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.

	Compound	Indication	Pre-clinical	Phase 1	Phase 2	Phase 3
Potassium Channel Openers	XEN1101	Focal Onset Seizures (FOS) *X-TOLE2/3*				
		Primary Generalized Tonic-Clonic Seizures (PGTCS) *X-ACKT*				
		Major Depressive Disorder (MDD) *X-NOVA*				
		Major Depressive Disorder (MDD) *Mount Sinai**				
Ion Channel Modulators		Neurological Disorders				

Partnered Programs

Sodium Channel Modulators	NBI-921352	Orphan Pediatric Epilepsy (SCN8A-DEE) *Neurocrine*				

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

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**.

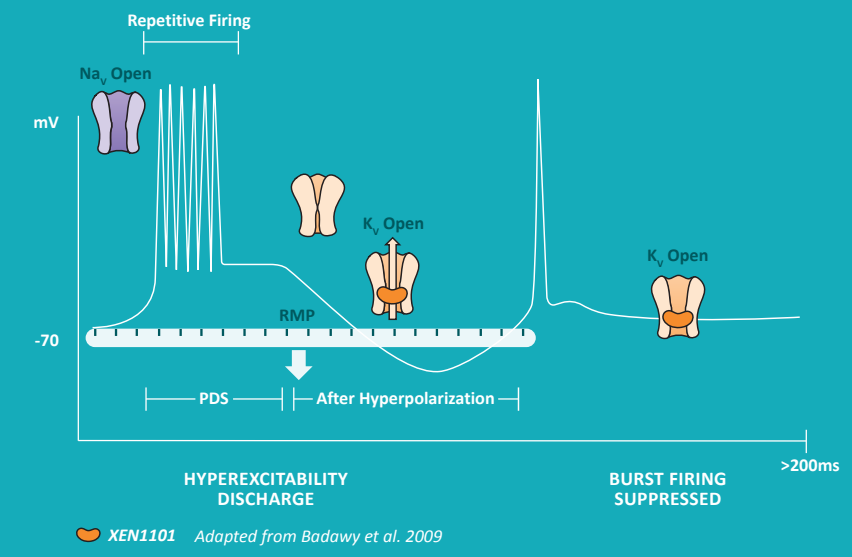
For other general questions, please contact **medicalaffairs@xenon-pharma.com**.

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 (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.* Published online October 9, 2023. doi:10.1001/jamaneurol.2023.3542.

Dean R, Lin S, Bankar G, et al. Preclinical *In Vitro* and *In Vivo* Comparison of the K_V7 Activator XEN1101 With Ezogabine. American Epilepsy Society 2020 Symposium. December 4-8, 2020, Seattle, WA.

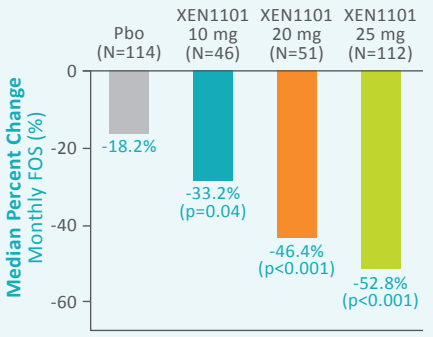
OUR COMPLETED PHASE 2B TRIAL FOR FOS

Phase 2b X-TOLE Study Design

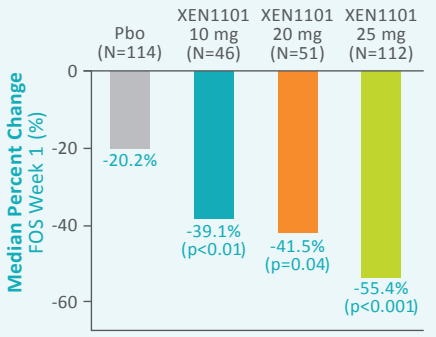
X-TOLE is a completed Phase 2b randomized, double-blind, placebo-controlled, parallel group, dose-ranging, multicenter study with an optional ongoing 5-year open-label extension. X-TOLE evaluated clinical efficacy, safety, and tolerability of XEN1101 administered with food as adjunctive treatment in 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 medication (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 **significant reduction in median 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 5-Year Open-Label Extension (OLE)

Continued seizure reduction has been observed during the ongoing 5-year 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, XEN1101 20 mg QD was generally well tolerated, and the safety profile observed 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).

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*. Published online October 9, 2023. 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 compelling data from the Phase 2b X-TOLE trial for XEN1101 in FOS.

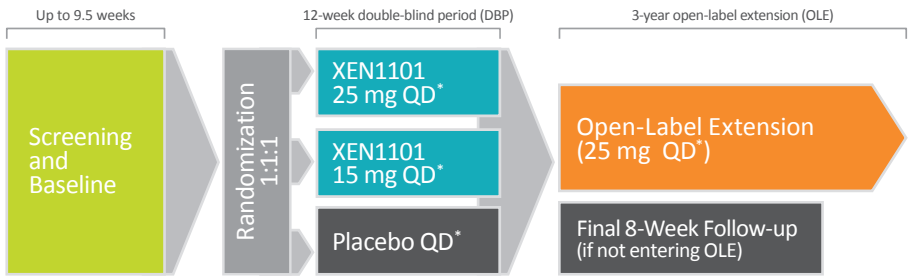
STUDY DESIGN

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 the evening meal) 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

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.

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 v2.0. October 20, 2022.

XPF-010-302 X-TOLE 3 Clinical Trial Protocol v2.0. October 24, 2022.

XPF-010-304 X-TOLE 2/3 & X-ACKT OLE Clinical Trial Protocol v2.0. October 28, 2022.

RATIONALE FOR 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.

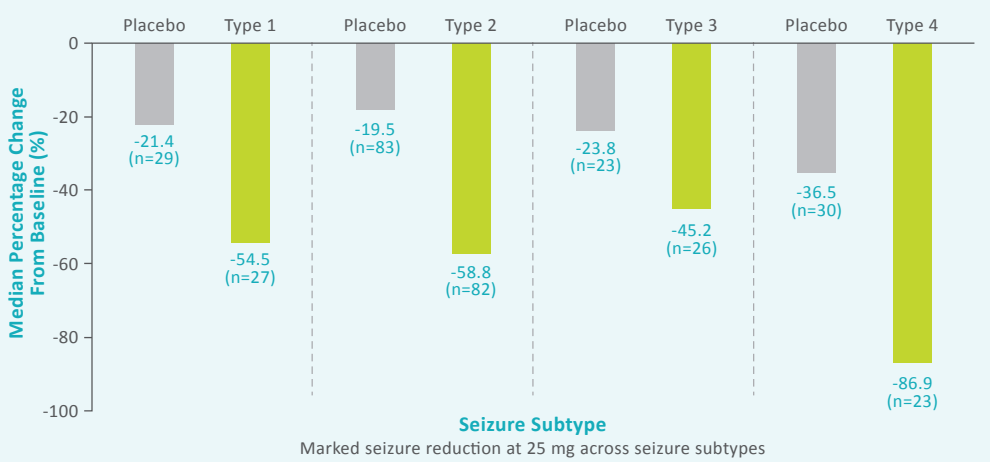
In patients with epilepsy and photosensitivity, a **K_V7 potassium channel opener** (no longer in development) **suppressed paroxysmal EEG activity.**

Levetiracetam, valproic acid, lamotrigine, and brivaracetam (not approved for PGTCS) suppressed photosensitivity in generalized epilepsy patients and demonstrated PGTCS efficacy.

In Phase 2b X-TOLE, XEN1101 demonstrated broad impact across all focal seizure subtypes, including those that progressed to generalized seizures.

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.

Kasteleijn-Nolst Trenité D et al. Kv7 potassium channel activation with ICA-105665 reduces photoparoxysmal EEG responses in patients with epilepsy. *Epilepsia.* 2013;54(8):1437-43.

Verotti A et al. Photosensitivity: epidemiology, genetics, clinical manifestations, assessment, and management. *Epileptic Disord*. 2012;14(4):349-62.

Aycardi E et al. A first-in-human study to assess the safety, tolerability, pharmacokinetics and preliminary pharmacodynamics of a novel small molecule $K_V7.2/7.3$ positive allosteric modulator (XEN1101) in healthy subjects. Abstract 3.282. American Epilepsy Society. November 30-December 4, 2018, New Orleans, LA.

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. Poster 27. American Society for Experimental Neurotherapeutics. March 13–15, 2023, Virtual.

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

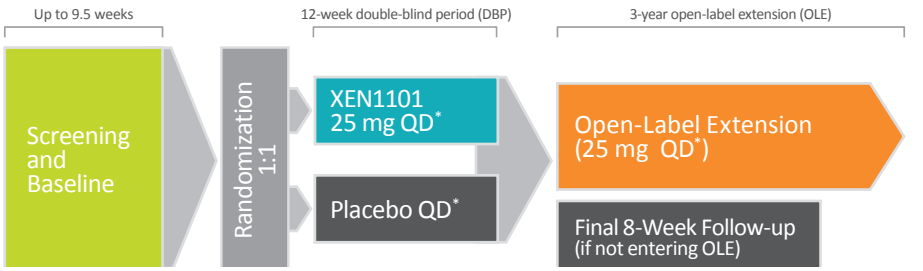
STUDY DESIGN

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 adults aged ≥18 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 (XEN1101 25 mg: placebo, taken QD with the evening meal).

- **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

X-ACKT



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

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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 October 19, 2023. https://clinicaltrials.gov/ct2/show/NCT05667142

XPF-010-303 X-ACKT Clinical Trial Protocol v2.0. October 24, 2022.

XPF-010-304 X-TOLE 2/3 & X-ACKT OLE Clinical Trial Protocol v2.0. October 28, 2022.

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 clinical stage biopharmaceutical company committed to developing innovative therapeutics to improve the lives of patients with neurological disorders.

As a leader in small molecule, ion channel drug development, we are advancing a novel product pipeline of neurology-focused therapies to address areas of high unmet medical need, with a focus on epilepsy.

XENON