# Xenon Expands Ion Channel Neurology Pipeline with Addition of XEN496, a "Phase 3 Ready" Potassium Channel Modulator for the Treatment of Epilepsy

September 6, 2018

***Single, Pivotal Phase 3 Clinical Trial in Approximately 20 KCNQ2-EE Patients Expected to be Initiated in Mid-2019***

***Conference Call Today at 8:00 am ET***

***Xenon to Webcast Update on Epilepsy Pipeline from Biocentury NewsMakers Conference on September 7, 2018***

BURNABY, British Columbia, Sept. 06, 2018 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq:XENE), a clinical stage, neurology-focused biopharmaceutical company, today reported the expansion of its ion channel product pipeline with XEN496 (active ingredient ezogabine), a Kv7 potassium channel modulator for the potential treatment of epilepsy. Based on feedback from the U.S. Food and Drug Administration (FDA), Xenon anticipates initiating a single, pivotal Phase 3 clinical trial in approximately mid-2019 examining XEN496's efficacy as a precision medicine treatment of KCNQ2 epileptic encephalopathy (KCNQ2-EE) or EIEE7, which is a rare, severe, pediatric epilepsy caused by loss-of-function missense mutations in the KCNQ2 gene that encodes for the Kv7.2 channel. Published case reports where physicians have used ezogabine in infants and young children with KCNQ2-EE suggest that XEN496 may be efficacious in this often hard-to-treat patient population.

Ezogabine, also known as retigabine, is the only anti-epileptic drug previously approved by the FDA with a mechanism of action that potentiates Kv7-mediated potassium current. Ezogabine was originally approved by the FDA in June 2011 as an adjunctive treatment for adults with focal seizures with or without secondary generalization. GlaxoSmithKline (GSK) marketed ezogabine in various jurisdictions – as Potiga® in the U.S. and Trobalt™ in Europe – but withdrew the drug from the market worldwide in June 2017 citing commercial reasons.

Dr. Simon Pimstone, Xenon's Chief Executive Officer, said, "We have done an immense amount of diligence leading up to the addition of XEN496 to our novel and robust pipeline of ion-channel, anti-epileptic drugs. Based on feedback from key opinion leaders, advocacy groups, pre-existing literature, and promising data generated to date, we believe there is tremendous support for us to vigorously pursue the development and commercialization of XEN496 in order to reach the pediatric KCNQ2-EE patient population as rapidly as possible."

Dr. Pimstone added, "We have already completed a number of critical steps to expedite our plans for XEN496. We have obtained a right of reference authorization from GSK so that the FDA can reference GSK's regulatory filings to support Xenon's own regulatory submissions, and we have also received orphan drug designation (ODD) from the FDA for XEN496 as a treatment of KCNQ2-EE. Additionally, our completed pre-IND interactions with the FDA, supported by the KCNQ2 Cure Alliance, key opinion leaders and parents of children with KCNQ2-EE, have been very positive and we believe they indicate support for a small, single, pivotal Phase 3 clinical trial in approximately 20 pediatric patients to support registration. Our ongoing work includes final pediatric formulation development in order to start the XEN496 Phase 3 clinical trial in approximately mid-2019."

Jim Johnson, President, KCNQ2 Cure Alliance, stated, "To date, no drug has been specifically studied in clinical trials and approved for the treatment of KCNQ2 epileptic encephalopathy. There is a substantial unmet medical need for new therapies, especially those that target the underlying genetic cause of the seizures and cognitive decline observed in children with KCNQ2-EE. We are excited by Xenon's announcement today outlining plans to develop XEN496 and their commitment to studying this drug in KCNQ2-EE. The KCNQ2 Cure Alliance is striving to identify and support the development of new and better treatments, and our hope is that XEN496 could represent a genetically targeted treatment that improves the lives of children living with this debilitating disease."

As requested by Xenon, GSK authorized the FDA to refer to the information contained in GSK's regulatory submissions for the purpose of the FDA's review of Xenon's regulatory filings. After consulting with clinical experts and patient advocacy groups, Xenon submitted a pre-IND briefing package to the FDA that outlined the proposed clinical development plans for XEN496. In response, the FDA indicated that it was acceptable to study XEN496 in infants and children up to 4 years old, and that a single pivotal trial in approximately 20 patients may be considered adequate in order to demonstrate XEN496's efficacy in KCNQ2-EE. Recently, Xenon received ODD from the FDA for ezogabine as a treatment of KCNQ2-EE.

Xenon has formally established a steering committee made up of key opinion leaders in the epilepsy field to help guide the clinical development of XEN496. With input from this steering committee on the proposed trial design, dosing, and endpoints, the protocol development for the XEN496 Phase 3 clinical trial is currently underway. Xenon is working on a pediatric-specific formulation for XEN496 that may also address certain pigmentation issues associated with ezogabine, and it is anticipated that the Phase 3 clinical trial examining XEN496's efficacy as a treatment of KCNQ2-EE will be initiated in approximately mid-2019. Additional details regarding the proposed clinical development of XEN496 are anticipated over the coming months.

There is strong human genetic validation and pharmacologic evidence, including published case studies that support the use of XEN496 as a potential treatment for KCNQ2-EE. The KCNQ2 gene encodes for the Kv7.2 voltage-gated potassium channel. Loss-of-function missense mutations in KCNQ2 can cause KCNQ2-EE, which is characterized in general, by multiple, daily, treatment-resistant seizures often presenting within the first week of life. XEN496 may have a greater potential to improve long term outcomes in KCNQ2-EE, as ezogabine enhances transmembrane potassium currents mediated by the Kv7.2/7.3 channels, thus potentially reversing the underlying genetic abnormality of KCNQ2-EE. By activating Kv7.2/7.3 channels, it is expected that XEN496 should stabilize the resting membrane potential and reduce brain excitability and may have the potential to improve brain function and cognitive development, in addition to decreasing seizures. In one previously published case report of 11 patients (Millichap 2016), ezogabine was associated with improvement in seizures and/or development in three of the four infants treated before six months of age, and two of the seven treated later. No serious adverse effects were observed in that study. Another study that included a review of medical records and structured interviews with families of eight children with KCNQ2-EE who had previously been prescribed ezogabine (Olson 2017), also suggested that ezogabine was effective and tolerable. Sustained improvement in seizure frequency was observed in five of the six patients with at least weekly seizures, along with improvements in development or cognition in all eight patients. The only adverse event reported was urinary retention in 3 patients and overall, ezogabine was well tolerated.

**About KCNQ2-EE**

KCNQ2 epileptic encephalopathy (KCNQ2-EE), otherwise known as EIEE7, is a rare, severe neurodevelopmental disorder with a significant seizure burden and profound developmental impairment. KCNQ2-EE is uniquely characterized by multiple, daily, refractory seizures presenting within the first week of life with a prominent tonic component and autonomic signs. Seizures are often accompanied by clonic jerking or complex motor behavior. The electroencephalogram (EEG) at onset of the disease shows a burst suppression pattern later evolving into multifocal epileptiform activity. The infants usually develop a severe to profound intellectual disability with axial hypotonia which can be accompanied by limb spasticity. The seizure activity typically decreases with age with patients often becoming seizure free or experiencing more minor seizure burden by 3 to 5 years of age; however, thereafter seizures can reoccur in clusters. The intellectual disability and other co-morbidities are not reversed or improved with age and patients generally require life-long care. Patients are often non-verbal and some children may also have autistic features. Seizure-related bradycardia and oxygen desaturation with cyanosis have been observed, and are thought to contribute to the significant risk of Sudden Unexpected Death in Epilepsy (SUDEP) in these children. KCNQ2-EE is rare, representing around 10% of patients with epileptic encephalopathy with onset in the first three months of life; however, the incidence of KCNQ2-EE is approximately 2.8/100,000 live births, which is roughly half the number of births of Dravet Syndrome, the most common genetic cause of early infantile epileptic encephalopathy.

**Conference Call and Webcast Information**

Xenon will host a conference call and webcast today at 8:00 a.m. Eastern Time (5:00 a.m. Pacific Time) to provide a corporate update and discuss its newly added XEN496 program. To participate in the call, please dial (855) 779-9075, or (631) 485-4866 for international callers and provide conference ID number 8287437. 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.

In addition, Xenon will be presenting an update on its epilepsy pipeline during a company presentation at the Biocentury “NewsMakers in the Biotech Industry” Conference in New York, NY on September 7, 2018 at 9:30 am Eastern Time (6:30 am Pacific Time). The webcast will be broadcast live on the “Investors” section of Xenon's website and will be available for replay following the event.

**About Xenon Pharmaceuticals Inc.**

We are a clinical stage, neurology-focused 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 central nervous system, or CNS, 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 our expectations regarding the timing of and results from clinical trials and pre-clinical development activities, including those related to XEN1101, XEN901, XEN496, XEN007, and our other product candidates, the plans of our collaboration partners, the potential efficacy, safety profile, future development plans, addressable market, regulatory success and commercial potential of XEN1101, XEN901, XEN496, XEN007, and our other product candidates, the anticipated timing of IND, or IND equivalent, submissions and the initiation of future clinical trials for XEN1101, XEN901, XEN496, XEN007, and our other product candidates, the efficacy of our clinical trial designs, our ability to successfully develop and achieve milestones in the XEN1101, XEN901, XEN496, XEN007, and other development programs, the potential addition of new programs to our pipeline, the potential to advance XEN007 directly into a Phase 2 or later clinical trial, the potential to initiate a single, pivotal Phase 3 clinical trial in approximately 20 pediatric patients with XEN496, the design of our clinical trials and anticipated enrollment, the progress and potential of our other ongoing development programs, and the timing of our public presentation and potential publication 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; our assumptions regarding our planned expenditures and sufficiency of our cash to fund operations may be incorrect; our efforts to expand our current pipeline may not be successful; 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 XEN007, XEN496 or other product candidates to advance directly into a Phase 2 or later clinical trial; the impact of competition; the impact of expanded product development and clinical activities on operating expenses; 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.

“Xenon” and the Xenon logo are registered trademarks or trademarks of Xenon Pharmaceuticals Inc. in various jurisdictions. All other trademarks belong to their respective owner.

**Xenon Investor/Media Contact**:
Jodi Regts
Phone: 778.999.5634
Email: investors@xenon-pharma.com

XENON

Xenon Pharmaceuticals Inc.