AZETUKALNER IN EPILEPSY

Phase 3 trials evaluating azetukalner as an adjunctive treatment in focal onset seizures or primary generalized tonic-clonic seizures.

X-TOLE2™ X-TOLE3™ X-ACKT™

XENON®

Scan the QR code to learn about the Phase 3 trials for azetukalner.

MED-US-AZET-2500008

OUR PIPELINE

At Xenon we are focused on advancing our ion channel neuroscience-focused pipeline, including our clinical stage candidate azetukalner, with a particular focus on epilepsy and depression.

Scan the QR code to learn about our pipeline of drug candidates currently undergoing clinical and preclinical testing in a variety of disease indications. The safety and efficacy of these investigational drug candidates have not been fully evaluated, and they have not yet been approved for use by any regulatory authorities.

To inquire about becoming an investigator for X-TOLE2 or X-TOLE3, please contact **X-TOLE@xenon-pharma.com**.

To inquire about becoming an investigator for X-ACKT, please contact **X-ACKT@xenon-pharma.com**.

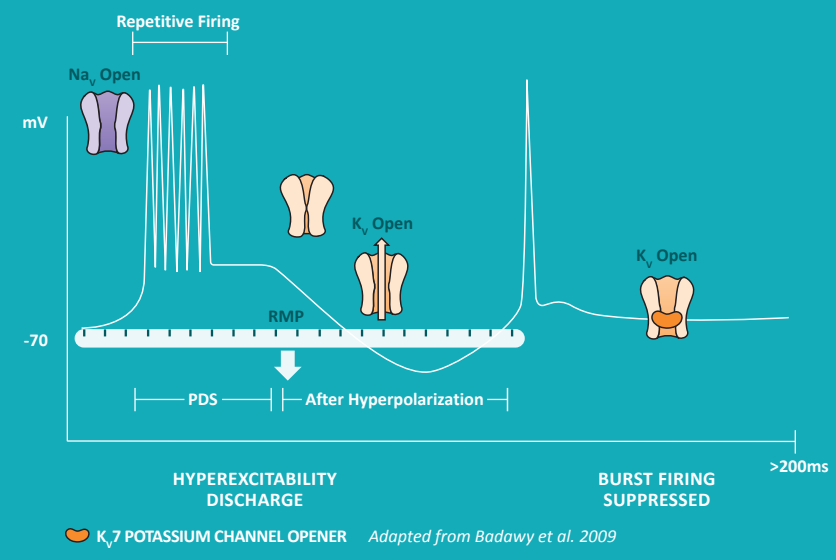
For other general questions, please contact **medicalaffairs@xenon-pharma.com**.

OVERVIEW OF AZETUKALNER

Azetukalner is a novel, potent K_V7 potassium channel opener being studied for the treatment of focal onset seizures (FOS) and primary generalized tonic-clonic seizures (PGTCS).

Potassium channels play an essential role in the control of neuronal excitability and represent a promising treatment target for epilepsy.

Azetukalner selectively potentiates the open state of KCNQ2/3 channels, which reduces the onset of rapid action potential spiking in neurons and favors a hyperpolarized resting state.



Adapted from Badawy et al. 2009

IN OUR PHASE 2B CLINICAL TRIAL FOR FOS (X-TOLE), AZETUKALNER WAS ADMINISTERED AS A ONCE-DAILY CAPSULE WITH FOOD WITH NO TITRATION.

Badawy RA, Harvey AS, Macdonell RA. Cortical hyperexcitability and epileptogenesis: understanding the mechanisms of epilepsy - part 1. *J Clin Neurosci.* 2009;16(3):355-365.

Porter RJ, Kenney C, Harden C, Sherrington R. The unmet need in epilepsy: the therapeutic potential of potassium channel modulators. Presented at: American Epilepsy Society 2021 Symposium. December 3, 2021; Chicago, IL.

Data on File. Xenon Pharmaceuticals Inc. Vancouver, British Columbia.

French JA, Porter RJ, Perucca E, et al. Efficacy and safety of XEN1101, a novel potassium channel opener, in adults with focal epilepsy a phase 2b randomized clinical trial. *JAMA Neurol.* 2023;80(11):1145-1154. doi:10.1001/jamaneurol.2023.3542

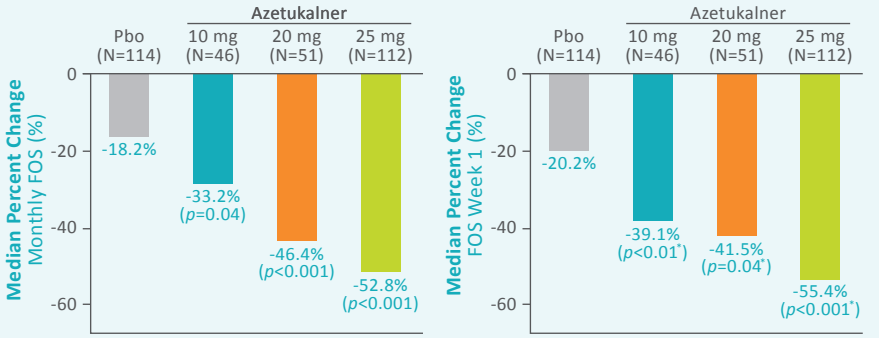
OUR COMPLETED PHASE 2B TRIAL FOR FOS

Phase 2b X-TOLE Study Design

X-TOLE is a completed Phase 2b randomized, double-blind, placebo-controlled, parallel group, dose-ranging, multicenter study with an optional ongoing 7-year open-label extension. X-TOLE evaluated clinical efficacy, safety, and tolerability of azetukalner administered with food as adjunctive treatment in adults with FOS who experienced ≥4 countable focal seizures per month, recorded on an eDiary during a planned 8-week baseline period, while receiving stable treatment with 1-3 anti-seizure medications (ASMs).

RESULTS OF THE PHASE 2B X-TOLE STUDY FOR FOS

X-TOLE met the primary and key secondary efficacy endpoints with azetukalner demonstrating a statistically significant reduction from baseline in monthly FOS frequency compared to placebo. Azetukalner was administered as a once-daily capsule with food with no titration.



*From a post hoc pairwise comparison.

There was a reduction in median monthly FOS frequency within 1 week for all doses compared with placebo (10 mg $p<0.01$; 20 mg $p=0.04$; 25 mg $p<0.001$ vs placebo from a post hoc pairwise comparison).

The most common (>10%) treatment-emergent adverse events (TEAEs) across all the azetukalner dose groups during the double-blind period (DBP) were dizziness (24.6%), somnolence (15.6%), and fatigue (10.9%).

Ongoing 7-Year Open-Label Extension (OLE)

During OLE study months 12-36, there was a sustained monthly reduction in seizure frequency (80%-87% MPC) from DBP baseline. Seizure freedom for any ≥12-month consecutive period was achieved in 18.2% of patients who entered the OLE (n=275) and 32.7% of patients who were treated in the OLE for ≥36 months (n=147).

As of October 2024, the safety profile of azetukalner 20 mg QD* was similar to that of the DBP. The most common (>10%) TEAEs during the OLE period were dizziness (23.3%), headache (17.5%), coronavirus infection (17.1%), somnolence (16.0%), fall (13.5%), weight increased (10.9%), and memory impairment (10.2%).

*Taken with food. Interim data cut October 7, 2024.

French JA, Porter RJ, Perucca E, et al. Efficacy and safety of XEN1101, a novel potassium channel opener, in adults with focal epilepsy a phase 2b randomized clinical trial. *JAMA Neurol*. 2023;80(11):1145-1154. doi:10.1001/jamaneurol.2023.3542

French JA, Porter RJ, Perucca E, et al. 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. Presented at American Epilepsy Society Annual Meeting; December 6-10, 2024; Los Angeles, CA.

Kenney C, French J, Porter R, et al. Rapid onset of efficacy of XEN1101, a novel potassium channel opener, in adults with focal epilepsy: results from a phase 2b study (X-TOLE). Presented at European Epilepsy Congress; July 9-13, 2022; Geneva, Switzerland.

X-TOLE2 & X-TOLE3 ENROLLING NOW

X-TOLE2 and X-TOLE3 were initiated based on data from the Phase 2b X-TOLE trial for azetukalner in FOS.

STUDY DESIGN

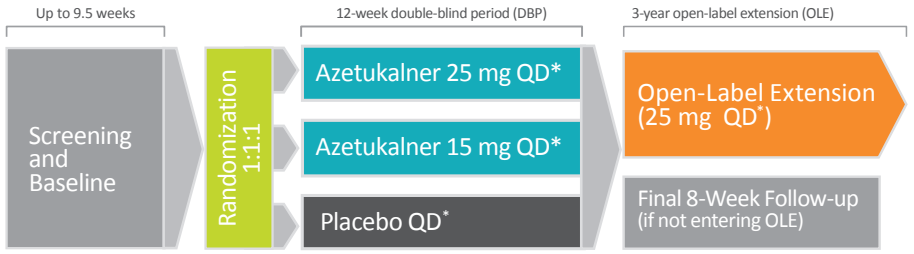
X-TOLE2 and X-TOLE3 are **identical** Phase 3, multicenter, randomized, double-blind, placebo-controlled trials designed to evaluate the clinical efficacy, safety, and tolerability of azetukalner as adjunctive treatment in adults aged ≥18 years diagnosed with FOS who are taking 1 to 3 ASMs.

Approximately 360 eligible participants will be randomized 1:1:1 (azetukalner 25 mg:15 mg: placebo, taken QD with food), per trial.

- **Screening/baseline period:** Up to 9.5-week duration to assess the frequency of seizures
- **Double-blind period (DBP):** 12-week duration, with no titration period
- **Follow-up period:** 8-week duration after the last dose of study drug for participants who do not complete the 12-week DBP or who complete the DBP but do not enter the open-label extension (OLE) study
- **OLE:** On completion of the DBP, eligible patients may enter an OLE study for up to 3 years

ASM, antiseizure medication; FOS, focal onset seizures.

X-TOLE 2 3™



*Administered as a once-daily capsule with food with no titration period.

Scan the QR code on the front cover to learn more about X-TOLE2 and X-TOLE3, and to find out how to enroll your patients or become a clinical trial site investigator.

Azetukalner is in Phase 3 clinical investigation and has not been approved by the U.S. FDA or other regulatory bodies.

NCT05614063: A Randomized Study of XEN1101 Versus Placebo in Focal-Onset Seizures (X-TOLE2). NIH U.S. National Library of Medicine ClinicalTrials.gov. Accessed July 8, 2024 https://clinicaltrials.gov/ct2/show/NCT05614063

NCT05716100: A Randomized Study of XEN1101 Versus Placebo in Focal-Onset Seizures (X-TOLE3). NIH U.S. National Library of Medicine ClinicalTrials.gov. Accessed July 8, 2024 https://clinicaltrials.gov/ct2/show/NCT05716100

Data on File. Xenon Pharmaceuticals Inc. Vancouver, British Columbia.

AZETUKALNER IN PGTCS

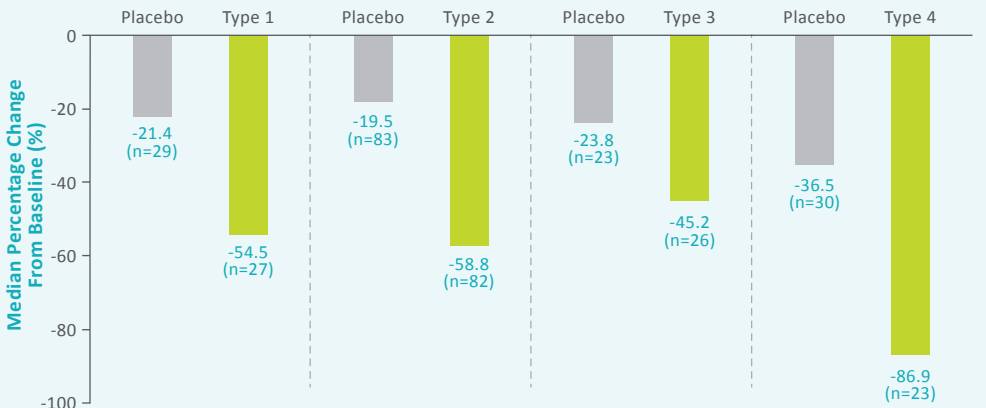
Azetukalner demonstrated anti-seizure activity in maximum electroshock seizure and pentylenetetrazole preclinical models, both shown to predict efficacy for primary generalized seizures.

In Phase 2b X-TOLE, azetukalner demonstrated seizure reduction across all focal seizure subtypes, including those that progressed to generalized seizures.

Phase 2B X-TOLE Study

Analysis of Seizure Reduction by Seizure Subtype

Azetukalner 25 mg QD*



Seizure Subtype

Marked seizure reduction at 25 mg across seizure subtypes

FOS Types

Type 1 Focal aware seizures with motor signs
Type 2 Focal seizures with impaired awareness with motor signs
Type 3 Focal seizures with impaired awareness with no motor signs
Type 4 Focal seizures progressing to bilateral tonic-clonic seizures

*All doses taken with food.

Gil-Nagel Rein A et al. A randomized, double-blind, placebo-controlled, phase 3 study to evaluate the safety and efficacy of XEN1101 as an adjunctive therapy in the treatment of primary generalized tonic-clonic seizures. Presented at International Epilepsy Congress. September 2–6, 2023; Dublin, Ireland.

Data on File. Xenon Pharmaceuticals Inc. Vancouver, British Columbia.

X-ACKT ENROLLING NOW

STUDY DESIGN

X-ACKT is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the pharmacokinetics, safety, and efficacy of azetukalner as adjunctive treatment in participants aged ≥12 years with a seizure frequency of ≥3 PGTCS during the last 8 weeks of the baseline period and taking 1 to 3 ASMs.

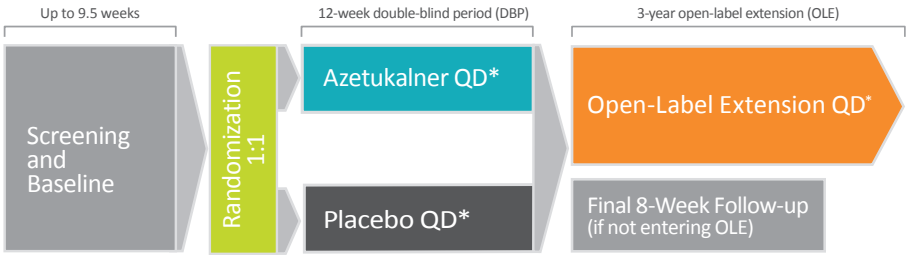
Approximately 160 eligible participants will be randomly assigned 1:1 to azetukalner or placebo, taken QD with food.*

- **Screening/baseline period:** Up to 9.5-week duration to assess the frequency of seizures
- **Double-blind period (DBP):** 12-week duration with no titration period
- **Follow-up period:** 8-week duration after the last dose of study drug for participants who do not complete the 12-week DBP or who complete the DBP but do not enter the open-label extension (OLE) study
- **OLE:** On completion of the DBP, eligible patients may enter an OLE study for up to 3 years

*Administered as a once-daily capsule with food with no titration period. Participants aged ≥12 years and <18 years will receive either azetukalner 15 mg, azetukalner 25 mg, or placebo; participants aged ≥18 years will receive either azetukalner 25 mg or placebo.

ASM, antiseizure medication; PGTCS, primary generalized tonic-clonic seizures.

X-ACKT™



*Administered as a once-daily capsule with food with no titration period. Participants aged ≥12 years and <18 years will receive either azetukalner 15 mg, azetukalner 25 mg, or placebo; participants aged ≥18 years will receive either azetukalner 25 mg or placebo. There is no placebo dose in the OLE.

Scan the QR code on the front cover to learn more about X-ACKT, and to find out how to enroll your patients or become a clinical trial site investigator.

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NCT05667142: A Study to Evaluate XEN1101 as Adjunctive Therapy in Primary Generalized Tonic-Clonic Seizures (X-ACKT). NIH. U.S. National Library of Medicine ClinicalTrials.gov. Accessed March 6, 2024. https://clinicaltrials.gov/ct2/show/NCT05667142

Data on File. Xenon Pharmaceuticals Inc. Vancouver, British Columbia.

ABOUT XENON

Study Sponsor for Phase 3 X-TOLE2 & X-TOLE3 trials in focal onset seizures (FOS) and Phase 3 X-ACKT trial in primary generalized tonic-clonic seizures (PGTCS).

We are a neuroscience-focused biopharmaceutical company committed to discovering, developing, and commercializing innovative therapeutics to improve the lives of people living with neurological and psychiatric disorders.

As a leader in small molecule, ion channel drug development, we are advancing a novel product pipeline to address areas of high unmet medical need, including epilepsy and depression.

XENON®