PRAX-562-102: A Phase 1 Trial Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of PRAX-562 in Healthy Volunteers

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Background

- Gain-of-function pathogenic variants in voltage-gated sodium channel (Na_V) genes can increase persistent sodium current (I_{NaP}) leading to neuronal hyperexcitability and seizures observed in severe developmental and epileptic encephalopathies (DEEs).[1-4]
- PRAX-562 is a next-generation anti-seizure small molecule with demonstrated potency and preference for disease state hyperexcitability present in multiple DEEs.
- Tailored for pediatric needs, this unique profile is expected to translate to a wider therapeutic window compared to current standard-of-care.
- Here we report findings from PRAX-562-102, a Phase 1 clinical trial characterizing the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of PRAX-562 in healthy adults.

Methods

- PRAX-562-102 was a 2-part randomized, placebo-controlled Phase 1 trial in healthy participants aged 18-55 years (***Fig. 1***).
- Part A evaluated the effects of 90 mg PRAX-562 over 28 days (QD) vs. placebo.
- Part B evaluated the effects of oxcarbazepine (OXC) in combination with 120 mg PRAX-562 (QD) vs. OXC alone over 28 days.
- PD effects were examined on quantitative EEG (qEEG; resting and vigilant conditions) and stimulated EEG using auditory steady state response (ASSR).

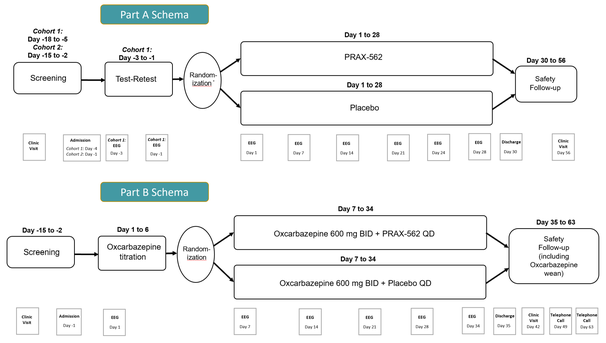

Figure 1. PRAX-562-102 Study Schema

Demographics

- A total of 48 participants were enrolled; Part A, n=30; Part B, n=18 (***Table 1***).

Table 1. Participant Demographics

Part A	PRAX-562 (N=18)	Placebo (N=12)
Age, *years*	38.7 (22, 53)	37.3 (24, 49)
Male, *n (%)*	15 (83.3)	8 (66.7)
Female, *n (%)*	3 (16.7)	4 (33.3)
Child-bearing potential, *n (%)*	3 (16.7)	4 (33.3)
Hispanic or Latino, *n (%)*	3 (16.7)	1 (8.3)
Not Hispanic or Latino, *n (%)*	15 (83.3)	11 (91.7)
Black or African American, *n (%)*	15 (83.3)	11 (91.7)
White, *n (%)*	3 (16.7)	1 (8.3)
BMI, kg/m^2	27.4 (18.6, 31.2)	27.3 (23.5, 30.9)

Part B	OXC + PRAX-562 (N=14)	OXC + PBO (N=4)
Age, *years*	36.9 (21, 55)	34 (25, 48)
Male, *n (%)*	12 (85.7)	4 (100)
Female, *n (%)*	2 (14.3)	0
Child-bearing potential, *n (%)*	2 (14.3)	0
Hispanic or Latino, *n (%)*	6 (42.9)	1 (25.0)
Not Hispanic or Latino, *n (%)*	8 (57.1)	3 (75.0)
Black or African American, *n (%)*	3 (75.0)	7 (50.0)
White, *n (%)*	1 (25.0)	7 (50.0)
BMI, kg/m^2	28.1 (22.2, 32.0)	25.2 (21.9, 29.2)

Mean (min, max) presented unless otherwise specified.

Safety and Tolerability

- There were no clinically significant safety findings in vital signs, physical exams, ECGs, or C-SSRS data. TEAEs were mostly mild or moderate (100% Part A; 96% Part B); the most common of which are summarized in **Table 2**.
- In Part A, there were 35 TEAEs across 13 participants: 71% mild in severity, 29% moderate, 0% severe.
- In Part B, there were 74 TEAEs across 16 participants: 51% mild in severity, 45% moderate, 4% severe.
  - TEAEs were observed in 13 (92.9%) patients receiving OXC + PRAX-562 and in 3 (75%) patients receiving OXC + Placebo.
  - A review of ALT/AST increases and rhabdomyolysis did not identify a causal association to PRAX-562.
  - One Part B participant experienced 3 study drug related SAEs leading to study drug discontinuation.
- Part B was stopped early after 5 participants receiving OXC + PRAX-562 (including the participant with SAEs) developed TEAEs.

Table 2. PRAX-562-102 Part A and B Most Common TEAEs by Preferred Term*

Part A

Preferred Term (PT)	PRAX-562 (N=18)	Placebo (N=12)
Dizziness	5 (27.8)	0
Headache	4 (22.2)	0
Hypoasthesia	2 (11.1)	0
Hypoasthesia (oral)	2 (11.1)	0
ALT Increased*	1 (5.6)	1 (8.3)

Part B

Preferred Term (PT)	OXC + PRAX-562 (N=14)	OXC + Placebo (N=4)
Headache	8 (57.1)	0
Nausea	7 (50.0)	0
Dizziness	6 (42.9)	0
Tremor	5 (35.7)	0
ALT increased	4 (28.6)	1 (25.0)
Hypoaesthesia oral	4 (28.6)	0
AST Increased	3 (21.4)	1 (25.0)
Fatigue	3 (21.4)	0
Amnesia	2 (14.3)	0
Balance disorder	2 (14.3)	0
Disorientation	2 (14.3)	0
Dysarthria	2 (14.3)	0
Vision blurred	2 (14.3)	0
Vomiting	2 (14.3)	0
Rhabdomyolysis*	1 (7.1)	1 (25.0)

> 1 participant reported TEAE PT or special interest AE*
Participants counted once per PT

Conclusions

- **PRAX-562 was well tolerated in healthy adults at 90 mg in Part A.**
- **The majority of AEs including SAEs in Part B were considered to be due to coadministration of projected supratherapeutic doses of PRAX-562 (120 mg) with OXC, and likely additive Na_V effects.**
- **Part A PK findings demonstrated a 13-fold increase in PRAX-562 concentrations over the human-equivalent dose required to achieve efficacy as measured in preclinical maximal electroshock seizure models (see also Poster P095).**
- **Our results are consistent with earlier work suggesting a wide therapeutic window for PRAX-562.**
- **Furthermore, PD findings indicate CNS modulation and expected target engagement for PRAX-562 across multiple qEEG measures.**
- **A PRAX-562 Phase 2 study (EMBOLD) is currently ongoing in pediatric patients with SCN2A-DEE and SCN8A-DEE (NCT05818553).**

EMBOLD

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics

- PRAX-562 90 mg administered for 28 days approaches steady state (Part A, ***Fig. 2***).
- PRAX-562 exposure did not appear to be altered with OXC coadministration (Part B, *data not shown*).
- Exposure to OXC and its primary metabolite, 10-Hydroxycarbamazepine, appeared to be similar when administered concomitantly with PRAX-562 vs administered alone (Part B, ***Table 3***).

Figure 2. Mean (+ SD) plasma concentration-time profile of PRAX-562 (90 mg, Part A). Semi-logarithmic scale.

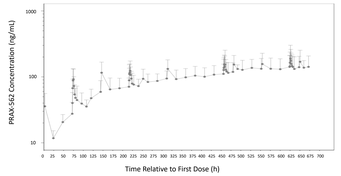

Table 3. Day 7 PRAX-562 exposure summary (120 mg, Part B)

Analyte	Parameter	OXC + PRAX-562 (N=13)	OXC + Placebo (N=4)
Oxcarbazepine	C_{max} (ng/mL)	1,776 (37.6)	1,525 (21.1)
	AUC_{last} (ng*h/mL)	5,564 (40.2)	5,828 (16.4)
10-Hydroxycarbamezapine	C_{max} (ng/mL)	17,017 (31.1)	18,175 (21.3)
	AUC_{last} (ng*h/mL)	151,595 (38.9)	172,658 (13.8)

Pharmacodynamics

- PD biomarker changes observed on qEEG and ASSR were exposure dependent; qEEG changes were observed across all spectral frequencies.
- Statistically significant differences between placebo and PRAX-562 were observed in Part A on qEEG (Delta and Theta power) and ASSR (phase-locking-factor (PLF) and Evoked Power) (***Fig. 3 and Fig. 4***). Effects on both low frequency qEEG power and ASSR appeared to be PRAX-562 concentration dependent.
- Statistically significant differences were observed in Part B participants receiving OXC + PRAX-562 vs. OXC alone on qEEG Delta, but not qEEG Theta or ASSR.

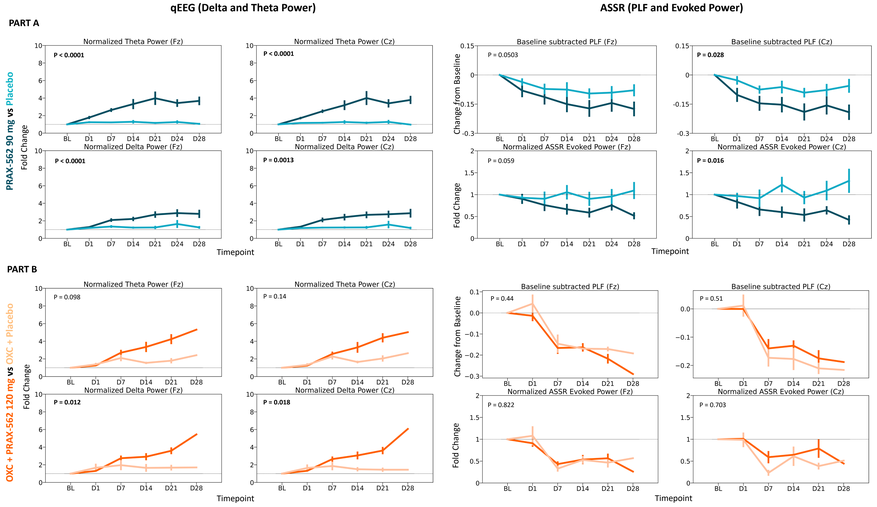

Figure 3. PD Effects of PRAX-562 on resting state qEEG measures, Delta and Theta Power. D1 baseline-normalized resting state qEEG power (mean ± SEM) for the C_{max} timepoint (2.5h) for each day. P values denote differences between PRAX-562 (n=17) and placebo (n=10) in Part A (*top*) and between OXC+PRAX-562 (n=12) and OXC+placebo (n=4) in Part B (*bottom*), based on MMRM analysis. In Part B, PRAX-562 vs placebo dosing began on D7.

Figure 4. PD Effects of PRAX-562 on ASSR measures, PLF and Evoked Power. Baseline-subtracted ASSR PLF and baseline-normalized ASSR Evoked Power (mean ± SEM) for the C_{max} timepoint (2.5h) for each day. P values denote differences between PRAX-562 (n=17) and placebo (n=10), in Part A (*top*) and between OXC+PRAX-562 (n=12) and OXC+placebo (n=4) in Part B (*bottom*), based on MMRM analysis. In Part B, PRAX-562 vs placebo dosing began on D7.

References

1. Wagnon et al 2015 *Hum Mol Genet*
2. Wagnon and Meisler 2019 *Front Neurol*
3. Ware et al 2019 *Epilepsia Open*
4. Wolff et al 2017 *Brain*

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.

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