A Clinical Drug Interaction Study to Assess the Effect of Vonoprazan on the Pharmacokinetics of Midazolam

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BACKGROUND

- Vonoprazan is a potassium-competitive acid blocker (P-CAB) that is being investigated for the treatment of erosive esophagitis, non-erosive reflux disease and, in combination with antimicrobials, *Helicobacter pylori* infection.[1-4]
- Clearance of vonoprazan occurs primarily by metabolism and to a minor extent by renal elimination.[5]
  - Vonoprazan is metabolized to inactive metabolites via multiple pathways by a combination of cytochrome P450 (CYP) isoforms along with sulfo- and glucuronosyl transferases.
  - Oxidative metabolism is mainly catalyzed by CYP3A4/5 and, to a lesser extent, by CYP2B6, CYP2C19, and CYP2D6.
- *In vitro*, vonoprazan showed mild reversible and time-dependent inhibition of CYP3A.[6]
- CYP3A is involved in the metabolism of many drugs[7] and mechanistic static modelling indicated that vonoprazan may result in the inhibition of sensitive CYP3A substrates *in vivo*.[6]
- Therefore, it is important to understand the potential for vonoprazan to inhibit CYP3A *in vivo* following therapeutic doses.

OBJECTIVES

To investigate the effects of vonoprazan on the pharmacokinetics of midazolam, a sensitive CYP3A index substrate (NCT04545944).

RESULTS

Participant disposition, demographics, and characteristics

- Of 32 participants screened, 20 entered the study.
- All 20 participants completed the study and were included in the safety and pharmacokinetic populations.
- The mean age of participants was 32.3 years and the mean body mass index was 25.5 kg/m^2 (**Table 1**).
- The majority were men (12/20; 60%, **Table 1**).

Table 1. Baseline Characteristics and Demographics

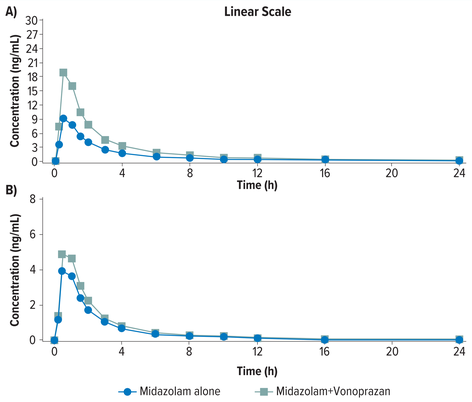
Characteristic	Study population (N=20)
Age, mean (SD)	32.3 (7.2)
Sex, n (%)	
Male	12 (60.0)
Female	8 (40.0)
Race, n (%)	
White	10 (50.0)
Black or African American	7 (35.0)
Asian	1 (5.0)
Native Hawaiian or Pacific Islander	1 (5.0)
Multi-racial	1 (5.0)
Ethnicity, n (%)	
Latinx	8 (40.0)
Not Latinx	12 (60.0)
BMI, mean (SD)	25.5 (2.3)

BMI, body mass index; SD, standard deviation.

Plasma concentrations of midazolam and 1-hydroxymidazolam

- Mean plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam were greater at all sampling times when midazolam was co-administered with vonoprazan compared with administration of midazolam alone (**Figure 2**).
- Peak mean concentrations of midazolam and 1-hydroxymidazolam were reached within 1 hour of dosing after either treatment.

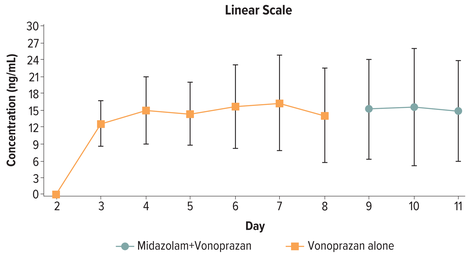
Figure 2. Mean Plasma Concentrations of A) Midazolam and B) 1-Hydroxymidazolam



Plasma concentrations of vonoprazan

- Steady state plasma concentrations of vonoprazan were achieved after 3 days of 20 mg twice-daily doses of vonoprazan, with mean C_{trough} values of 15.0, 14.3, and 15.7 ng/mL on Days 4, 5, and 6, respectively (**Figure 3**).
- Trough concentrations of vonoprazan were similar whether administered alone (Days 3–8) or following co-administration with midazolam (Days 9–11).

Figure 3. Mean Trough Plasma Concentrations of Vonoprazan



Effect of vonoprazan on midazolam pharmacokinetics

- Plasma exposure of midazolam increased following coadministration with vonoprazan, as reflected by 1.9-fold increases in C_{max} and AUC values (**Tables 2 and 3**).
- Plasma exposure of 1-hydroxymidazolam also increased following coadministration with vonoprazan, but to a lesser extent (1.3- to 1.4-fold) than midazolam exposure (**Tables 2 and 3**).
- Elimination of midazolam and 1-hydroxymidazolam was similar when midazolam was administered alone or concomitantly with vonoprazan, as reflected by no meaningful change in $t_{1/2}$ for either.

Table 2. Plasma Pharmacokinetic Parameter Estimates for Midazolam and 1-Hydroxymidazolam

	Treatment	
Parameter (units)	Midazolam Alone (N=20)	Midazolam + Vonoprazan (N=20)
Midazolam		
C_{max} (ng/mL)	10.3 (3.61)	20.3 (9.55)
$AUC_{(0-t)}$ (ng h/mL)	24.2 (8.8)	50.7 (39.8)
$AUC_{(0-inf)}$ (ng h/mL)	25.5 (9.00)	52.3 (39.8)
t_{max} (h) median (min, max)	0.67 (0.25, 1.00)	0.63 (0.50, 1.00)
$t_{1/2}$ (h)	6.21 (1.95)	6.58 (1.45)
1-Hydroxymidazolam		
C_{max} (ng/mL)	4.76 (2.42)	5.59 (2.00)
$AUC_{(0-t)}$ (ng h/mL)	9.7 (4.2)	13.1 (5.9)
$AUC_{(0-inf)}$ (ng h/mL)	10.5 (4.53)	13.8 (7.08)
t_{max} (h) median (min, max)	0.75 (0.25, 1.00)	0.75 (0.50, 1.00)
$t_{1/2}$ (h)	4.54 (1.96)	5.30 (3.16)

Data are presented as mean (standard deviation) unless otherwise specified.

AUC_{0-inf}, area under the plasma concentration versus time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal phase half-life; t_{max}, time to maximum concentration.

Table 3. Statistical Analysis of Plasma Pharmacokinetic Parameter Estimates for Midazolam and 1-Hydroxymidazolam

	LS means		
Parameter (units)	Midazolam alone	Midazolam + vonoprazan	Mean ratio (90% CI)
Midazolam			Decreased / Increased
C_{max} (ng/mL)	9.7	18.8	1.93 (1.61, 2.33)
$AUC_{(0-t)}$ (ng h/mL)	22.7	43.7	1.92 (1.53, 2.42)
$AUC_{(0-inf)}$ (ng h/mL)	24.0	45.4	1.89 (1.51, 2.37)
1-Hydroxymidazolam			
C_{max} (ng/mL)	4.2	5.2	1.25 (0.98, 1.59)
$AUC_{(0-t)}$ (ng h/mL)	8.9	12.2	1.37 (1.11, 1.70)
$AUC_{(0-inf)}$ (ng h/mL)	9.6	12.6	1.31 (1.03, 1.67)

AUC_{0-inf}, area under the plasma concentration versus time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; C_{max}, maximum concentration; LS, least square.

Safety

- Overall, 6 treatment-emergent adverse events (TEAEs) were reported in 4 subjects after receiving vonoprazan alone; 3 TEAEs were reported in 2 subjects after vonoprazan and midazolam coadministration. All TEAEs were mild in severity and resolved by the end of the study.
- Two TEAEs (somnolence and feeling drunk, in the same patient) were reported to be related to midazolam after vonoprazan and midazolam co-administration; no adverse events were considered related to vonoprazan.
- There were no deaths or serious TEAEs reported during the study, and no subjects discontinued from the study due to a TEAE.

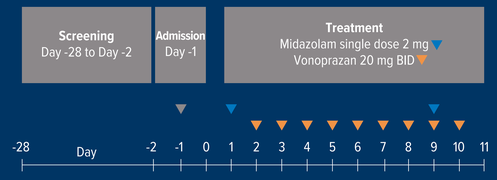
CONCLUSIONS

- Vonoprazan was a weak inhibitor of CYP3A4 *in vivo*, with a slightly less than two-fold increase in plasma exposure of midazolam after repeated doses of vonoprazan compared to when midazolam was given alone.
- These data suggest that plasma concentrations of other drugs that are primarily metabolized by CYP3A4 may increase when administered concomitantly with vonoprazan.
- Lower doses of sensitive CYP3A4 substrates with a narrow therapeutic index should be used when administered concomitantly with vonoprazan.
- Vonoprazan and midazolam were well tolerated when administered alone or concomitantly.

METHODS

- This was a Phase 1, open-label, clinical drug-drug interaction study.
- Healthy volunteers were given a single oral dose of midazolam 2 mg (syrup) on Day 1 and again on Day 9, and vonoprazan 20 mg twice daily (oral tablets) on Days 2 through 10 (**Figure 1**).
- Blood samples to measure midazolam and 1-hydroxymidazolam plasma concentrations were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours following midazolam dosing on Days 1 and 9.
  - Two additional blood samples were collected on Day 9 at 36 and 48 hours after dosing.
  - Blood samples to measure vonoprazan trough plasma concentrations were collected pre-dose on Days 2–11.
- PK parameters (AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, and $t_{1/2}$) for midazolam and 1-hydroxymidazolam were calculated using noncompartmental analysis.
- The effect of vonoprazan on the pharmacokinetics of midazolam was assessed using a linear mixed model performed on the natural log transformed values of C_{max}, AUC_{0-t} and AUC_{0-inf} for midazolam and 1-hydroxymidazolam.
  - Treatment was the fixed effect and subject was the random effect.
  - Treatment differences were expressed using point estimates and 90% confidence intervals with no effect boundaries of 0.8–1.25.

Figure 1. Clinical Study Design



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Acknowledgements

Medical writing support was provided by Abigail Killen-Devine Ph.D. and editorial support by Kyle Lambe, both of Synergy Medical Communications, funded by Phathom Pharmaceuticals in accordance with Good Publications Practice (GPP3) guidelines.

Conflicts of interest

DJM, **PB**, **NS** and **ED** are employed by Phathom Pharmaceuticals. **NS** and **ED** also report stock/options in Phathom Pharmaceuticals. **CS** discloses compensation from Phathom Pharmaceuticals as a consultant, advisory board member and speaker.

Meeting details

Presented at the Digestive Disease Week 2022®, May 21–24, San Diego, CA.