Vormatrigine Exhibits a Favorable Drug-Drug Interaction Profile Supporting Broad Combination Use with Antiseizure Medications

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Background

- Vormatrigine (PRAX-628), a functional state modulator that selectively targets the hyperexcitable state of CNS sodium channels, is currently in development for adult focal onset seizures and generalized epilepsy, with emerging preclinical and clinical data pointing to an ideal precision antiseizure medication (ASM) profile.
- Given that polytherapy is common in epilepsy management, understanding the drug-drug interaction (DDI) potential of vormatrigine is critical.

➢ ***A combination of preclinical studies and dedicated clinical DDI trials was undertaken to evaluate vormatrigine's liability for metabolic clearance drug interactions, with the goal of supporting its utilization alongside a broad spectrum of ASMs.***

Methods

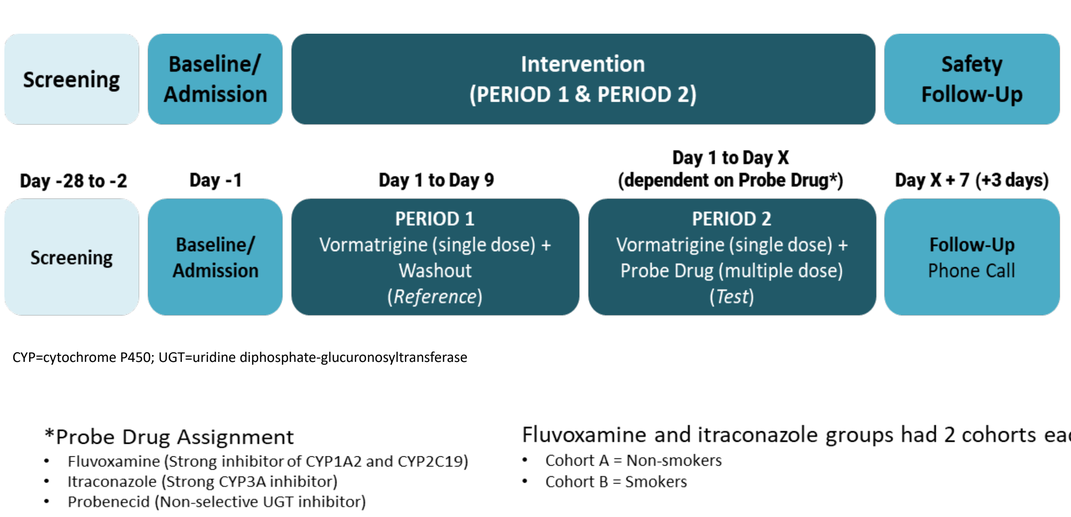
- An integrated nonclinical and clinical approach was used to assess the DDI profile of vormatrigine.

Preclinical Evaluations

- Preclinical evaluations included *in vitro* studies of cytochrome P450 (CYP450) and uridine diphosphate glucoronosyltransferase (UGT) metabolism, transporter interaction profiling, and hepatocyte induction assays.
- Key enzymes assessed included CYP1A2, 2C19, 3A4, and UGT isoforms, along with major efflux and uptake transporters.

Clinical Evaluations

- A Phase 1 PRAX-628-102 study in healthy adults evaluated how vormatrigine exposure is affected by co-administration with commonly used metabolic inhibitors:
  - Fluvoxamine (CYP1A2/2C19 inhibitor)
  - Itraconazole (CYP3A4 inhibitor)
  - Probenecid (non-selective UGT inhibitor)
- The study also assessed the effects of cigarette smoking, a known inducer of CYP1A2
- Vormatrigine PK was evaluated using non-compartmental analysis with linear mixed-effects modeling.



CYP=cytochrome P450; UGT=uridine diphosphate-glucuronosyltransferase

Figure 1. PRAX-628-102 DDI Evaluation Schema

Participant Demographics and Baseline Characteristics

- A total of 120 participants were enrolled, of which 43 were included in safety and PK analysis sets
- No clinically significant differences regarding medical and surgical history or prior medication use
- Drug screen results were negative for all participants at screening/admission, except cotinine positive for smokers
- Serology parameters were negative at screening for all participants
- Pregnancy test results were negative at screening for all females

Table 1. Summary of Demographics by Probe Group and Overall (Safety Set)

		Fluvoxamine (N=17)	Itraconazole (N=10)	Probenecid (N=16)	All (N=43)
Age (years)	Mean (SD)	36.0 (14.12)	38.4 (11.46)	35.5 (10.14)	36.4 (11.92)
Sex, n (%)	Male	14 (82.4)	6 (60.0)	11 (68.8)	31 (72.1)
	Female	3 (17.6)	4 (40.0)	5 (31.3)	12 (27.9)
Ethnicity, n (%)	Hispanic or Latino	2 (11.8)	0 (0)	1 (6.3)	3 (7.0)
	Not Hispanic or Latino	15 (88.2)	10 (100)	15 (93.8)	40 (93.0)
Race, n (%)	Asian	0 (0)	0 (0)	1 (6.3)	1 (2.3)
	White	17 (100)	9 (90.0)	14 (87.5)	40 (93.0)
	White + Asian	0 (0)	1 (10.0)	1 (6.3)	2 (4.7)
Height (cm)	Mean (SD)	180.8 (5.95)	171.9 (10.42)	176.1 (9.26)	177.0 (8.92)
Weight (kg)	Mean (SD)	77.48 (13.21)	73.90 (9.96)	75.23 (15.64)	75.81 (13.31)
BMI (kg/m^2)	Mean (SD)	23.66 (3.58)	25.00 (2.73)	24.09 (3.28)	24.13 (3.25)

Minimal DDI Risk on Combined Preclinical and Clinical Evaluation

- Preclinically, vormatrigine showed:
  - Low metabolic turnover in human hepatocytes
  - Minor involvement of CYPs and UGTs in its clearance
  - Weak inhibition of CYP2D6 and intestinal CYP3A at supratherapeutic concentrations
  - Minimal transporter interaction risk; some *in vitro* BCRP and MDR1 inhibition not expected to be clinically relevant

- Clinically, coadministration with:
  - Fluvoxamine increased vormatrigine exposure by about 15-25%, suggesting that CYP1A2 is involved in vormatrigine metabolism and that strong CYP1A2 inhibitors have a weak effect on vormatrigine exposure.
  - The effect of fluvoxamine on vormatrigine exposure was lower in smokers than in non-smokers.
  - Itraconazole had no significant impact on AUC, suggesting that vormatrigine is not a sensitive substrate of CYP3A4. Itraconazole reduced vormatrigine Cmax by nearly 40%.
  - This may reflect interaction in the GI tract between vormatrigine and one or more components (such as cyclodextrin) in the itraconazole dosing solution, potentially slowing the rate but not the extent of absorption.
  - Probenecid did not affect vormatrigine exposure, suggesting that vormatrigine is not a sensitive substrate of UGTs.

Table 2. Statistical Analysis of the Drug-Drug Interaction Between Vormatrigine and Probe Drugs

PK Parameter (Unit)	Ratio of GLSM (Test/Reference)	90% CIs for GLSM Ratio	
		Lower	*Upper*
Fluvoxamine (N =17)			
C_{max} (ng/mL)	1.17	1.044	1.304
$AUC_{0\text{-}inf}$ (h×ng/mL)	1.22	0.996	1.498
Itraconazole (N =10)			
C_{max} (ng/mL)	0.61	0.518	0.718
$AUC_{0\text{-}inf}$ (h×ng/mL)	1.06	0.913	1.226
Probenecid (N =16)			
C_{max} (ng/mL)	0.79	0.724	0.865
$AUC_{0\text{-}inf}$ (h×ng/mL)	0.89	0.851	0.926

CI = Confidence interval; GLSM= Geometric least squares mean; N= Number of participants

Safety Summary

- A single oral dose of 10 mg vormatrigine with or without concomitant treatment with 50 mg/100 mg fluvoxamine, 200 mg itraconazole, or 1000 mg probenecid was well tolerated in healthy participants.
- No deaths, SAEs, AESIs, or other clinically meaningful AEs occurred during the trial. There were 2 participants who discontinued the trial due to AEs; 1 in fluvoxamine cohort and 1 in probenecid cohort. Both AEs, vomiting and rash, were not related to the study drug.
- There were no clinically significant findings identified for clinical laboratory, vital signs, 12-lead ECGs, physical examinations, or C-SSRS.

Conclusions

- **Vormatrigine exhibits a favorable DDI profile, supported by both preclinical mechanistic studies and human PK data.**
- **Given no clinically meaningful interactions were observed with major CYP and UGT pathways, vormatrigine is well-suited for use in multi-drug epilepsy regimens, including a broad array of ASMs without the need for dose adjustments.**
- **These findings reinforce vormatrigine's potential as a best-in-class sodium channel modulator and support its continued clinical development in the ENERGY program for epilepsy.**

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