# A Phase 1b/2 Open-label Study of WVE-N531 in Patients with Duchenne Muscular Dystrophy: Part B (FORWARD-53) Study Design and Rationale

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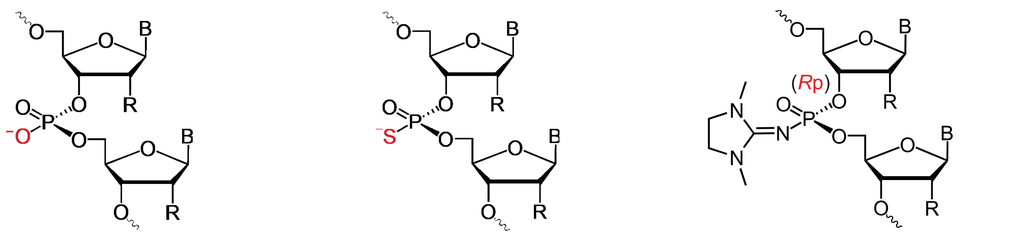
## SUMMARY

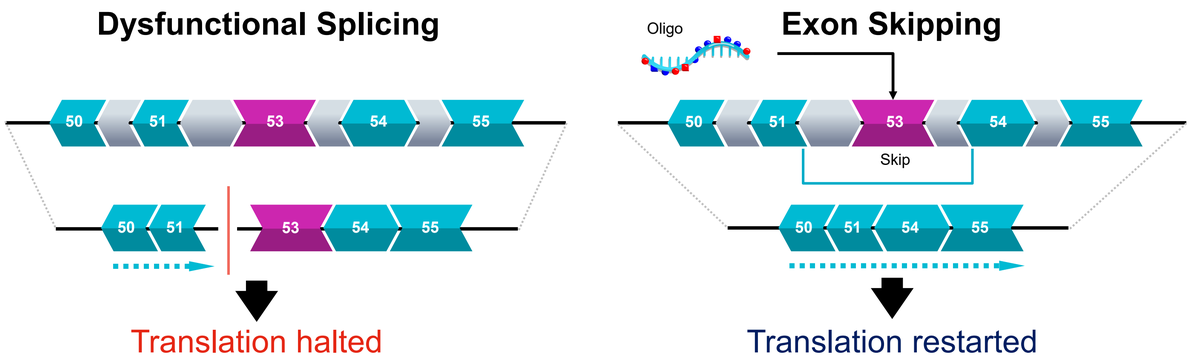
- WVE-N531 is an investigational stereopure antisense oligonucleotide with novel phosphoryl guanidine (PN) chemistry currently being developed as a potential therapy for patients with Duchenne muscular dystrophy (DMD) amenable to exon 53 skipping.
- In Part A (N=3) of a Phase 1b/2 clinical trial (NCT04906460), 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.
  - Mean dystrophin production was 0.27% (BLQ, western blot) of normal; extended dosing and follow up are needed to confirm increased production of dystrophin over time.
  - WVE-N531 was generally safe and well-tolerated with most adverse events (AEs) being mild in intensity.
- Part B (FORWARD-53, N=11) is designed to further evaluate WVE-N531:
  - FORWARD-53 includes ambulatory and non-ambulatory boys between 5 to 18 years of age.
  - All patients will receive intravenous (IV) infusions of WVE-N531 at 10 mg/kg every other week for 48 weeks.
  - Key clinical endpoints will include dystrophin levels, the North Star Ambulatory Assessment (NSAA), Stride Velocity 95$^{th}$ Centile (SV95C) and other functional outcomes and quality-of-life measures.
- Dosing is underway in FORWARD-53 with data expected in 3Q 2024.

## INTRODUCTION

- Duchenne muscular dystrophy is the most common genetic muscular dystrophy caused by mutations in the gene encoding dystrophin.[1]
- WVE-N531 is a stereopure antisense oligonucleotide, which contains PN chemistry (**Figure 1**).
- WVE-N531 was designed to induce exon 53 skipping and yield dystrophin protein production in patients with DMD amenable to exon 53 skipping.
- Part A of a Phase 1b/2 open-label study (NCT04906460) demonstrated that WVE-N531 was safe and well-tolerated, with a promising pharmacokinetic (PK) and pharmacodynamic (PD) profile in three ambulatory boys.
- Based on the encouraging results from Part A, the Phase 2 portion of the study (FORWARD-53, Part B) is designed to assess dystrophin protein generation over an extended period and in a larger population.

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

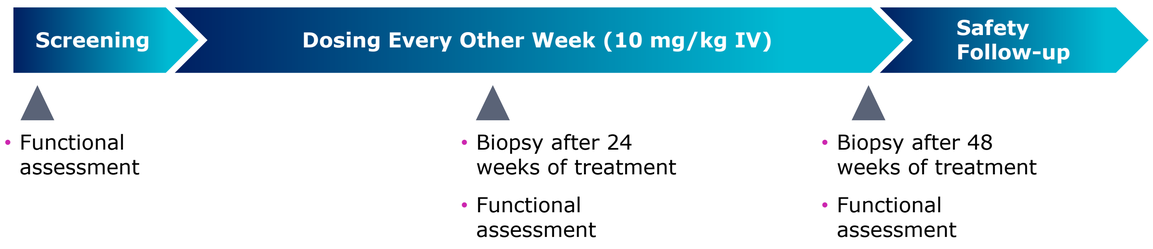



## STUDY DESIGN

- Part B (FORWARD-53) is a Phase 2 open-label study designed to evaluate the safety, tolerability, PD, PK, and clinical effects of WVE-N531 administered every other week in patients with DMD amenable to exon 53 skipping (**Figures 2-4**, **Table 1**).
  - All patients (N=11, between 5 to 18 years of age) will receive open-label WVE-N531 at 10 mg/kg every other week for 48 weeks.
  - Muscle biopsies will be performed after 24 and 48 weeks of treatment.
- The primary endpoint will be dystrophin protein levels as measured by western blot.
  - Patients will also be evaluated for functional outcomes and quality of life.
  - **Figure 3** displays key study endpoints.
- FORWARD-53 will also assess safety based on AEs, physical examinations, vital signs, and clinical laboratory evaluations.
- Safety monitoring will occur through 18 weeks after the last dose.

**Figure 2.** Dosing underway in FORWARD-53, a potentially registrational Phase 2 clinical trial of WVE-N531 in DMD (exon 53)




Abbreviation: IV, intravenous

**Table 1.** Key eligibility criteria

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

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

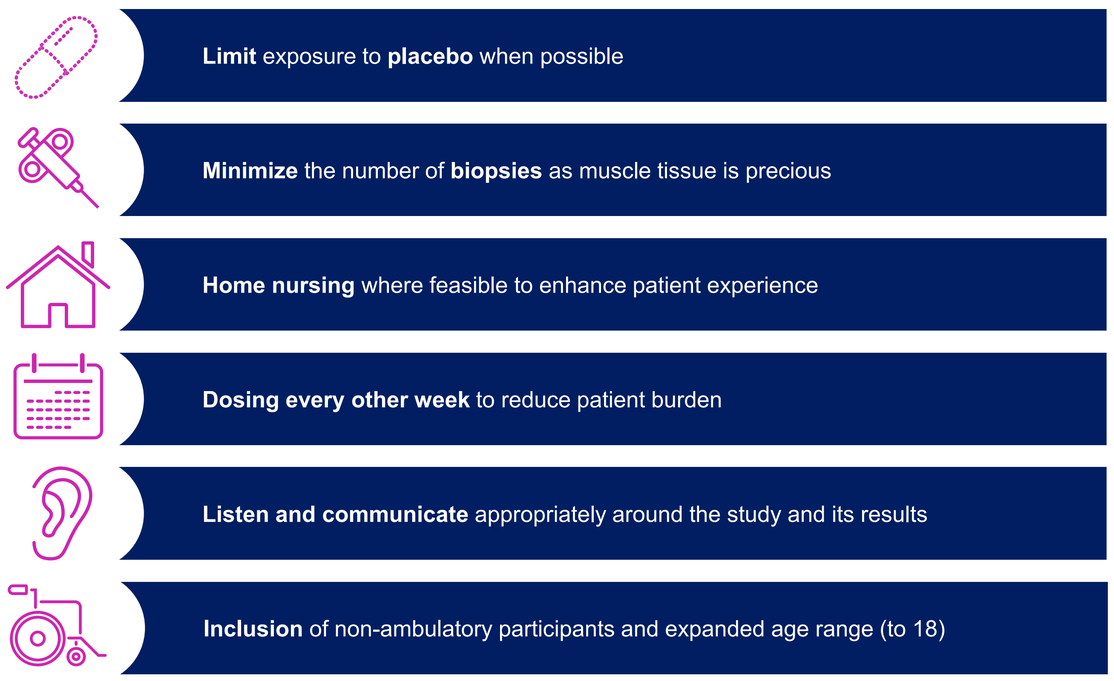
**Figure 3.** Key endpoints

| | |
|---|---|
| 1 Primary | • Dystrophin level (% of normal), as assessed by western blot of muscle tissue after 24 and 48 weeks of treatment |
| 2 Secondary | • NSAA (Version 2.0) including time to stand and a timed 10-meter walk/run<br>• Four-stair climb time<br>• PUL (Version 2.0)<br>• SV95C/upper limb outcome for non-ambulatory patients<br>• Upper limb proximal strength assessed by handheld myometer<br>• Pulmonary function tests (FVC, PFR, and CPF)<br>• Pharmacodynamic effect (exon 53 skipping, dystrophin immunofluorescence) |
| Exploratory | • DMD-QoL questionnaire<br>• WVE-N531 muscle concentration |

Abbreviations: CPF, cough peak flow; FVC, forced vital capacity; NSAA, North Star Ambulatory Assessment; PFR, peak flow rate; PUL, Performance of the Upper Limb; SV95C, Stride Velocity 95th Centile; QoL, Quality of Life.

## PATIENT-FOCUSED CLINICAL TRIAL DESIGN

**Figure 4.** Patient-focused design with input from DMD community expert




**References:** 1. Blake DJ, et al. *Physiol Rev.* 2002 Apr;82(2):291-329. **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. **Disclosures:** Laurent Servais is an employee of Oxford Children's Hospital; all other authors are employees of Wave Life Sciences.

For additional clinical trial information on this study, please contact clinicaltrials@wavelifesci.com or visit clinicaltrials.gov (NCT04906460)

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