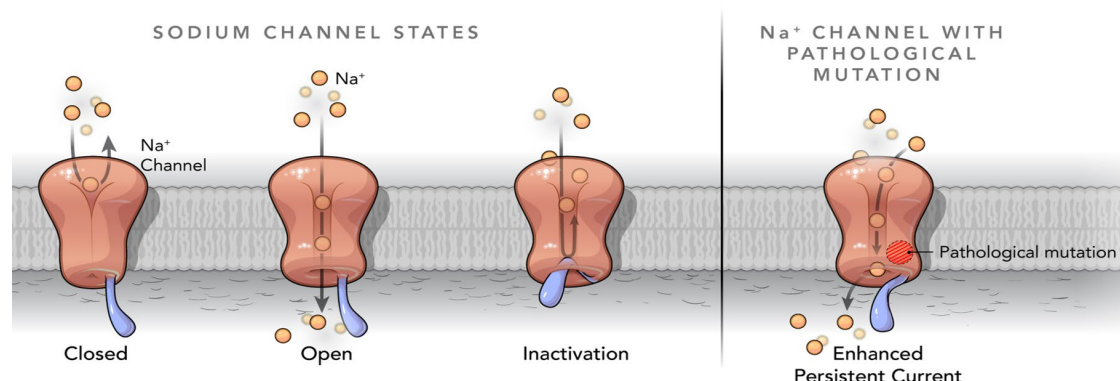


## Background

- Persistent sodium current ( $I_{NaP}$ ) is a subthreshold depolarizing current that contributes to the amplification of synaptic activity and enhancement of repetitive firing in neurons.<sup>1,2</sup>
- Gain of function (GOF) pathogenic mutations in voltage-gated sodium ( $Na_v$ ) channel genes can increase persistent  $I_{NaP}$  leading to neuronal hyperexcitability and severe epilepsies.<sup>3-8</sup>
- PRAX-628 is a next generation functionally selective small molecule targeting the hyperexcitable state of sodium channels in the brain, currently in development as a best-in-class treatment for adult focal epilepsy.<sup>9</sup>
- We have previously shown PRAX-628 potently inhibits persistent  $I_{NaP}$  with greater activity/use dependent block compared to standard of care anti-seizure medications (ASMs), carbamazepine and lamotrigine.



## Objective

➤ To define the *in vivo* efficacy profile of PRAX-628 in mice, relative to standard of care ASMs.

## Methods

### Acute seizure models

- Wildtype male CD-1 mice were used for maximal electroshock seizure (MES), 6-Hz and subcutaneous pentylenetetrazole (scPTZ) acute seizure experiments.
- Mice were administered either vehicle or PRAX-628 by oral gavage 30 min prior to the electrical stimulus or chemoconvulsant.
- Electroshocks (50 Hz, 0.8 s, 10 ms square pulse width, 50 mA or 6 Hz, 3 s, 0.2 ms rectangular pulse width, 32 mA) were delivered for MES and 6-Hz experiments, respectively.
- Mice were observed for the presence or absence of full tonic hindlimb extension (MES), or psychomotor seizures defined as stun/immobility, forelimb clonus, Straub tail and lateral head movement (6-Hz).
- PTZ (85 mg/kg) was administered as a subcutaneous injection and mice were observed for the presence or absence of generalized clonic seizure.
- PRAX-628 concentration in terminal plasma and brain samples was measured using mass spectrometry.
- For ASM comparator experiments, vehicle or test article were administered prior to electrical stimulus.
- Pre-treatment times: carbamazepine (30 min), cenobamate (4 h), lamotrigine (60 min), XEN1101 (60 min).

## In Vitro Pharmacology Profile

Table 1. PRAX-628 demonstrates greater potency and activity dependence for peak  $I_{NaP}$  compared with a panel of standard-of-care  $Na_v$ -targeting ASMs

IC <sub>50</sub> nM (Slope)	Persistent I <sub>NaP</sub>	Peak I <sub>NaP</sub> TB	Ratio to Pers. I <sub>NaP</sub>	Peak I <sub>NaP</sub> UDB-10Hz	Ratio to Pers. I <sub>NaP</sub>	Peak I <sub>NaP</sub> VDB	Ratio to Pers. I <sub>NaP</sub>
PRAX-628	128 (1.4)	8,707 (1.0)	68	200 (0.7) Max 100%	1.6	72 (1.0)	0.56
Cenobamate	71,690 (1.1)	1,719,000 (1.1)	24	749,300 (0.7)	11	66,710 (0.9)	0.9
Phenytoin	59,820 (0.8)	n/a**	--	876,600 (1.0)	15	47,780 (1.0)	0.8
Carbamazepine	77,490 (1.1)	2,307,000 (1.0)	30	1,418,000 (0.9)	18	44,370 (0.9)	0.6
Oxcarbazepine	123,700 (1.0)	1,035,000 (1.7)	8	n.d.	--	42,000 (1.1)	0.3
Lamotrigine	78,480 (1.0)	1,249,000 (0.8)	16	515,800 (1.0)	6.6	39,090 (0.9)	0.5
Lacosamide	832,700 (0.9)	n/a**	--	682,200 (1.3)	0.8	269,300 (1.2)	0.3
Valproic acid	2% @ 1 mM	11% @ 1 mM	--	8% @ 1 mM	--	18% @ 1 mM	--

Data are IC<sub>50</sub> (nM) with the hill slope in parenthesis. \*\*could not be determined due to compound solubility limit  
n.d.=not determined; Pers.=persistent; TB=tonic block; UDB=use-dependent block; VDB=voltage-dependent block

## PRAX-628 has Potent Anticonvulsant Activity Across Multiple Acute Seizure Models

- PRAX-628 (3 and 10 mg/kg) completely protected wildtype mice from tonic hindlimb extension induced by MES.
- PRAX-628 significantly reduced incidence of psychomotor seizures induced by 6-Hz.
- PRAX-628 significantly reduced incidence of clonic seizures induced by PTZ.

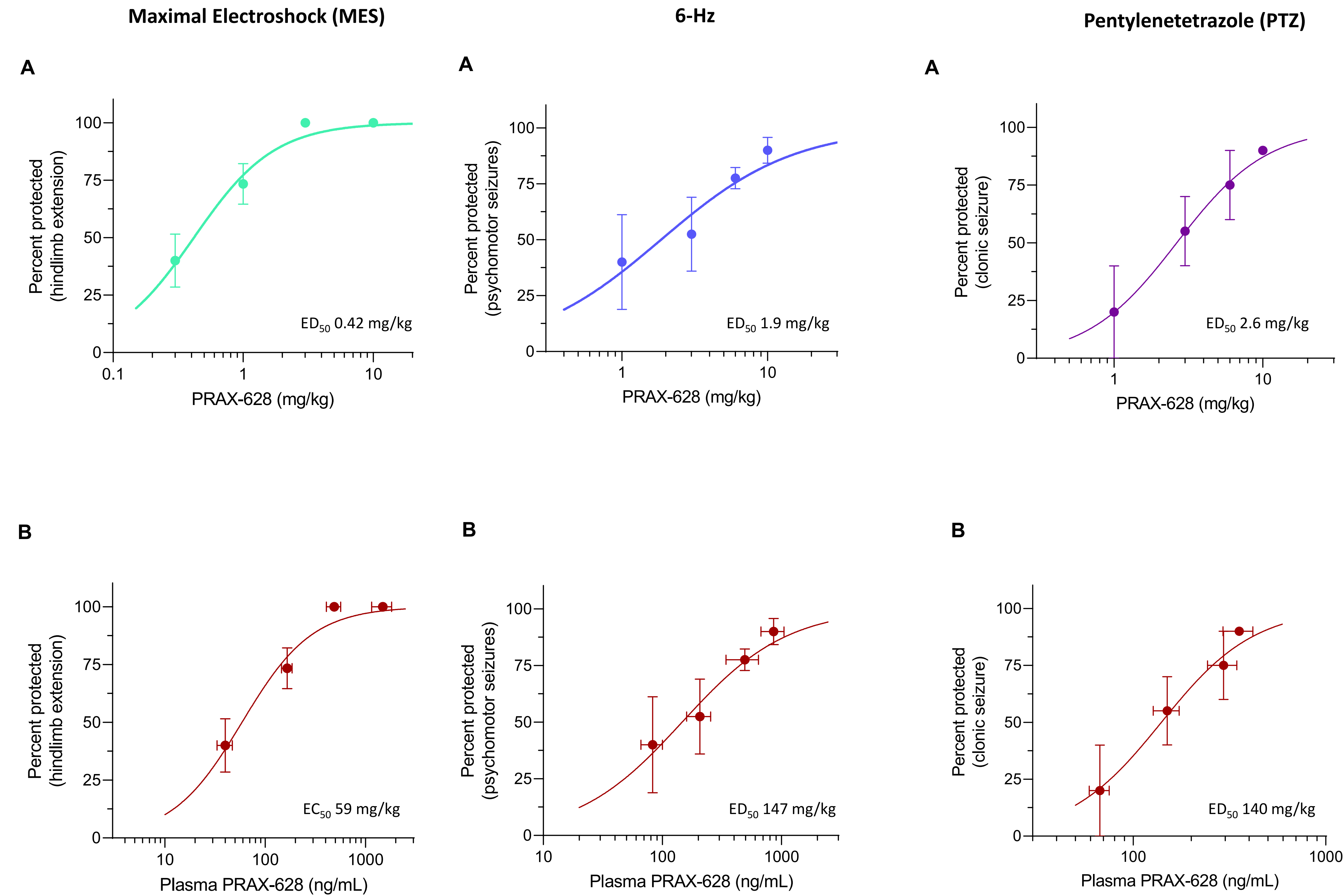


Figure 1. PRAX-628 is anticonvulsant against MES-induced seizures. A) Dose-response and B) concentration-response curves for protection from MES-induced tonic hindlimb extension. PRAX-628 (0.3-10 mg/kg) was administered as by oral gavage 30 min prior to electrical stimulation. Complete protection was achieved following treatment with 3 and 10 mg/kg PRAX-628. Data are presented as mean  $\pm$  SEM for three cohorts, with n = 10 per treatment each cohort. Curve represents fit to a four-parameter log function with ED<sub>50</sub> and EC<sub>50</sub> values of 0.42 mg/kg and 59 ng/mL, respectively.

Figure 2. PRAX-628 is anticonvulsant in the 6-Hz acute seizure model. A) Dose-response and B) concentration-response curves for protection from psychomotor seizures induced by 6-Hz. PRAX-628 (1-10 mg/kg) was administered by oral gavage 30 min prior to electrical stimulation. PRAX-628 (3-6 mg/kg) significantly reduced seizure incidence. Data are presented as mean  $\pm$  SEM for three to four cohorts, with n = 10 per treatment each cohort. Curve represents fit to a four-parameter log function with ED<sub>50</sub> and EC<sub>50</sub> values of 1.9 mg/kg and 147 ng/mL, respectively.

Figure 3. PRAX-628 is anticonvulsant in the scPTZ acute seizure model. A) Dose-response and B) concentration-response curves for protection from clonic seizures induced by PTZ (85 mg/kg, s.c.). PRAX-628 (1-10 mg/kg) was administered by oral gavage 30 min prior to PTZ administration. PRAX-628 (3-10 mg/kg) significantly reduced seizure incidence. Data are presented as mean  $\pm$  SEM for two cohorts, with n = 10 per treatment each cohort. Curve represents fit to a four-parameter log function with ED<sub>50</sub> and EC<sub>50</sub> values of 2.6 mg/kg and 140 ng/mL, respectively.

## PRAX-628 is Active at Lower Doses Compared to Standard ASMs in MES Acute Seizure Model

- The ED<sub>50</sub> value for PRAX-628 (0.42 mg/kg) is approximately ten times lower than that of carbamazepine, cenobamate, lamotrigine and XEN1101 (range 3.8-5.4 mg/kg).

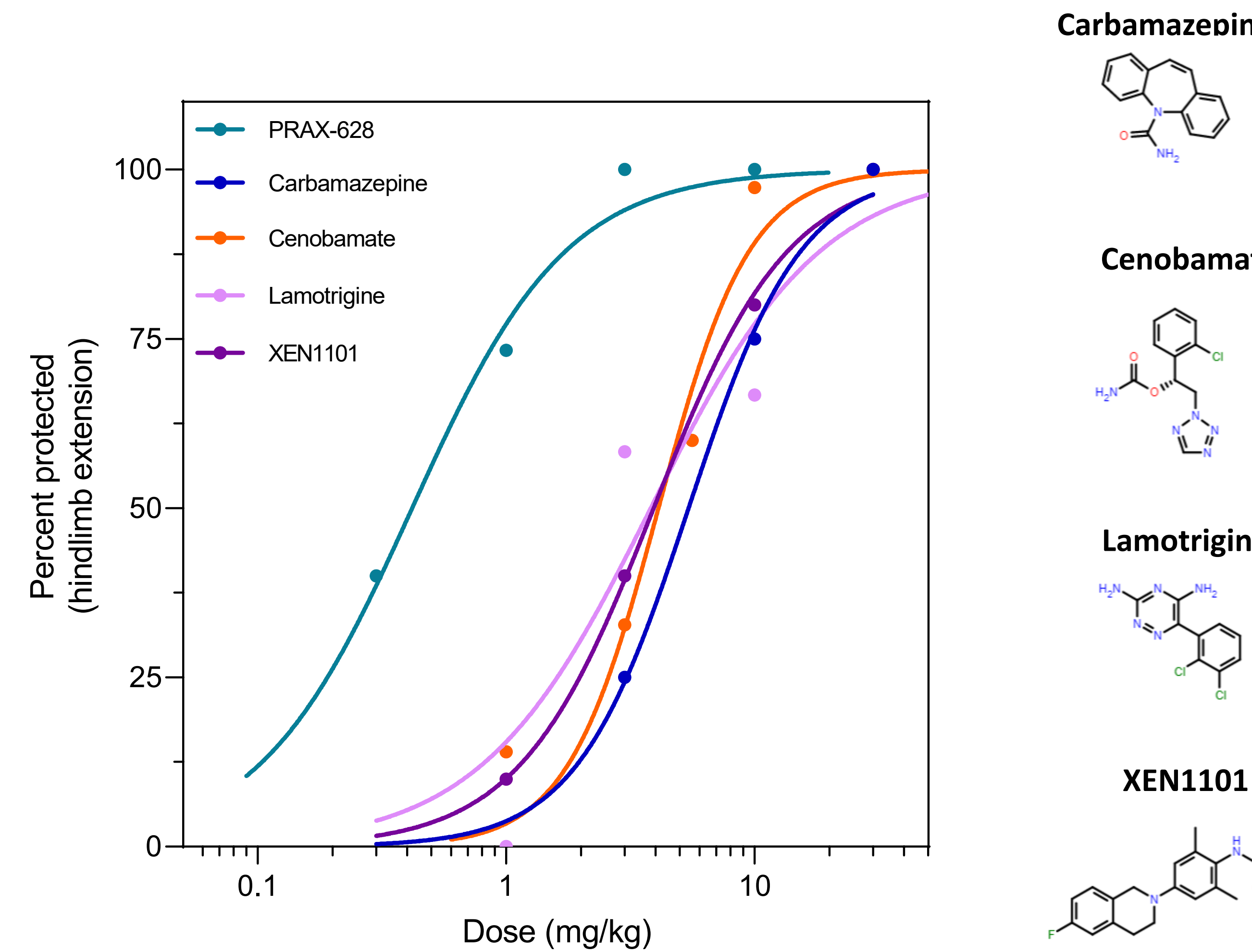


Table 2. Summary of MES ED<sub>50</sub> values

	PRAX-628	Carbamazepine	Cenobamate	Lamotrigine	XEN1101
ED <sub>50</sub> values (mg/kg)	0.42	5.4	4.1	3.8	3.9

Figure 4. PRAX-628 is anticonvulsant at lower doses than standard ASMs in the MES acute seizure model. Dose-response curves for protection from MES-induced tonic hindlimb extension for PRAX-628, carbamazepine, cenobamate, lamotrigine and XEN1101. Curves represent fits to a four-parameter log function and ED<sub>50</sub> values are presented in Table 2. Error bars removed for clarity.

## Conclusions

- PRAX-628 exhibited potent anticonvulsant activity in multiple acute seizure models
- PRAX-628 exhibited anticonvulsant activity at lower doses compared to standard of care ASMs in the MES acute seizure model
- Notably, first-in-human findings (poster P292) demonstrate PRAX-628 is well-tolerated at concentrations >15x the mouse MES EC<sub>50</sub>, with dose levels resulting in markedly higher multiples of MES EC<sub>50</sub> than cenobamate and XEN1101 shown to be well tolerated.

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**Ethical Statement** All *in vivo* studies were performed in accordance with local and institutional animal care and use guidelines.

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