X-TOLE2 & X-TOLE3

Identical global Phase 3 trials evaluating XEN1101 as an adjunctive treatment for adult patients with focal epilepsy

ENROLLING NOW

X-TOLE2 and X-TOLE3 are being initiated based on compelling data from the Phase 2b X-TOLE trial for XEN1101 in FOS

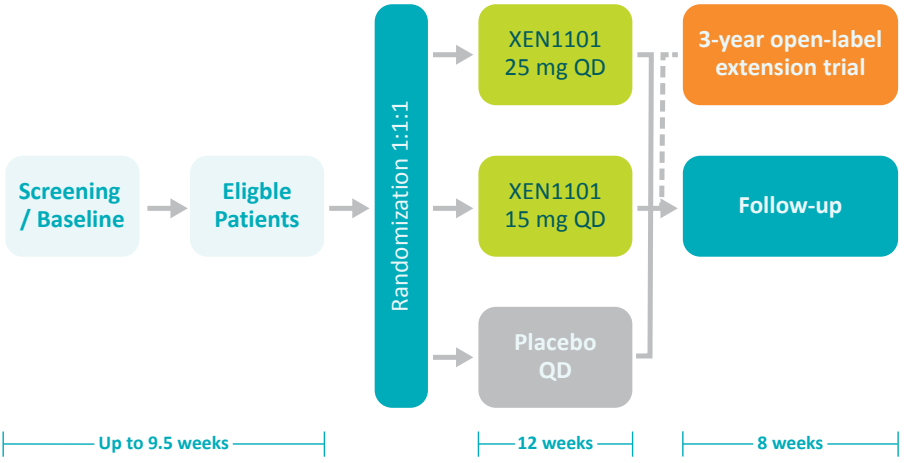
STUDY DESIGN

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 administered as adjunctive treatment in adult subjects diagnosed with FOS who are taking 1 to 3 anti-seizure medications (ASMs). Eligible subjects will be randomized 1:1:1 (XEN1101 25 mg: 15 mg: placebo).

- **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 (X-TOLE OLE) for up to 3 years

X-TOLE2 AND X-TOLE3 HAVE AN IDENTICAL TRIAL DESIGN AND WILL RUN IN PARALLEL.

X-TOLE2 & X-TOLE3 TRIAL DESIGN



ABOUT XENON

Study Sponsor for Phase 3 X-TOLE2 & X-TOLE3 Trials in focal onset seizures (FOS)

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.

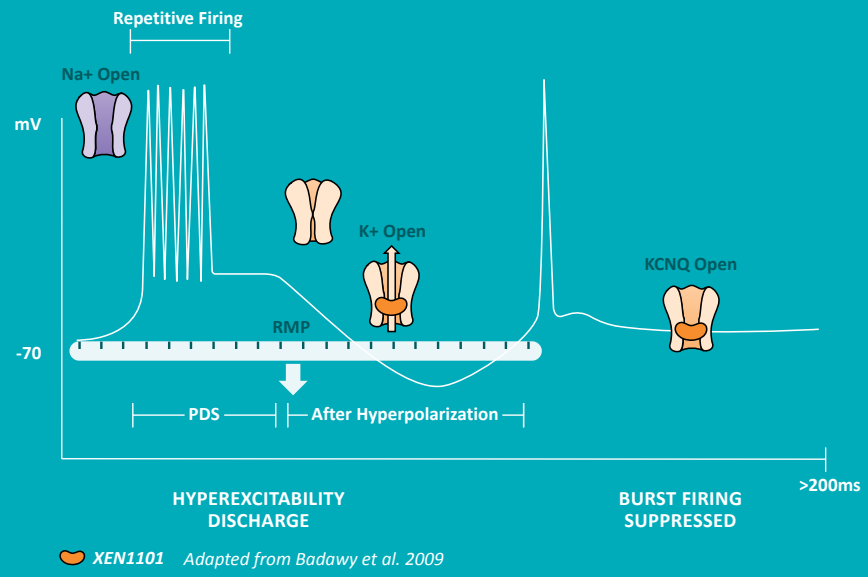
XENON

OVERVIEW OF XEN1101

XEN1101 is a novel, **potent, selective KCNQ2/3 (K_V7.2/7.3) potassium channel opener** under investigation 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, through subtypes K_v7.2 to K_v7.5, 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 DOSE, 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. doi:10.1016/j.jocn.2008.08.026

Porter RJ, Kenney C, Harden C, Sherrington R. The Unmet Need in Epilepsy: The Therapeutic Potential of Potassium Channel Modulators. AES 2021 Symposium. December 3, 2021, Chicago, IL.

Xenon Data on File.

French J, Porter R, Perucca E, *et al.* Phase 2b Efficacy and Safety of XEN1101, a Novel Potassium Channel Opener, in Adults with Focal Onset Seizures (X-TOLE). European Epilepsy Congress. July 9–13, 2022, Geneva, Switzerland.

Dean R, Lin S, Bankar G, *et al.* Preclinical *In Vitro* and *In Vivo* Comparison of the K_v7 Activator XEN1101 with Ezogabine. AES 2020 Symposium. December 4-8, 2020, Seattle, WA.

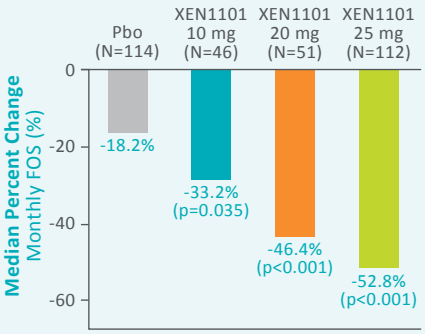
OUR COMPLETED PHASE 2B TRIAL FOR FOS

Phase 2b X-TOLE Study Design

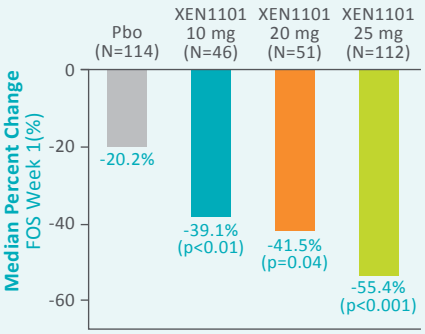
X-TOLE was a Phase 2b randomized, double-blind, placebo-controlled, parallel group, dose-ranging, multicenter study with an optional 5-year open-label extension. X-TOLE evaluated clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in adults with FOS who experienced ≥4 countable focal seizures per month, recorded on an eDiary during a planned 8-week baseline period, while receiving stable treatment with 1-3 ASMs.

TOPLINE 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.



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 **marked reduction in median FOS frequency within 1 week** for all doses compared with placebo.

The most common (>10%) treatment-emergent adverse events (TEAEs) across all the XEN1101 dose groups during the DBP were dizziness (24.6%), somnolence (15.6%), and fatigue (10.9%).

5-year Open-label Extension (OLE)

There is **continued seizure reduction during the ongoing 5-year OLE**.

During study months 14–20, there was a sustained monthly reduction in seizure frequency (80%-90% MPC) from DBP baseline. Seizure freedom for ≥6-month and ≥12-month consecutive durations was achieved in 17.5% and 10.5% of patients, respectively.

As of September 2022, 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 (20.7%), headache (13.5%), coronavirus infection (11.6%), and fall (11.3%).

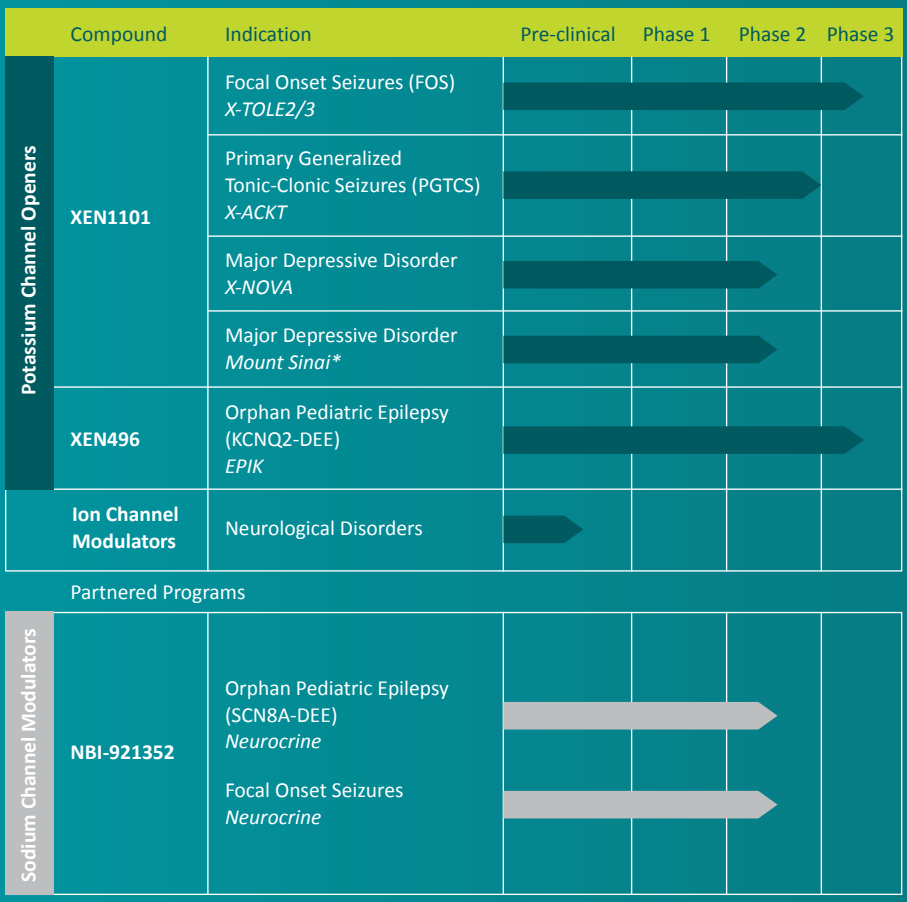
French J, Porter R, Perucca E, *et al.* XEN1101, a Novel Potassium Channel Modulator: Interim Data From an Ongoing, Long-Term, Open-Label Extension of a Phase 2B Study (X-TOLE) in Adults With Focal Epilepsy. American Epilepsy Society Annual Meeting, December 2–6, 2022, Nashville, TN.

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.

Xenon Data on File.

OUR PIPELINE

Xenon is focused on advancing our ion channel neurology pipeline. The products within our novel proprietary pipeline—including clinical-stage candidates XEN496 and XEN1101—are aimed at treating neurological disorders, with a particular focus on epilepsy.



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

We are also planning a Phase 3 clinical trial for primary generalized tonic-clonic seizures called X-ACKT in 2023. Please send any questions about the X-ACKT trial to **X-ACKT@xenon-pharma.com**.

To inquire about becoming an investigator for X-TOLE2 and X-TOLE3, please contact **X-TOLE@xenon-pharma.com**. For other general questions, please contact **medicalaffairs@xenon-pharma.com**.