Vigil Presents Key Findings from ILLUMINATE & IGNITE Studies in ALSP at the 2024 American Academy of Neurology Annual Meeting

Apr 17, 2024

- Findings from ILLUMINATE Natural History Study show that MRI and fluid biomarkers are emerging as key measures of ALSP pathophysiology -

- Positive interim IGNITE Phase 2 data demonstrating iluzanebart (VGL101) as potential disease-modifying therapy for ALSP

WATERTOWN, Mass., April 17, 2024 (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 the presentation of multiple oral and poster presentations on the Company's lead clinical candidate iluzanebart at the 2024 American Academy of Neurology (AAN) Annual Meeting.

"We are excited to see our enthusiasm for iluzanebart matched by clinical leaders in the ALSP community. The interim findings from both the IGNITE Phase 2 and ILLUMINATE Natural History studies support the potential of iluzanebart to become the first, disease-modifying therapy for those living with ALSP," said Petra Kaufmann, M.D., F.A.A.N, Chief Medical Officer of Vigil. "Both trials have led to an incredible step forward – not only in understanding ALSP disease progression, but also in drawing parallels between biomarkers and correlating clinical outcomes. We look forward to advancing the clinical development of iluzanebart in the hopes of providing a potentially transformative treatment option for those who have been impacted by this devastating disease."

Oral presentation presented by Zbigniew Wszolek, M.D., Mayo Clinic, Jacksonville: *Interim Results on iluzanebart (VGL101) From IGNITE: First Interventional Phase 2 Study in Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)*

"Vigil's interim IGNITE data demonstrated that iluzanebart was well-tolerated, and the data suggest a favorable impact on the protein product of the *CSF1R* gene whose dysfunction is the causal driver of ALSP," said Zbigniew Wszolek, M.D., consultant in the Department of Neurology at the Mayo Clinic. "Positive trends on MRI measurements support slowing in irreversible neurodegeneration, and to see these signals in patients as early as six months is very encouraging."

Interim analysis of the Phase 2 IGNITE proof-of-concept, multicenter, open-label study evaluating safety, tolerability, and clinical effects of iluzanebart demonstrated:

- A favorable safety and tolerability profile
- Predictable pharmacokinetic (PK) profile that is supportive of once-monthly dosing
- CNS target engagement and downstream pharmacological activity, including increased cerebrospinal fluid (CSF) levels of soluble colony-stimulating factor-1 receptor (sCSF1R), which is emerging as a key biomarker of ALSP disease pathophysiology
- Positive trends consistent with slowing of disease progression on key magnetic resonance imaging (MRI) measures in individual patients
- Encouraging trend emerging on changes in NfL reduction in individual patients

Poster presented by David S. Lynch, M.D., Ph.D., National Hospital for Neurology & Neurosurgery; University College London Institute of Neurology: *Findings from the ILLUMINATE Prospective Natural History Study (NHS) in Individuals with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)*

"The findings from ILLUMINATE highlight sensitive markers of ALSP pathophysiology that have the potential to provide valuable insight into clinical endpoints and improve the overall understanding of ALSP disease progression to inform future study designs," said David Lynch, Ph.D., Honorary Research Fellow, Department of Neuromuscular Diseases, University College London.

Data on clinical measures, biomarkers, and MRI from ILLUMINATE were presented at the conference. Key findings included:

- Baseline sCSF1R was substantially reduced in prodromal and symptomatic participants vs healthy volunteers, indicating reduced microglial activity
- At baseline, CSF and serum levels of neurofilament light chain (NfL), a marker of neuroaxonal injury, were elevated multifold in symptomatic participants vs prodromal and healthy volunteers
- Longitudinally, greater ventricle volume enlargement and gray matter volume reduction were observed in symptomatic vs prodromal participants
- Symptomatic participants demonstrated greater cognitive impairment at baseline and progression over time, as measured by the Montreal Cognitive Assessment scale (MoCA), vs prodromal participants
- Changes in ventricle volume over time demonstrated a statistically significant correlation with cognitive decline

Poster presented by Abbie Renoux, Ph.D., Vigil Neuroscience: *VGL101: An Immunotherapy that Enhances Microglial Survival for Adult Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)*

The preclinical study demonstrated iluzanebart as a highly potent human TREM2 (hTREM2) agonist monoclonal antibody, and preclinically validated its pharmacological potential to therapeutically circumvent CSF1R dysfunction in human microglia, the pathophysiological process underlying ALSP. Key supportive findings highlighting the mechanism of action of iluzanebart included:

- Demonstration that iluzanebart promotes human microglia resilience across multiple CSF1R loss-of-function states, including rescue in an ALSP-associated human genetic model system
- Mechanistic evidence that iluzanebart potently engages its target TREM2 and thereby indirectly modulates CSF1R biology, including the disease-associated biomarker sCSF1R
- Unbiased *in vivo* validation that TREM2-dependent activation of microglia is well-aligned with iluzanebart drug levels in mouse brains supporting its ability to achieve pharmacologically active CNS concentrations

The presentation and posters are accessible on the Publications page of the Company's website.

About Iluzanebart
Iluzanebart, Vigil's lead clinical candidate, is a fully human monoclonal antibody targeting human triggering receptor expressed on myeloid cells 2 (TREM2), which is responsible for maintaining microglial cell function. TREM2 deficiency is believed to be a driver of certain neurodegenerative diseases. Iluzanebart is in development for rare microgliopathies, such as ALSP, as well as other neurodegenerative diseases for which TREM2 and/or microglia deficiency is believed to be a key driver of disease pathology.

About ALSP
ALSP is a rare, inherited, autosomal dominant neurological disease with high penetrance. It is caused by a mutation to the CSF1R gene and affects an estimated 10,000 people in the United States, with similar prevalence in Europe and Japan. The disease generally presents in adults in their forties, is diagnosed through genetic testing and established clinical/radiologic criteria and is characterized by cognitive dysfunction, neuropsychiatric symptoms, and motor impairment. These symptoms typically exhibit rapid progression with a life expectancy of approximately six to seven years on average after diagnosis, causing significant patient and caregiver burden. There are currently no approved therapies for the treatment of ALSP, underscoring the high unmet need in this rare indication.

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) in genetically defined subpopulations.

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 potential therapeutic benefit of iluzanebart, beliefs about observations made analyzing preclinical study and clinical trial data to date; and our ability to advance the clinical development of iluzanebart. 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 related to uncertainties inherent in the development of product candidates, including the conduct of research activities and the conduct of clinical trials; whether results from preclinical studies and clinical trials will be predictive of the results of later preclinical studies and clinical trials; 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-K for the year ended December 31, 2023 and in 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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Investor Contact:
Leah Gibson
Vice President, Investor Relations & Corporate Communications
Vigil Neuroscience, Inc.
lgibson@vigilneuro.com

Media Contact:
Megan McGrath
MacDougall Advisors
mmcgrath@macdougall.bio