# Wave Life Sciences Announces Positive Results from Phase 1b/2a SELECT-HD Trial with First Clinical Demonstration of Allele-Selective Mutant Huntingtin Lowering in Huntington's Disease

June 25, 2024

*Statistically significant, potent, and durable allele-selective silencing: 46% mean reduction in CSF mutant huntingtin (mHTT) protein compared to placebo, preservation of wild-type huntingtin (wtHTT) protein, and generally safe and well-tolerated profile achieved in 30 mg multidose cohort*

*Statistically significant correlation between mHTT lowering and slowing of caudate atrophy - an imaging biomarker predictive of clinical outcomes*

*Wave to engage regulators on a clinical development path for WVE-003 that would support a potential accelerated approval, and will submit its opt-in package to program partner Takeda*

*Data provide further validation for Wave's RNA medicines platform, including PN chemistry, and pipeline; Wave remains on track to deliver 6-month dystrophin data for WVE-N531 in DMD in 3Q 2024 and RNA editing proof-of-mechanism data for WVE-006 in AATD in 2024, as well as to initiate a clinical trial for its INHBE GalNAc siRNA (WVE-007) for obesity in 1Q 2025*

*Wave to host investor conference call and webcast at 8:30 a.m. ET today*

CAMBRIDGE, Mass., June 25, 2024 (GLOBE NEWSWIRE) -- Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage biotechnology company focused on unlocking the broad potential of RNA medicines to transform human health, today announced positive results from its Phase 1b/2a SELECT-HD clinical trial of WVE-003, which is being developed as a potential disease modifying therapeutic for Huntington's disease (HD). WVE-003 is a first-in-class, allele-selective antisense oligonucleotide (ASO) designed to lower mutant huntingtin (mHTT) protein and preserve healthy, wild-type huntingtin (wtHTT) protein.

In the multidose portion of the SELECT-HD study (n=23), participants received either every-eight-week (Q8W) intrathecal doses of 30 mg WVE-003 (n=16) or placebo (n=7), with 12 weeks of follow up (total study period of 28 weeks). Key results are as follows:

- WVE-003 was generally safe and well-tolerated, with no Serious Adverse Events (SAEs) reported; ventricular volume was in line with natural history.
- Significant mHTT protein lowering was observed throughout the 28-week assessment period.
    - At 24 weeks (8 weeks after last dose), mean mHTT lowering in cerebrospinal fluid (CSF) was 46% versus placebo (p=0.0007).
    - At 28 weeks (12 weeks after last dose), mean mHTT lowering in CSF was 44% versus placebo (p=0.0002), which supports quarterly or less frequent dosing.
- wtHTT protein was preserved throughout the 28-week assessment period, validating allele-selective silencing. Additionally, statistically significant increases were observed in wtHTT protein versus placebo.
    - wtHTT protein supports the health and function of neurons and is crucial for CSF flow in the ventricles. mHTT also has a detrimental effect on wtHTT at the protein level, which further decreases wtHTT's function. Only selective lowering of mHTT has potential to relieve its negative impact on wtHTT protein function.
- Most WVE-003-treated participants had neurofilament light protein (NfL) levels that were in the range of placebo or had NfL levels that increased and returned to the range of placebo.
- At 24 weeks (the last MRI assessment), mHTT reduction was correlated with slowing of caudate atrophy (R=-0.50; p=0.047). Caudate atrophy is an imaging biomarker that is predictive of clinical outcomes, including clinically meaningful worsening of Total Motor Score (TMS).
- While not powered for clinical outcomes, a slowing of decline was observed for TMS for WVE-003 versus placebo (4.25 mean difference at 24 weeks, p=not significant).

"We are very proud to have demonstrated mHTT lowering of 46%, with preservation of wtHTT, and are encouraged to see these reductions in mHTT significantly correlating with a slowing in caudate atrophy after just 28 weeks. These results represent a significant achievement for Wave, for the oligonucleotide field, and most importantly, for the HD community," said Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS, Chief Development Officer at Wave Life Sciences. "Alongside the HD community, we have been working diligently to establish caudate volume as a biomarker for clinical development due to its association with clinical outcomes. We believe these strong data compel a case for accelerated approval for WVE-003, which we plan to discuss with regulators. We would like to express our immense gratitude to the HD community, the study participants, their families, and study site staff for their trust, support, and engagement that have helped us reach this important milestone."

"Wild-type huntingtin plays such a critical role in the central nervous system, and it's very exciting to finally have an opportunity to evaluate mHTT lowering in the context of allele-selectivity and to see positive signals emerging," said Ralf Reilmann, MD, founder of the George-Huntington Institute, Muenster, Germany, as well as the Primary Investigator and member of the Advisory Committee for SELECT-HD. "Additionally, these data have arrived at an opportune time when the HD community is coalescing around rapid, efficient registrational trial design utilizing sensitive clinical endpoints to detect early treatment effects, and Wave is well positioned to take advantage of this momentum with WVE-003. These data provide hope and a compelling path forward as the community continues to drive toward a long-awaited therapy to treat this devastating disease."

HD is a debilitating and ultimately fatal autosomal dominant neurological disorder. The HD population is significant – in the United States alone, approximately 30,000 people have clinical symptoms of HD and more than 200,000 are at risk of inheriting HD. WVE-003 is expected to address approximately 40% of individuals with HD, and up to 80% of HD may be addressed in the future with other SNP-targeted candidates.

"With these results, we have delivered the first-ever clinical demonstration of allele-selective silencing in any disease target. This was only possible due to the specificity, potency and durability enabled through our PRISM platform and it is validating of more than 10 years of chemistry innovation pioneered at Wave, including PN chemistry and stereochemistry," said Paul Bolno, MD, MBA, President and Chief Executive Officer at Wave Life Sciences. "The translation of genetic insights and preclinical data in the clinic is also highly encouraging and reinforces the broader value of our pipeline. We are looking forward to our Duchenne muscular dystrophy and Alpha-1 antitrypsin deficiency data this year, the continued advancement of our INHBE program for obesity, and new targets to be shared at R&D Day this Fall, which together will open up a substantial total addressable market for Wave. We are at a very exciting point in Wave's history as we advance our mission to unlock the broad potential of RNA medicines."

**Cash Runway**
Wave continues to expect that its current cash and cash equivalents will be sufficient to fund operations into the fourth quarter of 2025.

**Investor Conference Call and Webcast**
Wave will host an investor conference call today at 8:30 a.m. ET to review the SELECT-HD clinical trial results. A webcast of the conference call can be accessed by visiting "Investor Events" on the investor relations section of the Wave Life Sciences website: https://ir.wavelifesciences.com/events-publications/events. Analysts planning to participate during the Q&A portion of the live call can join the conference call at the audio-conferencing link available here. Once registered, participants will receive the dial-in information. Following the live event, an archived version of the webcast will be available on the Wave Life Sciences website.

**About SELECT-HD**
The SELECT-HD trial (NCT05032196) was 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. Additional objectives include assessing pharmacokinetics and exploratory pharmacodynamic and clinical endpoints.

**About WVE-003**
WVE-003 is a first-in-class, allele-selective antisense oligonucleotide that selectively lowers mutant huntingtin (mHTT) protein by targeting a single nucleotide polymorphism (SNP3) located on the mHTT messenger RNA that is not present on the wild-type huntingtin (wtHTT) mRNA. Wave's approach to Huntington's disease (HD) is guided by the recognition that, in addition to a gain of function of the mHTT protein, people with HD have lost one copy of the healthy wtHTT allele, leaving them with a smaller protective reservoir of wtHTT protein than unaffected individuals. wtHTT protein is critical for neuronal function, and suppression may have detrimental long-term consequences. For more information, please refer to Wave's published manuscript of WVE-003 preclinical data here.

**About Huntington's Disease**
Huntington's disease (HD) is a debilitating and ultimately fatal autosomal dominant neurological disorder, which is passed down from generation to generation within affected families. The symptoms of HD have been compared to having Alzheimer's disease, Amyotrophic lateral sclerosis, and Parkinson's disease all at once. 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, affecting thinking ability, emotions, and movement. Clinical symptom onset typically occurs during adulthood, between the ages of 30 and 50. It is characterized by cognitive decline, psychiatric illness, and chorea, and patients ultimately succumb to pneumonia, heart failure or other complications. There are no disease modifying treatments for HD.

**About Wave Life Sciences**
Wave Life Sciences (Nasdaq: WVE) is a biotechnology company focused on unlocking the broad potential of RNA medicines to transform human health. Wave's RNA medicines platform, PRISM ®, combines multiple modalities, chemistry innovation and deep insights in human genetics to deliver scientific breakthroughs that treat both rare and prevalent disorders. Its toolkit of RNA-targeting modalities includes editing, splicing, RNA interference and antisense silencing, providing Wave with unmatched capabilities for designing and sustainably delivering candidates that optimally address disease biology. Wave's diversified pipeline includes clinical programs in Duchenne muscular dystrophy, Alpha-1 antitrypsin deficiency and Huntington's disease, as well as a preclinical program in obesity. Driven by the calling to "Reimagine Possible", Wave is leading the charge toward a world in which human potential is no longer hindered by the burden of disease. Wave is headquartered in Cambridge, MA. For more information on Wave's science, pipeline and people, please visit www.wavelifesciences.com and follow Wave on X (formerly Twitter) and LinkedIn.

**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 beliefs as to what our WVE-003 data evidencing allele-selective mutant huntingtin lowering portend for our ability to deliver meaningful disease modifying therapies for people living with HD and their families; our understandings of the potential clinical efficacy of WVE-003, evidenced by correlations in exploratory pharmacodynamic and clinical endpoints and slowing of caudate atrophy, and our plans to engage regulators on a clinical development path that would support potential accelerated approval for WVE-003; our estimates of the HD patient population that would benefit from WVE-003 and other potential future SNP-targeted therapies; the potential benefits of our RNA medicines platform, PRISM, including PN chemistry, and pipeline; the benefits of RNA medicines generally for both rare and common diseases; our expectations and timing to deliver 6-month dystrophin data for WVE-N531 in DMD; our expectations and anticipated timing for delivering proof-of-mechanism clinical data in AATD patients treated with WVE-006; our expectations and anticipated timing to initiate a clinical trial for its INHBE GalNAc siRNA (WVE-007) for obesity; and our expectations on timing for announcing new targets at our R&D Day this Fall. 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.