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

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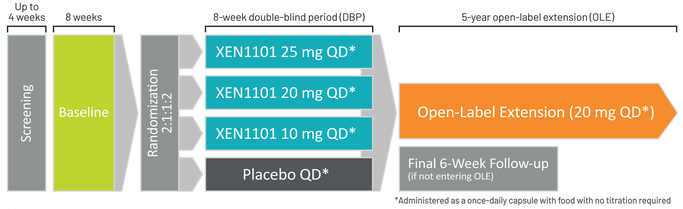
INTRODUCTION

- Quality of life (QoL) is an important measure when evaluating new antiseizure medications (ASM) as it is self-reported by patients 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 patients' self-perceived health status across specific functional and psychosocial domains[2]
- XEN1101 is a novel, potent K_v7 potassium channel opener in development for the treatment of epilepsy and major depressive disorder
  - X-TOLE (NCT03796962[3]) is a completed phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study with an ongoing optional 5-year open-label extension (OLE) evaluating the efficacy, safety, and tolerability of XEN1101 administered with food as adjunctive treatment in adults with focal onset seizures (FOS)
  - In the double-blind period (DBP), XEN1101 treatment yielded a dose-dependent, highly statistically significant, and rapid reduction of seizure frequency in a difficult-to-treat patient population. XEN1101 was generally well tolerated, with adverse events (AEs) consistent with other commonly prescribed ASMs[4]
  - An interim analysis (cutoff date September 22, 2022) of the ongoing X-TOLE OLE demonstrated that treatment with XEN1101 resulted in sustained monthly reduction in seizure frequency from DBP baseline, with AEs consistent with previous results and those seen with other ASMs; no new safety signals were identified[5]
- Here we report QoL (QOLIE-31) results from the same interim analysis of the X-TOLE OLE

METHODS

- The X-TOLE study design is shown in **Figure 1**

Figure 1. X-TOLE Study Design



QD, once daily.

- 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 y)[6]
  - ≥4 countable focal seizures per month during a planned 8-week baseline period
  - Receiving stable treatment with 1–3 ASMs
- Patients who successfully completed the DBP with a minimum of 80% compliance with the study medication were eligible to enroll in the OLE
- Patients enrolled in the OLE from all DBP arms received XEN1101 20 mg once daily taken with food, with no titration required from any 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 XEN1101 on QoL, the QOLIE-31 questionnaire was completed at baseline, at the end of the DBP, at OLE week-15, 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 12 months in the OLE were compared to the DBP baseline scores. Higher QOLIE-31 scores reflect a higher QoL
- Minimally important change thresholds in QOLIE-31 scores,[7] defined as a score change that represents a clinically meaningful benefit or worsening in patient health status, were used to evaluate the impact of XEN1101 on the QoL of all patients 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 data cut

RESULTS

- Of the 285 patients who completed the DBP, 275 (96.5%) enrolled in the OLE
- Demographics and baseline characteristics of patients in the OLE were consistent with those observed in the DBP (**Table 1**)

Table 1. Demographics and Baseline* Characteristics of the OLE Population

	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, kg/m^2, mean (SD)	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 12 months in the ongoing OLE, patient retention was 68% (n=188), and monthly FOS median reduction was 80%
- The SFG consisted of 29 patients (10.5% of those enrolled in the OLE)

QoL (QOLIE-31)

- At DBP baseline, patients in the OG and SFG reported the lowest mean QOLIE-31 scores for Seizure Worry (49.20 and 48.38, respectively), and the highest mean QOLIE-31 scores for Emotional Well-Being (67.15 and 65.93, respectively) (**Table 2**)

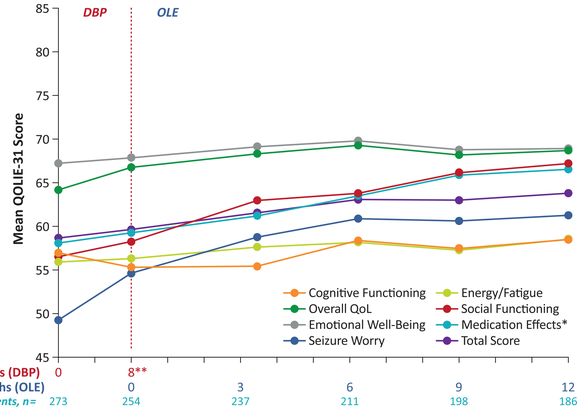
Table 2. QOLIE-31 Total and Subscale Scores at DBP Baseline

	OG (n=273*)	SFG (n=29)
Energy/Fatigue	55.86	56.03
Emotional Well-Being	67.15	65.93
Social Functioning	56.47	56.12
Cognitive Functioning	56.93	57.88
Medication Effects	58.03	56.23
Seizure Worry	49.20	48.38
Overall QoL	64.10	63.36
Total Score	58.65	58.46

*Note: QOLIE-31 total and subscale scores range from 0-100. Higher scores reflect higher QoL. *Two patients 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 at the end of the DBP and during the first 12 months of the OLE, compared to baseline (**Figure 2**)

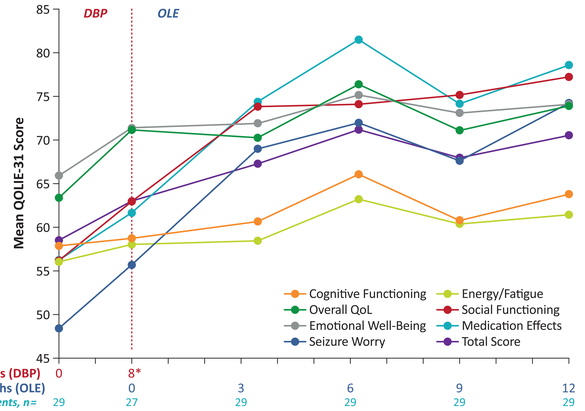
Figure 2. Mean QOLIE-31 Total and Subscale Scores from DBP Baseline to 12-Months of the OLE for the Overall Group



*Note: a positive change indicates improvement. *For medication effects, end of DBP (study week 8 n=253) and 3-months OLE (n=236). **Two patients did not complete the QOLIE-31 at DBP baseline. DBP, double-blind period; OLE, open-label extension; QoL, quality of life.*

- The SFG reported improvements in the total score and all subscales compared to baseline over the same time period (**Figure 3**)

Figure 3. Mean QOLIE-31 Total and Subscale Scores from DBP Baseline to 12-Months of the OLE for the Seizure-Free Group



*Note: a positive change indicates improvement. *Two patients in the SFG did not complete the QOLIE-31 at Week 8. DBP, double-blind period; OLE, open-label extension; QoL, quality of life.*

- At 12 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 (11.49 and 25.86 points, respectively), Social Functioning (8.45 and 21.06 points), and Medication Effects (6.06 and 22.32 points) (**Table 3**)
  - Energy/Fatigue (5.34 points), Emotional Well-Being (8.14 points), Cognitive Functioning (5.91 points), Overall QoL (10.52 points) and total QOLIE-31 total score (12.09 points) met the threshold for clinically important improvement in the SFG only (**Table 3**)
  - Neither group reported QOLIE-31 total and subscale mean change scores that met the criteria for clinically important worsening from DBP baseline

Table 3. Mean Changes from DBP for the QOLIE-31 Total and Subscale Scores at 12 Months in the OLE

	MIC (Borghs et al 2012)[7]	OG (n=186)	SFG (n=29)
Energy/Fatigue	5.25	2.58	5.34
Emotional Well-Being	4.76	1.63	8.14
Social Functioning	3.95	8.45	21.06
Cognitive Functioning	5.34	–1.14	5.91
Medication Effects	5.00	6.06	22.32
Seizure Worry	7.42	11.49	25.86
Overall QoL	6.42	4.57	10.52
Total Score	5.19	3.76	12.09

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

- XEN1101 was generally well tolerated, and the safety profile observed in the OLE was similar to that of 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 patients, with even greater improvements in the SFG
- The SFG achieved clinically important improvements in all QoL domains assessed by the QOLIE-31
- The improvements in Medication Effects across all patients is notable as this documented improved drug tolerability accompanied long-term seizure reduction in a difficult-to-treat epilepsy patient population

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