“Depression and Anhedonia: Acute Preclinical Efficacy for XEN1101, a Differentiated $K_{V7}$ Potassium Channel Modulator”

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Rationale for Testing XEN1101 in Preclinical “Mood” Models

- XEN1101 is a differentiated “next generation” Kv7 potassium channel modulator being developed for the treatment of epilepsy and potentially other neurological disorders.

- Preclinical and clinical studies suggest Kv7 channel potentiators, including ezogabine, may be beneficial for patients with depression and anhedonia.

- XEN1101 was assessed in acute rodent models of these conditions.

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**Forced Swim Test (FST)**
- Model of behavioral despair
- Vast majority of anti-depressants tested in the mouse FST decrease the time spent immobile by 20% or more.\(^2\)

**Progressive Ratio Test (PST)**
- Translational model of motivational performance and anhedonia
- Diminished effort in the PRT is observed in patients with depression.\(^3\)
- In rodents and humans, some anti-depressants improve motivational performance in reward-based tests, as does ezogabine.\(^4\)

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1 Krishnan et al. 2007; Friedman et al. 2014; Friedman et al. 2016; Tan et al., 2020
2 Borsisni and Meli 1988
4 Hughes et al. 1985, Yang et al. 2014; Tan et al. 2020
**XEN1101 Demonstrates Efficacy in FST Model of Depression**

- Mice received a single dose of 1 or 3 mpk XEN1101 or vehicle (n=10)

- After a period of vigorous activity, mice stop swimming and adopt an immobile posture (this is the “latency to immobility”)

- XEN1101 demonstrated a **trend towards increased latency to immobility**

- Total time spent immobile is also an indicator of efficacy

- Over a 6-minute test session, XEN1101 demonstrated a **significant dose-dependent reduction in time spent immobile**

- **Results indicate an anti-depressant effect of XEN1101**
XEN1101 Demonstrates Motivational Efficacy in the PRT

- Rats were trained to respond for food made available under a progressive schedule of reinforcement in which the number of lever presses required to obtain a food reward increased for each successive reward
  - Total number of lever presses in the test session, as well as the “break point” (defined as the cycle at which a rat failed to earn a food pellet in 20 minutes) were measured

- In a cross-over design, rats received a single dose of 1, 3, 8 mpk XEN1101 or vehicle (n=32)

- XEN1101 significantly increased the total number of lever presses in the test session

- XEN1101 also significantly increased the break point at doses of 3 and 8 mpk

- Results indicate XEN1101 improved motivation

(* p<0.05; *** p<0.001 compared to vehicle)
XEN1101 Impacts Anhedonia in Low Performing Rats

- 32 rats in the PRT were also ranked based on performance measured over 7 days prior to commencement of testing.
- Animals were classified as either low performers (n=11), or high performers (n=11) at baseline.
- An XEN1101 effect on total lever presses was only significant in the low performing subgroup (at 3 and 8 mpk).
  - Break point data is consistent, showing a significant effect in low performers only.
- Results suggest XEN1101 may preferentially exert an effect in depressed individuals with anhedonia.

(*p<0.05 compared to vehicle)
XEN1101 PK/PD in Mood & Epilepsy Animal Models

- Significant effects of XEN1101 in the FST occurred at and below the ED$_{50}$ for seizures in the MES model.
- Significant effects of XEN1101 in the PRT occurred at and above the ED$_{50}$ for seizures in the MES model*.
- These data support the hypothesis that XEN1101 may have beneficial impacts on mood at doses and plasma concentrations that are efficacious for seizure reduction.
- In addition, these efficacious effects on rodent seizure and “mood” endpoints occur at plasma levels achieved in a human Phase 1 MAD clinical trial of XEN1101.

*Note: species difference between PRT (rat) and MES (mouse) models.
Conclusions

- XEN1101 is a differentiated, next-generation Kv7 potassium channel modulator
- The results from the two preclinical studies presented here support a potential benefit of XEN1101 in mood disorders
  - XEN1101 demonstrated anti-depressant activity in the mouse FST model
  - XEN1101 improved motivation and anhedonia parameters in the PRT model, particularly in low performing rats
- Major depression is a common co-morbidity of persons with epilepsy and significantly impacts their quality of life
- The efficacious doses and plasma concentrations from the rodent depression, anhedonia, and MES studies overlap, suggesting that use of XEN1101 to treat epilepsy could have a beneficial impact on mood
- The Phase 2b “X-Tole” clinical trial is underway to evaluate the clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in approximately 300 adult patients with focal epilepsy
  - Topline results are expected in the third quarter of 2021

Please refer to these additional presentations at ASENT 2021 to learn more:

Dr. Robin Sherrington, “Kv7 Modulators in Epilepsy and Depression”

Dr. Ernesto Aycardi, “Addressing an Unmet Medical Need in Adult Focal Epilepsy with XEN1101, a Novel Kv7 Modulator”

Dr. J.P. Johnson, Jr., “Anticonvulsant Effects of the Differentiated Kv7 Channel Potentiator XEN1101 in Combination with Commonly Used Anti-Seizure Drugs”
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