Xenon Presents Azetukalner Phase 3 X-TOLE2 Study Results and 48-Month Long-term Data in Focal Onset Seizures at 2026 AAN Annual Meeting

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- *Azetukalner data show significant reductions in seizure frequency across weekly, monthly and multi-year time points*
- *X-TOLE2 data featured in Late-breaking Science session show 53.2% reduction in monthly seizure frequency in 25 mg group vs. 10.4% for placebo and increasing rates of 100% seizure reduction over time during 12-week double-blind period*
- *Long-term data from the ongoing X-TOLE OLE study at 48 months show nearly 40% of participants achieving at least 12 months of seizure freedom and one in four participants achieving at least 24 months of seizure freedom*
- *Real-world data reinforce the value of anti-seizure medications that do not require titration to reduce stress and simplify focal seizure management for both patients and physicians*

VANCOUVER, British Columbia and BOSTON, MA, April 19, 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 presented positive data from the Phase 3 X-TOLE2 study highlighting the efficacy and safety of azetukalner in focal onset seizures (FOS) at the American Academy of Neurology (AAN) Annual Meeting, taking place April 18-22, 2026 in Chicago, Illinois. Xenon is also presenting data at the AAN meeting that reinforce the significant opportunity for azetukalner in epilepsy, including 48-month data from the ongoing X-TOLE open-label extension (OLE) study, as well as real-world data reinforcing the potential value that no-titration options like azetukalner would bring to epilepsy management. Azetukalner (AZK) is a novel, potent, K_V7 potassium channel opener currently in clinical development for epilepsy and depression.

“Our data at the 2026 AAN meeting highlight the potential of azetukalner to become a preferred medication for addressing uncontrolled seizures,” said Chris Kenney, MD, Chief Medical Officer of Xenon. “In X-TOLE2, azetukalner demonstrated the best placebo-adjusted efficacy ever observed in a pivotal FOS study, to our knowledge. These data are particularly striking considering nearly 60% of the patient population were taking or had already discontinued cenobamate and were experiencing a high seizure burden with a median of 13 seizures per month at baseline. Equally remarkable was the ability for some of these patients to gain complete seizure control, with increasing rates of 100% seizure reduction the longer patients were on therapy. This trend is reinforced by the long-term data from our X-TOLE OLE study, showing nearly 40% of patients treated for at least 48 months achieved at least 12 months of seizure freedom, which is the clinically defined timepoint for seizure freedom across the field.”

“Across the X-TOLE, X-TOLE OLE, and X-TOLE2 studies, we have observed robust efficacy as early as week 1, increasing seizure control through the double-blind and open-label periods, impressive seizure freedom over time, including the ability to regain extended periods of seizure freedom with azetukalner in the event of a breakthrough seizure, and a consistent and generally well-tolerated safety profile,” said Ian Mortimer, President and CEO of Xenon. “Taken together, this robust body of data underscores our belief that azetukalner has the potential to deliver much needed innovation for ASMs, with strong efficacy, a different mechanism that may enable rational polytherapy, and ease-of-use benefits like no titration, once-daily dosing, and no dose adjustments for other ASMs. We are working hard toward submitting our New Drug Application to the FDA in the third quarter of 2026, bringing azetukalner one step closer to reaching clinicians and patients.”

Clinical Data for Azetukalner (AZK) in Epilepsy

Oral & Poster Presentation #7 (LS1 – Late-breaking Science Session 1): ***Results from the Phase 3 X-TOLE2 Study Evaluating Azetukalner, a Novel, Potent K_V7 Channel Opener, in Adults with Focal Onset Seizures (FOS)***

X-TOLE2 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the clinical efficacy, safety, and tolerability of AZK as adjunctive treatment in adults with FOS over a 12-week double-blind period (DBP). Participants had highly treatment-resistant epilepsy, with a median baseline seizure frequency of 12.75 per month, a median of five prior anti-seizure medications (ASMs), and 51.3% using three concomitant ASMs. Approximately 40% of participants entering the study were taking concomitant cenobamate, while 19% had previously tried and discontinued cenobamate.

- **Early and significant reductions in seizure frequency (Median Percent Change in FOS):** Treatment with 25 mg or 15 mg AZK resulted in a statistically significant -53.2% or -34.5% Median Percent Change (MPC), respectively, from baseline through the DBP in monthly FOS, compared to a -10.4% MPC for placebo ($p<0.0001$ for both 25 and 15 mg vs. placebo). Dose-dependent MPC reductions in weekly FOS were observed from baseline to week 1, which were sustained through the DBP with both AZK doses.
- **Dose-dependent increase in 50%, 75%, and 90% Responder Rates:** There was a statistically significant, dose-dependent increase in the proportion of participants with a ≥50% reduction in monthly seizure frequency from

baseline through the DBP. Dose-dependent increases in the proportion of participants with a ≥75% and a ≥90% reduction in monthly seizure frequency were also observed.

- **Improvements in 100% Responder Rate observed over time:** A 100% reduction in monthly FOS frequency from baseline through the DBP was attained by a greater proportion of participants with AZK 25 mg than with placebo (6.5% vs. 0.8%, respectively; nominal p<0.05). A post hoc analysis showed that a greater proportion of participants achieved a 100% Responder Rate over time with AZK in the last eight, six and four weeks of the DBP (nominal p<0.05) as AZK reached steady-state levels.
    - Last 8 weeks: 25 mg: 10.5%, 15 mg: 5.6%, placebo: 2.4%
    - Last 6 weeks: 25 mg: 11.3%, 15 mg: 8.0%, placebo: 4.0%
    - Last 4 weeks: 25 mg: 13.7%, 15 mg: 12.8%, placebo: 4.0%
- **Consistent safety and tolerability profile with X-TOLE:** The most common treatment-emergent adverse events (TEAEs) across both AZK 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%). 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. No notable weight gain, severe allergic rashes, retinal pigment epithelium or macular abnormalities, or notable cardiovascular adverse events occurred during the DBP. These results are consistent with the Phase 2b X-TOLE safety and tolerability results.

Poster Presentation #10-001 (P11 – Poster Session 11): ***Azetukalner, a Novel, Potent K_V7 Channel Opener, in Adults with Focal Epilepsy: ≥48-Month Interim Analysis of the Ongoing 7-Year X-TOLE Open-Label Extension***

AZK demonstrated long-term efficacy and safety in the ≥48-month interim analysis of the X-TOLE OLE study, including continued reductions in seizure frequency and improvements in seizure freedom over time. X-TOLE is a completed Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study, with an ongoing seven-year OLE evaluating the efficacy, safety, and tolerability of 20 mg azetukalner as adjunctive treatment in adults with FOS.

- **Continued reductions in monthly FOS frequency (MPC) with longer AZK treatment:** Participants treated for ≥48 months (n=131) in the OLE had an MPC reduction in monthly FOS frequency of -69.8% at month one in the OLE, which further increased to -85.1% at month 12 and reached -90.9% at month 48.
- **Greater MPC reductions in less refractory participants:** Those receiving one or two ASMs at the beginning of the X-TOLE DBP (n=60) had greater MPC reductions in monthly FOS frequency than those receiving three ASMs (n=69) at month 48 (100% vs. 81.8% reduction in monthly FOS frequency, respectively).
- **Sustained periods of seizure freedom**: The clinically accepted definition of seizure freedom is no seizures for at least 12 months. Among the participants treated for ≥48 months in the OLE (n=131), seizure freedom for any ≥12-month consecutive duration was attained by 38.2% of participants. Seizure freedom for any ≥24-, ≥36-, and ≥48- month consecutive duration was attained by 25.2%, 19.8% and 10.7% of the participants respectively.
- **Consistent safety and tolerability:** As of data cut-off, the OLE has generated more than 775 patient-years of safety and exposure data. Long-term safety of AZK in the OLE was comparable with the safety observed in the X-TOLE DBP.

Real-World Data on ASM Titration

Poster Presentation #11-007 (P3 – Poster Session 3)*: Treatment Experiences with Anti-seizure Medications (ASMs): Patient–Clinician Perspectives on Titration Burden, Quality of Life, and No-Titration Options*

In a real-world analysis, patient and healthcare professional (HCP) perspectives suggest that ASM titration imposes a meaningful burden for both groups, with patients reporting challenges related to medication schedules, daily life and quality-of-life during titration periods, and physicians reporting challenges related to treatment complexity and cross-titration. When questioned on their perceptions of ASMs without titration, most patients noted that they either agree or strongly agree that initiating an ASM without needing to titrate to a stable dose would boost their confidence (90%), reduce anxiety (77%), and improve adherence (84%). Physicians noted that no-titration options would cause less stress and increase simplicity for both physicians and patients, as many patients are already on complex drug regimens. These findings suggest using ASMs that do not require titration may offer benefits and underscore the potential value of avoiding a titration period to reduce stress and simplify FOS management for both patients and physicians. They also suggest an opportunity to further simplify care and integrate the patient voice into decision-making.

More Information About Xenon's AAN Presentations

For more information about Xenon's presence at AAN 2026 and for the full list of presentations, including additional epilepsy real-world data and pre-clinical data for Xenon's $Na_V1.1$ program for Dravet syndrome, please visit this link. Posters will be available after the live presentations.

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 X-TOLE2

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.

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, selective 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.

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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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