Wave Life Sciences Announces New Data for Leading RNA Editing Capability Across Multiple Tissues and Provides Update on AATD Program During Analyst and Investor Research Webcast

September 28, 2021

Durable ADAR editing in vivo in preclinical models, including in CNS tissues with editing out to at least four months

Chemistry optimization yields a four-fold increase over PBS control in AAT protein restoration in vivo preclinically (or more than 15 micromolar)

CAMBRIDGE, Mass., Sept. 28, 2021 (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 presented new data for its ADAR-mediated RNA editing capability (ADAR editing), including new preclinical editing data across multiple tissues, as well as an update on its discovery-stage alpha-1 antitrypsin deficiency (AATD) program during the company's 2021 Analyst and Investor Research Webcast. The webcast also included updates on the company's PRISM™ platform and initial results from the application of ADAR editing to neurology targets.

"Our presentations today represent robust and meaningful contributions to the rapidly advancing field of RNA editing, where we are at the forefront defining both new levels of editing, as well as the tissues and cell types amenable to this approach," said Chandra Vargeese, PhD, Chief Technology Officer of Wave Life Sciences. "The application of PRISM to RNA editing means that there is the potential for therapeutic applications extending beyond the restoration of protein function, such as upregulation of protein expression, modification of protein function by altering post-translational modifications or protein-protein interactions, or alteration of protein stability. Additionally, with our AATD program, we have shown an ability in preclinical experiments to drive alpha-1 antitrypsin protein significantly above levels that are potentially therapeutically meaningful and increase the overall percentage of secreted wild-type M-AAT protein."

A summary of the RNA editing presentations is below. A replay of the Analyst and Investor Research Webcast is available on Wave's Investor Relations website.

Leading RNA Editing Capability Using Endogenous ADAR

- Wave's RNA editing capability leverages widely expressed endogenous ADAR enzymes to achieve highly specific A-to-I (G) RNA editing using stereopure oligonucleotides, called "AIMers," without the need for lipid nanoparticles (LNPs) or viral vectors, and without altering the genome.
- Wave is developing short, fully-chemically modified AIMers with and without GalNAc conjugation, with the objective of achieving productive editing in the liver, central nervous system (CNS), and other tissues.
- **CNS**: Wave presented new *in vivo* data that demonstrated potent editing (up to 65%) and durable editing of UGP2 mRNA out to at least four months in multiple regions of the CNS in a mouse model with human ADAR.
    - Wave is applying ADAR editing to multiple therapeutic targets in the CNS, including MECP2, seeking to correct a nonsense mutation and potentially restore functional protein in Rett Syndrome.
    - Additionally, *in vitro* data were presented demonstrating the potential to target protein-protein interactions and upregulate downstream gene expression with AIMers.
- **Ophthalmology**: Wave also presented preclinical data demonstrating up to 50% editing of UGP2 mRNA in the posterior of the eye of mice at one-month post-single intravitreal injection.
- **New tissue and cell types:** Wave shared ACTB RNA editing in non-human primates (NHPs) using systemic administration, including in the kidneys, liver, lungs and heart, as well as editing of ACTB in multiple immune cell types *in vitro*, including CD4+ T-cells, CD8+ T-cells, and others.

ADAR Editing Provides Promising Treatment Approach for Alpha-1 Antitrypsin Deficiency (AATD)

- Wave's AATD program, its first investigational ADAR editing program, uses AIMers to potentially correct the single base mutation in mRNA coded by the *SERPINA1* Z allele. ADAR editing may provide an ideal approach for addressing AATD by increasing circulating levels of functional alpha-1 antitrypsin (M-AAT) protein and reducing mutant protein aggregation in the liver, thus potentially addressing both the lung and liver manifestations of the disease.
- Today Wave shared new *in vivo* data demonstrating durable restoration of M-AAT protein in the liver of transgenic mice with human *SERPINA1* and human ADAR following initial doses of a GalNAc-conjugated SERPINA1 AIMer. Serum concentrations of human AAT protein remained at least three-fold higher over PBS control for 30 days post-last dose with the SERPINA1 AIMer.
- Wave also shared data demonstrating progress in enhancing editing activity and protein restoration following PRISM chemistry optimization.
    - These AIMers achieved mean editing of approximately 50% of SERPINA1 mRNA *in vivo*.
    - Also with chemistry optimization, Wave demonstrated *in vivo* a four-fold increase over PBS control in AAT protein restoration in serum (or more than 15 micromolar), representing an improvement over the three-fold increase achieved with Wave's initial AIMers. Approximately 85% of circulating AAT was confirmed to be M-AAT in treated transgenic mice with human *SERPINA1* and human ADAR.
- Wave's ADAR editing appears highly specific with nominal off-target edits observed following transcriptome analysis, nor were there bystander edits observed in the SERPINA1 transcript.

- Ongoing and planned preclinical studies are assessing durability, dose response, pharmacokinetics, and pharmacodynamics. Wave also plans to assess reduction of Z-AAT aggregates in the liver and changes in liver pathology in its transgenic mouse model.
- Wave expects to have an AATD development candidate in 2022.

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 application of PRISM to RNA editing and the anticipated therapeutic benefits of RNA editing capabilities using endogenous ADAR; our beliefs regarding the learnings gained from our first-generation clinical programs and our initial chemistry; our understanding of AIMers and their expected capabilities; the anticipated therapeutic benefits of our ADAR editing program for AATD; the anticipated timing for our AATD development candidate; and the potential benefits of PRISM, including our stereopure oligonucleotides. The words "may," "represent," "expect," "plan," "objective," "achieve," "demonstrate," "represent," "predict," "appear," "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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