



**AES 2023
ANNUAL
MEETING**

PRAX-628: A Next Generation Functionally Selective Small Molecule with Potent Anticonvulsant Activity and Potential as Best-in-Class Treatment for Focal Epilepsy

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Disclosure

- Kris Kahlig is a current employee of Praxis Precision Medicines and is a Praxis stockholder

Learning Objectives

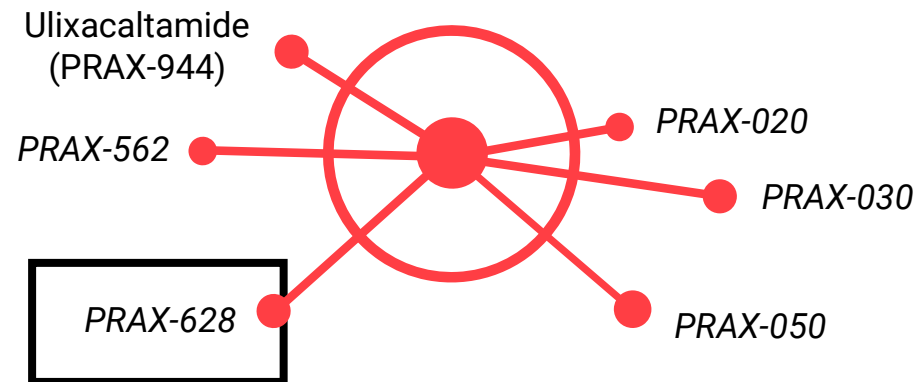
- Understand key differentiating features of PRAX-628 relative to
 - Approved sodium channel blockers (SCBs)
 - Molecules in development for adult Focal Onset Seizure

Developing treatments inspired by the genetics of epilepsy

ENABLED BY TWO PLATFORMS

CEREBRUM™

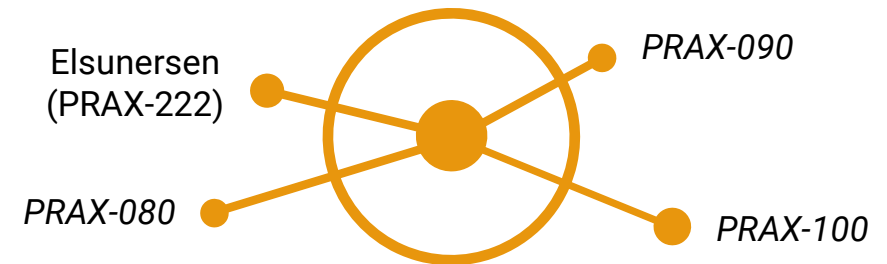
SMALL MOLECULE PLATFORM



Cerebrum™ utilizes deep understanding of neuronal excitability and neuronal networks and applies a series of computational and experimental tools to develop orally available precision therapies

SOLIDUS™

ANTISENSE OLIGONUCLEOTIDE (ASO) PLATFORM



Solidus™ is an efficient, targeted precision medicine discovery and development engine for ASOs anchored on proprietary, computational methodology

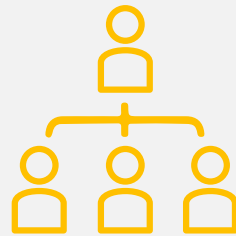
Focal epilepsy affects ~2 million people in the US



Defined as epilepsy that originates in one side or area of the brain and affects one side of the body



Most common type of epilepsy in adults and children - occurs in 60% of epilepsy cases



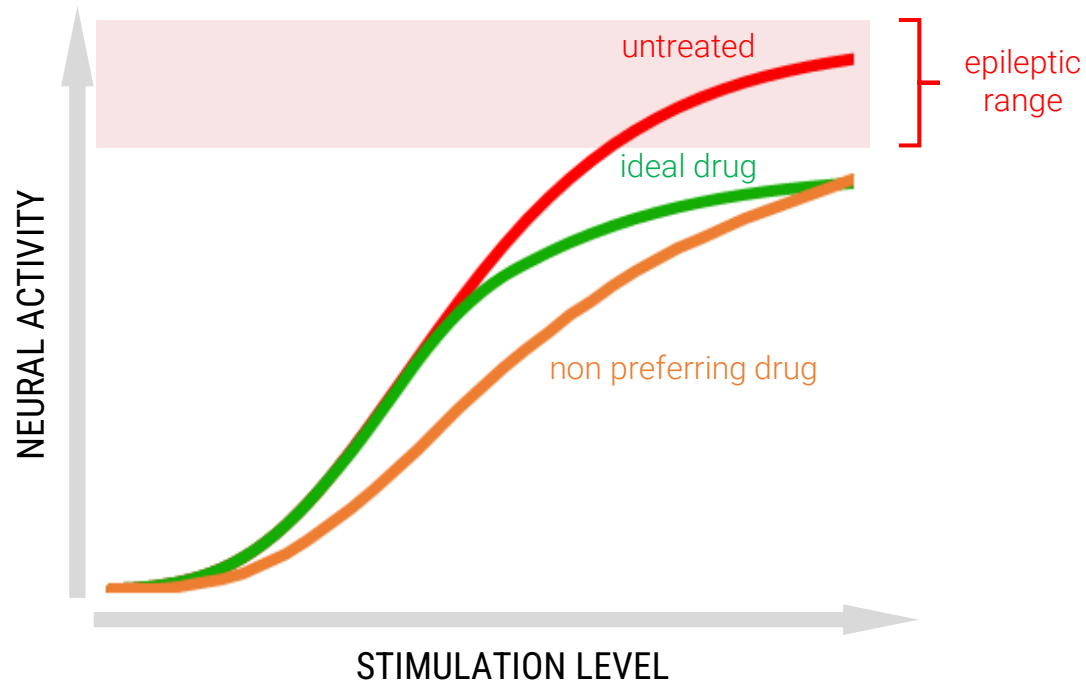
~ 50% have family history but genetics is not well understood



Most common age of onset is in the first year of life and in the 6th and 7th decade

Restoring physiological neural activity by precisely modulating biophysics

Preferential Action Against Hyperexcitability



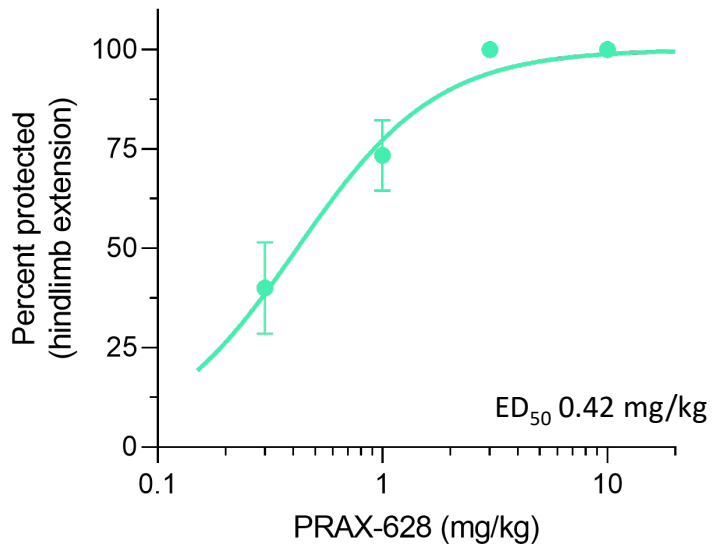
Biophysical “Levers” to Achieve Preferential Action

- A. Reduce pro-excitatory channel function
 - Inhibit persistent current
- B. Dynamic block of channels during high activity
 - Inhibit voltage dependent current
 - Inhibit use dependent current
- C. Maintain channel availability during low activity
 - Reduce potency against steady state peak current

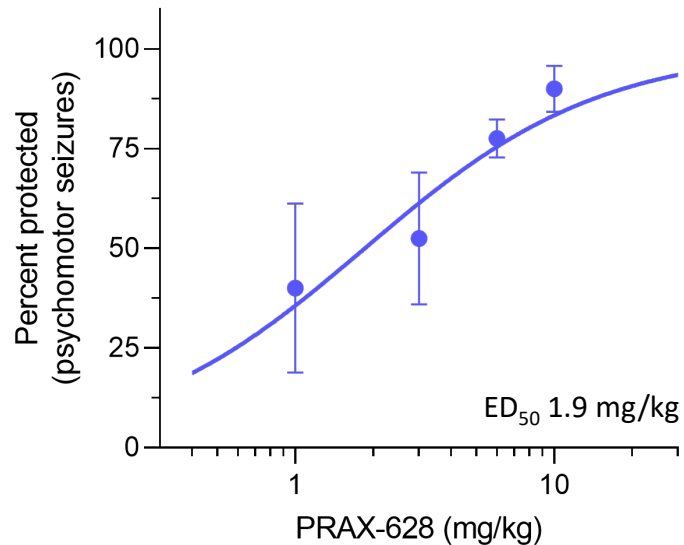
Ideal profile by precision sodium channel modulation

PRAX-628 has potent anticonvulsant activity across multiple acute seizure models

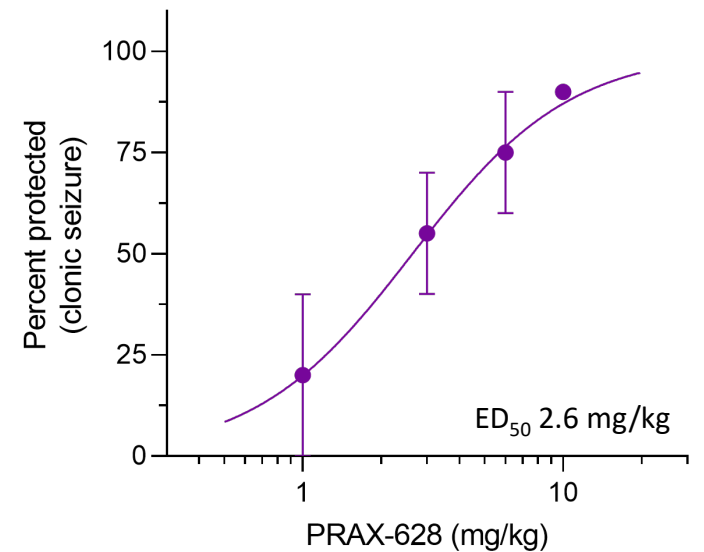
Complete protection from MES-induced tonic hindlimb extension



Significant reduction of 6-Hz induced psychomotor seizures



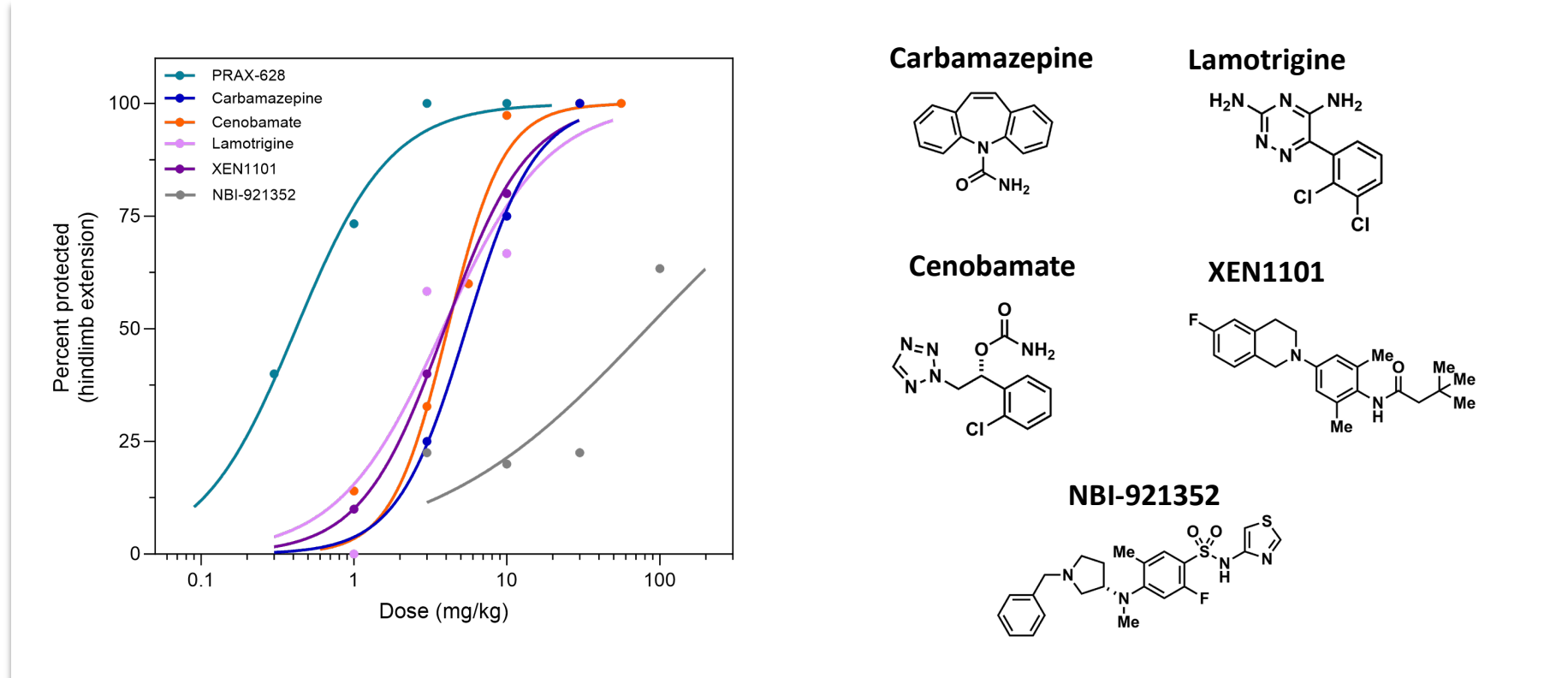
Significant reduction of PTZ-induced clonic seizures



Preclinical profile of PRAX-628 suggests broad, potent anticonvulsant activity

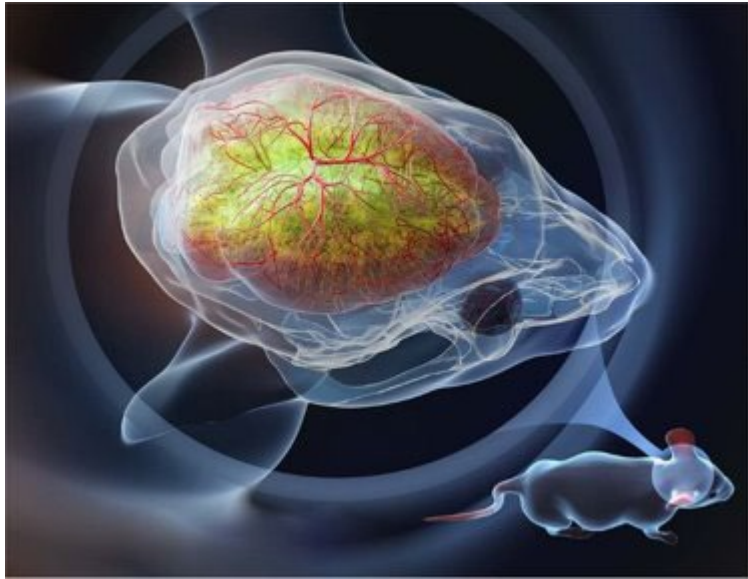
PRAX-628 is more potent than standard ASMs in the MES acute seizure model

The ED₅₀ value for PRAX-628 is approximately 10x lower than standard of care ASMs



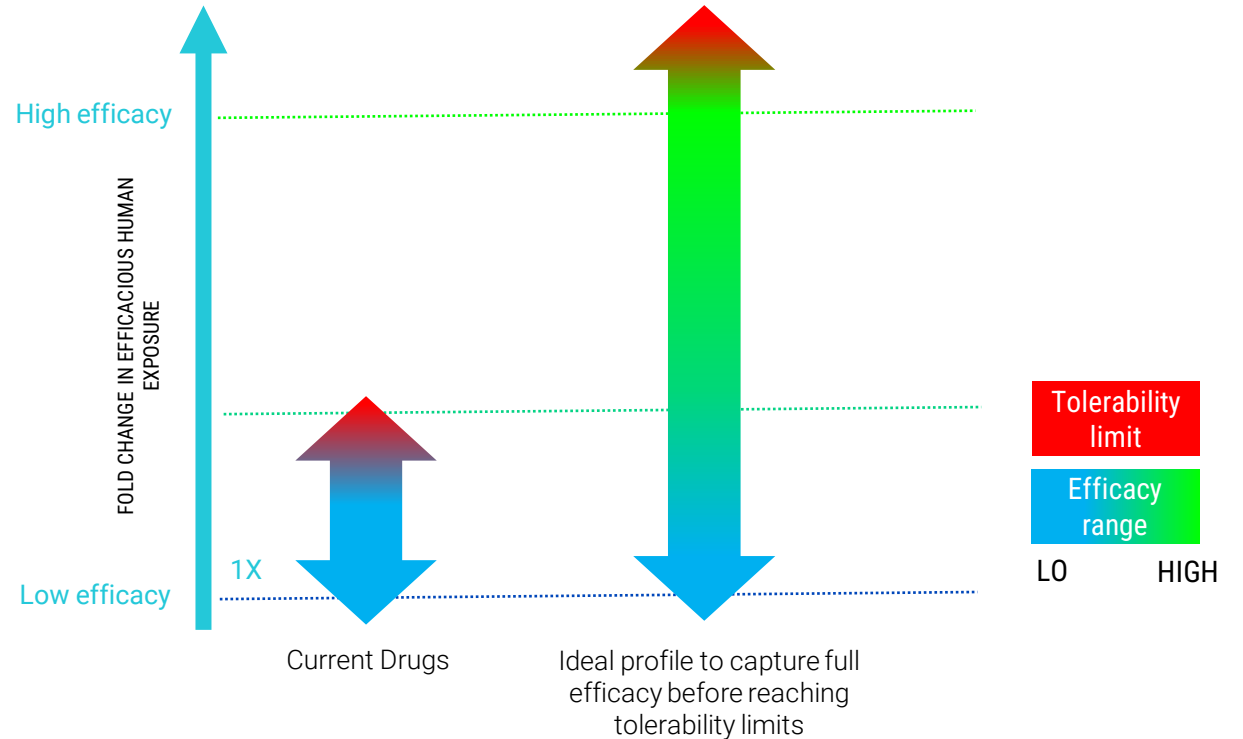
	PRAX-628	Carbamazepine	Cenobamate	Lamotrigine	XEN1101	NBI-921352
ED₅₀ values (mg/kg)	0.42	5.4	4.1	3.8	3.9	82

MES is a rapidly deployable, efficient pre-clinical assay that predicts efficacy and clinical exposure in focal onset seizure



“Maximal electroshock seizure (MES) is an experimental paradigm that induces synchronous neural discharges in the brain through artificial current input (Kamei et al., 1978), and is used to induce acute epileptic behaviors (Fischer & Muller, 1988)”

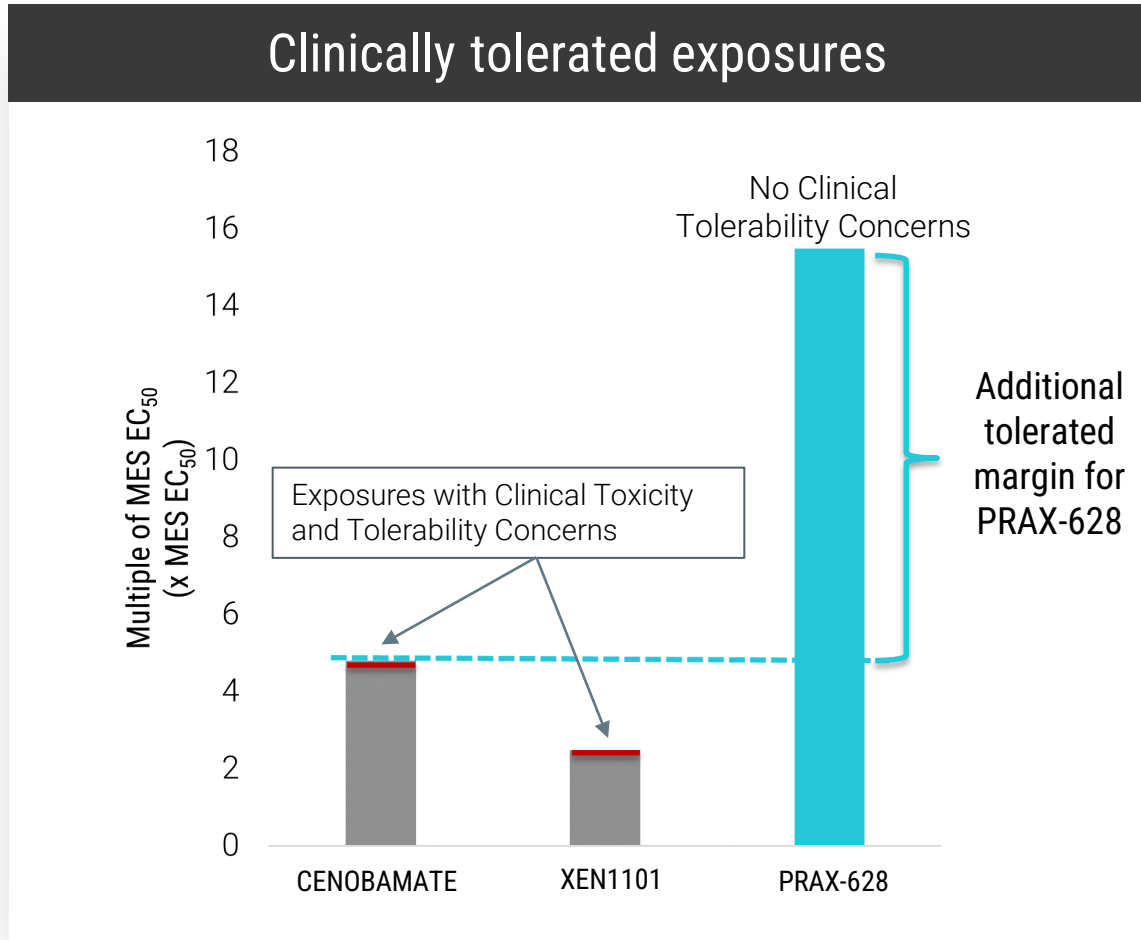
Combining MES and human safety studies for predictive translation



Efficacious exposures in MES models correspond to efficacious exposures in human focal onset seizures

See poster 3.458

PRAX-628 has a significantly larger therapeutic margin based on MES efficacy and human clinical tolerability



	MULTIPLE OF MES EC ₅₀ TOLERATED CLINICALLY
Cenobamate	4.8x
XEN1101	2.5x
PRAX-628	>15.5x*

Cenobamate C_{max}: >46,100 ng/mL, 400 mg C_{max} (Vernillet et al 2020)
 XEN1101 C_{max}: >107 ng/mL (Phase 1 data, Aycardi et al 2018 AES Annual Meeting)
 *No limit due to toxicity was identified for PRAX-628 to date
 x MES EC₅₀ = multiple of predicted human EC₅₀ based on the rodent MES model

Preclinical and Phase 1 data demonstrate potential of PRAX-628 as best-in-class treatment for focal epilepsy

PRAX-628

Focal Epilepsy

Small Molecule

Functionally Selective

Superior selectivity for hyperexcitable state of sodium channels in the brain associated with disease

Unprecedented therapeutic window could translate to superior safety and efficacy

qEEG analysis confirms CNS activity for clinical doses above 5mg

[See poster 3.455](#)

Favorable safety and tolerability profile across broad concentration range in healthy volunteers

The Phase 2 PRAX-628 PPR study will provide insight into efficacy and inform dose selection for pivotal studies

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Questions?



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Additional Praxis Posters at the Scientific Sessions



PRAX-628 is a Next Generation, Functionally Selective Small Molecule with Potent Anti-Seizure Activity and Potential as Best-in-Class Treatment for Focal Epilepsy

[Poster 3.258](#)



A Novel Method to Define an EEG Composite for the Detection of Drug Effects of Next Generation Small Molecules for Epilepsy

[Poster 3.455](#)



Translational Concordance of Preclinical Seizure Models in Focal and Generalized Epilepsies

[Poster 3.458](#)



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