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

Antonio Gil-Nagel,[1] David Vossler,[2] Elinor Ben-Menachem,[3] W. Curt LaFrance Jr,[4] Cynthia Harden,[5] Jenny Qian,[5] Gregory N. Beatch,[5] Christopher Kenney[5]

[1]Hospital Ruber Internacional, Madrid, Spain; [2]University of Washington, Seattle, WA, and UW Medicine/Valley Medical Center, Renton, WA, USA; [3]Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden; [4]Rhode Island Hospital, Brown University, Providence, RI, USA; [5]Xenon Pharmaceuticals Inc., Burnaby, BC, Canada

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-105665, 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
- 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[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)

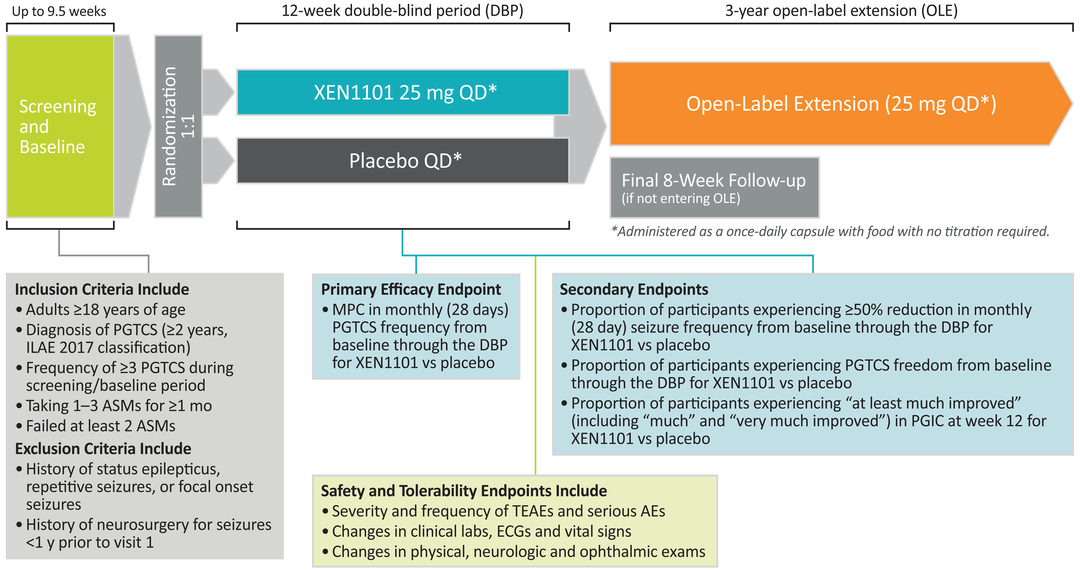
Table 1. X-ACKT Primary and Key Secondary Objectives and Endpoints

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 and with no titration required

ACKNOWLEDGMENTS Medical writing support was provided by Robin Smith, PhD, of The Curry Rockefeller Group, LLC (Tarrytown, NY), and was funded by Xenon Pharmaceuticals Inc.

FUNDING Xenon Pharmaceuticals Inc.

DISCLOSURES Antonio Gil-Nagel: personal fees from advisory boards and as a speaker from Arvelle/Angelini, Bial, Biocodex, Eisai, Esteve, GW Pharma, Jazz Pharmaceuticals, Pharvaris, PTC Therapeutics, Stoke, UCB Pharma, EISAI, and Zogenix, and research grants from Biocodex, GW Pharma, PTC Therapeutics, Zogenix and UCB Pharma. David Vossler: Consultant for Biocodex, Longboard, and Xenon Pharmaceuticals Inc. Institution research support from Longboard, SK Life Science, and Xenon Pharmaceuticals Inc. Elinor Ben-Menachem: consultant for Theracule, Congugard, Angelini, UCB, Xenon Pharmaceuticals Inc. Speaker for UCB, and Angelini. Compensation from Wiley as chief editor *Acta Neurologica Scandinavica*. W. Curt LaFrance, Jr: editorial boards of *Epilepsia*, *Epilepsy & Behavior*, *Journal of Neurology*, *Neurosurgery and Psychiatry*, and *Journal of Neuropsychiatry and Clinical Neurosciences*. Royalties from Cambridge University Press and Oxford University Press. Research support from Department of Defense, NIH, Providence VAMC, Center for Neurorestoration and Neurotechnology, Rhode Island Hospital, American Epilepsy Society, Epilepsy Foundation, Brown University, and the Siravo Foundation; serves on the Epilepsy Foundation New England Professional Advisory Board, Functional Neurological Disorder Society Board of Directors, American Neuropsychiatric Association Advisory Council. Honoraria for the American Epilepsy Society Annual Meeting. Consultant at University of Colorado Denver, Cleveland Clinic, Spectrum Health, Emory University, Oregon Health Sciences University and Vanderbilt University. Cynthia Harden, Jenny Qian, Gregory N. Beatch, Christopher Kenney: employees of and own stock or stock options in Xenon Pharmaceuticals Inc.

REFERENCES **1.** Xenon. Data on file. **2**. Kasteleijn-Nolst Trenite DG, et al. *Epilepsia*. 2013;54(8):1437-1443. **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.** Biondi A, et al. *Sci Rep.* 2022;12(1):1919. **5.** Premoli I, et al. *Ann Clin Transl Neurol.* 2019;6(11):2164-2174. **6.** 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.