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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

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 Life Sciences Ltd., 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.”

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.

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.

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