**Phase 2b Efficacy and Safety of XEN1101, a Novel Potassium Channel Modulator, in Adults With Focal Epilepsy (X-TOLE)**

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XEN1101 is an oral, small-molecule, selective Kv3.1A (KCNQ1) potassium channel opener being developed for the treatment of focal-onset seizures and major motor disabilities. In phase 2b clinical trials, XEN1101 demonstrated a high rate of seizure reduction in adults with drug-resistant focal seizures treated for up to 24 weeks. In the current phase 2b trial, XEN1101 showed statistically significant and clinically meaningful improvements in focal seizures up to 10 weeks in adults with drug-resistant focal seizures. In addition, XEN1101 was generally well tolerated with a low incidence of serious adverse events. In this clinical trial, safety and pharmacokinetic data will be presented.

**Research Design and Methods**

The X-TOLE study was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in adults with drug-resistant focal seizures. A total of 364 subjects were randomized 2:1:1:2 to active treatment arms of XEN1101 10 mg (N= 114), 20 mg (N= 311), 25 mg (N= 113), and placebo (N= 120) to one of four fixed dose groups. Overall, 347 subjects completed the 10-week double-blind period. The primary endpoint was the monthly focal seizure frequency change from baseline to week 10. Secondary endpoints included a change in weekly seizure frequency, qualitative changes in seizure frequency, responder rates, and safety assessments. The trial was conducted at 257 centers in the U.S., Canada, Europe, and Israel. The study was approved by institutional review boards and conducted in accordance with the Declaration of Helsinki and applicable regulatory requirements.

**RESULTS**

**Safety**

XEN1101 was generally well tolerated in this study with a low SAE incidence and balanced across treatment arms. In total, 4% of subjects discontinued due to SAEs with no treatment group having a difference of more than 1%. The most common TEAEs leading to discontinuation across XEN1101 groups were dizziness (4.7%), balance disturbance (3.4%), and headache (3.3%). There were no treatment-related SAEs of pigmentary abnormalities. The most common AEs of urinary retention were reported in the active treatment groups, one of which required a dose reduction, and 2 subjects who required a dose reduction with no other changes or intervention.

**Efficacy**

Highly significant dose response for reduction in focal seizures, across primary & secondary FOS endpoints

Highly significant and dose-dependent reduction in seizures

**Exploratory endpoint: time to event analysis showed marked dose-dependent decrease in rate of seizure recurrence**

**Safety and tolerability profile inline with commonly used ASMs**

**OVERALL ADVERSE EVENT PROFILE**

- **XEN1101** showed dose-dependent, consistent, highly statistically significant and clinically meaningful reduction in focal seizures across a 2:1:1:2 fixed dose group with similar low SAEs in all treatment arms compared to placebo (2.6%).
- **XEN1101** was generally well tolerated with a similar low SAE incidence (3.3%) as seen in placebo (2.6%) and no deaths in the study.
- The most common TEAEs leading to discontinuation across XEN1101 groups were dizziness (3.3%), balance disturbance (3.3%), and headache (3.3%).
- There were no treatment-related SAEs of pigmentary abnormalities.
- Based on the strong Phase 2b topline results from the XEN1101 study, Xenon intends to gather input from the U.S. FDA and other regulatory agencies to continue planning the future clinical development of XEN1101.

**CONCLUSIONS**

- XEN1101 demonstrated a high rate of seizure reduction in adults with drug-resistant focal seizures treated for up to 24 weeks.
- XEN1101 was generally well tolerated with a low incidence of serious adverse events. The most common TEAEs leading to discontinuation across XEN1101 groups were dizziness (3.3%), balance disturbance (3.3%), and headache (3.3%).
- There were no treatment-related SAEs of pigmentary abnormalities.
- Based on the strong Phase 2b topline results from the XEN1101 study, Xenon intends to gather input from the U.S. FDA and other regulatory agencies to continue planning the future clinical development of XEN1101.