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ESOPHAGUS

Vonoprazan is Efficacious for Treatment of Heartburn in Non-erosive Reflux Disease: A Randomized Trial

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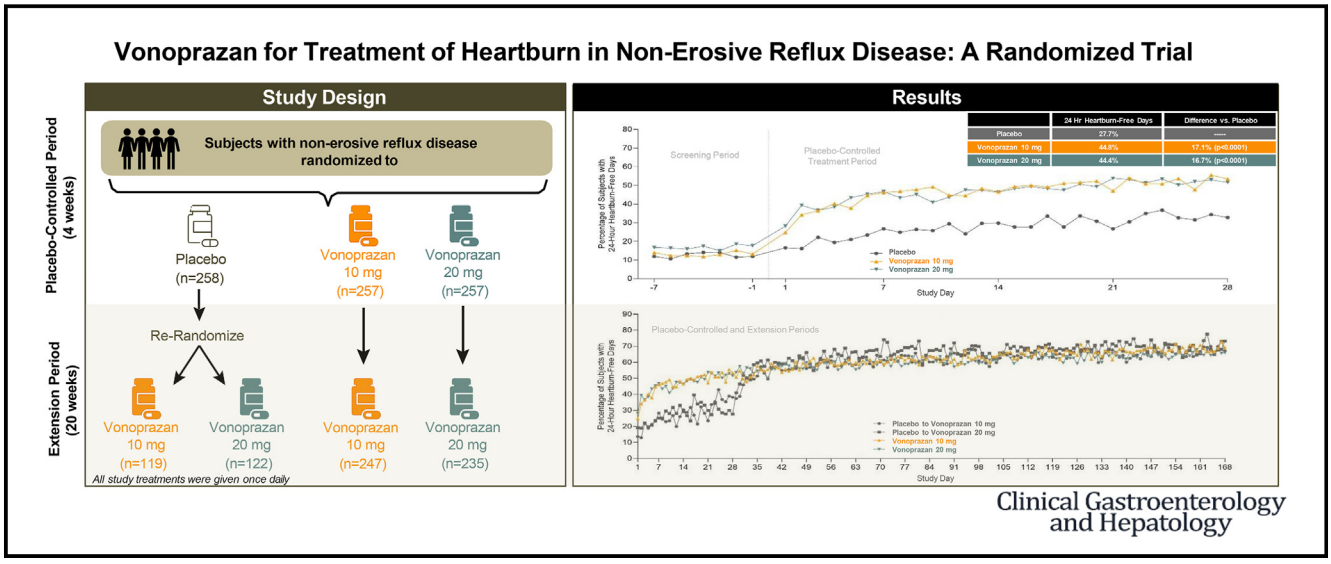

BACKGROUND & AIMS: **Potassium-competitive acid blockers have documented efficacy for erosive esophagitis. We performed a randomized trial in United States subjects diagnosed with non-erosive reflux disease of vonoprazan vs placebo for 4 weeks, followed by a 20-week active-treatment extension.**

METHODS: **Adult subjects with heartburn ≥4 days/week during screening without erosive esophagitis on endoscopy were randomized to placebo, vonoprazan 10 mg, or vonoprazan 20 mg. After 4 weeks, subjects on placebo were re-randomized to vonoprazan 10 mg or 20 mg, and those already on vonoprazan continued at the same dose for 20 weeks. Electronic diaries were completed twice daily. The primary endpoint was percentage of days without daytime or nighttime heartburn (24-hour heartburn-free days).**

RESULTS: **Among 772 randomized subjects, the percentage of 24-hour heartburn-free days was 27.7% for placebo vs 44.8% for vonoprazan 10 mg (least squares mean difference, 17.1%; $P < .0001$) and 44.4% for vonoprazan 20 mg (least squares mean difference, 16.7%; $P < .0001$). Differences in percentage of subjects with a 24-hour heartburn-free day for vonoprazan 10 mg vs placebo and vonoprazan 20 mg vs placebo were 8.3% and 11.6% on day 1 and 18.1% and 23.2% on day 2.**

Abbreviations used in this paper: GERD, gastroesophageal reflux disease; IQR, interquartile range; NERD, non-erosive reflux disease; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; U.S, United States.

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The mean/median percentages of 24-hour heartburn-free days over the extension period were similar across the 4 study arms: 61%-63%/76%-79%.

CONCLUSIONS: **Vonoprazan reduced heartburn symptoms in subjects diagnosed with non-erosive reflux disease, with the benefit appearing to begin as early as the first day of therapy. Treatment effect persisted after the initial 4-week placebo-controlled period throughout the 20-week extension period. The 2 vonoprazan doses (10 mg and 20 mg) were similar in efficacy. (ClinicalTrials.gov: NCT05195528)**

Keywords: Gastroesophageal Reflux; Heartburn; Potassium-competitive Acid Blocker.

Patients who have typical symptoms (heartburn, regurgitation) of gastroesophageal reflux disease (GERD) without erosive esophagitis at endoscopy are commonly classified as having non-erosive reflux disease (NERD). Proton pump inhibitors (PPIs) are the most commonly prescribed medication for GERD, with relief of heartburn that is superior to placebo and H2-receptor antagonists,[1,2] but their efficacy is less for NERD than erosive esophagitis.[1,3] One reason PPIs may be less effective in patients with NERD is that a proportion of these patients do not have acid reflux but rather have functional heartburn or symptoms related to non-acid/weakly acid reflux.

A potential alternative to PPI therapy is a potassium-competitive acid blocker (PCAB), a new class of antisecretory agents that provide more potent inhibition of gastric acid secretion than PPIs.[4] A small observational study found that 18 of 26 patients (69%) with PPI-resistant NERD had improvement in symptoms when changing to the PCAB vonoprazan.[5] However, initial randomized trials in patients with NERD from Japan failed to show benefit of the PCAB vonoprazan vs placebo in their primary endpoints.[6,7] We therefore performed a randomized trial of United States (U.S.) patients diagnosed with NERD to assess heartburn control with vonoprazan vs placebo over 4 weeks followed by a 20-week active-treatment extension period to assess longer term treatment effect of vonoprazan in patients with NERD.

Methods

The study was conducted by a clinical research organization (PPD, Inc) and funded by Phathom Pharmaceuticals. The study was approved by the institutional review boards of the 91 participating centers (see Supplementary Appendix for list of investigators and centers). All authors had access to the study data and reviewed and approved the final manuscript.

Subjects

Subjects ≥18 years old who had a diagnosis of symptomatic GERD with heartburn as their predominant symptom and onset ≥6 months prior to screening were eligible if they reported heartburn ≥4 days during any consecutive 7-day period during screening and did not have erosive esophagitis on endoscopy performed during screening (esophageal biopsies were not performed). Other key exclusion criteria included H. pylori infection (subjects underwent H. pylori testing during screening and were required to be free of antibiotics and bismuth ≥4 weeks and of H2-receptor antagonists and PPIs ≥2 weeks before testing) and Barrett's esophagus.

Treatment

Eligible subjects were enrolled and randomly assigned with concealed allocation by site investigators using an interactive response technology to access a central randomization sequence generated with SAS software Version 9.4 (SAS Institute, Inc) by PPD, Inc. Patients were randomized in a 1:1:1 ratio in the 4-week placebo-controlled period to vonoprazan 10 mg, vonoprazan 20 mg, or placebo once-daily in blocks of 6. For the extension period, those initially given vonoprazan remained on the same dose, whereas those on placebo were re-randomized in a 1:1 ratio to vonoprazan 10 mg or 20 mg once daily in blocks of 4. Randomization was not stratified. Study therapies had identical appearance and subjects, providers, and those assessing outcomes were all blinded to treatment allocation. Subjects also received rescue antacid (Gelusil, WellSpring Pharmaceutical) during the screening and active-treatment portions of the study to be used as needed by subjects for heartburn symptoms. Compliance was assessed by questioning of subjects and counting returned capsules at site visits. Noncompliance was defined as <80% or >120% use of study drug.

Study Flow

The study took place at ambulatory locations at 91 sites in the U.S. The screening period prior to randomization was ≤5 weeks. Eligible patients then entered the 4-week placebo-controlled period followed by the 20-week extension period. A 4-week follow-up period followed the 24 weeks of study treatment. Subjects completed an electronic diary for heartburn and use of rescue antacids twice daily (every morning upon waking

[to record the previous night's maximum heartburn severity] and every night before bedtime [to record that day's maximum heartburn severity]) throughout the screening period, placebo-controlled period, extension period, and follow-up period. Heartburn severity was graded on a scale of 0 (no heartburn) to 4 (very severe heartburn).

Endpoints

The primary endpoint was percentage of days without daytime or nighttime heartburn (24-hour heartburn-free days) over the 4-week placebo-controlled treatment period. The secondary endpoint was percentage of days without rescue antacid use over the placebo-controlled treatment period. Other exploratory endpoints assessed during the placebo-controlled period included percentage of days without daytime and without nighttime heartburn, mean severity of heartburn, and time to onset of sustained resolution of heartburn (period of $\geq$7 consecutive days with no heartburn). Exploratory endpoints for the extension period included percentage of days without heartburn, daytime heartburn, or nighttime heartburn; percentage of days without rescue antacid use; and mean severity of heartburn. Percentage of days without heartburn and without rescue antacid use were also assessed during the follow-up period.

A diary day was considered heartburn-free if both morning and evening diary entries were completed and were heartburn-free and no rescue antacid, H2 receptor antagonist, or PPI use was reported. For subjects who discontinued treatment before completing the placebo-controlled period, percentage of heartburn-free days after treatment discontinuation was imputed as the percentage of heartburn-free days during the screening period. For subjects with less than 4 days with diary entries during the placebo-controlled period, percentage of heartburn-free days was imputed as the percentage of heartburn-free days during the screening period.

Statistical Analysis

A sample size of 250 subjects per treatment group provided >90% power at the 0.05 2-sided level of significance using a 2-sample *t*-test assuming efficacy of 50% for a vonoprazan dose in the percentage of days without daytime or nighttime heartburn over the 4-week placebo-controlled treatment period and a difference of 20% between a vonoprazan dose and placebo with a common standard deviation of 35% (based on U.S. placebo-controlled studies of PPIs[8–11]).

Efficacy analyses for the placebo-controlled and extension periods were conducted on the intent-to-treat population, defined as all subjects randomized into that period who received at least 1 dose of study drug, categorized based on study drug assignment. Safety analyses were conducted on randomized subjects who received at least 1 dose of study drug, categorized based on the medication they actually received.

Primary and secondary endpoints were assessed using a fixed-sequence testing procedure. Comparisons were 2-sided and performed at the $\alpha = 0.05$ level in the prespecified order until a test was not significant. The prespecified order was: (1) vonoprazan 20 mg vs placebo for percentage of days without heartburn; (2) vonoprazan 10 mg vs placebo for percentage of days without heartburn; (3) vonoprazan 20 mg vs placebo for percentage of days without rescue antacid use; and (4) vonoprazan 10 mg vs placebo for percentage of days without rescue antacid use.

Each vonoprazan treatment group was compared with placebo using a general linear model, with treatment group as factor and severity and frequency of heartburn at baseline as covariates, with the least squares mean difference presented. A sensitivity analysis for the primary endpoint was also performed in which all days with missing diary entries were imputed as a day with heartburn. Subgroup analyses of the primary endpoint were performed for age (<45, ≥45 to <65, ≥65 years), sex, body mass index (<25, ≥25 to <30, ≥30 kg/m^2), mean severity of baseline heartburn (0, >0 to ≤1, >1 to ≤2,>2 to ≤3, >3 to 4), and baseline frequency of heartburn (0 to 3, 4 to 5, 6 to 7 days/week); post hoc analysis based on response to prior PPIs also was performed. Time to sustained resolution was estimated using the Kaplan-Meier method, and comparisons between vonoprazan and placebo were performed using the log-rank test.

What You Need to Know

Background

Proton pump inhibitors are the most commonly prescribed medication for relief of heartburn in patients diagnosed with non-erosive reflux disease (NERD). A new class of medication, potassium-competitive acid blockers, provides more potent gastric acid inhibition than proton pump inhibitors and may be an alternative therapy.

Findings

The potassium-competitive acid blocker vonoprazan reduced heartburn symptoms in subjects diagnosed with NERD in a 4-week placebo-controlled trial, and the treatment effect persisted throughout a subsequent 20-week extension period.

Implications for patient care

Vonoprazan appears to be an effective therapy for relief of heartburn in patients diagnosed with NERD.

Results

From February 2022 to October 2022, 776 subjects were randomized in the placebo-controlled phase; 739

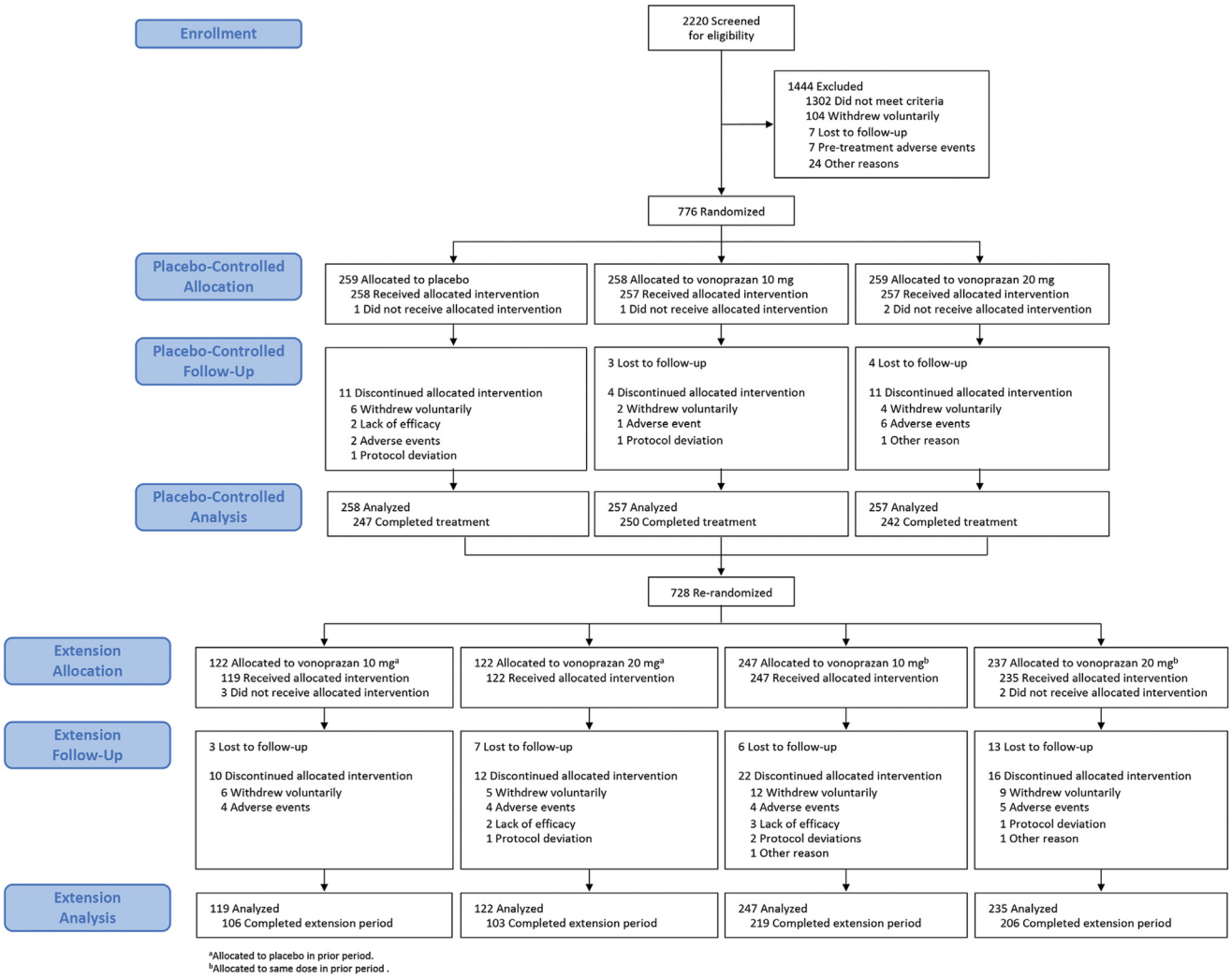

Figure 1. Flow diagram showing progression of patients through study.

completed this phase, and 728 were randomized into the extension phase (Figure 1).

Four-week Placebo-controlled Period

Baseline characteristics are shown in Table 1. Noncompliance was found in 12 of 258 (4.7%), 11 of 257 (4.3%), and 8 of 257 (3.1%) of the placebo, vonoprazan 10 mg, and vonoprazan 20 mg groups, respectively. Results for the primary endpoint showed that the percentage of 24-hour heartburn-free days was 27.7% for placebo vs 44.8% for vonoprazan 10 mg (least squares mean difference, 17.1%; $P < .0001$) and 44.4% for vonoprazan 20 mg (least squares mean difference, 16.7%; $P < .0001$) (Table 2). Median percentages of 24-hour heartburn-free days were 16.7% (interquartile range [IQR], 0.0%–46.2%) for placebo, 48.1% (IQR, 3.7%–78.6%) for vonoprazan 10 mg, and 46.4% (IQR, 3.6%–82.1%) for vonoprazan 20 mg. A sensitivity analysis with all days with missing diary entries imputed as a day with heartburn showed differences similar to the primary analysis for vonoprazan vs placebo: 17.4% for vonoprazan 10 mg and 16.7% for vonoprazan 20 mg ($P < .0001$ for both comparisons).

The percentage of subjects without heartburn on each day of the last 7 days of the screening period and the placebo-controlled period is shown in Figure 2: the separation in percentage of patients with 24-hour heartburn-free days between vonoprazan and placebo appears to begin on the first day of therapy, with differences on day 1 of 8.3% and 11.6% for vonoprazan 10 mg and 20 mg vs placebo and differences on day 2 of 18.1% and 23.2%, respectively.

Results for the secondary efficacy endpoint of percentage of days without rescue antacid revealed significant differences for both vonoprazan doses vs placebo: vonoprazan 10 mg, 15.8% and vonoprazan 20 mg, 13.7% ($P < .0001$ for both) (Table 2). Differences between mean and median for primary and secondary endpoints are due to the non-normal distribution of these endpoints in each of the 3 study arms (Shapiro-Wilk test $P < .0001$).

The time to sustained resolution of heartburn occurred sooner in each vonoprazan group compared

Table 1. Selected Baseline Characteristics of Treatment Groups in Placebo-controlled Period

	Placebo (n = 258)	Vonoprazan 10 mg (n = 257)	Vonoprazan 20 mg (n = 257)
Age, *years*	51.5 (14.7)	51.0 (14.0)	50.4 (14.4)
Female sex	179 (69.4)	182 (70.8)	166 (64.6)
Race			
White	205 (79.5)	186 (72.4)	185 (72.0)
Black	33 (12.8)	38 (14.8)	52 (20.2)
Asian	12 (4.7)	22 (8.6)	11 (4.3)
Other/unknown	8 (3.1)	11 (4.3)	9 (3.5)
Latin ethnicity	77 (29.8)	87 (33.9)	80 (31.1)
BMI, kg/m^2	30.4 (6.9)	30.5 (6.5)	29.9 (6.7)
Current smoker	35 (13.6)	29 (11.3)	34 (13.2)
Any alcohol use	133 (51.6)	136 (52.9)	135 (52.5)
Prior PPI	164 (63.6%)	182 (70.8%)	162 (63.0%)
Heartburn severity score (0–4)[a]	1.4 (0.8)	1.4 (0.8)	1.4 (0.9)
Days without heartburn in screening period, %[a]	11.9 (15.8)	11.4 (17.6)	13.6 (17.3)

Note: Data are presented as number (%) or mean (standard deviation).
BMI, Body mass index; PPI, proton pump inhibitor.
[a]Baseline heartburn frequency and severity based on diary entries from the 7 days before randomization. Mean heartburn severity score incorporates all days within the 7-day period, including days with a score of zero (no heartburn).

with placebo ($P < .0001$ for both) (Supplementary Figure 1). As compared with placebo, both doses of vonoprazan had more days without daytime heartburn (least squares mean difference for vonoprazan 10 mg, 14.4% and vonoprazan 20 mg, 14.8%; $P < .0001$ for both) and nighttime heartburn (least squares mean difference for vonoprazan 10 mg, 16.5% and vonoprazan 20 mg, 13.1%; $P < .0001$ for both) as well as reduced severity of heartburn (Table 2). The magnitude of the treatment effect favoring vonoprazan vs placebo was generally comparable across all subgroup analyses (Supplementary Figure 2), although the magnitude of this treatment effect was possibly lower in the small number of patients (vonoprazan 10 mg, n = 9; vonoprazan 20 mg, n = 9; placebo, n = 13) with baseline mean heartburn severity >3 to 4. Post hoc analysis of subjects with prior PPI use based on response vs no response to PPIs showed a possible trend to fewer (7%–9%) 24-hour heartburn-free days with vonoprazan in those without prior PPI response (Supplementary Table 1).

Adverse events are shown in Supplementary Table 2. Overall adverse events were somewhat higher in the vonoprazan groups, with 1 clearcut imbalance noted on review of individual events being nausea: placebo, 0.4%; vonoprazan 10 mg, 2.3%; and vonoprazan 20 mg, 3.1%. Serious adverse events occurred in no placebo patients, 1 vonoprazan 10 mg patient (viral pericarditis) and 2 vonoprazan 20 mg patients (salivary calculus, bone fracture)—all considered unrelated to study treatment by site investigators. Adverse events leading to study discontinuation occurred in 5 (2.0%), 3 (1.2%), and 6 (2.3%) patients, respectively. Serum gastrin increased by a median of 0 ng/L (range, −559 to 1681), 65.5 ng/L (−426 to 849), and 116 ng/L (−656 to 1466) with placebo, vonoprazan 10 mg, and vonoprazan 20 mg.

Extension and Follow-up Period

Baseline characteristics of subjects in the extension period are shown in Supplementary Table 3. Noncompliance was found in 7 of 119 patients (5.9%) re-randomized from placebo to vonoprazan 10 mg, 5 of 122 (4.1%) patients re-randomized from placebo to vonoprazan 20 mg, 14 of 247 patients (5.7%) remaining on vonoprazan 10 mg, and 10 of 235 patients (4.3%) remaining on vonoprazan 20 mg.

Mean and median percentages of days without heartburn over the extension period were similar in the 4 groups: placebo re-randomized to vonoprazan 10 mg (61.9%/78.3%) or 20 mg (62.9%/76.2%) and remaining on vonoprazan 10 mg (62.6%/77.7%) and 20 mg (60.7%/79.4%) (Table 3). Figure 3 shows those re-randomized from placebo to vonoprazan very rapidly reached proportions of 24-hour heartburn-free days comparable to those who continued on vonoprazan after the 4-week placebo-controlled period. Other exploratory efficacy endpoints also showed very similar results across the 4 groups (Table 3). Adverse events are shown

Table 2. Primary, Secondary, and Exploratory Efficacy Endpoint Analyses for 4-week Placebo-controlled Period

	Placebo (n = 258)		Vonoprazan 10 mg (n = 257)		Vonoprazan 20 mg (n = 257)		LS mean difference (SE): vonoprazan 10 mg vs placebo	LS mean difference (SE): vonoprazan 20 mg vs placebo
	LS mean (SE)	Median (IQR)	LS mean (SE)	Median (IQR)	LS mean (SE)	Median (IQR)		
24-hour days without heartburn, %	27.7 (1.9)	16.7 (0.0–46.2)	44.8 (1.9)	48.1 (3.7–78.6)	44.4 (1.9)	46.4 (3.6–82.1)	17.1 (2.7)[a]	16.7 (2.7)[a]
24-hour days without rescue antacid, %	47.6 (2.1)	50.0 (10.3–77.8)	63.3 (2.1)	75.9 (34.5–96.2)	61.2 (2.1)	73.9 (25.0–93.8)	15.8 (3.0)[a]	13.7 (3.0)[a]
Days without daytime heartburn, %	38.9 (2.0)	33.3 (6.7–69.2)	53.3 (2.0)	62.1 (12.0–86.2)	53.6 (2.0)	66.7 (14.3–88.9)	14.4 (2.8)[a]	14.8 (2.8)[a]
Days without nighttime heartburn, %	43.3 (1.9)	45.5 (8.0–71.4)	59.9 (1.9)	70.4 (25.0–92.3)	56.4 (1.9)	71.0 (13.8–92.9)	16.5 (2.6)[a]	13.1 (2.7)[a]
Severity of heartburn (scale 0–4)	1.0 (0.04)	0.8 (0.4–1.5)	0.7 (0.04)	0.4 (0.1–1.0)	0.7 (0.04)	0.4 (0.1–1.0)	−0.4 (0.05)[a]	−0.3 (0.05)[a]

IQR, Interquartile range; LS, least squares; SE, standard error.
[a]$P < .0001$.

in Supplementary Table 4; all serious adverse events were considered unrelated to study treatment by site investigators. Nausea occurred in 4 of 366 subjects (1.1%) on vonoprazan 10 mg and 6 of 357 subjects (1.7%) on vonoprazan 20 mg during the extension period.

The mean and median percentage of days without heartburn during the follow-up period off treatment decreased but was similar among the 4 groups: placebo to vonoprazan 10 mg (44.0%/39.3%), placebo to vonoprazan 20 mg (44.2%/41.1%), vonoprazan 10 mg to 10 mg (46.7%/46.7%), vonoprazan 20 mg to 20 mg (44.4%/42.3%); mean and median percentage of days without rescue antacid also decreased to similar levels in the 4 groups: 60.1%/69.8%, 59.3%/62.5%, 59.6%/70.6%, and 57.7%/60.6%.

The mean serum gastrin at baseline of the placebo-controlled period was 54.6 ng/L. At the beginning of the extension period, gastrin levels were lower in those re-randomized from placebo than in those continuing vonoprazan, but by the end of the extension period, the levels were similar whether patients had been on placebo or vonoprazan prior to the extension period—with levels higher in those receiving vonoprazan 20 mg (Supplementary Table 5). Four weeks after discontinuation of vonoprazan, mean serum gastrin dropped to a mean of 66.2 ng/L, with similar levels in all 4 groups.

Discussion

Our 4-week double-blind randomized comparison showed that the mean percentage of 24-hour heartburn-free days was 17% greater with vonoprazan than with placebo in subjects diagnosed with NERD. Similar differences were seen in both daytime and nighttime heartburn, as well as in the need for rescue antacid. This separation appeared to begin very rapidly: ~10% difference between the vonoprazan and placebo groups in the percentage with a 24-hour heartburn-free day was seen after the first dose of study medication and ~20% difference occurred after the second dose.

The long-term portion of our study showed that the treatment effect of vonoprazan persisted over 6 months without evidence of a reduction in heartburn-free days. Although an increase in mean and median percentage of 24-hour heartburn free days occurred through the 20-week extension after the 4-week placebo-controlled period, caution needs to be exercised in interpreting these results: lack of a placebo group potentially may influence the patient-reported outcome of heartburn.

Scant evidence is available from prior prospective trials regarding the benefit of daily antisecretory therapy when used over longer periods in patients with NERD. The only such studies assessing PPI efficacy for

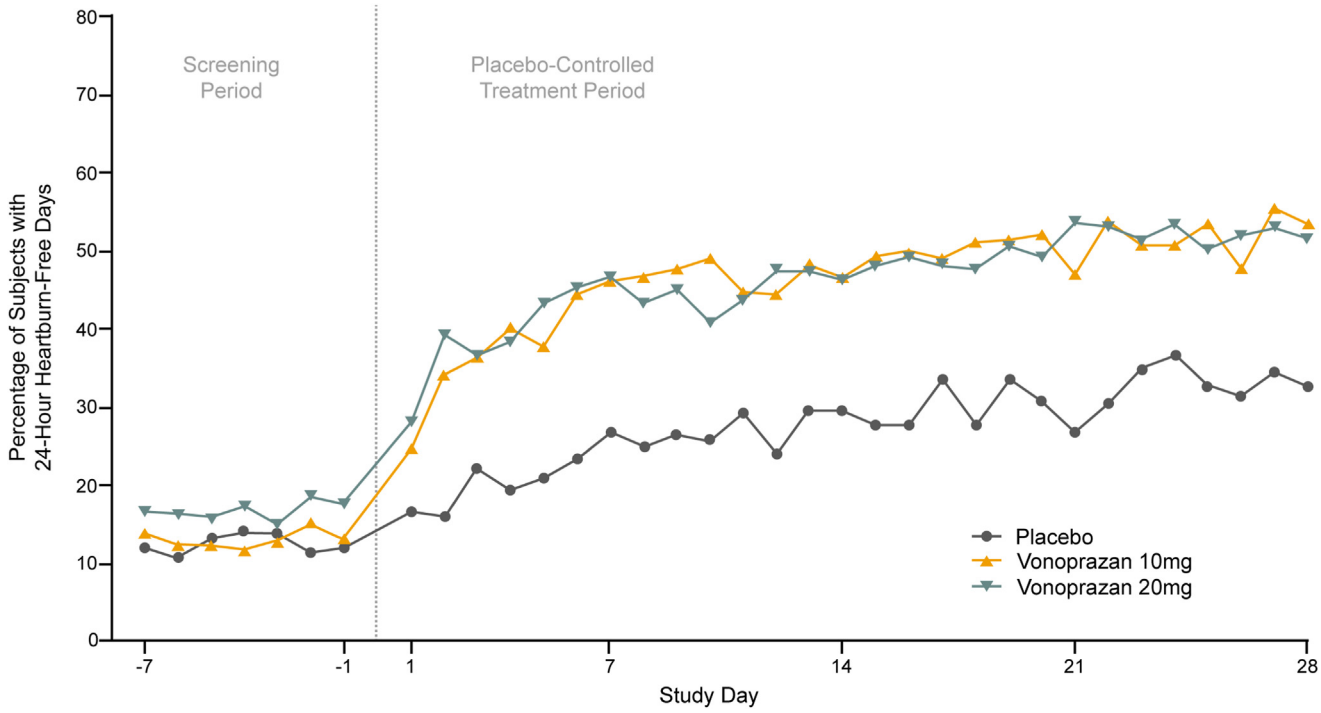

Figure 2. Percentage of subjects without heartburn on each day of the last week of the screening period and the placebo-controlled period.

6 months have been done in a selected population of patients with NERD who had all achieved symptomatic response prior to entry, and studies generally assessed outcomes such as willingness to continue, acceptable symptom control, and satisfaction—but not heartburn-free days.[12–14]

We found that efficacy was similar between the higher and lower doses of vonoprazan. This is not surprising given that most PPI studies also suggest no increase in efficacy with higher vs lower doses in achieving symptomatic relief in patients with NERD.[15,16] Previous 4-week randomized trials also have provided the percentages of heartburn-free 12 or 24-hour periods for PPIs vs placebo,[8–11,17,18] with differences in means ranging from 12% to 32%,[9,18] and differences in medians up to 36% reported.[11] We found least squares mean differences of 17% and differences in medians of 30% to 31% in 24-hour heartburn-free days between vonoprazan and placebo.

Two previous 4-week double-blind randomized trials from Japan compared vonoprazan with placebo in patients with NERD. The first randomly assigned 827 patients to placebo, vonoprazan 10 mg, or vonoprazan 20 mg.[6] The median proportion of days without heartburn was extremely low in all groups, without significant difference between placebo (7.4%) and vonoprazan 10 mg (10.3%) or 20 mg (12.0%). This study included a 1-week run-in period, and participants were required to have ≥2 days of moderate or higher severity heartburn in this week while taking antacid therapy ≥75% of the week. By excluding patients responsive to antacids, the study population was presumably enriched in patients without acid-related reflux symptoms, explaining the very poor results in all study groups. The second trial randomly assigned 483 patients to placebo vs vonoprazan 10 mg: the median proportion of days without heartburn was 61.5% vs 72.3% ($P = .06$), and the cumulative improvement in heartburn over 4 weeks was higher with vonoprazan ($P = .0003$, log-rank test).[7]

Our exploratory endpoint of mean heartburn severity score incorporates heartburn severity on all days, including days without heartburn (score = 0) and thus is a function of both severity and frequency of heartburn. We did not evaluate the minimal clinically important difference for heartburn severity in our study, which employed a 5-point severity scale, nor has it been defined for a 5-point scale in other NERD studies to the best of our knowledge. Junghard and Wiklund reported clinically relevant mean changes in heartburn severity were 0.35 for a 7-point scale and 0.29 for a 4-point scale.[19]

One subgroup in whom the magnitude of the treatment effect favoring vonoprazan vs placebo may have been less was subjects with the highest heartburn severity scores. Notably, this group was very small, and the confidence intervals around the estimates are wide, preventing us from drawing firm conclusions regarding this finding. It is conceivable this group included a higher proportion of subjects with functional heartburn, a condition that is generally not responsive to acid inhibition. As mentioned, our

Table 3. Efficacy Endpoints in Extension Period

	Placebo to vonoprazan 10 mg (n = 119)		Placebo to vonoprazan 20 mg (n = 122)		Vonoprazan 10 mg to 10 mg (n = 247)		Vonoprazan 20 mg to 20 mg (n = 235)	
	Mean (SD) %	Median (IQR) %	Mean (SD) %	Median (IQR) %	Mean (SD) %	Median (IQR) %	Mean (SD) %	Median (IQR) %
24-hour days without heartburn	61.9 (37.6)	78.3 (21.4–95.6)	62.9 (37.2)	76.2 (35.7–95.2)	62.6 (36.5)	77.7 (29.3–95.6)	60.7 (38.5)	79.4 (17.7–94.3)
24-hour days without rescue antacid	73.1 (34.7)	91.5 (55.9–98.6)	76.9 (32.9)	93.2 (74.3–99.3)	73.7 (34.1)	90.0 (60.4–98.5)	72.5 (35.4)	91.7 (47.1–98.0)
Days without daytime heartburn	70.5 (35.0)	88.5 (46.8–98.3)	71.2 (35.1)	87.4 (59.4–98.0)	69.8 (35.8)	85.9 (52.1–97.8)	68.0 (37.4)	90.1 (37.9–97.7)
Days without nighttime heartburn	70.7 (35.4)	88.2 (44.1–97.8)	71.2 (35.6)	89.1 (57.9–97.8)	72.5 (33.8)	88.4 (58.6–98.3)	70.2 (36.2)	91.5 (43.1–97.9)
Severity of heartburn (scale 0-4)	0.4 (0.7)	0.1 (0.0–0.6)	0.4 (0.6)	0.2 (0.0–0.5)	0.4 (0.6)	0.1 (0.0–0.5)	0.4 (0.7)	0.1 (0.0–0.6)

IQR, Interquartile range; SD, standard deviation.

severity score is a function of frequency and severity, so this subgroup had frequent, severe heartburn. Patients with functional heartburn have been reported to have more frequent (but not more severe) symptoms.[20–23] Post hoc analysis raised the possibility that patients who previously had not responded to PPIs may have a somewhat lower response to vonoprazan. This is not unexpected, given that patients not responding to PPIs are less likely to have heartburn due to acid reflux.

As previously shown with both PPIs and PCABs, serum gastrin was increased with 4 weeks of therapy and increased somewhat further over an additional 20 weeks of treatment. The serum gastrin levels returned to near baseline by 4 weeks after discontinuation. The duration of our study was too short to adequately evaluate long-term risks of PCABs. Although no clear signals have been identified at present, whether the potent acid inhibition and increased levels of gastrin seen with PCABs induce relevant histological or clinical effects with long-term administration requires further study.

A limitation of our study, and most prior studies of NERD, is that subjects enrolled likely include individuals for whom acid reflux is not a cause of their symptoms (eg, patients with functional heartburn, patients with symptoms related to weakly acid/non-acid reflux. When NERD is defined as requiring both negative endoscopy and positive pH monitoring, relief of heartburn is reported to be higher than in those defined by negative endoscopy alone.[24,25] However, we sought to simulate standard clinical practice, in which the great majority of patients with heartburn do not undergo ambulatory reflux monitoring. Nevertheless, further evaluation of PCABs in patients with NERD with positive reflux testing and in symptomatic patients without endoscopic or reflux testing will be useful to define their potential role in the management of patients with GERD-like symptoms.

Strengths of our study include the double-blind randomized design, the subsequent 20-week active-treatment extension for all patients enrolled rather than just those with response to initial therapy, and the high proportions of Black (16%) and Latino (32%) subjects enrolled, improving the generalizability of the study for a U.S. population.

Conclusion

In conclusion, the PCAB vonoprazan was efficacious in reducing heartburn symptoms in patients with NERD, with the benefit appearing to begin as early as the first day of therapy. This treatment effect persisted after the initial 4-week placebo-controlled period throughout the 20-week extension period. The two vonoprazan doses (10 mg and 20 mg) were similar in efficacy.

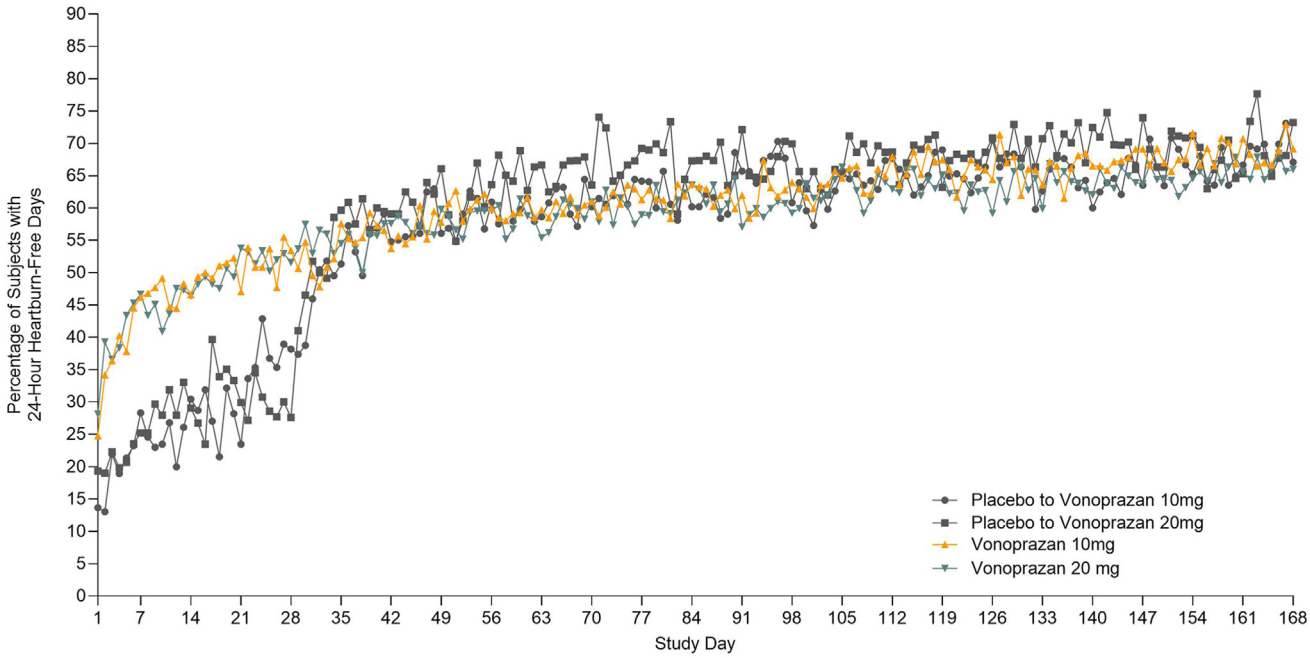

Figure 3. Percentage of subjects without heartburn on each day of the placebo-controlled period and extension period.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.05.004.

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Conflicts of interest

The authors disclose the following: Loren Laine reports consultant for Phathom Pharmaceuticals and Medtronic. Stuart Spechler reports consultant for Phathom Pharmaceuticals, Ironwood Pharmaceuticals, ISOThrive, and Castle Biosciences. Rena Yadlapati reports consultant for Medtronic, Phathom Pharmaceuticals, StatLinkMD, Braintree Pharmaceuticals, and Reckitt Benckiser Healthcare Ltd; research support from Ironwood Pharmaceuticals; and advisory board with stock options for RJS Mediagnostix. Felice H. Schnoll-Sussman reports advisory board for Medtronic, Ethicon, Braintree/Sebela, and Implantica. Neila Smith, Eckhard Leifke, Tom Harris, and Barbara Hunt report employees and stock/stock options for Phathom Pharmaceuticals. Ronnie Fass reports advisor for Takeda, Medtronic, Phathom Pharmaceuticals, GERDCare, Celexio, Dexcal, J&J, Carnot, Veritas, Syneos, BrainTree Labs/Sebela, and Renexxion; and speaker for AstraZeneca, Takeda, J&J, Medicamenta, Adcock-Ingram, Carnot, and Daewoong. Philip Katz reports consultant for Phathom Pharmaceuticals, Sebella, Syneos, Medtronic, and Medpace.

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Data Availability

Individual participant data will not be shared.

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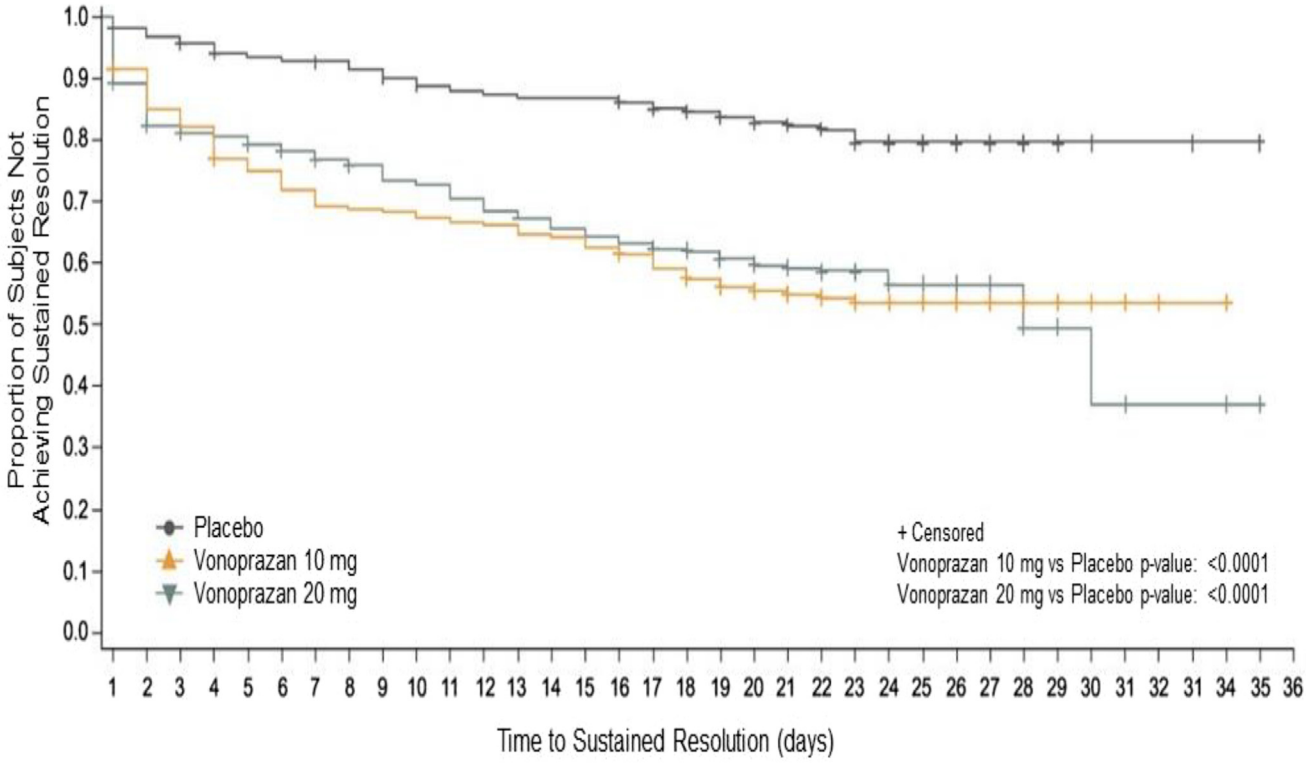
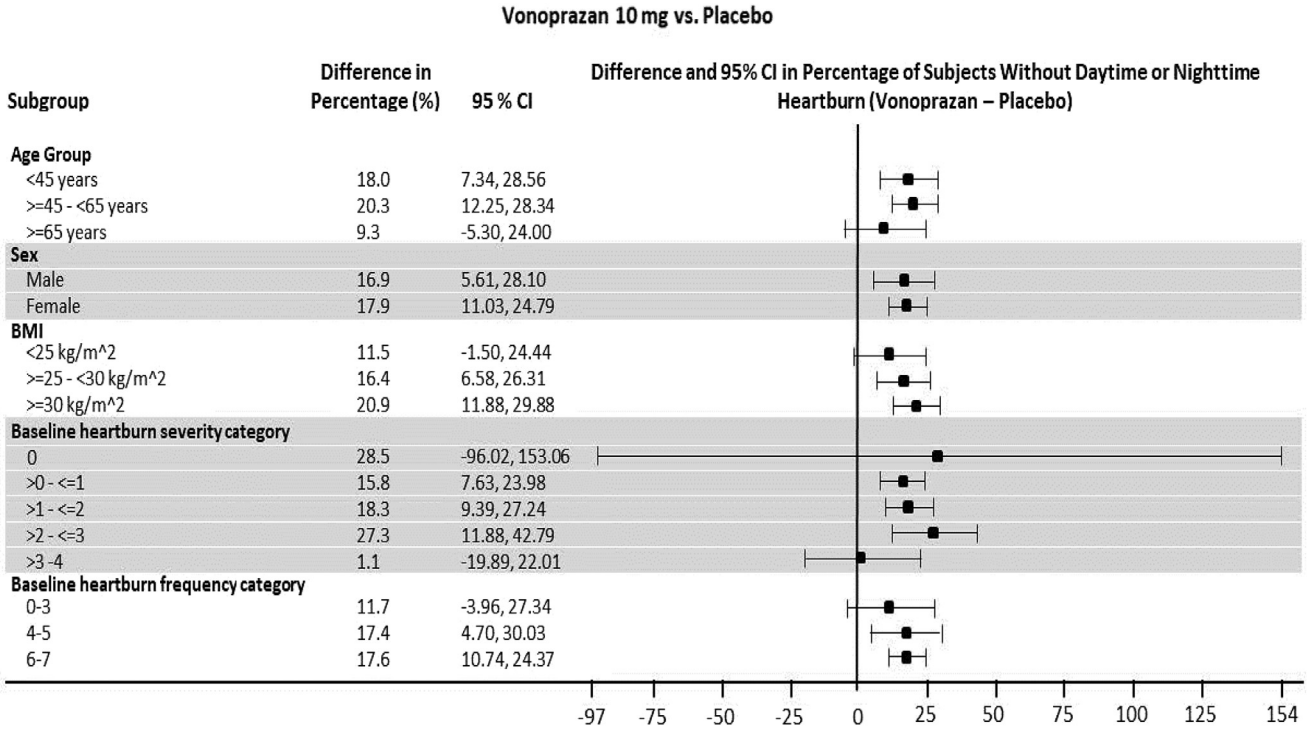
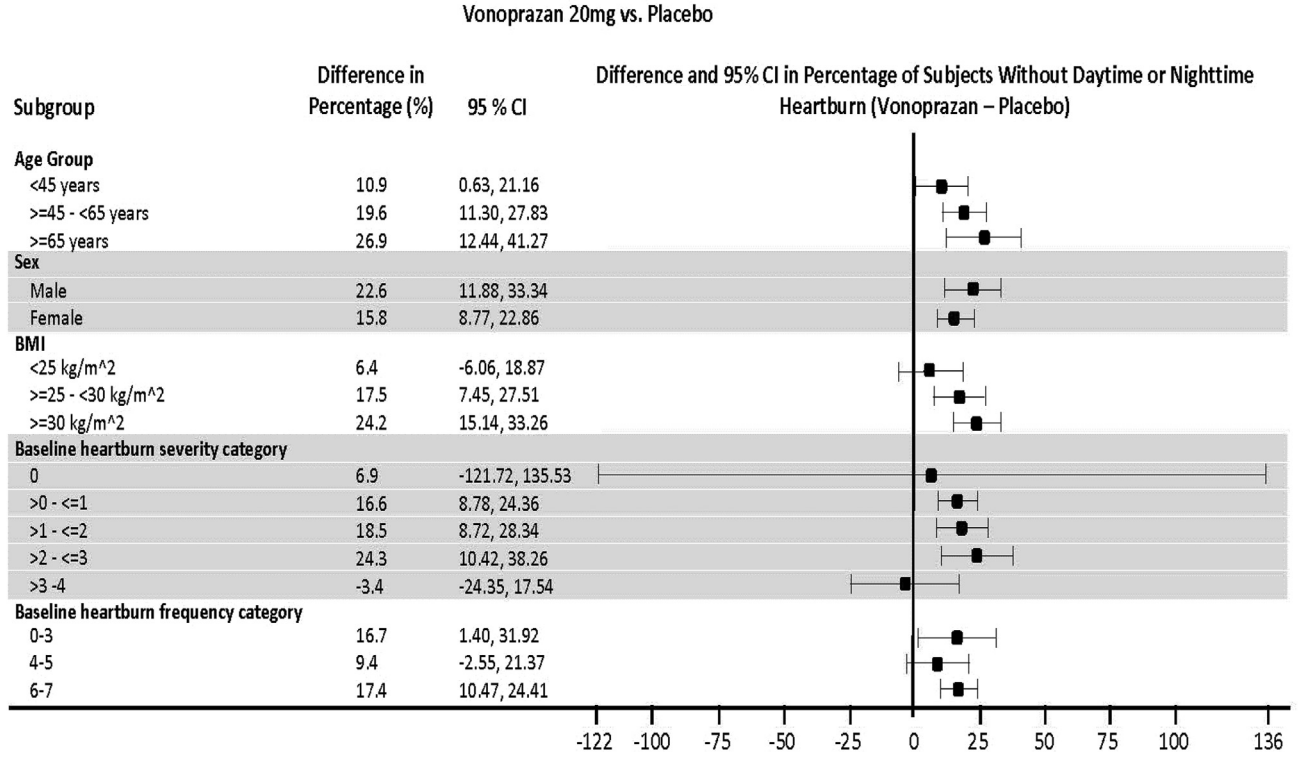


Supplementary Figure 1. Kaplan-Meier curve of time to sustained resolution of heartburn in placebo-controlled period.





Supplementary Figure 2. Sugroup analyses of percentage of days without heartburn over the placebo-controlled period.[a] CI, Confidence interval. [a]Baseline heartburn severity and frequency categories of 0 reflect 8 subjects who had no heartburn in the 7 days prior to randomization but did report heartburn ≥4 days during a consecutive 7-day period earlier in the screening period.

Supplementary Table 1. Twenty-four Hour Heartburn-free Days in Subjects With Prior PPI Use Related to their Prior Symptomatic Response to PPI

	Placebo LS mean, 95% CI (N)	Vonoprazan 10 mg LS mean, 95% CI (N)	Vonoprazan 20 mg LS mean, 95% CI (N)
Prior PPI use, %	25.7, 20.8-30.5 (n = 163[a])	44.9, 40.3-49.5 (n = 181)	47.3, 42.4-52.2 (n = 162)
PPI response, %	25.8, 20.0-31.7 (n = 114)	48.2, 42.4-54.1 (n = 112)	49.7, 43.7-55.8 (N-107)
No PPI response, %	26.0, 17.0-34.9 (n = 48)	39.2, 31.7-46.6 (n = 69)	42.5, 34.2-50.9 (n = 55)

CI, Confidence interval; LS, least squares; PPI, proton pump inhibitor.
[a]One placebo subject with prior PPI use did not have data on response to PPI.

Supplementary Table 2. Adverse Events in the Placebo-controlled Period

	Placebo (n = 256) n (%)	Vonoprazan 10 mg (n = 259) n (%)	Vonoprazan 20 mg (n = 257) n (%)
Any adverse event	41 (16.0)	56 (21.6)	67 (26.1)
Serious adverse event	0	1 (0.4)	2 (0.8)
Adverse event leading to treatment discontinuation	5 (2.0)	3 (1.2)	6 (2.3)
COVID-19	2 (0.8)	3 (1.2)	4 (1.6)
Bone fracture	0	0	1 (0.4)
C. difficile	0	0	0
Alanine aminotransferase >3× upper limit of normal	0	2 (0.8)	1 (0.4%)

Supplementary Table 3. Selected Baseline Characteristics of Treatment Groups in Extension Period

	Placebo to vonoprazan 10 mg (n = 119)	Placebo to vonoprazan 20 mg (n = 122)	Vonoprazan 10 mg to 10 mg (n = 247)	Vonoprazan 20 mg to 20 mg (n = 235)
Age, *years*	50.6 (15.3)	52.2 (14.2)	50.9 (14.0)	50.4 (14.3)
Female sex	85 (71.4)	82 (67.2)	175 (70.9)	151 (64.3)
Race				
White	94 (79.0)	98 (80.3)	180 (72.9)	169 (71.9)
Black	12 (10.1)	17 (13.9)	38 (15.4)	46 (19.6)
Asian	6 (5.0)	6 (4.9)	18 (7.3)	11 (4.7)
Other/unknown	7 (5.9)	1 (0.8)	11 (4.5)	9 (3.8)
Latin ethnicity	40 (33.6)	30 (24.6)	83 (33.6)	69 (29.4)
BMI, kg/m^2	30.5 (7.8)	30.6 (6.1)	30.5 (6.5)	29.8 (6.7)
Current smoker, %	16 (13.4)	18 (14.8)	27 (10.9)	27 (11.5)
Any alcohol use, %	60 (50.4)	63 (51.6)	129 (52.2)	122 (51.9)
Heartburn severity score (0–4)[a]	1.4 (0.9)	1.3 (0.8)	1.4 (0.8)	1.4 (0.9)
Days without heartburn in screening period, %[a]	11.4 (15.6)	12.3 (15.6)	11.7 (17.8)	13.5 (17.1)

Note: Data are presented as number (%) or mean (standard deviation).
BMI, Body mass index.
[a]Baseline heartburn frequency and severity based on diary entries from the 7 days before randomization.

Supplementary Table 4. Adverse Events in Extension Period

	Placebo to vonoprazan 10 mg (n = 118) n (%)	Placebo to vonoprazan 20 mg (n = 121) n (%)	Vonoprazan 10 mg to 10 mg (n = 248) n (%)	Vonoprazan 20 mg to 20 mg (n = 236) n (%)
Any adverse event	37 (31.4)	40 (33.1)	83 (33.5)	80 (33.9)
Serious adverse event	2 (1.7)	4 (3.3)	7 (2.8)	3 (1.3)
Adverse event leading to treatment discontinuation	2 (1.7)	3 (2.5)	2 (0.8)	4 (1.7)
COVID-19	12 (10.2%)	3 (2.5%)	11 (4.4%)	20 (8.5%)
Bone fracture	0	2 (1.7)	4 (1.6)	0
C. difficile	0	0	0	0
Alanine aminotransferase >3× upper limit of normal	0	0	3 (1.2)	0

Supplementary Table 5. Serum Gastrin Levels Throughout Study From Baseline to End of 4-week Follow-up Period

	Placebo to vonoprazan 10 mg	Placebo to vonoprazan 20 mg	Vonoprazan 10 mg to 10 mg	Vonoprazan 20 mg to 20 mg
Baseline, placebo-controlled period, *ng/L*	43.9 (87.6) (n = 114)	58.9 (117.8) (n = 113)	50.4 (116.7) (n = 230)	43.7 (115.9) (n = 219)
Baseline, extension period, *ng/L*	36.1 (84.6) (n = 118)	61.8 (247.4) (n = 120)	156.8 (177.8) (n = 247)	211.5 (250.8) (n = 235)
End of extension period, *ng/L*	199.5 (290.3) (n = 97)	257.4 (274.7) (n = 95)	218.9 (306.1) (n = 203)	296.7 (271.6) (n = 196)
End of follow-up period, *ng/L*	65.6 (170.5) (n = 101)	63.3 (129.0) (n = 96)	65.9 (114.5) (n = 205)	68.3 (141.9) (n = 199)

Data are presented as mean (standard deviation).