Background

- Major depressive disorder (MDD) is a highly prevalent mental health disorder and one of the leading causes of disability worldwide. With available treatments, 35-50% of patients fail to show a substantial improvement in symptoms, and 20-30% of patients discontinue treatment for multiple reasons, including tolerability.

- The most commonly used antidepressants largely share the same mechanism of action. Therefore, a new antidepressant, acting on a different target, could potentially benefit patients who do not respond to common treatments, or who have undesirable adverse effects.

KV7 potassium channels in depression

- KV7 potassium channels (Kv7) are gated by voltage and are regulated by neurotransmitters. kv7 channelopathies are observed in the chronic social defeat stress model (CSDS).

- Friedman et al. demonstrated that overexpression of Kv7.3 in the VTA dopaminergic neurons normalizes normal hyperactivity and depressive behaviors in the CSDS model in mice. The same effect was achieved with local (via VTA) or systemic infusion of XEN1101.

- Enhancing the open-state of KV7.2/3 in neurons favors a hyperpolarized resting state, reducing rapid action potential spiking. This mechanism has been clinically proven in mice. The same effect was achieved with local (via VTA) or systemic infusion of XEN1101.

- The same effect was observed during treatment of epilepsy patients with ezogabine.

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XEN1101

- XEN1101 is a next generation Kv7 potassium channel opener currently being developed. It was generally well-tolerated, with dose-dependent tolerability. The most common treatment-emergent adverse events observed in this study were dizziness, somnolence, fatigue, and headache.

- XEN1101 was assessed in the progressive ratio test, a protocol that evaluates motivational performance and decisional anhedonia in rats. In this test, XEN1101 maintained the number of lever presses, indicating improved motivation versus vehicle (Fig. 2).

Methods

Figure 2. Results of the progressive ratio test

Figure 3. Study design

Table 1. Key eligibility criteria

Table 2. Efficacy objectives and endpoints

CONCLUSIONS

- XEN1101 represents a novel molecular mechanism to potentially treat depression. The double-blind, placebo-controlled, proof-of-concept study described above will help evaluate the efficacy and safety of this compound in subjects with MDD and inform further development.

References

3. Costi S, Morris LS, Kirkwood KA et al. Impact of the KCNQ2/3 channel opener ezogabine on reward circuit activity and motivational performance and decisional anhedonia in rats. In this test XEN1101 maintained the number of lever presses, indicating improved motivation versus vehicle (Fig. 2).

Figure reproduced from Costi et al. Depression symptoms assessed by the Montgomery-Åsberg Depression Rating Scale, antidepressant symptoms assessed by the Sneddon Hamilton Profile.