Wave Life Sciences Announces First-Ever Therapeutic RNA Editing in Humans Achieved in RestorAATion-2 Trial of WVE-006 in Alpha-1 Antitrypsin Deficiency

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Achieved proof-of-mechanism for Wave's RNA editing platform; restoring levels of wild-type (edited) M-AAT that are consistent with the heterozygous "MZ" genotype with low risk of AATD lung and liver disease

A single subcutaneous dose of WVE-006 in the first two patients with homozygous "ZZ" AATD resulted in mean plasma total AAT levels of ~11 micromolar, with mean wild-type M-AAT representing more than 60% of total AAT; durable editing with M-AAT protein observed through 57 days

Wave expects to share multidose data from the RestorAATion-2 trial in 2025

Annual Research Day on October 30th will highlight WVE-006 proof-of-mechanism data and Wave's new wholly owned GalNAc-RNA editing programs, in addition to an obesity program update with new preclinical data for WVE-007 (INHBE GalNAc-siRNA)

CAMBRIDGE, Mass., Oct. 16, 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 proof-of-mechanism data from the ongoing Phase 1b/2a RestorAATion-2 study of WVE-006 in alpha-1 antitrypsin deficiency (AATD). WVE-006 is a GalNAc-conjugated, subcutaneously delivered, A-to-I RNA editing oligonucleotide (AIMer) that was developed with Wave's best-in-class oligonucleotide chemistry platform. It is uniquely designed to address AATD-related lung disease, liver disease, or both.

Today's proof-of-mechanism data are the first-ever clinical demonstration of RNA editing in humans. These data are from the first single dose cohort (200 mg) in RestorAATion-2 and include the first two patients with "ZZ" AATD (Pi*ZZ AATD) to reach day 57. Individuals with Pi*ZZ AATD do not naturally produce wild-type alpha-1 antitrypsin (M-AAT) protein; therefore, the presence of M-AAT protein is confirmation of successful editing of mutant Z-AAT mRNA. Additionally, restoring 50% M-AAT would be consistent with the heterozygous "MZ" genotype with low risk of AATD lung and liver disease.

Circulating wild-type M-AAT protein in plasma reached a mean of 6.9 micromolar at day 15, representing more than 60% of total AAT. Increases in neutrophil elastase inhibition from baseline were consistent with production of functional M-AAT. Mean total AAT protein increased from below the level of quantification at baseline to 10.8 micromolar at day 15, meeting the level that has been the basis for regulatory approval for AAT augmentation therapies. Increases in total AAT from baseline and M-AAT protein were observed as early as day 3 and through day 57.

WVE-006 has been well-tolerated with a favorable safety profile to date. All adverse events in RestorAATion-2, as well as in the ongoing RestorAATion-1 trial of healthy volunteers, are mild to moderate, with no Serious Adverse Events reported. The RestorAATion-2 trial is ongoing and Wave expects to share multidose data in 2025.

"Achieving the first-ever therapeutic RNA editing in humans is a significant milestone for our organization, for our GSK collaboration, and for the entire oligonucleotide field. It also unlocks and derisks Wave's RNA editing platform, in light of the continued strong clinical translation of our proprietary best-in-class chemistry, including PN, stereochemistry and our N3U AIMer modification," said Paul Bolno, MD, MBA, President and Chief Executive Officer at Wave Life Sciences. "The level of mRNA editing we are observing with a single dose exceeded our expectations and we expect M-AAT levels to continue to increase with repeat dosing, based on our preclinical data. These initial data, alongside WVE-006's durability and convenient subcutaneous administration, are all supportive of a best-in-class profile for WVE-006 relative to other editors and in the broader AATD space. These data also increase our confidence in our wholly owned pipeline, including our HD, DMD and obesity programs, as well as our next RNA editing targets. We look forward to introducing the next RNA editing programs, as well as providing an update on our INHBE GalNAc-siRNA program in obesity, at our Research Day on October 30."

There are an estimated 200,000 individuals living with AATD in the US and Europe who are homozygous for the SERPINA1 Z mutation. Treatment options are currently limited to weekly IV augmentation therapy for lung disease only (representing over $1.4 billion in worldwide sales in 2023). There are no approved therapies to address AATD liver disease, which ultimately requires many individuals living with AATD to undergo liver transplantation.

GSK has the exclusive global license for WVE-006. Development and commercialization responsibilities will transfer to GSK after Wave completes the RestorAATion-2 study. In total, Wave is eligible for up to $525 million in milestones, as well as tiered royalties on net sales, for WVE-006.

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-006 as a therapy for AATD and our estimates of the AATD patient population that may benefit from WVE-006; our plans and estimated timing to share multidose data from the RestorAATion-2 trial; our understanding of the mRNA being generated by WVE-006; our expectations that M-AAT levels may to continue to increase with repeat dosing; our understanding of the safety profile of WVE-006; potential milestone payments that we may earn for WVE-006; and the potential benefits of our RNA editing platform and our proprietary best-in-class chemistry, including PN, stereochemistry and our N3U AIMer modification. 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.

Investor Contact:
Kate Rausch
+1 617-949-4827
krausch@wavelifesci.com

Media Contact:
Alicia Suter
+1 617-949-4817
asuter@wavelifesci.com

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