Wave Life Sciences Announces Topline Results from Phase 1b/2a FOCUS-C9 Study of WVE-004 for C9orf72-associated Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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Potent and durable target engagement observed across cohorts, including with 10 mg doses administered every 12 weeks which were also generally safe and well-tolerated

WVE-004 did not show clinical benefit compared with placebo; additionally, poly(GP) reductions did not correlate with clinical outcomes -- Wave to discontinue development of WVE-004

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

CAMBRIDGE, Mass., May 23, 2023 (GLOBE NEWSWIRE) -- Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage RNA medicines company committed to delivering life-changing treatments for people battling devastating diseases, today announced topline results from the Phase 1b/2a FOCUS-C9 study evaluating WVE-004 as an investigational treatment for C9orf72-associated amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (C9-ALS/FTD). The results include data from a planned analysis of the study, where participants received multiple 10 mg doses of WVE-004 or placebo every 12 weeks (Q12W) or every 4 weeks (Q4W), as well as an additional 20 mg single dose cohort.

WVE-004 was generally safe and well-tolerated across doses, with most adverse events presenting as mild in intensity. There were no clinically meaningful changes in cerebrospinal fluid (CSF) protein or white blood cell count and no new safety signals since the previous data update in April 2022.

Robust, sustained reductions in poly(GP) from baseline were observed, with a maximal mean reduction of 48% ($p<0.0001$) in the Q12W dose and 50% ($p=0.0001$) in the Q4W dose of WVE-004. Poly(GP) is a pharmacodynamic biomarker indicating WVE-004 is lowering C9orf72 hexanucleotide repeat expansion (G_4C_2) transcripts, which are hypothesized to contribute to pathogenesis in C9-ALS/FTD. However, no clinical benefit was observed at 24 weeks, and reductions in poly(GP) were not associated with stabilization or improvement in functional outcomes. Based on these data, and in the absence of biomarkers reasonably likely to predict clinical outcomes, Wave has decided to discontinue development of WVE-004.

“Following our initial positive single dose data last year, we advanced WVE-004 with the hope that its potency and differentiated pharmacology may deliver a better result than C9orf72-targeting oligonucleotides discontinued by others in the field. While we again saw substantial reductions of poly(GP) with multiple doses, we are deeply disappointed that we were not able to see any evidence of potential benefits that would be expected to drive meaningful outcomes for these patients,” said Paul Bolno, MD, MBA, President and CEO of Wave Life Sciences. “C9-ALS/FTD is complex and made all the more challenging by the absence of a clinically validated biomarker. Our hope is that these data can help advance future research, and we are committed to sharing results with the community at an upcoming medical congress. On behalf of everyone at Wave, I wish to sincerely thank the participants, their families, the clinical sites, and our study advisory committees for their participation and support.”

Continued Dr. Bolno: “These data do reinforce that our preclinical data on target engagement and pharmacology are translating in the clinic. Looking forward, our lead programs in Huntington’s disease, Duchenne muscular dystrophy and Alpha-1 antitrypsin deficiency are designed to leverage biomarkers correlated with functional outcomes, making us more confident in the future of these programs and our emerging preclinical pipeline.”

Wave remains on track to share data from its Phase 1b/2a SELECT-HD study in Huntington’s disease investigating WVE-003 in the second half of 2023. The company is also rapidly advancing WVE-N531 for Duchenne muscular dystrophy amenable to exon 53 skipping into the potentially registrational Part B (Phase 2) clinical study, following its best-in-class exon skipping data observed in the Part A proof-of-concept study. Wave is also on track to bring the industry’s first RNA editing compound, WVE-006, into a clinical trial in Alpha-1 antitrypsin deficiency in the second half of 2023. In addition, the company continues to advance preclinical research with its modalities that restore or repair endogenous proteins, including additional RNA editing programs, and expects to share an update on its preclinical pipeline highlighting new data in the third quarter of 2023.

Topline FOCUS-C9 Results
The FOCUS-C9 study initially evaluated single doses of 10, 30 or 60 mg of WVE-004 or placebo. Based on potency and durability observed in the single dose cohorts, Wave added a 20 mg single dose cohort (n=8) and advanced 10 mg as the dose for the repeat dose phase, administered every 12 weeks (Q12W; n=8) or every four weeks (Q4W; n=5) and compared with placebo (n=7).

Participants in the Q12W cohort receive two 10 mg doses and participants in the Q4W cohort receive four 10 mg doses; participants are followed for 24 weeks. Key observations from the planned analysis of the study include:

Safety/tolerability results

- WVE-004 was generally safe and well-tolerated across the single and multidose cohorts (n=26 unique WVE-004-treated participants) and the most common adverse events (AEs) in the study were related to disease progression and intrathecal administration.
- AEs were mostly mild in intensity across all treatment groups.
- Among WVE-004-treated participants, there was one SAE in the study reported by the investigator as related to study drug that occurred in the 60 mg single dose cohort, as previously reported in April 2022. There was also one SAE reported that was procedure related. All other SAEs were associated with disease progression.
- There were no AEs indicative of antisense oligonucleotide class effects, including no clinically meaningful changes in blood chemistry or hematology.
- There was no evidence of inflammation in the CSF as indicated by no clinically meaningful changes in CSF white blood cell count or protein.

Poly(GP) results

- In the multidose cohorts, the mean, maximal poly(GP) reduction from baseline was 48% (95% CI, 0.36, 0.58; $p<0.0001$) for the 10 mg Q12W cohort at week 16 and 50% (95% CI: 0.29, 0.64, $p=0.0001$) for the 10 mg Q4W cohort at week 24.

- In the 20 mg single dose cohort, the mean, maximal poly(GP) reduction from baseline was 51% (95% CI, 0.29, 0.67; p=0.0006) at week 24.

Exploratory biomarker results: CSF neurofilament light chain (NfL)

- NfL elevations were observed in the WVE-004 20 mg single dose cohort and the 10 mg Q4W cohort; the 10 mg Q12W cohort and placebo had overlapping confidence intervals.
- There was no correlation (absolute correlation coefficient <0.1) between CSF NfL increases and ALSFRS-R change.

Exploratory clinical outcomes

- There was no benefit observed for WVE-004-treated participants compared with placebo on any exploratory clinical outcome measure, including the Revised ALS Functional Rating Scale (ALSFRS-R).
- In the Q12W cohort, there was no statistically significant difference in ALSFRS-R mean change between WVE-004 and placebo at any timepoint.
- In the Q4W cohort, participants treated with WVE-004 showed greater reduction in ALSFRS-R mean change than placebo patients at week 24 (p<0.0001); however, ALSFRS-R scores were not statistically different from the decline seen in natural history (using a matched natural history control group from the PRO-ACT database).
- Additionally, there was no benefit observed for WVE-004 treated participants with FTD compared with placebo on the Dementia Staging Instrument plus National Alzheimer's Coordinating Center (NACC) frontotemporal lobar degeneration (FTLD) Behavior and Language Domains (CDR® plus NACC FTLD).
- Reductions in poly(GP) did not associate with improvement on ALSFRS-R and CDR plus NACC FTLD and as such, Wave determined it will discontinue development of WVE-004, including stopping the FOCUS-C9 study and the open label extension study.

Investor Conference Call
Wave will host an investor conference call today at 8:30 a.m. ET to review the FOCUS-C9 clinical trial results. A webcast of the conference call can be accessed by visiting “Investor Events” on the investor relations section of the Wave Life Sciences website: https://ir.wavelifesciences.com/events-and-presentations. Analysts planning to participate during the Q&A portion of the live call can join the conference call at the following audio conferencing link**:** available here. Once registered, participants will receive the dial-in information. Following the live event, an archived version of the webcast will be available on the Wave Life Sciences website.

About FOCUS-C9
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 poly(GP) dipeptide repeat (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 was provided by the Alzheimer’s Drug Discovery Foundation.

About WVE-004
WVE-004 is an antisense oligonucleotide (ASO) designed with Wave’s proprietary and best-in-class chemistry, which selectively targets transcriptional variants containing the hexanucleotide repeat expansion (G_4C_2) associated with the C9orf72 gene, thereby sparing normal C9orf72 protein.

About Wave Life Sciences
Wave Life Sciences (Nasdaq: WVE) is a clinical-stage RNA 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 hope that our FOCUS-C9 data may be used to advance future research; our plans to share these results with the community at an upcoming medical congress; our expectations regarding the potential benefits and the anticipated timing of our upcoming milestones for our lead programs in Huntington’s disease, Duchenne muscular dystrophy and Alpha-1 antitrypsin deficiency and our confidence in these programs because they leverage biomarkers correlated with functional outcomes; and our expectations regarding the timing and substance of upcoming datasets from our preclinical pipeline using modalities that restore or repair endogenous proteins, including our RNA editing capability. 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.

Investor Contact:
Kate Rausch
617-949-4827
krausch@wavelifesci.com

Media Contact:
Alicia Suter
617-949-4817
asuter@wavelifesci.com

ALS and FTD Community Contact:
Chelley Casey
617-949-2900
ccasey@wavelifesci.com

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