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

Jacqueline French,1 Roger Porter,2 Emilio Perucca,3 Martin Brodie,4 Michael A. Rogawski,5 Cynthia Harden,6 Jenny Qian,7 Constanza Luzon Rosenbutl,8 Christopher Kenney,9 Gregory N. Beatch9

1New York University Comprehensive Epilepsy Center, New York, NY, USA; 2University of Pennsylvania, Philadelphia, PA, USA; 3University of Melbourne and Monash University, Melbourne, VIC, Australia; 4University Department of Medicine and Therapeutics, Western Infirmary, Glasgow, Scotland, UK; 5School of Medicine, University of California, Davis, Sacramento, CA, USA; 6Xenon Pharmaceuticals Inc., Burlingame, CA, USA

RATIONAL

- Despite the availability of several antiepileptic medications (AEMs), 37% of patients with focal onset seizures (FOS) do not achieve a year of seizure freedom after a trial of 2 AEMs; the incremental benefit of achieving seizure freedom with each subsequent AEM is limited.
- XEN1101 is a novel, potent, small molecule, selective Kv7.2/7.3 potassium channel opener developed for the treatment of FOS, primary generalized tonic-clonic seizures, and major depressive disorder.
- X-TOLE is a phase 2B, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study with an optional 15-year open-label extension (OLE) evaluating the efficacy, safety, and tolerability of XEN1101 administered with food as adjunctive treatment in adults with FOS.

METHODS

- The study design for the 2B-TOLE study (ClinicalTrials.gov identifier: NCT03736612) is shown in Figure 1. The OLE Study Design

RESULTS

Patients

- 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).

Efficacy in the OLE was evaluated by median percent change (MPC) in monthly FOS frequency from baseline observed during study months 14–20 (Figure 2).

Patients who continued to participate in the OLE included those who received XEN1101 20 mg QD during the DBP.

The key eligibility criteria for the DBP were as follows:

- Age 18–75 years, inclusive
- A diagnosis of focal epilepsy per International League Against Epilepsy criteria
- Aged 18–75 years (inclusive) with a diagnosis of focal epilepsy per International League Against Epilepsy criteria

Consecutive Months of Seizure Reduction

- 10.5% of patients achieved seizure freedom for any consecutive 12-month duration, and 17.5% (9/52) were seizure free for any 12-month consecutive months. Responder rates are summarized in Figure 4

Safety

- XEN1101 20 mg QD was generally well tolerated, and the safety profile observed was similar to that of the DBP. No new safety signals were identified.

- The most common reasons for discontinuation were lack of efficacy and adverse events.

- During study months 14–20, there was a sustained monthly reduction in seizure frequency (90% reduction in 90% of patients during OLE baseline cutoff).

EFFICACY

- In patients treated with XEN1101 20 mg QD during the OLE, monthly FOS reduction was maintained with 90%–96% MPC from DBP baseline observed in patients with ≥50% reduction in DBP baseline in monthly FOS frequency.

- XEN1101 continues to be generally well-tolerated in the OLE with AEs consistent with prior results and no new safety signals were identified.

CONCLUSIONS

- XEN1101 20 mg QD yielded long-term efficacy in this interim analysis with 68% retention at 12 months.

- In addition to the TEAEs summarized in Table 2, patients reported urinary retention, 1 reported as mild and the other as mild to the end of the first year, no dose changes were made in either case.

- There was 1 sudden unexplained death in epilepsy reported, determined by the investigator not to be related to the study drug.