# 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

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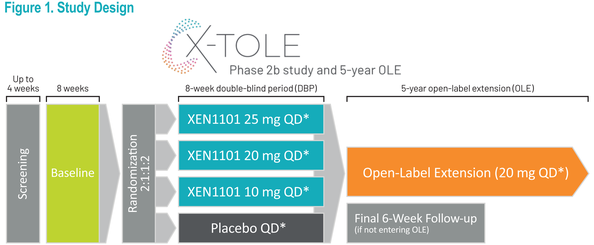
## INTRODUCTION

- XEN1101 is a novel, potent, K$_v$7 potassium channel opener in development for the treatment of focal onset seizures (FOS), primary generalized tonic-clonic seizures, and major depressive disorder[1-5]
  - X-TOLE is a completed Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study with an ongoing optional 5-year open-label extension (OLE) evaluating the efficacy, safety, and tolerability of XEN1101 administered with food as adjunctive treatment in adults with FOS[6]
  - In the double-blind period (DBP), XEN1101 treatment yielded a dose-dependent, consistent, highly statistically significant reduction in FOS across endpoints in a difficult-to-treat patient population[6]
  - XEN1101 was generally well tolerated with a low incidence of serious adverse events (AEs), and no cardiovascular safety signals were identified[6]
- The results presented here are interim data (cutoff date September 5, 2023) from the OLE of X-TOLE in which patients received open-label XEN1101 at a dose of 20 mg once daily (QD) with food

## METHODS

- The study design for the X-TOLE study (ClinicalTrials.gov identifier, NCT03796962)[1] is shown in **Figure 1**

**Figure 1. Study Design**




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

- The key eligibility criteria for the DBP were as follows:
  - Aged 18–75 years (inclusive) with a diagnosis of focal epilepsy per International League Against Epilepsy criteria (≥2 years)[7]
  - Receiving stable treatment with 1 to 3 antiseizure medications (ASMs)
  - Countable seizure frequency over the 8-week baseline period of ≥4 focal seizures per month on average, recorded in an eDiary
- Patients who successfully completed the DBP with a minimum of 80% compliance with the study medication were eligible to enroll in the OLE
- Patients enrolled in the OLE received XEN1101 20 mg QD taken with the evening meal
- Efficacy in the OLE was evaluated by median percentage change (MPC) in monthly FOS frequency from DBP baseline and percentage of patients with ≥50% reduction from DBP baseline in monthly FOS frequency
- Safety was assessed as severity and frequency of treatment-emergent AEs (TEAEs) and serious AEs, clinically significant changes in laboratory findings, and other measures
- Assessments occurred at week 3 in the OLE (study day 77, week 11 from randomization) and 3-month intervals thereafter for the first year
- After the first year, on-site visits occurred at 6-month intervals with teleconferences at 3 months between each on-site visit

## RESULTS

### Patients

- A total of 325 patients were randomized (placebo n=114, 10-mg group n=46, 20-mg group n=51, 25-mg group n=114). Of the 285 patients who completed the DBP, 275 (96.5%) enrolled in the OLE
- Demographics and baseline characteristics of patients in the OLE were consistent with those observed in the DBP (**Table 1**)

**Table 1. Demographics and Baseline* Characteristics of the OLE Population**

| 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 America | 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) |

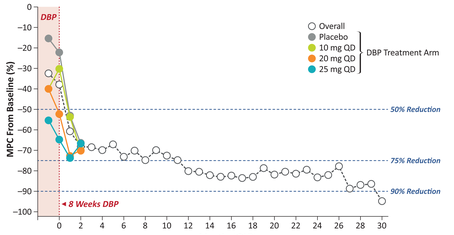
**DBP baseline. ASM, antiseizure medication; BMI, body mass index; CYP3A4, cytochrome P450 3A4; DBP, double-blind period; IQR, interquartile range; OLE, open-label extension.*

- At the analysis cutoff (September 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%)
- A total of 182 patients were treated in the OLE for ≥12 months; 165 patients were treated for ≥24 months at the time of the analysis cutoff
  - The percentage of patients continuing XEN1101 at 12 months and 24 months into the OLE study period were 66% and 60%, respectively

### Efficacy

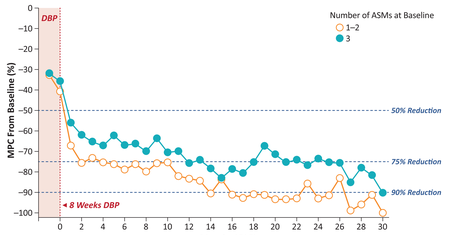
- For ongoing OLE patients, monthly MPC reductions in FOS frequency ranged from 61% to 95% from DBP baseline and were maintained at 78% to 95% in OLE study months 12 to 30 (**Figure 2**)
- Higher reductions were observed for patients who were receiving 1 to 2 ASMs at baseline compared with those receiving 3 ASMs (**Figure 3**)
- 37.5% (103/275) of all patients who entered the OLE achieved seizure freedom for any consecutive ≥3-month duration, 22.2% (61/275) were seizure free for any ≥6 consecutive months, and 14.9% (41/275) were seizure free for ≥12 consecutive months. Responder rates are summarized in **Figure 4**
  - For those patients who reached at least 24 months in the OLE (n=165) the percentages of seizure freedom were 56.4% (93/165) for ≥3 months, 34.5% (57/165) for ≥6 months, and 23.6% (39/165) for ≥12 months

**Figure 2. MPC in Monthly FOS Frequency During DBP and OLE**




*Notes: 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. 1 patient was not included in seizure frequency data because of non-compliance with seizure diary. DBP, double-blind period; FOS, focal onset seizure; MPC, median percentage change; OLE, open-label extension; QD, once daily.*

**Figure 3. MPC in Monthly FOS Frequency During DBP and OLE by Baseline Number of ASMs**




*Note: Monthly seizure rate was calculated for 28 days per month. ASM, antiseizure medication; DBP, double-blind period; FOS, focal onset seizures; MPC, median percentage change; OLE, open-label extension.*

### Safety

- XEN1101 20 mg QD 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 from the start of the OLE
- TEAEs occurred in 87.3% of the safety population; the most common TEAEs are summarized in **Table 2**

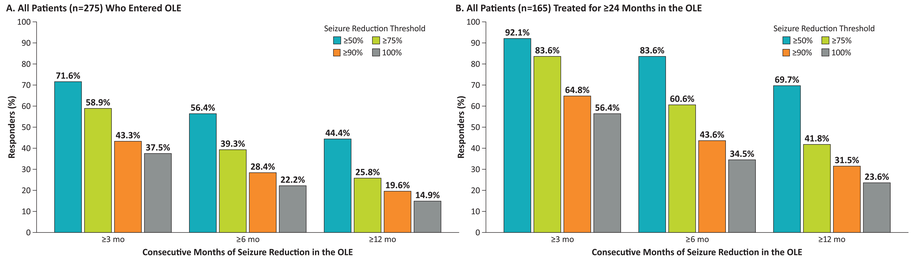
**Table 2. TEAEs During OLE Period**

| Summary of TEAEs, n (%) | XEN1101 20 mg (n=275) |
|---|---|
| At least 1 TEAE | 240 (87.3) |
| At least 1 serious TEAE | 35 (12.7) |
| At least 1 TEAE leading to permanent treatment discontinuation | 30 (10.9) |
| At least 1 serious TEAE leading to death | 1 (0.4) |
| Most common AEs (≥5% of overall OLE population), n (%) | |
| Dizziness | 60 (21.8) |
| Headache | 42 (15.3) |
| Coronavirus infection | 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) |

*AE, adverse event; OLE, open-label extension; TEAE, treatment-emergent adverse event.*

- In addition to the TEAEs summarized in **Table 2**, 3 patients reported urinary retention, 1 reported as mild and the 2 other as moderate; no dose changes were made in any case
- As shown in **Table 2**, serious TEAEs were reported in 35 (12.7%) patients. The only serious TEAEs reported in >1 patient were change in seizure presentation in 6 (2.2%) patients, and pneumonia, deep vein thrombosis, and fall reported in 2 (0.7%) patients each
- There was 1 sudden unexplained death in epilepsy (SUDEP) reported, determined by the investigator not to be related to the study drug

**Figure 4. Fraction of Patients Maintaining Specific Levels of Monthly Median Percentage Seizure Reduction From Baseline for Consecutive Periods of ≥3, ≥6, and ≥12 Months During the OLE**




*OLE, open-label extension.*

## CONCLUSIONS

- XEN1101 20 mg QD with food yielded long-term efficacy in this interim analysis with 60% retention at 24 months
- During OLE study months 18 to 30, there was a sustained monthly reduction in seizure frequency (78%–95% MPC) from DBP baseline
- Seizure freedom for ≥3-month, ≥6-month, and ≥12-month consecutive durations was achieved in 37.5%, 22.2%, and 14.9% of all patients enrolled in the OLE, respectively
- Seizure freedom for ≥3-month, ≥6-month, and ≥12-month consecutive durations was achieved in 56.4%, 34.5% and 23.6% of those patients with at least 24 months treatment in the OLE (n=165)
- XEN1101 continues to be generally well-tolerated in the OLE with AEs consistent with prior results and other ASMs AEs; no new safety signals were identified
- These promising data suggest long-term efficacy and tolerability of XEN1101 in a difficult-to-treat population

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