Xenon Announces Final Results of XEN1101 Phase 1 Clinical Trial and Update on XEN901 Phase 1 Clinical Trial at the American Epilepsy Society (AES) Annual Meeting

December 3, 2018

XEN1101 CTA Accepted by Health Canada for Initiation of Phase 2 Clinical Trial in Adult Focal Epilepsy; U.S. IND Filing Targeted in Q1 2019

Conference Call to Discuss Xenon's Epilepsy Programs at 9 am ET Today

BURNABY, British Columbia, Dec. 03, 2018 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq:XENE), a clinical stage biopharmaceutical company, today provided clinical updates on XEN1101, a Kv7 potassium channel modulator being developed for the treatment of epilepsy and potentially other neurological disorders and XEN901, a potent, highly selective Nav1.6 sodium channel inhibitor being developed for the treatment of epilepsy. Xenon announced final results from its XEN1101 Phase 1 clinical trial and the related transcranial magnetic stimulation (TMS) studies, along with interim results from its XEN901 Phase 1 clinical trial, in posters at the American Epilepsy Society (AES) Annual Meeting held in New Orleans, LA. In addition, Xenon today outlined plans for a XEN1101 Phase 2 clinical trial, with patient enrollment expected to begin early in the new year.

Dr. Simon Pimstone, Xenon's Chief Executive Officer, said, "With three epilepsy product candidates within our development pipeline, the AES Annual Meeting is an important event for us as it provides a venue to both present data as well as connect with key opinion leaders and world-class clinicians who provide input on our development plans. We are excited to announce the final results of the XEN1101 Phase 1 clinical trial and present the related TMS data at AES. These Phase 1 data support the continued advancement of XEN1101 into a Phase 2 clinical trial in adult patients with focal epilepsy and we look forward to initiating patient enrollment in the Phase 2 clinical trial in the near term."

Dr. Pimstone added, "We are pleased to be presenting additional data from our XEN901 Phase 1 clinical trial at the AES meeting. The next steps in the XEN901 program are to complete the Phase 1 clinical trial and continue planning for XEN901's Phase 2 clinical development as a treatment for adult focal seizures or for rare, pediatric forms of epilepsy, including SCN8A gain-of-function epilepsy patients, depending on feedback from planned discussions with regulatory agencies."

Summary of XEN1101 Phase 1 Data
The objectives of the XEN1101 Phase 1 clinical trial were to evaluate the safety, tolerability and pharmacokinetics of both single ascending doses (SAD) and multiple ascending doses (MAD) using a powder-in-capsule formulation of XEN1101 in healthy subjects. The XEN1101 Phase 1 clinical trial included a pharmacodynamic read-out from TMS studies that were designed to assess XEN1101's ability and potency to modulate cortical excitability, thereby demonstrating activity in the target CNS tissue. The XEN1101 Phase 1 results include data from six SAD cohorts ranging in dose from 5 to 30 mg (n=34, placebo=8), including a crossover food effect cohort (n=10) with a single 20 mg dose. MAD results included three cohorts ranging in dose from 15 to 25 mg (n=18, placebo=6) including two cohorts of 15 mg evaluated in a fasted and fed state over 7 and 10 days, respectively, and one cohort of 25 mg evaluated in a fed state over 10 days.

Final results from the XEN1101 Phase 1 clinical trial and TMS studies were presented in posters entitled, "A First-in-Human Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Pharmacodynamics of a Novel Small Molecule KV7.2/7.3 Positive Allosteric Modulator (XEN1101) in Healthy Subjects" and "A Phase 1 Study Utilizing Transcranial Magnetic Stimulation to Assess the Pharmacodynamic Effects of a Novel Potassium Channel Opener (XEN1101) on Human Cortical Excitability."

Highlights from these poster sessions include:

- **Pharmacokinetics:** The PK profile of XEN1101 (including an effective half-life greater than 24 hours) supports a once-per-day dosing schedule with expected steady state in approximately one week without the need for titration.

- **Safety:** The majority of adverse events (AEs) were mild or moderate, resolved spontaneously and were consistent with antiepileptic drugs of this class. Sedation (including somnolence, drowsiness) and dizziness (including light-headedness and presyncope) were the most common AEs, while mild cognitive effects (memory and speech impairment) and blurred vision were also observed in a dose dependent manner. There were no SAEs, deaths, or clinically significant ECG or laboratory findings. Phase 1 results suggest that that XEN1101 is generally safe and well tolerated in the doses examined (single doses of up to 30 mg and multiple doses of up to 25 mg once daily).

- **TMS Measures**: The TMS Phase 1b double-blind, placebo-controlled, randomized cross-over study included 20 healthy male subjects. TMS measurements were taken at 2 and 4 hours for all subjects and, due to a prolonged absorption phase displayed by XEN1101 pharmacokinetics, an additional TMS assessment time-point was added at 6 hours for a subset of

subjects. Subjects were randomized initially to either a 20 mg dose of XEN1101 or placebo and then, after a wash-out period, crossed over to the other treatment arm.

Consistent with the Phase 1a TMS pilot study, XEN1101 reduced corticospinal excitability, as demonstrated by a concentration dependent elevation in resting motor threshold (RMT), the key TMS-EMG measure. Single 20 mg doses of XEN1101 resulted in plasma levels of 15.9 ng/mL, 30.2 ng/mL and 42.1 ng/mL at 2, 4 and 6 hours, respectively. RMT increased in proportion to XEN1101 plasma concentration showing a mean ± standard error of mean increase of 4.9 ± 0.7% ($p<0.01$) at 6 hours. Active motor threshold (AMT) also increased in proportion to plasma concentration of XEN1101 with an increase of 2.0 ± 0.4% at 6 hours.

In addition, XEN1101 statistically significantly modulated TMS-evoked EEG potentials (TEPs) in a pattern consistent with reductions in cortical excitability. Relative to time-matched placebo, at peak plasma levels, XEN1101 decreased the amplitude of TEPs vs placebo at 25, 45 and 180 ms after the TMS pulse. Additional measures of cortical excitability including global mean field power were similarly impacted. XEN1101 also shifted the power spectra of resting state EEGs toward lower frequencies.

These TMS studies provided evidence of the CNS effects of a 20 mg dose of XEN1101 as indicated by suppression of cortical and corticospinal excitability, and helped with dose selection for the upcoming XEN1101 Phase 2 clinical trial.

Based on the encouraging Phase 1 data and TMS results, Xenon is continuing the advancement of XEN1101 into Phase 2 development in adult patients with focal epilepsy. A Clinical Trial Application (CTA) has been accepted by Health Canada enabling the start of patient screening, and the first patient in the XEN1101 Phase 2 clinical trial is expected to be enrolled early in the new year. Xenon anticipates submitting regulatory filings to support the clinical development of XEN1101 in other jurisdictions, including the United States and Europe, in the first quarter of 2019.

About the XEN1101 Phase 2 Clinical Trial

The XEN1101 Phase 2 clinical trial is designed as a randomized, double-blind, placebo-controlled, multicenter study to evaluate the clinical efficacy, safety and tolerability of XEN1101 administered as adjunctive treatment in adult patients aged 18 to 75 years diagnosed with focal epilepsy. Approximately 300 patients will be randomized in a blinded manner to one of three active treatment groups or placebo in a 2:1:1:2 fashion (XEN1101 25 mg : 20 mg : 10 mg : Placebo). The trial is designed to show at least a 15% difference between highest active dose and placebo powered at 88%. After screening, patients will have 8 weeks of baseline to assess frequency of seizures, followed by 8 weeks of treatment and a 4-week post treatment follow-up period. In order to be included in the study, patients must already be treated with a stable dose of 1 to 3 allowable current anti-epileptic drugs (AEDs) for at least one month prior to screening, during baseline, and throughout the duration of the study. During the treatment period, patients will be given XEN1101 or placebo once daily in the evening.

In addition to standard safety measurements, the primary endpoint is:

- the median percent change in monthly focal seizure frequency from baseline compared to treatment period of active versus placebo

Secondary endpoints include:

- assessment of patients experiencing greater than or equal to 50% reduction in monthly focal seizure frequency from baseline to treatment period
- median absolute, change, and percent change from baseline in weekly focal seizure frequency for each week in the double-blind treatment period
- clinical and patient global impression of change scores during the double-blind treatment period

The patients who successfully complete this trial on their assigned study medication through the treatment phase may be considered for an open-label safety extension study.

Depending upon the rate of enrollment, top-line results from the XEN1101 Phase 2 clinical trial are anticipated in the second half of 2020.

Summary of XEN901 Interim Phase 1 Clinical Data

Interim results from the ongoing XEN901 Phase 1 clinical trial were summarized in a poster entitled “A First in Human Phase 1 Study to Assess the Safety, Tolerability and Pharmacokinetics of a Novel Nav1.6 Selective Small Molecule Sodium Channel Inhibitor (XEN901) in Healthy Subjects.”

- The XEN901 interim Phase 1 results include data from six single ascending dose (SAD) cohorts ranging in dose from 5 to 80 mg (n=30, placebo=10) and from four multiple ascending dose (MAD) cohorts ranging in dose from 15 mg twice daily to 75 mg once daily (n=23, placebo=7). A food effect (FE) cohort received single doses of XEN901 in fed and fasted states in a crossover design. In addition, XEN901’s effects on TMS measurements and EEG were assessed in two of the multiple dose cohorts.

- Favorable pharmacokinetics (PK) data show dose proportionality with predicted half-life of 8 to 11 hours suggesting that XEN901 could be compatible with a once or twice daily dosing regimen.

- The majority of adverse events (AEs) for the SAD, MAD, and FE cohorts were deemed unrelated to XEN901, were mild or moderate, transient and resolved spontaneously. All AEs considered possibly related to XEN901 were mild; only nausea and dizziness were reported in more than 1 subject. There have been no SAEs, deaths, or clinically significant ECG, vital signs or laboratory findings. The interim preliminary safety results suggest XEN901 is overall generally safe and well tolerated in the doses examined.

- XEN901's effects on TMS measurements and EEG were assessed in a pilot study of 8 subjects from the 50 and 75 mg once daily cohorts and compared to 3 placebo subjects. TMS measures were recorded at baseline and on Day 5/6. In this pilot study, XEN901 showed increases in resting motor threshold (RMT) of 2.0% (versus 0.67% in placebo); increases in active motor thresholds (AMT) of 2.25% (versus 0% in placebo); decrease in amplitude of TMS evoked potential (TEP) at 180 ms (P180), and an increase in delta power in the resting state EEG. The observed changes in TMS-EMG and TMS-EEG parameters suggest activity of XEN901 in the target CNS tissue in this exploratory pilot study.

Xenon also presented posters at the AES annual meeting related to XEN901 pre-clinical research entitled "Preclinical Safety Margins of the Potent and Nav1.6 Selective Inhibitor, XEN901, in Relation to Non-Selective Sodium Channel Blockers" and "Efficacy of Sodium Channel Inhibitors as Anticonvulsants in the Rat MES Assay is Predictive of the Therapeutic Plasma Concentration in Humans." In its poster entitled "Repeat Dosing of Novel Selective Inhibitors of Nav1.6 Enhances Efficacy in the Mouse Maximal Electroshock Model," Xenon outlined new pre-clinical data suggesting that enhanced efficacy with chronic dosing of Nav1.6 modulating compounds in mice may result from knock-down of the Nav1.6 protein in mouse brain, suggesting that alterations in target protein levels may provide a mechanism for seizure protection. Xenon continues to evaluate selective Nav1.6 compounds and Nav1.2/1.6 dual acting compounds for development behind XEN901.

Conference Call Information

Xenon will host a conference call and live audio webcast today at 9:00 am Eastern Time (6:00 am Pacific Time) to provide an update on its XEN1101 and XEN901 epilepsy programs. To participate in the call, please dial (855) 779-9075, or (631) 485-4866 for international callers, and provide conference ID number 5369265. The webcast will be broadcast live on the "Investors" section of Xenon's website at www.xenon-pharma.com and will be available for replay following the call for 30 days.

About Xenon Pharmaceuticals Inc.

We are a clinical stage biopharmaceutical company focused on developing innovative therapeutics to improve the lives of patients with neurological disorders. Building upon our extensive knowledge of human genetics and diseases caused by mutations in ion channels, known as channelopathies, we are advancing – both independently and with our collaborators – a novel product pipeline of neurology therapies to address areas of high unmet medical need, such as epilepsy, migraine and pain. 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 and Section 21E of the Securities Exchange Act of 1934 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 XEN496, XEN901, XEN1101 and our other product candidates, the potential efficacy, safety profile, future development plans, addressable market, regulatory success and commercial potential of XEN496, XEN901, XEN1101 and our other product candidates, the anticipated timing of IND, or IND equivalent, submissions and the initiation of future clinical trials for XEN496, XEN901, XEN1101 and our other product candidates, the efficacy of our clinical trial designs, our ability to successfully develop and achieve milestones in the XEN496, XEN901, XEN1101 and other development programs, the potential to advance certain of our product candidates directly into a Phase 2 or later clinical trial, the anticipated benefits of the unique mechanisms of action of XEN901 and XEN1101, the design of our clinical trials and anticipated enrollment, the potential for XEN1101 to support once daily dosing, the potential for XEN901 to support once or twice daily dosing, the progress and potential of our other ongoing development programs, 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: 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 not permit certain of our product candidates to advance directly into a Phase 2 or later clinical trial; the impact of competition; 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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