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

XEN1101 is a novel, potent $K_V$7 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.

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

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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.
**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

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**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.

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**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%).

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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/jama-neurol.2023.3542


NCT05614063: A Randomized Study of XEN1101 Versus Placebo in Focal-Onset Seizures (X-TOLE2).

NCT05716100: A Randomized Study of XEN1101 Versus Placebo in Focal-Onset Seizures (X-TOLE3).

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.
**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 Kv7 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.

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**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

**Analysis of Seizure Reduction by Seizure Subtype**

<table>
<thead>
<tr>
<th>Seizure Subtype</th>
<th>Placebo Type 1</th>
<th>Placebo Type 2</th>
<th>Placebo Type 3</th>
<th>Placebo Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Percentage Change from Baseline (%)</td>
<td>-21.4 (n=29)</td>
<td>-19.5 (n=83)</td>
<td>-22.8 (n=23)</td>
<td>-36.5 (n=30)</td>
</tr>
<tr>
<td>-54.5 (n=27)</td>
<td>-56.3 (n=82)</td>
<td>-45.2 (n=26)</td>
<td>-86.9 (n=23)</td>
<td></td>
</tr>
</tbody>
</table>

**Seizure Subtype**
- 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

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

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

XENON IN EPILEPSY
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.

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