Wave Life Sciences Announces Initiation of Dosing in Phase 1b/2a SELECT-HD Clinical Trial of WVE-003 in Huntington's Disease

September 9, 2021

Only clinical-stage candidate for Huntington's disease designed to selectively lower mutant HTT and spare wild-type HTT

Adaptive trial design to enable faster optimization of dosing and decision-making on next steps for WVE-003; data to be generated through 2022

WVE-003 preclinical data and SELECT-HD trial to be highlighted at EHDN 2021 Remote Meeting September 9-11, 2021

CAMBRIDGE, Mass., Sept. 09, 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 initiation of dosing in the company's Phase 1b/2a SELECT-HD clinical trial evaluating investigational WVE-003 as a treatment for Huntington's disease (HD). WVE-003 is a stereopure antisense oligonucleotide designed to target SNP3, a single nucleotide polymorphism on the mutant huntingtin (mHTT) allele, thereby selectively lowering mHTT protein and sparing healthy, wild-type huntingtin (wtHTT) protein.

"WVE-003 reflects the significant evolution of our chemistry and the many learnings gained from our first-generation clinical programs," said Michael Panzara, MD, MPH, Chief Medical Officer and Head of Therapeutics Discovery and Development at Wave Life Sciences. "Our enthusiasm for this program is bolstered by a compelling set of preclinical data that demonstrated selectivity, potency, and durability of WVE-003 with effects in relevant brain regions. Further, emerging data continue to indicate that a fundamental requirement for clinical success in HD treatment will be the need to preserve wild-type HTT protein, supporting our allele-selective approach to mutant HTT protein reduction."

Wave's approach to HD and the WVE-003 program is guided by the recognition that, in addition to a gain of function of the mHTT protein, people with this disease have lost one copy of the wtHTT allele, leaving them with a smaller protective reservoir of healthy protein than unaffected individuals. A growing body of scientific evidence suggests that preserving as much of this essential wtHTT protein as possible, when in the setting of stress from the toxic mHTT protein, may be important for favorable clinical outcomes.

WVE-003 incorporates the company's novel PN backbone chemistry modifications (PN chemistry), which have been shown in preclinical studies to enhance potency, exposure, and durability. In preclinical studies, WVE-003 demonstrated dose-dependent and selective reduction of mHTT mRNA *in vitro* and potent and durable knockdown of mHTT mRNA *in vivo,* in both the cortex and striatum. Data from several preclinical models evaluating pharmacokinetic to pharmacodynamic relationships for WVE-003 have informed the starting dose for the SELECT-HD trial.

The SELECT-HD trial is a global, multicenter, randomized, double-blind, placebo-controlled Phase 1b/2a clinical trial to assess the safety and tolerability of single- and multiple-ascending intrathecal doses of WVE-003 in people with a confirmed diagnosis of HD who are in the early stages of the disease and carry SNP3 in association with their cytosine-adenine-guanine (CAG) expansion. It is estimated that approximately 40 percent of adults with HD carry SNP3 in association with the HD mutation. Additional objectives include assessing the plasma pharmacokinetic profile and exposure in the cerebrospinal fluid, as well as exploratory pharmacodynamic (mHTT, wtHTT and neurofilament light chain) and clinical endpoints. The SELECT-HD trial is expected to enroll approximately 36 patients. It is designed to be adaptive, with dose escalation and dosing frequency being guided by an independent committee.

The SELECT-HD trial design and WVE-003 preclinical data will be highlighted in plenary and poster sessions at the EHDN 2021 Remote Meeting, taking place September 9-11, 2021. Presentation details are as follows:

- **Friday, September 10 at 8:05 a.m. EDT (2:05 p.m. CEST)**
  SELECT-HD, an adaptive first-in-human clinical trial to evaluate WVE-003, an investigational allele-selective mHTT-lowering oligonucleotide, in early manifest Huntington's disease (Vissia Viglietta, MD, PhD, Vice President of Clinical Development and Medical Affairs at Wave Life Sciences)
  Plenary Session III: Clinical Trial Session
- **Thursday, September 9 – Saturday, September 11**
  Design of an Adaptive Randomized Controlled Phase 1b/2a Trial of WVE-003 in Participants with Huntington's Disease (Danlin Xu, PhD, Medical Director at Wave Life Sciences)
  Poster Available On Demand

About Huntington's Disease
Huntington's disease (HD) is a debilitating and ultimately fatal autosomal dominant neurological disorder, characterized by cognitive decline, psychiatric illness, and chorea. HD causes nerve cells in the brain to deteriorate over time, affecting thinking ability, emotions, and movement. HD is caused by an expanded cytosine-adenine-guanine (CAG) triplet repeat in the huntingtin (HTT) gene that results in production of mutant HTT (mHTT) protein. Accumulation of mHTT causes progressive loss of neurons in the brain. Wild-type, or healthy, HTT (wtHTT) protein is critical for neuronal function and suppression may have detrimental long-term consequences. Approximately 30,000 people in the United States have symptomatic HD and more than 200,000 others are at risk for developing the disease. There are currently no approved disease-modifying therapies available.

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 anticipated therapeutic benefit of WVE-003 as an investigational therapy for HD; our belief regarding the learnings gained from our first-generation clinical programs; the anticipated timing of data to enable decision-making on next steps for WVE-003; the predicted pharmacology of WVE-003 and the associated trial protocol, design and endpoints; our beliefs related to the cause of HD; our understanding of how mHTT and wtHTT impact HD to guide our WVE-003 program; expected patient enrollment in the SELECT-HD trial; the anticipated therapeutic benefits of our potential therapies, including our compounds containing PN chemistry, compared to others; and the potential benefits of PRISM, including our novel PN backbone chemistry modifications, and our stereopure oligonucleotides compared with stereorandom oligonucleotides. 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.

Investor Contact:
Kate Rausch
617-949-4827
krausch@wavelifesci.com

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

Patient Community Contact:
Wave Patient Advocacy
patientadvocacy@wavelifesci.com

Source: Wave Life Sciences USA, Inc.