



XENON

ASENT 2021

VIRTUAL NEUROTHERAPEUTICS CONFERENCE

“Depression and Anhedonia: Acute Preclinical Efficacy for XEN1101, a Differentiated K_v7 Potassium Channel Modulator”

DR. ALISON CUTTS

VP, SCIENTIFIC AFFAIRS | XENON PHARMACEUTICALS INC.

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Rationale for Testing XEN1101 in Preclinical “Mood” Models

- XEN1101 is a differentiated “next generation” K_v7 potassium channel modulator being developed for the treatment of epilepsy and potentially other neurological disorders
- Preclinical and clinical studies suggest K_v7 channel potentiators, including ezogabine, may be beneficial for patients with depression and anhedonia¹
- XEN1101 was assessed in acute rodent models of these conditions

¹ Krishnan et al. 2007; Friedman et al. 2014; Friedman et al. 2016; Tan et al., 2020

² Borsisni and Meli 1988

³ Hershenberg et al. 2016; Der-Avakian et al. 2016

⁴ Hughes et al. 1985; Yang et al. 2014; Tan et al. 2020

Forced Swim Test (FST)

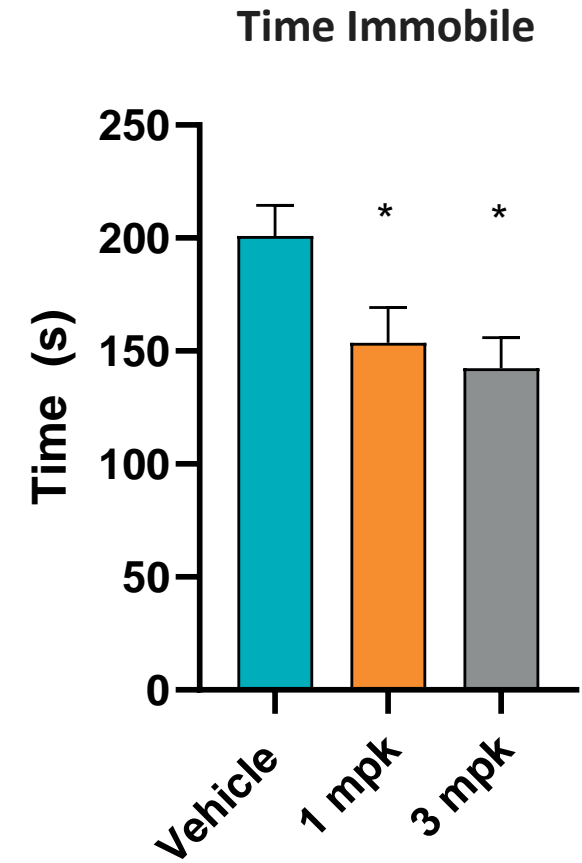
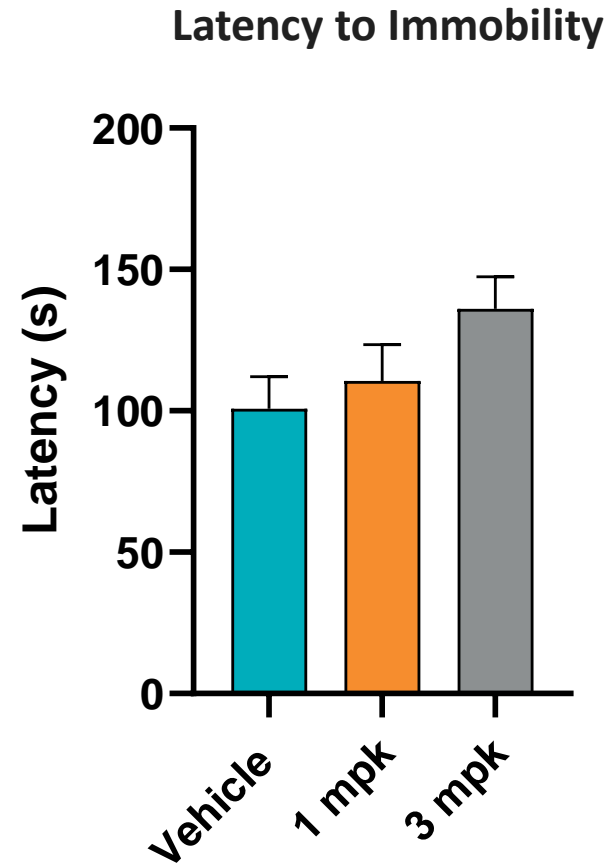
- Model of behavioral despair
- Vast majority of anti-depressants tested in the mouse FST decrease the time spent immobile by 20% or more²

Progressive Ratio Test (PST)

- Translational model of motivational performance and anhedonia
- Diminished effort in the PRT is observed in patients with depression³
- In rodents and humans, some anti-depressants improve motivational performance in reward-based tests, as does ezogabine⁴

XEN1101 Demonstrates Efficacy in FST Model of Depression

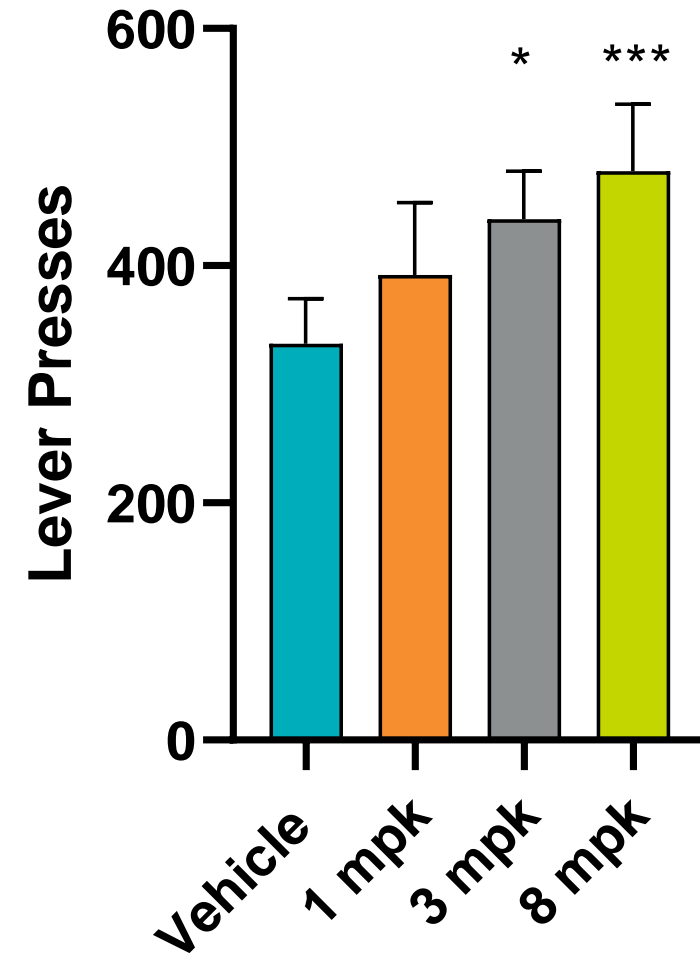
- Mice received a single dose of 1 or 3 mpk XEN1101 or vehicle (n=10)
- After a period of vigorous activity, mice stop swimming and adopt an immobile posture (this is the “latency to immobility”)
- XEN1101 demonstrated a **trend towards increased latency to immobility**
- Total time spent immobile is 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**



(*p<0.05 compared to vehicle)

XEN1101 Demonstrates Motivational Efficacy in the PRT

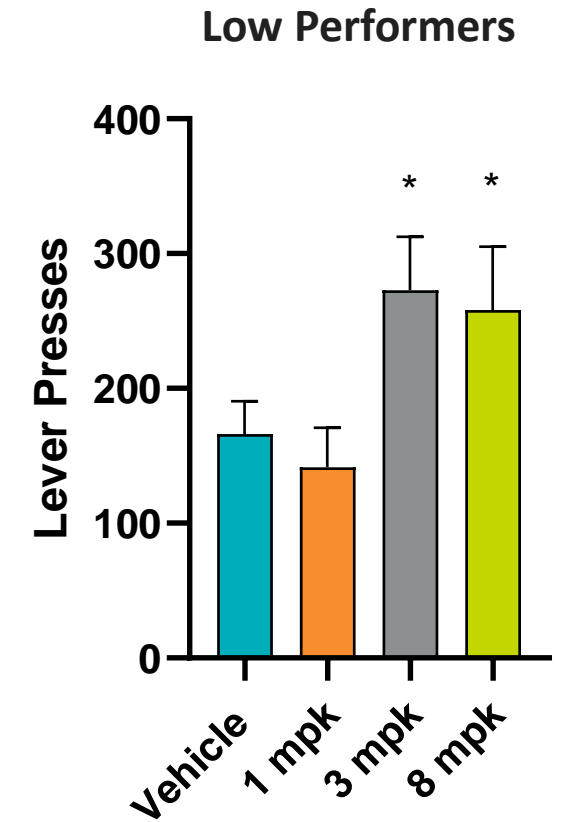
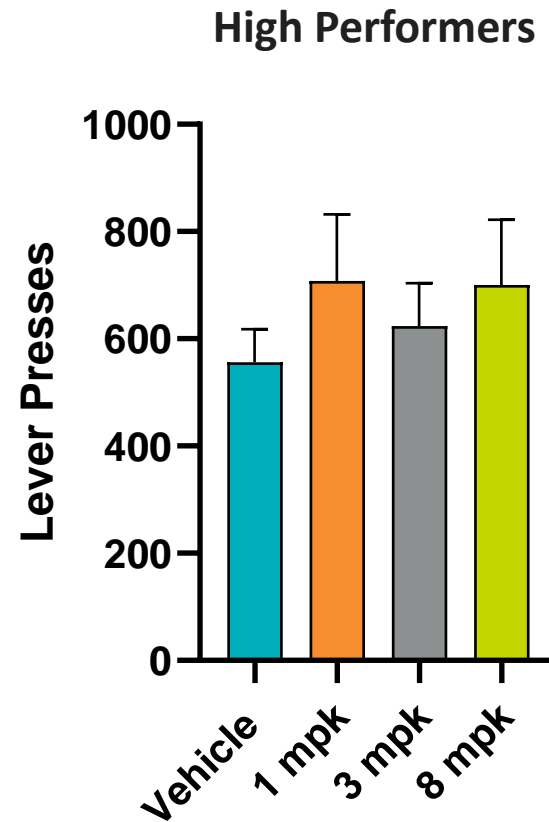
- Rats were trained to respond for food made available under a progressive schedule of reinforcement in which the number of lever presses required to obtain a food reward increased for each successive reward
 - Total number of lever presses in the test session, as well as the “break point” (defined as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

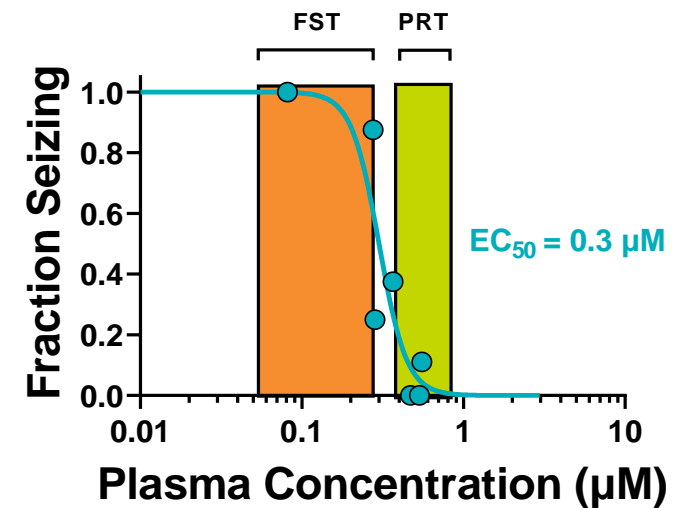
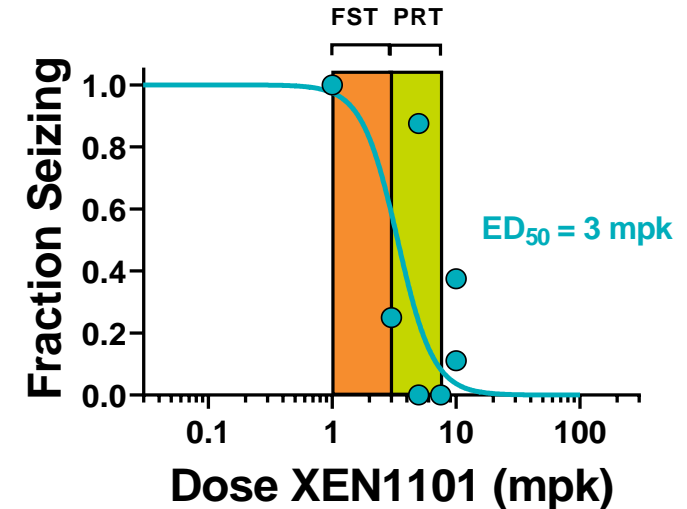
- 32 rats in the PRT were also ranked based on performance measured over 7 days prior to commencement of testing
- Animals were classified as either low performers (n=11), or high performers (n=11) at baseline
- An XEN1101 effect on total lever presses was only significant in the low performing subgroup (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 K_v7 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,
“ K_v7 Modulators in Epilepsy and Depression”*

*Dr. Ernesto Aycardi,
“Addressing an Unmet Medical Need in Adult Focal Epilepsy with XEN1101, a Novel K_v7 Modulator”*

*Dr. J.P. Johnson, Jr.,
“Anticonvulsant Effects of the Differentiated K_v7 Channel Potentiator XEN1101 in Combination with Commonly Used Anti-Seizure Drugs”*

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