Design of Two Parallel Randomized, Double-Blind, Placebo-Controlled Phase 3 Studies to Evaluate the Safety and Efficacy of XEN1101 as Adjunctive Therapy in the Treatment of Focal Onset Epilepsy
Authors

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Disclosures

Introduction

- XEN1101 is a potent, selective $K_{v7}$ potassium channel opener being developed for the treatment of epilepsy and major depressive disorder$^{1-4}$

- The clinical efficacy, safety and tolerability of XEN1101 in adults with FOS$^5$ was evaluated in X-TOLE (NCT03796962), a completed phase 2b randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study with an ongoing optional 5-year OLE

FOS, focal onset seizure; OLE, open-label extension.
X-TOLE Results

- In the double-blind period (DBP), XEN1101 demonstrated a statistically significant, dose-dependent reduction from baseline in monthly FOS frequency compared to placebo in a difficult-to-treat population\(^1\)

![Change From Baseline Seizure Frequency](image1)

![Responder Rate (RR50)](image2)

- There was a marked reduction in median FOS frequency within 1 week for all doses compared with placebo (post-hoc \(P<0.05\) at week 1 for all doses)\(^2\)
- Heavily pre-treated patient population failed a median of 6 ASMs; 50.5% were on 3 background ASMs
- Median baseline seizure frequency of 13.5 FOS per month
- XEN1101 was generally well-tolerated during the DBP, with AEs consistent with other commonly prescribed ASMs
- In an interim analysis of the OLE, XEN1101 yielded long-term efficacy and continued to be well-tolerated with AEs consistent with prior results; no new safety signals were identified\(^3\)

AE, adverse event; ASM, anti-seizure medication; DBP, double-blind period; FOS, focal onset seizure; OLE, open-label extension.

Phase 3 X-TOLE2 AND X-TOLE3 TRIALS

Based on the strong results from the X-TOLE study, Xenon is conducting 2 identical phase 3 trials in focal onset seizures (X-TOLE2\(^1\) and X-TOLE 3\(^2\))

- X-TOLE2 (NCT05614063)\(^1\) and X-TOLE3 (NCT05716100)\(^2\) are identical phase 3, multicenter, randomized, double-blind, placebo-controlled studies to evaluate the clinical pharmacokinetics, safety, and efficacy of XEN1101 as adjunctive therapy in patients with FOS
  - XEN1101 is also in phase 3 development for primary generalized tonic-clonic seizures (X-ACKT)\(^3\)
- X-TOLE2 will run in parallel with X-TOLE3. Each study will enroll approximately 360 patients
- Patients will be randomized 1:1:1 (25 mg: 15 mg: placebo QD taken with food) to a 12-week DBP without titration
- Dose selection was informed by safety and efficacy data from the X-TOLE trial\(^4\) as well as by pharmacokinetic/pharmacodynamic modeling completed last year
- Based on the X-TOLE data, the study has >90% power for the primary endpoint at both 15- and 25-mg doses

DBP, double-blind period; FOS, focal onset seizure.

**Study Design**

**Inclusion Criteria Include**
- Adults ≥18 years of age
- Diagnosis of focal epilepsy (≥2 years, ILAE 2017 classification)
- Frequency of ≥4 FOS per month during 8 weeks prior to randomization
- Taking 1–3 stable ASMs for ≥1 month
- Failed at least 2 ASMs

**Exclusion Criteria Include**
- History of status epilepticus, repetitive seizures, or primary generalized seizures
- History of neurosurgery for seizures <1 year prior to visit 1

ASM, antiseizure medication; FOS, focal onset seizure; ILAE, International League Against Epilepsy; QD, once daily.
### X-TOLE2 and X-TOLE 3 Efficacy and Safety Endpoints

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<tr>
<th><strong>Primary Efficacy (EMA)</strong>*</th>
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<td>• Proportion of patients experiencing ≥50% reduction in monthly (28 day) FOS frequency from baseline through the DBP</td>
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<th><strong>Key Secondary Efficacy (EMA)</strong>*</th>
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<tr>
<td>• MPC in monthly (28 days) FOS frequency from baseline through the DBP</td>
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<td>• Proportion of patients experiencing ≥50% reduction in weekly (7 day) FOS frequency from baseline to week 1</td>
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<td>• Proportion of patients experiencing “at least much improved” (including “much” and “very much improved”) in the Patient Global Impression of Change at week 12</td>
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<th><strong>Safety and Tolerability</strong>*</th>
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<tr>
<td>• Severity and frequency of treatment-emergent AEs and serious AEs</td>
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<td>• Changes in clinical labs, ECGs and vital signs</td>
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<td>• Changes in physical, neurologic and ophthalmological exams</td>
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*XEN1101 vs placebo.

AE, adverse event; DBP, double-blind treatment period; ECG, electrocardiogram; EMA, European Medicines Agency; FOS, focal onset seizure; MPC, median percentage change; PGTCs, primary generalized tonic-clonic seizure; QD, once daily.
Summary

- X-TOLE2 and X-TOLE3 will provide additional insight into the safety, tolerability, and efficacy of XEN1101 in FOS
- These studies are designed to further evaluate the therapeutic potential of XEN1101 and support registration of XEN1101 as a novel ASM for the treatment of FOS
- XEN1101 has a novel mechanism of voltage-gated potassium channel opening and would be the only-in-class, $K_v7.2/7.3$ opener ASM, if approved

Further Trial Contact Details: To inquire about becoming an investigator, please contact: X-TOLE@xenon-pharma.com. For other general questions, please contact medicalaffairs@xenon-pharma.com

ASM, antiseizure medication; FOS, focal onset seizures.
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References


