720LBP

Interim Data Following 24 Weeks of Treatment with WVE-N531 in the Phase 2 Open-label FORWARD-53 Study

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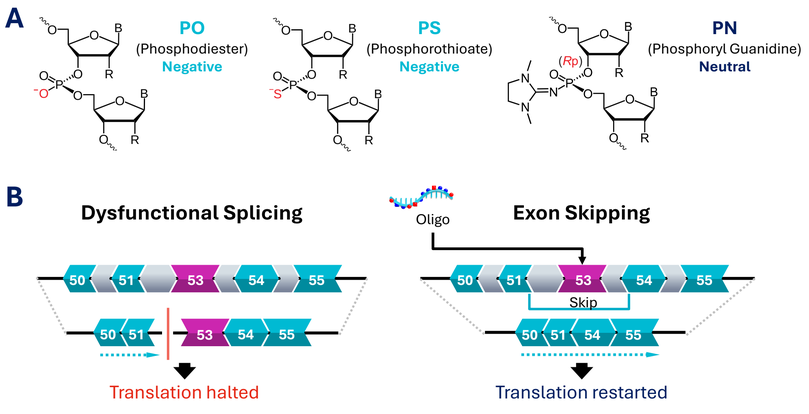
SUMMARY

- WVE-N531 is an investigational stereopure splicing oligonucleotide with novel PN (phosphoryl guanidine) chemistry currently being developed as a potential therapy for boys with Duchenne muscular dystrophy (DMD) amenable to exon 53 skipping.
- FORWARD-53 is an ongoing Phase 2 open-label study (NCT04906460) designed to evaluate the safety, tolerability, pharmacodynamics (PD), pharmacokinetics (PK), and clinical effects of WVE-N531 administered at 10 mg/kg every other week (Q2W) in boys with DMD amenable to exon 53 skipping.
- Eleven boys amenable to exon 53 skipping (age 5-11; 10 ambulatory and 1 non-ambulatory) are enrolled in the FORWARD-53 study, and WVE-N531 has demonstrated positive interim results following 24 weeks of dosing Q2W at 10 mg/kg.
  - In a prespecified analysis of ambulatory participants, mean absolute muscle content-adjusted dystrophin expression was 9.0%, and mean absolute unadjusted dystrophin was 5.5%, with high consistency across participants as measured by western blot; 89% of ambulatory participants achieved muscle content-adjusted dystrophin levels of at least 5%.
  - Data showed meaningful improvement in serum biomarkers for muscle health, with localization of WVE-N531 in myogenic stem cells and regeneration of myofibers.
  - Skeletal muscle concentrations of ~41,000 ng/g combined with 61-day tissue half-life support monthly dosing going forward.
  - WVE-N531 was safe and well tolerated: treatment-related adverse events were all mild, with no serious adverse events, no discontinuations, and no oligonucleotide class-related events.
- These data highlight the therapeutic potential of WVE-N531 in DMD, as well as other stereopure PN-containing splicing oligonucleotides being developed by Wave.
- FORWARD-53 is ongoing, and participants will be transitioned to a monthly dosing regimen. Wave expects to deliver 48-week FORWARD-53 data in 1Q 2025.

INTRODUCTION

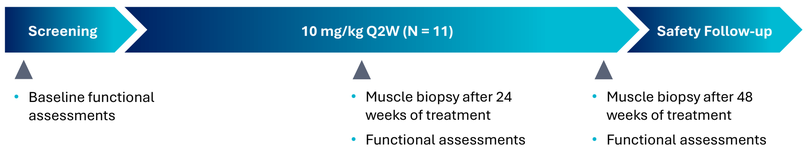
- DMD is the most common genetic muscular dystrophy caused by mutations in the gene encoding dystrophin.[1] DMD remains a relentless disease,[2] where lack of dystrophin protein results in severe, progressive muscle atrophy, eventual loss of ambulation, respiratory insufficiency, cardiomyopathy and premature death.[3,4]
- WVE-N531 is an investigational stereopure splicing oligonucleotide being developed as a potential therapy for boys with DMD amenable to exon 53 skipping (**Figure 1A**).
- Exon skipping oligonucleotides are designed to bind to pre-mRNA, causing cellular machinery to bypass exon(s) during splicing to restore the translational reading frame and protein production for out-of-frame mutations (**Figure 1B**).[5]
- WVE-N531 incorporates Wave's novel PN backbone chemistry, which demonstrated a substantial impact on muscle exposure, exon skipping, dystrophin restoration, survival, and both respiratory and skeletal muscle function in preclinical studies.[6]
- In Part A (N=3) of a Phase 1b/2 clinical trial (NCT04906460), WVE-N531 yielded 53% mean exon skipping (RT-PCR) and reached a mean concentration of 42,400 ng/g in muscle tissue after three doses administered at 10 mg/kg every other week.
- Based on the encouraging results from Part A, the Phase 2 open-label study (FORWARD-53) is designed to assess dystrophin protein restoration over an extended period and in a larger population.
- Here, we present the results from an interim analysis of the ongoing Phase 2 FORWARD-53 study.

Figure 1. WVE-N531 is an investigational stereopure splicing oligonucleotide with novel PN backbone chemistry



STUDY DESIGN

Figure 2. FORWARD-53: An ongoing open-label Phase 2 clinical trial of WVE-N531 in boys with DMD amenable to exon 53 skipping



Abbreviations: IV, Intravenous; Q2W, Every 2 Weeks; PK, Pharmacokinetics; PD, Pharmacodynamics

Table 1. Key eligibility criteria

✓ Diagnosis of DMD based on clinical phenotype	✓ Age of ≥5 and ≤18 years at time of screening
✓ Documented mutation associated with DMD that is amenable to exon 53 intervention	✓ Stable pulmonary and cardiac function
✓ Ambulatory or non-ambulatory patients	✓ Adequate muscle at screening to perform open muscle biopsies
✓ Score of ≥1 on item 1 or 2 of the shoulder component of the PUL	✓ Currently on a stable corticosteroid therapy regimen

National Clinical Trial number: NCT04906460; PUL, Performance of the Upper Limb.

- FORWARD-53 is an ongoing Phase 2 open-label study designed to evaluate the safety, tolerability, PD, PK, and clinical effects of WVE-N531 administered every other week in boys with DMD amenable to exon 53 skipping (**Figure 2**, **Table 1**).
- All participants are receiving open-label WVE-N531 Q2W at 10 mg/kg; participants will be transitioned to a monthly dosing regimen. Muscle biopsies are performed after 24 and 48 weeks of treatment.
  - The primary endpoint is dystrophin protein levels as measured by western blot.
  - PD: Exon skipping.
  - PK: Drug tissue concentrations.
- Additionally, patients will also be evaluated for functional outcomes and quality of life.
- Safety monitoring will continue for 18 weeks after the last dose.

RESULTS

Table 2. Baseline patient characteristics

Baseline DMD Patient Characteristics	FORWARD-53 population (n=11)
Age (years) (mean [SD])	8.2 (2.1)
Age 5-7 (n [%])*	5 (45)
Age 8-11 (n [%])*	6 (55)
BMI (kg/m^2) (mean [SD])	19.1 (4.0)
Years since DMD diagnosis (mean [SD])	4.0 (2.5)
Patients on oral steroids (n [%])	11 (100)
Prednisone	4 (36.4)
Deflazacort	7 (63.6)
Ambulatory (n [%])	10 (90.9)
Exon Deletion (n [%])	
45-52	6 (54.5)
52-52	2 (18.2)
Others**	3 (27.3)

*The progression of muscle weakness in patients with DMD is age-dependent, and separating these groups helps to account for these differences in disease progression. **Other deletions include 48-52, 49-52 and 50-52.

- The FORWARD-53 study has enrolled 11 boys (**Table 2**; age 5-11; 10 ambulatory and 1 non-ambulatory).
- The baseline characteristics showed that all participants had deletions expected to be amenable to treatment with WVE-N531.
  - There were five different underlying mutations occurring in the exon 45 – 52 region.
- All of the participants are on stable steroid regimens.

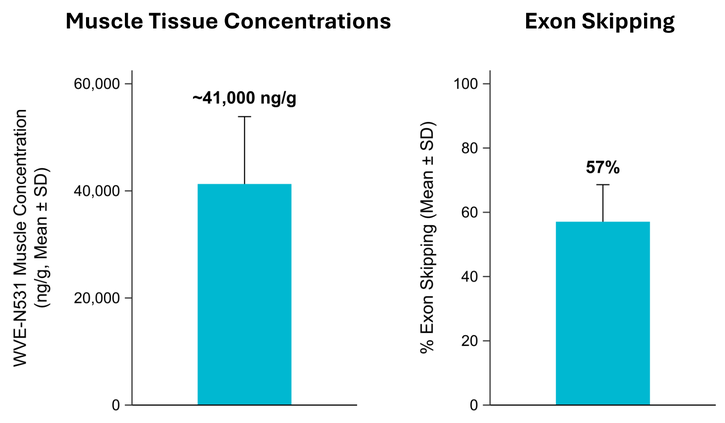
Table 3. WVE-N531 was safe and well tolerated

TEAE Category	WVE-N531 10 mg/kg (n=11)	
		Patients (%)
Any TEAE	10	90.9
Any drug-related TEAE	3	27.3
Mild	3	27.3
Moderate	0	0
Severe	0	0
Any serious TEAE	0	0
Any severe TEAE	0	0
Any TEAE leading to discontinuation	0	0
Any TEAE leading to death	0	0

TEAE: Treatment emergent adverse event; Data as of August 19, 2024

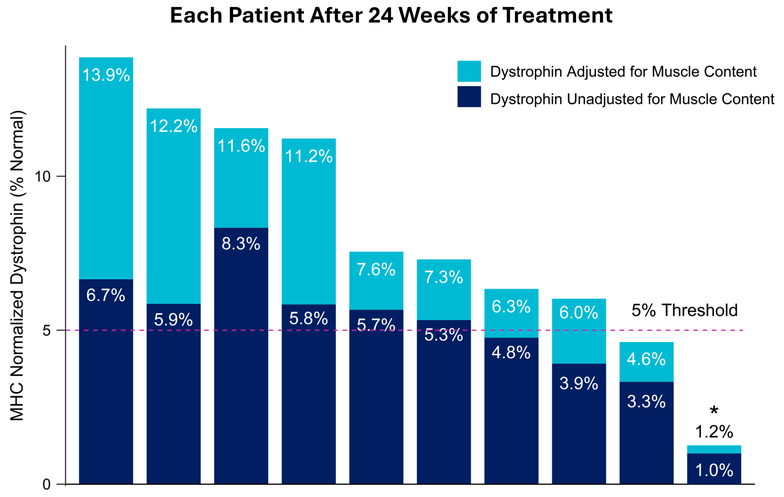
- WVE-N531 was safe and well tolerated (**Table 3**).
- Treatment-related adverse events (four events total in three participants) were mild in intensity.
- There were no serious adverse events and no study discontinuations due to any causes.
- There were no oligonucleotide class-related safety events.

Figure 3. High muscle concentrations and exon skipping indicate WVE-N531 is engaging target



- Mean exon skipping was 57% (range: 31-75%) as measured by RT-PCR (**Figure 3**; n=11).
- WVE-N531 reached high muscle concentrations (mean ~41,000 ng/g [~5,900 nM]).
- The muscle tissue half-life of WVE-N531 is estimated to be 61 days. Along with the muscle concentration data, this supports a monthly dosing regimen for WVE-N531 moving forward.

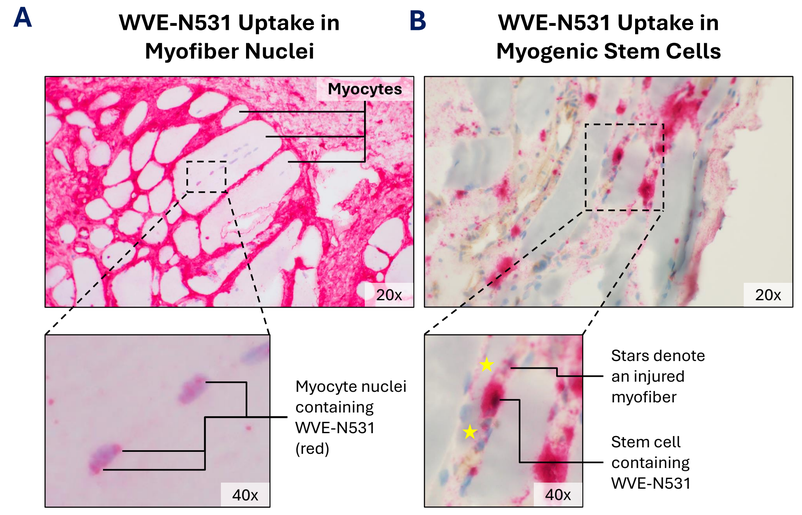
Figure 4. Dystrophin expression of up to 14% with high consistency across participants



*Excluded from prespecified mean analysis of ambulatory patients; Muscle content adjustment was done using the formula: MHC-normalized dystrophin/(total myofiber area/total area of biopsy section); Graph shows all patients (including non-ambulatory) with appropriate biopsy sample; dystrophin measured by Western Blot (AB15277). Muscle biopsies were collected 2 weeks after the 24-week dose was administered.

- Dystrophin results from a pre-specified analysis of ambulatory boys showed (**Figure 4**):
  - Mean absolute muscle content-adjusted dystrophin expression was 9.0% (range: 4.6-13.9%) and mean absolute unadjusted dystrophin expression was 5.5% of normal (range: 3.3-8.3%), as measured by western blot.
  - The dystrophin expression was quantified from two isoforms.
  - 89% of ambulatory participants achieved muscle content-adjusted dystrophin levels of at least 5%.

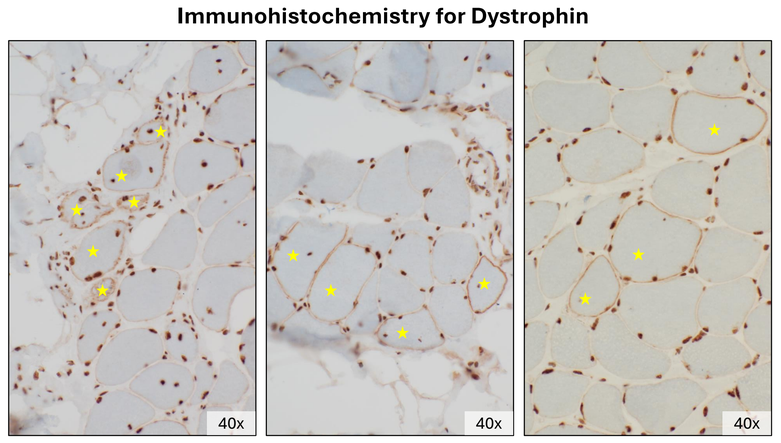
Figure 5. WVE-N531 was localized in myofiber nuclei and myogenic stem cells



(A) In situ hybridization for WVE-N531. Multiple myonuclei contain WVE-N531. Also note internalized myonuclei consistent with regeneration. (B) Dual staining utilizing in-situ hybridization for WVE-N531 and PAX7 immunohistochemistry for stem cells.

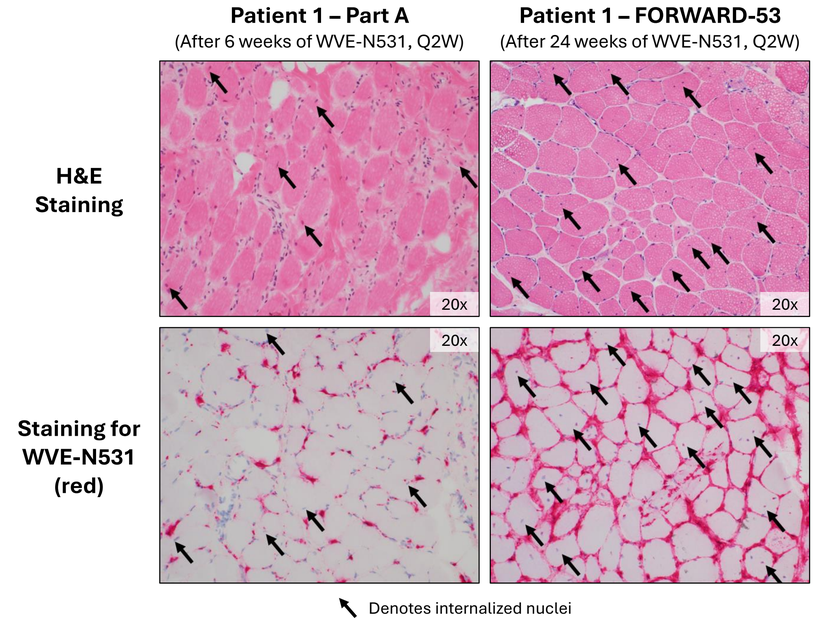
- WVE-N531 was detected in myocyte nuclei in all participants and in myogenic stem cells in the majority of participants (**Figure 5A**,**B**).

Figure 6. Dystrophin is localized to the sarcolemma membrane



Immunohistochemistry staining of anti-dystrophin antibody of a representative patient. Immunohistochemistry stains dystrophin brown (☆).

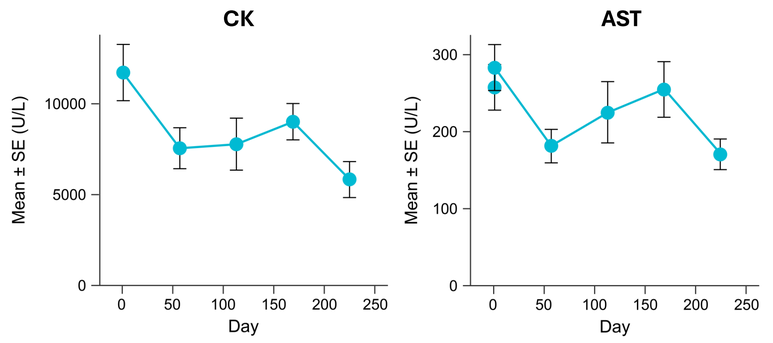
Figure 7. Evidence of myocyte regeneration and improvement in muscle health



Q2W: Every other week dosing. Staining for WVE-N531 (red): RNA Scope (in situ hybridization).

- Participants showed multiple indicators of improvement in muscle health, including an increase in the mean percentage of myocytes with internalized nuclei consistent with regeneration of myofibers between the previously completed Part A study and FORWARD-53 (**Figure 7**).

Figure 8. WVE-N531 treatment led to substantial decreases in muscle-related biomarkers



CK: Creatine Kinase; AST: Aspartate Aminotransferase.

- In the interim data, there were significant decreases in creatine kinase (CK) and aspartate aminotransferase (AST) levels from baseline. The reduction in CK was numerically larger than is typically seen with the introduction of steroids in DMD (**Figure 8**).
- Changes in CK and AST were highly correlated (p<0.0001).

References: 1. Blake DJ, et al. *Physiol Rev.* 2002 Apr;82(2):291-329; 2. Verhaart IEC and Aartsma-Rus A. *Nat Rev Neurol.* 2019 Jul;15(7):373-386; 3. Mah JK. *Neuropsychiatr Dis Treat.* 2016 Jul 22;12:1795-807; 4. Boland BJ, et al. *Pediatr Neurol.* 1996 Jan;14(1):7-12; 5. Hoffman EP and McNally EM. *Sci Transl Med.* 2014 Apr;6(230):230fs14. **Acknowledgments:** For development of this poster, the authors thank Amy Donner and Alexander Lin (Wave Life Sciences) for medical writing support and Eric Smith for graphics support. This work was funded by Wave Life Sciences.

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