Vaccinex, Inc.'s Phase 2 "SIGNAL" Study to Evaluate Pepinemab Antibody in Huntington's Disease is Published in Nature Medicine along with Detailed Mechanism of Action Study in Journal of Neuroinflammation

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Data suggest that pepinemab slows or prevents cognitive decline in Huntington's Disease (HD)

Results highlight the potential for impact on other neurodegenerative and neuroinflammatory diseases including Alzheimer's

ROCHESTER, N.Y., Aug. 08, 2022 (GLOBE NEWSWIRE) -- Vaccinex, Inc. (Nasdaq: VCNX), a clinical-stage biotechnology company pioneering a differentiated approach to treating cancer and neurodegenerative disease through the inhibition of semaphorin 4D (SEMA4D), today announced that results of its Phase 2 SIGNAL study to evaluate its SEMA4D-blocking antibody, pepinemab, in patients with Huntington's Disease (HD) were published in the August 8, 2022 issue of *Nature Medicine*[1], a leading journal for publication of translational and clinical research. In parallel, a second report has been published in the *Journal of Neuroinflammation*[2] detailing the pathologic impact of SEMA4D on neuroinflammatory cells in both HD and Alzheimer's disease (AD).

The *Nature Medicine* article, titled "*Pepinemab antibody blockade of SEMA4D in early Huntington's Disease: a randomized, placebo-controlled, Phase 2 trial*," provides a comprehensive analysis of results from the Phase 2 study showing that while the trial did not meet its pre-specified primary efficacy endpoints, brain imaging measures showed a significant reduction in atrophy of the brain caudate nucleus (characteristic of HD) and prevented loss of metabolic activity in most brain regions (characteristic of both HD and AD). Multiple other exploratory and post-hoc assessments indicate a cognitive benefit to treatment. Pepinemab was well-tolerated by participants in the trial. The *Journal of Neuroinflammation* article, titled "*Semaphorin 4D is upregulated in neurons of diseased brains and triggers astrocyte reactivity*," demonstrates that SEMA4D is upregulated on neurons that are stressed or damaged during HD and AD disease progression and this triggers physiological changes in astrocytes that reduce their ability to facilitate energy metabolism in the brain and to control levels of neurotransmitters required for efficient signaling. Experiments in an animal model of Alzheimer's disease demonstrate that treatment with SEMA4D-blocking antibody inhibits reactive transformation of astrocytes, restores neuronal transmitters, and prevents or reduces cognitive deficits.

These findings encourage continued development of pepinemab as a potential therapy for patients with early manifest symptoms of HD and potentially AD. Accordingly, a phase 1b/2a study of pepinemab in Alzheimer's disease has been initiated and is actively enrolling patients (NCT04381468). The mechanism of action of pepinemab, targeting neuroinflammation[2], may provide an alternative to other AD therapies that target aggregates of Aβ amyloid. The *Nature Medicine* publication is available online at https://www.nature.com/articles/s41591-022-01919-8 and *Journal of Neuroinflammation* at https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-022-02509-8; both articles will also be posted on the Vaccinex website.

"Vaccinex is very pleased to publish the results of the Phase 2 SIGNAL HD study of pepinemab antibody in *Nature Medicine* demonstrating the effects of treatment along with a separate report in *Journal of Neuroinflammation* describing how it works and why this is also relevant to Alzheimer's disease," said Maurice Zauderer, Ph.D., President and Chief Executive Officer. "To summarize what we believe we have learned about the role of neuroinflammation in neurodegenerative diseases, including considerable prior work by other investigators, a primary injury, which is different in HD and AD, causes damage or stress to neurons which induces them to upregulate SEMA4D. Astrocytes that are in intimate contact with neurons express plexin-B1/B2 receptors for SEMA4D and this signal triggers them to undergo a dramatic physiological change, reactive astrogliosis, an inflammatory state. Through crosstalk among brain cells, astrocytes may also recruit microglia and other potentially inflammatory cells. These cells act together to neutralize or contain damage. These mechanisms contribute to good natural local defenses, but chronic inflammation over an extended period of disease progression can eventually cause loss of normal function and widespread neural dysfunction. Pepinemab binds to SEMA4D and inhibits its activity, thereby preventing the increase in damaging inflammation and preserving essential normal brain functions."

"We believe that overall our clinical results provide compelling evidence of cognitive benefit to treatment with pepinemab. In surveys of HD patients and their families, cognitive decline is regularly identified as a major concern. It was, therefore, of particular interest that post-hoc subgroup analysis suggested that patients with early signs of mild cognitive deficits appeared to derive the greatest benefit from treatment. Pepinemab treatment also prevented characteristic decline in brain metabolic activity in HD which multiple clinical trials in Alzheimer's disease have previously shown to correlate with cognitive decline[3]. To our knowledge, pepinemab is the first intervention shown to reverse this trend in a neurodegenerative disease. Since we believe we have already demonstrated an effect of pepinemab on a key cognitive endpoint in HD together with the supporting FDG-PET biomarker that will be central to success in AD, we are excited to have initiated the SIGNAL-AD clinical trial in Alzheimer's disease. We are extremely grateful to work together with the community of patients and caregivers to evaluate new potential treatment options for these impactful neurodegenerative diseases."

Summary of Key Findings from the SIGNAL HD trial Highlighted in the *Nature Medicine* Article

The *Nature Medicine* article highlights results that support the potential of pepinemab as a novel therapeutic approach for treating cognitive impairment in patients with HD, particularly those initially presenting with mild cognitive deficits. Key Findings from the Phase 2 SIGNAL HD trial include:

- significantly improved cognition in patients with early manifest disease, as reflected in the HD-Cognitive Assessment Battery of 6 different cognitive measures (HD-CAB Index, p=0.007).
- significantly reduced apathy severity (p=0.02), measured by the Problem Behaviors Assessment (PBA-s) which has previously been reported to correlate with cognitive decline.

- reduced atrophy (p=0.017) in the caudate nucleus, a brain region known to undergo early degeneration in HD.
- significantly improved brain metabolic activity as detected by FDG-PET in the majority of brain regions examined. FDG-PET signal has been reported to correlate with cognitive decline and clinical progression in AD.
- was well-tolerated with a low frequency of treatment-emergent adverse events (5% with pepinemab vs 9% with placebo) and a low treatment discontinuation rate (13/265) over the 18-month treatment period.

SIGNAL was a phase 2, multi-center, randomized, double-blinded, placebo-controlled clinical trial in 265 subjects including 179 early manifest and 86 late prodromal subjects all confirmed to carry the Huntington's disease mutation. Subjects were randomized 1:1 for monthly intravenous infusion with either 20 mg/kg pepinemab or placebo for at least 18 months at 32 centers in the U.S. and Canada. The study is now complete, and we believe the program is Phase 3-ready.

About Huntington's disease

Huntington's disease (HD) is an inherited condition that compromises brain functions through progressive damage to neurons that is believed to be triggered by a mutation in the huntingtin gene. Data of our own and others suggest that the major inflammatory cells of the brain, astrocytes and microglia, contribute importantly to disease pathology[2]. People with HD develop problems with cognition, judgement, emotion, behavior, and motor activity which becomes progressively worse over time. There is no known cure for HD and currently no approved disease modifying treatment. Most patients start developing symptoms between the ages of 30 to 50 although HD can also occur in young adults. Today, there are approximately 41,000 patients in the U.S. with symptomatic disease and more than 200,000 at-risk of inheriting the disease, with approximately equal numbers in Europe[4].

References:

1. Feigin A et al. Nature Medicine 2022, https://www.nature.com/articles/s41591-022-01919-8*; 2. Evans EE et al. J Neuroinflammation 19, 200 (2022).* https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-022-02509-8*; 3. Khosravi M et al. J Alzheimers Dis 70, 1197-1207 (2019).*
4. https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/;

About Pepinemab
Pepinemab is a humanized IgG4 monoclonal antibody that inhibits SEMA4D, which regulates the actin cytoskeleton of cells that play an important role in both tumor immunity and in inflammatory reactions in the brain. Preclinical and clinical data show that by preventing inflammatory reactivity during disease progression[2], pepinemab preserves the normal function of astrocytes and microglia, two types of glial cells that play a crucial role in maintaining the health and function of neurons in the brain[2]. Additional data show that in cancer pepinemab promotes infiltration and activation of dendritic cells and CD8+ T-cells and reverses immunosuppression within the tumor microenvironment. Pepinemab is being evaluated in several clinical studies in oncology and neurodegenerative disease.

About Vaccinex, Inc.
Vaccinex, Inc. is pioneering a differentiated approach to treating cancer and slowly progressive neurodegenerative diseases through the inhibition of SEMA4D. The Company's lead drug candidate, pepinemab, blocks SEMA4D, a potent biological effector that it believes prevents immune infiltration into tumors and triggers inflammation in chronic diseases of the brain. Pepinemab is being evaluated in a Phase 1b/2 study in recurrent or metastatic head and neck cancer and in a Phase 1/2a study in Alzheimer's Disease, with ongoing exploration of potential Phase 3 development in Huntington's disease. The Company has also developed a proprietary drug discovery platform, ActivMAb®, that it is leveraging thru strategic collaborations, particularly by exploiting its unique capability to select high value antibodies against important multi-pass membrane receptors.

Forward Looking Statements
To the extent that statements contained in this presentation are not descriptions of historical facts regarding Vaccinex, Inc. ("Vaccinex," "we," "us," or "our"), they are forward-looking statements reflecting management's current beliefs and expectations. Such statements include, but are not limited to, statements about our plans, expectations and objectives with respect to the results and timing of our clinical trials of pepinemab in various indications, the use and potential benefits of pepinemab in Huntington's and Alzheimer's disease and other indications, and other statements identified by words such as "may," "will," "appears," "expect," "hope", "planned," "anticipate," "estimate," "intend," "hypothesis," "potential," "suggest", "advance," and similar expressions or their negatives (as well as other words and expressions referencing future events, conditions, or circumstances). Forward-looking statements involve substantial risks and uncertainties that could cause the outcome of our research and pre-clinical and clinical development programs, future results, performance, or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, uncertainties inherent in the execution, cost, enrollment and completion of preclinical studies and clinical trials, uncertainties related to regulatory approval, risks related to our dependence on our lead product candidate pepinemab, the impact of the COVID-19 pandemic, and other matters that could affect our development plans or the commercial potential of our product candidates. Except as required by law, we assume no obligation to update these forward-looking statements. For a further discussion of these and other factors that could cause future results to differ materially from any forward-looking statement, see the section titled "Risk Factors" in our periodic reports filed with the Securities and Exchange Commission ("SEC") and the other risks and uncertainties described in the Company's most recent year-end Annual Report on Form 10-K and subsequent filings with the SEC.

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