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

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INTRODUCTION: **We assessed pharmacodynamics and pharmacokinetics of a potassium-competitive acid blocker and proton pump inhibitor in US subjects.**

METHODS: **Healthy adults were randomized to 7-day periods of vonoprazan 20 mg once daily followed by lansoprazole 30 mg once daily or the reverse order, separated by ≥ 7 days of washout.**

RESULTS: **Vonoprazan (N = 40) had higher proportions of 24-hour periods with intragastric pH > 4 than lansoprazole (N = 41,38) on day 1 (62.4% vs 22.6%, *P* < 0.0001) and day 7 (87.8% vs 42.3%, *P* < 0.0001). Separation in pH started ~2.5 hours after the first dose.**

DISCUSSION: **Vonoprazan provided more rapid and potent inhibition of intragastric acidity than lansoprazole in US subjects.**

Am J Gastroenterol 2022;117:1158–1161. https://doi.org/10.14309/ajg.0000000000001735

INTRODUCTION

Potassium-competitive acid blockers (PCABs) suppress gastric acid secretion by competitively inhibiting parietal cell hydrogen, potassium-adenosine triphosphatase (H,K-ATPase, also called the proton pump) through a mechanism different than proton pump inhibitors (PPIs) (Figure 1) (1–4).

Vonoprazan is a PCAB 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. We performed a randomized crossover study assessing pharmacodynamics and pharmacokinetics of vonoprazan and lansoprazole in healthy US subjects.

METHODS

Study design

Participants were *Helicobacter pylori*-negative nonsmoking healthy subjects aged 18–55 years. Subjects were randomized 1:1 using a computer-generated sequence with concealed allocation to vonoprazan followed by lansoprazole or lansoprazole followed by vonoprazan. Open-label 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.

Subjects fasted overnight for ≥10 hours, and study drug was given each morning, within 1 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.

The study was approved by Advarra Institutional Review Board (Columbia, MD). All subjects provided written informed consent.

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 (Sleuth/ZepHr, Sandhill Scientific, Highlands Ranch, CO). Intragastric pH time and holding-time ratio (percentage 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, maximum concentration (C_{max}), time to C_{max} (T_{max}), and first-order terminal-elimination half-life ($t_{½}$).

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Received November 28, 2021; accepted March 14, 2022; published online March 16, 2022

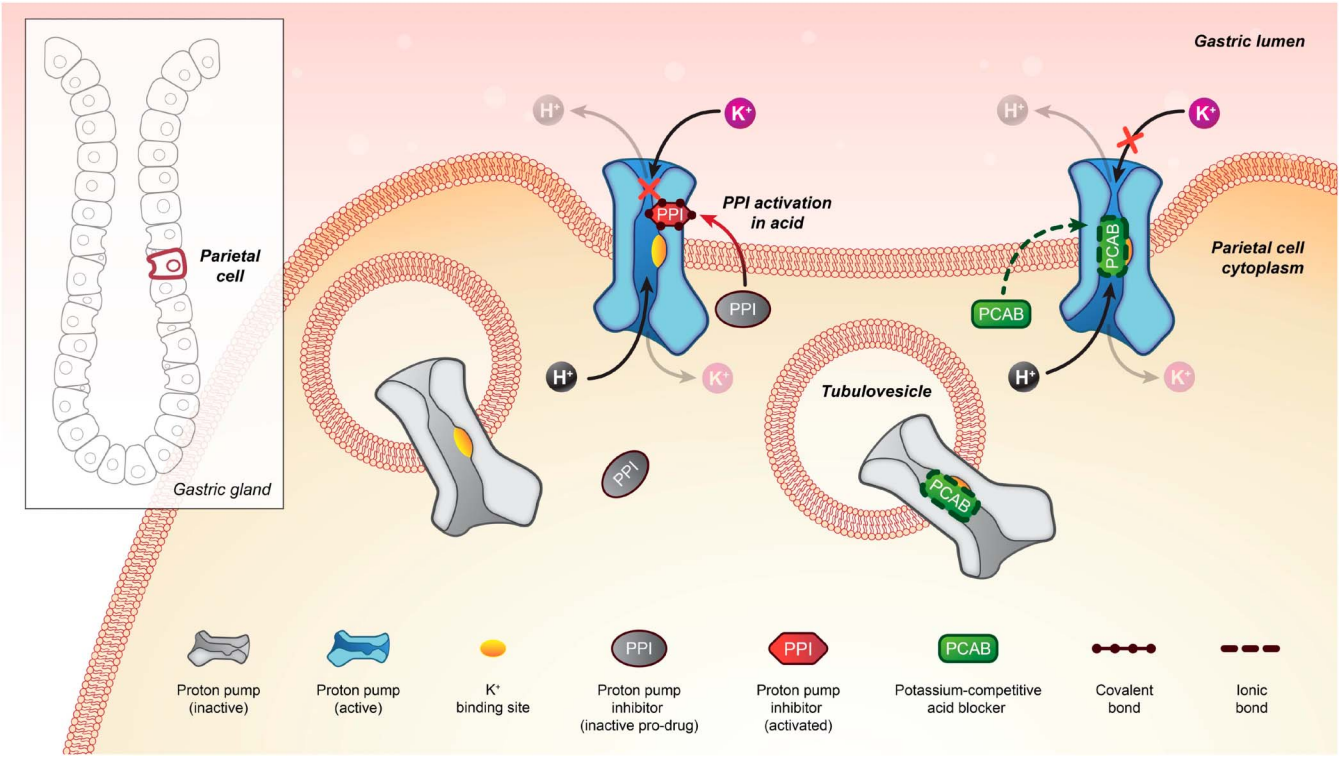

Figure 1. Mechanism of action of proton pump inhibitors (PPIs) and potassium-competitive acid blockers (PCABs) in a parietal cell. Proton pumps (H^+, K^+-ATPase) are stored in tubulovesicles in the cytoplasm in an inactive state. Activation of pumps occurs after their insertion into the extracytoplasmic secretory canalicular membrane at the luminal border. PPIs are prodrugs that are converted to sulfenamides, which covalently bind to cysteines on active proton pumps, blocking exchange of hydrogen and potassium ions. PPIs require an acidic environment for activation, and because the extracytoplasmic secretory canaliculus is acidic, it is the site of PPI accumulation and activation. PCAB accumulation and binding are not pH-dependent, and PCABs bind to both inactive and active proton pumps (in cytoplasmic and extracytoplasmic locations, respectively). PCABs act through ionic (reversible) binding, competing with luminal potassium ions that are necessary for hydrogen ion exchange by blocking access of potassium ions to the potassium-binding site of the pump (1–4).

Statistical analysis

The primary endpoint was 24-hour holding-time ratio for pH > 4 on day 7. The other key pharmacodynamic parameters were 24-hour holding-time ratio for pH > 4 on day 1 and 24-hour mean intragastric pH on days 1 and 7. Differences between vonoprazan and lansoprazole holding-time ratio and intragastric pH were calculated using analysis of variance with treatment, sequence, and period as fixed effects and subject-within-sequence as a random effect.

Sample size of 40 subjects (20 in each sequence group [vonoprazan-lansoprazole, lansoprazole-vonoprazan]) was required, based on detecting a difference between groups of ≥10% in pH > 4 holding-time ratio on day 7, assuming common SD of 17%, correlation coefficient between periods of 0.5, and a 10% (4 of 40 subjects) dropout rate.

RESULTS

Forty-four subjects were enrolled:12 (27%) women; mean age = 36 years; 32 (73%) White, 5 (11%) Black, and 21 (48%) Latinx; and mean body mass index = 25.5 kg/m^2. One subject was a poor CYP2C19 metabolizer. One subject discontinued prematurely and was not included in any analysis. Forty-three subjects were included in the baseline analysis, 40 in day-1 and day-7 vonoprazan analyses, and 41 and 38 in day-1 and day-7 lansoprazole analyses, respectively (Table 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 1). Mean intragastric pH 0–2 hours after initial dosage 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 to 24 hours also was 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).

Pharmacokinetics

Pharmacokinetic results are shown in Table 1. Mean $t_{½}$ was 7.9 hours for vonoprazan and 1.4 hours for lansoprazole.

DISCUSSION

This study demonstrated vonoprazan provided significantly more potent inhibition of intragastric acidity than lansoprazole in healthy US subjects. The proportion of a 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 on day 7. Differences in reduction of intragastric acidity were maintained throughout the 24-hour dosing

Table 1. Pharmacodynamic and pharmacokinetic results for vonoprazan 20 mg and lansoprazole 30 mg once daily

	Pharmacodynamics: 24-hour intragastric pH measurements				Pharmacokinetics		
	Holding-time ratio pH > 4 (mean ± SD %)	Holding-time ratio pH > 5 (mean ± SD %)	Holding-time ratio pH > 6 (mean ± SD %)	pH (mean ± SD)	AUC (mean ± SD ng*hr/mL)	C_{max} (mean ± SD ng/mL)	T_{max} (median, range; hrs)
Baseline (N = 43)	3.9 ± 3.8	2.5 ± 2.7	1.3 ± 1.9	1.8 ± 0.3	—	—	—
Day 1 vonoprazan (N = 40[a])	62.4 ± 23.4	52.4 ± 25.2	33.1 ± 20.6	4.6 ± 1.1	201 ± 81	21.8 ± 8.3	2.0, 1.0–5.0
Day 1 lansoprazole (N = 41[b])	22.6 ± 17.3	14.6 ± 13.8	7.4 ± 8.5	2.8 ± 0.8	2,677 ± 1,357	1,110 ± 412	1.5, 0.8–4.0
Difference in least-squares means (95% CI)[e]	39.0 (31.9–46.0)	37.1 (29.5–44.7)	25.4 (19.2–31.6)	1.7 (1.4–2.0)	—	—	—
Day 7 vonoprazan (N = 40[c])	87.8 ± 15.7	79.8 ± 19.9	62.5 ± 22.1	5.9 ± 0.8	261 ± 104	27.4 ± 10.0	2.0, 1.5–5.0
Day 7 lansoprazole (N = 38[d])	42.3 ± 25.6	28.4 ± 24.2	16.4 ± 20.6	3.8 ± 1.2	3,246 ± 2,396	1,164 ± 507	1.5, 0.8–4.0
Difference in least-squares means (95% CI)[e]	44.6 (37.6–51.7)	50.9 (43.6–58.2)	46.3 (38.2–54.4)	2.1 (1.7–2.4)	—	—	—

AUC, area under the plasma-concentration curve (0–24 hours, day 1; 0-tau, day 7); C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration.
[a]Three excluded (study personnel failed to start pH recording).
[b]Two excluded (study personnel failed to start pH recording—1; premature discontinuation because of nausea—1).
[c]Three excluded (did not take study drug that morning—2; pH recorder malfunction because of showering—1).
[d]Five excluded (premature discontinuation because of nausea—1 and personal reasons—1; did not take study drug that morning—2; pH recorder malfunction because of showering—1).
[e]$P < 0.0001$ for all differences.

interval: Nocturnal intragastric acidity also was markedly lower with vonoprazan than with lansoprazole.

Although lansoprazole's T_{max} was 1.5 hours, the pharmacokinetic profile of PPIs does not translate into concurrent pharmacodynamic effect because PPIs are prodrugs that need to be converted to sulfenamide derivatives before binding to proton pumps (1). Vonoprazan's T_{max} was similar to lansoprazole at 2.0 hours. However, because PCABs are not prodrugs, their pharmacodynamic effect more closely mirrors their pharmacokinetic profile, as suggested by the separation in intragastric pH between vonoprazan and lansoprazole beginning at ~2.5 hours after the first dose.

The longer half-life of vonoprazan than lansoprazole (7.9 vs 1.4 hours) probably also helps account for its longer duration of gastric acid inhibition. Mean intragastric pH 24 hours after the sixth daily doses of vonoprazan and lansoprazole were 5.5 and 2.7, respectively.

The pharmacokinetic and pharmacodynamic profiles for vonoprazan 20 mg were similar to those reported in studies from Japan and the United Kingdom (5–7). Our 24-hour holding-time results for lansoprazole fall just below the lower end of ranges reported for lansoprazole in other US and European studies (8–11). Possible explanations include the following: Our study was restricted to *H. pylori*-negative subjects, and PPIs provide greater acid inhibition in *H. pylori*-positive individuals; and

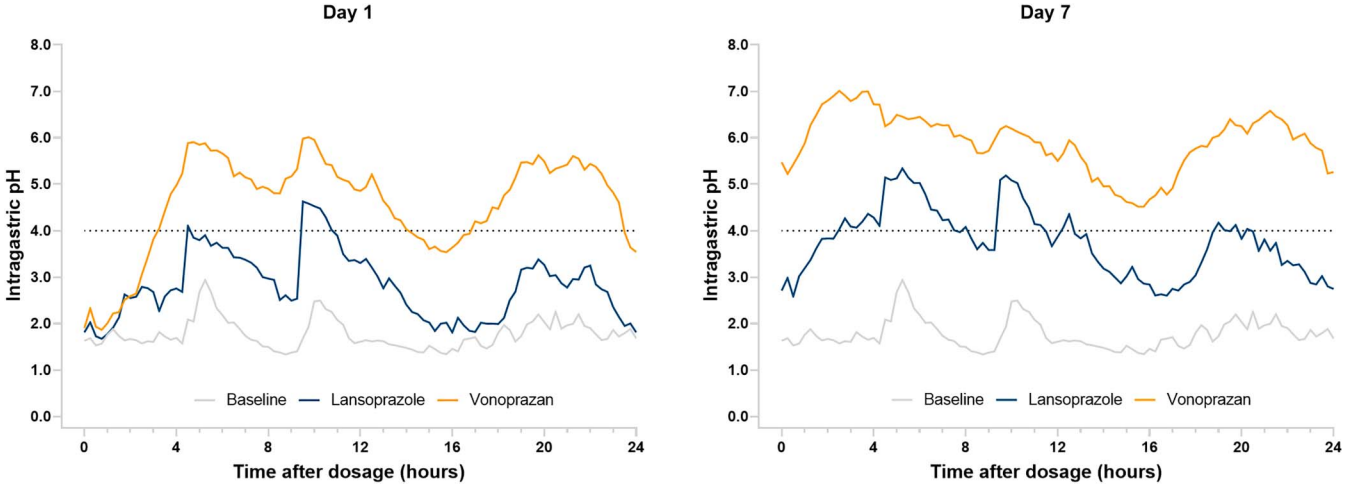

Figure 2. Mean 24-hour intragastric pH profiles for vonoprazan 20 mg and lansoprazole 30 mg on day 1 and day 7 in comparison with baseline.

subjects received lansoprazole 4 hours before a meal to eliminate the food effect on pH, but PPIs are more effective when taken soon before meals. Previous studies in Japanese studies also have shown significantly greater holding-time ratios with vonoprazan 20 mg vs esomeprazole 20 mg and rabeprazole 10 mg (7).

In summary, vonoprazan provided more rapid, potent, and prolonged inhibition of intragastric acidity than lansoprazole in healthy *H. pylori*-negative subjects from the United States. Future trials are needed to assess the impact of these pharmacodynamic differences on clinical outcomes in Western populations.

CONFLICTS OF INTEREST

Guarantor of the article: Loren Laine, MD.

Specific author contributions: L.L.: planning study, interpreting data, and drafting manuscript; P.S.: interpreting data and drafting manuscript; D.M.: planning study, interpreting data, and critical revision of manuscript; B.H.: planning study, interpreting data, and critical revision of manuscript; E.K.: planning study, interpreting data, and critical revision of manuscript; N.S.: planning study, interpreting data, and critical revision of manuscript; C.W.H.: interpreting data and drafting manuscript.

Financial support: Study performed by a clinical research organization (Celerion, Tempe, AZ) and funded by Phathom Pharmaceuticals (Buffalo Grove, IL). The sponsor participated in study design and analysis, and the authors from Phathom Pharmaceuticals participated in writing the manuscript. The manuscript was drafted by the authors without external writing assistance.

Potential competing interests: L.L.: consulting: Phathom Pharmaceuticals. P.S.: consulting: Phathom Pharmaceuticals. D.J.M.: employee of Phathom Pharmaceuticals. B.H.: employee of Phathom Pharmaceuticals. E.L.: employee of Phathom Pharmaceuticals. N.S.: employee of Phathom Pharmaceuticals. C.H.: consulting: Phathom Pharmaceuticals.

Clinical trial number: CLINICALTRIALS.GOV, NCT04729101.

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