Long-Term Safety and Efficacy of Azetukalner, a Novel, Potent K_V7 Potassium Channel Opener in Adults With Focal Epilepsy: Update From the Ongoing 7-Year Open-Label Extension of X-TOLE

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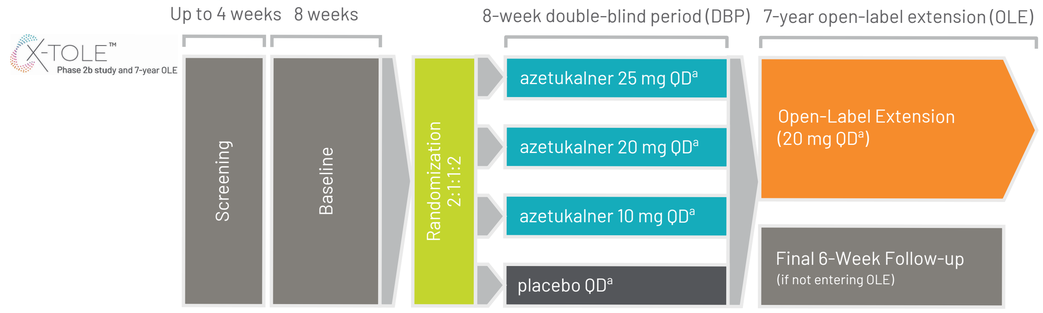
INTRODUCTION

- 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, 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 7-year open-label extension (OLE) evaluating the efficacy, safety, and tolerability of azetukalner administered with food as adjunctive treatment in adults with FOS[6]
  - In the double-blind period (DBP), azetukalner treatment yielded a dose-dependent, statistically significant reduction from baseline in FOS across treatment arms in a difficult-to-treat participant population[6]
  - Azetukalner 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 October 7, 2024) from the OLE of X-TOLE in which participants received open-label azetukalner at a dose of 20 mg once daily (QD) with food

METHODS

- The study design for the X-TOLE study (NCT03796962)[1] is shown in **Figure 1**
- 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
- Participants who successfully completed the DBP with a minimum of 80% compliance with the study medication were eligible to enroll in the OLE
- Participants enrolled in the OLE received azetukalner 20 mg QD taken with food
- Efficacy in the OLE was evaluated by median percentage change (MPC) in monthly FOS frequency from DBP baseline and percentage of participants with ≥50% reduction from DBP baseline in monthly FOS frequency

Figure 1. Study Design



[a]Administered as a once-daily capsule with food with 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.

- 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

Participants

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

Table 1. Demographics and Baseline[a] 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)

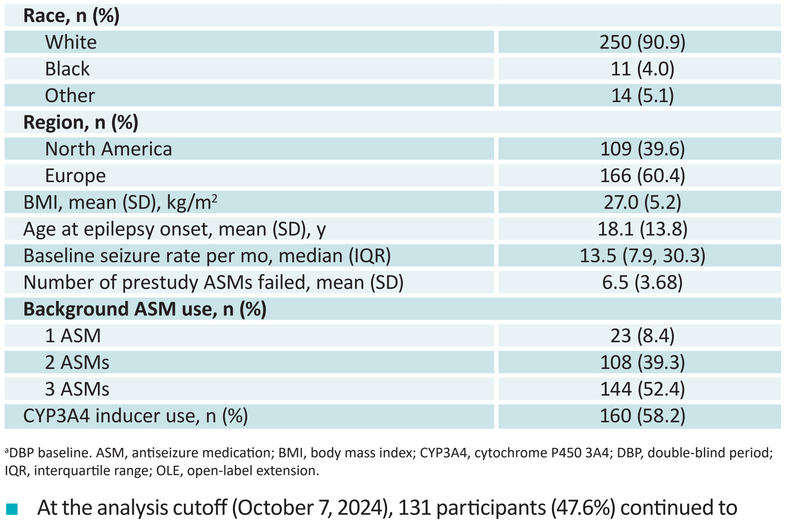
[a]DBP baseline. ASM, antiseizure medication; BMI, body mass index; CYP3A4, cytochrome P450 3A4; DBP, double-blind period; IQR, interquartile range; OLE, open-label extension.

- At the analysis cutoff (October 7, 2024), 131 participants (47.6%) continued to participate in the OLE
  - The most common reasons for discontinuation were lack of efficacy (17.5%), withdrawal by participant (14.9%), and AEs (12.7%)
- A total of 182 participants were treated in the OLE for ≥12 months, 165 participants were treated for ≥24 months, and 143 participants were treated for ≥36 months at the time of the analysis cutoff
  - Retention rates with azetukalner at 12, 24, and 36 months into the OLE study period were 66%, 60%, and 52%, respectively

Efficacy

- For ongoing OLE patients, monthly MPC reductions in FOS frequency ranged from 61%-82% during month 1 to OLE study month 24 and were maintained at 85% at OLE study month 36 (**Figure 2**)

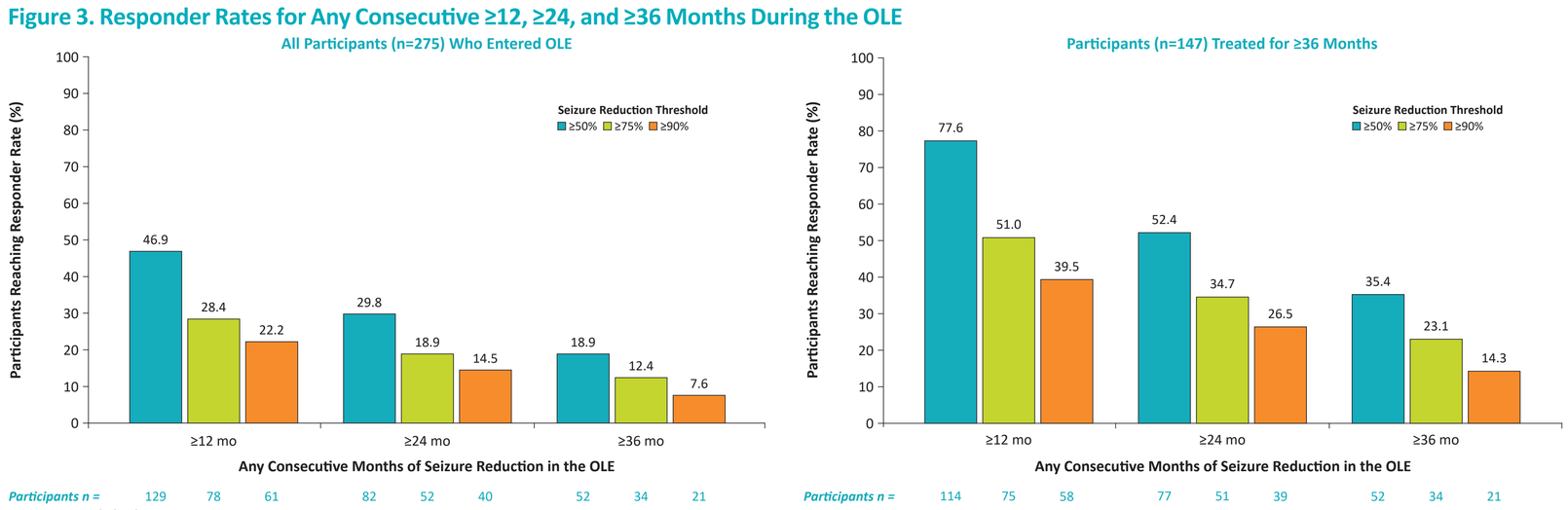
Figure 2. MPC in Monthly FOS Frequency During DBP and OLE



Participants n = 275 251 232 206 196 193 187 177 170 167 167 166 165[b] 162 161 161 156 148 147

[a]Following DBP, all patients received 20 mg at start of OLE as a once-daily capsule with food and no titration period. During the DBP participants received azetukalner 10 mg, 20 mg, or 25 mg, or placebo with food with no titration. [b]For the September 3, 2023 data cutoff, only 164 patients were included at OLE month 24; one participant was not counted due to delayed data entry. Monthly seizure rate was calculated for 28 days per month. DBP, double-blind period; FOS, focal onset seizure; MPC, median percentage change; OLE, open-label extension; QD, once daily.

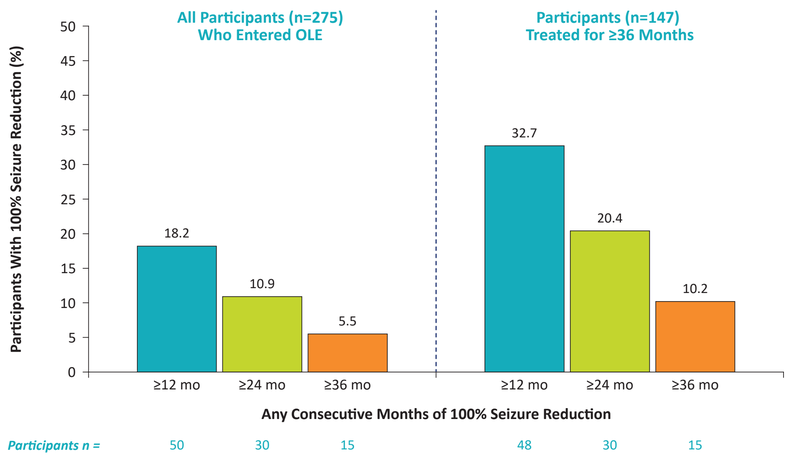
Figure 3. Responder Rates for Any Consecutive ≥12, ≥24, and ≥36 Months During the OLE



OLE, open-label extension.

- At OLE month 36, higher monthly MPC reductions in FOS frequency from baseline were observed for patients who were receiving 1-2 ASMs (100%, n=67) at baseline compared to those receiving 3 ASMs (80.6%, n=80; data not shown)
- Responder rates for ≥50, ≥75, and ≥90 seizure reduction for any consecutive ≥12, ≥24, and ≥36 months during the OLE are summarized in **Figure 3**
- 18.2% (50/275) of all participants who entered the OLE achieved 100% seizure reduction (seizure freedom) for any consecutive ≥12-month duration, 10.9% (30/275) were seizure free for any ≥24 consecutive months, and 5.5% (15/275) were seizure free for ≥36 consecutive months (**Figure 4**)
  - For those participants who were treated for ≥36 months in the OLE (n=147), the percentages of seizure freedom were 32.7% (48/147) for ≥12 months, 20.4% (30/147) for ≥24 months, and 10.2% (15/147) for ≥36 months

Figure 4. Percentage of Participants Who Achieved Any Consecutive ≥12, ≥24, and ≥36 Months of 100% Seizure Reduction During the OLE



OLE, open-label extension.

Safety

- Azetukalner 20 mg QD was generally well tolerated, and the safety profile observed was similar to that of the DBP
- At the end of the third year, participants recorded a mean (SD) weight change of 0.75 (8.7) kg from the start of the OLE
- TEAEs occurred in 88.7% of the safety population; the most common TEAEs are summarized in **Table 2**

Table 2. TEAEs During OLE Period

Summary of TEAEs, n (%)	Azetukalner 20 mg (n=275)
At least 1 TEAE	244 (88.7)
At least 1 serious TEAE	40 (14.5)
At least 1 TEAE leading to permanent treatment discontinuation	33 (12.0)
At least 1 serious TEAE leading to death	2 (0.7)[a]
Most common AEs (≥5% of overall OLE population), n (%)	
Dizziness	64 (23.3)
Headache	48 (17.5)
COVID-19	47 (17.1)
Somnolence	44 (16.0)
Fall	37 (13.5)
Weight increased	30 (10.9)
Memory impairment	28 (10.2)
Gait disturbance	27 (9.8)
Fatigue	25 (9.1)
Urinary tract infection	25 (9.1)
Aphasia	22 (8.0)
Confusional state	18 (6.5)
Nasopharyngitis	17 (6.2)
Change in seizure presentation	16 (5.8)
Disturbance in attention	16 (5.8)
Arthralgia	15 (5.5)
Balance disorder	15 (5.5)
Tremor	15 (5.5)
Anxiety	14 (5.1)
Paresthesia	14 (5.1)
Vertigo	14 (5.1)

[a]1 death from sudden unexplained death in epilepsy (SUDEP), and 1 death from viral pneumonia.
OLE, open-label extension; TEAE, treatment-emergent adverse event.

- 3 participants reported urinary retention, 1 reported as mild and the 2 other as moderate; no dose changes were made in any case
- Serious TEAEs were reported in 40 (14.5%) participants. Serious TEAEs reported in >1 participant were change in seizure presentation and seizure reported in 4 (1.5%) participants each, paresthesia, seizure cluster, influenza, deep vein thrombosis, and fall reported in 2 (0.7%) participants each
- There was 1 sudden unexplained death in epilepsy (SUDEP) reported, determined by the investigator not to be related to the study drug

CONCLUSIONS

- Azetukalner 20 mg QD with food yielded long-term efficacy in this interim analysis with 52% retention at 36 months
- During OLE study months 24 to 36, there was a sustained monthly reduction in seizure frequency (77%–87% MPC) from DBP baseline
- Seizure freedom for ≥12-month, ≥24-month, and ≥36-month consecutive durations was achieved in 18.2%, 10.9%, and 5.5% of all participants enrolled in the OLE, respectively
- Seizure freedom for ≥12-month, ≥24-month, and ≥36-month consecutive durations was achieved in 32.7%, 20.4%, and 10.2% of those participants with at least 36 months treatment in the OLE (n=147)
- Azetukalner continues to be generally well tolerated in the OLE, with AEs consistent with prior results and other ASM AEs; no new safety signals were identified
- These promising data suggest long-term efficacy and tolerability of azetukalner in a difficult-to-treat population

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