Despite the availability of several antiseizure medications (ASMs), 37% of patients with focal onset seizures (FOS) do not achieve 24-year seizure freedom after a trial of 2 ASMs, the incremental likelihood of achieving seizure control decreases with each subsequent ASM.

XEN1101 is a novel, potent K-7 potassium channel opener in development for the treatment of epilepsy and major depressive disorder.

X-TOLE (NCT03796962) is a completed, phase 2b, randomized, double-blind, placebo-controlled, parallel group, dose-ranging, multicenter, open-label 5-year extension study (OLE) evaluating the safety, tolerability, and efficacy of XEN1101 administered as a fixed-dose treatment in adults with FOS.

In the double-blind period (DBP), XEN1101 treatment yielded a dose-dependent, consistent, highly statistically significant reduction in FOS across endpoints in a hard-to-treat patient population.

XEN1101 was generally well tolerated with a low incidence of serious adverse events (SAEs), and no cardiovascular safety signals were identified.

The study design for the X-TOLE study is shown in Figure 1.

In which patients received open-label XEN1101 at a dose of 20 mg once daily (QD) with food with no titration required.

In addition to the TEAEs summarized in Table 2, 2 patients reported urinary retention, 1 reported as mild and the other moderate; no dose changes were made in either case.

In Table 2, SAEs were reported in 26 (9.5%) patients. The only SAEs reported in >1 patients were seizures in 5 (1.8%) patients, and pancreatitis 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.

CONCLUSIONS

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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METHODS

The study design for the X-TOLE study is shown in Figure 1.

Figure 1. X-TOLE Study Design

At the analysis cutoff (September 22, 2022), 168 patients continued to participate in the OLE.

– The key eligibility criteria for the DBP were as follows:
  – Age 18–75 years (inclusive) with a diagnosis of focal epilepsy per International League Against Epilepsy criteria (2 years)2
  – Receiving stable treatment with 3–4 ASMs.
  – Countable seizure frequency over the 8-week baseline period of 4 focal seizures per month on average, recorded in an eDiary
  – 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 received XEN1101 20 mg QD taken with the evening meal.

In the OLE, the efficacy was evaluated by median percentage change (MPC) in monthly FOS frequency from DBP baseline and percentage of patients with ≥50% reduction from DBP baseline in monthly FOS frequency.

Safety was assessed as severity and frequency of treatment-emergent adverse events (TEAEs) and SAEs, clinically significant changes in laboratory findings, and other measures.

Assessments occurred in the OLE (daily study day 71 from randomization) and 3-month intervals thereafter for the first year. After the first year, on-site visits occurred at 6-month intervals with teleconsultations at 3 months between each visit on site.

At the analysis cutoff (September 22, 2022), 168 patients continued to participate in the OLE.

– The most common reasons for discontinuation were lack of efficacy (12.7%), adverse events (AEs), 30.5%, and study drug dose reduction (11.3%).
– A total of 188 (68%) patients had been treated in the OLE for ≥12 months, 112 patients had reached 18 months in OLE as of data cutoff.
– The percentage of patients continuing XEN1101 at 6 months and 12 months in the OLE study period was 76% and 68%, respectively.

Efficacy

For ongoing OLE patients, monthly MPC reductions in FOS frequency ranged from 40–50% from DBP baseline and were maintained at 80–90% in OLE study months 14–20 (Figure 2).

Higher reductions were observed for patients who were receiving 1–2 ASMs at baseline compared with those receiving ≥3 ASMs (Figure 3).

30.5% of patients (29/96) achieved seizure freedom for any consecutive 12-month duration, and 17.5% (18/102) were seizure free for any of the 3 consecutive months. Responsive rates are summarized in Figure 4.

CONCLUSIONS


ACKNOWLEDGMENTS

Medical writing support was provided by Robin Smith, PhD, of The Curry Rockefeller Group, LLC (Tarrytown, NY), and was funded by Xenon Pharmaceuticals Inc.

REFERENCES