Pharmacokinetics , Tolerability and Cardiac Safety for PRAX-628, a Precision Medicine Therapeutic Set to Initiate Registration Enabling Studies for Focal Onset Seizures

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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, with current standard-of-care limited by tolerability issues and a need for titration to avoid side effects.[3]
- These limitations are likely due to inability to selectively target disease related hyperexcitability vs. normal neuronal function (***Fig. 1***).
- PRAX-628 is a next generation functionally selective small molecule targeting the hyperexcitable state of sodium channels in the brain that is currently in development as a best-in-class treatment for adult focal onset seizures and generalized epilepsy.[4,5]
- Emerging preclinical and clinical data highlight a differentiated profile over current standard-of-care, with ability to significantly exceed therapeutic concentrations while well tolerated.[5]

➢ **Here we report clinical pharmacology and tolerability data at multiples of the predicted efficacious concentration based on the mouse maximal electroshock seizure (MES) model and provide preliminary cardiac safety findings from the PRAX-628-101 study.**

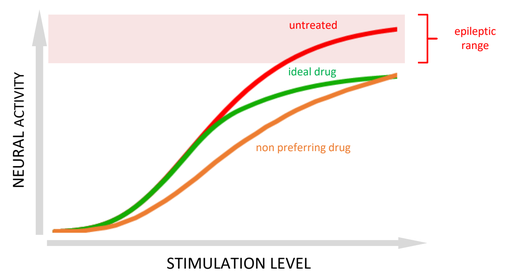


Figure 1. Preferential action against disease-related hyperexcitability

Methods

- PRAX-628-101 was a randomized, double-blinded, placebo-controlled Phase 1 trial investigating the safety, tolerability and pharmacokinetics (PK) of single (SAD, Part A) and multiple (MAD, Part B) ascending doses of PRAX-628 in healthy adults aged 18-55 years (***Fig. 2***).
- Participants were randomized 3:1 to receive either PRAX-628 or placebo in the fasted state, with SAD cohorts receiving single oral doses (5-45 mg) and MAD cohorts receiving multiple doses (20 and 30 mg for 10 days).
- Blood samples were collected for PK analysis. Safety and tolerability assessments included AE incidence and severity, vital signs, physical examinations, clinical lab tests and 12-lead ECGs including PK time-matched recordings up to 24h post-dose.
- ECG parameters included HR, PR, QRS, and QT.
- QTcF (calculated using Fridericia's method)[6] and Bazett's-corrected QT interval (QTcB)[7] were derived.

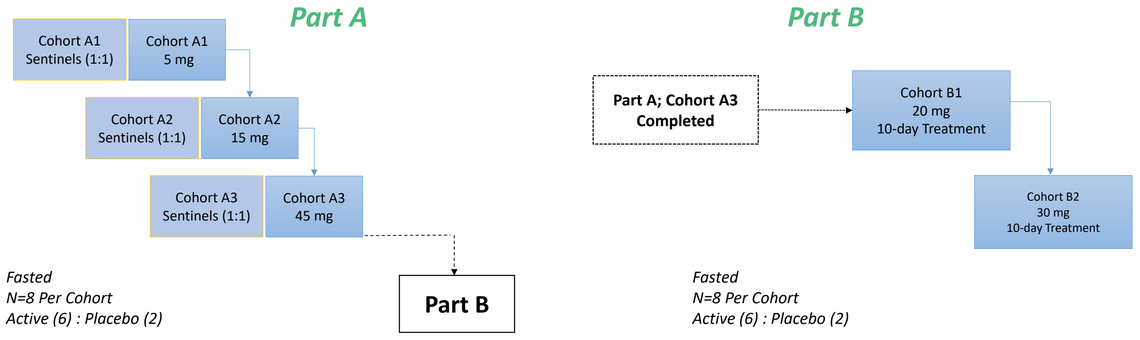


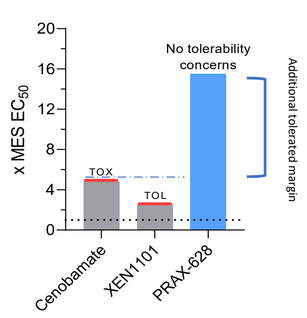
Figure 2. PRAX-628-101 Study Schema: Part A (Single Ascending Dose) and Part B (Multiple Ascending Dose)

Demographics

- A total of 40 participants completed the study (n=30 PRAX-628, n=10 placebo).
- All 40 participants were included in safety and PK analysis sets.
- Demographics and other baseline characteristics were generally similar across groups.
- Overall, the majority of participants were white, and not Hispanic or Latino.
- Part B (MAD) had a higher percentage of males, while in Part A (SAD), the PRAX-628 15-mg group had more males.

Conclusions

- ❖ **First-in-human results highlight PRAX-628 as a well-tolerated, next-generation functionally selective small molecule with potential for best-in-class efficacy in focal onset seizures & generalized epilepsy.**
- ❖ **PRAX-628 demonstrated a favorable safety and tolerability profile in healthy participants, with preliminary cardiac safety findings showing no adverse ECG effects.**
- ❖ **Preclinical and clinical data to date support once-daily dosing of PRAX-628 without titration to achieve *multiples of the predicted* therapeutically effective concentrations based on MES.**



	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 6. MES Predicted Human Therapeutic Window

Red lines denote respective toxicity and tolerability 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)

*No limit due to toxicity was identified for PRAX-628 to date

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

- ❖ **Praxis expects to initiate two efficacy studies in patients with focal onset seizures, as part of the PRAX-628 ENERGY Program, in the fourth quarter of 2024 and first half of 2025.**

Pharmacokinetics

- PK data demonstrated dose-dependent exposure.
- PRAX-628 rapidly appeared in plasma with median t_{max} 1.5-2.3h and a geometric mean half-life of 45-66h (MAD).
- In Part A (SAD), following single doses of 5 to 45 mg PRAX-628, plasma concentrations were quantifiable throughout the dosing interval in all participants (***Fig. 3***).
- In Part B (MAD), following multiple oral doses of PRAX-628 20 and 30 mg QD, there was an increase in exposure from Day 1 to Day 10 in all participants (***Fig. 4***).
- Concentrations which exceeded the human equivalent of mouse MES EC_{50} were reached in all cohorts (***Fig. 3 & 4***). In the SAD cohorts, average concentrations 2-4x the human equivalent MES EC_{50} were maintained for 8 hours with a single dose of 15 mg. In the MAD cohorts, concentrations in excess of 15x the human equivalent MES EC_{50} were achieved at C_{max} with average C_{trough} around 3-5x the MES EC_{50} at steady-state.

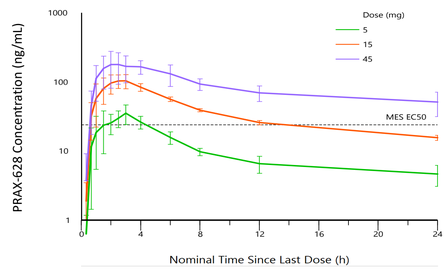


Figure 3. Mean Plasma Concentration-Time Profile of PRAX-628 by Dose (Part A, SAD).
Data are shown as mean ± SD, with PRAX-628 concentration-time profiles shown on a semi-log scale.

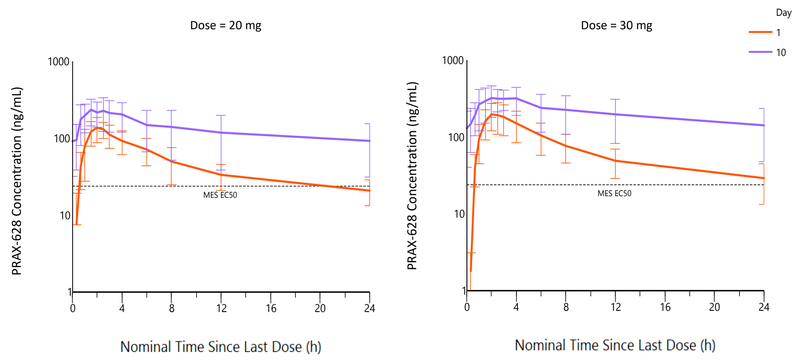


Figure 4. Mean Plasma Concentration-Time Profile of PRAX-628 on Day 1 and 10 (Part B, MAD).
Data are shown as mean ± SD, with PRAX-628 concentration-time profiles shown on a semi-log scale.

Tolerability and Preliminary Cardiac Safety

- PRAX-628 was well-tolerated at all doses evaluated – single doses up to 45 mg (Part A, SAD) and multiple doses up to 30 mg daily for 10 days (Part B, MAD).
- All AEs were mild, mostly transient (lasting minutes to hours), and resolved spontaneously; none led to study drug withdrawal.
  - Most common AEs were CNS related (fatigue, dizziness), which were typically observed and resolved within 4 hours post dosing.
  - Dizziness had no apparent temporal correlation with point of maximum change in QTcB, based on QTc interval categorical analyses.
- Part A (SAD): most common AEs (≥ 2 subjects) were fatigue, dizziness, and headache.
- Part B (MAD): most common AEs (≥ 2 subjects) were fatigue, dizziness, somnolence, headache, disturbance in attention, nausea, presyncope, insomnia, and vision blurred.
- No SAEs, clinically meaningful findings on labs, vital signs or neurological examination were observed.
- Cardiac safety assessments showed no clinically meaningful change in ECG parameters across all doses, with no dose-related trends.
- By-timepoint QTc analysis demonstrated no discernible effect on the QT interval in SAD or MAD cohorts (***Fig. 5***).

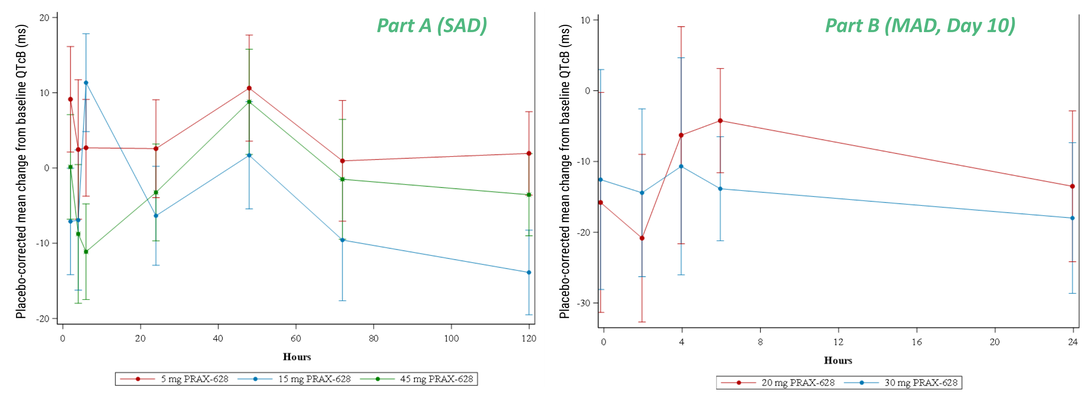


Figure 5. Placebo-corrected Change from Baseline QTcB (ΔΔQTcB) Interval by Treatment and Timepoint (Safety Population) for Part A, SAD (left) and Part B, MAD Day 10 (right). Data shown as mean ± 90% CI

Preclinical Cardiac Safety Findings

Cardiac Ion Channel	% Inhibition @ 10μM	Ratio to target[b]
$K_{ir}2.1$ (maximum inward current)	0.9 ± 7.2	**>50x**
$K_V1.5$ (peak current)	2.4 ± 6.0	
$K_V1.5$ (steady state current)	7.0 ± 6.6	
$K_V4.3$ (peak current)	14.1 ± 3.0	
$K_V4.3$ (area under curve)	42.1 ± 6.3[a]	
$K_V7.1$/mink (steady state current)	10.5 ± 9.8	
HCN4 (steady state current)	-4.6 ± 1.7	
$Ca_V1.2$ (peak current)	25.1 ± 4.8[a]	
$Ca_V3.2$ (peak current)	26.5 ± 2.4[a]	
hERG (peak tail current)	IC_{50} = 5.0 μM (GLP)	**25x**

Data are mean ± SEM (n=3). SEM=standard error of the mean.
[a] Statistically significant difference from control group as determined by one-way ANOVA with Dunnett's Multiple Comparison Test. Ca_V=voltage-gated calcium channel; hERG=human ether-a-go-go-related gene; HCN=hyperpolarization-activated cyclic nucleotide-gated channel; K_{ir}=inwardly-rectifying potassium channel; K_V=voltage-gated potassium channel.
[b] Based on primary pharmacology studies for $hNa_V1.6$ UDB-10Hz (IC_{50} 0.2μM)

Table 1. In vitro non-GLP safety pharmacology study evaluating the ability of 10μM PRAX-628 to modulate recombinant, human non-I_{Na} cardiac channels, stably expressed in either CHO or HEK293 cells.

References

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Acknowledgments We thank the participants and their families, as well as Dr. Kris Kahlig and our collaborators for their contributions to this work.

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

Disclosures KH, JC, MT, DP, HJ, SF, SP and MS are current or former employees/consultants of Praxis Precision Medicines and may be Praxis shareholders.

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Presented at:
European Epilepsy Congress
7 – 11 September 2024
Rome, Italy