XEN1101 is a novel, potent, selective KCNQ2/3 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 pentyleneetetrazole preclinical models, both known to predict efficacy for primary generalized seizures.

ICA-105665, a K₇ potassium channel opener, suppressed photosensitivity (electroencephalogram model) in patients with generalized epilepsy.

Levetiracetam, valproic acid, lamotrigine, and brivaracetam (not approved for PGTCS) suppressed photosensitivity in patients with generalized epilepsy and demonstrated PGC efficacy.

XEN1101 demonstrates higher in vitro and in vivo potency compared to the first generation K₇.2-7 opener, azagagine.

XEN1101’s pharmacokinetic properties support once-daily (QD) oral dosing with food without the need for titration at initiation of dosing or tapering at termination of dosing.

XEN1101 has been evaluated in phase 1 clinical studies, including a companion pharmacodynamic crossover study using transcranial magnetic stimulation. These data demonstrated that dosing XEN1101 at 25 mg QD was generally well-tolerated and reduced cortical excitability, with a strong pharmacodynamic/pharmacokinetic 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.

These data support the broad-spectrum antiseizure potential of XEN1101 and the rationale for its development in patients with PGTCS.

The X-ACKT study for XEN1101 in patients with PGTCS is designed to support FDA registration of XEN1101 for treatment of the primary generalized tonic-clonic seizures (PGTCS) endpoint.

**Objective and Endpoints**

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
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<tr>
<td>Primary</td>
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<tr>
<td>To assess the effect of XEN1101 vs placebo on reducing PGI frequency</td>
<td>MPC in monthly (28 day) PGTCS frequency from baseline through the DBP (12 weeks)</td>
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<tr>
<td>To assess the effect of XEN1101 vs placebo on reducing PGTCS frequency</td>
<td>Proportion of participants experiencing ≥50% reduction in monthly (28 day) PGTCS frequency from baseline through the DBP</td>
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<tr>
<td>To assess the safety and tolerability of XEN1101 on seizure impact</td>
<td>Proportion of participants experiencing at least much improved (including &quot;much&quot; and &quot;very much improved&quot;) in the POGC at week 12</td>
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**Secondary Endpoints**

- **PGTCS freedom from baseline through the DBP for XEN1101 vs placebo**
- **Propotion of participants experiencing ≥50% reduction in monthly (28 day) seizure frequency from baseline through the DBP for XEN1101 vs placebo**
- **Proportion of participants experiencing ≥50% reduction in generalized tonic-clonic seizures (PGTCS) frequency from baseline through the DBP**
- **Proportion of participants experiencing at least much improvement (including "much" and "very much improved") in POGC at week 12 for XEN1101 vs placebo**

**Safety and Tolerability Endpoints**

- **Incidence of adverse events**
- **Changes in clinical labs, ECGs and vital signs**
- **Changes in physical, neurologic and psychiatric exams**

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 double-blind period or who complete the DBP but do not enter the open-label extension study.

**Further Trial 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**

- XEN1101 will provide insight into the safety, tolerability, and efficacy of XEN1101 as an 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 K₇.2-7 opener ASM with once-daily administration and with no titration required.