Wave Life Sciences Announces Positive Update from Phase 1b/2a SELECT-HD Trial with Initial Results Indicating Allele-Selective Target Engagement with WVE-003 in Huntington's Disease

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Single doses of WVE-003 appear generally safe and well-tolerated

CSF mutant huntingtin (mHTT) protein was reduced following single doses of 30 or 60 mg; mean mHTT reduction across both cohorts was 22% (median reduction 30%) from baseline 85 days post-single dose

Wild-type huntingtin (wtHTT) protein levels through day 85 appear consistent with allele-selectivity

Expanding single dose cohorts to optimize dose level with data expected in 1H 2023

Continued clinical validation of PRISM platform and PN stereochemistry

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

CAMBRIDGE, Mass., Sept. 20, 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 announced a positive update to the ongoing Phase 1b/2a SELECT-HD clinical trial of WVE-003, the company's clinical candidate for Huntington's disease (HD). SELECT-HD (NCT05032196) is an adaptive trial designed to rapidly optimize dose level and frequency based on early indicators of target engagement. The trial update announced today is being driven by the observation of reductions in mutant huntingtin (mHTT) protein in cerebrospinal fluid (CSF) after study participants received either a single 30 or 60 mg dose of WVE-003. Additionally, wild-type huntingtin (wtHTT) protein was preserved, which appears consistent with allele-selectivity.

"These preliminary data suggest WVE-003 is working as intended: to selectively reduce the toxic mHTT protein while avoiding targeting the healthy, wild-type huntingtin protein, thereby preserving its beneficial effects in the central nervous system," said Ralf Reilmann, MD, founder of the George-Huntington Institute, Muenster, Germany and member of the SELECT-HD Clinical Advisory and Dose Escalation Committees. "Additionally, I am encouraged by the safety and tolerability data. Taken together, WVE-003 appears to have a unique profile with the potential to overcome prior therapeutic challenges in this field. Furthermore, as a clinician and researcher focused on HD, it is my hope that innovative adaptive trial designs like SELECT-HD become more commonplace to optimize dosing in early proof-of-concept studies. It is also exciting to finally see an assay measuring wtHTT being developed and used successfully in a clinical trial – a long awaited, big step forward for the HD research community. The availability of this assay has potential to significantly increase our understanding of how best to treat this challenging disease."

"Based on these initial data, it appears that our preclinical data for WVE-003 are translating in the clinic," said Michael Panzara, MD, MPH, Chief Medical Officer and Head of Therapeutics Discovery and Development at Wave Life Sciences. "We are encouraged to see a mean CSF mHTT reduction from baseline of 22% at day 85 after participants received just a single dose of WVE-003, demonstrating a compelling pharmacological profile for individuals with HD. We are grateful to the HD community, including the SELECT-HD participants, study sites and advisors, for their continued partnership and support of this program. We look forward to continuing to expand this study and sharing additional data next year."

Eighteen (18) participants have been dosed in the SELECT-HD trial (30 mg, n=4; 60 mg, n=4; 90 mg, n=4; placebo, n=6). Participants enrolled at 30 mg, 60 mg and placebo had adequate follow-up to day 85 for biomarker analysis. At the time of analysis, none of the participants dosed with 90 mg had reached day 85 so this cohort is not included in the biomarker analysis.

Key observations include:

- Single doses of WVE-003 up to 90 mg appeared generally safe and well-tolerated
  - Adverse events (AEs) were balanced across treatment groups, including placebo, and all were mild to moderate in intensity
  - No serious adverse events (SAEs) were observed
  - No participants discontinued from the study
- Among participants in the 30 and 60 mg WVE-003 cohorts, the mean reduction in CSF mHTT from baseline was 22% (median reduction 30%) at 85 days following a single dose
  - The difference in the mean reduction in CSF mHTT compared to placebo was 35% at 85 days post-single dose
  - For these analyses, the 30 and 60 mg single dose cohorts were pooled as there was no apparent dose response between these two cohorts. Wave will continue to evaluate dose response in the expanded single dose cohorts
- In the 30 and 60 mg cohorts, wtHTT protein was preserved, which appears consistent with allele-selectivity
- Increases in neurofilament light chain (NfL) from baseline were observed in some participants. Wave will continue to monitor trends in NfL as SELECT-HD advances
- There were no clinically meaningful elevations in CSF white blood cell counts or protein that would indicate inflammation in the CNS

- There were no meaningful changes in clinical outcome measures, although the dataset and duration were not sufficient to assess clinical effects

Based on these data, Wave is adapting the SELECT-HD clinical trial to expand the single dose cohorts and will also continue advancing the 90 mg cohort for biomarker analysis at day 85. Additional single dose biomarker and safety data are expected in the first half of 2023.

Wave's approach to HD 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. wtHTT protein is critical for neuronal function and suppression may have detrimental long-term consequences.

WVE-003 is the only allele-selective HD candidate in clinical development. It is designed to preferentially lower mHTT by targeting a single nucleotide polymorphism (SNP3) that appears on the mHTT allele and is not present on the wtHTT allele. Based upon scientific literature, it is estimated that approximately 40 percent of adults with HD carry SNP3 in association with the HD mutation.

"These SELECT-HD data are the first to support the feasibility of allele-selective mHTT knockdown in the clinic – a precision approach enabled by our PRISM discovery and drug development platform," said Paul Bolno, MD, MBA, President and Chief Executive Officer at Wave Life Sciences. "SELECT-HD is the second clinical trial this year to demonstrate clinical translation of Wave's PN backbone chemistry modifications, as well as the impact of rational design through control of stereochemistry, increasing our conviction in our platform. We look forward to sharing data from our splicing clinical program in muscle – WVE-N531 for exon 53 skipping in Duchenne muscular dystrophy – in the fourth quarter of 2022."

Investor Conference Call and Webcast
Wave management will host an investor conference call today at 8:30 a.m. ET to discuss the SELECT-HD clinical trial update. The webcast of the conference call may be accessed by visiting "Events" on the investor relations section of the Wave Life Sciences corporate website: ir.wavelifesciences.com/events-and-presentations. 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. It is recommended that participants register at least 15 minutes in advance of the call. 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 the SELECT-HD Clinical 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. 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 participants. It is designed to be adaptive, with dose escalation and dosing frequency being guided by an independent committee.

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.

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 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 concerning our goals, beliefs, expectations, strategies, objectives and plans and other statements that are not necessarily based on historical facts, which are within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding: our belief as to what our initial WVE-003 data indicating allele-selective target engagement announced above portend for our ability to deliver meaningful therapies for people living with HD and their families; the first-in-class nature of our initial WVE-003 data to support the feasibility of allele-selective mHTT knockdown in the clinic; the continued dosing and generation of data to complete our SELECT-HD adaptive study and the announcement of such events; our expectations regarding the timing of additional data in the SELECT-HD study; the potential of our *in vitro* and *in vivo* preclinical data and modelling to predict the relevant dosing and behavior of our compounds in humans; the potential benefits of PRISM, including our novel PN backbone chemistry modifications and the impact of rational design through control of stereochemistry; and our expectations regarding the timing of sharing data from our third clinical candidate containing PN chemistry, WVE-N531 for exon 53 skipping in Duchenne muscular dystrophy. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including the following: our ability to finance our drug discovery and development efforts and to raise additional capital when needed; the ability of our preclinical programs to produce data sufficient to support our clinical trial applications and the timing thereof; the clinical results of our programs and the timing thereof, which may not support further development of product candidates; actions of regulatory

agencies, which may affect the initiation, timing and progress of clinical trials, including their receptiveness to our adaptive trial designs; our effectiveness in managing future clinical trials and regulatory interactions; the effectiveness of PRISM, including our novel PN backbone chemistry modifications; the effectiveness of our novel ADAR-mediated RNA editing platform capability and our AIMers; the continued development and acceptance of oligonucleotides as a class of medicines; our ability to demonstrate the therapeutic benefits of our candidates in clinical trials, including our ability to develop candidates across multiple therapeutic modalities; our dependence on third parties, including contract research organizations, contract manufacturing organizations, collaborators and partners; our ability to manufacture or contract with third parties to manufacture drug material to support our programs and growth; our ability to obtain, maintain and protect our intellectual property; our ability to enforce our patents against infringers and defend our patent portfolio against challenges from third parties; competition from others developing therapies for similar indications; our ability to maintain the company infrastructure and personnel needed to achieve our goals; the severity and duration of the COVID-19 pandemic and variants thereof, and its negative impact on the conduct of, and the timing of enrollment, completion and reporting with respect to our clinical trials; and any other impacts on our business as a result of or related to the COVID-19 pandemic, as well as the information under the caption “Risk Factors” contained in our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) and in other filings we make with the SEC from time to time. We undertake no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances.

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