Vigil Neuroscience Reports Positive Data from its Phase 1 Clinical Trial Evaluating VG-3927 for the Potential Treatment of Alzheimer's Disease

Jan 23, 2025

- Safety, tolerability, pharmacokinetic, and pharmacodynamic profile supports continued development of VG-3927 as potential once-daily oral therapy for Alzheimer's disease (AD) -

- Robust and dose-dependent reductions of sTREM2 were achieved demonstrating sustained functional target engagement –

- Company plans to advance VG-3927 into a Phase 2 trial in the third quarter of 2025; Selects 25mg QD oral as a dose that fully engages desired pharmacology -

WATERTOWN, Mass., Jan. 23, 2025 (GLOBE NEWSWIRE) -- Vigil Neuroscience, Inc. (Nasdaq: VIGL), a clinical-stage biotechnology company committed to harnessing the power of microglia for the treatment of neurodegenerative diseases, today announced positive data from its completed Phase 1 clinical trial evaluating VG-3927 for the potential treatment of AD. Collectively, the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profile supports the advancement of VG-3927 into a Phase 2 clinical trial as a potential once-daily oral therapy for AD.

"We are very excited by these positive Phase 1 data, which further support continued development of VG-3927 as a potential next-generation therapy for AD," said Ivana Magovčević-Liebisch, Ph.D., J.D., President and Chief Executive Officer of Vigil. "As the first and only Phase 2-ready oral, once-daily small molecule TREM2 agonist, VG-3927 is designed to provide a differentiated profile that can go beyond targeting amyloid plaques to address additional contributors of disease progression and has the potential to offer a more convenient treatment regimen for those struggling with the immense burden of this disease. We are delighted to have reached this key clinical milestone enabling VG-3927 to advance into a Phase 2 trial."

The Phase 1 single and multiple ascending dose (SAD/MAD) trial assessed the safety, tolerability, PK, and PD of VG-3927 across 14 cohorts. As part of this trial, the Company evaluated 8 SAD cohorts of healthy volunteers up to a 140mg/kg dose and 4 MAD cohorts of healthy volunteers up to a 50mg/kg dose. The trial also included an elderly cohort and a single dose cohort of 11 AD patients, including some participants who carry TREM2 or other genetic risk factors for AD. The trial enrolled a total of 115 participants. Eighty-nine (89) participants received VG-3927, including 34 who were 55 years of age and older.

Key takeaways from the Phase 1 clinical trial of VG-3927 include the following:

- Demonstrated a favorable safety and tolerability profile across all cohorts, including the elderly cohort.
    - All related adverse events were mild or moderate in severity and self-resolving without drug discontinuations. No serious AEs were reported.
- Highly brain penetrant with a favorable and predictable PK profile that supports once-daily dosing.
- Achieved robust and dose-dependent reduction of sTREM2 of up to approximately 50% in the cerebral spinal fluid (CSF) demonstrating a strong PK/PD relationship, sustained target engagement and TREM2 agonist activity.
- PK and sTREM2 reduction observed in the AD cohort was consistent with healthy volunteers and was similar across evaluated TREM2 and ApoE genetic variants supporting development in AD across genotypes.
- PK and sTREM2 reduction observed in the elderly cohort was consistent with healthy volunteers.
- Combined clinical and *in vivo* preclinical data confirm VG-3927 elicits neuroprotective activation of microglia downstream of TREM2 signaling.
- Vigil expects to provide additional data in an oral presentation at the AD/PD™ 2025 International Conference on Alzheimer's and Parkinson's Disease taking place April 1-5, 2025, in Vienna, Austria and online.

Based on the Phase 1 results and preclinical profile of VG-3927, the Company plans to advance a once-daily oral dose of 25mg that fully engages the desired pharmacology and expects to initiate the Phase 2 trial in the third quarter of 2025.

"We are happy to report that following our strong Phase 1 results, VG-3927 is a Phase 2-ready candidate that has demonstrated a favorable safety and tolerability profile," said Petra Kaufmann, M.D., F.A.A.N., Chief Medical Officer of Vigil. "Based on our comprehensive dataset, we are confident that VG-3927 is a well-characterized molecule that is highly brain penetrant and engages TREM2 to harness the neuroprotective potential of microglia. We continue to work toward the goal of providing a potential new and differentiated therapy to those impacted by AD, a disease with significant unmet need."

VG-3927 is a potent orally bioavailable small molecule TREM2 agonist. Its novel mode of action as both an agonist and a positive allosteric modulator

(PAM) may amplify functional responses around sites of pathology leading to strong modulation of microglia and potentially greater neuroprotection. VG-3927 is designed to enhance protective microglial responses to aggregated amyloid and tau without increasing inflammation. In contrast to antibody TREM2 agonists, VG-3927 maximizes receptor activation and microglial function because it does not bind to sTREM2, which may increase its access to the site of therapeutic action in AD. Additionally, VG-3927 does not have an Fc (fragmented crystallizable region) domain, which engages elements of the immune system that have been associated with increased risk of amyloid-related imaging abnormalities (ARIA). Collectively across preclinical and clinical data, these key differentiators create a compelling profile for VG-3927 as an investigational next-generation therapy for the treatment of AD.

About Vigil Neuroscience

Vigil Neuroscience is a clinical-stage biotechnology company focused on developing treatments for both rare and common neurodegenerative diseases by restoring the vigilance of microglia, the sentinel immune cells of the brain. Vigil is utilizing the tools of modern neuroscience drug development across multiple therapeutic modalities in its efforts to develop precision-based therapies to improve the lives of patients and their families. Iluzanebart, Vigil's lead clinical candidate, is a fully human monoclonal antibody agonist targeting human triggering receptor expressed on myeloid cells 2 (TREM2) in people with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), a rare and fatal neurodegenerative disease. Vigil is also developing VG-3927, a novel small molecule TREM2 agonist, to treat common neurodegenerative diseases associated with microglial dysfunction, with an initial focus on Alzheimer's disease (AD).

Forward-Looking Statements

This press release includes certain disclosures that contain "forward-looking statements" of Vigil Neuroscience ("Vigil" or the "Company") that are made pursuant to the safe harbor provisions of the federal securities laws, including, without limitation, express or implied statements regarding: the Company's strategy, business plans and focus; the potential therapeutic benefit of the Company's product candidates; the progress and timing of the clinical development of Vigil's programs, including the expected progress and timing to advance VG-3927 into a Phase 2 clinical trial in the third quarter of 2025; and beliefs about observations made analyzing preclinical study and clinical trial data to date, including with respect to VG-3927. Forward-looking statements are based on Vigil's current expectations and are subject to inherent uncertainties, risks and assumptions that are difficult to predict. Factors that could cause actual results to differ include, but are not limited to, risks and uncertainties inherent in the development of product candidates, including the conduct of research activities and clinical trials; whether results from prior preclinical studies and clinical trials will be predictive of the results of subsequent preclinical studies and clinical trials; whether Vigil's cash resources will be sufficient to fund its foreseeable and unforeseeable operating expenses and capital expenditure requirements; and the timing and content of additional regulatory information from the FDA; as well as the risks and uncertainties identified in the Company's filings with the Securities and Exchange Commission (SEC), including Vigil's Quarterly Report on Form 10-Q for the quarter ended September 30, 2024 and any subsequent filings Vigil makes with the SEC. Forward-looking statements contained in this announcement are made as of this date, and Vigil undertakes no duty to update such information except as required under applicable law. Readers should not rely upon the information on this page as current or accurate after its publication date.

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