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Platform session; Drug Therapy, **Sunday, September 3, 16:10-16:20**

Design of 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

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

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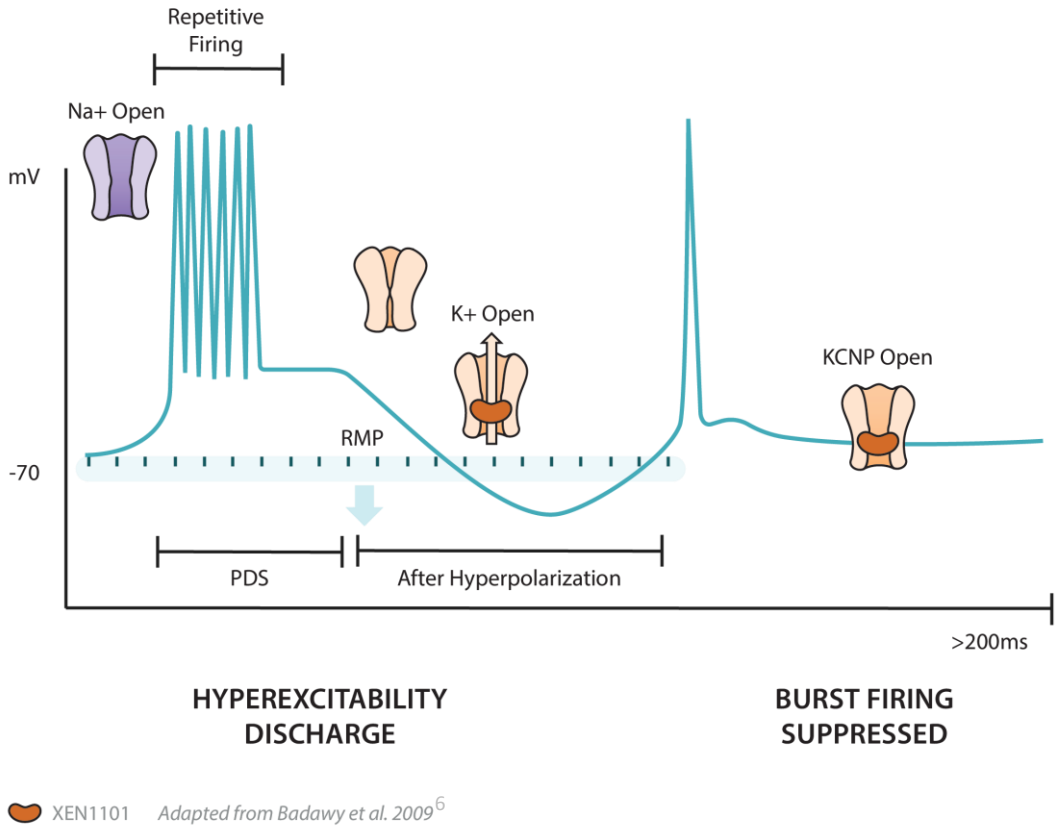
Disclosures

Emilio Perucca: speaker/consultancy fees from Angelini, Arvelle, Biogen, Eisai, GW Pharma, Janssen, PMI Life Sciences, Sanofi, Shackelford Pharma, SK Life Science, Sun Pharma, Takeda, UCB Pharma, Xenon Pharmaceuticals Inc., Zogenix. **Jacqueline French**: numerous relationships on behalf of the Epilepsy Study Consortium with various commercial and academic entities (consulting, salary support, research support, travel reimbursement, or served on the editorial board), including Xenon Pharmaceuticals Inc. Salary support from Epilepsy Study Consortium. **Elinor Ben-Menachem**: consultant for Theracule, Congugard, Angelini, UCB, Xenon Pharmaceuticals Inc. Speaker for UCB, and Angelini. Chief editor *Acta Neurologica Scandinavica*. **David Gloss** and **Philippe Ryvlin**: no conflict of interest. **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 Oxford and Cambridge University Presses. Research support from Department of Defense, NIH, Providence VAMC, Center for Neurorestoration and Neurotechnology, Rhode Island Hospital, AES, 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 AES Annual Meeting. Consultant at University of Colorado Denver, Cleveland Clinic, Spectrum Health, Emory University, Oregon Health Sciences University and Vanderbilt University. **Mona Sazgar**: scientific advisory boards of UCB, Eisai, Biocodex, Idorsia, and speaker for UCB, SK Lifesciences, Neurelis. **Manuel Toledo**: participated in drug-resistant epilepsy clinical trials with different antiseizure mediations development. Consulting fees from Angelini, Bial, Eisai Inc, GSK, GW Pharmaceuticals, and UCB Pharma. **Torbjörn Tomson**: grants from NordForsk (Nordic Register-Based Study of Antiepileptic Drugs in Pregnancy [SCAN-AED] project). Grants from Angelini Pharma, Accord, Eisai, GSK, UCB, Bial, Sanofi, GW Pharma, Zentiva, Glenmark, EcuPharma, and Teva. Speaker for Eisai, GSK, Angelini, and UCB. Advisory boards for Arvelle and GW Pharma. **Eugen Trinka**: personal fees from EVER Pharma, Marinus, Arvelle, Angelini, Argenx, Medtronic, Bial-Portela & Cª, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, UCB, Biogen, Sanofi, Jazz Pharmaceuticals, and Actavis. Institutional grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Osterreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank. **Vicente Villanueva**: advisory boards/industry-sponsored symposia by Angelini, Bial, Eisai Inc, Jazz Pharmaceuticals, Novartis, Takeda, UCB Pharma, and Xenon. **Robert Wechsler**: investigator for Aquestive, Biogen, Cavion, Cerevel, Eisai, Engage Pharma, Greenwich Biosciences, Lundbeck, Otsuka, Pfizer, SK Life Science, Sunovion, UCB Pharma, Xenon, and Zogenix. Advisory boards/consulting work for Brain Sentinel, Cerevel, Eisai, Engage Pharma, Greenwich Biosciences, Lundbeck, Otsuka, SK Life Science, Sunovion, and UCB Pharma. Speaker for Aquestive, Eisai, Greenwich Biosciences, LivaNova, Neurelis, SK Life Science, Sunovion, and UCB Pharma. Member of Epilepsy Study Consortium. **Cynthia Harden, Jenny Qian, Constanza Luzon Rosenblut, Christopher Kenney,** and **Gregory N. Beatch**: employees of and own stock or stock options in Xenon Pharmaceuticals Inc.

Introduction

- XEN1101 is a potent, selective K_V7 potassium channel opener being developed for the treatment of epilepsy and major depressive disorder[1-4]
- The clinical efficacy, safety and tolerability of XEN1101 in adults with FOS[5] was evaluated in X-TOLE (NCT03796962), a completed phase 2b randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study with an ongoing optional 5-year OLE

Potassium channels play a major role in the control of neuronal excitability and represent a promising treatment target for epilepsy

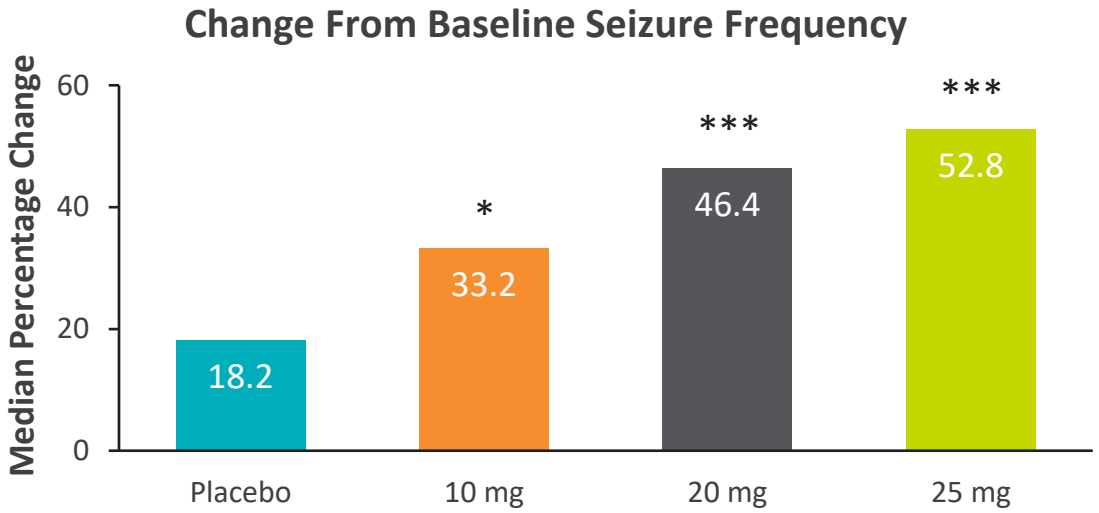


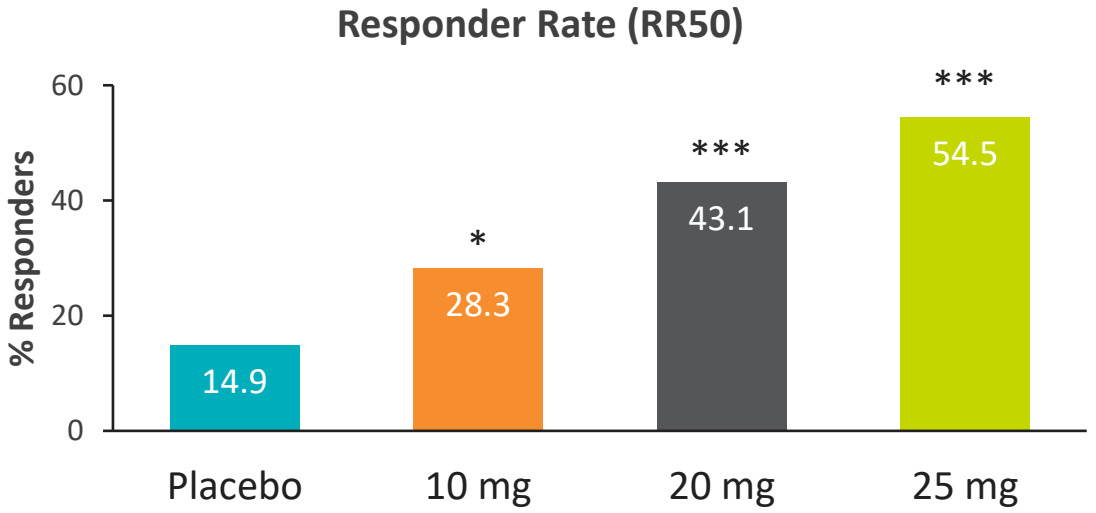
FOS, focal onset seizure; OLE, open-label extension.

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). 6. Badawy RA, et al. *J Clin Neurosci.* 2009;16(3):355-365.

X-TOLE Results

- In the double-blind period (DBP), XEN1101 demonstrated a statistically significant, dose-dependent reduction from baseline in monthly FOS frequency compared to placebo in a difficult-to-treat population[1]





*P<0.05 ***P<0.001

- There was a marked reduction in median FOS frequency within 1 week for all doses compared with placebo (post-hoc P<0.05 at week 1 for all doses)[2]
- Heavily pre-treated patient population failed a median of 6 ASMs; 50.5% were on 3 background ASMs
- Median baseline seizure frequency of 13.5 FOS per month
- XEN1101 was generally well-tolerated during the DBP, with AEs consistent with other commonly prescribed ASMs
- In an interim analysis of the OLE, XEN1101 yielded long-term efficacy and continued to be well-tolerated with AEs consistent with prior results; no new safety signals were identified[3]

AE, adverse event; ASM, anti-seizure medication; DBP, double-blind period; FOS, focal onset seizure; OLE, open-label extension.

1. 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 P12.8.006]. *Neurology*. 2022;98(18 SUPPL). 2. Kenney C, et al. Rapid Onset of Efficacy of XEN1101, a Novel Potassium Channel Opener, in Adults With Focal Epilepsy: Results From a Phase 2b Study (X-TOLE)[Abstract 2.236]. AES 2022. 3. French J, et al. XEN1101, a novel potassium channel modulator: interim data from an ongoing, long-term, open-label extension of a phase 2B study (X-TOLE) in adults with focal epilepsy [Abstract 2.235]. AES 2022.

Phase 3 X-TOLE2 AND X-TOLE3 TRIALS

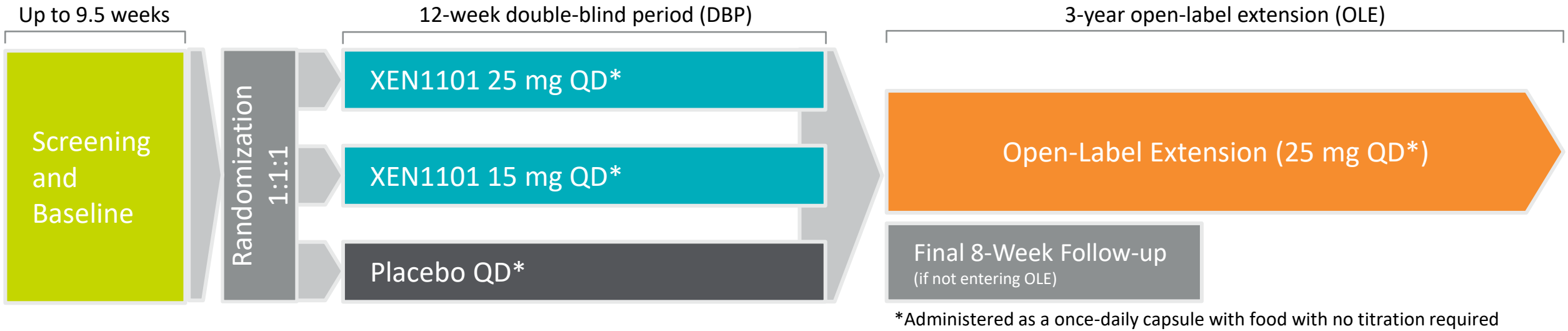
Based on the strong results from the X-TOLE study, Xenon is conducting 2 identical phase 3 trials in focal onset seizures (X-TOLE2[1] and X-TOLE 3[2])

- X-TOLE2 (NCT05614063)[1] and X-TOLE3 (NCT05716100)[2] 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
  - XEN1101 is also in phase 3 development for primary generalized tonic-clonic seizures (X-ACKT)[3]
- X-TOLE2 will run in parallel with X-TOLE3. Each study will enroll approximately 360 patients
- Patients will be randomized 1:1:1 (25 mg: 15 mg: placebo QD taken with food) to a 12-week DBP without titration
- Dose selection was informed by safety and efficacy data from the X-TOLE trial[4] as well as by pharmacokinetic/pharmacodynamic modeling completed last year
- Based on the X-TOLE data, the study has >90% power for the primary endpoint at both 15- and 25-mg doses

DBP, double-blind period; FOS, focal onset seizure.

1. https://clinicaltrials.gov/ct2/show/record/NCT05614063 2. https://clinicaltrials.gov/ct2/show/record/NCT05716100. 3. https://clinicaltrials.gov/ct2/show/NCT05667142. 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 P12.8.006]. *Neurology*. 2022;98(18 SUPPL).

Study Design



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

Inclusion Criteria Include

- Adults ≥18 years of age
- Diagnosis of focal epilepsy (≥2 years, ILAE 2017 classification)
- Frequency of ≥4 FOS per month during 8 weeks prior to randomization
- Taking 1–3 stable ASMs for ≥1 month
- Failed at least 2 ASMs

Exclusion Criteria Include

- History of status epilepticus, repetitive seizures, or primary generalized seizures
- History of neurosurgery for seizures <1 year prior to visit 1

ASM, antiseizure medication; FOS, focal onset seizure; ILAE, International League Against Epilepsy; QD, once daily.

X-TOLE2 and X-TOLE 3 Efficacy and Safety Endpoints

Primary Efficacy (EMA)*

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

Key Secondary Efficacy (EMA)*

- MPC in monthly (28 days) FOS frequency from baseline through the DBP Proportion of patients experiencing ≥50% reduction in weekly (7 day) FOS frequency from baseline to week 1
- Proportion of patients experiencing “at least much improved” (including “much” and “very much improved”) in the 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; EMA, European Medicines Agency; FOS, focal onset seizure; MPC, median percentage change; PGTCS, primary generalized tonic-clonic seizure; QD, once daily.

Summary

- X-TOLE2 and X-TOLE3 will provide additional 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 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

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

ASM, antiseizure medication; FOS, focal onset seizures.

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