Wave Life Sciences Announces Initiation of Dosing in RestorAATion Clinical Program Evaluating First-Ever RNA Editing Candidate, WVE-006, for Alpha-1 Antitrypsin Deficiency

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WVE-006 is uniquely designed to correct the disease-causing RNA mutation in AATD, thereby restoring circulation of wild-type M-AAT protein and reducing Z-AAT protein levels to address both lung and liver manifestations of the disease

Wave earned $20 million USD milestone from GSK for initiation of dosing; eligible for additional development, launch, and sales-related milestones of up to $505 million for WVE-006

Proof-of-mechanism data in individuals with AATD, as measured by restoration of M-AAT protein, expected in 2024

As shared at recent R&D Day, Wave is also advancing a pipeline of wholly owned RNA editing therapeutics beyond WVE-006 and across a range of high-impact GalNAc-hepatic and extra hepatic targets

CAMBRIDGE, Mass., Dec. 06, 2023 (GLOBE NEWSWIRE) -- Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage RNA medicines company committed to delivering life-changing treatments for people battling devastating diseases, today announced the initiation of dosing in healthy volunteers in the RestorAATion clinical trial program, which is investigating WVE-006 as a potential treatment for alpha-1 antitrypsin deficiency (AATD).

WVE-006 is a first-in-class, GalNAc-conjugated RNA editing oligonucleotide (AIMer). It is designed to restore circulation of healthy, wild-type alpha-1 antitrypsin (M-AAT) protein and reduce dysfunctional Z-AAT protein, thereby potentially addressing AATD-related lung disease, liver disease, or both.

“Initiating dosing in RestorAATion represents an important milestone for the alpha-1 community, where treatment options are limited and there are no medicines that address the underlying genetic mutation that most commonly causes AATD. In preclinical studies, WVE-006 led to potent and durable RNA editing and restoration of AAT protein up to 30 micromolar, underscoring the impact of our novel chemistry. WVE-006 has the potential to transform the treatment paradigm for this disease, and we are well-positioned to achieve this vision as part of our collaboration with GSK,” said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. “Moreover, with the first RNA editing therapeutic to ever be dosed in humans, we are making a significant contribution to the scientific field by bringing an entirely new class of medicines into clinical development, and we expect to continue unlocking the potential of RNA editing more broadly.”

The RestorAATion clinical program includes healthy volunteers (RestorAATion-1) as well as individuals with AATD who have the homozygous PiZZ mutation (RestorAATion-2) and is designed to provide an efficient path to proof-of-mechanism as measured by restoration of M-AAT protein in serum. Wave expects to deliver proof-of-mechanism data in individuals with AATD in 2024.

“This represents an important milestone for GSK’s growing oligonucleotide pipeline,” said Tony Wood, Chief Scientific Officer, GSK. “Throughout this year, we’ve demonstrated our commitment to realizing the potential of oligonucleotide therapeutics in areas of unmet need for patients. Beyond WVE-006, we’re also excited to continue our collaboration with Wave Life Sciences using their best-in-class PRISM™ platform.”

With initiation of dosing in RestorAATion, Wave has achieved its first WVE-006 milestone in its collaboration with GSK, resulting in a $20 million payment to Wave. For WVE-006, Wave is eligible to receive up to $505 million in additional development, launch, and sales-related milestone payments, as well as tiered royalties on net sales, from GSK. Development and commercialization responsibilities will transfer to GSK after Wave completes the RestorAATion-2 study.

Beyond WVE-006, Wave is advancing a pipeline of wholly owned RNA editing therapeutics designed to either correct or upregulate mRNA across a range of high impact targets. The company’s discovery and development efforts in RNA editing are powered by its proprietary “edit-verse”, which leverages genetic datasets and deep learning models to identify new RNA editing targets and edit sites. These targets leverage easily accessible biomarkers, offer efficient paths to proof-of-concept in humans, and represent meaningful commercial opportunities. At its R&D Day in September 2023, Wave shared *in vivo* and *in vitro* proof-of-concept data on several undisclosed targets, achieving at least 2-fold mRNA upregulation in liver and kidney targets and more than 60% mRNA correction in liver and lung targets.

About Alpha-1 Antitrypsin Deficiency
Alpha-1 antitrypsin deficiency (AATD) is an inherited genetic disorder that is commonly caused by a G-to-A point mutation (Z allele) in the *SERPINA1* gene. This mutation leads to lung disease due to insufficient levels of circulating M-AAT protein, which protects the lungs from proteolytic enzymes, and it leads to liver disease due to aggregation of misfolded Z-AAT protein in hepatocytes. There are approximately 200,000 patients in the United States and Europe who have Z mutations on both alleles, known as the PiZZ genotype. Augmentation therapy via delivery of AAT protein is currently the only treatment option for AATD lung disease and requires weekly intravenous infusions. There are no treatments for AATD liver disease, other than liver transplantation.

About WVE-006
WVE-006 is a first-in-class, GalNAc-conjugated and subcutaneously administered RNA editing oligonucleotide designed to correct the single base mutation in messenger RNA (mRNA) coded by the *SERPINA1* Z allele, thereby enabling restoration and circulation of functional M-AAT protein. In preclinical studies, WVE-006 demonstrated potent and durable editing of SERPINA1 Z transcript in mice, restoration of AAT protein up to 30 micromolar, and improvement in several markers of liver disease. WVE-006 is also highly specific with no evidence of bystander editing. Together, these data demonstrate the potential of WVE-006 to address AATD-related liver disease, lung disease, or both.

About AIMers
Wave’s A-to-I RNA editing oligonucleotides (AIMers) are designed to target single bases on an RNA transcript and recruit proteins that exist in the body, called ADAR (adenosine deaminases acting on RNA) enzymes, which naturally possess the ability to change an adenine (A) to an inosine (I), which cells read as guanine (G). This approach enables both the correction of G-to-A point mutations, as well as the modulation of RNA to upregulate protein expression, modify protein-protein interactions, or alter RNA folding and processing. AIMers enable simplified delivery and avoid the risk of permanent changes to the genome and irreversible off-target effects with DNA-targeting approaches. AIMers are short in length, fully chemically modified, and use novel chemistry, including proprietary PN backbone modifications and chiral control, which make them distinct from other

ADAR-mediated editing approaches.

About Wave Life Sciences
Wave Life Sciences (Nasdaq: WVE) is a clinical-stage RNA 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 X (formerly 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 expectations for our GalNAc-conjugated RNA editing oligonucleotides (AIMers), including WVE-006, and the anticipated therapeutic benefits thereof, including the potential of WVE-006 to treat AATD; the future performance and results of our clinical programs; our expectations and anticipated timing for delivering proof-of-mechanism clinical data in AATD patients treated with WVE-006; our understanding that WVE-006 is the most advanced candidate for AATD designed to restore functional wild-type AAT protein and reduce Z-AAT protein aggregation; our expectations regarding the ability of our AIMers, and RNA editing broadly, to address diseases of many different tissues and cell types; the potential benefits of our AIMers compared with other RNA base editing approaches; the potential benefits that our "edit-verse" map may offer to identify new RNA editing targets; and the potential achievement of development, launch and sales-related milestones for WVE-006 under our GSK collaboration and receipt of cash payments therefor. 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 circumstance.

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