# Wave Life Sciences Announces Proof-of-Concept Preclinical Data for ADAR Editing Program in Alpha-1 Antitrypsin Deficiency

June 2, 2021

*First proof-of-concept in vivo data for RNA editing using endogenous ADAR enzymes in alpha-1 antitrypsin deficiency*

*ADAR editing resulted in therapeutically meaningful restoration of circulating functional AAT protein*

*Wave's program in alpha-1 antitrypsin deficiency aims to correct the single base mutation in mRNA derived from the SERPINA1 Z allele, thereby addressing both lung and liver manifestations of the disease*

CAMBRIDGE, Mass., June 02, 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 announced the first proof-of-concept preclinical data for its ADAR (adenosine deaminases acting on RNA)-mediated RNA editing ("ADAR editing") program in alpha-1 antitrypsin deficiency (AATD). Up to 40 percent editing of human *SERPINA1* Z-allele mRNA in the liver was observed at a single timepoint, which resulted in a therapeutically meaningful increase in circulating functional wild-type AAT protein. This initial *in vivo* study utilized Wave's proprietary transgenic mouse model, which has both the human *SERPINA1* Z-allele as well as human ADAR that is expressed comparably to human cells.

"These findings are a critical contribution to the genetic medicines field, as they represent the first proof-of-concept *in vivo* data for RNA editing using endogenous ADAR enzymes in AATD. They also reinforce Wave's leadership position in the RNA editing field, as we continue to observe meaningful and significant levels of editing in animal models, including in mice and NHPs, which paves the way for translating this technology to the clinic," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "Wave's approach to RNA editing using endogenous ADAR and our AATD program have advanced quickly, with the team demonstrating immense creativity and tenacity to reach this important milestone. We look forward to presenting additional *in vivo* data in the second half of this year and continuing our progress towards the clinic."

Wave's AATD program, the first to utilize its ADAR editing modality, uses GalNAc-conjugated oligonucleotides to correct the single base mutation in mRNA derived from the *SERPINA1* Z allele. ADAR editing provides a simple and efficient approach to treating AATD by simultaneously reducing aggregation of mutated, misfolded alpha-1 antitrypsin protein (Z-AAT) and increasing circulating levels of wild-type protein (M-AAT), thus having the potential to address both the lung and liver manifestations of the disease while avoiding risk from permanent off-target changes to the DNA. Wave is initially focusing on homozygous "ZZ" patients who have the highest risk of disease and where RNA editing may result in a heterozygous "MZ" phenotype, which would result in a substantially lower risk of disease.

The goals of Wave's first *in vivo* proof-of-concept study were: 1) achieve editing of *SERPINA1* Z allele mRNA in the liver at levels that approach the MZ phenotype; 2) restore human M-AAT protein in serum; and 3) demonstrate functionality of the restored human M-AAT protein. Results were analyzed at a single timepoint (day 7) and demonstrated:

- Up to 40 percent editing of Z allele mRNA was observed in the liver of Wave's transgenic human ADAR mice, correlating with levels nearing correction to an MZ phenotype.
- Editing was highly specific with no bystander edits.
- A three-fold increase in circulating human AAT compared with placebo was observed, similar to the fold difference seen between ZZ and MZ patients.
- 75 percent of circulating AAT protein was confirmed as M-AAT. This also suggests a reduction of Z-AAT in the liver and serum.
- Confirmation of functionality of the M-AAT protein using a neutrophil elastase inhibition assay.

Wave's preclinical studies for its AATD program are ongoing and additional data on durability and dose response are expected in the second half of 2021. Wave also continues to evaluate ADAR editing compounds for other disease targets, leveraging its proprietary mouse model which expresses human ADAR and is crossed with disease-specific mouse models.

These proof-of-concept preclinical data were also presented at the Jefferies Virtual Healthcare Conference on June 2, 2021 and the presentation can be viewed by visiting the investor relations page of the Wave Life Sciences corporate website at http://ir.wavelifesciences.com.

**About ADAR Editing**
Wave's novel RNA editing platform capability uses endogenous ADAR (adenosine deaminases acting on RNA) enzymes via free uptake of A-to-I (G) RNA editing oligonucleotides. ADAR editing may provide an attractive alternative to DNA editing, as the effects of RNA editing are both reversible and titratable, and avoid potential long-term risks associated with permanent off-target genome edits. Wave's ADAR editing modality also offers potential advantages over other RNA editing approaches, including the use of short oligonucleotides that are freely taken up by cells and do not require viral or nanoparticle delivery. Wave's design also reduces the risk of immunogenicity from exogenous proteins and off-target effects.

**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, the potential significance of Wave's first proof-of-concept *in vivo* data for RNA editing with respect to AATD and the genetic medicines field; the anticipated plans, type of data and timing from Wave's ongoing preclinical studies for its AATD program; Wave's evaluation of additional ADAR-amenable disease targets. 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, 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
617-949-4827
krausch@wavelifesci.com

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

Source: Wave Life Sciences USA, Inc.