Pharmacodynamics and Pharmacokinetics of the Potassium-Competitive Acid Blocker Vonoprazan and the Proton Pump Inhibitor Lansoprazole in U.S. Subjects

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BACKGROUND

- Potassium-competitive acid blockers (P-CABs) suppress gastric acid secretion by competitively inhibiting parietal cell H,K-ATPase (the proton pump) via a mechanism different than proton pump inhibitors (PPIs).
- Vonoprazan is a P-CAB approved for use in Japan and other countries. Most studies of this compound have been conducted in Japan, and no studies have provided comparative pharmacodynamic data for vonoprazan and PPIs in Western subjects.

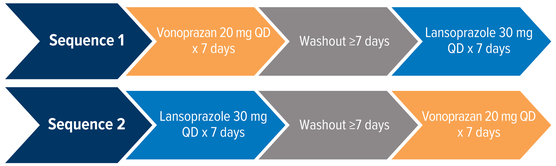
OBJECTIVES

To assess the pharmacodynamics and pharmacokinetics of vonoprazan and lansoprazole in healthy U.S. subjects (NCT04729101).

METHODS

- Randomized, open-label, crossover design.
- Participants were *H. pylori*-negative, non-smoking, healthy subjects aged 18–55 years.
- Subjects were randomized 1:1 to vonoprazan followed by lansoprazole or lansoprazole followed by vonoprazan. Vonoprazan 20 mg tablets and lansoprazole 30 mg capsules were administered orally once daily for a 7-day period, separated by a washout interval of ≥7 days (**Figure 1**).

Figure 1. Clinical Study Design



- Subjects fasted overnight for ≥10 hours and study drug was given each morning, within one hour of the dosing time established on day 1 of the 7-day period.
- Standardized meals and snacks were provided at the same times relative to dosing each day.
- On days 1 and 7 of each 7-day period, breakfast was held and subjects received meals at 4 hours and 9 hours after their dose, and a snack at 12 hours after their dose.

QD, once daily.

Pharmacodynamics

- Intragastric pH was recorded continuously for 24 hours the day before the first 7-day period and on days 1 and 7 of each 7-day period.
- Intragastric pH time and holding-time ratio (percentage of time pH above threshold) for pH >4, >5, and >6, and mean intragastric pH were assessed.
- Mean intragastric pH 12–24 hours after dosing was determined to assess nocturnal acidity.

Pharmacokinetics

- Blood samples to measure plasma vonoprazan and lansoprazole concentrations were collected on days 1 and 7 during each 7-day period.
- Parameters assessed included area under the plasma concentration-time curve (AUC), maximum concentration (C_{max}), time to C_{max} (t_{max}), and first-order terminal-elimination half-life ($t_{½}$).

RESULTS

- A total of 44 subjects were enrolled (**Table 1**).
  - One subject discontinued prematurely and was not included in any analysis; 43 subjects were included in the baseline pH analysis.

Table 1. Demographics (n=44)

Women	12 (27%)
Mean age	36 years
Race/ethnicity, n (%)	
White	32 (73%)
Black	5 (11%)
Latinx	21 (48%)
Mean body mass index	25.5 kg/m^2
CYP2C19 poor metabolizer	1

Pharmacodynamics

- The primary endpoint of 24-hour holding-time ratio for pH>4 on day 7 was significantly higher with vonoprazan than lansoprazole [87.8% vs. 42.3% (p<0.0001)] as were the other pharmacodynamic endpoints on days 1 and 7 (**Table 2**).
- Mean intragastric pH 0–2 hours after initial dose on day 1 was similar for vonoprazan and lansoprazole (2.2 vs. 2.1), with separation beginning ~2.5 hours after the first dose (**Figure 2**).
- Mean intragastric pH from 12–24 hours was also higher with vonoprazan than lansoprazole on day 1 (4.6 ± 1.5 vs. 2.5 ± 0.9) and day 7 (5.6 ± 1.2 vs. 3.4 ± 1.4).

Figure 2. Mean 24-Hour Intragastric pH Profiles for Vonoprazan 20 mg and Lansoprazole 30 mg on Day 1 and Day 7 with Comparison to Baseline

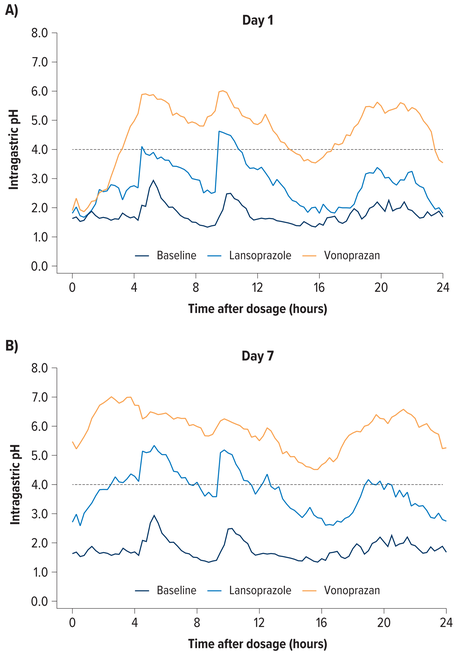


Table 2. Mean 24-Hour Intragastric pH Holding Time Ratios and Intragastric pH with Differences in Least Squares Means for Vonoprazan 20 mg and Lansoprazole 30 mg Once-Daily

	Baseline	Day 1			Day 7		
		Vonoprazan	Lansoprazole	Difference (95% CI)*	Vonoprazan	Lansoprazole	Difference (95% CI)*
Subjects (N)	43	40[a]	41[b]		40[c]	38[d]	
pH >4 (mean ± SD; %)	3.9 ± 3.8	62.4 ± 23.4	22.6 ± 17.3	39.0 (31.9–46.0)	87.8 ± 15.7	42.3 ± 25.6	44.6 (37.6–51.7)
pH >5 (mean ± SD; %)	2.5 ± 2.7	52.4 ± 25.2	14.6 ± 13.8	37.1 (29.5–44.7)	79.8 ± 19.9	28.4 ± 24.2	50.9 (43.6–58.2)
pH >6 (mean ± SD; %)	1.3 ± 1.9	33.1 ± 20.6	7.4 ± 8.5	25.4 (19.2–31.6)	62.5 ± 22.1	16.4 ± 20.6	46.3 (38.2–54.4)
pH (mean ± SD)	1.8 ± 0.3	4.6 ± 1.1	2.8 ± 0.8	1.7 (1.4–2.0)	5.9 ± 0.8	3.8 ± 1.2	2.1 (1.7–2.4)

[a]3 excluded (study personnel failed to start pH recording).
[b]2 excluded (study personnel failed to start pH recording-1; premature discontinuation due to nausea-1).
[c]3 excluded did not take study drug that morning-2; pH recorder malfunction due to showering-1).
[d]5 excluded (premature discontinuation due to nausea-1 and personal reasons-1; did not take study drug that morning-2; pH recorder malfunction due to showering-1).
*p<0.0001 for all differences.

Table 3. Pharmacokinetic Parameters for Vonoprazan 20 mg and Lansoprazole 30 mg Once-Daily on Days 1 and 7

	Vonoprazan	Lansoprazole
Day 1		
Subjects (N)	40	41
$AUC_{0–24}$ (mean ± SD; ng*h/mL)	201 ± 81	2677 ± 1357
$AUC_{0–inf}$ (mean ± SD; ng*h/mL)	230 ± 99	2679 ± 1361
C_{max} (mean ± SD; ng/mL)	21.8 ± 8.3	1110 ± 412
T_{max} (median, range; h)	2.0, 1.0–5.0	1.5, 0.8–4.0
$T_{½}$ (mean ± SD; h)	7.9 ± 1.9	1.4 ± 0.5
Day 7		
Subjects (N)	40	38
$AUC_{0–tau}$ (mean ± SD; ng*h/mL)	261 ± 104	3246 ± 2396
C_{max} (mean ± SD; ng/mL)	27.4 ± 10.0	1164 ± 507
T_{max} (median, range; h)	2.0, 1.5–5.0	1.5, 0.8–4.0

AUC, area under plasma-concentration curve; C_{max}, maximum plasma concentration; inf, infinity; tau, end of dosing period; T_{max}, time to maximum plasma concentration; $T_{½}$, terminal elimination half-life.

CONCLUSIONS

- **Vonoprazan provided more rapid, potent, and prolonged inhibition of intragastric acidity than lansoprazole in healthy *H. pylori*-negative subjects from the U.S.**
  - The proportion of the 24-hour period during which intragastric pH was >4 was nearly 3-fold higher with vonoprazan than lansoprazole after a single dose, and approximately 2-fold higher after the 7th once-daily dose.
  - Differences in reduction of intragastric acidity were maintained throughout the 24-hour dosing interval: nocturnal intragastric acidity also was markedly lower with vonoprazan than with lansoprazole.
- **Future trials are needed to assess the impact of these pharmacodynamic differences on clinical outcomes in Western populations.**

Potential Conflicting Interests

LL Consulting: Phathom Pharmaceuticals; **PS** Consulting: Phathom Pharmaceuticals; **DJM** Employee of Phathom Pharmaceuticals; **BH** Employee of Phathom Pharmaceuticals; **EL** Employee of Phathom Pharmaceuticals; **NS** Employee of Phathom Pharmaceuticals; **CH** Consulting: Phathom Pharmaceuticals.

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