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Platform session; Drug Therapy **Sunday, September 3, 15:40-15:50**

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

THIS STUDY IS SPONSORED AND FUNDED BY XENON® PHARMACEUTICALS INC.

Authors

ANTONIO GIL-NAGEL,[1] DAVID G. 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., Vancouver, BC, Canada

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Disclosures

Antonio Gil-Nagel: Personal fees from advisory boards and as a speaker for 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.

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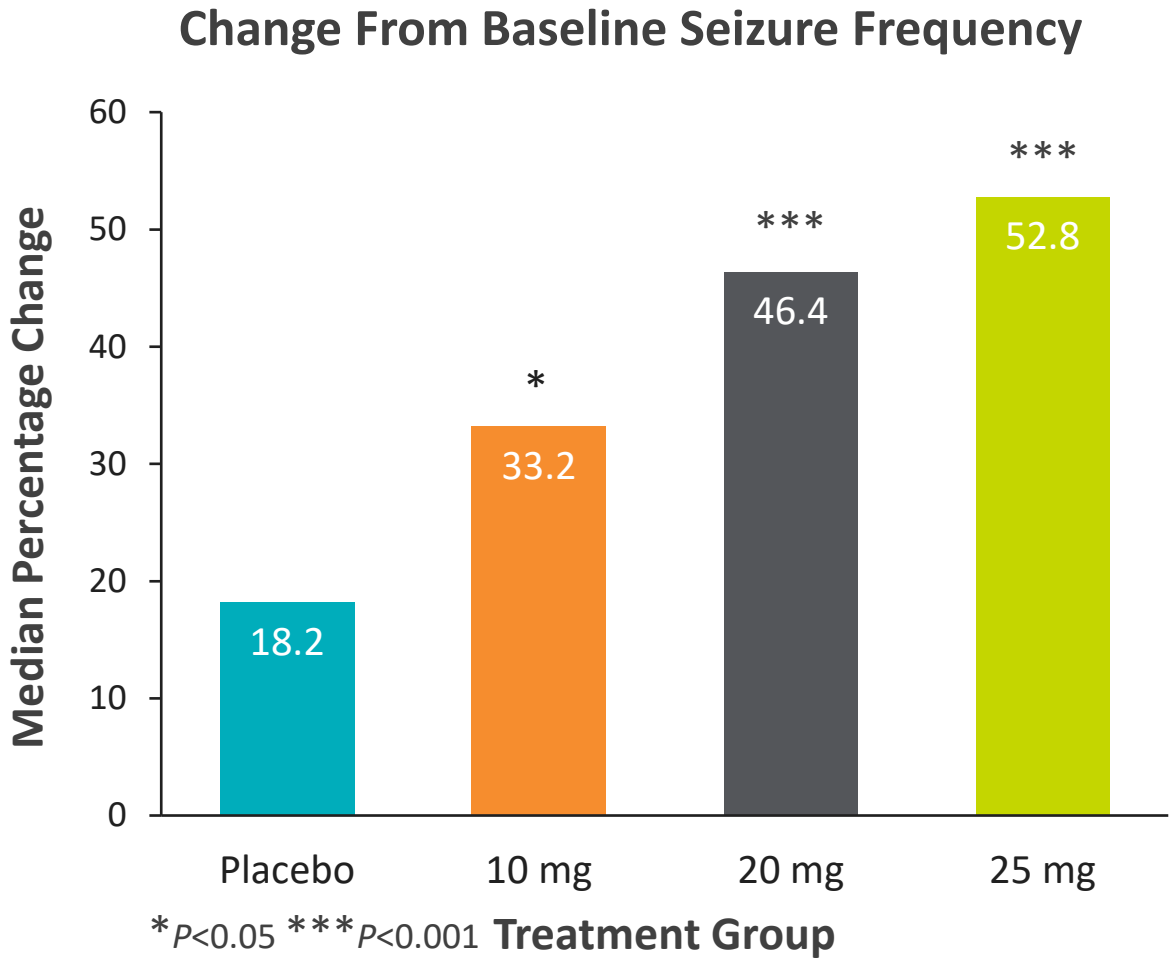
XEN1101

- XEN1101 is a novel, potent K_V7 potassium channel opener in development for the treatment of epilepsy and major depressive disorder[1-4]
- In the phase 2b X-TOLE study in patients with FOS,[1] XEN1101 demonstrated a statistically significant, dose-dependent reduction from baseline in monthly FOS frequency compared to placebo in a difficult-to-treat population[1]
- XEN1101 was generally well tolerated with AEs consistent with other commonly prescribed ASMs[5]

X-TOLE Efficacy Results



AE, adverse event; ASM, antiseizure medication; FOS, focal onset seizure.

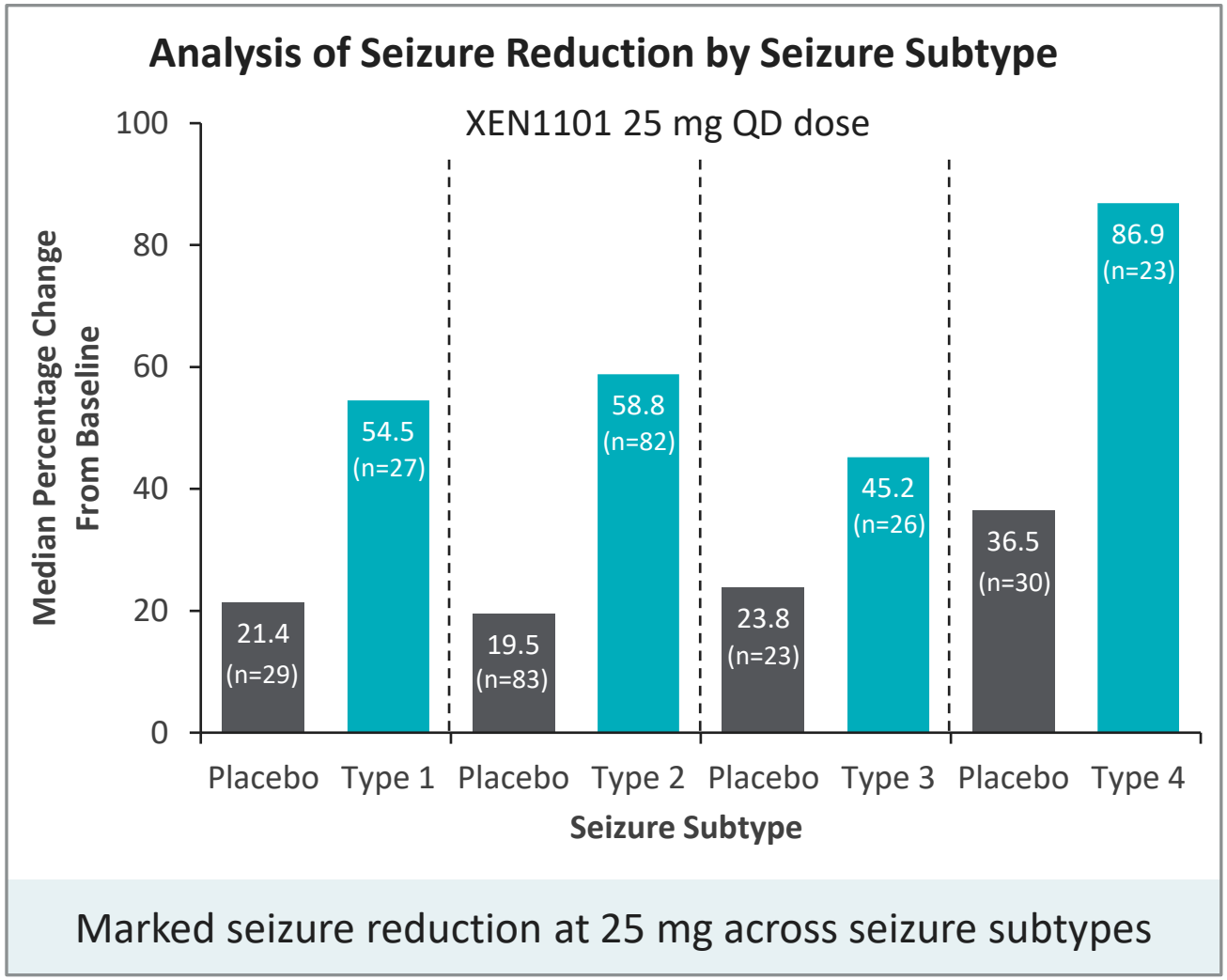
1. https://clinicaltrials.gov/ct2/show/record/NCT05614063. 2. https://clinicaltrials.gov/ct2/show/record/NCT057161. 3. https://clinicaltrials.gov/ct2/show/record/NCT0571610000. 4. https://clinicaltrials.gov/ct2/show/record/NCT04827901. 5. French J, Porter R, Perucca E, et al. Phase 2b efficacy and safety of XEN1101, a novel potassium channel opener, in adults with focal onset seizures (X-TOLE)[Abstract P12.8.006]. *Neurology*. 2022;98(18 SUPPL).

XEN1101 Efficacy in Focal to Bilateral Tonic-Clonic Seizures

- In X-TOLE, seizure reduction was noted across all focal seizure subtypes, including those that progressed to bilateral tonic-clonic seizures

Focal Onset Seizure Types

- **Type 1** Focal aware seizures with motor signs
- **Type 2** Focal seizures with impaired awareness with motor signs
- **Type 3** Focal seizures with impaired awareness with NO motor signs
- **Type 4** Focal seizures progressing to bilateral tonic-clonic seizures



Marked seizure reduction at 25 mg across seizure subtypes

Xenon Pharmaceuticals Inc. Data on file.

Rationale for the Development of XEN1101 in PGTCS

- In preclinical studies, XEN1101 has been shown to selectively potentiate the open state of K_V7.2/7.3 channels, favoring a hyperpolarized resting state, which reduces neuronal hyperexcitability[1]
- XEN1101 suppresses seizures in the maximal electroshock seizure and pentylenetetrazole preclinical models[1], both considered predictive of human PGTCS[2]
- In a phase 1 pharmacodynamic crossover study using transcranial magnetic stimulation, XEN1101 up to 25 mg QD reduced cortical excitability[3]
- In patients with epilepsy and photosensitivity, ICA-105665, a K_V7 potassium channel opener (no longer in development) suppressed paroxysmal EEG activity[4]
  - Levetiracetam, valproic acid, and lamotrigine suppressed photosensitivity in generalized epilepsy and reduced PGTCS frequency[5]; carbamazepine did not[6]

Collectively, these data support the broad-spectrum antiseizure potential of XEN1101 and provide the rationale for the clinical development of XEN1101 in patients with PGTCS

EEG, electroencephalogram; PGTCS, primary generalized tonic-clonic seizure; QD, once daily.

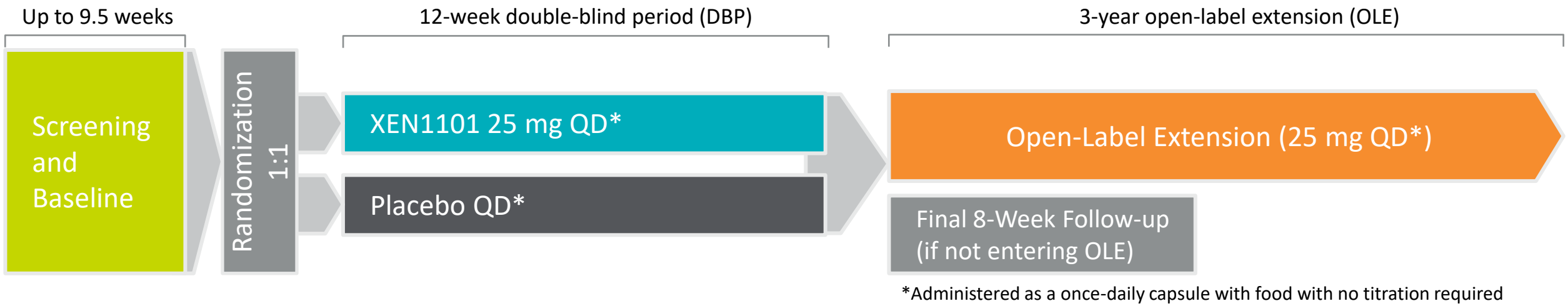
1. Xenon Pharmaceuticals Inc. Data on file. 2. Loscher W. *Seizure*. 2011;20(5):359-368. 3. Premoli I, et al. *Ann Clin Transl Neurol*. 2019;6(11):2164-2174. 4. Kasteleijn-Nolst Trenite DG, et al. *Epilepsia.* 2013;54(8):1437-1443. 5. Verrotti A, et al. *Epileptic Disord*. 2012;14(4):349-362. 6. French JA, et al. *Neurotherapeutics*. 2014;11(2):412-418.

Phase 3 X-ACKT TRIAL

- X-ACKT (NCT05667142) is a phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate PK, safety, and efficacy of XEN1101 in the fed state in adults aged ≥18 years with a seizure frequency of ≥3 PGTCS over the 8 weeks prior to randomization who were taking 1–3 ASMs
- Study will enroll approximately 160 patients, randomized 1:1 to 25 mg XEN1101 or placebo taken QD with food, without titration to a 12-week DBP to assess seizure frequency
- Patients completing the DBP may be eligible for an OLE trial
- X-ACKT is designed to support the FDA registration for XEN1101 in patients with PGTCS

ASM, antiseizure medication; DBP, double-blind treatment period; FDA, US Food and Drug Administration; PK, pharmacokinetics; OLE, open-label extension; PGTCS, primary generalized tonic-clonic seizure; QD, once daily.

Study Design



*Administered as a once-daily capsule with food with no titration required

Inclusion Criteria Include

- Adults ≥18 years of age
- Diagnosis of PGTCS (≥2 years, ILAE 2017 classification)
- Frequency of ≥3 PGTCS during 8 weeks prior to randomization
- Taking 1–3 ASMs for ≥1 month
- Failed at least 2 ASMs

Exclusion Criteria Include

- History of status epilepticus or repetitive seizures <1 year prior to visit 1
- Concomitant diagnosis of focal onset seizures
- History of neurosurgery for seizures <1 year prior to visit 1

ASM, antiseizure medication; ILAE, International League Against Epilepsy; PGTCS, primary generalized tonic-clonic seizure; QD, once daily.

X-ACKT Efficacy and Safety Endpoints

X-ACKT

Primary Efficacy (EMA)*

- Proportion of patients experiencing ≥50% reduction in monthly (28 day) PGTCS frequency from baseline through the DBP

Key Secondary Efficacy (EMA)*

- MPC in monthly (28 days) PGTCS frequency from baseline through the DBP
- Proportion of patients experiencing PGTCS freedom from baseline through the DBP
- Proportion of patients experiencing at least “much improved” (including “much improved” and “very much improved”) in Patient Global Impression of Change at week 12

Safety and Tolerability*

- Severity and frequency of treatment-emergent AEs and serious AEs
- Changes in clinical labs, ECGs and vital signs
- Changes in physical, neurologic and ophthalmological exams

*XEN1101 vs placebo.

AE, adverse event; DBP, double-blind treatment period; ECG, electrocardiogram; MPC, median percentage change; PGIC, Patient Global Impression of Change; PGTCS, primary generalized tonic-clonic seizure; QD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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

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.*

ASM, antiseizure medication; FDA, US Food and Drug Administration; PGTCS, primary generalized tonic-clonic seizure.

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