Design of X-TOLE2 and X-TOLE3: 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

INTRODUCTION

- XEN1101 is a novel, small-molecule, selective KCNQ2/3 (K_v7.2/7.3) potassium channel opener being developed for the treatment of focal onset seizures (FOS), primary generalized tonic-clonic seizures, and major depressive disorder
- The pharmacokinetic properties of XEN1101 support once-daily (QD) oral dosing without the need for titration at initiation of dosing or tapering at termination of dosing
- XEN1101 demonstrates higher in vitro and in vivo potency compared to the first generation K_v7.2-7.5 opener, ezogabine, and lacks the chemical properties that could form pigmented dimers
- XEN1101 has been evaluated in phase 1 clinical studies, including a companion pharmacodynamic crossover study using transcranial magnetic stimulation.[1-3] These data demonstrated that dosing XEN1101 up to 25 mg QD was generally well tolerated and reduced cortical excitability, with a strong pharmacokinetic/pharmacodynamic relationship in healthy volunteers

X-TOLE PHASE 2B STUDY

- X-TOLE (NCT03796962) is a phase 2b randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study with an optional 5-year open-label extension that evaluated clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in adults with FOS.[4] All data presented are from the double-blind treatment period (DBP)
- XEN1101 showed a dose-dependent and highly statistically significant reduction ($P<0.001$ for 20 mg and 25 mg QD) in FOS across endpoints in a patient population who had failed a median of 6 antiseizure mediations (ASMs); 50.8% of the population were on 3 background ASMs
- XEN1101 was generally well tolerated with a similar low incidence of serious adverse events (AEs) (3.3%) compared with the placebo group (2.6%), and there were no deaths in the DBP of the study
- The most common treatment-emergent AEs leading to discontinuation across XEN1101 groups were dizziness (4.7%), balance disorder (2.4%), dysarthria (1.9%), and gait disturbance (1.9%). There were no cardiovascular signals of concern in electrocardiograms or vital signs
- **Based on the strong topline results from the X-TOLE study, Xenon initiated its XEN1101 phase 3 development program, which includes 2 identical phase 3 clinical trials in FOS (X-TOLE2 and X-TOLE3) and a planned phase 3 trial in primary generalized tonic-clonic seizures (X-ACKT)**

X-TOLE2 AND X-TOLE3 PHASE 3 STUDIES

- X-TOLE2 (NCT05614063) and X-TOLE3 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

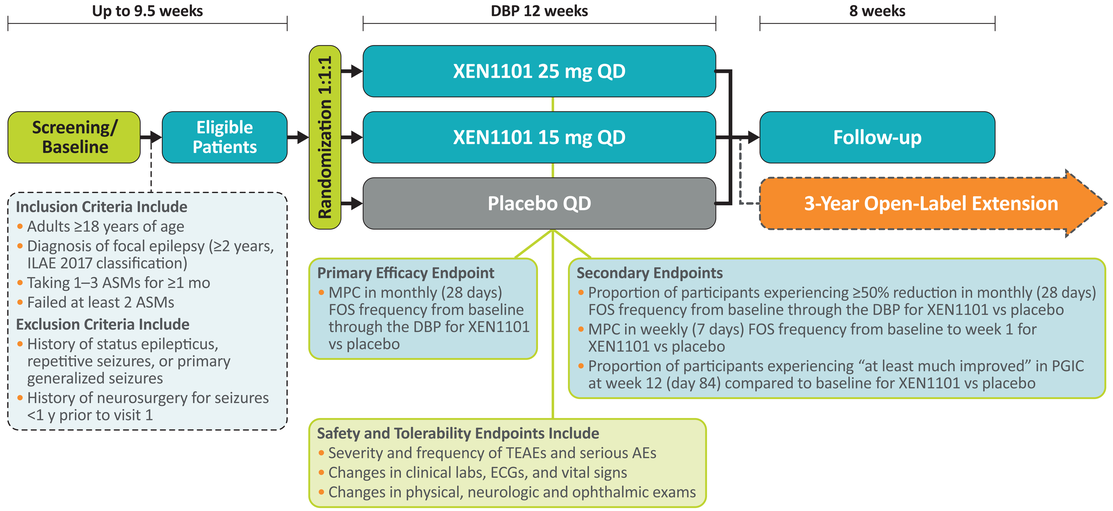
Table 1. X-TOLE2 and X-TOLE3 Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of XEN1101 vs placebo on reducing FOS frequency	MPC in monthly (28 day) FOS frequency from baseline through the DBP (12 weeks/84 days)
Key Secondary	
To assess the effect of XEN1101 vs placebo on reducing FOS frequency	Proportion of participants experiencing ≥50% reduction in monthly (28 day) FOS frequency from baseline through the DBP
To assess the early treatment effect of XEN1101 vs placebo on FOS frequency	MPC in weekly (7 day) FOS frequency from baseline to week 1
To assess the effect of XEN1101 vs placebo on seizure impact	Proportion of patients experiencing "at least much improved" (including "much" and "very much improved") in the PGIC at week 12
To assess the safety and tolerability of XEN1101	Severity and frequency of adverse events

DBP, double-blind treatment period; FOS, focal onset seizure; MPC, median percentage change; PGIC, Patient Global Impression of Change.

- X-TOLE2 will run in parallel with X-TOLE3. Each study will enroll approximately 360 patients who will be randomized 1:1:1 (25 mg: 15 mg: placebo QD taken with the evening meal) to a 12-week DBP without titration following an 8-week baseline to assess seizure frequency (**Figure 1**)
- Dose selection for these phase 3 studies was informed by the safety and efficacy data from the X-TOLE trial[4] as well as by pharmacokinetic/pharmacodynamic modeling completed earlier this year
- Based on the X-TOLE data, the study has >90% power for the primary endpoint at both 15- and 25-mg doses

Figure 1. Study Design of the X-TOLE2 and X-TOLE3 Studies



AE, adverse event; ASM, antiseizure medication; DBP, double-blind treatment period; ECG, electrocardiogram; FOS, focal onset seizure; ILAE, International League Against Epilepsy; MPC, median percentage change; PGIC, Patient Global Impression of Change; QD, once daily; TEAE, treatment-emergent adverse event.

Each trial consists of 3 parts

1. Screening/baseline period of up to 9.5 weeks duration to assess the frequency of seizures
2. DBP of 12 weeks
3. Follow-up period: 8 weeks duration after the last dose of study drug for participants who do not complete the 12-week DBP or who complete the DBP but do not enter the open-label extension study

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

SUMMARY

- X-TOLE2 and X-TOLE3 will provide 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 adults with 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

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REFERENCES **1.** Biondi A, et al. *Sci Rep*. 2022;12(1):1919. **2.** Premoli I, et al. *Ann Clin Transl Neurol*. 2019;6(11):2164-2174. **3.** 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]. Presented at: American Epilepsy Society; November 30-December 4, 2018; New Orleans, LA. **4.** French J, et al. Phase 2b efficacy and safety of XEN1101, a novel potassium channel opener, in adults with focal onset seizures (X-TOLE) [Abstract P12.006]. Presented at: American Academy of Neurology; April 2-7, 2022; Seattle, WA.

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