Wave Life Sciences Announces Publication of Foundational Preclinical Data Supporting Development of WVE-004 for C9orf72-associated ALS and FTD

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Preclinical data published in Molecular Therapy Nucleic Acids demonstrate that WVE-004 potently reduces C9orf72 transcriptional variants and poly(GP) dipeptide repeat proteins in mice for at least six months while maintaining C9orf72 protein levels

Recently reported clinical data from ongoing Phase 1b/2a FOCUS-C9 trial of WVE-004 suggest these preclinical data translate in the clinic

CAMBRIDGE, Mass., April 25, 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 the publication of preclinical data for WVE-004, the company's clinical candidate for C9orf72-associated amyotrophic lateral sclerosis (C9-ALS) and frontotemporal dementia (C9-FTD), in *Molecular Therapy Nucleic Acids* (MTNA). The paper includes *in vivo* data demonstrating that WVE-004 led to potent, sustained reductions in pathogenic C9orf72 RNA transcripts and poly(GP) dipeptide repeat proteins (DPRs) for six months in C9 BAC transgenic mice after only two doses, without altering C9orf72 protein levels. The paper, titled "Preclinical evaluation of WVE-004, an investigational stereopure antisense oligonucleotide for the treatment of C9orf72-associated ALS or FTD," is available here.

WVE-004 is currently being investigated in the Phase 1b/2a FOCUS-C9 clinical trial in individuals with C9-ALS and/or C9-FTD. Wave recently shared initial, positive data from the study (here), demonstrating target engagement with potent, durable reductions of poly(GP) after low, single doses.

"On the heels of the first clinical data from FOCUS-C9, we are excited to be publishing our preclinical data for WVE-004, which helped enable accurate prediction of pharmacodynamically active starting doses in patients with C9-ALS/FTD," said Michael Panzara, MD, MPH, Chief Medical Officer and Head of Therapeutics Discovery and Development at Wave Life Sciences. "These preclinical data demonstrate that WVE-004 distributes widely throughout the CNS in mice, potently and durably lowering the toxic transcripts and poly(GP) driven by a *C9orf72* expansion mutation. We also recently reported our first human data from FOCUS-C9 where low, single doses of WVE-004 significantly reduced CSF poly(GP) levels, which were still declining after three months, suggesting translation of the preclinical data to the clinic. We are looking forward to sharing additional clinical data from the WVE-004 program this year."

WVE-004 is a stereopure antisense oligonucleotide designed with Wave's proprietary chemistry, including PN backbone chemistry modifications (PN chemistry), to selectively target transcriptional variants containing a hexanucleotide repeat expansion (G_4C_2) associated with the *C9orf72* gene, thereby sparing C9orf72 protein. A G_4C_2 expansion in *C9orf72* is the most common known genetic cause of the sporadic and inherited forms of ALS and FTD. Despite being distinct disorders, studies have found that ~20-50% of patients have both C9-ALS and C9-FTD. The overlap in genetics, pathology and clinical presentation has led to the idea that these diseases are manifestations of a clinical spectrum.

C9-ALS and C9-FTD are believed to be caused by multiple factors related to the G_4C_2 expansion. The expansion leads to production of modified sense and antisense transcripts that can form nuclear RNA foci and encode 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.

Data from the MTNA publication include:

- WVE-004 led to dose-dependent, potent, and selective decreases of repeat-containing transcripts *in vitro* in patient-derived motor neurons under free-uptake conditions.
- After two 50 microgram doses in mice, WVE-004 distributed widely throughout the CNS, including spinal cord and cortex, the tissues most profoundly affected in C9-ALS/FTD, through 24 weeks.
- WVE-004 led to a 66-87% ($P<0.001$) and 35-49% ($P<0.01$) mean reduction of pathogenic RNA transcripts in the spinal cord and cortex, respectively, through 24 weeks after dosing in mice.
- WVE-004 led to a ≥94% ($P<0.05$) and ≥84% ($P<0.01$) reduction of poly-GP DPRs in the spinal cord and cortex, respectively, through 24 weeks after dosing in mice.
- C9orf72 protein levels remained consistent at 24 weeks following WVE-004 treatment in mice, confirming the healthy V2 transcriptional variants were preserved.
- WVE-004 (up to 30 mM) did not induce cytotoxicity and induced relatively low cytokine production compared to a positive control *in vitro* in human peripheral blood mononuclear cells.

"This MTNA publication details the profound potency and durability of WVE-004, one of our next-generation clinical candidates optimized through our PRISM platform and using PN chemistry. Earlier this year we also published a paper on the profound impact of PN chemistry on enhancing pharmacology for silencing oligonucleotides in the CNS, compared with traditional oligonucleotide chemistry," said Chandra Vargeese, PhD, Chief Technology Officer and Head of Platform Discovery Sciences at Wave Life Sciences. "As we begin to share data from our PN chemistry-containing clinical candidates, it is abundantly clear that this novel backbone modification and the enhanced resolution provided through controlling stereochemistry has resulted in highly differentiated molecules, with the potential to overcome issues previously experienced by Wave and others developing antisense oligonucleotides for CNS diseases."

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.

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 within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, our understanding of the potential of WVE-004 preclinical data and modeling to predict the relevant dosing and behavior of our compounds in humans, and how this may translate into the clinic; the anticipated therapeutic benefits of WVE-004; our understandings of the causes of C9-ALS and C9-FTD and interplay between these two diseases; the continued dosing and generation of data to complete our FOCUS-C9 adaptive study and the announcement of such events; 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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