Wave Life Sciences Provides Update on Phase 1b/2a PRECISION-HD Trials

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mHTT results from PRECISION-HD trials do not support further development of WVE-120102 and WVE-120101

No observed change in wtHTT and NfL during trials

Advancing Phase 1b/2a trial for WVE-003 (SNP3) program in HD; WVE-003 uses new PN backbone chemistry modifications, which demonstrate improved preclinical pharmacology

Wave to host investor conference call and webcast today at 4:30 p.m. ET

CAMBRIDGE, Mass., March 29, 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 data from the Phase 1b/2a PRECISION-HD2 and PRECISION-HD1 trials evaluating investigational treatments WVE-120102 and WVE-120101, respectively, in Huntington's disease (HD).

In the PRECISION-HD2 core trial, results from all participants (n=88) showed no statistically significant change in mutant huntingtin protein (mHTT) versus placebo after single or multiple doses of WVE-120102 up to and including 32 mg monthly. There was no evidence of a dose response across the dose levels tested.

In the PRECISION-HD2 open label extension (OLE) trial, results from all participants (n=28) showed modest reductions in mHTT after a mean of 8.1 monthly doses (range: 1-17), but effects were inconsistent over the course of the trial. While there was a correlation between WVE-120102 cerebrospinal fluid (CSF) concentrations and mHTT lowering, pharmacokinetic (PK) modeling suggests that additional dose escalation is unlikely to achieve drug concentrations needed for robust mHTT knockdown. Given the lack of consistent and significant reductions in mHTT and the PK modeling projections, Wave will stop clinical development of WVE-120102. Trial participants will have a final follow-up visit but receive no further doses.

Results in all participants through 16 mg (n=51) from the PRECISION-HD1 core trial are similar to those in PRECISION-HD2 at those dose levels. Given these and results from Wave's previous clinical trials, as well as current understanding of the limitations of the company's first-generation candidates, Wave will also stop clinical development of WVE-120101. Dosing in the 32 mg cohort of the PRECISION-HD1 core trial is complete, and core and OLE trial participants will have a final follow-up visit but receive no further doses. Wave expects to complete analysis of the 32 mg cohort in the second quarter of 2021.

"We are disappointed not to have better news to share with the HD community and would like to extend our gratitude to the trial participants and their families for their commitment to these programs," said Michael Panzara, MD, MPH, Chief Medical Officer and Head of Therapeutics Discovery and Development at Wave Life Sciences. "However, we have learned an enormous amount from these trials and are encouraged by data that suggest our SNP targeting approach may achieve allele-selectivity. We look forward to continuing our collaboration with our research partners to advance our first HD clinical candidate that incorporates our next-generation PN backbone chemistry, WVE-003, and remain committed to the science of HD and, in particular, selective mutant huntingtin lowering."

WVE-003 is an investigational drug designed to selectively lower mHTT by targeting a specific single nucleotide polymorphism (SNP3) that is commonly found on the expanded CAG allele. This allele-selective approach is guided by the recognition that, in addition to a gain of function of mHTT, people with HD have lost one copy of the wild-type HTT allele, leaving them with a smaller protective reservoir of healthy, wild-type HTT protein (wtHTT) than unaffected individuals. A growing body of scientific evidence suggests that preserving as much of this essential protein as possible is important for favorable health outcomes.

Wave expects to initiate dosing in a Phase 1b/2a clinical trial for WVE-003 in 2021. As people with HD can carry multiple SNPs, participants from the PRECISON-HD trials will be offered the opportunity to undergo screening for potential enrollment in the WVE-003 trial. It is estimated that approximately 40% of adults with HD carry SNP3 in association with the HD mutation.

"Everyone at Wave wishes our PRECISION-HD programs had yielded different results, but we believe our WVE-003 program will enable us to address deficiencies with our first-generation candidates while maintaining our commitment to developing wild-type sparing therapies for HD," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "Our next generation of investigational clinical candidates, which also includes WVE-004 for amyotrophic lateral sclerosis and frontotemporal dementia and WVE-N531 for Duchenne, as well as our current preclinical and discovery programs, all use novel PN chemistry, which has been shown to increase potency, exposure, and durability across our silencing, splicing, and editing modalities in preclinical studies. Our clinical candidates have also been optimized with pharmacodynamic and pharmacokinetic insights from *in vivo* models, which were not available for our first-generation compounds. For example, we selected WVE-003 as our next HD candidate after years of optimization and demonstrated target engagement *in vivo*. Moreover, we are implementing innovative, adaptive designs across our new clinical programs to speed development and help us make data-driven decisions more quickly. These collective advances and learnings will improve our ability to deliver transformative genetic medicines."

Additional Results from the PRECISION-HD Trials

mHTT Assessments

- PRECISION-HD2 core trial participants who received three or four 32 mg doses of WVE-120102 had a non-statistically significant median reduction of 9.9% in mHTT in the CSF (p=0.74) as compared to a pooled placebo group who had a median decrease in mHTT of 0.8%.
- PRECISION-HD1 core trial participants who received three or four 16 mg doses of WVE-120101 had a non-statistically significant median reduction of 11.6% in mHTT in the CSF (p=0.56) as compared to a pooled placebo group who had a median decrease in mHTT of 10.0%.

wtHTT and Neurofilament Light Chain (NfL) Assessments

- Observations from PRECISION-HD2 OLE participants with >20% reduction in mHTT were used to determine whether wtHTT was similarly affected by treatment. There was no correlation between mHTT reduction and wtHTT change, suggesting allele-selectivity.
    - This analysis was not performed for the PRECISION-HD2 or the PRECISION-HD1 core trials given insufficient mHTT reduction.
- In the PRECISION-HD trials (core and OLE), there were no changes in CSF NfL over time. NfL is a protein component of the neuronal cytoskeleton, which has been shown to increase in the CSF with disease severity in HD.
- In the PRECISION-HD trials (core and OLE), there was no worsening of disease progression in treated participants versus progression expected based upon natural history studies.

Safety and Tolerability
Overall, adverse events (AEs) were balanced across treatment groups in the PRECISION-HD2 core trial (83% of WVE-120102-treated participants versus 90% on placebo) and most events were mild to moderate in intensity. The most common AEs (those occurring in at least 10% of participants receiving WVE-120102) were headache, procedural pain, back pain, falls, viral upper respiratory tract infection, dizziness, and post-lumbar puncture syndrome. There was an increase in serious adverse events (SAEs) in the 32 mg group as compared to lower doses. Seven of 13 participants in the 32 mg group were reported with an SAE related to treatment and six participants discontinued treatment due to an AE. SAEs were transient and included disorientation, delirium, ataxia, slurred speech, amnesia, meningitis, fever, and vertigo.

Adverse events were similar in the PRECISION-HD2 OLE to those that occurred in the core trial. Thirty-six participants reported with an event over 327 person/months of exposure. The incidence of SAEs related to treatment with 32 mg WVE-120102 was lower than in the core trial. Three participants discontinued treatment due to AEs (two receiving 16 mg, one receiving 32 mg).

In the PRECISION-HD1 core trial, 91% of participants who received up to 16 mg of WVE-120101 were reported with an AE compared with 75% who received placebo, most of which were mild to moderate in intensity. The most common AEs were headache, procedural pain, dizziness, back pain, falls and viral upper respiratory infection. There were no participants with SAEs related to WVE-120101 up through 16 mg. Two participants discontinued treatment due to AEs, one participant each in the 2 mg and 4 mg groups.

Adverse events were similar in the PRECISION-HD1 OLE as in the core trial, with 25 participants experiencing an event over 95 person/months of exposure. There were no discontinuations due to AEs. One participant experienced a related SAE of gait disturbance.

Across both PRECISION-HD programs (core and OLE), there were no clinically meaningful trends in clinical laboratory values including no CSF white blood cell and protein elevations.

WVE-003 Targeting SNP3 in HD To Begin Dosing in 2021
Site activation and enrollment in the Phase 1b/2a clinical trial of WVE-003 for adults with HD that carry SNP3 are currently underway and Wave expects to begin dosing in 2021. Preclinical models that have established pharmacologic activity have informed the starting dose for this trial. Additionally, Wave will incorporate an adaptive design, intended to support data-driven decisions regarding dosing and to potentially accelerate time to proof-of-concept.

In preclinical studies, WVE-003 showed dose-dependent and selective reduction of mHTT mRNA *in vitro*, and potent and durable knockdown of mHTT mRNA and protein *in vivo*. Based on the modeling of the pharmacokinetic-pharmacodynamic (PK-PD) relationship for WVE-003, the model predicts that WVE-003 will attain sufficient concentrations to engage mHTT transcript in both the cortex and striatum and decrease expression of mHTT protein.

Additional Clinical Trials Initiating in 2021
Wave also expects to initiate dosing in two other clinical trials this year, which will assess target engagement, impact on key disease biomarkers, and initial safety of WVE-004 (targeting C9orf72) for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) and WVE-N531 (targeting exon 53) for Duchenne muscular dystrophy (DMD). Wave submitted a clinical trial application (CTA) for WVE-N531 in March 2021. These clinical candidates also utilize PN backbone chemistry modifications and have been optimized based on the evolution of Wave's PRISM ™ discovery and drug development platform.

Cash Guidance
Wave expects that its existing cash and cash equivalents, together with expected and committed cash from its existing collaboration, will enable the company to fund its operating and capital expenditure requirements into the second quarter of 2023.

Investor Conference Call and Webcast
Wave management will host an investor conference call today at 4:30 p.m. ET to discuss these results and provide a business update. The conference call may be accessed by dialing (866) 220-8068 for participants based in the United States, or +1 (470) 495-9153 for participants based outside the United States, and entering conference ID 9608737. The live webcast may be accessed by visiting the investor relations section of the Wave Life Sciences corporate website at www.ir.wavelifesciences.com. Following the webcast, a replay will be available on the website.

About the PRECISION-HD Clinical Trials
PRECISION-HD1 and PRECISION-HD2 were Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled trials, which evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of WVE-120101 and WVE-120102 in adults with early manifest HD who carried a targeted single nucleotide polymorphism (SNP) rs362307 (SNP1) and rs362331 (SNP2), respectively. The trials included both single and multi-dose portions where participants were randomized to either active drug or placebo, with five cohorts in the multi-dose portion, ranging from 2-32 mg dosed intrathecally every four weeks. Upon completing the core trials, eligible participants were transitioned to OLE trials and dose escalated to the highest doses tested. The primary objective of both the core and OLE trials was to evaluate safety and tolerability, and secondary objectives included evaluation of PK and PD to assess plasma concentration and disease biomarkers (respectively).

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 protein (mHTT). Accumulation of mHTT causes progressive loss of neurons in the brain. Wild-type, or healthy, HTT protein (wtHTT) 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 inheriting the disease. There are currently no approved disease-modifying therapies available. Wave's

allele-selective approach may also enable treatment in the premanifest setting, before onset of clinical disease.

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, including statements regarding the following, among others: our commitment to developing wild-type sparing therapies for people living with HD; our plans to stop clinical development of WVE-120102 and WVE-120101 following the results received from our PRECISION-HD trials; our encouragement by PRECISION-HD trial data that suggest our SNP targeting approach may achieve allele-selectivity; the anticipated benefits of our allele-selective approach to lowering mutant huntingtin while sparing wild-type huntingtin; our understanding of the growing body of scientific evidence suggesting that preserving as much wild-type huntingtin protein as possible is important for favorable health outcomes; our plans to advance development of and begin dosing in 2021 for WVE-003, our first HD clinical candidate that incorporates our next-generation PN backbone chemistry modifications; our belief that additional preclinical modeling for and optimization of WVE-003 and our plans to use adaptive clinical trial designs to support data-driven decisions regarding dosing may assist in potentially accelerating time to proof-of-concept; our expectations regarding dosing for two other PN-containing clinical candidates, including WVE-004 for ALS and FTD and WVE-N531 targeting exon 53 for DMD; our ability to deliver on the promise of our current and future pipeline; the future performance and results of our programs in clinical trials and in preclinical development; the potential benefits of PRISM and our stereopure oligonucleotides compared with stereorandom oligonucleotides; the benefit of nucleic acid therapeutics generally; and the anticipated duration of our cash runway. 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; our ability to maintain the company infrastructure and personnel needed to achieve our goals; the clinical results of our programs, which may not support further development of product candidates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; our effectiveness in managing future clinical trials and regulatory interactions; the effectiveness of PRISM and our next generation therapeutic candidates, including our novel PN backbone chemistry modifications; the effectiveness of our novel ADAR-mediated RNA editing platform capability; 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; the severity and duration of the COVID-19 pandemic 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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