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

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XEN1101

- XEN1101 is a novel, potent, selective *KCNQ2/3* (K_v7.2/7.3) potassium channel opener being developed for the treatment of focal onset seizures, primary generalized tonic-clonic seizures (PGTCS), and major depressive disorder
- XEN1101 has shown antiseizure activity in maximum electroshock seizure and pentylenetetrazole preclinical models, both known to predict efficacy for primary generalized seizures[1]
- ICA-105665m, a K_v7 potassium channel opener, suppressed photosensitivity (electroencephalogram model) in patients with generalized epilepsy[2]
- Levetiracetam, valproic acid, lamotrigine, and brivaracetam (not approved for PGTCS) suppressed photosensitivity in patients with generalized epilepsy and demonstrated PGTCS efficacy[2]
- 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's pharmacokinetic properties support once-daily (QD) oral dosing without the need for titration at initiation of dosing or tapering at termination of dosing[3]
- XEN1101 has been evaluated in phase 1 clinical studies, including a companion pharmacodynamic crossover study using transcranial magnetic stimulation.[3-5] 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
- In the phase 2b X-TOLE study in patients with focal onset seizures, XEN1101 demonstrated broad impact across all focal seizure subtypes, including those that progressed to generalized seizures[6]
- These data support the broad-spectrum antiseizure potential of XEN1101 and provide the rationale for a trial of XEN1101 in patients with PGTCS
- The X-ACKT study for XEN1101 in patients with PGTCS is designed to support US Food and Drug Administration (FDA) registration

X-ACKT STUDY

- X-ACKT (NCT05667142) is a phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the pharmacokinetics, safety, and efficacy of XEN1101 in the fed state in adults aged ≥18 years with a seizure frequency of ≥3 PGTCS over an 8- to 9.5-week screening/baseline and taking 1–3 antiseizure medications (ASMs)

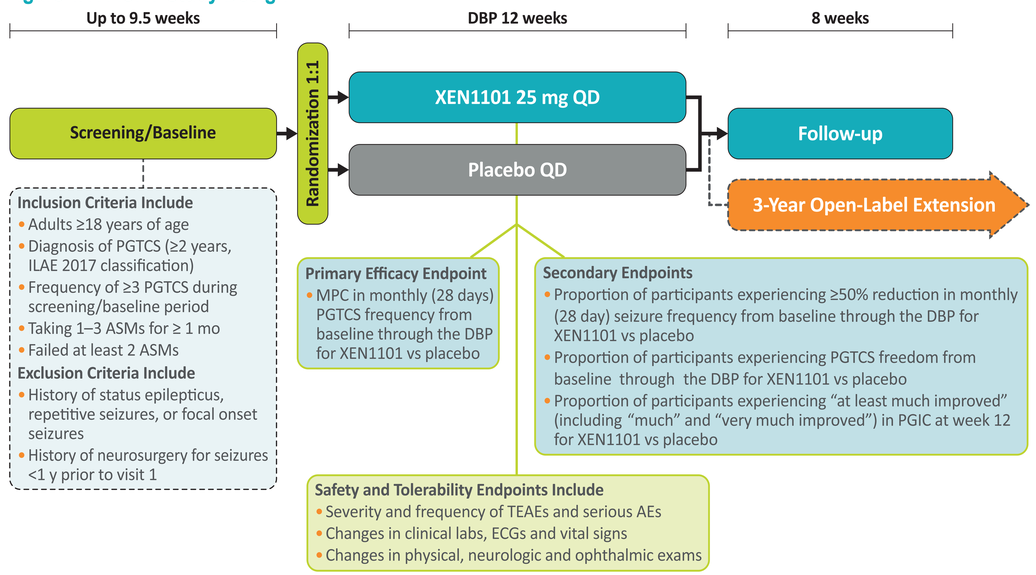
Table 1. X-ACKT Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of XEN1101 vs placebo on reducing PGTCS frequency	MPC in monthly (28 day) PGTCS frequency from baseline through the DBP (12 weeks)
Key Secondary	
To assess the effect of XEN1101 vs placebo on reducing PGTCS frequency	Proportion of participants experiencing ≥50% reduction in monthly (28 day) PGTCS frequency from baseline through the DBP
To assess the effect of XEN1101 vs placebo on the frequency of PGTCS freedom	Proportion of participants experiencing PGTCS freedom from baseline through the DBP
To assess the effect of XEN1101 vs placebo on seizure impact	Proportion of participants 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; MPC, median percentage change; PGTCS, primary generalized tonic-clonic seizures; PGIC, Patient Global Impression of Change.

- The study will enroll approximately 160 participants who will be randomized 1:1 (25 mg: placebo taken QD with the evening meal; no titration required) to a 12-week double-blind treatment period (DBP) following an 8- to 9.5-week baseline period to assess seizure frequency (**Figure 1**)
- Participants completing the DBP may be eligible for an open-label extension trial under a separate protocol

Figure 1. X-ACKT Study Design



AE, adverse event; ASM, antiseizure medication; DBP, double-blind treatment period; ECG, electrocardiogram; ILAE, International League Against Epilepsy; MPC, median percentage change; PGTCS, primary generalized tonic-clonic seizures; PGIC, Patient Global Impression of Change; QD, once daily; TEAE, treatment-emergent adverse event.

The trial consists of 3 parts

1. Screening/baseline period of up to 9.5 weeks of duration to assess the frequency of seizures
2. DBP of 12 weeks
3. Follow-up period: 8 weeks of 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

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

SUMMARY

- X-ACKT will provide insight into the safety, tolerability, and efficacy of XEN1101 as adjunctive therapy in the treatment of PGTCS and is designed to support FDA registration of XEN1101 for the treatment of PGTCS
- If approved, this would be the only-in-class K_v7.2/7.3 opener ASM with once-daily administration with no titration required

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