PRAX-628: A Next Generation Functionally Selective Small Molecule with Potent Anticonvulsant Activity

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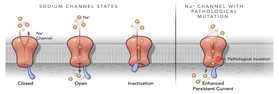
Background

- Persistent sodium current (I_{Na}) is a subthreshold depolarizing current that contributes to the amplification of synaptic activity and enhancement of repetitive firing in neurons.[1,2]
- Gain of function (GOF) pathogenic mutations in voltage-gated sodium (Na_V) channel genes can increase persistent I_{Na}, leading to neuronal hyperexcitability and severe epilepsies.[3-8]
- 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. [9]
- We have previously shown PRAX-628 potently inhibits persistent I_{Na} 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 dependance for peak I_{Na} compared with a panel of standard-of-care Na_V-targeting ASMs

IC_{50}, nM (Slope)	Persistent I_{Na}	Peak I_{Na} TB	Ratio to Pers. I_{Na}	Peak I_{Na} UDB-10Hz	Ratio to Pers. I_{Na}	Peak I_{Na} VDB	Ratio to Pers. I_{Na}
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** (0.6)	**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_{50} (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.

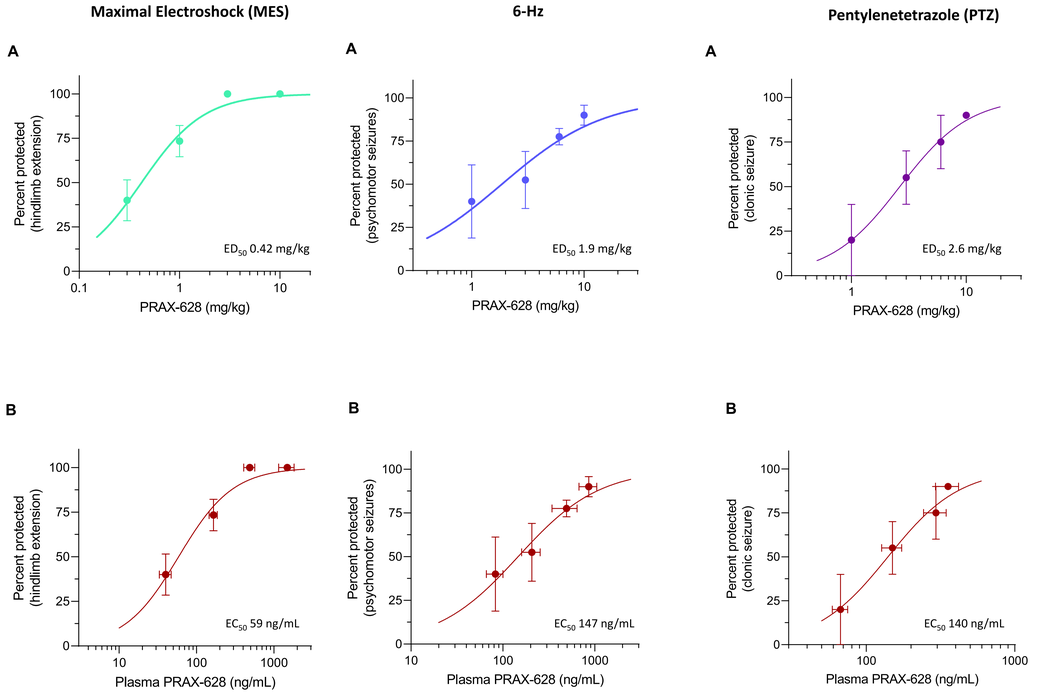


Figure 1. PRAX-628 is anticonvulsant against MES-induced seizures. **A)** Dose-response and **B)** concentration-response curves for protection from MES-induced tonic hindlimb extension. PRAX-628 (0.3-10 mg/kg) was administered as by oral gavage 30 min prior to electrical stimulation. Complete protection was achieved following treatment with 3 and 10 mg/kg PRAX-628. Data are presented as mean ± SEM for three cohorts, with n = 10 per treatment each cohort. Curve represents fit to a four-parameter log function with ED_{50} and EC_{50} 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 ± SEM for three to four cohorts, with n = 10 per treatment each cohort. Curve represents fit to a four-parameter log function with ED_{50} and EC_{50} 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 ± SEM for two cohorts, with n = 10 per treatment each cohort. Curve represents fit to a four-parameter log function with ED_{50} and EC_{50} 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_{50} 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).

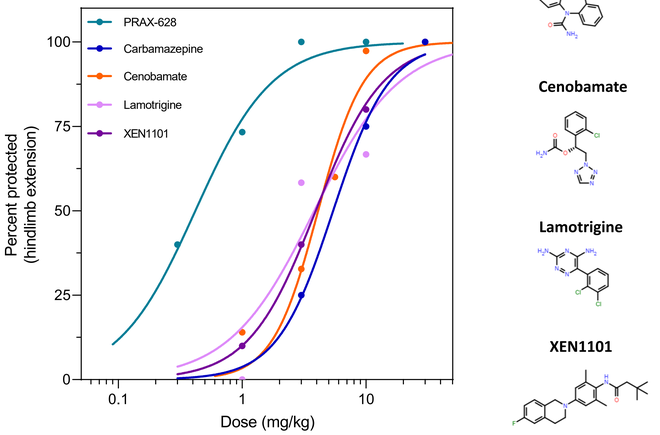


Table 2. Summary of MES ED_{50} values

	PRAX-628	Carbamazepine	Cenobamate	Lamotrigine	XEN1101
ED_{50} 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_{50} 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_{50}; with dose levels resulting in markedly higher multiples of MES EC_{50} than cenobamate and XEN1101 shown to be well tolerated.**

References

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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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