Wave Life Sciences Provides Positive Update on Proof-of-Concept Study for WVE-N531 in Duchenne Muscular Dystrophy

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53% mean exon skipping and <1% (BLQ) mean dystrophin expression six weeks after initiating biweekly multidosing

PN chemistry improved pharmacology of WVE-N531 compared with Wave's first-generation DMD program – demonstrated high muscle concentrations with a mean of 42 micrograms/gram

WVE-N531 appeared safe and well tolerated

Third Wave clinical trial evaluating a PN chemistry-containing compound to achieve target engagement in 2022

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

CAMBRIDGE, Mass., Dec. 19, 2022 (GLOBE NEWSWIRE) -- Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases, announced today a positive update from the initial cohort of the Phase 1b/2a proof-of-concept study of WVE-N531 in three boys with Duchenne muscular dystrophy (DMD) amenable to exon 53 skipping. High muscle concentrations of WVE-N531 and exon skipping were observed six weeks after initiating biweekly multidosing at 10 mg/kg, achieving proof-of-concept in the study. WVE-N531 also appeared safe and well-tolerated.

"These data provide early evidence that WVE-N531 is working as intended, leading to substantial exon skipping after just three consecutive doses. This is the earliest timepoint at which exon skipping has been reported in a clinical trial of boys with DMD," said Anne-Marie Li-Kwai-Cheung, Chief Development Officer of Wave Life Sciences. "While dystrophin was below the lower limit of detection, it is expected that dystrophin protein production would lag splicing of the RNA transcript. We are encouraged by these early results and are evaluating next steps for the program, including the continuation of this initial cohort. We would like to express our sincerest gratitude to the boys, their families, and the investigators who participated in the study."

"There remains a significant unmet need in DMD for new treatment options. It is exciting to see this level of exon skipping in a short period of time, especially since skipping would be expected to increase over a longer dosing interval," said Laurent Servais, MD, PhD, professor of pediatric neuromuscular diseases at the MDUK Oxford Neuromuscular Center and primary investigator in the WVE-N531 study. "Based on the data, it appears Wave's next-generation chemistry has led to significantly improved pharmacology. Expression of dystrophin after longer exposure will, of course, be key to confirm the promise of these early data. I look forward to the continued progression of clinical research for WVE-N531."

Three ambulatory boys participated in this open-label, intra-patient dose escalation clinical trial (NCT04906460). The boys received single escalating doses of 1, 3, 6 and 10 mg/kg; and in the multidose portion of the study, the same boys received three doses of 10 mg/kg every other week. A muscle biopsy was taken two weeks after the third and final dose (six weeks after the first dose).

Results included:

- WVE-N531 resulted in a mean tissue concentration of 42 micrograms/gram (6.1 micromolar)
- RNAscope results indicated WVE-N531 is reaching the nucleus in muscle cells
- WVE-N531 resulted in mean exon skipping of 53% (range: 48-62%) as measured by RT-PCR
- Mean dystrophin production was 0.27% of normal as measured by Western blot, which was below the level of quantification (BLQ: 1%)
- Plasma concentrations and other pharmacokinetic parameters following a single dose of 10 mg/kg demonstrate a half-life of 25 days, which may support monthly dosing
- Adverse events were all mild, except for a COVID-19 infection of moderate intensity. There were no serious adverse events, no trends in labs, and no oligonucleotide class-related safety events.

"These data indicate PN chemistry can improve potency, distribution and durability of splicing oligonucleotides without needing peptide or antibody conjugates, clearly demonstrating the increasing potential of Wave's PRISM platform," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "This is Wave's third clinical trial in 2022 to demonstrate the impact of PN chemistry, as well as our third clinical trial to demonstrate translation of preclinical data in humans. In 2023, we are looking forward to determining next steps for WVE-N531, advancing our silencing clinical programs, and bringing a whole new modality into the clinic with our RNA editing and upregulation capability."

Investor Conference Call and Webcast
Wave management will host an investor conference call today at 8:30 a.m. ET to discuss results from this WVE-N531 proof-of-concept study. The webcast of the conference call and corresponding slide presentation may be accessed by visiting "Events" on the investor relations section of the Wave Life Sciences corporate website: ir.wavelifesciences.com/events-and-presentations.

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 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 PRISM™
PRISM is Wave Life Sciences' proprietary discovery and drug development platform that enables genetically defined diseases to be targeted with stereopure oligonucleotides across multiple therapeutic modalities, including silencing, splicing and editing. PRISM combines the company's unique ability to construct stereopure oligonucleotides with a deep understanding of how the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry impacts key pharmacological properties. By exploring these interactions through iterative analysis of *in vitro* and *in vivo* outcomes and machine learning-driven predictive modeling, the company continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles.

About Wave Life Sciences®
Wave Life Sciences (Nasdaq: WVE) is a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. Wave aspires to develop best-in-class medicines across multiple therapeutic modalities using PRISM, the company's proprietary discovery and drug development platform that enables the precise design, optimization, and production of stereopure oligonucleotides. Driven by a resolute sense of urgency, the Wave team is targeting a broad range of genetically defined diseases so that patients and families may realize a brighter future. To find out more, please visit www.wavelifesciences.com and follow Wave on Twitter @WaveLifeSci.

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 understanding of the cause of DMD and the potential addressable patients amenable to treatment with an exon 53 skipping therapy; our expectations that the level of exon skipping would be expected to increase over a longer dosing interval; our expectation that dystrophin protein production would lag splicing of the RNA transcript; our beliefs regarding the learnings gained from our first-generation DMD program; our expectation regarding the continued progression of clinical research for 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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