Safety, Tolerability and Pharmacokinetic Findings from a First-In-Human, Randomized, Double-blind, Placebo-Controlled Trial of Single and Multiple Ascending Doses of PRAX-628 in Healthy Participants

Karl Hansen, Dharit Patel, Angela Wehr, Marjie Hard, Silvana Frizzo, Steven Petrou, Marcio Souza

Praxis Precision Medicines, Boston, MA 02110 USA

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] which are likely due to the inability to selectively target disease related hyperexcitability over 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 epilepsy.[4]

➢ Here we report preliminary first-in-human safety and tolerability at multiples of the predicted efficacious concentration based on the mouse maximal electroshock seizure (MES) model.

➢ We demonstrate that PRAX-628 achieved >15x the predicted therapeutic dose, while being safe and tolerable with mild, transient CNS related adverse events (AEs).

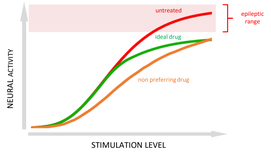


Figure 1. Preferential action against disease-related hyperexcitability

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 mg starting dose) and MAD cohorts receiving multiple doses (for 10 days).
- Safety and tolerability assessments included incidence and severity of AEs, vital signs, 12-lead ECGs, physical examinations, clinical laboratory tests, and the Columbia-Suicide Severity Rating Scale (MAD only).
- Blood samples were collected for measurement of PRAX-628 plasma concentrations.

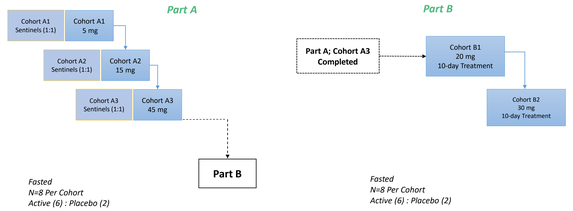


Figure 2. PRAX-628-101 Study Schema: Part A (Single Ascending Dose) and Part B (Multiple Ascending Dose)

Demographics

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

Pharmacokinetics

- PK data demonstrated dose-dependent exposure.
- PRAX-628 rapidly appeared in plasma with time to observed maximum concentration (t_{max}) between 2.5 to 3 hours, and a terminal elimination half-life consistent with once daily dosing.
- In Part A (SAD), following single doses of 5 to 45 mg PRAX-628, plasma concentrations were quantifiable throughout the entire dosing interval in all participants (***Fig. 3***).
- In Part B (MAD), administration of 20 to 30 mg PRAX-628 QD, plasma concentrations were quantifiable throughout the entire dosing interval on Days 1 and 10 in all participants (***Fig. 4***).
- Concentrations which exceeded the predicted efficacious level based on the mouse MES EC_{50} were reached in all cohorts (***Fig. 3 & 4***). In the SAD cohorts, average concentrations 2-4x the 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 MES EC_{50} were achieved at C_{max} with average C_{trough} around 3-5x the MES EC_{50} at steady-state.

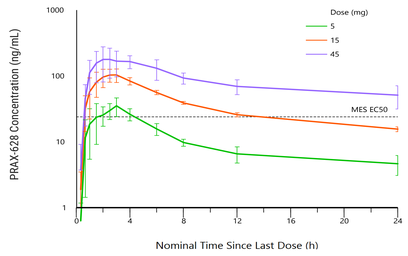


Figure 3. Mean Plasma Concentration-Time Profile of PRAX-628 by Dose (Part A, SAD).
Data are shown as mean ± SD, with PRAX-628 concentration-time profiles shown on a semi-log scale.

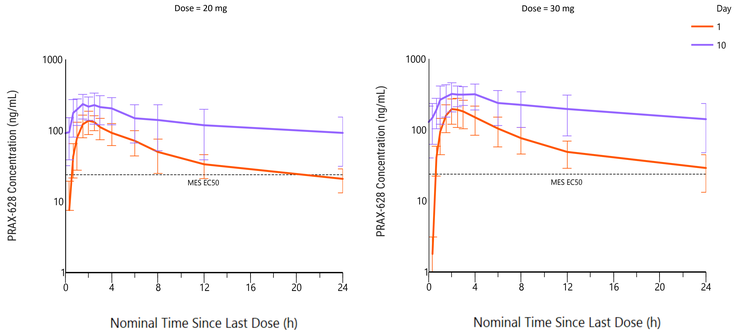
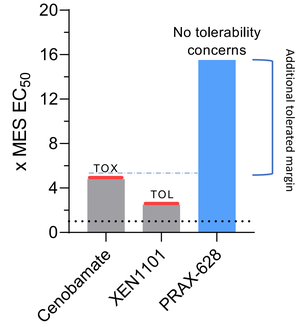


Figure 4. Mean Plasma Concentration-Time Profile of PRAX-628 on Day 1 and 10 (Part B, MAD).
Data are shown as mean ± SD, with PRAX-628 concentration-time profiles shown on a semi-log scale.

Safety and Tolerability

- PRAX-628 was well-tolerated at tested doses – 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.
  - Most common AEs were CNS related (fatigue, dizziness), which were typically observed and resolved within 4 hours post dosing.
- 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, AESI or AE led to study drug withdrawal, and no clinically significant findings on vital signs, ECG or neurological examination were observed.
- There were no clinically significant changes in safety laboratory assessment.



	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 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

PRAX-628 has unprecedented margins based on its MES efficacy and clinical tolerability in humans

Conclusions

- **PRAX-628 demonstrated a favorable safety and tolerability profile in healthy volunteers.**
- **Building on preclinical work, these findings support once-daily dosing of PRAX-628 without titration to achieve *multiples of the predicted* therapeutically effective concentrations based on MES.**
- **First-in-human results 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*

Acknowledgments We thank the participants and their families, as well as 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 All authors are current or former employees/consultants of Praxis Precision Medicines and may be Praxis stockholders.

@PraxisMedicines
Praxismedicines.com
clinicaltrials@praxismedicines.com

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