Characterization of Long-Term Seizure Freedom in the Ongoing Open-Label Extension of X-TOLE: Potential Implications for Future Clinical Practice

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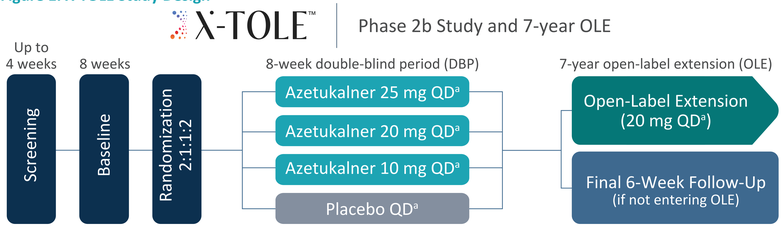
INTRODUCTION

- Seizure freedom is a primary goal of epilepsy management, yet its definition and importance can vary among patients[1]
- Patients with epilepsy value different timeframes of seizure freedom, ranging from weeks to years, depending on their personal treatment goals, risks and benefits of antiseizure medications (ASMs), and health-related quality of life factors[2-5]
- Understanding patterns of seizure freedom epochs following a breakthrough seizure is clinically relevant for guiding patient expectations and treatment planning
  - As most patients with epilepsy experience a fluctuating clinical course of attaining, losing, and regaining variable periods of seizure control, a single standardized duration of seizure freedom may set unrealistic treatment expectations for seizure management[2]
  - Provoked (e.g., due to missed medication) or unprovoked breakthrough seizures can disrupt periods of seizure control, complicating long-term management[6]
- Long-term open-label extension (OLE) studies investigating ASMs allow continuous observation of seizure patterns, enabling the calculation of various seizure-free epochs to better characterize the dynamic patterns of treatment response
- Azetukalner is a novel, potent K_v7 channel opener currently being evaluated in the ongoing 7-year X-TOLE OLE of participants with focal onset seizures,[7] for which ≥48-month data in the OLE are being presented[8]
- Using long-term data from the X-TOLE OLE study, we report multiple seizure freedom analyses to better understand how periods of complete seizure control were attained, lost, and regained in a difficult-to-treat patient population

METHODS

- The study design for the X-TOLE study (NCT0379692) is shown in **Figure 1**
- The key eligibility criteria and endpoints for X-TOLE and the X-TOLE OLE have been published[7,9]
- Participants enrolled in the OLE on azetukalner 20 mg once daily (QD) taken with food. Azetukalner dose adjustments and changes in concomitant ASMs were allowed during the OLE
- Among participants who had completed ≥48 months in the OLE as of the data cutoff (October 6, 2025), rates of seizure freedom, defined as 100% reduction in seizure frequency from OLE baseline, were assessed:
  - Proportions of participants with ≥12 consecutive months of seizure freedom at the time of last study visit, and subsets of these participants with ≥24 and ≥36 consecutive months of seizure freedom at the time of last study visit
  - Among participants who had initially attained an epoch of ≥6 consecutive months of seizure freedom but subsequently had a breakthrough seizure, proportions of these participants who subsequently attained any ≥3, ≥6, or ≥12 consecutive months of seizure freedom

Figure 1. X-TOLE Study Design



[a]Administered as a QD 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

- Of the 285 participants who completed the X-TOLE double-blind period (DBP), 275 (96.5%) enrolled in the OLE (**Figure 1**, population characteristics shown in **Table 1**); all 275 participants had an opportunity to complete 48 months of treatment in the OLE
- 131 of the original 275 participants (47.6%) continued in the OLE for ≥48 months (calculated for 28 days per month). As of October 6, 2025, 122 (44.4%) participants continued to participate in the OLE
- At the cutoff date, the OLE has generated >775 patient-years of safety data exposure
- Long-term safety of azetukalner 20 mg QD in the OLE was comparable with the safety observed in the DBP

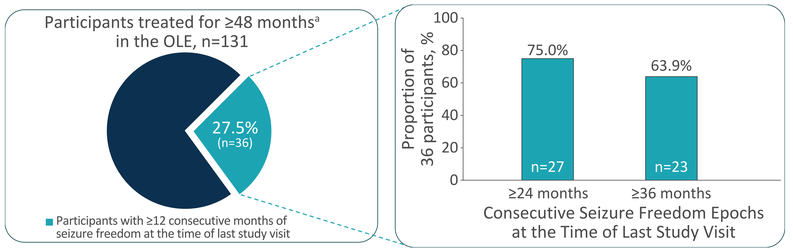
Table 1. Demographics and Baseline[a] Characteristics of the OLE Population

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.

- Seizure freedom analyses for the OLE participants treated for ≥48 months who attained ≥12 consecutive months of seizure freedom at the time of last study visit are shown in **Figure 2**
  - Of the 131 participants in the OLE who had been treated for ≥48 months, 36 (27.5%) attained ≥12 consecutive months of seizure freedom at the time of last study visit
  - Of these 36 participants, 27 (75.0%) and 23 (63.9%) attained ≥24 months and ≥36 consecutive months of seizure freedom at the time of last study visit, respectively

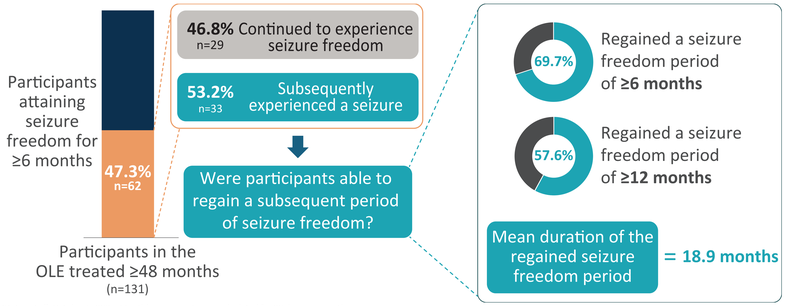
Figure 2. Sustained Seizure Freedom in Participants Treated for ≥48 Months in the OLE at the Time of Last Study Visit: Proportion With ≥12 Consecutive Months of Seizure Freedom, and Among Those Participants, Proportions With ≥24 and ≥36 Consecutive Months of Seizure Freedom



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

- Seizure freedom pattern analysis for the OLE participants treated for ≥48 months who attained any ≥6 consecutive months of seizure freedom, had a breakthrough seizure, and regained seizure freedom are shown in **Figure 3**
  - Of the 131 OLE participants who had been treated for ≥48 months, 62 (47.3%) attained any ≥6 consecutive months of seizure freedom
  - Among these 62 participants, 29 participants (46.8%) continued to experience seizure freedom (duration mean [SD] of 41.7 [20.6] months), and the other 33 participants (53.2%) subsequently had a breakthrough seizure
    - Of these 33 participants who subsequently had a breakthrough seizure, 27 (81.8%, data not shown), 23 (69.7%), and 19 (57.6%) participants attained a subsequent seizure-free epoch of ≥3, ≥6 or ≥12 consecutive months, respectively, with a mean (SD) duration of regained seizure freedom of 18.9 (16.7) months

Figure 3. Participants Treated for ≥48 Months in the OLE[a] Who Attained Any ≥6 Consecutive Months of Seizure Freedom, Had a Subsequent Breakthrough Seizure, and Regained Seizure Freedom



[a]Data cutoff: October 6, 2025. Monthly seizure rate was calculated for 28 days per month.
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CONCLUSIONS

- This interim analysis of the X-TOLE OLE highlights extended seizure freedom with long-term use of azetukalner
  - Seizure freedom for ≥12 consecutive months at the time of last study visit was attained by 36 (27.5%) of 131 participants with ≥48 months of treatment in the OLE; 27 (75.0%) and 23 (63.9%) of those 36 participants attained ≥24 and ≥36 consecutive months of seizure freedom, respectively, at the time of the last study visit
- Seizure freedom can be attained, maintained, and, if lost, regained with long-term azetukalner treatment, even in patients with difficult-to-treat disease
  - Of the 33 participants who had a breakthrough seizure after one epoch of seizure freedom for any ≥6 consecutive months, 23 (69.7%) and 19 (57.6%) regained ≥6 and ≥12 months of subsequent seizure freedom, respectively
- Collectively, these findings highlight that assessing only a single epoch of seizure freedom may underestimate the full scope of treatment response to azetukalner over time and offer a deeper understanding of treatment response patterns that may inform future clinical decision-making

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ACKNOWLEDGMENTS Medical writing support was provided by Oishika Panda, PhD, CMPP, from Citrus Health Group, Inc. (Chicago, Illinois) and was funded by Xenon Pharmaceuticals Inc (Vancouver, BC, Canada).

DISCLOSURES Danielle Becker is a consultant/speaker for Neurelis, Inc; SK Life Science; Jazz Pharmaceuticals; LivaNova; Neuropace; and Xenon Pharmaceuticals Inc. (advisory board). Jacqueline A. 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. Jenny Qian and Lee Gervitz are employees of and own stock or stock options in Xenon Pharmaceuticals Inc.

FUNDING This study was funded by Xenon Pharmaceuticals Inc.

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