Xenon Showcases New Long-Term Azetukalner Data from X-TOLE OLE Study in FOS at AES 2024

December 6, 2024

– OLE data shows sustained monthly reduction in seizure frequency, impressive seizure freedom rates, and consistent AE safety profile suggesting long-term efficacy and tolerability of azetukalner

– Approximately one in three patients on drug for at least 36 months achieved seizure freedom for a period of one year or longer

– Sustained monthly reductions in seizure frequency maintained at 85% at OLE study month 36

– Patient-reported survey data and literature review illustrate significant mental health and comorbidity burdens of focal onset seizures highlighting areas of unmet need for people living with epilepsy

– New pre-clinical data shows Nav1.1 potentiator provides protection against spontaneous seizures and SUDEP in pre-clinical Dravet model

VANCOUVER, British Columbia and BOSTON, Dec. 06, 2024 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq: XENE), a neuroscience-focused biopharmaceutical company dedicated to discovering, developing, and delivering life-changing therapeutics for patients in need, today announced new compelling long-term data from its ongoing X-TOLE open-label extension (OLE) study of azetukalner in patients with focal onset seizures (FOS) presented at the American Epilepsy Society Annual Meeting (AES 2024) taking place December 6-10, 2024 at the Los Angeles Convention Center in Los Angeles, CA.

"We are excited for this opportunity to engage with the broad epilepsy community at AES 2024 and share new long-term azetukalner data from our ongoing X-TOLE open-label extension study showing compelling evidence of sustained seizure reduction and seizure freedom rates," stated Dr. Christopher Kenney, Chief Medical Officer of Xenon. "Approximately one-third of patients who have been on azetukalner for at least 36 months achieved 100% seizure reduction, or seizure freedom, for a period of one year or longer. This is a meaningful metric for epileptologists who tell us that seizure freedom translates directly into improved quality of life for people living with epilepsy. Further, we continue to see an impressive, sustained monthly reduction in seizure frequency – approximately 85% at month 36 – while importantly maintaining a consistent safety profile that suggests azetukalner continues to be generally well-tolerated."

Dr. Kenney added, "There remains a substantial need for new, efficacious and well-tolerated epilepsy therapies, especially for those patients who continue to experience the debilitating impacts of focal seizures even while taking multiple anti-seizure medications. As we continue to build upon the foundation of strong X-TOLE results, amass a growing amount of supportive data from the ongoing open-label extension study, and drive towards Phase 3 completion, we believe that azetukalner could be paradigm-shifting in the treatment of epilepsy in the future."

Poster Presentation #2.361: *Long-term Safety and Efficacy of Azetukalner, a Novel, Potent Kv7 Potassium Channel Opener in Adults With Focal Epilepsy: Update From the Ongoing 7-year Open-Label Extension of X-TOLE*

The results presented at AES 2024 are interim data from the X-TOLE OLE in which participants received open-label azetukalner at a dose of 20 mg once daily (QD) with food.

- **Sustained reductions in seizure frequency:** For ongoing OLE patients, monthly median percent change (MPC) reductions in FOS frequency ranged from 61%-82% during month 1 to OLE study month 24 and were maintained at 85% at OLE study month 36. Patients who were receiving 1 to 2 anti-seizure medications (ASMs) at baseline experienced higher monthly MPC reductions in FOS frequency from baseline at OLE study month 36 (100% seizure reduction, n=67), compared to those receiving 3 ASMs (80.6% seizure reduction, n=80).
- **Achieving seizure freedom:** For those participants who were treated for >36 months in the OLE, 32.7% (48/147) achieved seizure freedom for a period of at least 12 months.
- **Consistent tolerability and safety profile**: Azetukalner continues to be generally well-tolerated in the OLE, with AEs consistent with prior results in the double-blind period and other ASMs; no new safety signals were identified.
- **Long-term retention:** A total of 182 participants were treated in the OLE for ≥12 months, 165 participants were treated for ≥24 months, and 143 participants were treated for ≥36 months at the time of the analysis cutoff (October 7, 2024). Retention rates with azetukalner at 12, 24, and 36 months into the OLE study period were 66%, 60%, and 52%, respectively.

"With over 600 patient-years of azetukalner exposure in people living with epilepsy – and some patients now on drug for more than 5 years – these latest long-term OLE results further validate our substantial clinical experience with azetukalner and reinforce

our belief that azetukalner represents a potentially best-in-class anti-seizure medication," stated Ian Mortimer, President and Chief Executive Officer of Xenon. "In addition to the interim long-term OLE data, we will present important results from a patient-survey and a literature review study looking at the impacts of the mental health burden and comorbidities of focal onset seizures. We will also highlight new data from our Nav1.1 potentiator program that showed protection against spontaneous seizures and SUDEP in a pre-clinical model, suggesting that targeting Nav1.1 could potentially address the underlying cause and symptoms of Dravet Syndrome," added Mr. Mortimer.

Poster Presentation #2.347: *Is the Mental Health Burden of Epilepsy Under-Recognized in Patients Reporting Focal Onset Seizures? A Patient-Reported Outcomes Study*

- Patients with epilepsy reporting FOS experience considerable mental health burden in addition to their recurring seizure burden. Most patients experienced ≥3 non-seizure symptoms despite ongoing treatment with existing anti-seizure medications, with most experiencing mood issues (e.g., depression, anxiety) that ranged from moderate to severe.
- The high positive screening rates for depression and anxiety, in contrast to lower self-reported physician-diagnosed depression and anxiety, suggest mental health burden may be under-recognized in patients with epilepsy reporting FOS.

Poster Presentation #2.338: *A Targeted Literature Review of Comorbidity Burden in Focal Onset Seizures*

- Patients with FOS and comorbid conditions experience greater disease burden compared to those without comorbidities, highlighting an area of unmet need in this population.
- Enhanced understanding of the association between comorbidities, particularly mental health comorbidities like depression and the burden of FOS may enable personalized treatment and help in improving patient outcomes.

Poster Presentation #3.389: *Nav1.1 Potentiators Modulate Brain Rhythms Measured Through Quantitative Electrocorticography (qECoG) in a Dravet Mouse Model*

- These data suggest *Scn1a*$^{+/-}$ mouse brain activity is differentiated from that in wild-type littermates. XPC-418, a Nav1.1 potentiator, altered brain activity in *Scn1a*$^{+/-}$ mice, making the phenotype more similar to that of wild-type animals, and also changed brain activity in wild-type mice in a dose- and time-dependent manner.
- These pre-clinical data indicate that Nav1.1 potentiation could normalize the power spectrum phenotype of Dravet mice to the wild-type phenotype.

Poster Presentation #3.395: *Selective Potentiation of Nav1.1 Channels in Dravet Mice Restores Interneuron Function and Improves Motor Function*

- Acute dosing of XPC-837 – an orally available, small molecule, CNS-penetrant, highly selective Nav1.1 potentiator – suppressed induced seizures in the 6Hz assay and improved motor performance in the Rotarod assay, supporting the potential for improvements in Dravet patient motor function. Chronic dosing over 14 days with XPC-837 in chow suppressed spontaneous seizures, prevented sudden unexpected death in epilepsy (SUDEP) and increased long-term potentiation, a potential cellular correlate of learning and memory.
- These pre-clinical data suggest that XPC-837 could represent a novel, mechanistically differentiated, orally available compound with the potential to provide an improved therapeutic profile for the overarching treatment of Dravet Syndrome.

Scientific Exhibit

Xenon is hosting a Scientific Exhibit to provide an overview of its clinical and research programs on Sunday, December 8, 2024 from 2 pm to 5 pm PT in Room 406A on level 2. In addition to the posters noted above, the exhibit will provide information related to the azetukalner Phase 3 epilepsy program, including its ongoing clinical trials in focal onset seizures and primary generalized tonic-clonic seizures. The exhibit will also feature the topline results from the Phase 2 X-NOVA clinical trial that evaluated azetukalner in major depressive disorder.

Exhibit Hall

In addition to Booth #1721 in the Exhibit Hall, Xenon is hosting a dedicated Mindfulness Zone (#1827) to rest, recharge, and learn more about the mental health burden associated with epilepsy. As part of Xenon's commitment to raising awareness about mental health, visitors are invited to join the cause with donations going to the Epilepsy Foundation of America to support comprehensive mental health programming, which strives to ensure that all individuals living with epilepsy and seizure disorders have access to quality, affordable mental health care. The Exhibit Hall will open on Saturday, December 7 at 12 pm PT and close on Monday, December 9 at 2 pm PT.

About Xenon Pharmaceuticals Inc.

Xenon Pharmaceuticals (Nasdaq: XENE) is a neuroscience-focused biopharmaceutical company dedicated to discovering, developing, and delivering life-changing therapeutics. We are advancing an ion channel product portfolio to address areas of high unmet medical need, including epilepsy and depression. Azetukalner, a novel, highly potent, selective Kv7 potassium channel opener, represents the most advanced, clinically validated potassium channel modulator in late-stage clinical development for multiple indications. 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 potential results from clinical trials; the potential efficacy, safety profile, future development plans in current and anticipated indications, addressable market, regulatory success and commercial potential of our and our partners' product candidates; the efficacy of our clinical trial designs; our ability to successfully develop and achieve milestones in our azetukalner and other pipeline and development programs; and our ability to successfully develop and obtain regulatory approval of azetukalner and our other product candidates. 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; promising results from pre-clinical development activities or early clinical trial results may not be replicated in later clinical trials; 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, including azetukalner, 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; the impact of market, industry, and regulatory conditions on clinical trial enrollment; the impact of competition; the impact of expanded product development and clinical activities on operating expenses; the impact of new or changing laws and regulations; as well as the other risks identified in our filings with the U.S. 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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