# 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

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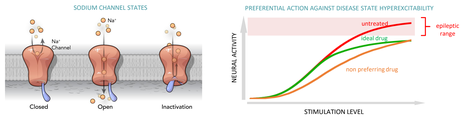
## Background

- Approximately 3 million people in the US have epilepsy; nearly 2 million of whom have focal epilepsy.[1,2]
- Focal epilepsy is characterized by localized neuronal hyperexcitability. Current standard-of-care is limited by tolerability issues and a need to titrate up to an effective dose to minimize side effects.[3] This profile may reflect the inability to selectively target disease related hyperexcitability over normal neuronal activity.
- PRAX-628 is a next generation, functionally selective small molecule targeting the hyperexcitable states of sodium channels in the brain that is currently in development as a best-in-class treatment for adult focal epilepsy.[4]
- We have previously shown that PRAX-628 potently inhibits persistent sodium current ($I_{NaP}$) and has greater activity/use dependent block of peak $I_{Na}$ compared to standard-of-care anti-seizure medications (ASMs), carbamazepine and lamotrigine.

➢ *Here we define the in vivo efficacy profile of PRAX-628 in mice, compared to standard-of-care ASMs. We relate preclinical findings based on the mouse maximal electroshock seizure (MES) model to first-in-human safety and tolerability studies.*




## Methods

*Acute Seizure Models*

- Wildtype male CD-1 mice were used for MES, 6-Hz and subcutaneous pentylenetetrazole (scPTZ) acute seizure experiments.
- MES – Electrical stimulation was 50 Hz, 0.8 s, 10 ms square pulse width, 50 mA. Mice were observed for the presence or absence of full tonic hindlimb extension.
- 6-Hz – Electrical stimulation was 6 Hz, 3 s, 0.2 ms rectangular pulse width, 32 mA. Mice were monitored for psychomotor seizures defined as stun/immobility, forelimb clonus, Straub tail and lateral head movement.
- scPTZ (85 mg/kg) was administered as a subcutaneous injection and mice were observed for the presence or absence of generalized clonic seizure.
- Mice were administered either vehicle or PRAX-628 by oral gavage 30 min prior to the electrical stimulus or chemoconvulsant. 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: carbamazepine (30 min), cenobamate (4 h), lamotrigine (60 min), XEN1101 (60 min), NBI-921352 (60 min).
- MES findings were related to safety and tolerability findings from PRAX-628-101, a randomized, double-blinded, placebo-controlled Phase 1 trial investigating single and multiple ascending doses in healthy adults.

## 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.

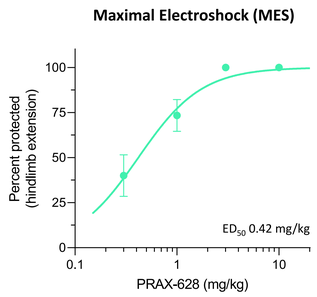



*Figure 1. PRAX-628 is anticonvulsant against MES-induced seizures.* Dose-response curves for protection from MES-induced tonic hindlimb extension. PRAX-628 (0.3-10 mg/kg) was administered by oral gavage 30 min prior to electrical stimulation. Complete protection was achieved following treatment with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

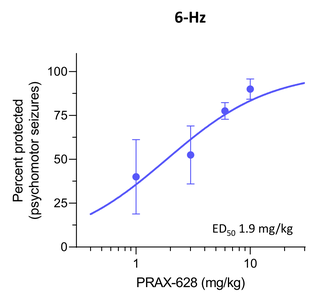



*Figure 2. PRAX-628 is anticonvulsant in the 6-Hz acute seizure model.* Dose-response curves for protection from psychomotor seizures induced by 6-Hz. PRAX-628 (1-10 mg/kg) was administered by oral gavage 30 min prior to electrical stimulation. PRAX-628 (3-6 mg/kg) significantly reduced seizure incidence. Data are presented as mean ± SEM for three to four cohorts, with n = 10 per treatment for each cohort. Curve represents fit to a four-parameter log function.

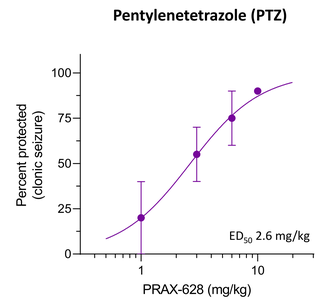



*Figure 3. PRAX-628 is anticonvulsant in the scPTZ acute seizure model.* Dose-response curves for protection from clonic seizures induced by PTZ (85 mg/kg, s.c.). PRAX-628 (1-10 mg/kg) was administered by oral gavage 30 min prior to PTZ administration. PRAX-628 (3-10 mg/kg) significantly reduced seizure incidence. Data are presented as mean ± SEM for two cohorts, with n = 10 per treatment for each cohort. Curve represents fit to a four-parameter log function.

## PRAX-628 is More Potent than 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).

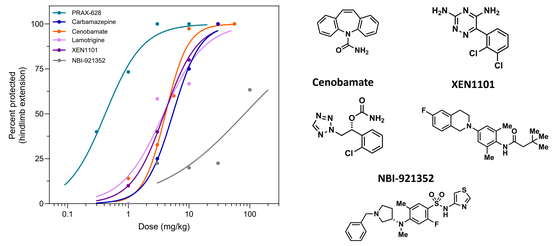






*Table 2. Summary of MES $ED_{50}$ Values*

| | PRAX-628 | Carbamazepine | Cenobamate | Lamotrigine | XEN1101 | NBI-921352 |
|---|---|---|---|---|---|---|
| **$ED_{50}$ values (mg/kg)** | 0.42 | 5.4 | 4.1 | 3.8 | 3.9 | 82 |

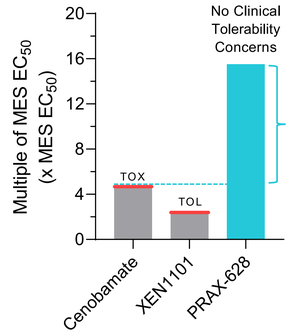
*Figure 4. PRAX-628 is anticonvulsant at lower doses than standard ASMs in the MES acute seizure model.* Dose-response curves for protection from MES-induced tonic hindlimb extension for PRAX-628, carbamazepine, cenobamate, lamotrigine, XEN1101 and NBI-921352. Curves represent fits to a four-parameter log function and $ED_{50}$ values are presented in **Table 2**. Error bars removed for clarity.

## PRAX-628 has Unprecedented Margins Based on Preclinical MES Efficacy and Human Clinical Tolerability

- Recent analysis of the clinical translation of efficacy in commonly used seizure models highlights MES as a rapidly deployed and efficient pre-clinical assay with high predictive validity in focal onset seizures [see also Poster 3.458].

***Combining preclinical MES efficacy with clinical tolerability from first-in-human Phase 1 trials supports predictive translation of clinically tolerated exposures***

**CLINICALLY TOLERATED EXPOSURES**




| | Human Equivalent of Mouse MES $EC_{50}$, ng/mL | Multiples of MES $EC_{50}$ Tolerated Clinically |
|---|---|---|
| Cenobamate | 9,600 | 4.8x |
| XEN1101 | 42 | 2.5x |
| PRAX-628 | 24 | >15.5x* |

*Figure 5. MES Predicted Human Therapeutic Window*

Red lines denote respective toxicity (TOX) or tolerability (TOL) levels: 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 el 2018 AES Annual Meeting)

*No limit due to toxicity was identified for PRAX-628 in the SAD/MAD study PRAX-628-101

xMES $EC_{50}$ = multiple of predicted human $EC_{50}$ based on the rodent MES model

## 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.**
- **First-in-human findings (PRAX-628-101) demonstrate PRAX-628 is well-tolerated at exposures >15x the predicted efficacious exposure from mouse MES.**
- **Higher multiples of the mouse MES $EC_{50}$ human equivalent were well-tolerated compared to cenobamate and XEN1101.**
- **Combined preclinical and clinical findings highlight PRAX-628 as a next-generation functionally selective small molecule with potential for best-in-class efficacy in focal epilepsy.**

## References

1. CDC 2015 US Prevalence Data
2. Gupta et al 2017 *Epilepsia Open*
3. Seiden & Connor 2022 *Epilepsy & Behavior*
4. Kahlig et al 2022 *AAN*

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