

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).

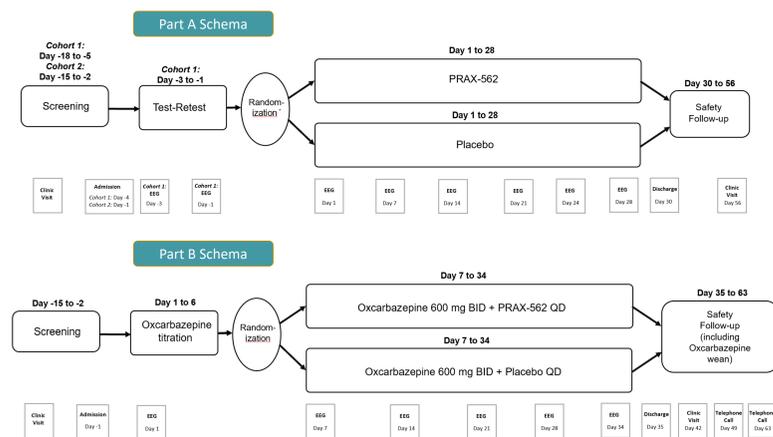


Figure 1. PRAX-562-102 Study Schema

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)	Part B	OXC + PRAX-562 (N=14)	OXC + PBO (N=4)
Age, years	38.7 (22, 53)	37.3 (24, 49)	Age, years	36.9 (21, 55)	34 (25, 48)
Male, n (%)	15 (83.3)	8 (66.7)	Male, n (%)	12 (85.7)	4 (100)
Female, n (%)	3 (16.7)	4 (33.3)	Female, n (%)	2 (14.3)	0
Child-bearing potential, n (%)	3 (16.7)	4 (33.3)	Child-bearing potential, n (%)	2 (14.3)	0
Hispanic or Latino, n (%)	3 (16.7)	1 (8.3)	Hispanic or Latino, n (%)	6 (42.9)	1 (25.0)
Not Hispanic or Latino, n (%)	15 (83.3)	11 (91.7)	Not Hispanic or Latino, n (%)	8 (57.1)	3 (75.0)
Black or African American, n (%)	15 (83.3)	11 (91.7)	Black or African American, n (%)	3 (75.0)	7 (50.0)
White, n (%)	3 (16.7)	1 (8.3)	White, n (%)	1 (25.0)	7 (50.0)
BMI, kg/m ²	27.4 (18.6, 31.2)	27.3 (23.5, 30.9)	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	PRAX-562 (N=18)	Placebo (N=12)
Dizziness	5 (27.8)	0
Headache	4 (22.2)	0
Hypoesthesia	2 (11.1)	0
Hypoesthesia (oral)	2 (11.1)	0
ALT Increased*	1 (5.6)	1 (8.3)

Part B	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)
Hypoesthesia 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).



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-Hydroxycarbamezapine, 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.

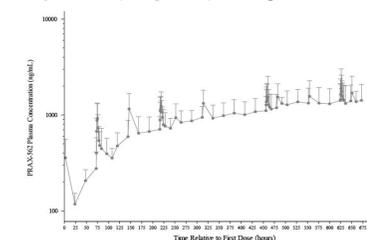


Table 3. Day 7 PRAX-562 exposure summary (120 mg, Part B)

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 ₀₋₂₄ (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 ₀₋₂₄ (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.

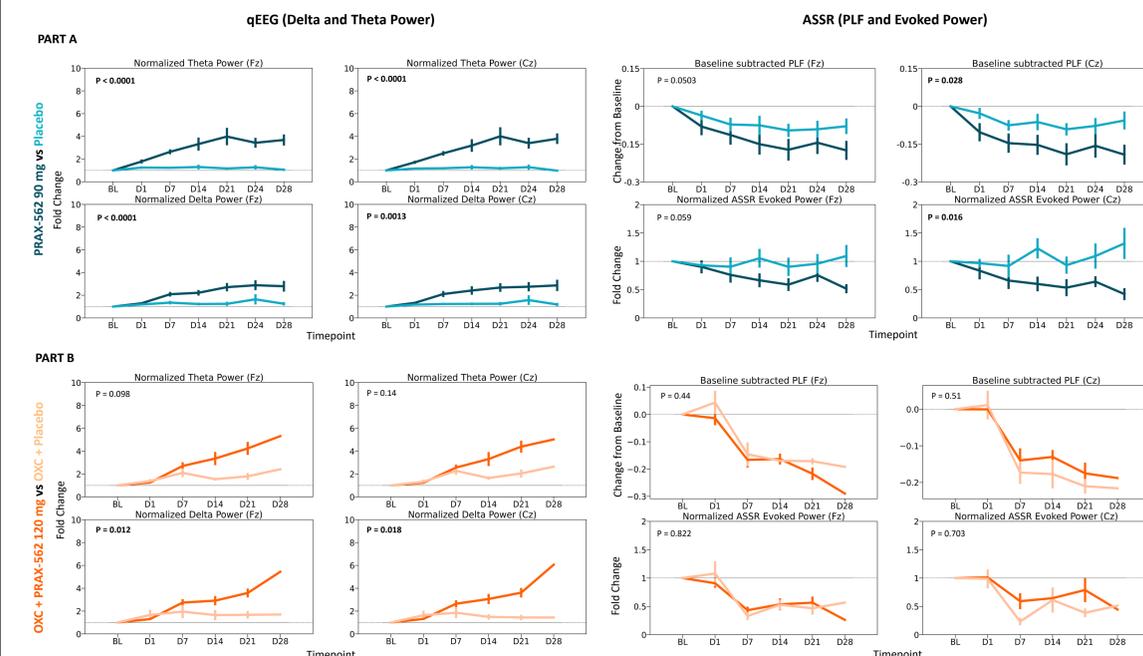


Figure 3. PD Effects of PRAX-562 on resting state qEEG measures, Delta and Theta Power. D1 baseline-normalized resting state qEEG power (mean ± SEM) for the C_{max} timepoint (2.5h) for each day. P values denote differences between PRAX-562 (n=17) and placebo (n=10) in Part A (top) and between OXC+PRAX-562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

- Wagnon et al 2015 Hum Mol Genet
- Wagnon and Meisler 2019 Front Neural
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