XEN1101 IN EPILEPSY

Phase 3 trials evaluating XEN1101 as an adjunctive treatment in focal onset seizures or primary generalized tonic-clonic seizures.

X-TOLE 2/3™

X-ACKT™

XENON®

Scan the QR code to learn about the Phase 3 trials for XEN1101.

OUR PIPELINE

At Xenon we are focused on advancing our ion channel neurology pipeline, including our clinical stage candidate XEN1101, with a particular focus on epilepsy and depression.

	Compound	Indication	Pre-clinical	Phase 1	Phase 2	Phase 3
Potassium Channel Openers	XEN1101	Focal Onset Seizures (FOS) *X-TOLE2*				
		Focal Onset Seizures (FOS) *X-TOLE3*				
		Primary Generalized Tonic-Clonic Seizures (PGTCS) *X-ACKT*				
		Major Depressive Disorder (MDD) *X-NOVA*				
		Major Depressive Disorder (MDD)* *Mount Sinai*				
Other Ion Channel Modulators		K_V7 (Potassium Channel) Openers				
		Na_V 1.1 (Sodium Channel) Openers				
		Na_V 1.7 (Sodium Channel) Inhibitors				
Partnered Programs						
Sodium Channel Inhibitor	NBI-921352	Orphan Pediatric Epilepsy (SCN8A-DEE) *Neurocrine*				

*Investigator-Sponsored Phase 2 Proof-of-Concept Study

Products mentioned are investigational and have not been approved by the U.S. FDA or other regulatory bodies.

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**.

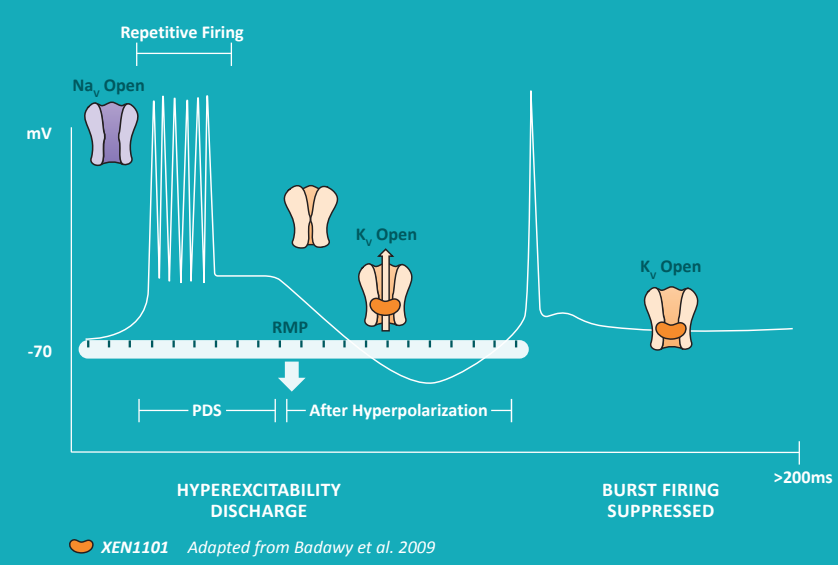
For other general questions, please contact **medicalaffairs@xenon-pharma.com**.

OVERVIEW OF XEN1101

XEN1101 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 a major role in the control of neuronal excitability and represent a promising treatment target for epilepsy.

XEN1101 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.



IN OUR PHASE 2B CLINICAL TRIAL FOR FOS (X-TOLE), XEN1101 WAS ADMINISTERED AS A ONCE-DAILY CAPSULE WITH FOOD WITH NO TITRATION REQUIRED.

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. American Epilepsy Society 2021 Symposium. December 3, 2021, Chicago, IL.

Xenon Pharmaceuticals Inc. Data on file.

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.

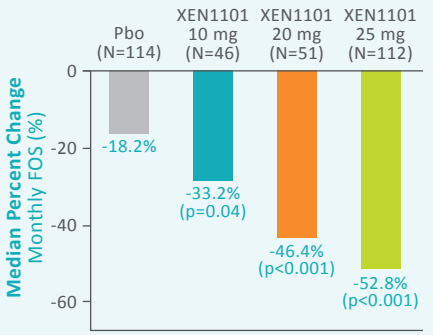
OUR COMPLETED PHASE 2B TRIAL FOR FOS

Phase 2b X-TOLE Study Design

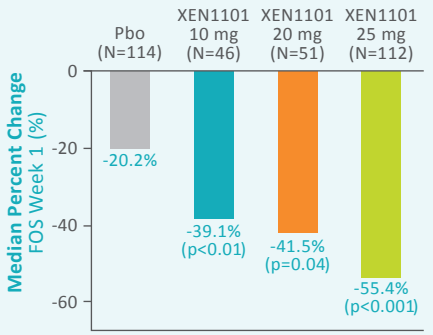
X-TOLE is a completed Phase 2b randomized, double-blind, placebo-controlled, parallel group, dose-ranging, multicenter study with an optional ongoing 7-year open-label extension. X-TOLE evaluated clinical efficacy, safety, and tolerability of XEN1101 administered with food as adjunctive treatment in 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 XEN1101 demonstrating a statistically significant reduction from baseline in monthly FOS frequency compared to placebo. XEN1101 was administered as a once-daily capsule with food with no titration required.



Overall Median Percent Change from Baseline in Monthly Focal Onset Seizure (FOS) Frequency in the Double-Blind Period



Median Percent Change from Baseline in Weekly Focal Onset Seizure (FOS) Frequency During Week 1 of the Double-Blind Period

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 XEN1101 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 12-24, there was a sustained monthly reduction in seizure frequency (79%-84% MPC) from DBP baseline. Seizure freedom for ≥3-month, ≥6-month, and ≥12-month consecutive durations was achieved in 37.5%, 22.2% and 14.9% of patients,* respectively.

As of September 2023, the safety profile of XEN1101 20 mg QD was similar to that of the DBP. The most common (>10%) TEAEs during the OLE period were dizziness (21.8%), coronavirus infection (15.3%), headache (15.3%), fall (12.7%), somnolence (12.7%), and memory impairment (10.9%).

*All patients who entered the OLE (n=275). Interim data cut September 5, 2023.

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 J, Porter R, Perucca E, et al. Interim Long-Term Safety and Efficacy of XEN1101, a Potent, Selective Potassium Channel Opener: Update From an Ongoing, Open-Label Extension of a Phase 2b Study (X-TOLE) in Adults with Focal Epilepsy. American Epilepsy Society Annual Meeting. December 1-5, 2023, Orlando, FL.

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). 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 XEN1101 in FOS.

STUDY DESIGN

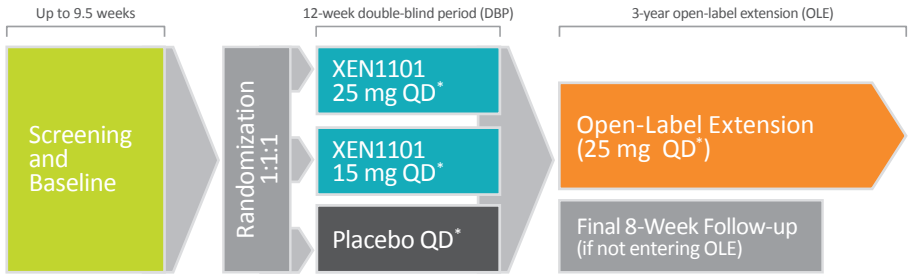
X-TOLE2 and X-TOLE3 are **identical** Phase 3, multicenter, randomized, double-blind, placebo-controlled trials designed to evaluate the clinical efficacy, safety, and tolerability of XEN1101 as adjunctive treatment in adults aged ≥18 years diagnosed with FOS who are taking 1 to 3 ASMs.

Approximately 360 eligible subjects will be randomized 1:1:1 (XEN1101 25 mg: 15 mg: placebo, taken QD with food) per trial.

- **Screening/baseline period:** Up to 9.5 weeks duration to assess the frequency of seizures
- **Double-blind period (DBP):** 12 weeks duration, with no titration period
- **Follow-up period:** 8 weeks duration after the last dose of study drug for subjects 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 required.

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.

XEN1101 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 October 19, 2023 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 October 19, 2023 https://clinicaltrials.gov/ct2/show/NCT05716100

XPF-010-301 X-TOLE 2 Clinical Trial Protocol v4.0. February 13, 2024.

XPF-010-302 X-TOLE 3 Clinical Trial Protocol v3.0. October 27, 2023.

XPF-010-304 X-TOLE 2/3 & X-ACKT OLE Clinical Trial Protocol v4.0 November 14, 2023.

XEN1101 IN PGTCS

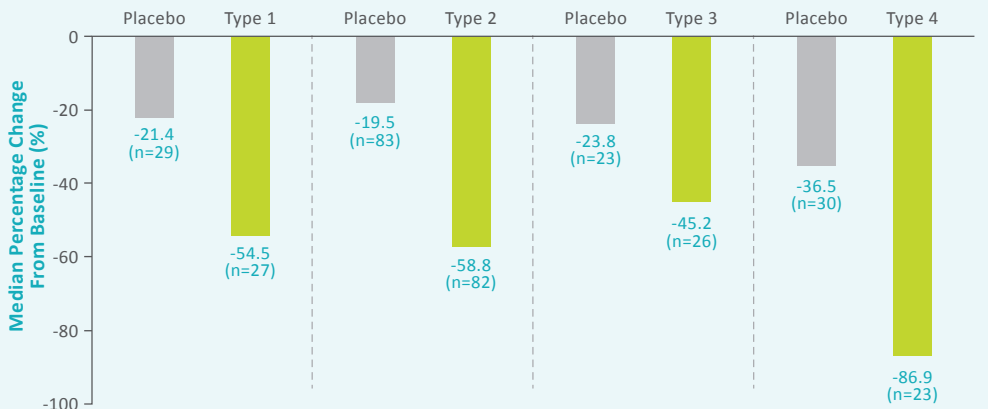
XEN1101 demonstrated anti-seizure activity in maximum electroshock seizure and pentylenetetrazole preclinical models, both shown to predict efficacy for primary generalized seizures.

In Phase 2b X-TOLE, XEN1101 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

XEN1101 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. Platform Session. International Epilepsy Congress. September 2–6, 2023, Dublin, Ireland.

Xenon Pharmaceuticals Inc. Data on file.

X-ACKT ENROLLING NOW

STUDY DESIGN

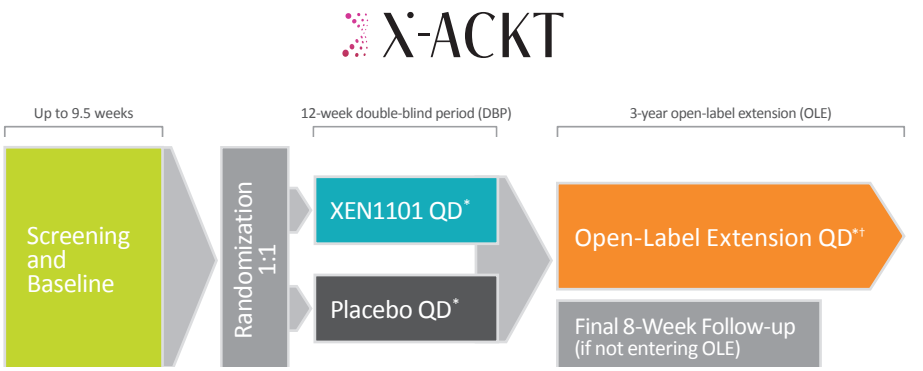
X-ACKT is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the pharmacokinetics, safety, and efficacy of XEN1101 as adjunctive treatment in subjects aged ≥12 years with a seizure frequency of ≥3 PGTCS during the last 8 weeks of the baseline period and taking 1 to 3 ASMs.

Approximately 160 eligible subjects will be randomly assigned 1:1 to XEN1101 or placebo, taken QD with food.*

- **Screening/baseline period:** Up to 9.5 weeks duration to assess the frequency of seizures
- **Double-blind period (DBP):** 12 weeks duration with no titration period
- **Follow-up period:** 8 weeks duration after the last dose of study drug for subjects 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 required. Subjects aged ≥12 years and <18 years will receive either XEN1101 15 mg, XEN1101 25 mg, or placebo; subjects aged ≥18 years will receive either XEN1101 25 mg or placebo.

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



*Administered as a once-daily capsule with food with no titration required. Subjects aged ≥12 years and <18 years will receive either XEN1101 15 mg, XEN1101 25 mg, or placebo; subjects aged ≥18 years will receive either XEN1101 25 mg or placebo.

†No placebo in 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.

XEN1101 is in Phase 3 clinical investigation and has not been approved by the U.S. FDA or other regulatory bodies.

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

XPF-010-303 X-ACKT Clinical Trial Protocol v4.0. December 04, 2023.

XPF-010-304 X-TOLE 2/3 & X-ACKT OLE Clinical Trial Protocol v4.0. November 14, 2023.

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

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