# Wave Life Sciences Announces Initiation of Dosing in Phase 1b/2a FOCUS-C9 Clinical Trial of WVE-004 in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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*First clinical dosing of a compound using PN backbone chemistry modifications*

*Enrolling participants with C9-ALS, C9-FTD or mixed phenotype*

*FOCUS-C9 is adaptive to enable rapid optimization of WVE-004 dosing*

*Clinical data to enable decision-making on next steps for WVE-004 program expected in 2022*

CAMBRIDGE, Mass., July 20, 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 that multiple participants have initiated dosing in the Phase 1b/2a FOCUS-C9 clinical trial evaluating WVE-004 as an investigational treatment for C9orf72-associated amyotrophic lateral sclerosis (C9-ALS) and frontotemporal dementia (C9-FTD). WVE-004 is a stereopure antisense oligonucleotide designed to selectively target transcriptional variants containing a hexanucleotide repeat expansion ($G_4C_2$) associated with the *C9orf72* gene, thereby sparing C9orf72 protein. $G_4C_2$ expansions in *C9orf72* are one of the most common genetic causes of the sporadic and inherited forms of ALS and FTD.

"ALS and FTD are devastating illnesses where therapeutic progress has been extremely limited. Advancing discovery and development of new treatments for ALS and FTD is an urgent need that requires creativity, expediency and innovative thinking," said Michael Panzara, MD, MPH, Chief Medical Officer and Head of Therapeutics Discovery and Development at Wave Life Sciences. "The predicted pharmacology of WVE-004, afforded by PN chemistry and based upon *in vivo* models, allowed us to design FOCUS-C9 to be adaptive, enabling data-driven decisions regarding dose level and frequency as the trial proceeds and potentially accelerating time to proof-of-concept. Opening the FOCUS-C9 trial to those diagnosed with C9orf72-associated ALS or FTD may also facilitate the ability to pursue both indications in the future. We anticipate generating clinical data in 2022 that will enable decision-making on next steps for the program."

C9-ALS and C9-FTD are believed to be caused by multiple factors related to the $G_4C_2$ expansion. The expansion may lead to accumulation of repeat-containing RNA transcripts and aberrantly translated dipeptide repeat proteins (DPRs) leading to neurotoxicity, as well as insufficient levels of C9orf72 protein, affecting normal regulation of neuronal function and the immune system.

Preclinical studies of WVE-004 demonstrated potent and durable knockdown of repeat-containing transcripts in spinal cord and cortex, as well as knockdown of more than 90% of DPRs in the spinal cord and at least 80% of DPRs in the cortex, an effect that persisted for at least six months. C9orf72 protein was relatively unchanged over the same time period.

The FOCUS-C9 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-004 for people with C9-ALS and/or C9-FTD. Additional objectives include measurement of polyGP DPR proteins in the cerebrospinal fluid (CSF), plasma and CSF pharmacokinetics (PK), and exploratory biomarkers and clinical outcomes. The FOCUS-C9 trial is expected to enroll approximately 50 participants. It is designed to be adaptive, with dose escalation and dosing frequency being guided by an independent committee.

WVE-004 incorporates Wave's novel PN backbone chemistry modifications (PN chemistry), which have been shown in preclinical studies to enhance potency, exposure, and durability. In addition to WVE-004, Wave is advancing two other proof-of-concept trials with PN chemistry-containing investigational candidates: WVE-003 targeting SNP3 in Huntington's disease and WVE-N531 targeting exon 53 in Duchenne muscular dystrophy.

**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.

ALS and FTD can be caused by mutations in the *C9orf72* gene, which provides instructions for making protein found in various tissues, including nerve cells in the cerebral cortex and motor neurons. In the United States, mutations of the *C9orf72* gene are present in approximately 40% of familial ALS cases and 8% to 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 within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, the anticipated therapeutic benefit of WVE-004 as an investigational therapy for C9-ALS and C9-FTD; the anticipated timing of data to enable decision-making on next steps for WVE-004; the predicted pharmacology of WVE-004 and the associated trial protocol, design and endpoints; our beliefs related to the cause of C9-ALS and C9-FTD and our understandings of the effects of $G_4C_2$ expansion; 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.

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