Updates from the First-in-human Phase 1 Clinical Trial Evaluating the Safety, Tolerability, Pharmacokinetics and Food Effect of Vormatrigine in Healthy Participants

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Background

- There are ~50 million individuals worldwide living with epilepsy, the majority of whom have focal epilepsy.
- 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.
- These limitations are likely due to inability to selectively target disease related hyperexcitability vs. normal neuronal function.
- Vormatrigine is a potent 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.
- Emerging preclinical and clinical data highlight a differentiated profile over current standard-of-care.
- PK and cardiac safety data from PRAX-628-101, a first-in-human Phase 1 trial demonstrated a favorable safety and tolerability profile in doses up to 45 mg in Part A (SAD), and up to 30 mg in Part B (MAD), and an ability to significantly exceed therapeutic concentrations while being well tolerated.

➢ ***Here, we provide an update from 45 mg arm in the MAD cohort, including food effect data.***

Methods

- PRAX-628-101 was a randomized, double-blinded, placebo-controlled Phase 1 trial investigating the safety, tolerability and PK of single and multiple ascending doses and the effect of food of vormatrigine in healthy adults aged 18-55 years (Fig. 1).
- The MAD and SAD cohorts were randomized, double-blinded, and placebo-controlled, with participants assigned 3:1 to receive vormatrigine or placebo under fasting conditions.
- SAD cohorts received single oral doses (5-45 mg) and MAD cohorts receiving multiple doses (20, 30 and 45 mg for 10 days) of vormatrigine.
- The food effect cohort was an open-label, crossover design with participants receiving two 30 mg doses (fasted and fed states) separated by a 7-day washout. Participants were randomized 1:1 to be in either the fasted or fed state prior to the first dose.
- Blood samples were collected for PK analysis. Safety and tolerability assessments included adverse events (AEs), vital signs, 12-lead ECGs, physical examinations, clinical laboratory tests, and the Columbia-Suicide Severity Rating Scale.

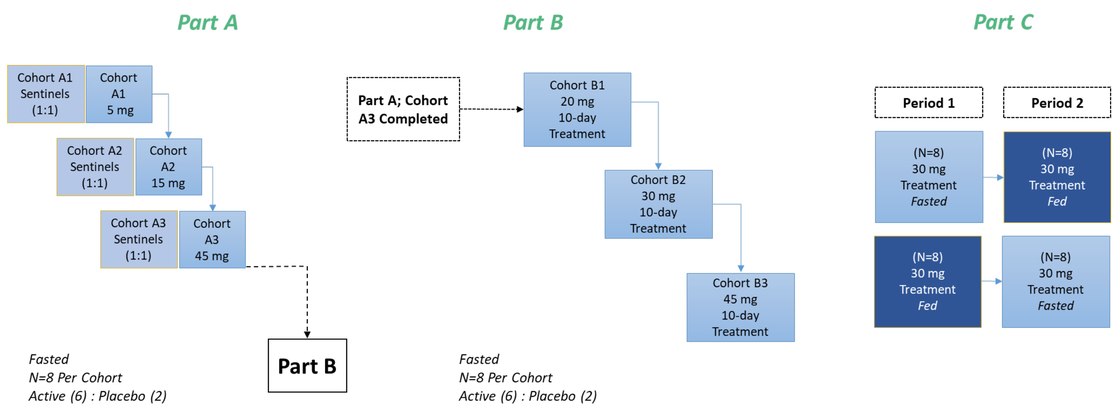

Figure 1. PRAX-628-101 Study Schema: Part A (Single Ascending Dose), Part B (Multiple Ascending Dose) and Part C (Food Effect Evaluation)

Demographics Summary

- Vormatrigine has been administered to 52 healthy participants in Parts A (n=18), B (n=18) and C (n=16).
- Overall, the majority of participants were white, and not Hispanic or Latino.
- Demographics and other baseline characteristics were generally similar across treatment groups.

Vormatrigine Continues To Be Well Tolerated

- Vormatrigine was well tolerated at tested doses up to 45 mg QD for 10 days.
- No deaths, SAEs, AESIs or adverse event-related discontinuations were reported.
- TEAEs were mostly mild, transient, and self-resolving. No severe TEAEs were reported.
- No safety findings were observed on clinical lab test results, ECGs, physical exam, or vital signs and no participants exhibited suicidal ideation and behavior, as determined from the C-SSRS.

Table 2. PRAX-628-101 Tolerability Summary for Vormatrigine 45 mg (Part B, MAD)

	Vormatrigine (N=6)	Placebo (N=6)
ANY TEAE	**6 (100%)**	**3 (50%)**
TEAEs ≥ 2 Subjects		
Dizziness	6 (100%)	0
Paraesthesia oral	5 (83.3%)	0
Asthenia	2 (33.3%)	0
Headache	3 (50%)	1 (16.7%)
Nausea	2 (33.3%)	1 (16.7%)
Somnolence	2 (33.3%)	2 (33.3%)
Fatigue	2 (33.3%)	2 (33.3%)

Exposure at 45 mg MAD Cohort

- Exposure data from MAD showed a dose-dependent increase of exposure up to 45 mg .
- The 45 mg dose C_{max} showed a modest increase on Day 1 (1.1-fold) and a more pronounced increase on Day 10 (1.3-fold).
- $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}tau}$ demonstrates a consistent and linear dose proportional increase on Day 1 and 10 respectively, indicating that drug exposure is proportional to increasing dose up to 45 mg.
- Consistent with data from Part B 20 and 30 mg cohorts, concentrations exceeding the predicted efficacious level based on the mouse MES EC_{50} were reached in the 45 mg cohort.
- Highest MES EC_{50} reported to date, with concentrations in excess of 20x the human equivalent MES EC_{50} achieved in the 45 mg MAD cohort.
- These findings support the use of up to the 45 mg dose to achieve optimal therapeutic levels.

Table 1. Geometric Means (%CV) of Vormatrigine 45 mg on Day 1 and 10 (Part B, MAD)

	Day 1 (N=5)	Day 10 (N=5)
C_{max} (ng/mL)	235.8 (21.9)	471.59 (19.2)
AUC_{tau} (ng*h/mL)	2407.06 (22.6)	6489.01 (29.1)

AUC_{tau}: area under the plasma concentration-time curve over the dosing interval

Vormatrigine Has No Clinically Significant Food Effect

- Food effect analysis revealed no clinically significant impact to C_{max} or AUC at steady state.
- Modeling and simulation with a population PK model of the effect of fed/fasted states on drug exposure at steady state showed that the decrease in fed C_{max} is within the bioequivalence range (***Fig. 2***, ***Table 3***).
- The effectiveness and safety profile of vormatrigine are thus likely to remain unchanged, regardless of whether vormatrigine is taken with or without respect to food.

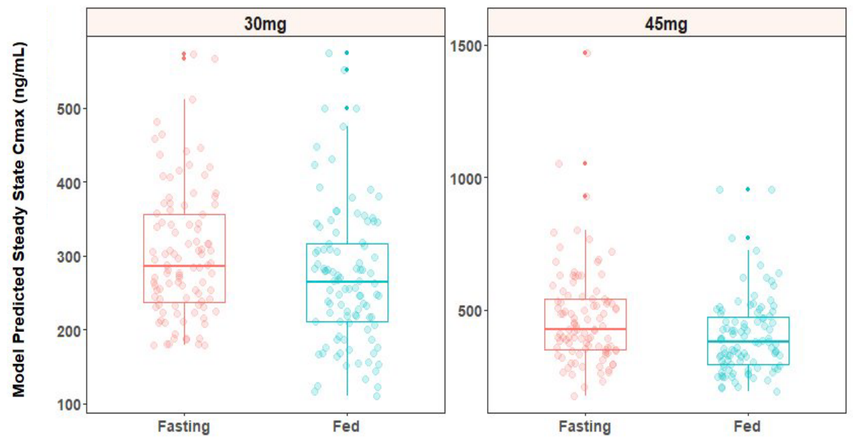

Figure 2. Model Predicted Steady State C_{max} for Vormatrigine Administered Under Fasted and Fed Conditions (Part C, FE). Results shown for modelling based on 30 mg and 45 mg doses.

Table 3. Model Predicted Steady State C_{max} for Vormatrigine Administered Under Fasted and Fed Conditions (Part C, FE)

	30 mg		45 mg	
C_{max} (ng/mL)	**Fasted (N=100)**	**Fed (N=100)**	**Fasted (N=100)**	**Fed (N=100)**
Median	285.75	264.76	427.80	378.13
Mean (Range)	301.97 (178.59, 572.79)	271.04 (110.07, 574.24)	470.67 (175.54, 1469.00)	400.85 (194.28, 954.85)

Conclusions

- **Vormatrigine demonstrated consistent safety, tolerability, and PK profiles in healthy adults, with no significant food effect.**
- **Findings from the 45 mg cohort highlight the highest multiples of the predicted therapeutically effective concentration achieved to date, with expected translation to patient benefit.**
- **These results support flexible dosing regimens up to 45 mg in the ongoing vormatrigine ENERGY program.**
- **Recent topline results from the RADIANT study in patients with focal onset seizures demonstrated robust, well-tolerated seizure reduction, and freedom on top of current standard-of-care, supporting vormatrigine's potential as a best-in-disease ASM.**

radiant

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