dystrophin, a protein that plays a key structural role in muscle fiber function.[1]
- DMD affects approximately 1 in 5000 newborn boys around the world.[2,3]
- Mutations in the *dystrophin* (*DMD*) gene result in absent or defective dystrophin protein.[4]
- Lack of dystrophin protein results in severe, progressive muscle loss, leading to eventual loss of ambulation and premature death in the early thirties, often due to respiratory or cardiac failure.[4,5]
- Approximately 13% of patients with DMD have mutations amenable to exon 51 skipping.[6]

Exon Skipping With Suvodirsen (WVE-210201)

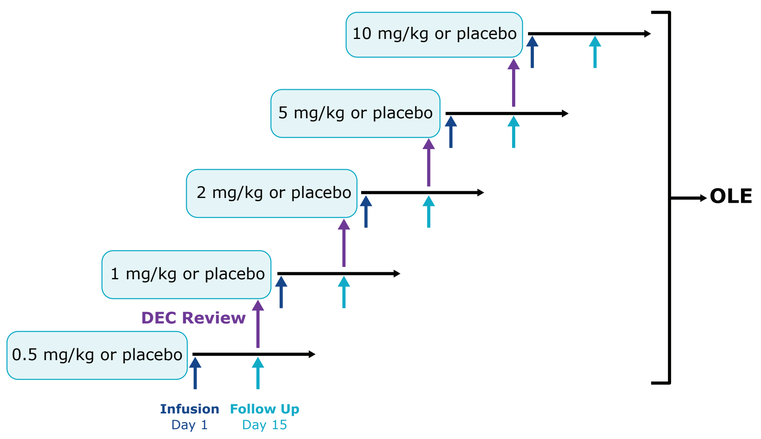
- Oligonucleotides that induce exon 51 skipping during mRNA processing in DMD may enable restoration of functional dystrophin protein, which is expected to result in therapeutic benefits.[4]
- Suvodirsen (WVE-210201) is an investigational stereopure oligonucleotide that is being developed as a potential disease-modifying therapy for patients with DMD amenable to exon 51 skipping.
- We present safety, tolerability, and pharmacokinetics (PK) from the Phase 1 clinical trial of suvodirsen in patients with DMD amenable to exon 51 skipping.

Methods

Study Design

- This was a Phase 1, multicenter, double-blind, placebo-controlled, single ascending dose clinical trial with 12-week follow-up (NCT03508947) and optional open-label extension (OLE) conducted under a separate protocol (**Figure 1**) at 13 sites in North America and Europe.
- The study was reviewed and approved by institutional review boards/independent ethics committees and conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice and the European Guidelines for First-in-Human Studies.[7] All patients or their parents/legal guardians provided written informed consent and minor assent, as applicable.
- Patients were randomized 3:1 to receive a single intravenous infusion of suvodirsen or placebo in ascending dose cohorts (**Figure 1**). Study drug was to be administered over a 1-hour infusion period.
- Dosing was staggered, beginning with 2 sentinel patients observed for 48 hours. If neither experienced a serious adverse event (SAE), the remaining patients in the cohort were treated and observed for 24 hours. Decision regarding escalation to each subsequent dose level was made based on the recommendation of the Dose Escalation Committee with endorsement by the Safety Monitoring Committee (SMC).
- Stopping criteria were based upon the European Guidelines for First-in-Human Studies:[7]
  - A single patient experienced an SAE assessed as related to treatment.
  - ≥2 patients experienced a treatment-emergent adverse event (AE) graded as severe and related to treatment.

Figure 1. Study Design



DEC=Dose Escalation Committee; OLE=open-label extension.

Key Enrollment Criteria

- The trial enrolled ambulatory and nonambulatory male patients, age 5–18 years (inclusive), with a confirmed *DMD* mutation amenable to exon 51 skipping.
- Patients may have been previously treated with eteplirsen or ataluren, with appropriate washout, but previous treatment with drisapersen or gene therapy was not permitted.

Endpoints and Statistical Analyses

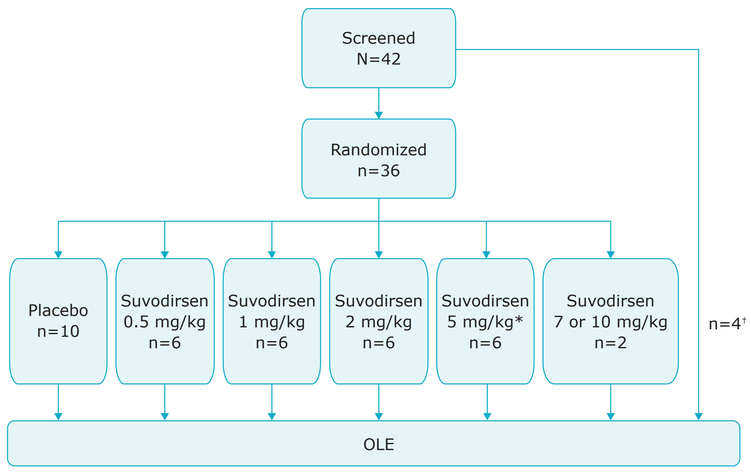
- The primary endpoint was safety and tolerability of single ascending doses of suvodirsen.
  - Safety assessments included AEs, physical examination, vital signs, electrocardiogram, and clinical laboratory evaluations at specified time points through week 12.
  - The safety population included all patients who were randomly assigned to treatment and received study drug.
- The secondary endpoint was the PK profile of suvodirsen after single-dose administration.
- Plasma PK samples were collected predose, at end of infusion (EOI), and at specified intervals ≤7 days after EOI.
  - The PK population included all patients in the safety population who had sufficient plasma concentration data for analysis.
- All data were analyzed descriptively and are presented as mean (SD) or frequency (%).

Results

Patient Disposition and Baseline Characteristics

- Thirty-six patients received a single dose of placebo or suvodirsen 0.5, 1, 2, 5, 7, or 10 mg/kg and were followed for 85 days (**Figure 2**).
- No patients discontinued the study.

Figure 2. Patient Disposition



IAR=infusion-associated reaction; OLE=open-label extension; SMC=Safety Monitoring Committee.
*1 patient who was randomly assigned to receive suvodirsen 5 mg/kg received 2.75 mg/kg due to a dosing error.
†Based on IARs in the patients who received 7 or 10 mg/kg suvodirsen, the remaining 4 patients screened are expected to enroll directly into the OLE.

- Baseline characteristics were well balanced between suvodirsen- and placebo-treated patients (**Table 1**). Mean (SD) age across all cohorts was 8.1 (2.1) years, and mean (SD) time since diagnosis was 4.7 (2.8) years.

Table 1. Patient Baseline Demographics and Clinical Characteristics

Characteristic	Placebo n=10	Total Suvodirsen n=26	Suvodirsen 0.5 mg/kg n=6	Suvodirsen 1 mg/kg n=6	Suvodirsen 2 mg/kg n=6	Suvodirsen 5 mg/kg n=6	Suvodirsen 7 or 10 mg/kg n=2
Age*, mean (SD), y	8.5 (1.72)	8.0 (2.24)	8.2 (2.56)	8.0 (2.28)	8.7 (2.34)	6.8 (1.94)	9.0 (2.83)
Time since diagnosis, mean (SD), y	4.8 (3.25)	4.6 (2.64)	3.6 (3.18)	5.0 (1.85)	5.4 (1.52)	4.2 (3.58)	5.2 (4.08)
Ambulatory, n (%)	9 (90.0)	22 (84.6)	5 (83.3)	5 (83.3)	5 (83.3)	6 (100.0)	1 (50.0)
Prior treatment, n (%)	10 (100.0)	26 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	2 (100.0)
Eteplirsen	1 (10.0)	5 (19.2)	3 (50.0)	0.0	1 (16.7)	1 (16.7)	0.0
Deflazacort	8 (80.0)	22 (84.6)	4 (66.7)	6 (100.0)	4 (66.7)	6 (100.0)	2 (100.0)
Oral prednisone	2 (20.0)	6 (23.1)	2 (33.3)	1 (16.7)	2 (33.3)	0.0	1 (50.0)

*At the time of informed consent.

Safety and Tolerability

Suvodirsen 0.5–5 mg/kg Cohorts

- Sixteen of 24 patients who received 0.5–5 mg/kg suvodirsen (67%) and 8 of 10 patients who received placebo (80%) experienced ≥1 AE (**Table 2**).
- We took a conservative approach and classified any event occurring within 24 hours of start of infusion as infusion-associated reactions (IARs).
- Using this definition, the most common AEs (those occurring in ≥2 patients) were IARs, consisting of pyrexia, headache, vomiting, and tachycardia (**Table 2** and **Table 3**).
  - The IARs were nonserious and mild or moderate in intensity.
  - Only 1 case of pyrexia was deemed significant per the analysis, defined as >38°C or an increase of ≥1°C.
- In patients receiving 5 mg/kg, the IARs were associated with transient increases in the inflammatory marker high-sensitivity C-reactive protein (hsCRP) from a mean (SD) of 0.588 (0.693) mg/L at baseline to 39.706 (45.125) mg/L on day 2, which had resolved by the next measured time point (day 8). Similarly, there was a transient increase in complement factor Bb from a mean (SD) of 0.885 (0.195) µg/mL at baseline to 2.100 (0.746) µg/mL on day 2 that had resolved by the next measured time point (day 8). There was no change in complement C3.
- No other notable changes were observed in clinical laboratory results including renal, hepatic, or hematologic (eg, platelets) parameters.

Table 2. Summary of Adverse Events

AE, n (%)	Placebo n=10	Suvodirsen 0.5 mg/kg n=6	Suvodirsen 1 mg/kg n=6	Suvodirsen 2 mg/kg n=6	Suvodirsen 5 mg/kg n=6
Patients with any AE*	8 (80.0)	3 (50.0)	5 (83.3)	4 (66.7)	4 (66.7)
Mild	6 (60.0)	3 (50.0)	5 (83.3)	4 (66.7)	2 (33.3)
Moderate	0.0	0.0	0.0	0.0	2 (33.3)
Severe	2 (20.0)	0.0	0.0	0.0	0.0
Serious AE†	1 (10.0)	0.0	0.0	0.0	0.0
Discontinued due to AE	0.0	0.0	0.0	0.0	0.0
Death	0.0	0.0	0.0	0.0	0.0
AE occurring in ≥2 patients in an active treatment group‡					
Headache	0.0	0.0	2 (33.3)	1 (16.7)	3 (50.0)
Pyrexia	0.0	0.0	0.0	0.0	4 (66.7)
Vomiting	0.0	1 (16.7)	0.0	0.0	2 (33.3)
Tachycardia	1 (10.0)	0.0	0.0	0.0	1 (16.7)

AE=adverse event.
*Defined as an adverse event that was first identified, or identified to worsen in intensity, at a time point occurring during or after study drug infusion.
†Defined as any event that resulted in death, was immediately life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect not present at screening.
‡Number of patients with events. Patients could have been counted more than once if they had >1 AE.

Table 3. Infusion-Associated Reactions

IAR, n (%)	Placebo n=10	Suvodirsen 0.5 mg/kg n=6	Suvodirsen 1 mg/kg n=6	Suvodirsen 2 mg/kg n=6	Suvodirsen 5 mg/kg n=6
Patients with any IAR*	2 (20.0)	0.0	3 (50.0)	1 (16.7)	4 (66.7)
IAR occurring in ≥2 patients in any treatment group†					
Pyrexia	0.0	0.0	0.0	0.0	4 (66.7)
Headache	0.0	0.0	1 (16.7)	0.0	3 (50.0)
Vomiting	0.0	0.0	0.0	0.0	2 (33.3)
Tachycardia	1 (10.0)	0.0	0.0	0.0	1 (16.7)

AE=adverse event; IAR=infusion-associated reaction.
*IARs included any AE with onset occurring within 24 h of start of infusion.
†Number of patients with events. Patients could have been counted more than once if they had >1 IAR.

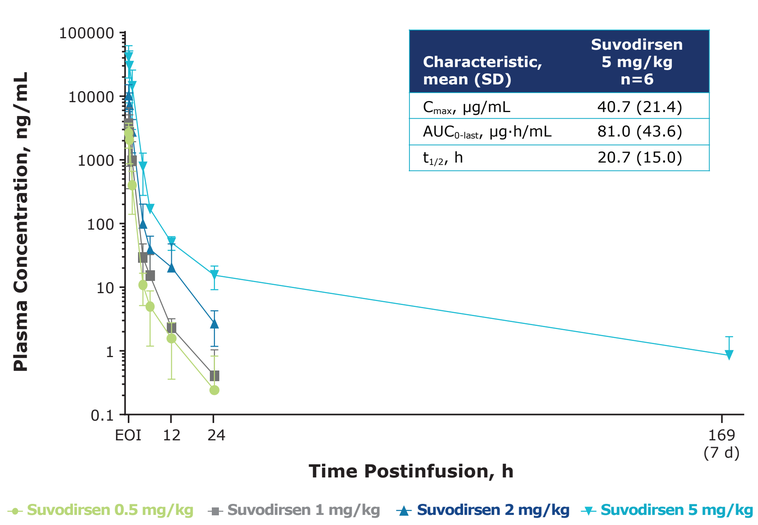
Dose Exploration Above 5 mg/kg

- Based on results of the first 4 ascending dose cohorts, the SMC endorsed exploration of a higher dose per the planned protocol.
  - Following dose escalation, 2 patients received a single dose of either 10 mg/kg or placebo infused over 1 hour. The patient who received suvodirsen 10 mg/kg experienced an IAR consisting of pyrexia (39.6°C), headache, tachycardia, and vomiting approximately 4 hours after EOI. The reaction was characterized by the investigator as nonserious but severe. The patient was treated with 2 doses of hydrocortisone and acetaminophen with resolution of symptoms.
  - Two patients then received a single dose of either 7 mg/kg or placebo, with an infusion time of 2 hours, in the setting of pretreatment with hydrocortisone and acetaminophen. The patient who received suvodirsen 7 mg/kg experienced isolated pyrexia to 39.5°C occurring 6 hours after EOI that resolved with acetaminophen treatment. The investigator characterized the IAR as nonserious but severe.
  - These IARs were associated with transient changes in inflammatory markers hsCRP (from a mean [SD] at baseline of 0.245 [0.064] mg/L to a peak of 88.100 [94.611] mg/L at day 2) and complement factor Bb (from a mean [SD] at baseline of 0.660 [0.042] µg/mL to a peak of 2.520 [1.853] µg/mL at day 2).
  - No other notable changes were observed in clinical laboratory results including renal, hepatic, or hematologic (eg, platelets) parameters.
  - Based on the safety and tolerability data of the 2 patients treated with suvodirsen 7 or 10 mg/kg, the predefined stopping criteria were met. The SMC reviewed all available data and agreed that dosing could proceed at 5 mg/kg.
  - Given that the study objectives were considered met, a decision was made in agreement with the SMC that the 4 remaining patients would move directly into the OLE at the 5 mg/kg dose level.

Pharmacokinetic Parameters

- Preliminary PK parameters are summarized in **Figure 3** (inset).
- For suvodirsen 5 mg/kg, mean (SD) maximum plasma concentration was 40.7 (21.4) µg/mL (**Figure 3**).
- Approximately dose-proportional increases were seen in $AUC_{0\text{-last}}$ and C_{max}.

Figure 3. Preliminary Pharmacokinetic Analysis of Suvodirsen



Characteristic, mean (SD)	Suvodirsen 5 mg/kg n=6
C_{max}, µg/mL	40.7 (21.4)
$AUC_{0\text{-last}}$, µg·h/mL	81.0 (43.6)
$t_{1/2}$, h	20.7 (15.0)

$AUC_{0\text{-last}}$=area under the plasma concentration-time curve from time zero to the last quantifiable concentration; C_{max}=maximum plasma concentration; EOI=end of infusion; $t_{1/2}$=terminal half-life.

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