# The Impact of Disease Severity on Responder Rates in a Phase 2b Study of XEN1101, a Potent, Selective Potassium Channel Opener, in Adults With Focal Epilepsy (X-TOLE)

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## INTRODUCTION

- XEN1101 is a novel, potent $K_V7$ 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 X-TOLE, XEN1101 (10, 20, and 25 mg once daily [QD] with food) showed a dose-dependent, highly statistically significant, and rapid-onset reduction in FOS frequency[6,7]
- XEN1101 was generally well tolerated, with adverse events consistent with commonly prescribed antiseizure medications (ASMs)[6]
- Compared to other recent adult FOS clinical studies (**Table 1**), X-TOLE included a difficult-to-treat patient population given the baseline seizure burden, number of tried and stopped ASMs, and number of concomitant ASMs during the study[6]

### Table 1. Summary of Recent FOS Trials: Baseline Seizure Frequencies and Concomitant ASMs

| Drug | Phase (Study Years) | Total N (Population) | BL Median Monthly Seizure Frequency, Mean (SD)* | BL Median Monthly Seizure Frequency, Median (Min, Max)† | Allowed Concomitant ASMs | Concomitant ASMs ≤2, % of Patients | Concomitant ASMs = 3, % of Patients |
|---|---|---|---|---|---|---|---|
| XEN1101[6] | Phase 2b (2019–2021) | 325 (Safety) | N/A‡ | 13.5 (13.5,13.5) | 1 to 3 | 49.5% | 50.5% |
| Cenobamate[8,9] | Phase 2 and 3 (2011–2015) | 659 (Safety) | 8.5 (1.9) | 8.7 (5.5, 11) | 1 to 3 | 70.1% | 29.6%§ |
| Brivaracetam[10-14] | Phase 2 and 3 (2005–2014) | 1919 (ITT) | 9.1 (1.3) | 9.0 (7.0, 11.8) | 1 to 2 | 96.1% | 3.8%¶ |
| Perampanel[15-18] | Phase 2 (2005–2007) | 153 (Safety) | N/A# | N/A# | 1 to 2 | 99.3%‖ | 0% |
| | Phase 2 and 3 (2007–2010) | 1526 (Safety) | 11.9 (1.8) | 11.9 (9.3, 14.3) | 1 to 3 | 64.8% | 35.2% |
| Lacosamide[19-21] | Phase 2 (2002–2004) | 415 (Safety) | N/A** | 11-13‖ | 1 to 2 | 100% | 0% |
| | Phase 2 and 3 (2004–2006) | 879 (Safety) | 12.5 (2.7) | 11.5 (9.9, 16.5) | 1 to 3 | 67.6% | 32.4% |

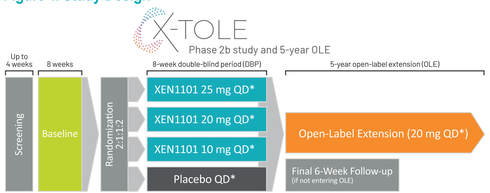
*ASM, antiseizure medication; BL, baseline; FOS, focal onset seizure. *Calculated as the mean (SD) of median monthly seizure frequency reported in each referenced study. †Calculated as the median (min, max) of median monthly seizure frequency reported in each referenced study. ‡Requires multiple studies for analysis. §Some additional patients received temporary treatment with a fourth ASM. ¶Subset of patients used benzodiazepines as needed. #Not reported. ‖As reported. **Not calculated due to method used to report baseline median monthly seizures.*

- The study population of X-TOLE included a spectrum of disease severity, allowing for comparison of the effect of baseline disease severity characteristics on efficacy outcomes
- A prior post hoc analysis of X-TOLE suggested that the efficacy of XEN1101 25 mg QD with food, measured by the median percentage change (MPC) in monthly FOS frequency, may be most pronounced in patients with less-severe disease[22]
- Another widely used efficacy endpoint for evaluating ASM efficacy is the percentage of patients with a ≥50% reduction in seizure frequency during a given treatment period compared with baseline, known as the responder rate or RR50. We report the potential impact of baseline disease severity on the RR50 in patients treated with XEN1101 25 mg QD in X-TOLE

## METHODS

- Key eligibility criteria: aged 18–75 years with a diagnosis of focal epilepsy per International League Against Epilepsy criteria (≥2 years),[23] ≥4 countable focal seizures per month during a planned 8-week baseline period, and receiving stable treatment with 1 to 3 ASMs
- A total of 325 patients were randomized to an 8-week double-blind period (DBP) and treated across 3 active treatment groups or placebo in a 2:1:1:2 ratio (25 mg: 20 mg: 10 mg: placebo, QD with food; **Figure 1**)

### Figure 1. Study Design




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

- Post hoc analyses were performed to assess the influence of baseline disease severity as indicated by seizure frequency (≤8.5 and >8.5 seizures per month), number of concomitant ASMs (≤2 or =3), and number of previously tried and stopped ASMs (median of ≤6 and >6) on the responder rate, defined as the RR50 in monthly FOS frequency from baseline to the DBP. The post hoc analysis data presented below pertain to patients given 25 mg QD with food (25 mg group)
  - The ≤8.5 and >8.5 seizures per month frequency was based on the average median baseline seizure frequencies of the cenobamate randomized controlled trials (**Table 1**)

## RESULTS

### Demographics and Baseline Characteristics

- At DBP baseline, patients in the 25 mg group (n=114) had a median of 12.8 monthly seizures and had tried and discontinued a median of 6 ASMs; 48.2% were taking 3 concomitant ASMs[6] (**Table 2**)
- Patients in the placebo group (n=114) had a median of 13.4 monthly seizures and had tried and discontinued a median of 6 ASMs at DBP baseline; 49.1% were taking 3 concomitant ASMs[6] (**Table 2**)

### Table 2. Demographic and DBP Baseline Characteristics of the Placebo and 25 mg Groups[6]

| | Placebo (n=114) | XEN1101 25 mg (n=114) |
|---|---|---|
| Age at study entry, mean (SD), y | 42.9 (13.7) | 38.7 (13.1) |
| ≥65 | 5 (4.4) | 1 (0.9) |
| <65 | 109 (95.6) | 113 (99.1) |
| Sex, n (%) | | |
| Female | 61 (53.5) | 54 (47.4) |
| Male | 53 (46.5) | 60 (52.6) |
| Region, n (%) | | |
| Europe | 67 (58.8) | 68 (59.6) |
| North America | 47 (41.2) | 46 (40.4) |
| Baseline seizure frequency per mo | | |
| Mean (SD) | 27.3 (38.5) | 23.5 (30.4) |
| Median | 13.4 | 12.8 |
| Background ASM use, n (%) | | |
| 1 ASM | 12 (10.5) | 11 (9.6) |
| 2 ASMs | 46 (40.4) | 48 (42.1) |
| 3 ASMs | 56 (49.1) | 55 (48.2) |
| Number of prestudy ASMs failed, n (%) | | |
| ≤3 ASMs | 29 (25.4) | 31 (27.2) |
| >3 ASMs, | 85 (74.6) | 83 (72.8) |
| Median (IQR) | 6.0 (4.0–8.0) | 6.0 (3.0–9.0) |

*ASM, antiseizure medication; IQR, interquartile range.*

### Efficacy Results: Baseline Disease Severity Impact on RR50 in the 25 mg Group

#### *Baseline Seizure Sub-Group Analysis*

- RR50 was achieved by 65.5% of patients with ≤8.5 seizures per month at baseline and 50.6% with >8.5 seizures per month; with placebo treatment, RR50 was higher (20.0% vs 13.1%) in the ≤8.5 vs >8.5 seizure per month sub-group (**Figure 2**)

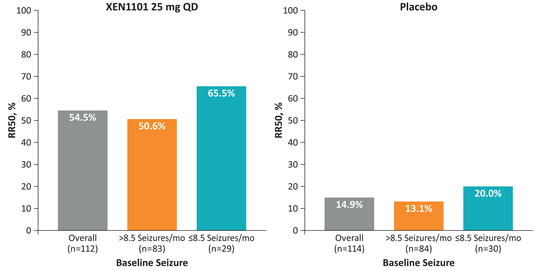
#### *Number of Tried and Stopped ASMs Sub-Group Analysis*

- RR50 was achieved by 64.2% of patients with ≤6 tried and stopped ASMs and 40.0% with >6 ASMs; with placebo treatment, RR50 was higher (19.4% vs 8.5%) in the ≤6 vs >6 tried and stopped ASMs sub-group (**Figure 3**)

#### *Concomitant ASMs Sub-Group Analysis*

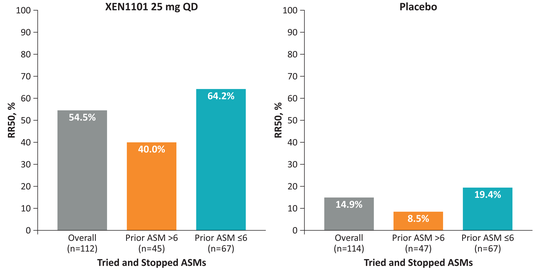
- RR50 was achieved by 56.9% of patients treated with 1–2 concomitant ASMs throughout and 51.9% treated with 3 concomitant ASMs throughout the study (**Figure 4**)

### Figure 2. Baseline Seizure Sub-Group Analysis



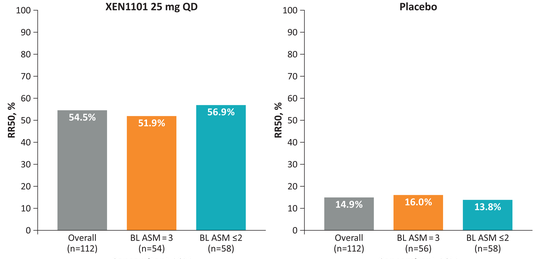

*Note: All doses taken with food. RR50, percentage of patients with a ≥50% reduction in seizure frequency.*

### Figure 3. Tried and Stopped Sub-Group Analysis




*Note: All doses taken with food. ASM, antiseizure medication; RR50, percentage of patients with a ≥50% reduction in seizure frequency.*

### Figure 4. Concomitant ASMs Sub-Group Analysis




*Note: All doses taken with food. ASM, antiseizure medication; BL, baseline; RR50, percentage of patients with a ≥50% reduction in seizure frequency.*

## CONCLUSIONS

- Consistent with the significant MPC reduction in X-TOLE, 54.5% of the patients in the 25 mg group achieved the benchmark of RR50
- This effect was observed in a difficult-to-treat patient population
- XEN1101 was relatively more effective in patients with indicators of less-severe disease in the trial population
- These findings suggest that XEN1101 may be appropriate for use in patients with focal epilepsy across the spectrum of disease severity

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**REFERENCES**

**1.** ClinicalTrials.gov. A Study to Evaluate XEN1101 as Adjunctive Therapy in Focal Epilepsy (X-TOLE). https://clinicaltrials.gov/study/NCT03796962 **2.** ClinicalTrials.gov. A Study to Evaluate XEN1101 as Adjunctive Therapy in Primary Generalized Tonic-Clonic Seizures (X-ACKT). https://clinicaltrials.gov/ct2/show/NCT05667142 **3.** ClinicalTrials.gov. A Randomized Study of XEN1101 Versus Placebo in Focal-Onset Seizures (X-TOLE3). https://clinicaltrials.gov/study/NCT05716100 **4.** ClinicalTrials.gov. A Study to Evaluate the Safety, Tolerability and Efficacy of XEN1101 in Major Depressive Disorder (X-NOVA). https://clinicaltrials.gov/study/NCT05376150 **5.** ClinicalTrials.gov. A Randomized Study of XEN1101 Versus Placebo in Focal-Onset Seizures (X-TOLE2). https://clinicaltrials.gov/study/NCT05614063 **6.** French JA, et al. *JAMA Neurol.* 2023;doi:10.1001/jamaneurol.2023.3542 **7.** 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 number: 2.236]. 2022. https://cms.aesnet.org/abstractslisting/rapid-onset-of-efficacy-of-xen1101--a-novel-potassium-channel-opener--in-adults-with-focal-epilepsy--results-from-a-phase-2b-study-(x-tole) **8.** Chung SS, et al. *Neurology.* 2020;94(22):e2311-e2322. **9.** Krauss GL, et al. *Lancet Neurol.* 2020;19(1):38-48. **10.** Biton V, et al. *Epilepsia.* 2014;55(1): 57-66. **11.** Klein P, et al. *Epilepsia.* 2015;56(12):1890-1898. **12.** French JA, et al. *Neurology.* 2010;75(6):519-525. **13.** Rylvin P, et al. *Epilepsia.* 2014;55(1):47-56. **14.** Van Paesschen W, et al. *Epilepsia.* 2013;54(1):89-97. **15.** French JA, et al. *Neurology.* 2012;79(6):589-596. **16.** French JA, et al. *Epilepsia.* 2013;54(1):117-125. **17.** Krauss GL, et al. *Acta Neurol Scand.* 2012;125(1):8-15. **18.** Krauss GL, et al. *Neurology.* 2012;78(18):1408-1415. **19.** Ben-Menachem E, et al. *Epilepsia.* 2007;48(7):1308-1317. **20.** Chung S, et al. *Epilepsia.* 2010;51(6):958-967. **21.** Halasz P, et al. *Epilepsia.* 2009;50(3):443-453. **22.** Leung J, et al. The impact of disease severity on efficacy from a phase 2b study of XEN1101, a novel potassium channel opener, in adults with focal epilepsy (X-TOLE) [Abstract number: 2.233]. 2022. https://aesnet.org/abstractslisting/the-impact-of-disease-severity-on-efficacy-from-a-phase-2b-study-of-xen1101--a-novel-potassium-channel-opener--in-adults-with-focal-epilepsy-(x-tole) **23.** Fisher RS, et al. *Epilepsia.* 2017;58(4):522-530.



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