Wave Life Sciences Announces Positive Update from Ongoing RestorAATion-2 Trial of WVE-006 in Alpha-1 Antitrypsin Deficiency

September 3, 2025

Achieved durable production of serum AAT protein at levels associated with a lower risk of AATD liver and lung diseases following repeat 200 mg doses of WVE-006 (11.9 µM total AAT, 7.2 µM M-AAT)

*First-ever demonstration of therapeutically restored physiological serum AAT production in a Pi*ZZ individual during a non-drug related acute phase response (20.6 µM total AAT, 10.3 µM M-AAT)*

Single dose of 400 mg achieved 12.8 µM total AAT and 5.3 µM M-AAT; ongoing 400 mg multidose cohort has potential to deliver further increases in serum AAT

Data from 200 mg and 400 mg cohorts support monthly or less frequent subcutaneous dosing; 400 mg monthly multidose cohort data expected in 1Q 2026

WVE-006 continues to be well tolerated with a favorable safety profile to date

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

CAMBRIDGE, Mass., Sept. 03, 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 200 mg single and multidose and 400 mg single dose cohorts of the ongoing Phase 1b/2a RestorAATion-2 study evaluating WVE-006 as a treatment for alpha-1antitrypsin deficiency (AATD). WVE-006 is a GalNAc-conjugated, subcutaneously delivered A-to-I RNA editing oligonucleotide (AIMer) developed with Wave's best-in-class oligonucleotide chemistry platform.

Approximately 200,000 people in the US and Europe living with AATD are homozygous for the Z mutation (Pi*ZZ) in the SERPINA1 gene, which can lead to severe lung disease, liver disease, or both. Pi*ZZ individuals make only mutant Z-AAT protein, which gets trapped in the liver, and their ability to produce protective levels of AAT protein during an acute phase response is compromised, thus leaving the lungs vulnerable to damage. WVE-006 is designed to address both lung and liver manifestations of AATD by correcting the Z mutation in SERPINA1 mRNA, thereby converting Z-AAT to wild-type M-AAT without altering the endogenous transcriptional regulation of the SERPINA1 gene.

"Today's data represent a significant clinical milestone for individuals living with AATD, as well as the field of RNA editing, with WVE-006 enabling the dynamic generation of wild-type M-AAT protein when needed. We have demonstrated the potential for WVE-006 to achieve a long-standing goal by restoring expression of AAT under endogenous physiologic control, which allows for upregulation of this protective protein during exacerbations. WVE-006 continues to translate in the clinic across all participants to consistently drive production of M-AAT, which is protective of lung function, as well as reduce mutant Z-AAT, a cause of liver disease. Furthermore, these data support monthly or less frequent dosing. Collectively, our data highlight WVE-006's potential to provide a transformative treatment option for people living with AATD," said Paul Bolno, MD, MBA, President and Chief Executive Officer at Wave Life Sciences. "Today's update reinforces the strength of our platform as we continue to advance additional wholly owned editing programs toward the clinic. We look forward to sharing more about these at our Research Day this fall."

The data reported today include RestorAATion-2 cohort 1 (200 mg, n=8), where participants received a single subcutaneous dose of WVE-006 and then received seven subcutaneous doses administered every other week under the multidose protocol, as well as the single dose portion of cohort 2 (400 mg, n=8). Circulating M-AAT, Z-AAT, and total (M + Z) AAT protein in the serum were measured by highly selective and sensitive LC-MS/MS assays (LLOQ: 0.096 µM (M), 0.029 µM (Z)) and reported as mean maximums.

Production of M-AAT protein indicates WVE-006 led to RNA editing in all treated participants, with durable production of serum AAT at levels associated with a lower risk of liver and lung disease following repeat 200 mg doses.

In the 200 mg multidose cohort, total AAT reached therapeutically relevant levels of 11.9 micromolar (µM). Wild-type M-AAT increased from below the level of quantitation at baseline to 7.2 µM, which was significantly increased from levels achieved during the single dose portion of the cohort (4.8 µM; p=0.012). Further, M-AAT levels reached 64.4% of total AAT, and mutant Z-AAT protein declined from baseline by 60.3%. M-AAT levels were durable and sustained at >50% of total AAT for at least two months following the last dose. Increases in neutrophil elastase inhibition from baseline were confirmed with production of functional M-AAT.

Notably, following a single 200 mg dose of WVE-006, a total AAT level of 20.6 µM, including a M-AAT level of 10.3 µM, was observed in one individual during an acute phase response due to a kidney stone. These data demonstrate that treatment with WVE-006 enables endogenous regulation and dynamic increased secretion of AAT protein during an acute phase response as indicated by a concurrent C-reactive protein elevation.

In the 200 mg single dose cohort, total AAT reached 12.9 µM, M-AAT increased to 4.8µM, and Z protein decreased by 47.3%. Excluding the individual with an acute phase response, total AAT reached 11.8 µM, M-AAT increased to 4.0 µM, and Z protein decreased by 48.8%.

A single 400 mg dose of WVE-006 resulted in achievement of total AAT of 12.8 µM and M-AAT of 5.3 µM. Circulating serum M-AAT levels reached 47.2% of total AAT and Z-AAT decreased by 49% versus baseline. Data from both the 200 mg and 400 mg (single dose only) cohorts support a monthly or less frequent subcutaneous dosing regimen. Dosing is ongoing in the 400 mg multidose cohort with a monthly dosing regimen, for which Wave expects to deliver data in the first quarter of 2026.

WVE-006 continues to be well tolerated with a favorable safety profile to date. All adverse events (AEs) were mild to moderate in intensity, and there were no SAEs or discontinuations.

"Wave's clinical trial provides two important findings. First, RNA editing resulted in the endogenous production of M protein in ZZ individuals. Second, serendipitously the study observed that the stress of a kidney stone was associated with marked upregulation of M protein production. This suggests that RNA editing has the potential to restore, at least in part, both endogenous M protein production and its normal regulation in AATD. These results

are extremely exciting," said Stephen Rennard, MD, Professor of Medicine in the Division of Pulmonary, Critical Care and Sleep Medicine at the University of Nebraska Medical Center.

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.

Behind WVE-006, Wave is continuing to advance a wholly owned pipeline of RNA editing candidates which utilize its proprietary chemistry in a variety of hepatic and extrahepatic tissues. The company plans to share new preclinical data from these programs at Research Day in the fall of 2025 and to initiate clinical development of additional RNA editing programs in 2026.

Investor Conference Call and Webcast
Wave will host an investor conference call today at 8:30 a.m. ET to review the RestorAATion-2 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 Alpha-1 Antitrypsin Deficiency (AATD)
AATD can manifest as both lung and liver disease. It is a rare, inherited genetic disorder caused by a G-to-A point mutation in the SERPINA1 gene, and is referred to as the Z allele. Approximately 200,000 people in the US/EU are homozygous for the Z allele. In healthy individuals, wild-type, M-AAT protects the lung from proteolytic and inflammatory damage, particularly during exacerbations. AATD causes an aggregation of the mutant Z-AAT protein in the liver and a lack of functional AAT in the lungs. Instead of traveling through the bloodstream to the lungs, Z-AAT protein tends to get trapped in the liver. Further, Pi*ZZ individuals have a reduced capacity to produce incremental AAT protein during an acute phase response. These dynamics can lead to progressive lung damage (e.g. COPD, early onset emphysema), as well as liver damage (e.g. cirrhosis, liver cancer).

AATD treatment options are currently limited to weekly IV augmentation therapy in Pi*ZZ individuals for lung disease (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. Other investigational treatment approaches are often confined to either lung or liver manifestations, rely on exogenously delivered enzymes, and/or utilize complex delivery systems such as lipid nanoparticles.

About RestorAATion-2
RestorAATion-2 (NCT06405633) is an ongoing Phase 1b/2a open label study designed to evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of WVE-006 in individuals with AATD who have the homozygous Pi*ZZ mutation. The trial includes both single ascending dose and multiple ascending dose portions.

About WVE-006
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. By correcting the single RNA base mutation that causes a majority of AATD cases with the Pi*ZZ genotype, WVE-006 is designed to deliver a comprehensive treatment approach for AATD by increasing circulating levels of wild-type AAT protein and reducing mutant protein aggregation in the liver, thus simultaneously addressing both the lung and liver manifestations of the disease. 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 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, obesity, Duchenne muscular dystrophy, and Huntington's disease, 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 benefits of WVE-006 as a therapy for AATD and the potential to address both lung and liver manifestations of the disease; the potential for RNA editing to restore endogenous M protein production and its normal regulation in AATD; our understanding of the levels of AAT considered to be therapeutically relevant; our understanding that treatment with WVE-006 enables endogenous regulation and dynamic increased secretion of AAT protein during an acute phase response; our estimates of the AATD patient population that may benefit from WVE-006; our understanding of the dose levels and dosing frequency for WVE-006; our plans and estimated timing to share additional data from the RestorAATion-2 trial; our understanding of the safety profile of WVE-006; potential milestone payments that we may earn for WVE-006; preclinical activities and programs and their potential to transition into clinical-stage programs, and the timing and announcement of data related to such activities; the potential benefits of our RNA editing capabilities, generally, and our proprietary best-in-class chemistry. 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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