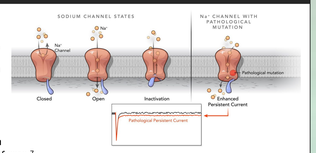
PRAX-562 is a Well-Tolerated, Next Generation Anti-Seizure Small Molecule with Broad Anticonvulsant Activity in Multiple DEE Mouse Models

Nikola Jancovski[2], Lyndsey Anderson[1], William A. Eckert, III[1], Erin Baker[3], Pravin K. Wagley[4], Snezana Maljevic[2], Chris Reid[2], Manoj K. Patel[4], Jennifer A. Kearney[3], Kristopher M. Kahlig[1], Steven Petrou[1]

[1]Praxis Precision Medicines, Boston, MA 02110 USA; [2]The Florey Institute of Neuroscience and Mental Health, Melbourne, VIC 3052, AUS; [3]Dept. Pharmacology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [4]Dept. Anesthesiology, University of Virginia Health System, Charlottesville, VA, 22908

Background

- Persistent sodium current (I_{Na}), a subthreshold depolarizing current, contributes to the amplification of synaptic activity and enhancement of repetitive firing.[1,2]
- Some voltage-gated sodium channel (Na_V) gain-of-function (GOF) variants cause pathological increases in persistent I_{Na} that contribute to the neuronal hyperexcitability observed in severe developmental and epileptic encephalopathies (DEE).[2-6]
- We previously showed PRAX-562 inhibits persistent I_{Na} with improved preference over peak I_{Na} compared to standard of care.[7]
- This profile was efficacious in DEE mouse models with GOF mutations in *Scn8a* ($Na_V1.6$) and *Scn2a* ($Na_V1.2$).[8]



Objective

➢ *To further profile the anticonvulsant efficacy of PRAX-562 and determine whether efficacy extends to non-Na_V DEE models: $Kcnq2^{K556E/+}$, $Kcnc1^{R320H/+}$ and $Hcn1^{M305L/+}$*

Methods

- *Acute seizure models.* Wild-type (WT) male CD-1 mice were used for maximal electroshock seizure (MES) and 6-Hz acute seizure experiments. Mice were administered either vehicle or PRAX-562 by oral gavage 30 min prior to electrical stimulus. Transauricular (50 Hz, 0.8 s, 10 ms square pulse width, 50 mA) and corneal electroshocks (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).
- *Na_V DEE models.* Anticonvulsant activity of PRAX-562 was evaluated by comparing the number of spontaneous seizures during a 30 min pre-treatment period with the number occurring during a 30 min post-treatment period in $Scn2a^{Q54}$ mice. $Scn8a^{N1768D/+}$ mice were treated with vehicle or PRAX-562 by oral gavage 60 min prior to acoustic stimulus (15 kHz). Mice were observed for the presence or absence of seizure.
- *Non-Na_V DEE models.* Mice ($Kcnq2^{K556E/+}$, $Kcnc1^{R320H/+}$, $Hcn1^{M305L/+}$) were pre-treated with vehicle or PRAX-562 by oral gavage 60 min prior to administration of PTZ (100 mg/kg, s.c.). Mice were observed until the onset of first tonic-clonic seizure with hindlimb extension or a time of 40 min was reached.

In Vitro Pharmacology Profile

Table 1. PRAX-562 demonstrates greater potency and preference for $hNa_V1.6$ persistent I_{Na} compared with a panel of standard Na_V-targeting ASMs

	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-562	**141** (1.2)	**8,472** (1.0)	60	**271** (1.3) **max 75%**	2	**317** (1.0)	2.2
Carbamazepine	**77,490** (1.1)	**2,307,000** (1.0)	**30**	**1,418,000** (0.9)	**18**	**44,370** (0.9)	**0.6**
Lamotrigine	**78,480** (1.0)	**1,249,000** (0.8)	**16**	**515,800** (1.0)	**6.6**	**39,090** (0.9)	**0.5**

Data are IC_{50} (nM) with the hill slope in parenthesis.
ASM=antiseizure medications; Pers.=persistent; TB=tonic block; UDB=use-dependent block; VDB=voltage-dependent block

PRAX-562 Demonstrates Potent Preclinical Anticonvulsant Activity as a Result of Potent Inhibition Of Persistent and Use-dependent Sodium Current

PRAX-562 demonstrates functional selectivity[7]

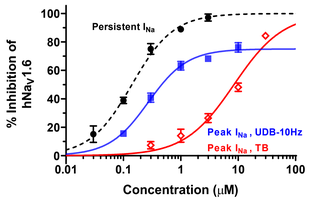


Figure 1. HEK-293 whole-cell patch clamp recordings with PRAX-562

PRAX-562 demonstrates increased potency[7]

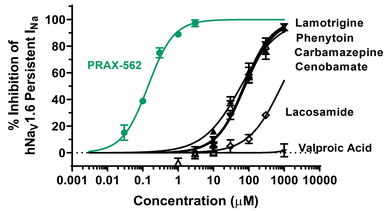


Figure 2. HEK-293 whole-cell patch clamp recordings with PRAX-562 and standards of care

PRAX-562 is anticonvulsant in MES model[7]

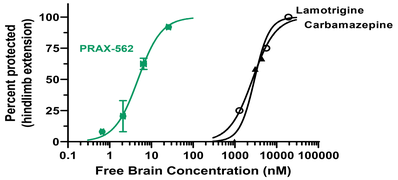


Figure 3. Efficacy of PRAX-562 in acute MES seizure model compared to standards of care

Preclinical profile of PRAX-562 suggests broad anticonvulsant activity

PRAX-562 has Potent Anticonvulsant Activity in *Scn2a* and *Scn8a* DEE Mouse Models

- Complete protection from spontaneous seizures in $Scn2a^{Q54}$ mice with PRAX-562 (10 mg/kg)
- PRAX-562 (10 mg/kg) also protects $Scn8a^{N1768D/+}$ mice from audiogenic-induced seizures.

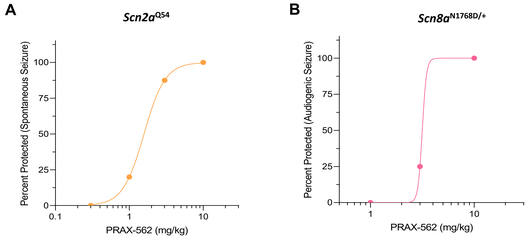


Figure 3. PRAX-562 is anticonvulsant in DEE mouse models with Na_V channel mutations. **A)** Dose-response curve for protection from spontaneous seizures in $Scn2a^{Q54}$ mice. Curve represents fit to a four-parameter log function and ED_{50} and EC_{50} values are presented in ***Table 2*** below. **B)** Dose-response curve for protection from audiogenic-induced seizures in $Scn8a^{N1768D/+}$ mice, with n = 8 per treatment. Curve represents fit to a four-parameter log function and ED_{50} and EC_{50} values are presented in ***Table 2*** below.

Table 2. PRAX-562 summary of ED_{50} and EC_{50} values

	Efficacy (MES)		*Scn2a*-Q54		*Scn8a*-N1768D	
	ED_{50} (mg/kg)	Plasma EC_{50} (ng/mL)	ED_{50} (mg/kg)	Plasma EC_{50} (ng/mL)	ED_{50} (mg/kg)	Plasma EC_{50} (ng/mL)
PRAX-562	2.2	102	1.6	34	3.3	101

PRAX-562 Has Been Generally Well-tolerated in Phase 1 Studies, with Phase 2 Study Underway

PRAX-562 has been generally well tolerated in over 130 healthy volunteers

See posters [P408 & P409]

All TEAEs mild to moderate as stand-alone therapy*, with headache & dizziness most common TEAEs

See posters [P408 & P409]

Significant changes observed between placebo and 90 mg of PRAX-562 on qEEG and on ASSR biomarkers

See poster [P409]

EMBOLD

Phase 2 EMBOLD study topline data expected 2H23

* Co-administration of proposed supra-therapeutic doses of PRAX-562 (120 mg) and oxcarbazepine led to additive sodium blocking effects, including resulting in SAEs

PRAX-562 Anticonvulsant Activity Extends to Some Non-Na_V DEE Mouse Models

- PRAX-562 (10 mg/kg) is anticonvulsant against PTZ-induced seizure in $Kcnq2^{K556E/+}$ and $Kcnc1^{R320H/+}$ mice.

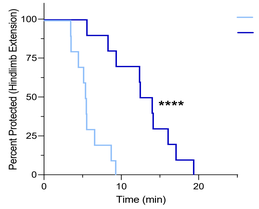


Figure 4. PRAX-562 increases latency to PTZ-induced seizures in $Kcnq2^{K556E/+}$ mice. Curves of tonic hindlimb extension incidence induced by PTZ in $Kcnq2^{K556E/+}$ ($Kcnq2^{KE/+}$) mice treated with vehicle or 10 mg/kg PRAX-562 administered orally 60 min before PTZ. The latency to tonic hindlimb extension in $Kcnq2^{KE/+}$ mice is significantly increased following treatment with PRAX-562, with n = 8-10 per group (****p < 0.0001, logrank Mantel-Cox).

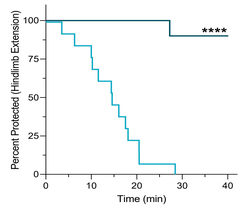


Figure 5. PRAX-562 increases latency to PTZ-induced seizures in $Kcnc1^{R320H/+}$ mice. Curves of tonic hindlimb extension incidence induced by PTZ in $Kcnc1^{R320H/+}$ ($Kcnc1^{RH/+}$) mice treated with vehicle or 10 mg/kg PRAX-562 administered orally 60 min before PTZ. The latency to tonic hindlimb extension significantly increases following treatment with PRAX-562, with n = 8-13 per group, (****p < 0.0001, logrank Mantel-Cox).

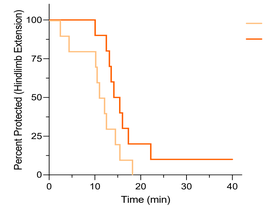


Figure 6. PRAX-562 has no effect on latency to PTZ-induced seizures in $Hcn1^{M305L/+}$ mice. Curves of tonic hindlimb extension incidence induced by PTZ in $Hcn1^{M305L/+}$ ($Hcn1^{ML/+}$) mice. Mice were treated with vehicle or 10 mg/kg PRAX-562 orally 60 min before PTZ. A non-significant trend toward increased latency to tonic hindlimb extension was observed.

Conclusions

- **PRAX-562 exhibits robust anticonvulsant activity across mechanistically divergent genetic models of pediatric DEEs.**
- **PRAX-562 is more potent than existing treatments in MES acute seizure model.**
- **The profile of PRAX-562 suggests a wide therapeutic window with potential for superior safety and efficacy.**

References

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Acknowledgments We thank the staff at ChemPartner for conducting MES studies and InterVivo Solutions for conducting 6-Hz studies. We also thank the animal care staff for husbandry of the animals involved in these studies.

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

Funding All studies were funded by Praxis Precision Medicines. Medical writing and editorial assistance were provided by Lillian G. Matthews in accordance with Good Publication Practice (GPP3).

Disclosures LA, BE, KK and SP are current or former employees/consultants of Praxis Precision Medicines and may be Praxis stockholders.

@PraxisMedicines
Praxismedicines.com
spetrou@praxismedicines.com

Presented at:
International Epilepsy Congress
2 - 6 September 2023
Dublin, Ireland