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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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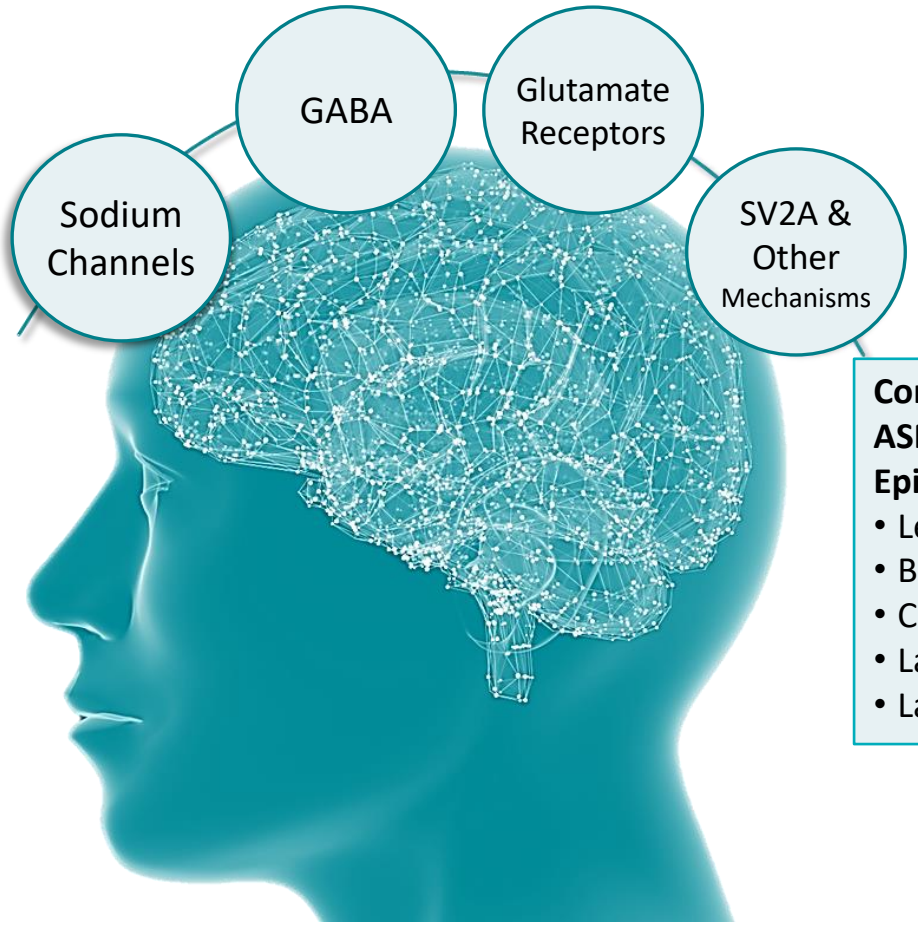
XEN1101 K_V7 Channel Opener

- XEN1101 is a novel, potent, selective *KCNQ2/3* ($K_V7.2/7.3$) potassium channel opener currently in development[1,2]
- Supports QD dosing with food with no titration
- Potential to treat common comorbidities, such as depression

Common Pharmacological Actions of Approved Anti-Seizure Medications (ASMs)



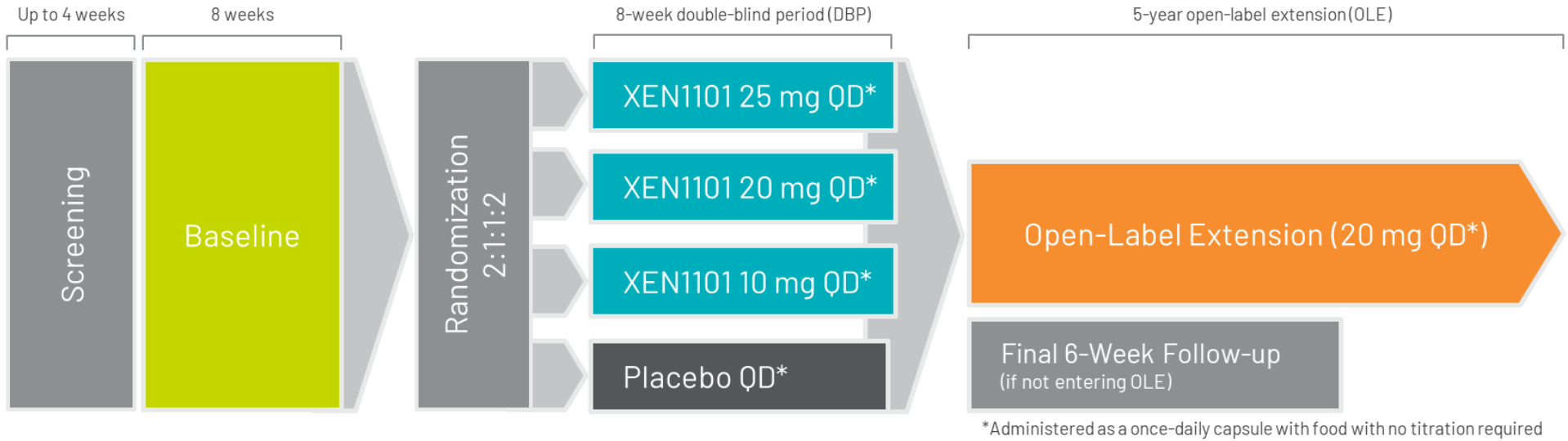
Commonly Prescribed ASMs for Adult Focal Epilepsy
- Levetiracetam
- Brivaracetam
- Carbamazepine
- Lamotrigine
- Lacosamide

1. French J, et al. *Neurology*. 2022;98(18 SUPPL). 2. Aycardi E, et al. Abstract 3.282. Presented at: American Epilepsy Society; Nov 30-Dec 4, 2018; New Orleans, LA.

X-TOLE and X-TOLE OLE

X-TOLE

Phase 2b study and 5-year 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[1]
- Key eligibility criteria included age 18–75 years with a diagnosis of focal epilepsy per International League Against Epilepsy criteria (≥2 years)[2], ≥4 countable focal seizures per month during a planned 8-week baseline period, and receiving stable treatment with 1–3 anti-seizure medications (ASMs)

DBP, double-blind period; FOS, focal onset seizure; QD, once daily.

1. French J, et al. Abstract P12.8.006. *Neurology*. 2022;98(18 SUPPL). 2. Fisher RS, et al. *Epilepsia*. 2017;58(4):522-530.

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

X-TOLE OLE Efficacy

- Median percentage change (MPC) in monthly FOS frequency from DBP baseline
- Percentage of patients with ≥50% reduction from DBP baseline in monthly FOS frequency

X-TOLE OLE Safety

- Severity and frequency of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Clinically significant laboratory findings, and other measures

**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.*

1. French J, et al. Abstract P12.8.006. *Neurology*. 2022;98(18 SUPPL).

X-TOLE OLE Patient Population

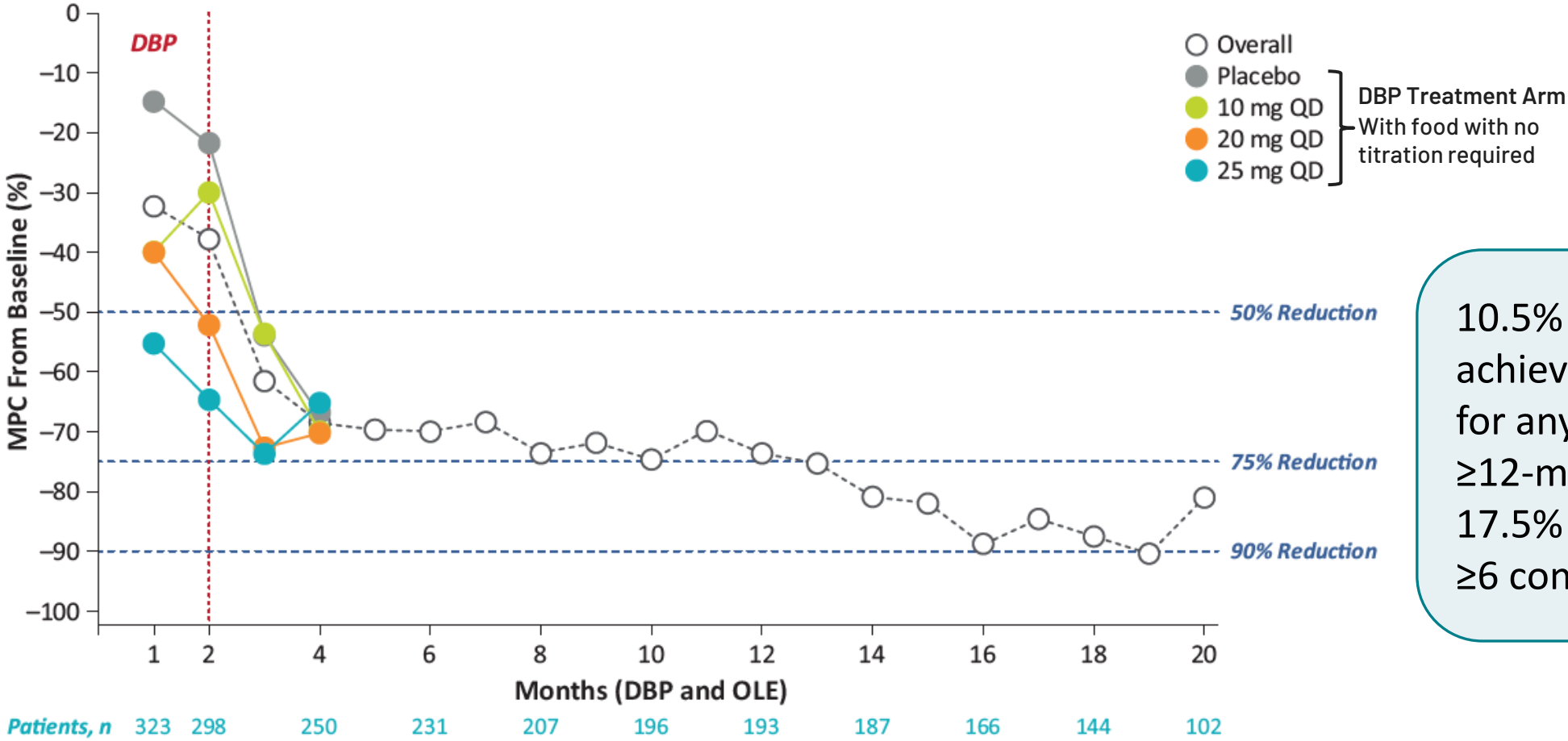
- 285 patients completed the DBP, 275 (96.5%) enrolled in the OLE
- At the analysis cutoff*:
  - 168 (61%) patients continued to participate in the OLE
    - Most common reasons for discontinuation were lack of efficacy (12.7%), AEs (10.5%), and study withdrawal by the patient (9.5%)
- The percentage 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.*

French J, et al. Abstract number: 2.235. Presented at: American Epilepsy Society; 2022; Nashville, TN, Dec 2-6, 2022.

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

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

X-TOLE
Phase 2b study and 5-year OLE

- 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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