Azetukalner (XEN1101), a Novel, Potent K_V7 Potassium Channel Opener: Interim Data From an Ongoing, Long-Term, Open-Label Extension of a Phase 2b Study (X-TOLE) in Adults With Focal Onset Seizures

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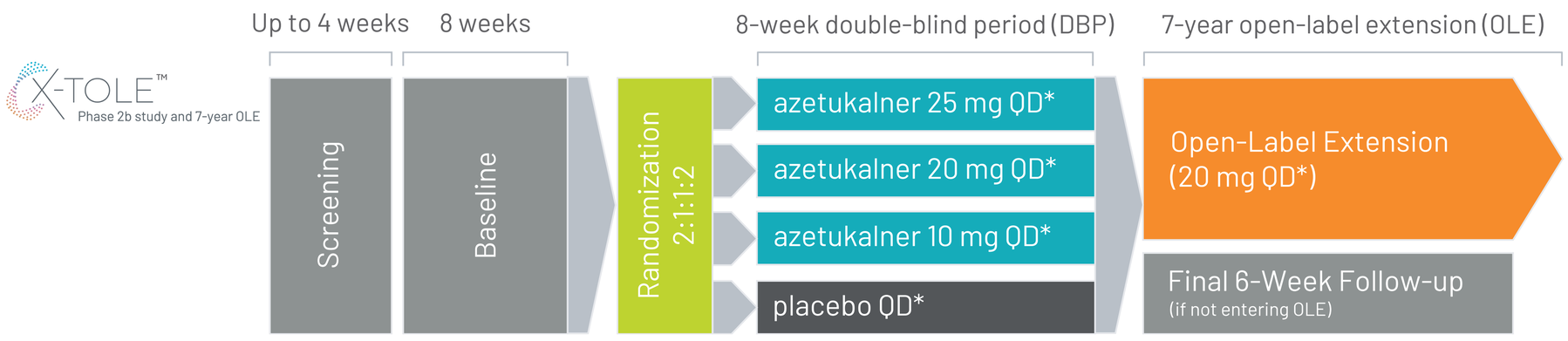
INTRODUCTION

- Azetukalner (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 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, consistent, highly statistically significant reduction in FOS across endpoints 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 September 5, 2023) 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 the evening meal
- 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
- 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

Figure 1. Study Design



*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.

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* 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)

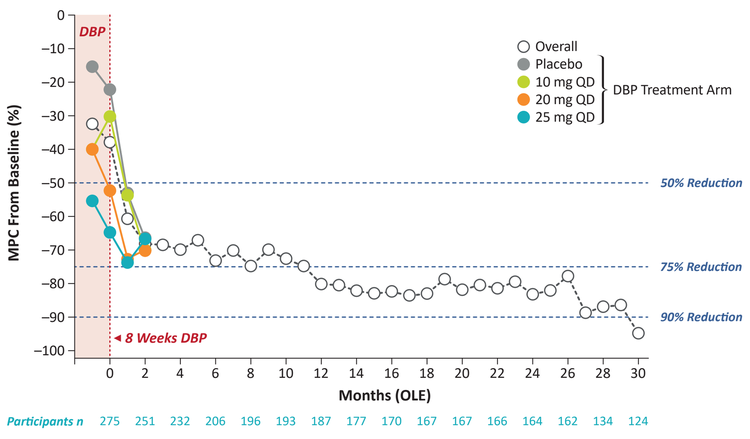
*DBP baseline. ASM, antiseizure medication; BMI, body mass index; CYP3A4, cytochrome P450 3A4; DBP, double-blind period; IQR, interquartile range; OLE, open-label extension.

- At the analysis cutoff (September 5, 2023), 153 participants (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 participant (12.0%)
- A total of 182 participants were treated in the OLE for ≥12 months; 165 participants were treated for ≥24 months at the time of the analysis cutoff
  - The percentage of participants continuing azetukalner at 12 months and 24 months into the OLE study period were 66% and 60%, respectively

Efficacy

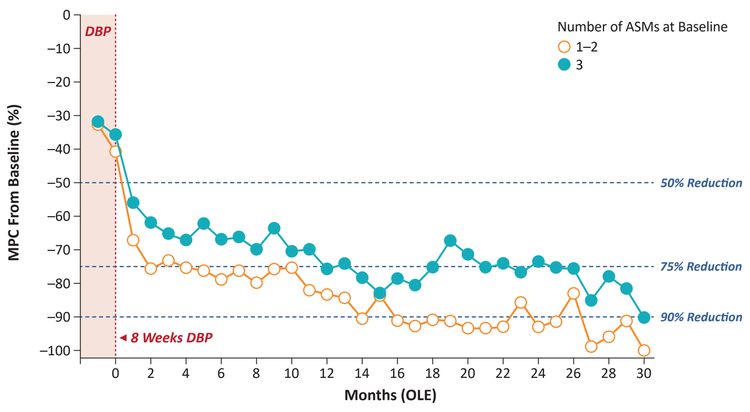
- For ongoing OLE participants, monthly MPC reductions in FOS frequency ranged from 61% to 95% from DBP baseline and were maintained at 78% to 95% in OLE study months 12 to 30 (**Figure 2**)
- Higher reductions were observed for participants who were receiving 1 to 2 ASMs at baseline compared with those receiving 3 ASMs (**Figure 3**)
- 37.5% (103/275) of all participants 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 participants 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 administered as a once-daily capsule with food with no titration period. Monthly seizure rate was calculated for 28 days per month. Following DBP, all participants received 20 mg QD with food at start of OLE. OLE participants separated by prior DBP treatment groups shown for first 2 months of OLE. 1 participant was not included in seizure frequency data because of noncompliance 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

- 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 second year, participants 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**

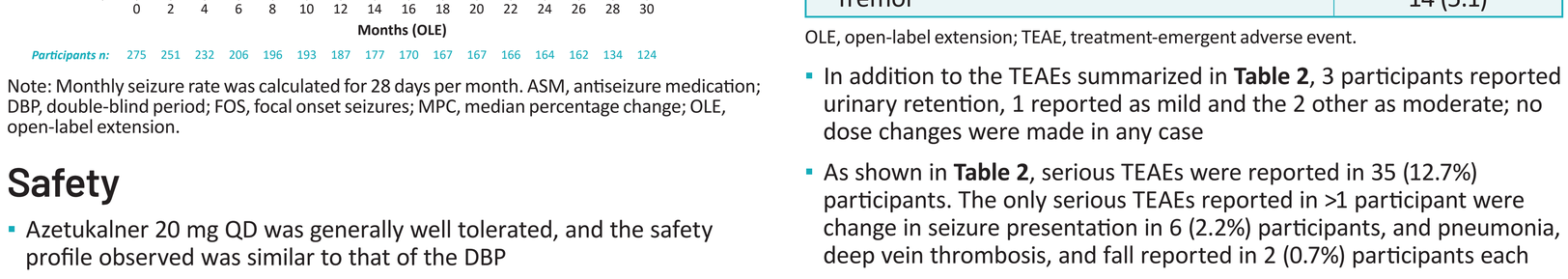
Table 2. TEAEs During OLE Period

Summary of TEAEs, n (%)	Azetukalner 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 TEAEs (≥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)

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

- In addition to the TEAEs summarized in **Table 2**, 3 participants 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%) participants. The only serious TEAEs reported in >1 participant were change in seizure presentation in 6 (2.2%) participants, and pneumonia, 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

Figure 4. Fraction of Participants 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

- Azetukalner 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 participants 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 participants with at least 24 months treatment in the OLE (n=165)
- 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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