PRAX-562-101: A Phase 1 Trial Evaluating the Safety, Tolerability, Pharmacokinetics and Food Effect of PRAX-562 in Healthy Volunteers

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Background

- Developmental and epileptic encephalopathies (DEEs) are devastating neurological disorders presenting in infancy and early childhood, characterized by severe and frequent seizures, developmental delay, intellectual disability, and other comorbidities.
- Poor prognosis, increased risk of early death, and limited treatment options constitute a significant burden for affected patients and caregivers.[1]
- Gain-of-function pathogenic variants in voltage-gated sodium channel (Na_v) genes cause several severe DEEs. These mutations can increase persistent sodium current (I_{NaP}), leading to neuronal hyperexcitability and seizures.[2-5]
- PRAX-562 is a next-generation anti-seizure small molecule in clinical development 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 a first-in-human trial evaluating safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending doses of PRAX-562, and the effect of food on PK of a single dose in healthy adults.

Methods

- PRAX-562-101 (ACTRN12620001292965) was a 3-part Phase 1 trial in healthy adults aged 18-55 years (***Fig. 1***).
  - Parts A and B were randomized, placebo-controlled and evaluated the effects of single (2.5-150 mg) and multiple (30-120 mg, 14 days QD) ascending oral doses of PRAX-562, respectively.
  - Part C was an open-label, randomized, crossover design evaluating the PK of a single oral dose (90 mg) in fasted and fed states.
- In Parts A (n=64) and B (n=32), participants were randomized 3:1 to PRAX-562 or placebo.
- In Part C (n=16), participants were randomized 1:1 to one of two treatment sequences receiving a single dose of 90 mg PRAX-562 in the fed (following a high-fat/high calorie meal) or fasted (≥10h after the last, and 4h before the next, meal) state.
- The pharmacodynamic (PD) effect of PRAX-562 on stimulated electroencephalography (EEG) endpoints using auditory steady state response (ASSR) and resting state EEG (qEEG) was also explored in Parts A and B (120-mg single-dose and multiple-dose cohorts, respectively).

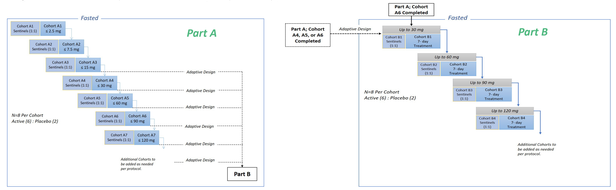
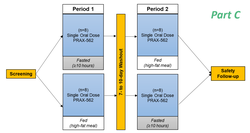


Figure 1. PRAX-562-101 Study Schema: Part A (Single Ascending Dose), Part B (Multiple Ascending Dose) and Part C (Food Effect)



Demographics

- 112 participants were enrolled across the PRAX-562-101 trial (n=88 PRAX-562, n=24 placebo).
- All participants were included in the Safety analysis sets; 48 (75%) Part A, 24 (76%) Part B, and 16 (100%) Part C participants were included in the PK analysis set.
- Overall, the majority of participants were male, white, and not Hispanic or Latino.
- Demographics and other baseline characteristics were generally similar across treatment groups, with the exception that all participants in the PRAX-562 60-mg group in Part A and 120-mg QD Group in Part B were male.

Safety and Tolerability

- PRAX-562 was well-tolerated with no clinically significant safety findings in vital signs, clinical laboratory results, physical exams, ECGs, or C-SSRS data.
- TEAEs were mild (>92%) and resolved without administration of concomitant medications; the most common of which were headache and catheter-site related.
- No severe TEAEs were reported across any of the parts of the trial.
- Drug class effects of Na_v blockers (dizziness and hypoaesthesia) were more frequently reported at higher doses (120 and 150 mg) vs placebo.
- In Part A, the most frequently reported study drug-related TEAEs were somnolence, headache, abdominal pain, diarrhea, nausea, and dizziness (***Table 1***).

Table 1. Summary of Study Drug–Related TEAEs Reported for ≥2 Participants Overall (Part A)

Part A	Placebo (N=16)	PRAX-562 2.5 mg (N=6)	PRAX-562 7.5 mg (N=6)	PRAX-562 15 mg (N=6)	PRAX-562 30 mg (N=6)	PRAX-562 60 mg (N=6)	PRAX-562 90 mg (N=6)	PRAX-562 120 mg (N=6)	PRAX-562 150 mg (N=6)	Overall (N=64)
Any Study Drug–Related TEAE*	2 (12.5)	0	0	5 (83.3)	2 (33.3)	0	2 (33.3)	3 (50.0)	2 (33.3)	16 (25.0)
Somnolence	1 (6.3)	0	0	0	0	0	1 (16.7)	2 (33.3)	0	4 (6.3)
Headache	0	0	0	0	1 (16.7)	0	0	2 (33.3)	0	3 (4.7)
Abdominal pain	0	0	0	1 (16.7)	1 (16.7)	0	0	1 (16.7)	0	3 (4.7)
Diarrhea	0	0	0	3 (50.0)	0	0	0	0	0	3 (4.7)
Nausea	0	0	0	0	0	0	1 (16.7)	1 (16.7)	0	2 (3.1)
Dizziness	0	0	0	0	0	0	0	1 (16.7)	1 (16.7)	2 (3.1)

*The first row denotes the number of participants with at least 1 TEAE. For each TEAE listed below, participants are counted once. Some participants had multiple TEAEs; only TEAEs present in ≥2 participants are listed.

- In Part B, the most commonly reported study drug–related TEAEs were somnolence and headache (***Table 2***); however, no dose response was apparent.
- One SAE (foreign body in gastrointestinal tract) occurred in Part B which was considered unrelated to study drug and not treatment emergent.

Table 2. Summary of Study Drug–Related TEAEs Reported for ≥2 Participants Overall (Part B)

Part B	Placebo (N=8)	PRAX-562 30 mg QD (N=6)	PRAX-562 45 mg QD (N=6)	PRAX-562 90 mg QD (N=6)	PRAX-562 120 mg QD (N=6)	Overall (N=32)
Any Study Drug–Related TEAE*	3 (37.5)	5 (83.3)	2 (33.3)	1 (16.7)	5 (83.3)	16 (50.0)
Somnolence	2 (25.0)	2 (33.3)	0	1 (16.7)	0	5 (15.6)
Headache	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	4 (12.5)
Hypoaesthesia	1 (12.5)	0	0	0	2 (33.3)	3 (9.4)
Vertigo	0	0	1 (16.7)	0	2 (33.3)	3 (9.4)
Disturbance in attention	0	0	0	0	2 (33.3)	2 (6.3)
Dizziness	0	0	0	1 (16.7)	2 (33.3)	3 (9.4)
Dysgeusia	0	0	0	0	2 (33.3)	2 (6.3)
Facial Spasm	0	0	0	0	2 (33.3)	2 (6.3)
Myoclonus	1 (12.5)	0	0	0	1 (16.7)	2 (6.3)
Paraesthesia	0	0	0	1 (16.7)	2 (33.3)	3 (9.4)
Sedation	1 (12.5)	1 (16.7)	0	0	0	2 (6.3)
Hypoaesthesia oral	0	0	0	0	3 (50.0)	3 (9.4)
Nausea	0	1 (16.7)	0	1 (16.7)	0	2 (6.3)

*The first row denotes the number of participants with at least 1 TEAE. For each TEAE listed below, participants are counted once. Some participants had multiple TEAEs; only TEAEs present in ≥2 participants are listed.

- In Part C, ≥1 TEAE was reported for 11 participants (68.8%) in the fasted state and 10 participants (62.5%) in the fed state; the majority were considered mild in severity.
  - ≥1 moderate TEAE was reported for 2 participants (12.5%) in the fasted state and 3 participants (18.8%) in the fed state.
- In Part C, ≥1 study drug–related TEAE was reported for 1 participant (6.3%) in the fasted state and 5 participants (31.3%) in the fed state.
  - The most common was dizziness, reported for 2 participants (12.5%) in the fed state. All other study drug–related TEAEs were reported for a single participant each.

Exploratory Pharmacodynamics

- qEEG-based absolute power analysis and composite metrics showed change from baseline for PRAX-562.
- ASSR-based measures of phase locking factor (PLF) were reduced from baseline in the 90-mg and 120-mg PRAX-562 QD groups in Part B after 14 days of dosing, suggesting modulation of cortical excitatory/inhibitory balance.
- These exploratory results are suggestive of central PD activity of PRAX-562, which has now been followed up in our subsequent Phase 1 trial (PRAX-562-102; Poster P409).

Pharmacokinetics and Food Effect

- Exposure increased dose proportionally over the evaluated dose range.
- PRAX-562 rapidly appeared in plasma with time to observed maximum concentration (t_{max}) between 2 and 3 hours.
- In Part A, following single doses of 2.5 to 150 mg PRAX-562, plasma concentrations were quantifiable up to 120 hours post-dose in all participants (***Fig. 2***).

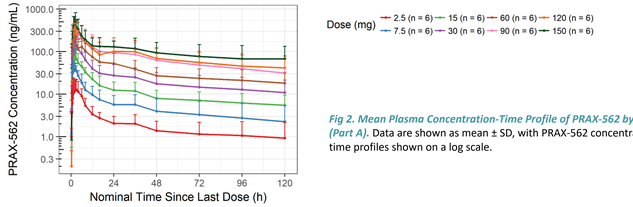


Fig 2. Mean Plasma Concentration-Time Profile of PRAX-562 by Dose (Part A). Data are shown as mean ± SD, with PRAX-562 concentration-time profiles shown on a log scale.

- In Part B, following administration of 30 to 120 mg PRAX-562 QD, plasma concentrations were quantifiable throughout the entire dosing interval on Days 1 and 7, and were quantifiable up to 120 hours post last dose on Day 14 in all participants (***Fig. 3***).

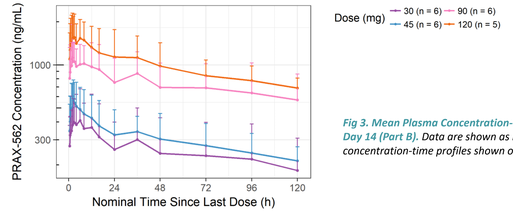


Fig 3. Mean Plasma Concentration-Time Profile of PRAX-562 by Dose on Day 14 (Part B). Data are shown as mean ± SD, with PRAX-562 concentration-time profiles shown on a log scale.

- In Part C, following administration of a single dose of 90 mg PRAX-562, plasma concentrations were quantifiable up to 120 hours post-dose in all participants (***Fig. 4***); 90 mg PRAX-562 in the fed state resulted in a slight increase in C_{max} (9%), delay in t_{max} (4 vs 2.5 h), and a modest increase in AUC (14%) compared to fasted state.

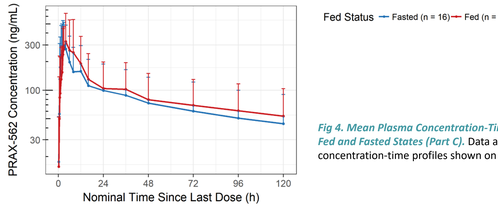


Fig 4. Mean Plasma Concentration-Time Profile of 90 mg PRAX-562 in the Fed and Fasted States (Part C). Data are shown as mean ± SD, with PRAX-562 concentration-time profiles shown on a log scale.

Conclusions

- **PRAX-562 was well tolerated in healthy participants at single doses up to 150 mg (fasted) in Part A, at multiple doses of up to 120 mg QD for 14 days (fasted) in Part B, and at a single dose of 90 mg in the fed and fasted states in Part C.**
- **Daily administration of PRAX-562 resulted in plasma concentrations that were detectable throughout the dose interval. Additionally, PRAX-562 can be administered without regard to food.**
- **A PRAX-562 Phase 2 study (EMBOLD) is currently ongoing in pediatric patients with SCN2A-DEE and SCN8A-DEE (NCT05818553).**

EMBOLD

References

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