# Wave Life Sciences Announces Positive Interim Data from FORWARD-53 Clinical Trial Evaluating WVE-N531 in Boys with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping

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*Mean muscle content-adjusted dystrophin expression of 9.0% and unadjusted dystrophin of 5.5%, with high consistency across participants, in a prespecified analysis; dystrophin was comprised of two isoforms consistent with Becker muscular dystrophy patients who display milder disease*

*Data demonstrated 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; preclinical data suggest participants may have even higher concentrations in heart and diaphragm*

*WVE-N531 was safe and well tolerated: treatment-related adverse events were all mild, no serious adverse events, no discontinuations and no oligonucleotide class-related events*

*Wave expects feedback on a pathway to accelerated approval from regulators, as well as the complete 48-week FORWARD-53 data, in 1Q 2025*

*Wave to host investor conference call and webcast at 8:30 a.m. ET today*

CAMBRIDGE, Mass., Sept. 24, 2024 (GLOBE NEWSWIRE) -- Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage biotechnology company focused on unlocking the broad potential of RNA medicines to transform human health, today announced positive interim data from the ongoing Phase 2 FORWARD-53 study of WVE-N531, which is an exon skipping oligonucleotide being investigated in boys with Duchenne muscular dystrophy (DMD) who are amenable to exon 53 skipping. The interim analysis was conducted after 24 weeks of 10 mg/kg dosing every two weeks (Q2W), and WVE-N531 demonstrated substantial dystrophin expression and that it was safe and well tolerated.

“The high and consistent dystrophin levels at this interim timepoint are compelling and speak to the potential of WVE-N531 for boys amenable to exon 53 skipping, where better therapeutic options are urgently needed,” said Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS, Chief Development Officer at Wave Life Sciences. “It is also known that dystrophin is expressed as multiple functional isoforms and we are encouraged that the two isoforms observed on our Western Blot data are consistent with Becker muscular dystrophy patients who display milder disease. This observation is further supported by our interim data showing myofiber regeneration and improvements in muscle health. We look forward to delivering data from the complete FORWARD-53 study in the first quarter of 2025, and would like to express our deepest gratitude to the boys, families and study staff who are participating in the study.”

“Exon skipping is a promising approach to treat DMD and is compatible with all others that are approved or in development. However, it has been challenging for the field to achieve dystrophin levels that can significantly improve clinical outcomes. Achieving mean muscle content-adjusted dystrophin of 9% is a meaningful step forward,” said Laurent Servais, MD, PhD, Professor of Paediatric Neuromuscular Disease at the University of Oxford and Principal Investigator in FORWARD-53. “The safe and tolerable profile and the option for monthly dosing is also encouraging and has the potential to greatly contribute to quality of life of treated boys in comparison with current weekly dosing.”

**Detailed Interim Results from FORWARD-53**
Eleven boys amenable to exon 53 skipping (age 5-11; 10 ambulatory and 1 non-ambulatory) are enrolled in the ongoing, open-label FORWARD-53 trial. The study is designed to administer 10 mg/kg infusions of WVE-N531 Q2W and muscle biopsies are taken after 24 and 48 weeks of dosing. Results from this interim analysis include:

*Safety and Tolerability*

- WVE-N531 was safe and well tolerated. 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.

*Efficacy*

- **Dystrophin:** Dystrophin results from a pre-specified analysis of ambulatory boys showed:
  - 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 consistent with those observed in Becker muscular dystrophy patients who display milder disease.
  - 89% of ambulatory participants achieved muscle content-adjusted dystrophin levels of at least 5%.
- **Exon skipping:** Mean exon skipping was 57% (range: 31-75%) as measured by RT-PCR.
- **Localization:** WVE-N531 was detected in myocyte nuclei in all participants and in myogenic stem cells in the majority of participants. Myogenic stem cells are the progenitor cells for new myoblasts, which give rise to new myocytes and ultimately aid in skeletal muscle regeneration.
- **Improvements in muscle health:** Participants showed multiple indicators of improvement in muscle health, including an increase in the mean percentage of myocytes with internalized nuclei and an improvement in myofiber size and diameter between the previously completed Part A study and FORWARD-53.
- **Serum biomarkers for muscle health:** Creatine kinase (CK) and aspartate aminotransferase (AST) are serum biomarkers that are elevated in the presence of muscle damage. In the interim data, there were significant decreases in CK and AST levels from baseline. The reduction in CK was numerically larger than is typically seen with the introduction of steroids in DMD. Changes in CK and AST were highly correlated ($p<0.0001$).
- **Muscle concentration:** Mean muscle concentration was ~41,000 ng/g (~5,900 nM).

    - Preclinical data for WVE-N531 demonstrate significantly higher drug concentrations in the heart and diaphragm versus skeletal muscle, suggesting the FORWARD-53 data from skeletal muscle biopsies may be underrepresenting activity in heart and diaphragm.
- **Half-life:** The muscle tissue half-life of WVE-N531 is estimated to be 61 days. Along with muscle concentration, this supports a monthly dosing regimen for WVE-N531 moving forward.

In the first quarter of 2025, Wave expects to complete the FORWARD-53 trial and receive feedback from regulators on a pathway to accelerated approval. Wave is also advancing a broader DMD pipeline of oligonucleotides for skipping other exons, with the goal of providing new and best-in-class treatment options for up to 40% of boys with DMD.

"We have long believed that our novel platform chemistry offered an opportunity to reimagine therapeutics for Duchenne, and we are looking forward to sharing further updates on WVE-N531," said Paul Bolno, MD, MBA, President and CEO of Wave Life Sciences. "We are also hard at work advancing our lead RNA editing and RNAi programs, which offer differentiated, best-in-class therapeutic approaches. In the fourth quarter of 2024, we expect proof-of-mechanism data for our WVE-006 program in Alpha-1 antitrypsin deficiency. In the first quarter of 2025, we expect to initiate our clinical trial for WVE-007 – a potentially breakthrough approach to obesity that leverages GalNAc-siRNA to target INHBE and induce healthy weight loss with muscle maintenance. Finally, we are looking forward to our annual R&D Day, which will take place this fall and where we will discuss the next wave of RNA innovations being advanced by our organization."

**Investor Conference Call and Webcast**
Wave will host an investor conference call today at 8:30 a.m. ET to review the interim data from FORWARD-53. A webcast of the conference call can be accessed by visiting "Investor Events" on the investor relations section of the Wave Life Sciences website: https://ir.wavelifesciences.com/events-publications/events. Analysts planning to participate during the Q&A portion of the live call can join the conference call at the audio-conferencing link available here. Once registered, participants will receive the dial-in information. Following the live event, an archived version of the webcast will be available on the Wave Life Sciences website.

**About WVE-N531**
WVE-N531 is an exon skipping oligonucleotide being developed as a disease modifying treatment for boys with Duchenne muscular dystrophy amenable to exon 53 skipping. WVE-N531 was designed using Wave's best-in-class oligonucleotide chemistry modifications, including PN backbone chemistry. WVE-N531 is being investigated in the ongoing Phase 2 FORWARD-53 clinical trial, with additional data expected in the first quarter of 2025. WVE-N531 has received Orphan Drug Designation and Rare Pediatric Disease Designation from the U.S. Food & Drug Administration.

**About FORWARD-53**
FORWARD-53 is a potentially registrational, open-label, Phase 2 clinical trial evaluating WVE-N531 as a treatment for boys with Duchenne muscular dystrophy (DMD) who are amenable to exon 53 skipping. Eleven boys are currently enrolled. WVE-N531 is being dosed at 10 mg/kg every two weeks, and endpoints include dystrophin expression after 24 and 48 weeks of treatment, as well as pharmacokinetic, safety and tolerability data, and functional assessments. FORWARD-53 is fully enrolled with final data from the study, including muscle biopsies after 48 weeks of treatment, expected in the first quarter of 2025.

**About Duchenne Muscular Dystrophy**
Duchenne muscular dystrophy (DMD) is a fatal X-linked genetic neuromuscular disorder caused predominantly by out-of-frame deletions in the dystrophin gene, resulting in absent or defective dystrophin protein. Dystrophin protein is needed for normal muscle maintenance and operation. Because of the genetic mutations in DMD, the body cannot produce functional dystrophin, which results in progressive and irreversible loss of muscle function, including the heart and lungs. Worldwide, DMD affects approximately one in 5,000 newborn boys. Approximately 8%-10% of DMD patients have mutations amenable to treatment with an exon 53 skipping therapy. Exon skipping aims to address the underlying cause of DMD by promoting the production of dystrophin protein to stabilize or slow disease progression.

**About Wave Life Sciences**
Wave Life Sciences (Nasdaq: WVE) is a biotechnology company focused on unlocking the broad potential of RNA medicines to transform human health. Wave's RNA medicines platform, PRISM®, combines multiple modalities, chemistry innovation and deep insights in human genetics to deliver scientific breakthroughs that treat both rare and prevalent disorders. Its toolkit of RNA-targeting modalities includes editing, splicing, RNA interference and antisense silencing, providing Wave with unmatched capabilities for designing and sustainably delivering candidates that optimally address disease biology. Wave's diversified pipeline includes clinical programs in Duchenne muscular dystrophy, Alpha-1 antitrypsin deficiency and Huntington's disease, as well as a preclinical program in obesity. Driven by the calling to "Reimagine Possible", Wave is leading the charge toward a world in which human potential is no longer hindered by the burden of disease. Wave is headquartered in Cambridge, MA. For more information on Wave's science, pipeline and people, please visit www.wavelifesciences.com and follow Wave on X (formerly Twitter) and LinkedIn.

**Forward-Looking Statements**
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, our understanding of the anticipated therapeutic benefit of WVE-N531 as a therapy for DMD; our plan and estimated timing to engage regulators with the interim results and complete the trial and deliver the results of the complete trial; our understanding of the dystrophin isoforms we are observing with WVE-N531; our understanding of the safety profile of WVE-N531; and the potential benefits of PRISM, including our novel PN backbone chemistry modifications, and our stereopure oligonucleotides compared with stereorandom oligonucleotides. The words "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release and actual results may differ materially from those indicated by these forward-looking statements as a result of these risks, uncertainties and important factors, including, without limitation, the risks and uncertainties described in the section entitled "Risk Factors" in Wave's most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC), as amended, and in other filings Wave makes with the SEC from time to time. Wave undertakes no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances.

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