Xenon Pharmaceuticals Announces Promising New Pre-Clinical Data and Provides Clinical Overview of its XEN1101 Program at ASENT 2021

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Pre-Clinical Data Support the Potential Benefit of XEN1101 to Treat Depression and Anhedonia

XEN1101, in Combination with Other Anti-Seizure Medications, Provides Robust Efficacy in Animal Models

Topline Data from XEN1101 Phase 2b X-TOLE Clinical Trial in Adult Focal Epilepsy on Track for Third Quarter of 2021

BURNABY, British Columbia, Feb. 22, 2021 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq:XENE), a neurology-focused biopharmaceutical company, announced that new pre-clinical data and a clinical overview of its XEN1101 program will be presented at ASENT 2021, the virtual annual meeting of the American Society for Experimental Neurotherapeutics. XEN1101 is a differentiated Kv7 potassium channel modulator being developed for the treatment of epilepsy and potentially other neurological disorders. The X-TOLE Phase 2b clinical trial is currently underway studying the efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in approximately 300 adult patients with focal epilepsy.

Today, Xenon hosted a symposium presentation entitled, “Addressing an Unmet Medical Need in Adult Focal Epilepsy with XEN1101, a Novel Kv7 Modulator,” which provided an update on XEN1101’s clinical development to date and outlined a number of its unique pharmaceutical properties including:

- Proven anti-seizure Kv mechanism of action
- Efficacious as monotherapy and in combination with other anti-seizure medications (ASMs) in pre-clinical models
- Well-tolerated in Phase 1 clinical studies, and low drop-out and high conversion to open label extension in blinded Phase 2b clinical trial to date
- Once daily (QD) evening dosing, low daily dose and no dose titration in ongoing Phase 2b clinical trial
- No significant drug-drug-interactions (DDI) predicted

Dr. Simon Pimstone, Xenon’s Chief Executive Officer, stated, “Our presentations at ASENT 2021 summarize our view that XEN1101 could potentially represent a highly differentiated profile in the focal epilepsy space with important “ease-of use” attributes that we believe are meaningful for physicians and patients combined with a favorable safety/tolerability profile to date. We are looking forward to the read-out of topline results from our ongoing Phase 2b X-TOLE clinical trial, anticipated in the third quarter of this year.”

Other presentations at ASENT 2021 include:

- A pipeline presentation entitled “Anticonvulsant Effects of the Differentiated Kv7 Channel Potentiator XEN1101 in Combination with Commonly Used Anti-Seizure Drugs” includes new pre-clinical data showing that combining sub-efficacious doses of XEN1101 and other ASMs provided robust efficacy in animal models, which was not an apparent DDI effect. In addition, the combination dosing was well tolerated in the dose ranges explored. This work suggests that XEN1101 may be well suited for use as a monotherapy or applied in a rational polypharmacy setting to treat seizures. Data were presented combining XEN1101 with commercially approved ASMs, including lacosamide, levetiracetam, cenobamate, phenytoin, and valproic acid.

- A symposium presentation entitled, “Kv7 Modulators in Epilepsy and Depression” outlines the scientific rationale, pre-clinical data, and clinical work to date supporting the use of Kv7 modulators for the treatment of depression and anhedonia. Pre-clinical work demonstrates a regulatory role for the KCNQ-type potassium channels in reversing depressive phenotypes following social defeat stress. Results from clinical studies using the first generation, Kv7 potassium channel modulator, ezogabine, supported the hypothesis that increasing KCNQ channel signaling can be beneficial for patients with depression and anhedonia. Major depression is a common co-morbidity of persons with epilepsy and significantly impacts their quality of life.

- A pipeline presentation entitled “Depression and Anhedonia: Acute Pre-clinical Efficacy for XEN1101, a Differentiated Kv7 Potassium Channel Modulator” included new pre-clinical data from the Forced Swim Test and Progressive Ratio Test animal models, which support a potential benefit of XEN1101 in mood disorders. Of note, the efficacious doses and plasma concentrations from the pre-clinical depression, anhedonia, and seizure studies overlap and occur at plasma levels achieved during a multi-ascending Phase 1 clinical trial suggesting that the current doses being used in the ongoing XEN1101 Phase 2b clinical trial to treat epilepsy may have a beneficial impact on depressed mood.

Mr. Ian Mortimer, Xenon’s President and Chief Financial Officer said, “In addition to the ongoing clinical development of our XEN1101 Phase 2b X-TOLE study in adult focal epilepsy, we have been exploring the use of XEN1101 in other non-epilepsy

indications. Based on our analysis and these promising pre-clinical data, we expect to initiate a Phase 2 proof-of-concept clinical trial this year examining XEN1101 in major depressive disorder (MDD) and anhedonia in partnership with academic collaborators at the Icahn School of Medicine at Mount Sinai. We look forward to updating you with further details in the coming months."

All of Xenon's presentations at ASENT 2021 will be made available on the Xenon website.

Scientific Rationale for Studying XEN1101 in MDD

In addition to the supporting evidence presented at ASENT 2021, previous 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 ventral tegmental area (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 be effective 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, relevant for the efficacy and safety 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. In addition, an open-label, proof-of-concept clinical study was conducted with eighteen medication-free 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).

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 IND, or IND-equivalent, submissions and the initiation of future clinical trials for XEN1101; the efficacy of our clinical trial designs; our ability to successfully develop and achieve milestones in the XEN1101 proprietary development program; the timing and results of our interactions with regulators; anticipated enrollment in our clinical trials and the timing thereof; the progress and potential of our other ongoing development programs; the potential receipt of milestone payments and royalties from our collaborators; 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; 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; promising results from trials involving a small number of patients may not be replicated in subsequent, larger trials; 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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