XEN1101, a Novel Potassium Channel Modulator: Interim Data From an Ongoing, Long-Term, Open-Label Extension of a Phase 2b Study (X-TOLE) in Adults With Focal Epilepsy

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XEN1101 \( K_v^7 \) Channel Opener

- XEN1101 is a novel, potent, selective \( KCNQ2/3 \) (\( K_v^7.2/7.3 \)) potassium channel opener currently in development\(^1,2\)
- Supports QD dosing with food with no titration
- Potential to treat common comorbidities, such as depression

X-TOLE and X-TOLE OLE

- X-TOLE 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 FOS

- Key eligibility criteria included age 18–75 years with a diagnosis of focal epilepsy per International League Against Epilepsy criteria (≥2 years), ≥4 countable focal seizures per month during a planned 8-week baseline period, and receiving stable treatment with 1–3 anti-seizure medications (ASMs)

\[\text{DBP, double-blind period; FOS, focal onset seizure; QD, once daily.}\]

X-TOLE Results and X-TOLE OLE Endpoints

- X-TOLE enrolled a heavily pre-treated patient population: participants tried and stopped a median of 6 ASMs prior to study entry; 50.8% were on 3 background ASMs with a median baseline seizure frequency of 13.5 FOS per month.

- The trial met its primary efficacy endpoint, with XEN1101 demonstrating a statistically significant, dose-dependent percent reduction from baseline in median monthly FOS seizure frequency of 33.2%, 46.4%, and 52.8% in the 10 mg, 20 mg, and 25 mg groups, respectively, compared to 18.2% in the placebo group.*

- XEN1101 was generally well-tolerated with adverse events (AEs) consistent with other commonly prescribed anti-seizure medications.

- Patients enrolled in the X-TOLE OLE from all DBP arms received XEN1101 20 mg QD taken with food.

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<tr>
<th>X-TOLE OLE Efficacy</th>
<th>X-TOLE OLE Safety</th>
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<tr>
<td>• Median percentage change (MPC) in monthly FOS frequency from DBP baseline</td>
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<td>• Percentage of patients with ≥50% reduction from DBP baseline in monthly FOS frequency</td>
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<tr>
<td>• Severity and frequency of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)</td>
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<td>• Clinically significant laboratory findings, and other measures</td>
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*XEN1101 10 mg group vs placebo P=0.035, XEN1101 20 & 25 mg groups vs placebo P<0.001. ASM, antiseizure medications; FOS, focal onset seizure; OLE, open-label extension.

X-TOLE OLE Patient Population

- 285 patients completed the DBP, 275 (96.5%) enrolled in the OLE
- At the analysis cutoff*:
  - 168 (61%) patients continued to participate in the OLE
    - Most common reasons for discontinuation were lack of efficacy (12.7%), AEs (10.5%), and study withdrawal by the patient (9.5%)
- The percentage of patients continuing XEN1101 into the OLE study period
  - At 6 months: 76% (n = 209)
  - At 12 months: 68% (n = 188)

*Analysis cut off: September 22, 2022. DBP, double-blind period; OLE, open-label extension.
X-TOLE OLE Efficacy: MPC in Seizure Frequency from Baseline

MPC in monthly FOS frequency During DBP and OLE

10.5% of patients (29/275) achieved seizure freedom for any consecutive ≥12-month duration, and 17.5% (48/275) for ≥6 consecutive months.

Note: Following DBP, all patients received 20 mg QD with food with no titration required at start of OLE (at month 2); OLE patients separated by prior DBP treatment groups shown for first 2 months of OLE (months 3–4). Not all patients have reached 18 months in OLE as of data cutoff. DBP, double-blind period; FOS, focal onset seizures; MPC, median percentage change; OLE, open-label extension; QD, once daily.
X-TOLE OLE Safety

- XEN1101 was generally well tolerated, and the safety profile observed was similar to that of the DBP
- No new safety signals were identified
- At the end of the first year, patients recorded a mean (SD) weight gain of 1.1 (5.9) kg
- TEAEs occurred in 85.8% of the safety population

**TEAEs During OLE Period**

- 2 patients reported urinary retention, 1 reported as mild and the other moderate; no dose changes were made in either case
- SAEs were reported in 26 (9.5%) patients
  - The only SAEs reported in >1 patients were seizures in 5 (1.8%) patients, and paresthesia and deep vein thrombosis reported in 2 (0.7%) patients each
- There was 1 sudden unexplained death in epilepsy reported, determined by the investigator not to be related to the study drug

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<tr>
<th>Summary of TEAEs, n (%)</th>
<th>XEN1101 20 mg (N=275)</th>
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<tr>
<td>At least 1 TEAE</td>
<td>236 (85.8)</td>
</tr>
<tr>
<td>At least 1 SAE</td>
<td>26 (9.5)</td>
</tr>
<tr>
<td>At least 1 TEAE leading to permanent treatment discontinuation</td>
<td>31 (11.3)</td>
</tr>
<tr>
<td>At least 1 SAE leading to death</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

**Most common AEs (≥5% of overall OLE population), n (%)**

- Dizziness 57 (20.7)
  - Headache 37 (13.5)
  - Corona virus infection 32 (11.6)
  - Fall 31 (11.3)
  - Somnolence 27 (9.8)
  - Weight increased 25 (9.1)
  - Gait disturbance 24 (8.7)
  - Fatigue 20 (7.3)
  - Aphasia 19 (6.9)
  - Urinary tract infection 18 (6.5)
  - Memory impairment 17 (6.2)
  - Confusional state 15 (5.5)
  - Disturbance in attention 14 (5.1)
  - Tremor 14 (5.1)

AE, adverse event; DBP, double-blind period; OLE, open-label extension; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.
Conclusions

- XEN1101 yielded long-term efficacy in this interim analysis with 68% retention at 12 months.
- During study months 14–20, there was a sustained monthly reduction in seizure frequency (80%–90% MPC) from DBP baseline.
- Seizure freedom for ≥6-month and ≥12-month consecutive durations was achieved in 17.5% and 10.5% of patients, respectively.
- XEN1101 continues to be generally well-tolerated in the OLE with AEs consistent with prior results and other ASMs; no new safety signals were identified.
- Based on the strong phase 2b results from the X-TOLE study, Xenon has initiated a XEN1101 phase 3 clinical program in FOS and primary generalized tonic-clonic seizures.

AE, adverse event; ASM, antiseizure medication, DBP, double-blind period; FOS, focal onset seizure; MPC, median percentage change; OLE, open-label extension.
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References


