Wave Life Sciences Announces Positive Data from FORWARD-53 Clinical Trial in DMD Including Significant Functional Benefit and Reversal of Muscle Damage after 48 Weeks of Dosing with WVE-N531

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Statistically significant and clinically meaningful improvement of 3.8 seconds in Time-to-Rise vs. natural history with largest effect observed relative to any approved dystrophin restoration therapy at 48 weeks; additional functional benefits observed in other outcome measures including NSAA

First-ever demonstration of substantial improvements in muscle health with exon skipping – statistically significant reduction in fibrosis driven by decreases in inflammation and necrosis, coupled with transition from regenerative to mature muscle; decreases in creatine kinase and circulating inflammatory biomarkers

Dystrophin expression stabilized between 24 and 48 weeks and averaged 7.8%, with 88% of boys above 5% average dystrophin; WVE-N531 remains safe and well-tolerated with no Serious Adverse Events

Following recent feedback from FDA, Wave intends to file a New Drug Application in 2026 for accelerated approval, with data to support monthly dosing at launch

Wave expects to file CTAs in 2026 for multiple DMD candidates for other exons, with preclinical data supporting a best-in-class exon skipping franchise

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

CAMBRIDGE, Mass., March 26, 2025 (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 data from the Phase 2 FORWARD-53 trial 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 analysis was conducted after 48 weeks of treatment with 10 mg/kg WVE-N531 dosed every two weeks (Q2W).

FORWARD-53 achieved all trial goals, demonstrating sustained and industry-leading exon skipping, muscle concentrations and dystrophin restoration through 48 weeks and a 61-day tissue half-life that supports monthly dosing. WVE-N531 continues to be safe and well-tolerated.

Additionally, the data demonstrate substantial decreases in inflammation and necrosis, a statistically significant reversal of muscle fibrosis (28.6% reduction between week 24 to 48; $p<0.01$), and a transition from regeneration to maturation of muscle. A 50% decline (<0.001) in creatine kinase (CK), as well as decreases in IL-6 and MCP-1, were also observed. Time-to-Rise (TTR) data demonstrate a statistically significant and clinically meaningful 3.8-second improvement versus natural history ($p<0.05$), which is the largest effect observed relative to any approved dystrophin restoration therapy at 48 weeks. Additional functional benefits were observed on the North Star Ambulatory Assessment (NSAA) versus natural history, and in hand grip strength versus baseline.

“Despite progress in Duchenne, there remains a significant unmet need for therapeutics that meaningfully impact disease progression. These data demonstrate a promising continuum from dystrophin restoration, to regeneration and maturation of muscle tissue, to functional improvement,” said Pat Furlong, founder and president of Parent Project Muscular Dystrophy. “Paired with monthly administration and a continued favorable safety profile, WVE-N531 represents a significant step forward – not just for individuals amenable to exon 53 skipping, but also for the broader exon skipping field. PPMD looks forward to working with Wave as they expediently bring WVE-N531 and their broader exon skipping pipeline to the Duchenne community.”

“As a clinician deeply involved in patient care and research in muscle diseases like Duchenne, I am encouraged by these data for WVE-N531 that show dystrophin restoration and several markers of improved muscle condition,” said Laurent Servais, MD, PhD, Professor of Paediatric Neuromuscular Disease at the University of Oxford and Principal Investigator in FORWARD-53. “To see a clinically meaningful and statistically significant difference on TTR versus natural history in a Phase 2 study is another encouraging finding. I am looking forward to the continued development of WVE-N531.”

Wave also announced today that the company met with the U.S. Food and Drug Administration (FDA) on WVE-N531 to discuss its interim 24-week data and initial plans for the confirmatory trial, where the Agency confirmed that the accelerated approval pathway using dystrophin expression as a surrogate endpoint remains open. Based on the FDA feedback and the 48-week data, Wave intends to file a New Drug Application (NDA) in 2026 for accelerated approval of WVE-N531. The NDA filing will be based on all FORWARD-53 data, which will include additional data to support monthly dosing. Furthermore, Wave will continue to engage the Agency with the new 48-week data, including functional outcomes, and its planned global confirmatory trial of WVE-N531.

“WVE-N531’s demonstrated ability to reach both myofibers and myogenic stem cells – the regenerative muscle cells – and sustain dystrophin restoration over time is impacting muscle health in ways never before seen in DMD,” said Paul Bolno, MD, MBA, President and Chief Executive Officer at Wave Life Sciences. “With these transformational data and feedback from FDA in hand, we are now moving toward our first NDA filing, which puts us on the path toward becoming a commercial company.”

Continued Dr. Bolno, “Most importantly, we are inspired by the opportunity ahead to deliver life-changing medicines to this community. We expect WVE-N531 to become the first-line treatment of choice for boys amenable to exon 53 skipping, including the 40-50% in the US who are not being treated with approved exon skippers due in part to the burden of weekly infusions coupled with limited efficacy. Additionally, we are accelerating our near-term clinical programs for other exons, which based on preclinical data, suggest a best-in-class exon skipping franchise. We are incredibly grateful to the trial participants and their families, as well as all our collaborators across the DMD community for their contributions to this program and all our DMD research over the past decade.”

WVE-N531, as well as Wave’s programs for exons 52, 51, 45 and 44, leverage best-in-class oligonucleotide chemistry, including PN backbone

chemistry and stereochemical control, enabling industry-leading muscle delivery and potency without requiring antibody or peptide conjugates. Preclinical data for Wave's PN chemistry-containing exon skipping candidates have also demonstrated significantly higher dystrophin and drug concentrations in the heart and diaphragm versus skeletal muscle. Collectively, WVE-N531 plus Wave's exon 52, 51, 45 and 44 programs would address ~40% of the DMD population and represent a >$2.4 billion total market opportunity in the United States alone. Wave expects to submit multiple clinical trial applications (CTAs) for other exon skipping programs in 2026.

Detailed 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. Biopsy data are from eight of the 11 boys (all ambulatory and who had biopsies at 24 and 48 weeks) while safety and functional outcome assessments were available for all participants. All 11 boys have advanced to the extension portion of the study where they are now receiving monthly doses of WVE-N531.

Results after 48 weeks of 10 mg/kg dosing every two weeks include:

Safety and Tolerability

- WVE-N531 was safe and well-tolerated through 48 weeks. All treatment-related adverse events were mild to moderate in intensity.
- There were no Serious Adverse Events and no discontinuations due to any causes.

Results from Muscle Biopsies

- **Dystrophin and exon skipping:** Dystrophin expression stabilized between 24 and 48 weeks of dosing with a mean of 7.8% [95% CI: 5.4-10.3%; 24-week dystrophin was 9.0% (95% CI: 6.5-11.5%) and 48-week dystrophin was 6.4% (95% CI: 3.8-9.0%); muscle content-adjusted dystrophin as measured by western blot]. The difference between the 24- and 48-week mean dystrophin measurements is within the established 30-35% inter-assay variability of the western blot, and consistency between these timepoints was confirmed with an orthogonal assay.
    - 88% of boys (7/8) achieved greater than 5% average dystrophin between 24 and 48 weeks.
    - Mean exon skipping reached steady state at 6 weeks and was consistent through 48 weeks of dosing with a mean of 54% (95% CI: 46-63%).
- **Reversal of muscle damage:** Participants showed significant and unprecedented improvements in multiple indicators of muscle health through 48 weeks, indicating a shift from dystrophic muscle towards healthy muscle. These data include:
    - Decreases of the median muscle necrosis and inflammation scores from 2 to 1(representing mild damage) in muscle pathology.
    - Decreases in markers of inflammation (MCP-1 and IL-6).
    - A statistically significant decline in the amount of muscle fibrosis between 24 and 48 weeks (mean decrease of 28.6%, $p<0.01$).
    - A 50% decrease ($p<0.001$) in serum creatine kinase (CK), which occurred on top of a stable corticosteroid regimen.
    - Improved organization and uniformity of myofibers in muscle tissue.
    - Decreases in number of stem cells and internalized nuclei, indicative of myofiber maturation between week 24 and 48.

Functional Assessments

- Benefits were seen in multiple functional assessments among WVE-N531-treated boys (n=10), including Time-to-Rise (TTR) and North Star Ambulatory Assessment (NSAA), compared with a matched exon 53 natural history control group (n=18).
    - TTR showed a statistically significant and clinically meaningful 3.8-second difference ($p<0.05$) favoring WVE-N531 compared with natural history. The minimal clinically important difference (MCID) for TTR was 1.4 seconds, based on the baseline functional characteristics of boys in the study.
    - NSAA showed positive trends favoring WVE-N531 relative to natural history (1.2-point improvement; not significant).
- Positive trends were also observed among WVE-N531-treated boys (n=11) on grip strength versus baseline.

Additional Upcoming Milestones Across Wave's Clinical RNA Medicines Pipeline
Wave expects multiple additional milestones across its clinical pipeline of RNA medicines in 2025, including:

- WVE-006 (GalNAc-conjugated RNA editing oligonucleotide for alpha-1 antitrypsin deficiency): Wave expects to deliver 200 mg multi-dose data and 400 mg single-dose data from the Phase 1b/2a RestorAATion-2 trial in 2025.
- WVE-007 (GalNAc-conjugated siRNA for obesity, designed to silence INHBE mRNA): Wave expects to deliver clinical data from the Phase 1 INLIGHT trial in the second half of 2025, including safety, tolerability and biomarkers reflective of healthy weight loss.
- WVE-003 (allele-selective silencing for Huntington's disease): Wave expects to submit an Investigational New Drug application in the second half of 2025 for its potentially registrational Phase 2/3 trial of WVE-003.

Investor Conference Call and Webcast
Wave will host an investor conference call today at 8:30 a.m. ET to review the FORWARD-53 data. 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 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 has received Orphan Drug Designation and Rare Pediatric Disease Designation from the U.S. Food & Drug Administration.

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 boys with DMD 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 common 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 Alpha-1 antitrypsin deficiency, Duchenne muscular dystrophy, Huntington's disease, and obesity, as well as several preclinical programs utilizing the company's broad RNA therapeutics toolkit. 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, and the broader exon skipping field; our understanding of the safety profile of WVE-N531; our plan and estimated timing to file an NDA for accelerated approval of WVE-N531, along with our expectations for commercialization; our expectations for WVE-N531 to become the first-line treatment of choice for boys amenable to exon 53 skipping; our plan to file CTA submissions for other exon skipping treatments and the potential for a best-in-class exon skipping franchise; addressable patient population estimates related to our therapeutic candidates; the potential commercial opportunities that our therapeutic candidates may address; anticipated milestones and anticipated benefits of our therapeutic candidates and pipeline compared to our competitors; 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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