American Academy of Neurology Annual Meeting • April 13–18, 2024 • Denver, CO
Oral #005. S19: Epilepsy Clinical Trials and Long-term Studies, Monday, April 15, 2024

Interim, Long-term, Safety and Efficacy of XEN1101, a Potent, Selective Potassium Channel Opener: Update From an Ongoing Open-Label Extension of a Phase 2b Study (X-TOLE) in Adults With Focal Epilepsy

JACQUELINE FRENCH,[1] ROGER PORTER,[2] EMILIO PERUCCA,[3] MARTIN BRODIE,[4] MICHAEL A. ROGAWSKI,[5] CYNTHIA HARDEN,[6] JENNY QIAN,[6] CONSTANZA LUZON ROSENBLUT,[6] CHRISTOPHER KENNEY,[6] GREGORY N. BEATCH[6]

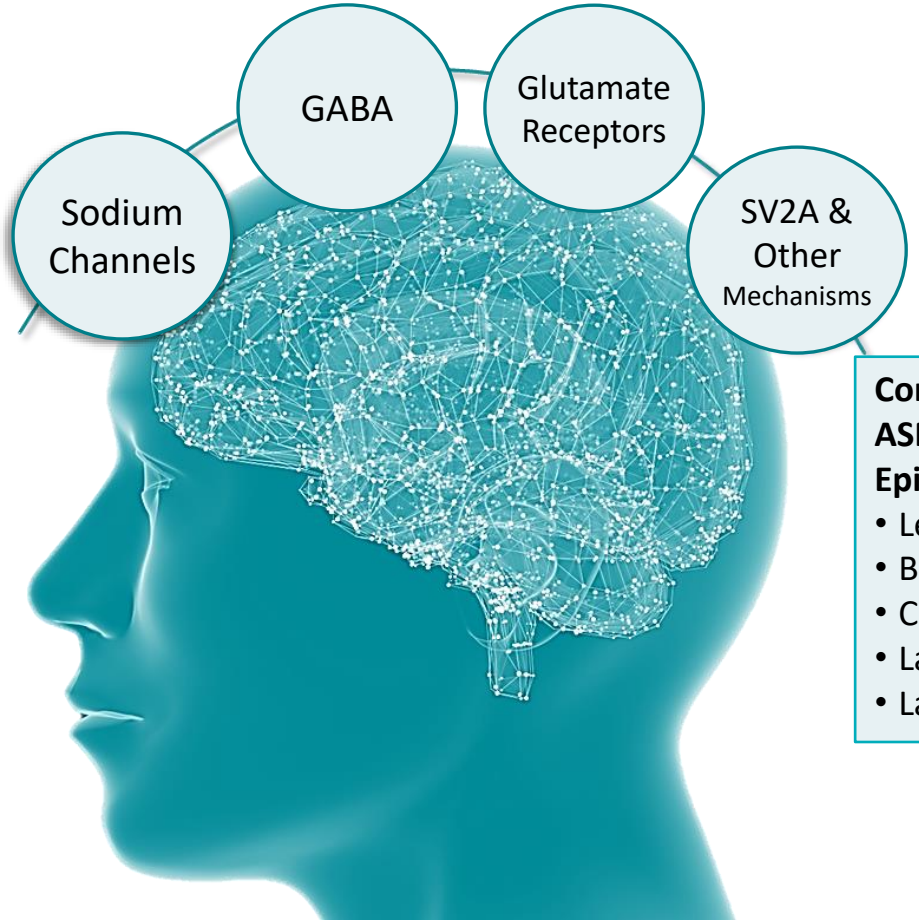
[1]New York University Grossman School of Medicine and NYU Langone Health, New York, NY, USA; [2]University of Pennsylvania, Philadelphia, PA, USA; [3]Monash University, Melbourne, VI, Australia, and University of Melbourne (Austin Health), Heidelberg, VI, Australia; [4]University of Glasgow Department of Medicine and Therapeutics, Western Infirmary, Glasgow, Scotland, UK; [5]School of Medicine, University of California, Davis, Sacramento, CA, USA; [6]Xenon Pharmaceuticals Inc., Vancouver, BC, Canada

Disclosures: Jacqueline French has 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. She receives salary support from the Epilepsy Study Consortium and no other income from these relationships.
Acknowledgments: Editorial assistance was provided by The Curry Rockefeller Group, LLC and funded by Xenon Pharmaceuticals Inc.

XEN1101 K_v7 Potassium Channel Opener

- XEN1101 is a novel, potent, K_v7 potassium channel opener currently in development for epilepsy and major depressive disorder[1-5]
- The pharmacokinetic properties support once-daily dosing with food, and no titration required[6]

Common Pharmacological Actions of Approved Antiseizure Medications (ASMs)[7,8]



Commonly Prescribed ASMs for Adult Focal Epilepsy

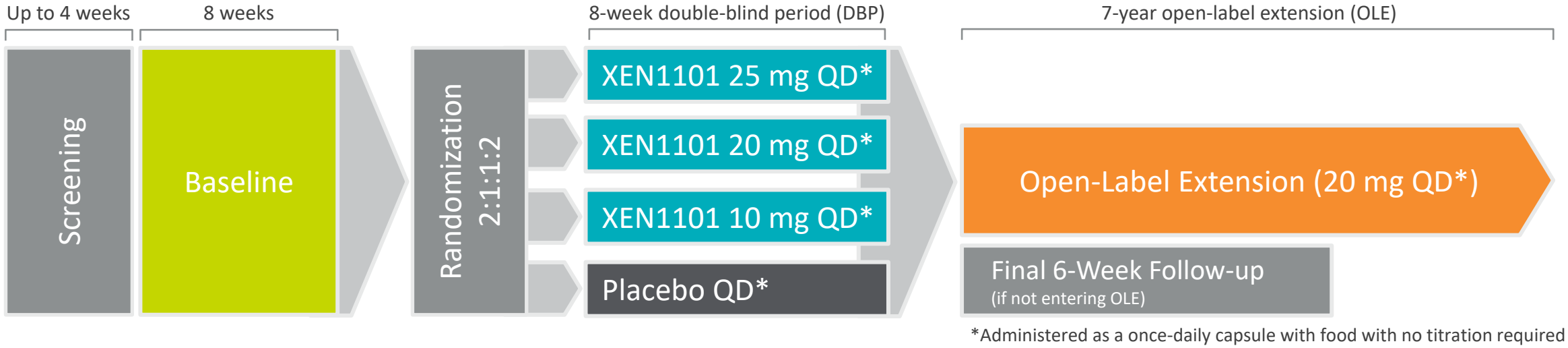
- Levetiracetam
- Brivaracetam
- Carbamazepine
- Lamotrigine
- Lacosamide

ASM, antiseizure medication; GABA, γ-aminobutyric acid; SV2A synaptic vesical protein A.

1. https://www.clinicaltrials.gov/study/NCT03796962. 2. https://clinicaltrials.gov/study/NCT05667142. 3. https://clinicaltrials.gov/study/NCT05614063
4. https://clinicaltrials.gov/study/NCT05716100. 5. https://clinicaltrials.gov/study/NCT05376150. 6. Bialer M, et al. *Epilepsia*. 2022;63(11):2883-2910. 7. Rogawski MA, et al. *Cold Spring Harb Perspect Med.* 2016;6(5):a022780. 8. Hakami T. *Neuropsychopharmacol Rep*. 2021;41(3):336-351.

X-TOLE and X-TOLE OLE

X-TOLE™
Phase 2b study and 7-year OLE



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

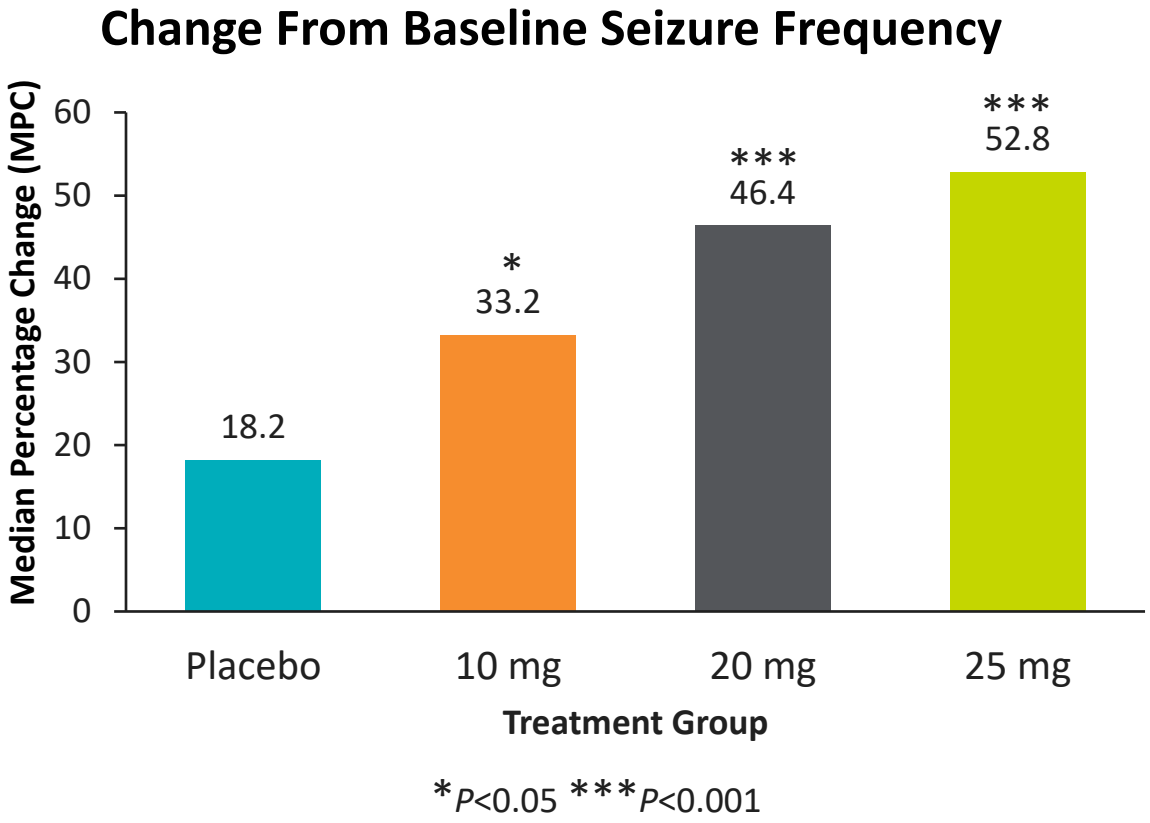
- X-TOLE is a completed Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study with an ongoing optional 7-year open-label extension (OLE) evaluating the efficacy, safety, and tolerability of XEN1101 administered with food as adjunctive treatment in adults with FOS[1]
- Key eligibility criteria included age 18–75 years with a diagnosis of focal epilepsy per the International League Against Epilepsy criteria (≥2 years)[2], ≥4 countable focal seizures per month during a planned 8-week baseline period, and receiving stable treatment with 1–3 antiseizure ASMs[1]

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

1. French JA, et al. *JAMA Neurol*. 2023;80(11):1145-1154. 2. Fisher RS, et al. *Epilepsia*. 2017;58(4):522-530.

X-TOLE DBP Results[1]

- The trial met its primary efficacy end point, with XEN1101 demonstrating a statistically significant, dose-dependent percent reduction from baseline in median monthly FOS seizure frequency
- XEN1101 was generally well tolerated, with a low incidence of serious adverse events (AEs), and no cardiovascular safety signals were identified



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

1. French JA, et al. *JAMA Neurol*. 2023;80(11):1145-1154.

X-TOLE OLE Patient Population*[1]

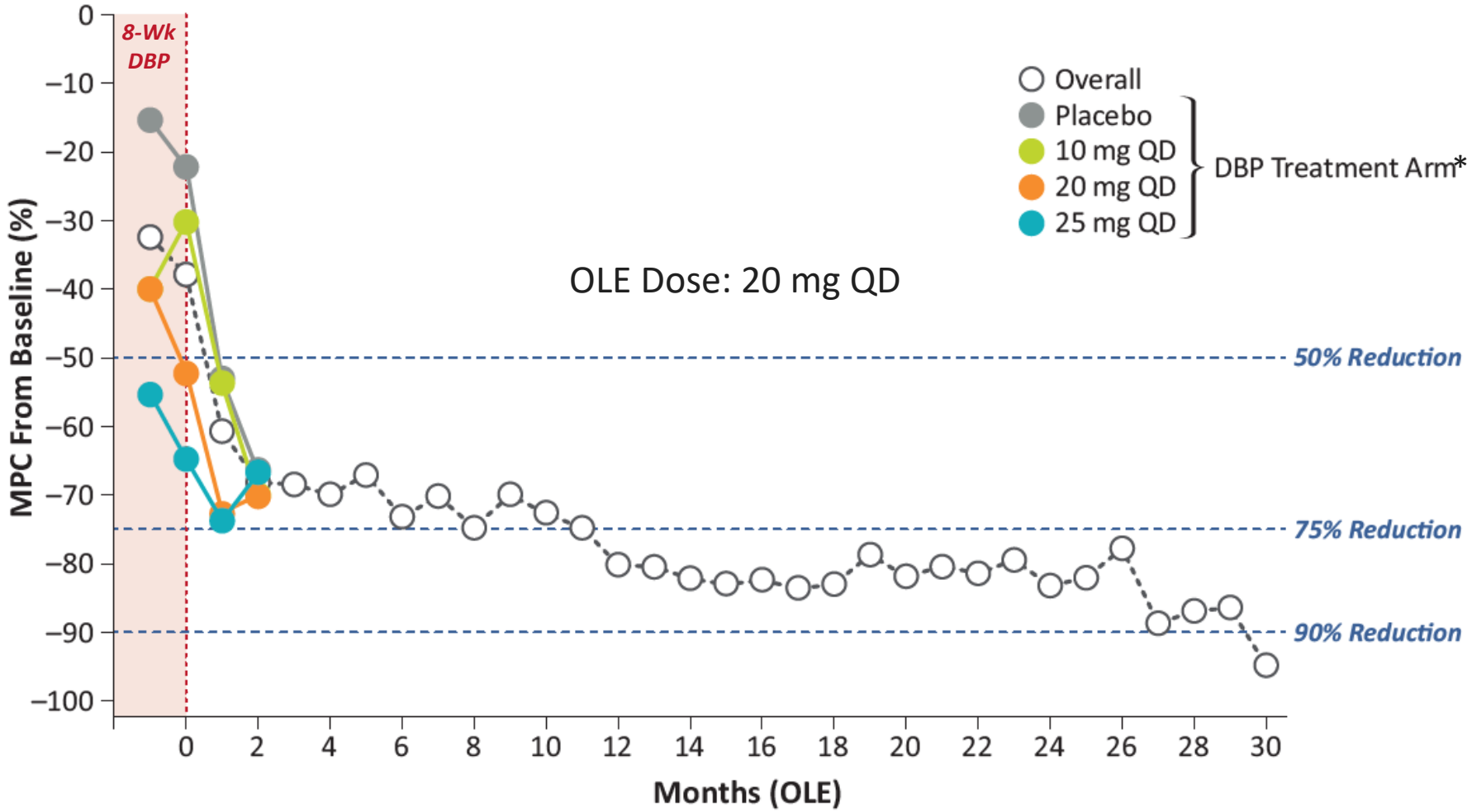
Characteristic	OLE Population (N=275)
Age at study entry, mean (SD), y	41.1 (13.3)
Sex, n (%)	
Male	137 (49.8)
Female	138 (50.2)
Race, n (%)	
White	250 (90.9)
Black	11 (4.0)
Other	14 (5.1)
Region, n (%)	
North American	109 (39.6)
Europe	166 (60.4)
BMI, mean (SD), kg/m^2	27.0 (5.2)
Age at epilepsy onset, mean (SD), y	18.1 (13.8)
Baseline seizure rate per mo, median (IQR)	13.5 (7.9, 30.3)
Number of prestudy ASMs failed, mean (SD)	6.5 (3.68)
Background ASM use, n (%)	
1 ASM	23 (8.4)
2 ASMs	108 (39.3)
3 ASMs	144 (52.4)
CYP3A4 inducer use, n (%)	160 (58.2)

- Of the 285 patients who completed the DBP, 275 (96.5%) enrolled in the OLE
- The percentage of patients continuing XEN1101 into the OLE study period
  - At ≥12 months: 66% (n=182)
  - At ≥24 months: 60% (n=165)
- At the analysis cutoff (Sept 5, 2023) 153 patients (55.3%) continued to participate in the OLE
- The most common reasons for discontinuation were lack of efficacy (13.8%), AEs (12.0%), and study withdrawal by the patient (12.0%)

**DBP baseline. AE, adverse event; ASM, antiseizure medication; BMI, body mass index; CYP3A4, cytochrome P450 3A4; DBP, double-blind period; IQR, interquartile range; OLE, open-label extension.*

1. French J, Porter R, Perucca E, et al. Poster 1.277. Presented at: American Epilepsy Society Annual Meeting. December 1–5, 2023; Orlando, FL.

X-TOLE OLE Efficacy: MPC in Seizure Frequency From Baseline

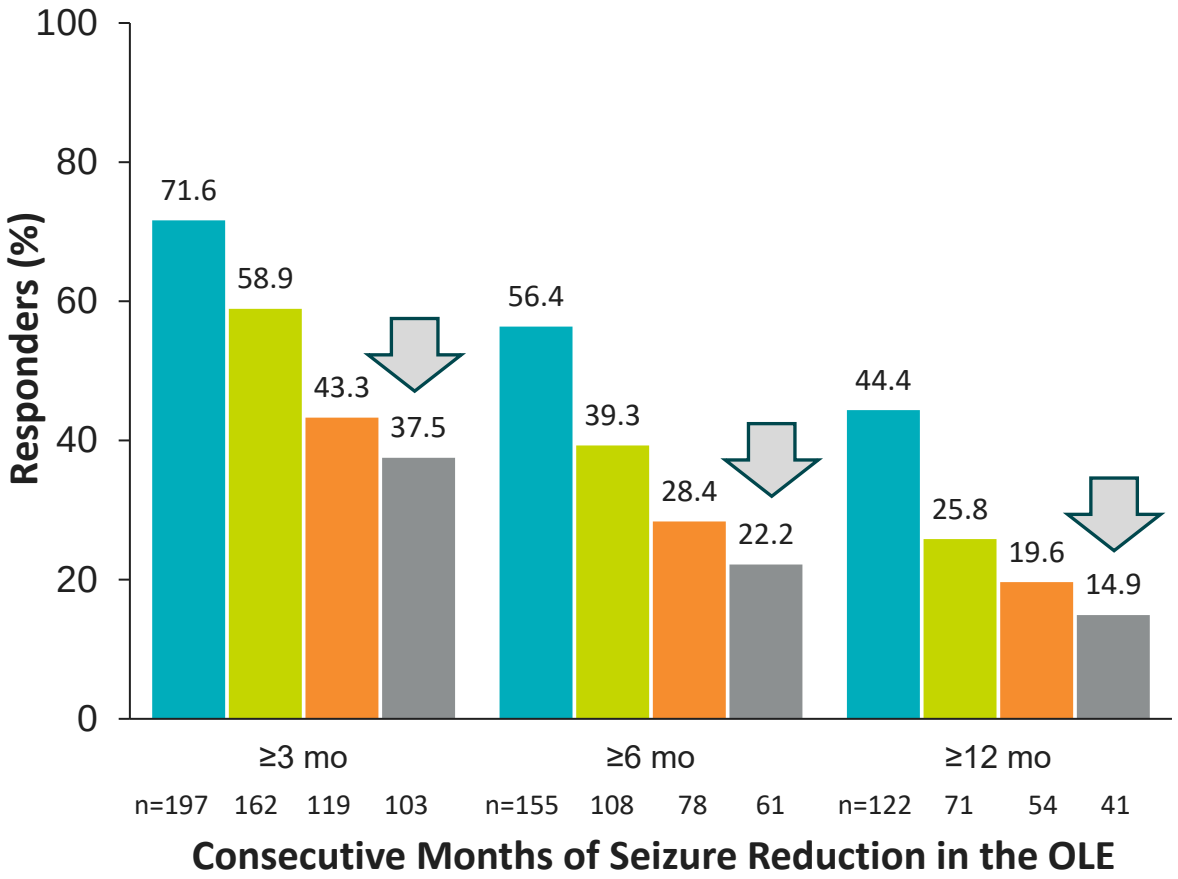


Patients n: 275 251 232 206 196 193 187 177 170 167 167 166 164 162 134 124

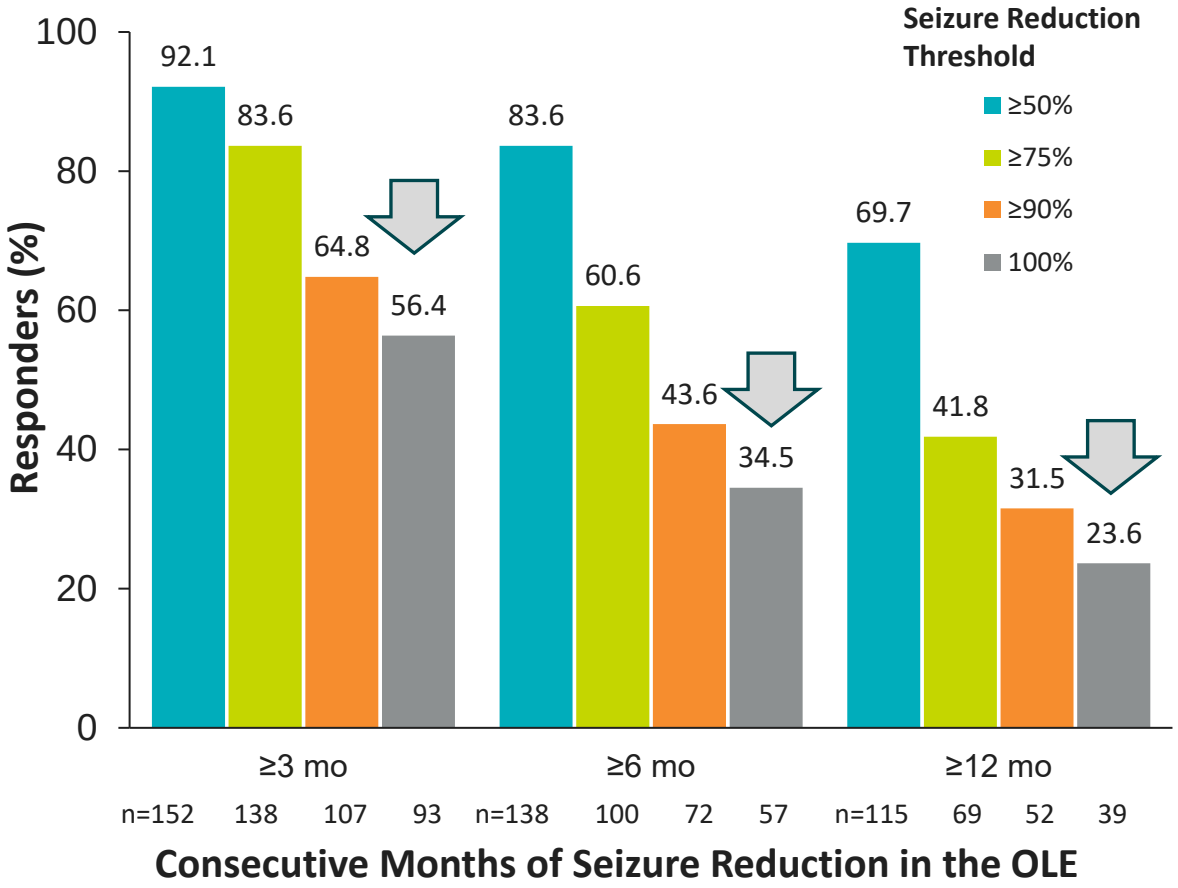
**All doses taken with food with no titration required. Monthly seizure rate was calculated for 28 days per month. Following DBP, all patients received 20 mg QD with food at start of OLE. OLE patients separated by prior DBP treatment groups shown for first 2 months of OLE. One patient was not included in seizure frequency data because of noncompliance with seizure diary.*
DBP, double-blind period; MPC, median percentage change; OLE, open-label extension; QD, once daily

Monthly Median Percentage Seizure Reduction From Baseline for Consecutive Periods of ≥3, ≥6, and ≥12 Months During the OLE

All Patients (n=275) Who Entered OLE



Patients (n=165) Treated for ≥24 Months in the OLE



OLE, open-label extension.

X-TOLE OLE Safety

- XEN1101 20 mg QD with food was generally well tolerated, and the safety profile observed was similar to that of the DBP
- At the end of the second year, patients recorded a mean (SD) weight change of -0.2 (8.8) kg
- TEAEs occurred in 87.3% of the safety population
- SAEs were reported in 35 (12.7%) patients
  - SAEs reported in >1 patient were change in seizure presentation in 6 (2.2%) patients, and paresthesia, pneumonia, deep vein thrombosis, and fall reported in 2 (0.7%) patients each
- 3 patients reported urinary retention, 1 reported as mild and 2 other as moderate; no dose changes were made in either case
- There was 1 sudden unexplained death in epilepsy reported, determined by the investigator not to be related to the study drug

AE, adverse event; DBP, double-blind period; OLE, open-label extension; QD, once daily; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.

Summary of TEAEs, n (%)	XEN1101 20 mg (n=275)
At least 1 TEAE	240 (87.3)
At least 1 SAE	35 (12.7)
At least 1 TEAE leading to permanent treatment discontinuation	30 (10.9)
At least 1 SAE leading to death	1 (0.4)
Most common AEs (≥5% of overall OLE population), n (%)	
Dizziness	60 (21.8)
Coronavirus infection	42 (15.3)
Headache	42 (15.3)
Fall	35 (12.7)
Somnolence	35 (12.7)
Memory impairment	30 (10.9)
Weight increased	26 (9.5)
Gait disturbance	23 (8.4)
Fatigue	22 (8.0)
Urinary tract infection	22 (8.0)
Aphasia	21 (7.6)
Change in seizure presentation	20 (7.3)
Nasopharyngitis	17 (6.2)
Confusional state	16 (5.8)
Disturbance in attention	15 (5.5)
Balance disorder	14 (5.1)
Paresthesia	14 (5.1)
Tremor	14 (5.1)

Conclusions

X-TOLE™
Phase 2b study and 7-year OLE

- XEN1101 20 mg QD with food yielded long-term efficacy in this interim analysis with 60% retention at 24 months
- In the patients that remained in the study for 18–30 months, there was a sustained monthly reduction in seizure frequency (78%–95% MPC) from DBP baseline
- Seizure freedom for ≥6-month, and ≥12-month consecutive durations was achieved in 22.2%, and 14.9% of all patients enrolled in the OLE, respectively
- XEN1101 continues to be generally well tolerated in the OLE with AEs consistent with prior results and other ASMs; no new safety signals were identified
- These promising data suggest long-term efficacy and tolerability of XEN1101 in a difficult-to-treat population

AE, adverse event; ASM, antiseizure medication, DBP, double-blind period; FOS, focal onset seizure; MPC, median percentage change; OLE, open-label extension; QD, once daily.