Efficacy of Azetukalner in Focal Onset Seizure (FOS) Subtypes: Results From the Double-Blind, Placebo-Controlled X-TOLE Study

Emilio Perucca,[1] Jacqueline A. French,[2] Cynthia Harden,[3] Jenny Qian,[3] Constanza Luzon Rosenblut,[3] Christopher Kenney,[3] Gregory N. Beatch[3]

[1]Monash University, Melbourne, VIC, Australia, and University of Melbourne (Austin Health), Heidelberg, VIC, Australia; [2]New York University Grossman School of Medicine and NYU Langone Health, New York, NY, USA; [3]Xenon Pharmaceuticals Inc., Vancouver, BC, Canada

BACKGROUND

- Azetukalner is a novel, potent K_V7 potassium channel opener in development for the treatment of focal onset seizures (FOS), primary generalized tonic-clonic seizures (PGTCS), and major depressive disorder[1-3]
- 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 azetukalner in adults with FOS who failed a median of 6 antiseizure medications (ASMs) and were on stable treatment with 1-3 ASMs[4]
- In the double-blind period (DBP), azetukalner administered once daily with food and no titration period yielded a dose-dependent, rapid, statistically significant reduction in FOS frequency vs placebo[4]
- Azetukalner was generally well tolerated with a low incidence of serious adverse events, and no cardiovascular safety signals were identified in the DBP[4]
- Moreover, azetukalner has been generally well tolerated in the OLE, and no new safety signals have been identified
  - As of the last safety data cut (October 2024), more than 600 participant-years of safety data have been generated through the OLE study

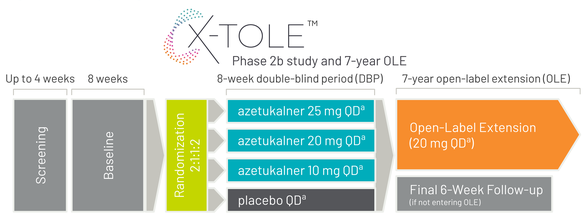
OBJECTIVE

- To report the efficacy of azetukalner by focal seizure subtype in the DBP of the X-TOLE study

METHODS

- The study design for the X-TOLE study (NCT03796962)[1] is shown in **Figure 1**

Figure 1. Study Design



[a]Administered as a once-daily capsule with food and no titration period.
Azetukalner is an investigational product and has not been approved by the FDA or other regulatory bodies.
FDA, US Food and Drug Administration; QD, once daily.

- In the 8-week DBP of X-TOLE, participants who experienced ≥4 FOS while on stable treatment (1-3 ASMs) were randomized 2:1:1:2 to receive azetukalner 25, 20, or 10 mg or placebo taken once daily with food and no titration period[4]
- The modified intention-to-treat population (mITT) consisted of treated patients with ≥1 post-treatment seizure diary entry; the safety population consisted of all patients who were randomized and treated[4]
- The median percentage change (MPC) in monthly (28 days) seizure frequency and the proportion of participants experiencing a ≥50% reduction in monthly seizure frequency (responder rate) were calculated by seizure subtypes as a prespecified exploratory analysis
- Seizure subtypes included in the prespecified exploratory analyses were focal aware with motor signs (type 1), focal impaired awareness with motor signs (type 2), focal impaired awareness with no motor signs (type 3), and focal to bilateral tonic-clonic (type 4)
- Safety outcomes included treatment-emergent adverse events (TEAEs) and serious TEAEs[4]
- The placebo (n=114) and azetukalner (25 mg; n=114) groups are included in this analysis

RESULTS

- A total of 325 participants were randomized and treated (safety population), 323 had ≥1 seizure diary entry (mITT population), and 285 completed the 8-week DBP[4]
  - Of the 325 participants, 114 each were randomized to receive placebo or azetukalner (25 mg)

Baseline Characteristics

- Demographic characteristics were generally similar across placebo and azetukalner (25 mg) groups (**Table 1**)

Table 1. Demographic and Baseline Characteristics (Safety Population)

Characteristic	Placebo (n=114)	Azetukalner 25 mg (n=114)
Age, mean (SD), y	42.9 (13.7)	38.7 (13.1)
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)
BMI, mean (SD), kg/m²	27.3 (5.4)	26.5 (5.1)
Age at disease onset, mean (SD), y	19.2 (14.7)	15.3 (12.1)
CYP3A4 inducer use, n (%)	69 (60.5)	65 (57.0)
Background ASM use, n (%)		
1	12 (10.5)	11 (9.6)
2	46 (40.4)	48 (42.1)
3	56 (49.1)	55 (48.2)
No. of prestudy ASMs failed, median (IQR)	6.0 (4.0-8.0)	6.0 (3.0-9.0)

ASM, antiseizure medication; BMI, body mass index.

- The median monthly baseline seizure frequencies by treatment were 12.8 for azetukalner (25 mg) and 13.4 for placebo
- Median monthly baseline seizure frequencies for seizure subtypes 1, 2, 3, and 4 for azetukalner (25 mg) were 12.6, 9.5, 11.2, and 2.9, respectively, and for placebo were 16.2, 9.0, 11.4, and 1.9 (**Table 2**)

Table 2. Baseline Seizure Characteristics (mITT Population)

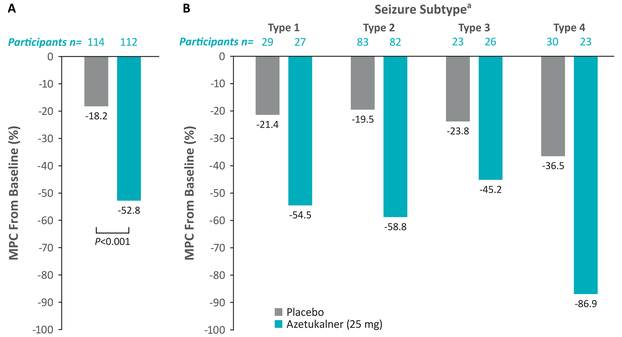
Characteristic	Placebo (n=114)	Azetukalner 25 mg (n=112)
Seizure subtype,[a] n (%)		
Focal aware, motor (type 1)	29 (25.4)	27 (24.1)
Focal impaired awareness, motor (type 2)	83 (72.8)	82 (73.2)
Focal impaired awareness, no motor (type 3)	23 (20.2)	26 (23.2)
Focal to bilateral tonic-clonic (type 4)	30 (26.3)	23 (20.5)
Monthly seizure frequency, median (Q1, Q3)		
Focal aware, motor (type 1)	16.2 (9.3, 23.5)	12.6 (6.4, 33.7)
Focal impaired awareness, motor (type 2)	9.0 (5.5, 24.3)	9.5 (4.3, 15.3)
Focal impaired awareness, no motor (type 3)	11.4 (7.0, 29.5)	11.2 (6.3, 23.8)
Focal to bilateral tonic-clonic (type 4)	1.9 (0.9, 5.0)	2.9 (1.2, 4.3)

[a]Patients could have experienced ≥1 seizure subtype.
mITT, modified intention-to-treat.

Efficacy

- MPC reduction from baseline was higher for azetukalner (25 mg) compared with placebo in the overall population (all FOS combined) and across seizure subtypes (1-4) (**Figure 2**)

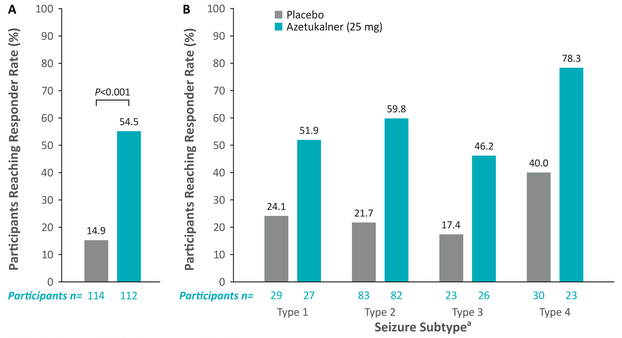
Figure 2. MPC in Monthly FOS Frequency During DBP (A) in the Overall Population (all FOS combined)[4] and (B) by Seizure Subtype (mITT Population)



DBP, double-blind period; FOS, focal onset seizure; mITT, modified intention-to-treat; MPC, median percentage change.
Azetukalner administered once daily with food and no titration period.
[a]Exploratory descriptive analysis; statistical significance was not assessed.

- The responder rate was also higher for azetukalner (25 mg) than placebo in the overall population (all FOS combined) and across seizure subtypes (1-4) (**Figure 3**)

Figure 3. Responder Rates During DBP (A) in the Overall Population (all FOS combined)[4] and (B) by Seizure Subtype (mITT Population)



DBP, double-blind period; FOS, focal onset seizure; mITT, modified intention-to-treat.
Azetukalner administered once daily with food and no titration period.
Responder rate was defined as the proportion of participants experiencing a ≥50% reduction in monthly seizure frequency.
[a]Exploratory descriptive analysis; statistical significance was not assessed.

Safety

- Azetukalner was generally well tolerated, with a safety profile that was similar to that of other commonly prescribed ASMs[4]
- The most common TEAEs for azetukalner (25 mg) were dizziness (31.6%), somnolence (14.9%), fatigue (12.3%), balance disorder (11.4%), and tremor (10.5) (**Table 3**)
  - Serious TEAEs were reported in 2.6% of participants in both the azetukalner (25 mg) and placebo groups

Table 3. Summary of TEAEs

TEAE, n (%)	Placebo (n=114)	Azetukalner 25 mg (n=114)
Summary of all TEAEs		
≥1 TEAE	71 (62.3)	97 (85.1)
≥1 serious TEAE	3 (2.6)	3 (2.6)
≥1 TEAE leading to permanent treatment discontinuation	4 (3.5)	18 (15.8)
≥1 serious TEAE leading to death	0	0
Most common TEAEs (≥10% in either group)		
Dizziness	8 (7.0)	36 (31.6)
Somnolence	8 (7.0)	17 (14.9)
Fatigue	6 (5.3)	14 (12.3)
Balance disorder	2 (1.8)	13 (11.4)
Tremor	2 (1.8)	12 (10.5)

TEAE, treatment-emergent adverse event.

CONCLUSIONS

- In the DBP of X-TOLE, azetukalner was efficacious and was well tolerated in a highly treatment-resistant patient population
- Compared with placebo, azetukalner (25 mg) reduced the seizure frequency rate across all focal seizure subtypes, including focal to bilateral tonic-clonic seizures, in the X-TOLE study
  - This exploratory analysis consisted of small subgroup sizes for the 4 different seizure subtypes
- The efficacy of azetukalner in FOS subtypes is being further investigated in ongoing Phase 3 studies (X-TOLE2 and X-TOLE3)
- In addition, a Phase 3, randomized, double-blind, placebo-controlled study to examine the pharmacokinetics, safety, and efficacy of azetukalner as adjunctive treatment in participants with PGTCS is currently enrolling participants (X-ACKT)[2]
  - This study will consist of a 12-week DBP with the option to enroll in a 3-year OLE
  - Primary efficacy endpoints will include MPC in monthly PGTCS frequency from baseline through the DBP (US Food and Drug Administration) or proportion of participants experiencing ≥50% reduction in monthly seizure frequency from baseline through the DBP (European Medicines Agency)[2]

ACKNOWLEDGMENTS Medical writing support was provided by Kirk W. Evanson, PhD, from The Curry Rockefeller Group, LLC, a Citrus Health Group, Inc., company (Chicago, IL), and was funded by Xenon Pharmaceuticals Inc.

FUNDING This study was funded by Xenon Pharmaceuticals Inc.

DISCLOSURES **Emilio Perucca** receives speaker or consultancy fees from Eisai, GRIN Therapeutics, Sintetica, SK Life Science, Sun Pharma, Takeda, UCB Pharma, and Xenon Pharmaceuticals Inc. **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. **Cynthia Harden**, **Jenny Qian**, **Constanza Luzon Rosenblut**, **Christopher Kenney**, and **Gregory N. Beatch** are employees of and own stock or stock options in Xenon Pharmaceuticals Inc.

REFERENCES **1.** ClinicalTrials.gov. A study to evaluate XEN1101 as adjunctive therapy in focal epilepsy (X-TOLE). https://www.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/NCT05687142 **3.** ClinicalTrials.gov. A study to evaluate the safety, tolerability and efficacy of XEN1101 in major depressive disorder (X-NOVA). https://clinicaltrials.gov/study/NCT05376150 **4.** French JA, et al. *JAMA Neurol*. 2023;80(11):1145-1154.

XENON