Xenon Pharmaceuticals Announces Collaboration with Researchers at Icahn School of Medicine at Mount Sinai to Conduct a Phase 2 Study of XEN1101 for the Treatment of Major Depressive Disorder (MDD)

March 8, 2021

U.S. FDA IND acceptance and IRB approval in place for investigator-sponsored trial, expected to be initiated in the second quarter of 2021

BURNABY, British Columbia, March 08, 2021 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq:XENE), a clinical stage biopharmaceutical company, today announced a collaboration with the Icahn School of Medicine at Mount Sinai (Mount Sinai) to facilitate an investigator-sponsored Phase 2 proof-of-concept, randomized, parallel-arm, placebo-controlled clinical trial of XEN1101 for the treatment of major depressive disorder (MDD) and anhedonia, which is an inability to feel pleasure. The principal investigator and sponsor of the Investigational New Drug (IND) application for the study is Dr. James W. Murrough, MD, PhD, Associate Professor of Psychiatry and Neuroscience at Mount Sinai. Xenon will supply the study drug, XEN1101, which is a proprietary, differentiated Kv7 potassium channel modulator being developed for the treatment of epilepsy and potentially other neurological disorders. The U.S. Food and Drug Administration (FDA) has accepted the IND, and study investigators have obtained Institutional Review Board (IRB) approval of the protocol in order to proceed with the Phase 2 XEN1101 MDD clinical trial, which is expected to be initiated in the second quarter of 2021.

Dysfunction of the dopamine neurons in the ventral tegmental area (VTA) of the brain reward system is an important feature of depressive disorders and other comorbidities, including anhedonia. Evidence from preclinical studies has highlighted KCNQ-type (Kv7) neuronal potassium channels as novel targets for the treatment of depressive disorders capable of reversing the observed dysfunction in the dopamine neurons. In addition, promising results were 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KCNQ channels as a treatment for MDD using ezogabine, an earlier-generation KCNQ potassium channel modulator that was withdrawn from the market for commercial reasons. Dr. Murrough and colleagues recently published the results from the randomized, placebo-controlled clinical trial of ezogabine in MDD and anhedonia in the *American Journal of Psychiatry*. For more information, refer to the news release issued by Mount Sinai on March 3, 2021: https://www.mountsinai.org/about/newsroom/2021/researchers-identify-brain-ion-channel-as-new-approach-to-treating-depression

Dr. Murrough stated, “MDD is one of the most disabling medical conditions worldwide, and new treatments are urgently needed to address this large, public health burden. Our previous clinical work using ezogabine suggests that KCNQ channel potentiation may represent a novel treatment approach for depression. Ezogabine was well-tolerated in patients with depression and resulted in a significant improvement in symptoms of depression and anhedonia. Our hope is that this new study will generate useful data that supports the utility of XEN1101 in depressive disorders such as MDD, given its common mechanism of action combined with an advantageous pharmacokinetic profile when compared to ezogabine.”

Dr. Simon Pimstone, Xenon’s Chief Executive Officer, said, “In addition to our ongoing Phase 2b X-TOLE study in adult patients with focal epilepsy, we have been exploring other neurological conditions for XEN1101. We have already completed Phase 1 and Phase 1b studies with XEN1101, establishing pharmacokinetic, toxicology, brain exposure and safety data. Dr. Murrough has generated promising, clinical results with the first generation Kv7 channel modulator ezogabine on reward circuit activity and clinical outcomes in patients with depression. This strategic collaboration allows us to further explore the potential we see for XEN1101 as a ‘next-gen’ Kv7 channel modulator in patients with depressive disorders such as MDD and also supports our ongoing epilepsy work as depression is a significant co-morbidity in many patients with focal epilepsy.”

About the Phase 2 XEN1101 MDD Clinical Trial

The Phase 2 investigator-sponsored XEN1101 MDD Study is designed as a multi-site, double-blind, randomized, parallel-arm, placebo-controlled clinical trial to test the antidepressant effect of XEN1101 compared to placebo in patients with MDD and significant anhedonia. Approximately 60 patients with a primary diagnosis of MDD according to Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) will be randomized in a 1:1 manner under double-blind conditions. Following a screening period, each subject will receive a daily dose of study drug or placebo for 8 weeks. The primary objective of the study is to investigate the effect of XEN1101 on brain measures of reward 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 a variety of clinical scales including the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Snaith-Hamilton Pleasure Scale (SHAPS). This Phase 2 Study is expected to initiate in the second quarter of 2021.

Scientific Rationale and Pre-Clinical Support for Studying XEN1101 in MDD

Pre-clinical work demonstrates a regulatory role for the KCNQ-type potassium channels in reversing depressive phenotypes following 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 VTA, 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 KCNQ channel openers, or (c) systemic injection of KCNQ channel openers. Repeated peripheral daily administration of the KCNQ channel opener ezogabine completely reversed the depressive/anhedonic phenotype in the susceptible mice. XEN1101, a next-generation, more potent KCNQ channel opener, has been shown to have activity in several *in vivo* rodent models of electrically and chemically induced seizures and exhibits a selectivity for Kv7 channels over other ion channels and receptors. Moreover, XEN1101 was found to be relatively more selective for Kv7.2/7.3 over Kv7.3/7.5 and Kv7.4 channels, which may be relevant for the clinical profile of the drug. *In vitro* studies suggested a low potential for drug-drug interactions through the inhibition of the cytochrome isoenzymes, and data from Phase 1 clinical studies showed a favorable pharmacokinetic profile.

Clinical Validation for Studying XEN1101 in MDD Based on Completed Studies with Ezogabine
Dr. Murrough conducted two clinical studies using the first-generation Kv7 potassium channel modulator, ezogabine, in order to test the hypothesis that increasing KCNQ channel signaling can be beneficial for patients with depression and anhedonia. An open-label, proof-of-concept study was conducted with eighteen individuals with MDD in a major depressive episode (MDE) who received ezogabine up to 900 mg/day orally (within the approved range for seizure disorder) over the course of ten weeks. After treatment with ezogabine, subjects exhibited a significant reduction of depressive symptoms MADRS score change: −13.7±9.7, $p<0.001$, $d=2.08$ and anhedonic symptoms (Snaith-Hamilton Pleasure Scale (SHAPS) score change: −6.1±5.3, $p<0.001$, $d=1.00$), which remained significant even after controlling for overall depression severity (Tan et al 2018).

The second study was a two-site, double-blind, randomized, placebo-controlled, proof-of-concept clinical trial designed as a preliminary test of the hypothesis that increasing KCNQ2/3 channel activity in the brain is a viable new approach for the treatment of depression. Forty-five adult patients diagnosed with a depressive disorder were assigned to a five-week treatment period with daily dosing of either ezogabine or matching placebo. All participants underwent clinical evaluations and functional magnetic resonance imaging (fMRI) during a reward task at baseline and at the end of the treatment period. Compared to patients treated with placebo, those treated with ezogabine showed a significant and large reduction in several key measures of depression severity, anhedonia, and overall illness severity. For example, significant improvements following treatment with ezogabine compared to placebo were observed using MADRS and the SHAPS clinical scales. In addition, the ezogabine group showed a trend towards an increase in response to reward anticipation in the brain compared to placebo. Relative to placebo (N=24), ezogabine (N=21; target dose 900 mg daily) was associated with a significantly larger improvement in symptoms of depression (MADRS score change: -7.9±3, $p<.001$), significantly larger improvement in symptoms of anhedonia (SHAPS score change: -6.9±3.2, $p<.001$), and other clinical endpoints. In both trials, ezogabine was well tolerated and no serious adverse events occurred. Overall, these results provide further support for the use of KCNQ channel potentiators as a novel treatment approach for MDD (Costi et al 2021).

About Xenon Pharmaceuticals Inc.

We are 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 anticipated timing of the initiation of future clinical trials for XEN1101; the efficacy of clinical trial designs; our ability to successfully develop and achieve milestones in the XEN1101 and other proprietary and partnered development programs; anticipated enrollment in 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 COVID-19 pandemic on our business, research and clinical development plans and timelines and results of operations, 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; 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; 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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