Wave Life Sciences Highlights Therapeutic Potential for WVE-006 for Alpha-1 Antitrypsin Deficiency and Progress Bringing RNA Editing to the Clinic During Analyst and Investor Event

September 28, 2022

WVE-006 is the most advanced candidate for AATD designed to restore functional wild-type AAT protein and reduce Z-AAT protein aggregation with potential for disease modification in both lung and liver phenotypes

IND-enabling activities for WVE-006 are underway and Wave expects to submit clinical trial applications for WVE-006 in 2023

Wave is also pioneering new therapeutic applications for RNA editing, including activating gene pathways and upregulating gene expression

CAMBRIDGE, Mass., Sept. 28, 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, today hosted a virtual event, "Towards the Clinic: Spotlight on RNA Editing for AATD," highlighting its WVE-006 program, which is Wave's preclinical A-to-I RNA base editing oligonucleotide ("AIMer") candidate for the treatment of alpha-1 antitrypsin deficiency (AATD). The event featured a presentation from an AATD clinical expert, D. Kyle Hogarth, MD, FCCP, Professor of Medicine in the Section of Pulmonary and Critical Care Medicine at the University of Chicago. The company also outlined future therapeutic applications of its leading RNA editing capability, including modulating protein interactions as well as addressing diseases outside the liver. A replay of the event and slide presentation are available here.

"Wave continues to lead the genetic medicines field in advancing therapeutic RNA editing toward the clinic with our WVE-006 AIMer program and we expect to submit clinical trial applications for our first-in-human study in 2023. WVE-006 is distinct from other approaches in development for AATD, as it offers the opportunity to treat the root genetic cause of the disease and restore functional, wild-type protein that remains under physiological regulation. This would be a holistic solution and applicable to those with lung disease, liver disease, or both," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "Additionally, the opportunity for AIMers is much broader than restoring or correcting protein function in genetic diseases, as we demonstrated today with our preclinical data supporting the use of AIMers to modulate protein-protein interactions and upregulate gene expression. RNA editing is emerging as a distinct class of therapeutics with potential to address disease biology in novel and innovative ways and reach patients suffering from an array of diseases, including neurological disorders, as well as renal, cardiometabolic, or immunologic diseases. We are proud to be pioneers in this new area of genetic medicine and to have a best-in-class RNA editing capability with our AIMers."

Highlights from today's event, "Towards the Clinic: Spotlight on RNA Editing for AATD," are below.

Best-in-Class Potential of WVE-006 for AATD
WVE-006 is a first-in-class, GalNAc-conjugated RNA editing candidate and the most advanced program currently in development using an oligonucleotide to harness an endogenous enzyme for editing. WVE-006 is designed to correct the single G-to-A base mutation in mRNA coded by the *SERPINA1* Z allele, thereby enabling functional, wild-type M-AAT protein to be produced.

Data for WVE-006 highlighted today include:

- At 13 weeks in an AATD mouse model (NSG-PiZ), treatment with WVE-006 resulted in approximately 50% RNA editing of SERPINA1 transcript. Additionally in this same preclinical study:
  - AAT protein levels in mice dosed with WVE-006 were approximately 7-fold greater than PBS-administered controls and well above the established protective threshold of 11 uM.
  - WVE-006 led to restoration of approximately 50% wild-type M-AAT protein in serum.
  - WVE-006 led to a 3-fold increase in neutrophil elastase inhibition activity, indicating the restored M-AAT protein was functional.
- An earlier lead (pre-optimization) AIMer reduced Z-AAT aggregates and inflammation in mouse livers (mouse model: huADARxSA1).
- Wave's AATD AIMers are highly specific *in vitro* and *in vivo* based on transcriptome-wide analyses.

WVE-006 Advancing Toward the Clinic
IND-enabling activities for WVE-006 are underway and Wave expects to submit clinical trial applications (CTAs) for WVE-006 in 2023.

In addition, Wave announced today initial plans for the anticipated first-in-human study of WVE-006. This Phase 1/2 study would evaluate safety, pharmacokinetics, and relevant biomarkers, including serum AAT. The study, which would use Wave's adaptive design approach, is expected to first enroll healthy volunteers to establish dose, followed by cohort expansion with Pi*ZZ patients to evaluate target engagement based on change in serum AAT levels.

Future Applications of AIMers
Wave is advancing research using AIMers for applications beyond correction of G-to-A driver mutations and today highlighted preclinical data supporting the use of AIMers to activate gene pathways and upregulate gene expression. These applications would significantly expand the universe of targets addressable with AIMers, including diseases with large patient populations. Highlights from the presentation include:

- GalNAc-AIMers can disrupt KEAP1 protein/NRF2 protein interactions, thereby enabling NRF2 downstream gene upregulation in the liver of mice.
- GalNAc-AIMers can edit RNA motifs to restore or upregulate gene expression in the liver of mice.

Wave is also advancing research using AIMers beyond hepatocytes and using free uptake instead of GalNAc conjugation. Preclinical *in vivo* data supports the ability to edit with systemic delivery in multiple tissues, including heart, kidney, lung, spleen, liver, white adipose tissue, and brown adipose tissue. Wave has also generated *in vivo* data demonstrating substantial and durable editing and supporting administration of AIMers with intrathecal or intracerebroventricular delivery in central nervous system tissues.

"Towards the Clinic: Spotlight on RNA Editing for AATD" Presentation and Slideshow
A replay of today's webcast and the full slideshow presentation can be accessed and downloaded by visiting "Events & Publications" on the investor relations section of the Wave Life Sciences corporate website: ir.wavelifesciences.com/events-and-presentations.

About AIMers
Wave's AIMers are designed to correct mutations in an RNA transcript, thereby avoiding permanent changes to the genome that occur with DNA-targeting approaches. Rather than using an exogenous editing enzyme, AIMers recruit proteins that exist in the body, called ADAR enzymes, which naturally edit certain adenine (A) bases to inosine (I). Because I is read as G (guanine) by the cellular translational machinery, sequence-directed editing with ADAR has the potential to revert transcripts with single G-to-A point mutations that cause genetic diseases. This approach redirects a natural system for therapeutic purposes, enables simplified delivery without viral particles or liposomes, and avoids the risk of irreversible off-target effects of DNA-targeting approaches. AIMers are short in length, fully chemically modified, and use novel chemistry, including proprietary PN backbone modifications and chiral control, that make them distinct from other ADAR-mediated editing approaches.

About Alpha-1 antitrypsin deficiency (AATD)
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 lack of wild-type alpha-1 antitrypsin (M-AAT) in lungs and 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 is the only treatment option for AATD lung disease and requires weekly intravenous infusions. There are no treatments for AATD liver disease, other than liver transplant. The average age of diagnosis of AATD lung disease is 46 years and the average age of adult-onset liver disease is 61 years.

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 expectations for our GalNAc-conjugated A-to-I(G) RNA base editing oligonucleotides (AIMers) and the anticipated therapeutic benefits thereof; our belief 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 to address diseases of many different tissues and cell types; the potential benefits of our AIMers compared with other RNA base editing approaches; the anticipated timing of future development milestones for our lead AIMer program, WVE-006; and our expectations regarding potential future applications of our AIMERs to activate genetic pathways and upregulate gene expression. 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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Source: Wave Life Sciences USA, Inc.