Xenon Announces Positive Topline Data from Phase 3 X-TOLE2 Study of Azetukalner in Focal Onset Seizures (FOS)

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- *X-TOLE2 met primary endpoint in both dose groups, including -53.2% median percent change (MPC) from baseline in monthly FOS frequency with 25 mg dose compared with -10.4% for placebo (p=0.000000000006)*
- *X-TOLE2 outperformed Phase 2b X-TOLE study, with a placebo-adjusted MPC of -42.7% in 25 mg group in X-TOLE2 compared to -34.6% in 25 mg group in X-TOLE*
- *Azetukalner was generally well-tolerated with a safety profile consistent with X-TOLE study*
- *Xenon anticipates submitting New Drug Application for azetukalner in FOS to the U.S. FDA in Q3 2026*
- *X-TOLE2 data to be featured in Late Breaking Science oral presentation at AAN Annual Meeting in April*
- *Company to host conference call and webcast today at 8:00 am ET*

VANCOUVER, British Columbia and BOSTON, MA, March 09, 2026 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq: XENE), a neuroscience-focused biopharmaceutical company dedicated to drug discovery, clinical development and commercialization of life-changing therapeutics for patients in need, today announced positive topline results from the Phase 3 X-TOLE2 study of azetukalner in focal onset seizures (FOS). Azetukalner is a novel, potent, K_V7 potassium channel opener currently in clinical development for epilepsy and depression.

The study met its primary endpoint of MPC in monthly FOS frequency from baseline to week 12 in both the 25 mg and 15 mg azetukalner dose groups compared to placebo [MPC of -53.2% (p=0.000000000006), -34.5% (p=0.00007) and -10.4%, respectively]. The placebo-adjusted MPC in the 25 mg group was -42.7%, outperforming the previously completed Phase 2b X-TOLE study, which demonstrated a -34.6% placebo-adjusted MPC in the 25 mg dose group over 8 weeks (-52.8% in the 25 mg group and -18.2% in the placebo group). Azetukalner also demonstrated a safety and tolerability profile consistent with prior studies. Xenon plans to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for the treatment of focal onset seizures in the third quarter of 2026. If approved, azetukalner would be the only K_V7 potassium channel opener available for the treatment of epilepsy.

“We are very happy to announce these data for azetukalner, which exceeded expectations and, to our knowledge, show the highest placebo-adjusted efficacy ever observed in a pivotal epilepsy study. The magnitude of effect in X-TOLE2 and favorable safety profile, along with its differentiated K_V7 mechanism of action and ease-of-use attributes, give us great confidence in azetukalner’s potential to become a preferred medication for patients living with uncontrolled seizures,” said Ian Mortimer, President and Chief Executive Officer of Xenon. “With a strong body of clinical evidence from two large placebo-controlled trials and more than 800 patient-years of exposure data, we are focusing next on submitting our new drug application to the FDA later this year, as well as advancing our commercial-readiness activities in anticipation of our first commercial launch.”

“Despite a large number of approved epilepsy treatments, there are only a handful of distinct mechanisms of action available, and the data from X-TOLE2 reinforce the value that azetukalner and its K_V7 mechanism may bring to the treatment armamentarium for focal seizures,” said Jacqueline A. French, MD, Professor in the Department of Neurology at NYU Langone Health, Co-director of Epilepsy Clinical Trials at NYU Langone's Comprehensive Epilepsy Center, Founder/Director of the Epilepsy Study Consortium, and Chair of the Steering Committee for X-TOLE2. “The data also continue to support a differentiated clinical profile for azetukalner relative to other antiseizure medications, including no need for titration, once-daily dosing, and no meaningful drug-drug interactions. I am pleased to see another successful pivotal trial for azetukalner that exceeds the strong X-TOLE data and look forward to this potential new medicine becoming available to more patients in the future.”

Study Design and Participant Disposition

The X-TOLE2 clinical trial (NCT05614063) was a randomized, double-blind, placebo-controlled, multicenter Phase 3 study evaluating the efficacy, safety, and tolerability of azetukalner, administered as an oral, adjunctive therapy once-daily with food in adult patients with FOS. The study randomized participants in a blinded manner to either azetukalner 25 mg, 15 mg, or placebo, and included a total of 380 randomized participants, with 374 participants in the safety and modified intent-to-treat (mITT) population for the safety and efficacy analyses. Participants had highly treatment-resistant epilepsy, with a median of five prior ASMs, a baseline seizure frequency of 12.75 per month, and 51.3% using three concomitant ASMs. Of the 332 participants who completed the double-blind period, 322 entered the open-label extension study.

Additional Study Results

In addition to meeting the primary endpoint of MPC in monthly FOS frequency, the study also met the key secondary endpoint of Responder Rate 50 (RR50), with 54.8% in the 25 mg group and 37.6% in the 15 mg group experiencing at least a 50% reduction in monthly FOS frequency from baseline, compared with 20.8% in the placebo group (p=0.00000008 and p=0.003 for 25 mg and 15 mg groups, respectively).

	Azetukalner 25 mg (n=124)	**Azetukalner 15 mg (n=125)**	**Placebo (n=125)**
Primary Endpoint: Median percent change (MPC) in monthly (28 days) FOS frequency from baseline to Week 12	-53.2% (p=0.000000000006)	-34.5% (p=0.00007)	-10.4%
Key Secondary Endpoint: Proportion of participants experiencing ≥50% reduction in monthly (28 days) FOS frequency from baseline to Week 12 (RR50)	54.8% (p=0.00000008)	37.6% (p=0.003)	20.8%

The safety and tolerability profile of azetukalner remains consistent with the previously disclosed data from the X-TOLE study. The most common treatment-emergent adverse events (TEAEs) across both azetukalner dose groups were dizziness (20.5%), headache (8.8%), somnolence (8.8%), and fatigue (7.6%) as compared to the placebo group, which reported dizziness (3.2%), headache (6.4%), somnolence (7.2%), and fatigue (6.4%). 14.5% of participants in the 25 mg group, 4.8% in the 15 mg group, and 3.2% in the placebo group had a TEAE leading to treatment discontinuation. The incidence of serious TEAEs was low and similar across treatment groups, with 5.6% in the 25 mg group, 3.2% in the 15 mg group, and 2.4% in the placebo group experiencing a serious TEAE.

“Epilepsy is one of the most common neurological diseases, and foundational antiseizure medications do not provide sufficient seizure control for up to 50% of patients, so we are very optimistic about the opportunity for azetukalner to meaningfully shift the epilepsy treatment paradigm,” said Chris Kenney, MD, Chief Medical Officer of Xenon. “We are grateful to the epilepsy community for their close partnership on azetukalner’s clinical development plan over the years. In particular, we wish to extend our appreciation to the patients, families, investigators, and clinical trial staff who participated in X-TOLE2. With their support, we believe we were able to execute a gold-standard clinical trial program for epilepsy and deliver a comprehensive and important dataset to support this potential new therapeutic option.”

Upcoming Congress Presentation

The X-TOLE2 efficacy and safety results will be featured as a Late Breaking Science oral presentation on Sunday, April 19th, at the American Academy of Neurology (AAN) Annual Meeting, taking place in Chicago, Illinois.

Conference Call Information

Xenon will host a conference call and webcast today at 8:00 am Eastern Time (5:00 am Pacific Time) to discuss the X-TOLE2 topline results. A listen-only webcast can be accessed on the Investors section of the Xenon website, with a replay available following the event. Participants can access the conference call by dialing (800) 715-9871 or (646) 307-1963 for international callers and referencing conference ID 7885306.

About Azetukalner

Azetukalner is a novel, potent K_V7 potassium channel opener currently in Phase 3 clinical trials for the treatment of epilepsy, major depressive disorder (MDD) and bipolar depression (BPD). It represents the most advanced, clinically validated potassium channel modulator in late-stage clinical development. Azetukalner is designed to open potassium channels in the central nervous system, allowing potassium ions to flow and hyperpolarizing neurons. This process helps reduce excessive neuronal firing, which is a key contributor to several neurologic and psychiatric disorders. It is the only K_V7 potassium channel opener in development for multiple indications that is backed by long-term efficacy and safety data in epilepsy patients and proof-of-concept data in MDD patients.

About Epilepsy and Focal Onset Seizures

Epilepsy is a neurological condition characterized by abnormal electrical activity in the brain that leads to spontaneous, recurrent and unprovoked seizures. It is the fourth most common neurological condition and affects approximately three million adults in the U.S. Focal epilepsy is the most common form of epilepsy. It is characterized by recurrent seizures that originate in a specific area of the brain (i.e. “focal onset seizures”), leading to various motor, sensory, autonomic, or cognitive symptoms depending on the affected region.

Epilepsy is often managed with polytherapy – or concurrent use of multiple antiseizure medications (ASMs) – in an attempt to improve seizure control. However, despite a large number of available epilepsy treatments, up to half of people with focal epilepsy still live with uncontrolled seizures. Epilepsy treatment is further complicated by often burdensome drug interactions and lengthy titration and dose-adjustment periods. These challenges highlight the critical need for a new therapeutic approach.

About Xenon Pharmaceuticals Inc.

Xenon Pharmaceuticals (Nasdaq: XENE) is a neuroscience-focused biopharmaceutical company dedicated to drug discovery, clinical development and commercialization of life-changing therapeutics for patients in need. Xenon's lead molecule, azetukalner, is a novel, potent K_V7 potassium channel opener in Phase 3 clinical trials for the treatment of epilepsy, major depressive disorder (MDD) and bipolar depression (BPD). Xenon is also advancing an early-stage portfolio of multiple promising potassium and sodium channel modulators, including K_V7 and $Na_V1.7$ programs in Phase 1 development for the potential treatment of pain. Xenon has offices in Vancouver, British Columbia, and Boston, Massachusetts. For more information, visit www.xenon-pharma.com and follow us on LinkedIn and X.

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 studies; 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 study designs; our ability to successfully develop and achieve milestones in our azetukalner and other pipeline and development programs, including the anticipated filing of investigational new drug applications and NDAs; the timing and results of our interactions with regulators, including the timing of any NDA submission; our ability to successfully develop and obtain regulatory approval of azetukalner and our other product candidates; and anticipated timing of topline data readout from our clinical studies of azetukalner. 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 studies 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 study results may not be replicated in later clinical studies; 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 or completion of clinical studies; the impact of market, industry, and regulatory conditions on clinical study 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; the impact of unstable economic conditions in the general domestic and global economic markets; adverse conditions from geopolitical events; 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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