Wave Life Sciences Announces Positive Update to Ongoing Phase 1b/2a FOCUS-C9 Study Driven by Potent, Durable Reductions of Poly(GP) with Low, Single Doses of WVE-004

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Reductions in poly(GP), a key disease biomarker indicating target engagement, observed across all treatment groups after single doses

Extending dose observation period from three months (day 85) to six months to identify the maximum reduction of poly(GP) and duration of effect of low, single doses

Dosing in multidose 10 mg cohort well underway; longer-term follow-up from single dose cohorts and multidose data expected throughout 2022

First human data supporting preclinical to clinical translation of next-generation PN chemistry-containing molecules; clinical data from HD and DMD programs also expected in 2022

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

CAMBRIDGE, Mass., April 04, 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 FOCUS-C9 trial of WVE-004, the company's clinical candidate for C9orf72-associated amyotrophic lateral sclerosis (C9-ALS) and frontotemporal dementia (C9-FTD). FOCUS-C9 (NCT04931862) is an adaptive trial that was 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 potent, durable reductions of poly(GP) dipeptide repeat proteins in cerebrospinal fluid (CSF) with low, single doses of WVE-004. Poly(GP) is a key C9-ALS/C9-FTD disease biomarker that, when reduced in CSF, indicates WVE-004's engagement of target in the brain and spinal cord.

"ALS and FTD are serious, life threatening disorders where advances in disease-modifying therapeutics have been extremely limited. While early, these data are encouraging and open an opportunity to target the disease at the RNA level," said Merit Cudkowicz, MD, Chief of the Neurology Department, Director of the Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital and chair of the FOCUS-C9 Clinical Advisory Committee. "Additionally, it is encouraging to see the benefits of the study's adaptive design, where this early analysis has already helped narrow the doses being explored and enabled more precise, real-time exploration of dose response and optimization."

Reductions in poly(GP) were observed across all active treatment groups (10 mg, n=2 patients; 30 mg, n=4 patients; 60 mg, n=3 patients), reaching statistical significance versus placebo (n=3 patients) after single 30 mg doses, with a 34% reduction in poly(GP) at day 85 (p=0.011). At the time of analysis, none of the patients dosed with 60 mg had reached day 85.

As the poly(GP) reduction in the 30 mg single dose cohort does not appear to have plateaued, Wave will extend the observation period from approximately three months (85 days) to approximately six months to identify the maximum reduction of poly(GP) and duration of effect of low single doses. Based on the durability and potency observed in the 30 mg cohort, FOCUS-C9 has been adapted to include additional patients receiving 20 mg and 30 mg single doses of WVE-004.

Additional exploratory assessments included monitoring of CSF neurofilament light chain (NfL) and clinical outcome measures. CSF NfL elevations were observed in some patients in the 30 mg and 60 mg single dose cohorts with no meaningful changes in clinical outcome measures, although the dataset and duration were not sufficient to assess clinical effects. Exploratory assessments will continue throughout the single and multidose phases of the FOCUS-C9 trial.

Adverse events (AEs) were balanced across treatment groups, including placebo, and were mostly mild to moderate in intensity. Four patients (including one on placebo) experienced severe and/or serious adverse events; three were reported by the investigators to be related to ALS or administration, and one was reported by the investigator to be related to study drug. There were no treatment-associated elevations in CSF white blood cell counts or protein and no other notable laboratory abnormalities were observed.

Dosing in a multidose cohort at 10 mg monthly is also well underway, and additional single and multidose data are expected throughout 2022.

The company anticipates that the additional single and multidose data will be used to optimize dose level and frequency and enable discussions with regulatory authorities later this year regarding the next phase of development.

"FOCUS-C9 was designed to deliver an early indication of target engagement so that we could rapidly optimize the dose and move toward the next stage of development. Based on our preclinical PK/PD modeling, we expected that relatively low doses would engage target; however, seeing this level of poly(GP) knockdown three months after a single 30 mg dose exceeded our expectations and we expect poly(GP) to reduce further with repeat administrations," said Michael Panzara, MD, MPH, Chief Medical Officer and Head of Therapeutics Discovery and Development at Wave Life Sciences. "The next step is to identify a regimen that maximizes knockdown with repeat dosing, while potentially enabling quarterly or less frequent dosing. We are incredibly grateful to the patients, families, researchers and clinicians in the study who helped us reach this initial milestone and we look forward to their continued partnership as we work to complete FOCUS-C9."

Upcoming milestones for other Wave programs
In addition to WVE-004, Wave is advancing two other Phase 1b/2a clinical trials with its next-generation PN chemistry-containing investigational candidates: WVE-003 targeting SNP3 in Huntington's disease (HD), which is being investigated in the SELECT-HD trial (NCT05032196), and WVE-N531 targeting exon 53 in Duchenne muscular dystrophy (DMD) (NCT04906460). Wave expects to share clinical data in 2022 for WVE-003 and WVE-N531 to provide further insight into the clinical effects of PN chemistry and enable decision-making for these programs.

Wave also continues to rapidly advance its alpha-1 antitrypsin deficiency (AATD) program, which is the company's first program using its novel GalNAc-conjugated A-to-I(G) RNA base editing oligonucleotides ("AIMers"). Wave expects to select an AATD development candidate and initiate IND-enabling toxicology studies in the third quarter of 2022.

"Wave was founded on the vision that rational drug design would allow us to realize the full potential of genetic medicines. This guiding principle has

enabled the continued evolution of our PRISM platform and the discovery that PN chemistry significantly improved potency, durability, and distribution in our therapeutic candidates. Today, these initial results from FOCUS-C9 demonstrate that our compelling preclinical data for PN-containing molecules are beginning to translate in the clinic," said Paul Bolno, MD, MBA, President and Chief Executive Officer at Wave Life Sciences. "Additionally, these data reinforce our confidence that we will see the advantages of PN chemistry manifest in our other clinical programs – WVE-003 in HD and WVE-N531 in DMD – as well as our first RNA editing program in AATD. We are well on our way to delivering meaningful therapies to patients and families."

Investor Conference Call and Webcast
Wave management will host an investor conference call today at 8:30 a.m. ET to discuss the FOCUS-C9 clinical trial update. The conference call may be accessed by dialing (866) 220-8068 for participants based in the United States, or (470) 495-9153 for participants based outside the United States, and entering conference ID 3157835. The live webcast may be accessed by visiting the investor relations section of the Wave Life Sciences corporate website at ir.wavelifesciences.com. Following the webcast, a replay will be available on the website.

About WVE-004
WVE-004 is a stereopure antisense oligonucleotide designed with Wave's proprietary chemistry, including PN backbone chemistry modifications, to selectively target transcriptional variants containing a hexanucleotide repeat expansion (G_4C_2) associated with the *C9orf72* gene, thereby sparing normal C9orf72 protein.

About the FOCUS-C9 Clinical Trial
The FOCUS-C9 trial is an ongoing, 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-004 for people with C9-ALS and/or C9-FTD. Additional objectives include measurement of poly(GP) DPR proteins in the cerebrospinal fluid (CSF), plasma and CSF pharmacokinetics (PK), and exploratory biomarkers and clinical outcomes. The FOCUS-C9 trial is designed to be adaptive, with dose escalation and dosing frequency being guided by an independent committee.

Support for FOCUS-C9 is provided by the Alzheimer's Drug Discovery Foundation.

About Amyotrophic Lateral Sclerosis and Frontotemporal Dementia
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease in which the progressive degeneration of motor neurons in the brain and spinal cord leads to the inability to initiate or control muscle movement. People with ALS may lose the ability to speak, eat, move and breathe. ALS affects as many as 20,000 people in the United States.

Frontotemporal dementia (FTD) is a fatal neurodegenerative disease in which progressive nerve cell loss in the brain's frontal lobes and temporal lobes leads to personality and behavioral changes, as well as the gradual impairment of language skills. It is the second most common form of early-onset dementia after Alzheimer's disease in people under the age of 65. FTD affects as many as 70,000 people in the United States.

A hexanucleotide repeat expansion (G_4C_2) is the most common known genetic cause of the sporadic and inherited forms of ALS and FTD. The expansion leads to production of modified sense and antisense transcripts that can form nuclear RNA foci and encode dipeptide protein repeats (DPRs), which are believed to drive disease pathology. Additionally, the G_4C_2 expansion can decrease expression of C9orf72 protein, affecting regulation of neuronal function and the immune system.

In the United States, mutations of the *C9orf72* gene are present in approximately 40% of familial ALS cases and ~8-10% of sporadic ALS cases. In FTD, the mutations appear in 38% of familial cases and 6% of sporadic cases.

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 the initial data demonstrating target engagement announced above reinforce for the rest of our pipeline and our progress toward delivering meaningful therapies for patients and families; the continued dosing and generation of data to complete our FOCUS-C9 adaptive study and the announcement of such events; our expectations regarding the timing of additional single and multidose data in the FOCUS-C9 study; our anticipation that such data will be used to optimize dosing and enable discussions with regulatory authorities regarding the next phase of development; our expectations regarding the potential frequency of dosing; 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; our expectations regarding the timing of generating clinical data for WVE-003 and WVE-N531; and our expectations regarding the timing of selecting our first AIMer development candidate and initiating IND-enabling toxicology studies. 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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