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

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RATIONALE

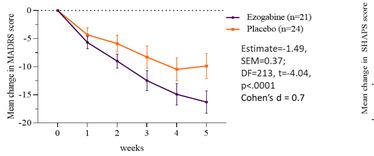
- XEN1101 is being developed for the treatment of epilepsy and potentially other indications, including Major Depressive Disorder (MDD)
- Preclinical and clinical studies suggest Kv7 channel potentiators, including ezogabine, may be beneficial for patients with depression and anhedonia [1,2,8]

Ezogabine Results in Meaningful Clinical Efficacy in MDD

- The Kv7 agonism mechanism of action was evaluated in a proof-of-concept randomized placebo controlled clinical trial (n=45)[2]
  - Ezogabine was dosed at 300 mg TID for 5 weeks
  - The MADRS[3] is a 10-item instrument used for the evaluation of depressive symptoms.
  - The SHAPS[4] is a validated 14-item self-report questionnaire commonly used to assess anhedonia.

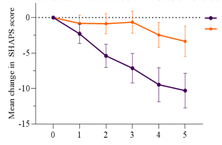
Inclusion	
DSM-V MDD or PDD	
Clinically significant anhedonia (SHAPS ≥ 20)	
Illness severity moderate or greater (CGI-S ≥ 4)	
Highlighted Demographics	**Active**	**Placebo**
Baseline MADRS	28.4	26.8
Baseline SHAPS	38.7	33.7

Montgomery–Åsberg Depression Rating Scale



Estimate=-1.49, SEM=0.37; DF=213, t=-4.04, p<.0001
Cohen's d = 0.7

Snaith-Hamilton Pleasure Scale

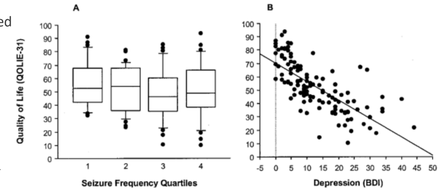


Estimate=-1.55, SEM=0.37; DF=212, t=-4.1, p<0001
Cohen's d = 0.6

Figures reproduced from Costi et al.

Depression Burden in Persons with Epilepsy

- Depression is a common co-morbidity of epilepsy, lifetime prevalence rate reported in the literature ~30-50%
- Greater severity of depression has been associated with higher seizure frequency[5]
- Depression is a strong and independent predictor of reduced QOL[6] and can be a significant cause of non-adherence to anti-seizure medications[9]
- Market research with 20 epileptologists highlighted the need for ASMs offering a mood benefit for patients that suffer from co-morbid depression
  - Majority of current ASMs do not adequately address depression
  - Some ASM side effect profiles can exacerbate mood-related co-morbidities (e.g., levetiracetam)
  - In later lines of treatment, physicians indicated the potential need to choose between improving seizure control at the expense of potentially worsening mood-related comorbidities



Figures reproduced from Boylan et al.

METHODS

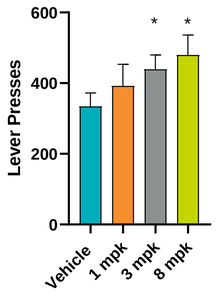
- Trained rats followed a progressive schedule of reinforcement in which the number of lever presses required to obtain a food reward is increased for successive reinforcers
- The break point was defined as the point at which a rat failed to earn a food pellet in 20 minutes
- Rats received a single oral dose of 1, 3, or 8 mpk XEN1101 or vehicle, or a single IP dose of 0.6 mpk amphetamine in a cross-over design
- The 32 rats in the PRT were also ranked based on their performance measured over 5 days prior to dosing
- In a sub-group analysis, animals were classified as either low performers (n=11), exhibiting lowered motivation and greater anhedonia, or high performers (n=11) at baseline
- XEN1101 data was analyzed by one-way repeated measures ANOVA. Amphetamine data vs. vehicle was analyzed by paired t-test
- To compare plasma exposures for efficacy across anti-seizure models with efficacy in the PRT, XEN1101 was also evaluated in the mouse Direct Current Maximal Electroshock Seizure (DC-MES) model at 1, 3, 5, 7.5 or 10 mpk

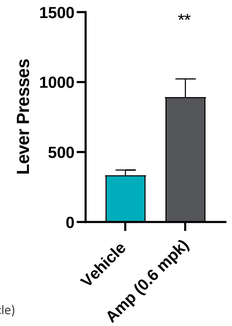
Progressive Ratio Test (PRT)

- Translational model of motivational performance and anhedonia
- Diminished effort in the PRT is observed in patients with depression[7]
- In rodents and humans, some anti-depressants, and ezogabine, improve motivational performance in reward-based tests[8]

RESULTS

XEN1101 and Amphetamine PRT Responses in Entire Cohort



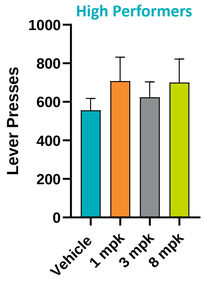


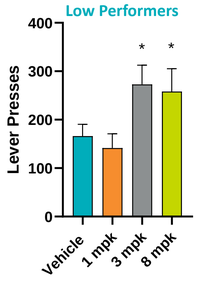
(* p<0.05; ** p<0.01 compared to vehicle)

- 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)
- The stimulant amphetamine was used as a positive assay control

XEN1101 Responses in High vs. Low Performers

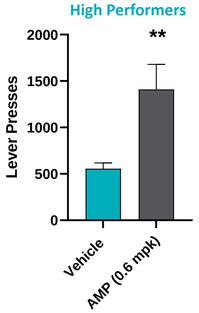
- In the sub-group analysis, the XEN1101 effect on total lever presses was significant in the low performing sub-group at doses of 3 and 8 mpk
- XEN1101 did not show a significant effect in the high performing sub-group
- Break point data was consistent, showing a significant effect in low performers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

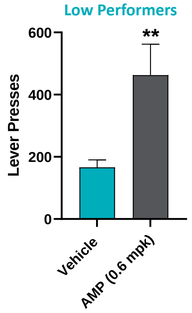




(*p<0.05 compared to vehicle)

Amphetamine Responses in High vs. Low Performers



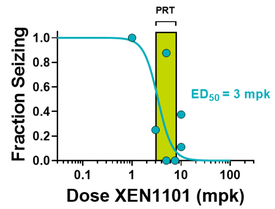


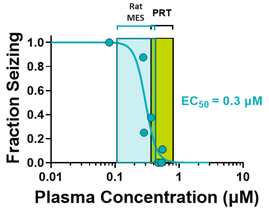
(**p<0.01 compared to vehicle)

- 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 reward/motivation, relative to the stimulant amphetamine

XEN1101 PK/PD in Preclinical Models of Mood & Epilepsy

- Significant effects of XEN1101 in the PRT occurred at and above the ED_{50} and plasma EC_{50} for seizures in the mouse 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





*Species differences noted between PRT (rat) and MES (mouse) models: in the rat MES model the ED_{50} is 0.79 mg/kg and the EC_{50} range is 104-408 nM .

XEN1101 Clinical Studies

- XEN1101 showed a dose-dependent statistically significant reduction in focal onset seizures in a recently completed Phase 2b study (X-TOLE)
- An investigator-initiated, Phase 2 study of XEN1101 in MDD is ongoing with collaborators at Icahn School of Medicine at Mount Sinai
  - Randomized, parallel-arm, placebo-controlled clinical trial of 60 patients with MDD
  - Subjects will be randomized in 1:1 fashion to XEN1101 (N=30) or matching placebo (N=30)
  - Primary endpoint: Change in activation within the bilateral ventral striatum as measured by fMRI
  - Secondary endpoint: Change in clinical measures of depression severity and anhedonia
- Xenon expects to initiate a company sponsored study of XEN1101 in MDD in the first half of 2022

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 Kv7 modulation 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 efficacious for seizure reduction
- 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-blinded clinical trial ongoing and a second study being planned

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