Phases 2b and 3a of XEN1101: A Novel Potassium Channel Modulator, in Adults With Focal Epilepsy (X-TOLE)

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XEN1101 was an oral, small-molecule, selective Kᵥ3.2 (data on file) potassium channel opener being developed for the treatment of focal onset seizures and major depressive disorder (MDD). Preclinical properties support daily oral dosing without the need for titration at initiation of therapy or monitoring at the termination of dosing. XEN1101 demonstrated higher in-research efficacy to stanozolol in a different seizure model, and showed an improved therapeutic index in a conditioned avoidance paradigm compared with stanozolol, a non-selective Kᵥ opener. Preclinical and clinical properties also suggested minimal cardiac liability for XEN1101.

TOLERABILITY

- XEN1101 was well tolerated in both Phase 2b and 3a trials. Most common treatment-related AEs were related to dose and included somnolence (28.3%), sedation (14.9%), and hallucinations (4.3%).
- No drug-related deaths occurred.
- There were no toxicities to the CNS observed, with a low incidence of serious AEs related to the CNS.
- No notable differences were observed in the likelihood of discontinuation due to AEs or in the number of patients who discontinued due to AEs. There were no significant differences in the incidence of severe AEs across treatment groups.
- No serious AEs leading to discontinuation were reported.
- No new safety signals were identified in Phase 3a compared with Phase 2b.
- All reported serious AEs were considered unrelated to treatment, including suicide attempt resulting in enhancer injury and a non-serious, non-life-threatening injury. Patients were reevaluated at the end of the study.
- Patients were not overrepresented with regard to age or sex attributes.
- There were no notable differences in the incidence of serious AEs or serious AEs leading to discontinuation between treatment groups.

OVERALL ADVERSE EVENT PROFILE

- XEN1101 was generally well tolerated in this study with common AEs in patient populations similar to those enrolled in the 2b- and 3a-phase trials. All AEs were considered mild to moderate in severity. No new safety signals were identified in Phase 3a compared with Phase 2b trials. There were no serious AEs reported.
- The most common AEs reported were somnolence (28.3%), dizziness (14.9%), and nausea (14.9%)
- Treatment-emergent serious AEs (SAEs) in double-blind period: N/A (>9 weeks). Time taken for the same number of patients to achieve 50% and 75% responder rates were N/A and N/A, respectively.

CONCLUSIONS

- Multiple doses of XEN1101 demonstrated consistent efficacy and tolerability in patients with focal onset seizures.
- XEN1101 was well tolerated in both Phase 2b and 3a trials. The most common AEs were somnolence, dizziness, and nausea.
- The therapeutic index of XEN1101 was demonstrated to be higher than that of stanozolol, a non-selective Kᵥ opener.
- XEN1101 demonstrated a consistent safety profile across both phases, with no new safety signals identified in Phase 3a.
- The study results support further development of XEN1101 for the treatment of focal onset seizures without the need for titration at initiation of therapy or monitoring at the termination of dosing, providing an improved therapeutic index compared to stanozolol.

Highly significant dose-dependent reduction in seizures

Change from Baseline in Seizure Frequency

Responder Rate (p=0.0001)

Dose dependent increase in the number of responders with >50% reduction in seizures

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

Safely and tolerability profile inline with commonly used ASMs

Tolerability profile consistent with other ASMs, with majority of TEAEs within the CN5 summary of all treatment emergent adverse events (SAEs) in the double-blind period within the safety window, based on the investigator's judgment.

Most common treatment emergent adverse events (TEAEs) are listed in any arm:

- Somnolence (28.3%), dizziness (14.9%), and nausea (14.9%)
- No new safety signals were identified in Phase 3a compared with Phase 2b trials.

Low incidence of SAEs and balanced across treatment arms

- Treatment-emergent serious adverse events (SAEs) in double-blind period.
- There were no cardiovascular signals of concern in ECG or vital signs.
- The most common TEAEs leading to discontinuation across XEN1101 groups were dizziness (4.7%), balance disturbance (2.2%), dizziness (2.2%), and gait disturbance (1.8%).

Clinical meaning and statistically significant, dose-dependent improvements in CGI-I/C-GI-P-C

Marked reduction in FOS (MPC from baseline)

Monthly Seizure Frequency in Baseline; n (%)

At least 1 improvement in CGI-I/C-GI-P-C

At least much improved in CGI-I/C-GI-P-C

10mg (N=46)

25mg (N=112)

Placebo 10 mg 20 mg 25 mg Study Arm

2.94 1.6 1.1 0.8

1.1 2.3

2.2 kg at 20 mg and 1.9 kg at 10 mg, 2.3 kg at 10 mg, 2.1 kg at 20 mg, 1.1 kg at 10 mg.

Most common treatment emergent adverse events (TEAEs) [N=211] are listed in any arm:

- Dizziness (14.9%), somnolence (7.8%), sedation (2.2%), nausea (6.3%)
- There were no cardiovascular signals of concern in ECG or vital signs.
- The most common TEAEs leading to discontinuation across XEN1101 groups were dizziness (4.7%), balance disturbance (2.2%), dizziness (2.2%), and gait disturbance (1.8%).

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