XENON

ASENT 2021

VIRTUAL NEUROTHERAPEUTICS CONFERENCE

"Anticonvulsant Effects of the Differentiated K_V7 Channel Potentiator XEN1101 in Combination with Commonly Used Anti-Seizure Drugs"

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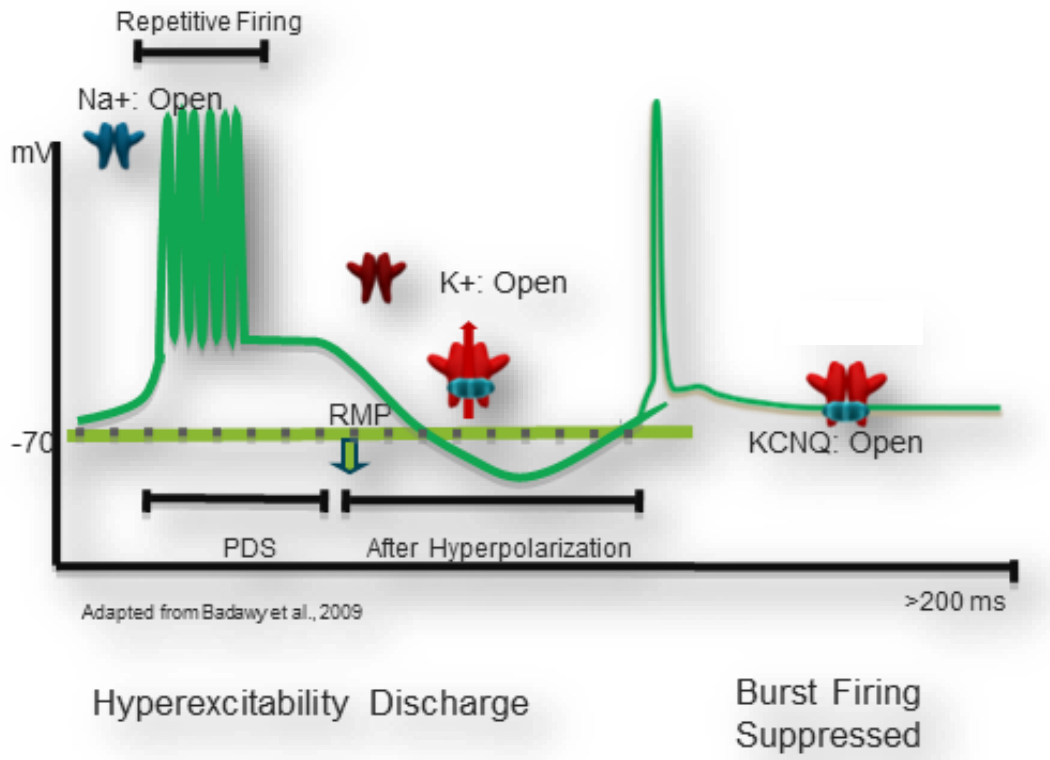
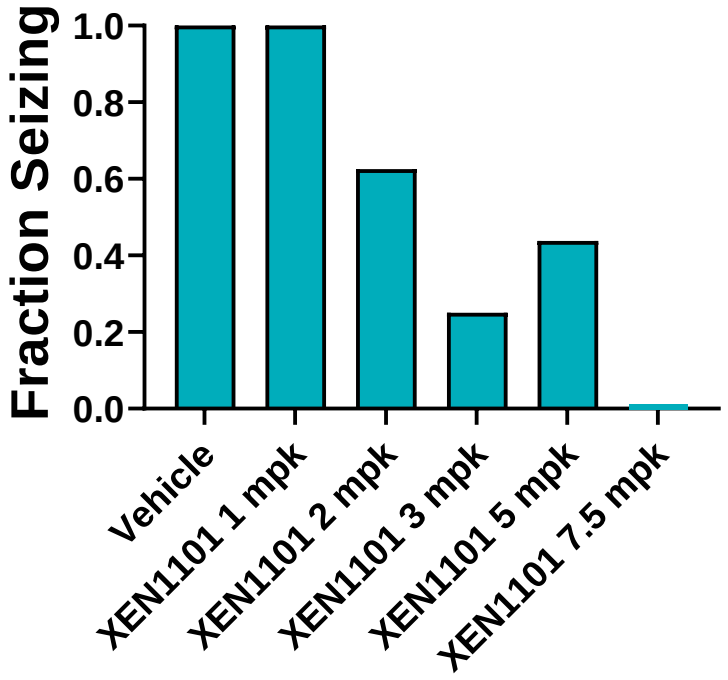
Rationale for Testing XEN1101 in Combination with Other ASMs

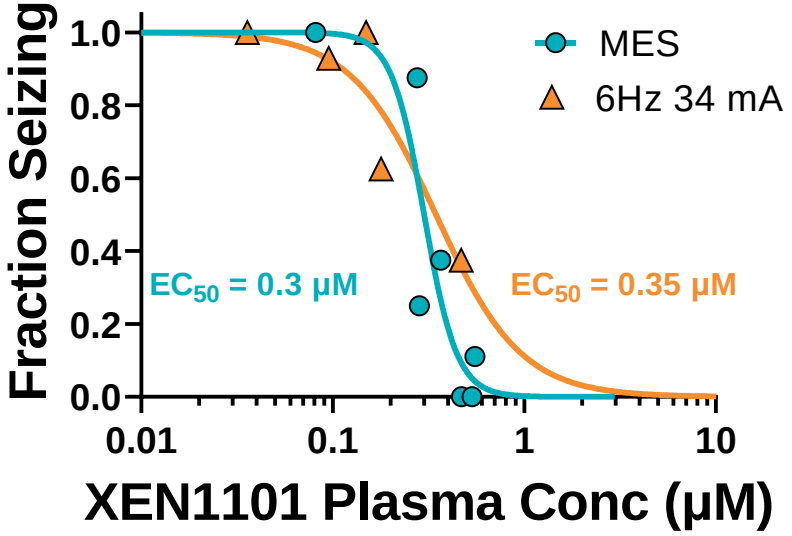
- XEN1101 is a differentiated “next generation” K_V7 potassium channel modulator being developed for the treatment of epilepsy and potentially other neurological disorders
- K_V7 channels are important modulators of neuronal resting membrane potential and XEN1101 potentiation of K_V7 is predicted to provide robust activity in epilepsy
- Rational polypharmacy is common in clinical practice
- XEN1101 mediated inhibition of neural activity was predicted to accentuate the efficacy of anti-seizure medications (ASMs) acting by other mechanisms



XEN1101 is a Potent Inhibitor of Seizures in Rodent Models

- XEN1101 inhibits seizures in rodent seizure models* at low plasma concentrations
- Low plasma levels reduce the likelihood of off-target activity

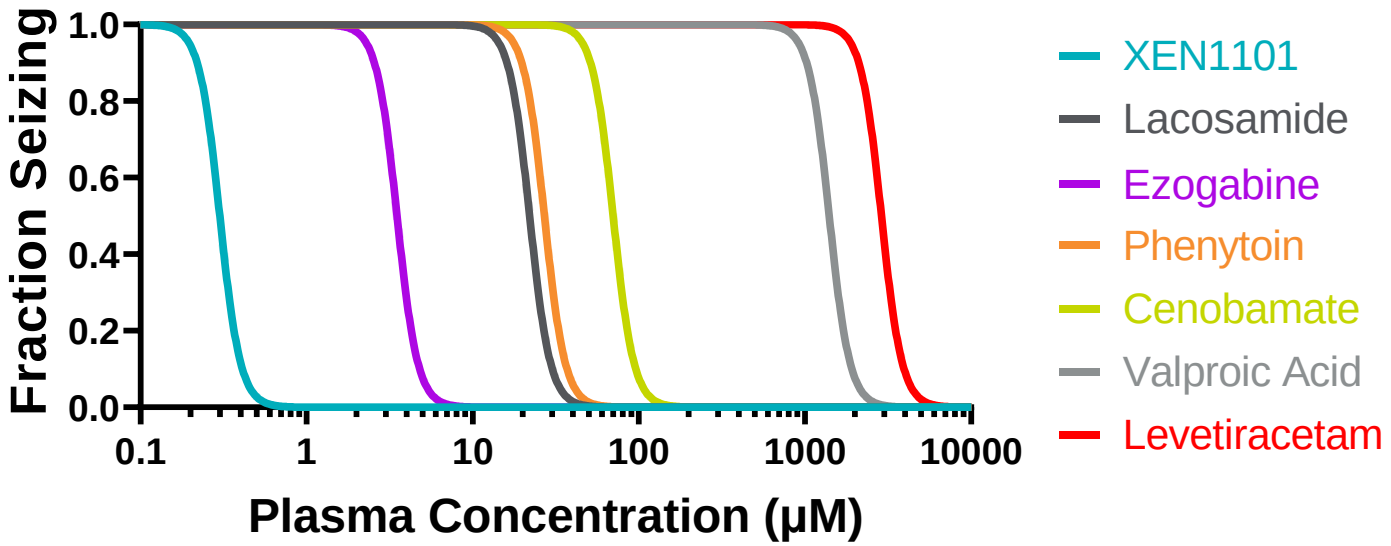




* Mouse Alternating Current Maximal Electroshock (MES) Assay and 6Hz Psychomotor Seizure Assay (34 mA)

Potency Differentiates XEN1101 from Established ASMs

- XEN1101 is more potent* than many current ASMs in preclinical models of epilepsy

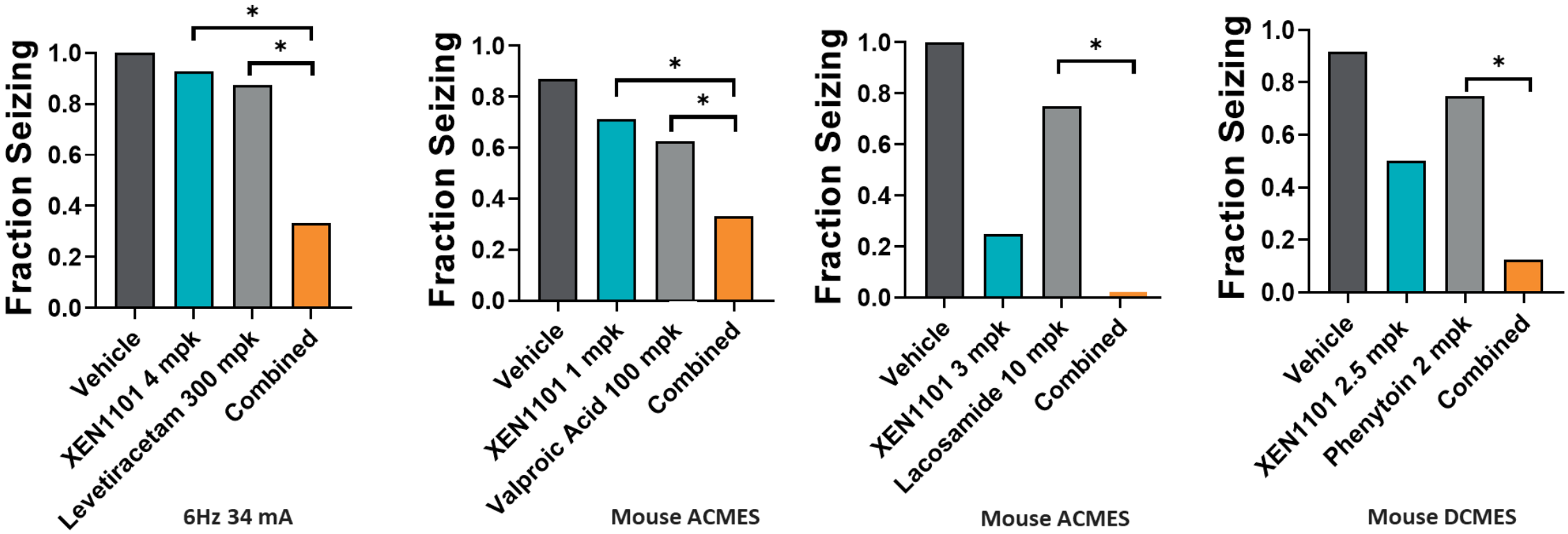


	XEN11101	ezogabine	lacosamide	phenytoin	cenobamate	valproic acid	levetiracetam
EC_{50}	0.3	3.5	22	27	70	1,400	2,900
Fold XEN1101	-	12	73	90	230	4,700	10,000

* Potency measures from Xenon data in mouse MES or 6Hz 34 mA assays

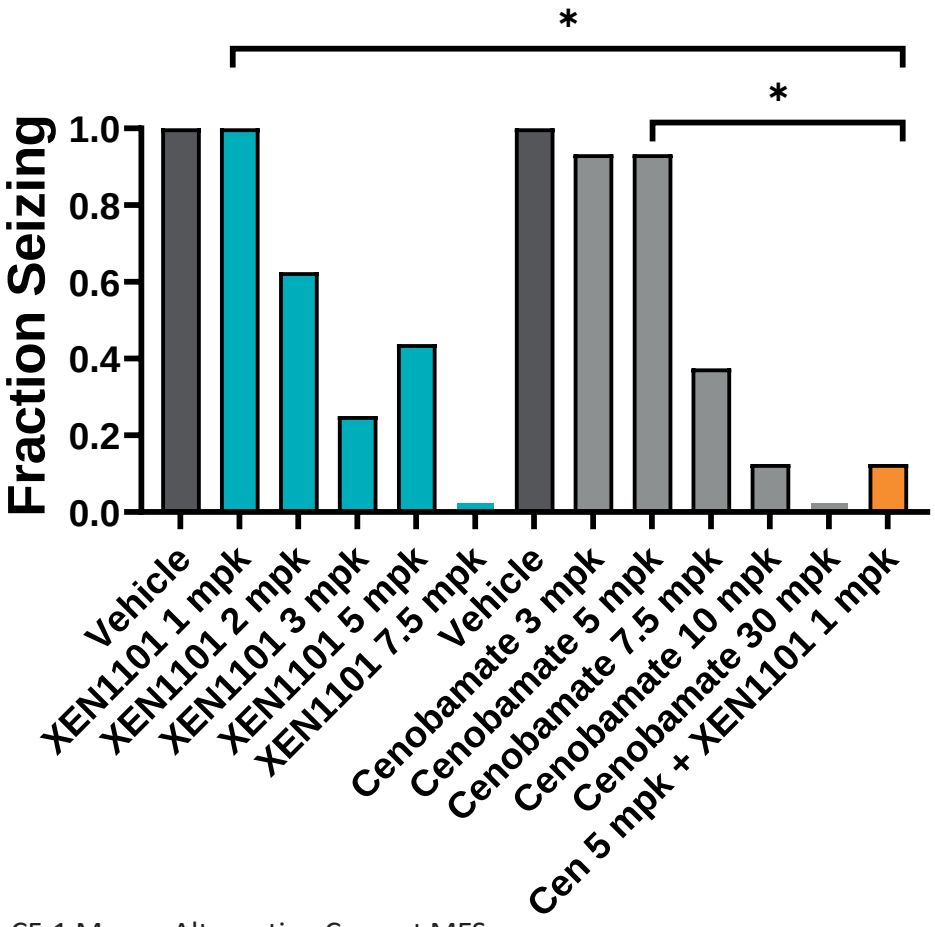
Combining XEN1101 with Common ASMs Provides Robust Seizure Protection

- Combining ineffective or weakly active doses of XEN1101 and common ASMs provides robust seizure protection
- Improved efficacy is not a drug-drug interaction phenomenon
- Enhanced efficacy is not explained by changes in plasma levels
- Combination doses were well tolerated

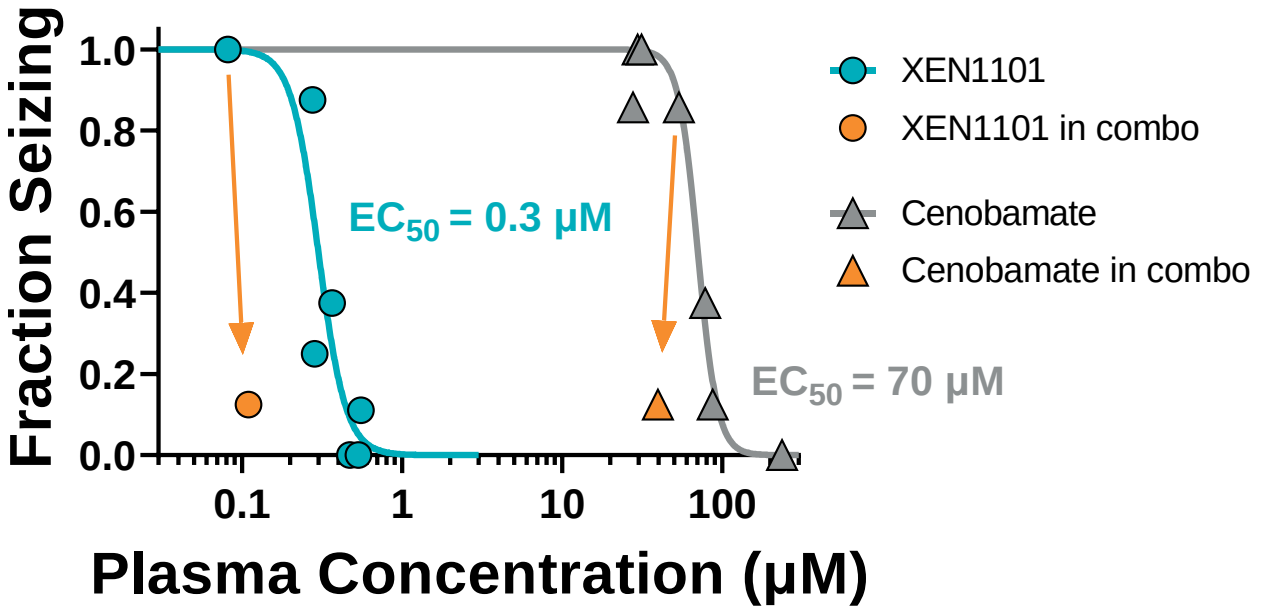


Combining XEN1101 with Cenobamate Provides Robust Seizure Protection

- Combining ineffective or weakly active plasma levels of XEN1101 and cenobamate provides robust seizure protection in the mouse MES assay



CF-1 Mouse Alternating Current MES



- Improved efficacy is not explained by increased plasma concentration of either agent - not a DDI effect
- Combination doses were well tolerated

Conclusions

- XEN1101 is a differentiated, next-generation K_V7 potassium channel modulator
- Combining sub-efficacious doses of XEN1101 and other ASMs provides robust efficacy
- Improved efficacy is not an apparent DDI effect
  - Not explained by increased plasma levels of XEN1101 or other ASMs
- Combination dosing was well tolerated in the dose ranges explored
- This work suggests that XEN1101 can be used as monotherapy or applied in rational polypharmacy to treat seizures
- 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. Alison Cutts,
"Depression and Anhedonia: Acute Preclinical Efficacy for XEN1101, a Differentiated K_V7 Potassium Channel Modulator"

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