Xenon Pharmaceuticals Announces Initiation of Phase 2 Clinical Trial to Evaluate XEN1101 as a Treatment for Major Depressive Disorder (MDD)

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BURNABY, British Columbia, May 03, 2022 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq:XENE), a neurology-focused biopharmaceutical company, today announced the initiation of a Phase 2 randomized, double-blind, placebo-controlled, multicenter clinical study – called the "X-NOVA" clinical trial – to evaluate the safety, tolerability, and efficacy of XEN1101 in Major Depressive Disorder (MDD).

Mr. Ian Mortimer, Xenon's President and Chief Executive Officer stated, "We are excited to announce the initiation of our Phase 2 'X-NOVA' clinical trial to evaluate XEN1101 as a potential treatment for major depressive disorder. Designed as a randomized, double-blind, placebo-controlled study, our clinical objective is to assess if XEN1101 improves depressive and anhedonia symptoms in patients with MDD. We have generated compelling pre-clinical evidence to support the use of XEN1101 in MDD, and we are encouraged by previously published clinical data using ezogabine that suggest that targeting Kv7 neuronal potassium channels could be a novel treatment approach for depression. The X-NOVA study complements an ongoing investigator-led study with our collaborators at Mount Sinai, which is investigating the effects of XEN1101 on brain measures of reward in subjects with MDD."

About the Xenon-Sponsored Phase 2 "X-NOVA" XEN1101 Clinical Trial in MDD
Based on promising pre-clinical data with XEN1101 and published clinical data generated from both an open-label study and a randomized, placebo-controlled clinical trial that explored the targeting of KCNQ channels as a treatment for MDD using ezogabine, Xenon is evaluating the efficacy, safety and tolerability of XEN1101 for the treatment of MDD in a Phase 2 randomized, double-blind, placebo-controlled, multicenter clinical study – called the "X-NOVA" clinical trial. Following a 4-week screening period, approximately 150 subjects with MDD will be randomized (on a 1:1:1 basis) to three arms for once-daily dosing of XEN1101 (10 mg), XEN1101 (20 mg) or placebo for 6 weeks. The primary objective is to assess the efficacy of 10 mg and 20 mg doses of XEN1101 compared to placebo on improvement of depressive symptoms in subjects diagnosed with moderate to severe MDD, using the Montgomery-Åsberg Depression Rating Scale (MADRS) score change through week six. Secondary endpoints include improvement of anhedonia symptoms assessed by the Snaith-Hamilton Pleasure Scale (SHAPS) score change through week six, as well as improvement of anxiety symptoms measured by the Beck Anxiety Inventory (BAI) score change through week six. Topline results from the X-NOVA study are anticipated in 2023.

About the Investigator-Led Phase 2 XEN1101 Clinical Trial in MDD
Xenon is collaborating with the Icahn School of Medicine at Mount Sinai to conduct an ongoing investigator-sponsored Phase 2 proof-of-concept, randomized, parallel-arm, placebo-controlled multi-site study of XEN1101 for the treatment of MDD in approximately 60 subjects. The primary objective of the study is to investigate the effect of XEN1101 on the brain reward circuit as measured by the change in bilateral ventral striatum activity as assessed by functional MRI (fMRI). The secondary objectives are to test the effect of XEN1101 compared to placebo on clinical measures of depression and anhedonia using the MADRS and SHAPS scales.

Scientific Rationale for Studying XEN1101 in MDD
Pre-clinical work demonstrates that increased activity of KCNQ type potassium channels reverses depressive phenotypes following chronic social defeat stress (Krishnan et al. 2007; Friedman et al. 2014; Friedman et al. 2016). Mice resilient to depression and anhedonia exhibit increased KCNQ channel activity within the ventral tegmental area (VTA) of the reward system, dampening the hyperexcitability of the dopamine neurons that is associated with depressive/anhedonia phenotypes observed in the susceptible mice. This susceptible phenotype can be reversed through (a) overexpression of KCNQ channels in the VTA dopamine neurons, (b) direct intra-VTA injection of small molecule KCNQ channel openers, or (c) systemic injection of KCNQ channel openers. Repeated peripheral daily administration of ezogabine, an earlier-generation KCNQ potassium channel modulator, completely reversed the depressive/anhedonic phenotype in the susceptible mice.

In addition to an open label study, statistically significant clinical results were generated from a randomized, placebo-controlled clinical trial that explored the targeting of KCNQ channels as a treatment for MDD and anhedonia using ezogabine (Costi et al. 2021). XEN1101, a next-generation KCNQ channel opener, has been studied in a Phase 2b clinical trial in adult patients with focal onset seizures, and demonstrated compelling efficacy results, with a statistically significant and dose-dependent reduction from baseline in monthly focal seizure frequency when compared to placebo (monotonic dose response; $p<0.001$).

About Xenon Pharmaceuticals Inc.
Xenon Pharmaceuticals (NASDAQ:XENE) is a clinical stage biopharmaceutical company committed to developing innovative therapeutics to improve the lives of patients with neurological disorders. We are advancing a novel product pipeline of neurology therapies to address areas of high unmet medical need, with a focus on epilepsy. For more information, please visit www.xenon-pharma.com.

Safe Harbor Statement

This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and the Private Securities Litigation Reform Act of 1995 and Canadian securities laws. These forward-looking statements are not based on historical fact, and include statements regarding the timing of and results from clinical trials and pre-clinical development activities, including those related to XEN1101; the potential efficacy, safety profile, future development plans, addressable market, regulatory success and commercial potential of XEN1101; the efficacy of our clinical trial designs; our ability to successfully develop and achieve milestones in the XEN1101 program; the timing and results of our interactions with regulators; anticipated enrollment in our clinical trials and the timing thereof; and the timing of potential publication or presentation of future clinical data. These forward-looking statements are based on current assumptions that involve risks, uncertainties and other factors that may cause the actual results, events, or developments to be materially different from those expressed or implied by such forward-looking statements. These risks and uncertainties, many of which are beyond our control, include, but are not limited to: the impact of the ongoing COVID-19 pandemic on our research and clinical development plans and timelines, including impact on our clinical trial sites, collaborators, and contractors who act for or on our behalf, may be more severe and more prolonged than currently anticipated; clinical trials may not demonstrate safety and efficacy of any of our or our collaborators' product candidates; our assumptions regarding our planned expenditures and sufficiency of our cash to fund operations may be incorrect; our ongoing discovery and pre-clinical efforts may not yield additional product candidates; any of our or our collaborators' product candidates may fail in development, may not receive required regulatory approvals, or may be delayed to a point where they are not commercially viable; we may not achieve additional milestones in our proprietary or partnered programs; regulatory agencies may impose additional requirements or delay the initiation of clinical trials; regulatory agencies may be delayed in reviewing, commenting on or approving any of our or our collaborators' clinical development plans as a result of the COVID-19 pandemic, which could further delay development timelines; the impact of competition; the impact of expanded product development and clinical activities on operating expenses; impact of new or changing laws and regulations; the impact of the COVID-19 pandemic on our business, adverse conditions in the general domestic and global economic markets; as well as the other risks identified in our filings with the Securities and Exchange Commission and the securities commissions in British Columbia, Alberta and Ontario. These forward-looking statements speak only as of the date hereof and we assume no obligation to update these forward-looking statements, and readers are cautioned not to place undue reliance on such forward-looking statements.

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