XEN1101, a Differentiated Kv7 Potassium Channel Modulator, Impacts Depression and Anhedonia

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RATIONAL

XEN1101 is being developed for the treatment of epilepsy and potentially other indications, including Major Depressive Disorder (MDD).

Practical and clinical studies suggest Kv7 channel potentiators, including ezogabine, may be beneficial for patients with depression and anhedonia.\(^1,2\)

Ezogabine Results in Meaningful Clinical Efficacy in MDD

- The 9/7 nitrogen mechanism of action was evaluated in a proof-of-concept randomized placebo-controlled clinical trial (\(^3\))
- Ezogabine was dosed at 300 mg TID for 4 weeks
- The MADRS is a 16-item instrument used for the evaluation of depression symptoms.
- The SIGH-P is a validated 16-item self-report questionnaire commonly used to screen anhedonia.

Depression Burden in Persons with Epilepsy

- Depression is a common co-morbidity of epilepsy, lifetime prevalence rate reported in the literature is ~30-50%.
- Greater severity of depression has been associated with higher seizure frequency.
- Depression is a strong and independent predictor of reduced QOL and can be a significant cause of non-adherence to anti-seizure medications.
- Market research w/20 épileptologists highlighted the need for ASMs offering a mood benefit for patients that suffer from comorbid depression.
- Majority of current AEDs do not adequately address depression.
- Some AED side effect profiles can exacerbate mood-related co-morbidities (e.g., somnolence).
- In later lines of treatment, physicians indicated the preferred trend is to choose between improving seizure control and potentially ameliorating mood-related co-morbidities.

METHODS

- Trained rats followed a progressive schedule of reinforcement in which the number of lever presses required to obtain a food reward is increased for successive reinforcers.
- The stimulant amphetamine was used to reward/motivation, relative to the vehicle group.
- The 32 rats in the PRT were also ranked based on their performance of XEN1101 on CNS systems relevant to reward/motivation.
- In the sub-group analysis, the XEN1101 effect on total lever presses was significant in the low performing sub-group at doses of 3 mpk and 8 mpk.
- XEN1101 did not show a significant effect in the high performing sub-group.
- Breakpoint data was consistent, showing a significant effect in low performers but not the high performers (data not shown).
- As a positive assay control.

RESULTS

XEN1101 and Amphetamine PRT Responses in Entire Cohort

- XEN1101 significantly increased the number of total lever presses at the 3 mpk and 8 mpk doses compared to vehicle control.
- Breakpoint data was consistent (data not shown).

XEN1101 Responses in High vs. Low Performers

- In the sub-group analysis, the XEN1101 effect on total lever presses was significant in the low performing sub-group at doses of 3 mpk and 8 mpk.
- XEN1101 did not show a significant effect in the high performing sub-group.
- Breakpoint data was consistent, showing a significant effect in low performers but not the high performers (data not shown).

Amphetamine Responses in High vs. Low Performers

- Amphetamine was efficacious in increasing total lever presses in both high and low performer sub-groups.
- This may suggest a more subtle effect of XEN1101 on CNS systems relevant to motivation/reward, relative to the direct amphetamine.

CONCLUSIONS

- Depression is a common co-morbidity of persons with epilepsy and significantly impacts their quality of life.
- This work confirms the beneficial impact of XEN1101 on motivation and anhedonia in the translational PRT model.
- Further, these data support the hypothesis that XEN1101 may have beneficial impacts on mood at plasma concentrations that are achievable in the clinic.
- Sub-group results suggest XEN1101 may preferentially exert an effect in animals with greater anhedonia at baseline.
- XEN1101 is being studied in patients with MDD with one randomized, placebo-controlled, double-blind clinical trial ongoing and a second study being planned.

REFERENCES


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