Long-Term, Quality of Life in Epilepsy Inventory-31 (QOLIE-31) Improvements in Adults With Focal Onset Seizures Treated With Azetukalner (XEN1101) in an Ongoing, Open-Label Extension of a Phase 2b Study (X-TOLE)

Christian Brandt,[1] Vicente Villanueva,[2] Cynthia Harden,[3] Jenny Qian,[3] Constanza Luzon Rosenblut,[3] Joanne Wagner,[3] Christopher Kenney,[3] Gregory N. Beatch[3]

[1]Bethel Epilepsy Centre, Mara Hospital, University Hospital for Epileptology, Bielefeld, Germany; [2]Refractory Epilepsy Unit, Hospital Universitario Y Politécnico La Fe, Valencia, Spain; [3]Xenon Pharmaceuticals Inc., Vancouver, BC, Canada

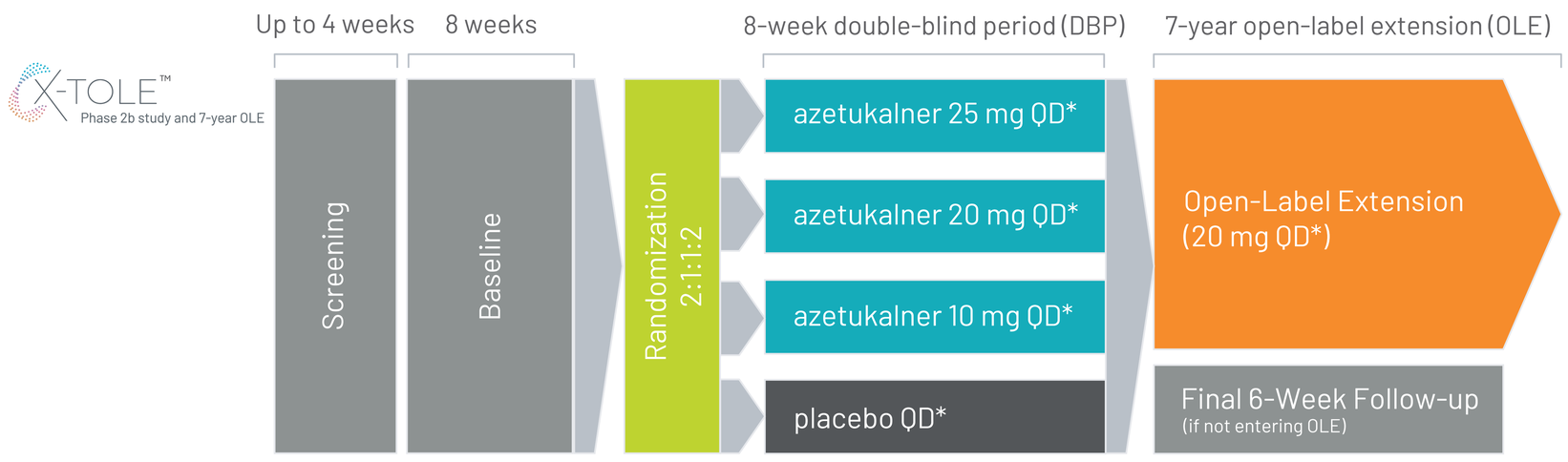
INTRODUCTION

- Quality of life (QoL) is an important measure when evaluating new antiseizure medications (ASMs) as it is self-reported by participants and is associated with patient satisfaction[1]
- The Quality of Life in Epilepsy Inventory-31 (QOLIE-31) is a validated tool that provides an overall QoL assessment and additional insight into participants' self-perceived health status across specific functional and psychosocial domains[2]
- Azetukalner (XEN1101) is a novel, potent K_V7 potassium channel opener in development for the treatment of epilepsy and major depressive disorder[3]
  - X-TOLE (NCT037969623[4]) 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 focal onset seizures (FOS)
  - In the double-blind period (DBP), azetukalner treatment yielded a dose-dependent, highly statistically significant, and rapid reduction of seizure frequency in a difficult-to-treat patient population[3]
  - Azetukalner was generally well tolerated, with adverse events (AEs) consistent with other commonly prescribed ASMs
  - A 12-month interim analysis of the ongoing X-TOLE OLE demonstrated that treatment with azetukalner resulted in sustained monthly reduction in seizure frequency from DBP baseline; no new safety signals were identified[5]
  - Analysis of QOLIE-31 data from the same interim analysis revealed clinically important improvements in multiple QoL domains. Participants who were seizure-free for ≥12 consecutive months in the OLE reported meaningful improvement in all QoL domains of the QOLIE-31[6]
- Here, we report QoL (QOLIE-31) results from a further interim analysis of the X-TOLE OLE at 24 months (datacut September 5, 2023)

METHODS

- The X-TOLE study design 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[7] (≥2 y)
  - ≥4 countable focal seizures per month during a planned 8-week baseline period
  - Receiving stable treatment with 1–3 ASMs
- Participants who successfully completed the DBP with a minimum of 80% compliance with the study medication were eligible to continue in the OLE
- Participants from all prior DBP treatment arms were dosed in the OLE at azetukalner 20 mg once daily taken with food with no titration period from any prior dose
- The primary measure of efficacy in the OLE was the median percentage change in monthly FOS frequency from DBP baseline
- Safety was assessed as severity and frequency of treatment-emergent AEs and serious AEs, clinically significant changes in laboratory findings, and other measures
- To assess the impact of azetukalner on QoL, the QOLIE-31 questionnaire was completed at baseline, at the end of the DBP, and at week 15 of the OLE, followed by 3-month intervals during the first 12 months of the OLE, then at 6-month intervals thereafter. Mean change in QOLIE-31 total and subscale scores at 24 months in the OLE were compared with the DBP baseline scores. Higher QOLIE-31 scores reflect a higher QoL
- Minimally important change thresholds in QOLIE-31 scores,[8] defined as a score change that represents a clinically meaningful benefit or worsening in patient health status, were used to evaluate the impact of azetukalner on the QoL of all participants enrolled in the OLE (overall group [OG]) and a group that was seizure-free (SFG) for ≥12 consecutive months in the OLE at the interim datacut

Figure 1. X-TOLE 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

- Of the 285 participants who completed the DBP, 275 (96.5%) continued 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 24 months in the ongoing OLE, participant retention was 60% (n=165), and monthly FOS median reduction was 83.2%
- The SFG consisted of 41 participants who had experienced seizure freedom for ≥12 months (14.9% of those enrolled in the OLE)

QoL (QOLIE-31)

- At DBP baseline, participants in the OG and SFG reported the lowest mean QOLIE-31 scores for Seizure Worry (49.20 and 44.56, respectively) and the highest mean QOLIE-31 scores for Emotional Well-Being (67.15 and 67.41, respectively) (**Table 2**)

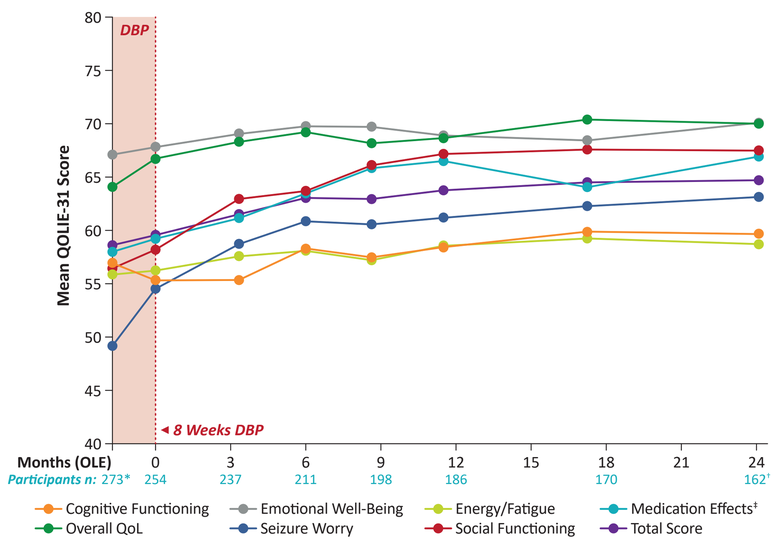
Table 2. QOLIE-31 Total and Subscale Mean Scores at DBP Baseline

	OG (n=273*)	SFG (n=41)
Energy/Fatigue	55.86	56.46
Emotional Well-Being	67.15	67.41
Social Functioning	56.47	55.76
Cognitive Functioning	56.93	57.23
Medication Effects	58.03	61.86
Seizure Worry	49.20	44.56
Overall QoL	64.10	63.96
Total Score	58.65	58.42

Note: QOLIE-31 total and subscale scores range from 0-100. Higher scores reflect higher QoL. *2 participants did not complete the QOLIE-31 at DBP baseline. DBP, double-blind period; OG, overall group; QoL, quality of life; QOLIE-31, Quality of Life in Epilepsy Inventory-31; SFG, seizure-free group.

- Improvements in mean QOLIE-31 total score and most subscale scores were reported by the OG during the first 24 months of the OLE compared with DBP baseline (**Figure 2**)

Figure 2. Mean QOLIE-31 Total and Subscale Scores From DBP Baseline to 24 Months of the OLE for the Overall Group



Note: a positive change indicates improvement. *2 participants did not complete the QOLIE-31 at DBP baseline. †3 participants did not complete the QOLIE-31 at 24 months in the OLE. ‡For medication effects, end of DBP (study week 8, n=253) and 3 months OLE (n=236). DBP, double-blind period; OLE, open-label extension; QoL, quality of life; QOLIE-31, Quality of Life in Epilepsy Inventory-31; SFG, seizure-free group.

- Mean QOLIE-31 total score and all subscale scores reported by the SFG improved over the first 24 months of the OLE, compared to DBP baseline (**Figure 3**)

Figure 3. Mean QOLIE-31 Total and Subscale Scores from DBP Baseline to 24 Months of the OLE for the SFG

Note: a positive change indicates improvement. *3 participants in the SFG did not complete the QOLIE-31 at Week 8. †2 participants in the SFG did not complete the QOLIE-31 at 24 months in the OLE. DBP, double-blind period; OLE, open-label extension; QoL, quality of life; QOLIE-31, Quality of Life in Epilepsy Inventory-31; SFG, seizure-free group.

- At 24 months in the OLE
  - QOLIE-31 subscale scores met the threshold for clinically important improvement in the OG and SFG as follows: mean change in Seizure Worry (13.42 and 28.54 points, respectively), Social Functioning (7.77 and 21.29 points, respectively), and Medication Effects (6.31 and 13.03 points, respectively) (**Table 3**)
  - Emotional Well-Being (5.64 points), Cognitive Functioning (7.41 points), Overall QoL (10.19 points) and total QOLIE-31 total score (11.85 points) met the threshold for clinically important improvement in the SFG (**Table 3**)
  - Neither group reported QOLIE-31 Energy/Fatigue scores that met the criteria for clinically important improvement or worsening from DBP baseline
  - This represents a maintenance or improvement in the number of QOLIE-31 subscale scores previously reported as clinically important at 12 months in the OLE[6]

Table 3. Mean Changes From DBP in the QOLIE-31 Total and Subscale Scores After 24 Months in the OLE

	MIC (Borghs et al 2012)[8]	24 Months*	
		OG (n=162*)	SFG (n=39*)
Energy/Fatigue	5.25	2.50	3.59
Emotional Well-Being	4.76	3.01	**5.64**
Social Functioning	3.95	**7.77**	**21.29**
Cognitive Functioning	5.34	0.12	**7.41**
Medication Effects	5.00	**6.31**	**13.03**
Seizure Worry	7.42	**13.42**	**28.54**
Overall QoL	6.42	6.10	**10.19**
Total Score	5.19	4.53	**11.85**

Bold type indicates that mean change exceeds minimal important change (improvement).
*3 participants in the OG and 2 in the SFG did not have QOLIE-31 data collected at month 24.
DBP, double-blind period; MIC, minimally important change; OG, overall group; OLE, open-label extension; QOLIE-31, Quality of Life in Epilepsy Inventory-31; SFG, seizure-free group.

Safety

- Azetukalner 20 mg QD was generally well tolerated, and the safety profile observed was similar to that seen in the DBP. No new safety concerns were identified

CONCLUSIONS

- Clinically important improvements in QOLIE-31 subscales of Seizure Worry, Social Functioning, and Medication Effects were seen across all participants, with even greater improvements in the SFG
- The SFG achieved clinically important improvements in all QoL domains assessed by the QOLIE-31 except for Energy/Fatigue
- The improvements in Medication Effects across all participants is notable as this documented improved drug tolerability accompanied long-term seizure reduction in a difficult-to-treat epilepsy patient population
- The rapid, marked improvements seen in Medication Effects, Seizure Worry, and Social Functioning in the SFG over the first 3 months of the OLE were sustained and continued to improve over the first 2 years of the OLE
- QoL improvements, as measured by the QOLIE-31, originally reported at year 1 were maintained or improved at year 2 of the X-TOLE OLE

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