Azetukalner, a Novel, Potent K_V7 Channel Opener, in Adults With Focal Epilepsy: ≥48-Month Interim Analysis of the Ongoing 7-Year X-TOLE Open-Label Extension

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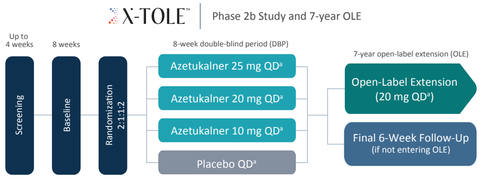
INTRODUCTION

- Azetukalner is a novel, potent K_V7 channel opener in development for the treatment of focal onset seizures (FOS), primary generalized tonic-clonic seizures, major depressive disorder, and bipolar depression[1-7]
  - 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[8,9]
  - In the double-blind period (DBP) of X-TOLE, treatment with azetukalner yielded a statistically significant dose-dependent reduction from baseline in monthly FOS in participants with difficult-to-treat disease[9]
  - Azetukalner was generally well tolerated with a low incidence of serious adverse events (SAEs)[9]
- We report interim efficacy and safety data (cutoff date October 6, 2025) from the ongoing OLE of X-TOLE in which participants enrolled at 20 mg of azetukalner once daily (QD)

METHODS

- The study design for the X-TOLE study (NCT03796962)[1] is shown in **Figure 1**
- Select eligibility criteria for the DBP and OLE of X-TOLE are outlined in **Table 1**

Figure 1. X-TOLE 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.

Table 1. X-TOLE DPB and OLE Eligibility Criteria

Select Inclusion Criteria
DBP
• Age 18-75 years (inclusive) • Diagnosis of focal epilepsy per International League Against Epilepsy criteria (≥2 years) • Receiving stable treatment with 1-3 ASMs • Countable seizure frequency (over the 8-week baseline period) of ≥4 focal seizures/month on average, recorded in an eDiary
OLE
• Successful completion of the DPB with ≥80% compliance with study medication

ASM, antiseizure medication; DBP, double-blind period; OLE, open-label extension.

- **Dosing in the OLE:** Azetukalner 20 mg QD taken with food. Azetukalner dose adjustments and changes in concomitant antiseizure medications (ASMs) were allowed during the OLE[8]
- **Select efficacy endpoints in the OLE:**
  - Median percent change (MPC) in monthly FOS frequency from DBP baseline
  - Proportion of participants with ≥50%, ≥75%, ≥90%, and 100% reduction from the DBP baseline in monthly FOS frequency for any consecutive ≥12-, ≥24-, ≥36-, and ≥48-month period during the OLE
  - Efficacy endpoints are reported for the overall group of participants who entered the OLE and for those treated for ≥48 months in the OLE
- **Safety endpoints in the OLE:**
  - Severity and frequency of treatment emergent adverse events (TEAEs) and SAEs
  - Clinically significant changes in laboratory findings
  - Other measures
- **Assessment schedule in the OLE:**
  - First year: Week 3 in the OLE (study day 77, week 11 from randomization) and 3-month intervals thereafter
  - After the first year: On-site visits at 6-month intervals with teleconferences at 3-month intervals between each on-site visit

RESULTS

Participants

- A total of 325 participants were randomized in the X-TOLE study (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 (**Table 2**) were consistent with those observed in the DBP
- At the analysis cutoff (October 6, 2025), 122 participants (44.4%) continued with the OLE
  - The most common reasons for discontinuation were lack of efficacy (17.8%), study withdrawal by the participant (17.5%), and adverse events (AEs; 13.1%)
- Retention rates with azetukalner at 1, 2, 3, and 4 years into the OLE study were 182 (66.2%), 165 (60.0%), 143 (52.0%), and 126 (45.8%) participants, respectively

Table 2. Demographics and Baseline[a] Characteristics of the OLE Population[8]

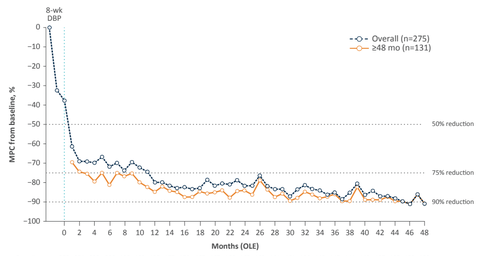
Characteristics	OLE Population (n=275)
Age at study entry, mean (SD), y	41.1 (13.3)
Sex, n (%)	
Male	137 (49.8)
Female	138 (50.2)
Race, n (%)	
White	250 (90.9)
Black	11 (4.0)
Other	14 (5.1)
Region, n (%)	
North America	109 (39.6)
Europe	166 (60.4)
BMI, mean (SD), kg/m^2	27.0 (5.2)
Age at epilepsy onset, mean (SD), y	18.1 (13.8)
Baseline seizure rate per mo, median (IQR)	13.5 (7.9-30.3)
Number of prestudy ASMs tried and discontinued before study entry, mean (SD)	6.5 (3.7)
Background ASM use, n (%)	
1	23 (8.4)
2	108 (39.3)
3	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; OLE, open-label extension.

Efficacy

- For the overall group, MPC reductions in monthly FOS frequency from DBP baseline ranged from 61.6%-81.9% during months 1-24 of the OLE study (n=266 to n=165) and increased further to a 90.9% reduction at OLE month 48 (n=129; **Figure 2**)
- Participants treated for ≥48 months in the OLE (n=131) had a MPC in monthly FOS frequency of -69.8% at month 1 in the OLE, which further increased to -85.1% at month 12, and -90.9% at month 48 in the OLE (**Figure 2**)
- At OLE month 48, higher monthly MPC reductions in FOS frequency from the DBP baseline were observed for the overall group of participants in the OLE who were receiving 1-2 ASMs at DBP baseline (n=60, 100%) compared with those receiving 3 ASMs (n=69, 81.8%; data not shown)

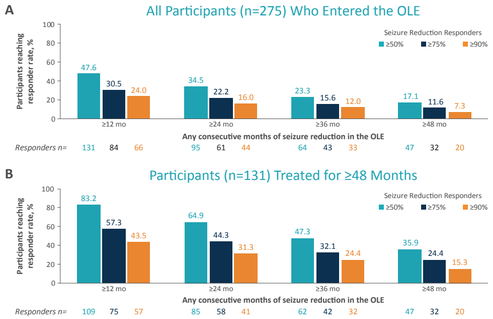
Figure 2. MPC in Monthly FOS Frequency During DBP and OLE[a] for the Overall OLE Participant Population and Participants Treated for ≥48 Months in the OLE[b]



[a]After the DBP, all participants received 20 mg azetukalner at start of OLE as a once-daily capsule with food and no titration period. [b]Data cutoff: October 6, 2025. Monthly seizure rate was calculated for 28 days per month. [c]Sample sizes for each month varied for the 131 participants treated for ≥48 months in the OLE due to non-compliance with daily seizure diary entries.
DBP, double-blind period; FOS, focal onset seizure; mo, month; MPC, median percent change; OLE, open-label extension.

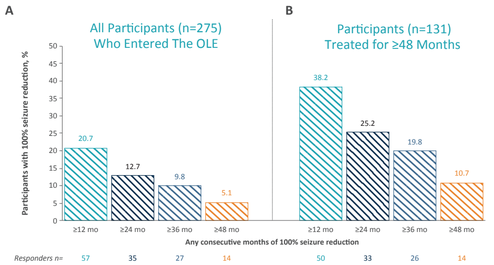
- For any consecutive ≥12, ≥24, ≥36, and ≥48 months during the OLE, responder rates for ≥50%, ≥75%, and ≥90% seizure frequency reduction are shown in **Figure 3**, and 100% seizure frequency reduction (seizure freedom) are shown in **Figure 4**
  - Among all 275 participants who entered the OLE, responder rates for any consecutive ≥12 months in the OLE were 47.6%, 30.5%, and 24.0% for ≥50%, ≥75%, and ≥90% seizure frequency reduction, respectively; 17.1% had ≥48 consecutive months of ≥50% reduction in seizure frequency (**Figure 3A**)
  - Among the 131 participants treated for ≥48 months in the OLE, these rates were 83.2%, 57.3%, and 43.5%, respectively; 35.9% had ≥48 consecutive months of ≥50% reduction in seizure frequency (**Figure 3B**)
  - Any consecutive ≥12 months of seizure freedom were attained by 20.7% of the participants entering the OLE, and 38.2% of the participants treated for ≥48 months in the OLE; 5.1% and 10.7% had ≥48 consecutive months of seizure freedom, respectively (**Figure 4**)

Figure 3. Responder Rates for Any Consecutive ≥12, ≥24, ≥36, and ≥48 Months During the OLE



Data cutoff: October 6, 2025. Monthly seizure rate was calculated for 28 days per month.
OLE, open-label extension.

Figure 4. Seizure Freedom Rates for Any Consecutive ≥12, ≥24, and ≥48 Months in the OLE



Data cutoff: October 6, 2025. Monthly seizure rate was calculated for 28 days per month.
OLE, open-label extension.

Safety

- As of October 6, 2025, the OLE has generated >775 patient-years of safety data exposure
- Long-term safety of azetukalner in the OLE was comparable with the safety observed in the DBP
- At the end of the fourth year of the OLE, participants recorded a mean (SD) weight increase of 0.91 (10.0) kg from the start of the OLE
- TEAEs and treatment-related TEAEs occurred in 89.5% and 65.8% of the safety population, respectively (**Table 3**)

Table 3. TEAEs During the OLE Period

Summary of TEAEs, n (%)	Azetukalner (n=275)
At least 1 TEAE	246 (89.5)
At least 1 serious TEAE	45 (16.4)
At least 1 TEAE leading to permanent treatment discontinuation	35 (12.7)
TEAE leading to death	2 (0.7)[a]
Most common AEs (≥5% of overall OLE population), n (%)	
Dizziness	69 (25.1)
Headache	52 (18.9)
COVID-19	47 (17.1)
Somnolence	47 (17.1)
Fall	40 (14.5)
Weight increased	31 (11.3)
Memory impairment	30 (10.9)
Gait disturbance	28 (10.2)
Seizure	27 (9.8)
Urinary tract infection	26 (9.5)
Fatigue	25 (9.1)
Aphasia	22 (8.0)
Nasopharyngitis	22 (8.0)
Tremor	19 (6.9)
Arthralgia	17 (6.2)
Balance disorder	17 (6.2)
Confusional state	17 (6.2)
Disturbance in attention	17 (6.2)
Vertigo	16 (5.8)
Back pain	15 (5.5)
Nausea	15 (5.5)
Diarrhea	14 (5.1)
Insomnia	14 (5.1)
Paresthesia	14 (5.1)
Pyrexia	14 (5.1)

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

- Four participants reported urinary retention, 1 reported as mild and the other 3 as moderate; no dose changes were made in any case
- Serious TEAEs were reported in 45 (16.4%) participants, and those occurring in >1 participant included seizure (n=12, 4.4%); deep vein thrombosis (n=3, 1.1%); and paresthesia, seizure cluster, influenza, pneumonia aspiration, rhabdomyolysis, and fall (n=2, 0.7% each)
- Two deaths considered unrelated to azetukalner treatment were reported (sudden unexplained death in epilepsy and viral pneumonia, n=1 each)

CONCLUSIONS

- Azetukalner showed long-term efficacy and safety in this interim analysis of the X-TOLE OLE, with 45.8% participant retention at 4 years in the OLE
- A sustained monthly reduction in FOS frequency from DBP baseline was observed during OLE study months 12-48 for 131 participants who were treated for ≥48 months in the OLE (MPC, 82.2%-90.9%)
- Seizure freedom in the OLE for any ≥12-, ≥24-, ≥36-, and ≥48-month consecutive durations was attained by 20.7%, 12.7%, 9.8%, and 5.1% of all 275 participants enrolled in the OLE, respectively
- Seizure freedom in the OLE for any ≥12-, ≥24-, ≥36-, and ≥48-month consecutive durations was attained by 38.2%, 25.2%, 19.8%, and 10.7% of the 131 participants with ≥48 months treatment in the OLE, respectively
- Long-term safety of azetukalner in the OLE was comparable with the safety observed in the DBP
- These promising data suggest long-term efficacy and tolerability of azetukalner in patients with difficult-to-treat disease

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