ESOPHAGUS

Vonoprazan Versus Lansoprazole for Healing and Maintenance of Healing of Erosive Esophagitis: A Randomized Trial

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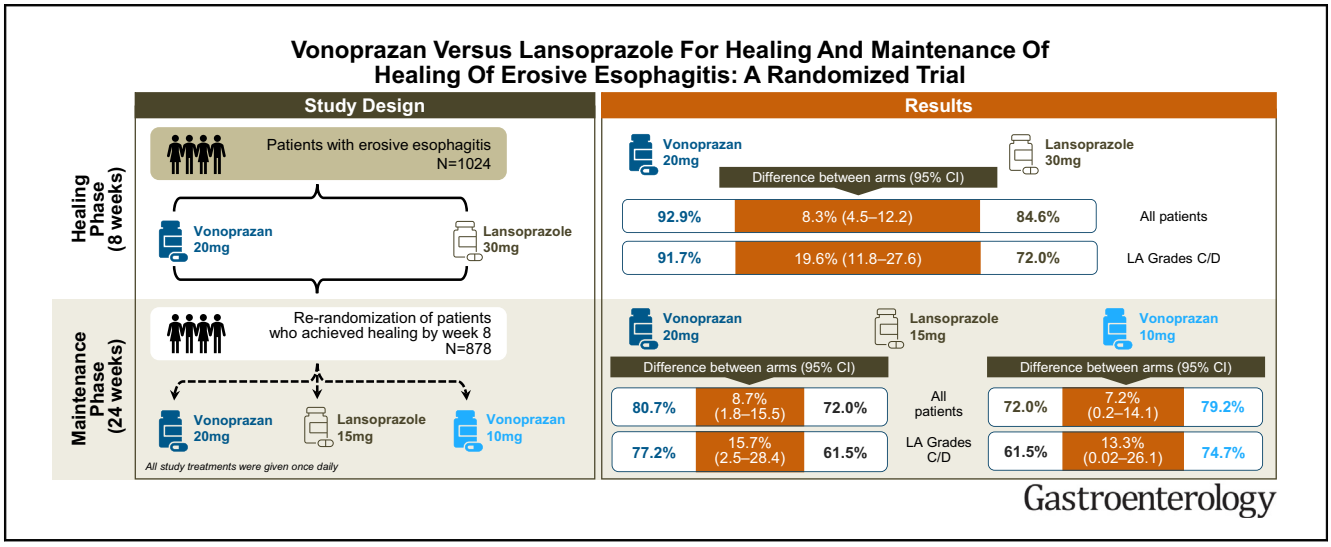

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BACKGROUND & AIMS: For decades, proton pump inhibitors (PPIs) have been the mainstay of treatment for erosive esophagitis. The potassium-competitive acid blocker vonoprazan provides more potent acid inhibition than PPIs, but data on its efficacy for erosive esophagitis are limited. **METHODS:** Adults with erosive esophagitis were randomized to once-daily vonoprazan, 20 mg, or lansoprazole, 30 mg, for up to 8 weeks. Patients with healing were rerandomized to once-daily vonoprazan, 10 mg, vonoprazan, 20 mg, or lansoprazole, 15 mg, for 24 weeks. Primary end points, percentage with healing by week 8 endoscopy, and maintenance of healing at week 24 endoscopy, were assessed in noninferiority comparisons (noninferiority margins, 10%), with superiority analyses prespecified if noninferiority was demonstrated. Analyses of primary and secondary end points were performed using fixed-sequence testing procedures. **RESULTS:** Among 1024 patients in the healing phase, vonoprazan was noninferior to lansoprazole in the primary analysis and superior on the exploratory analysis of healing (92.9 vs 84.6%; difference, 8.3%; 95% confidence interval [CI], 4.5%–12.2%). Secondary analyses showed vonoprazan was noninferior in heartburn-free days (difference, 2.7%; 95% CI, −1.6% to 7.0%), and superior in healing Los Angeles Classification Grade C/D esophagitis at week 2 (difference, 17.6%; 95% CI, 7.4%–27.4%). Among 878 patients in the maintenance phase, vonoprazan was noninferior to lansoprazole in the primary analysis and superior on the secondary analysis of maintenance of healing (20 mg vs lansoprazole: difference, 8.7%; 95% CI, 1.8%–15.5%; 10 mg vs lansoprazole: difference, 7.2%; 95% CI, 0.2%–14.1%) and secondary analysis of maintenance of healing Grade C/D esophagitis (20 mg vs lansoprazole: difference, 15.7%; 95% CI, 2.5%–28.4%; 10 mg vs lansoprazole: difference, 13.3%; 95% CI, 0.02%–26.1%). **CONCLUSIONS:** Vonoprazan was noninferior and superior to the PPI lansoprazole in healing and maintenance of healing of erosive esophagitis. This benefit was seen predominantly in more severe erosive esophagitis. (ClinicalTrials.gov: NCT04124926).

Keywords: Gastroesophageal Reflux; Proton Pump Inhibitors; Vonoprazan.

Abbreviations used in this paper: **CI, confidence interval; CD, cluster of differentiation; COVID-19, coronavirus disease 2019; ECL, enterochromaffin-like; GERD, gastroesophageal reflux disease; LA, Los Angeles; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; US, United States.**

Most current article

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Gastroesophageal reflux disease (GERD) is one of the most common disorders of the gastrointestinal tract, with a pooled prevalence of 21% in the United States (US),[1] accounting for >4.6 million ambulatory visits annually.[2] GERD's most common complication is erosive esophagitis, estimated to occur in ~25% to 50% of patients with GERD symptoms.[3,4]

Guidelines recommend proton pump inhibitors (PPIs) as the therapy of choice for erosive esophagitis.[5] Healing of erosive esophagitis is related to the degree and duration of gastric acid inhibition,[6,7] and PPIs are the most potent acid-inhibitory agents currently licensed to treat erosive esophagitis in the US and Europe. Long-term maintenance therapy with PPIs also is recommended to maintain healing in patients with more severe erosive esophagitis, defined as Los Angeles Classification (LA) Grade C or D, given that recurrence occurs in nearly 100% of such patients without therapy.[5]

Although PPIs are effective for healing erosive esophagitis, some patients do not achieve success with conventional PPI treatment. For example, lack of healing of erosive esophagitis with 8 weeks of PPI therapy can be expected in ~5% to 20% of patients,[8-11] with rates up to ~30% reported in patients with more severe esophagitis.[12] After healing, recurrence over 12 months occurs in ~10% to 45% despite PPI therapy,[8-11] with the higher rates associated with more severe baseline esophagitis.[13]

Furthermore, PPIs are restricted in their time of dosing. PPIs are prodrugs that are converted to their active form in the acidic environment of the secretory canaliculus, which is also the sole location of active proton pumps in the parietal cell.[14,15] Thus, PPIs only inhibit active proton pumps. Given their limited duration of action (half-life of ~1–2 hours), PPIs are taken 30 to 60 minutes before a meal so their presence in the secretory canaliculus coincides with the postprandial peak in active proton pumps.[15] An alternative therapy for patients who may not respond to PPIs and that does not have the requirement for dosing around meals might be of utility.

Such a potential alternative therapy is a potassium-competitive acid blocker (PCAB), a new class of antisecretory agent that provides more potent inhibition of gastric acid than PPIs.[15,16] However, clinical studies of PCABs have been conducted primarily in Asia. Three double-blind randomized trials in Asian patients with erosive esophagitis observed rates of healing at 8 weeks to be only 1.0% to 3.5% higher with the PCAB vonoprazan (20 mg daily) than the PPI lansoprazole (30 mg daily).[17-19] Because Asian and Western populations differ in factors that may influence acid inhibition, assessment of PCAB efficacy in Western subjects is crucial. We undertook a randomized, double-blind, parallel-group trial in which 2 doses of vonoprazan were compared with the approved doses of the PPI lansoprazole for healing and maintenance of healing in patients with erosive esophagitis from the US and Europe.

An active control (standard PPI therapy) rather than placebo was ethically required for a 32-week-long trial of patients with erosive esophagitis. As is common in studies with an active control being used for regulatory approval of a new alternative therapy, our primary efficacy analysis was a noninferiority comparison. Noninferiority comparisons also are used if a new therapy might have other advantages over a standard therapy, even if efficacy is similar.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Proton pump inhibitors have been the mainstay of treatment for erosive esophagitis for decades. A new type of medication (potassium-competitive acid blockers) provides more potent gastric acid inhibition than proton pump inhibitors.

NEW FINDINGS

The potassium-competitive acid blocker vonoprazan was noninferior and superior to the proton pump inhibitor lansoprazole in healing and maintenance of healing of erosive esophagitis. This benefit was seen predominantly in Los Angeles Grade C/D esophagitis.

LIMITATIONS

Results may not be generalizable to *Helicobacter pylori*-positive patients and those with reflux-like symptoms but no erosive esophagitis.

CLINICAL RESEARCH RELEVANCE

Vonoprazan is an effective alternative to lansoprazole for treatment of patients with erosive esophagitis, especially for those with more severe disease.

PCABs do not have the same restriction on timing of administration as PPIs because they have a longer half-life (~7–8 hours)[15,16] and appear to bind both active and inactive proton pumps based on preclinical data.[20] Thus, PCAB's ease of use may be an advantage. Although our primary analysis was a noninferiority comparison, we also hypothesized that vonoprazan might provide greater healing than PPIs, especially in patients with more severe esophagitis, because greater acid inhibition is associated with greater healing of erosive esophagitis.[6,7] Therefore, we also prespecified superiority comparisons if noninferiority was established.

Methods

The study protocol and statistical analysis plan (original and final versions) with summary of changes are provided as Supplementary Material. No important changes (eg, in eligibility criteria or outcomes) occurred after trial commencement. All authors had access to the study data and reviewed and approved the final manuscript. The study was conducted by a clinical research organization (PPD, Inc, Morrisville, NC) and funded by Phathom Pharmaceuticals (Buffalo Grove, IL).

Subjects

Adults found at endoscopy to have erosive esophagitis. as confirmed by blinded central reading of endoscopic photographs, were eligible for participation. Key exclusion criteria included *Helicobacter pylori* infection (patients underwent ^{13}C-urea breath testing during screening) and Barrett's esophagus. Subjects with *H pylori* infection were excluded for several reasons: European guidelines have previously indicated that "*H pylori* testing should be considered in patients receiving long

term maintenance treatment with PPIs" because "in patients with reflux esophagitis receiving long-term acid suppression, eradication of *H pylori* infection decreases inflammation and gastritis activity, and reverses corpus gastritis"[21]; other *H pylori*-associated conditions (ulcers, dyspepsia) may cause symptoms that are ascribed to GERD; and patients with *H pylori* require treatment, which would prevent eligibility for the trial (eg, high-dose PPI therapy) and can cause upper gastrointestinal symptoms. In addition, subjects with coronavirus disease 2019 (COVID-19) were excluded because it would prevent their meeting study obligations (eg, endoscopies) and might impact study results. Full details on eligibility are provided in the study protocol (Supplementary Material). Relevant Institutional Review Boards or Ethics Committees approved the study, and all participants gave written informed consent.

Treatment

Eligible subjects were enrolled and randomly assigned with concealed allocation by site investigators (see Supplementary Material for the list of investigators and sites) using an interactive response technology to access a central randomization sequence generated with SAS 9.4 software (SAS Institute, Inc, Cary, NC) by PPD, Inc. Randomization was stratified by baseline LA Grade of erosive esophagitis (A/B and C/D) using block sizes of 4 for the healing phase and 6 for the maintenance phase. For the healing portion of the study, patients were assigned in a 1:1 ratio to once-daily vonoprazan, 20 mg, or lansoprazole, 30 mg, for up to 8 weeks. Patients who achieved healing were rerandomized in a 1:1:1 ratio to once-daily vonoprazan, 10 mg, vonoprazan, 20 mg, or lansoprazole, 15 mg, for 24 weeks. Study medications were given 30 minutes before the morning meal and had identical appearance. 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.

The doses of lansoprazole chosen are the approved doses for healing and maintenance of healing in the US and Europe. When an active control is used in registration studies, the control is required to be an approved medication and at an approved dosage. The vonoprazan dose of 20 mg for the healing phase was chosen based on data from Japan showing that 20 mg was numerically superior to 5- and 10-mg doses for LA Grade C/D erosive esophagitis and was superior to lansoprazole, 30 mg, for healing of erosive esophagitis.[17,18] Doses for maintenance were based on a Japanese study showing that vonoprazan doses of 10 mg and 20 mg were superior to lansoprazole, 15 mg, and that vonoprazan, 20 mg, had numerically greater maintenance of healing than 10 mg for LA Grade C/D erosive esophagitis.[22]

Study Flow

The study took place at endoscopy units and ambulatory locations at 77 sites in the US and 34 in Europe (Poland, Czech Republic, Hungary, Bulgaria, and United Kingdom). Patients had visits at weeks 2 and 8 of the healing phase, weeks 4, 12, and 24 of the maintenance phase, and 4 weeks after the last dose of study drug. Subjects recorded maximum severity (5-point ordinal scale, none to very severe) of daytime and nighttime heartburn for $\geq$7 days during screening and daily throughout the study in an electronic diary.

Repeat endoscopy was performed at week 2 of the healing phase. If healing was confirmed by a central reading, the patient entered the maintenance phase. If not, upper endoscopy was again performed at week 8. Those with healing confirmed by a central reading entered the maintenance phase. Subjects in the maintenance phase had repeat endoscopy with gastric biopsies at week 24. All central readings of endoscopic photographs, at baseline and during healing and maintenance phases, were done by experts (P.K., K.D., S.S.) blinded to patient, clinical data, and week of endoscopy.

End Points

Healing phase. The primary end point was the percentage of subjects with healing by week 8. Secondary end points included percentage of subjects with healing at week 2, of subjects with baseline LA Grade C/D esophagitis with healing at week 2 and week 8, of 24-hour heartburn-free days, and of subjects with onset of sustained heartburn resolution ($\geq$7 consecutive days without heartburn) by day 3.

Maintenance phase. The primary end point was the percentage of subjects who maintained healing after 24 weeks. Secondary end points included the percentage of subjects with baseline LA Grade C/D erosive esophagitis who maintained healing after 24 weeks and of 24-hour heartburn-free days over the maintenance phase.

Statistical Analysis

Analyses were performed by the clinical research organization (PPD, Inc) and the sponsor (Phathom Pharmaceuticals), with full access by the authors.

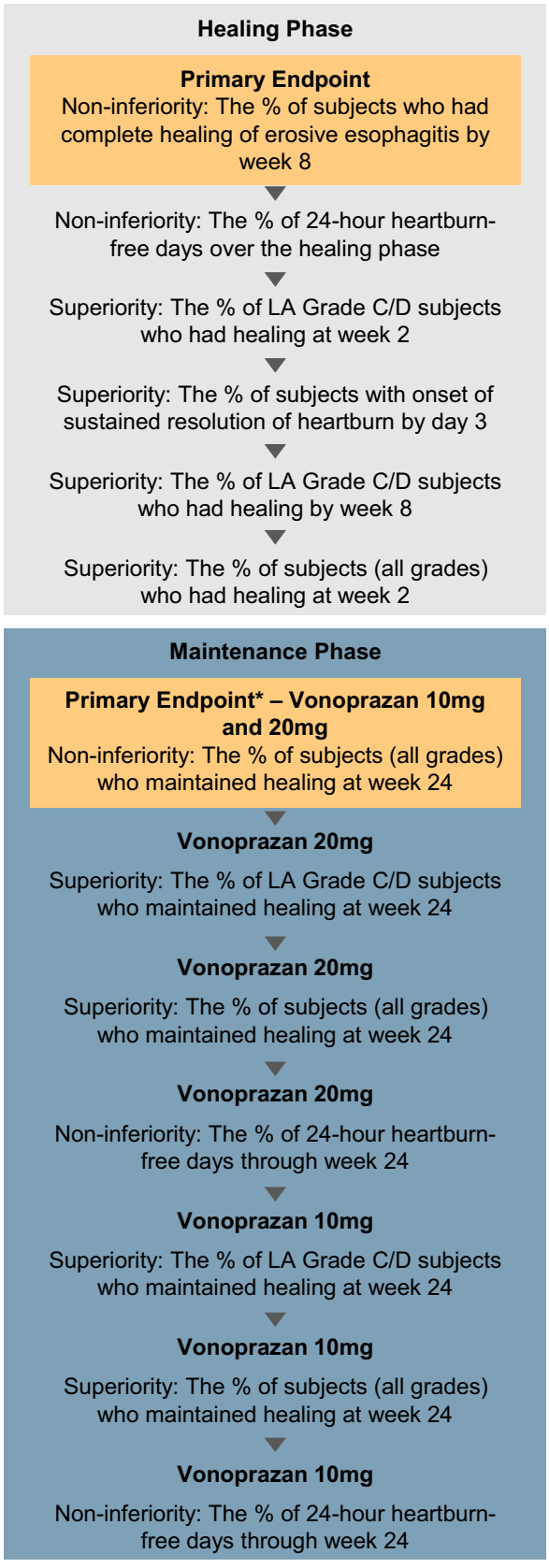
Healing phase. The primary analysis was a noninferiority comparison with a noninferiority margin of 10%, which retains $\geq$62% of the treatment effect of lansoprazole, 30 mg, based on prior placebo-controlled trials.[23,24] Assuming healing rates of 80% for both treatment arms, a sample size of 500 subjects per arm provides 97% power to demonstrate noninferiority using a Farrington-Manning test.

The primary and secondary end points were assessed using a fixed-sequence testing procedure (Figure 1). Comparisons were 2-sided and performed at the $\alpha = 0.05$ level in the sequence shown until a test was not significant. At that point, no further hypothesis testing was performed for subsequent end points. If noninferiority was shown for the primary analysis, superiority was assessed by the Farrington-Manning test as an exploratory analysis; if noninferiority was shown for the percentage of 24-hour heartburn-free days (margin of 15% based on Castell et al[23] with difference in means and 95% confidence interval [CI] computed using Welch's *t* test), superiority was assessed using Wilcoxon's rank sum test as an exploratory analysis.

Maintenance phase. The primary analysis was a noninferiority comparison with a noninferiority margin of 10%, which retains $\geq$74% of the treatment effect of lansoprazole, 15 mg, based on prior placebo-controlled trials.[8] A sample size of 265 subjects per treatment arm provides $\geq$90% power to demonstrate noninferiority and superiority using the Farrington-Manning test, assuming maintenance of healing rates of 82% for vonoprazan and 70% for lansoprazole.

Comparisons of the primary end point were adjusted using Hochberg's multiple comparisons method to test noninferiority of each vonoprazan dose group to lansoprazole. If both vonoprazan dose groups had $P \leq .05$, both were considered noninferior to lansoprazole. If 1 dose group had $P > .05$ and the other $P \leq .025$, the dose group with $P \leq .025$ was considered noninferior to lansoprazole. If noninferiority was declared for both vonoprazan dose groups from the primary analysis,

comparisons to lansoprazole for secondary end points were performed using a fixed-sequence testing procedure (Figure 1) until a test was not significant at the $\alpha = 0.05$ level. If non-inferiority was shown for the percentage of 24-hour heartburn-free days (margin of 15% based on Metz et al[25] with difference in means and 95% CI computed using Welch's t test), superiority was assessed using Wilcoxon's rank sum test as an exploratory analysis. Comparisons were 2-sided.



Gastric biopsies were taken from the greater and lesser curvature of the antrum and of the body during endoscopies at baseline and the final visit of the maintenance phase. Specimens were placed in 10% buffered formalin and shipped to a central pathology laboratory for processing (NeoGenomics, Aliso Viejo, CA, and Rolle, Switzerland). Hematoxylin and eosin staining was performed for biopsy specimens from the antrum and body. Immunohistochemistry staining for cluster of differentiation (CD) 56, synaptophysin, and chromogranin was performed for body biopsy specimens, with a negative control performed for each subject and stain. Histologic examination was performed by a single pathologist (NeoGenomics, Aliso Viejo, CA) blinded to clinical information, with assessments including presence or absence of gastric atrophy, intestinal metaplasia, dysplasia, or malignancy, as well as neuroendocrine cell proliferation (CD56, chromogranin, and synaptophysin) and enterochromaffin-like (ECL) cell hyperplasia in the gastric body specimens. Neuroendocrine cell proliferation was defined by the percentage of the total epithelial cells that were neuroendocrine cells positive for CD56, synaptophysin, or chromogranin. ECL cell hyperplasia was defined as linear or micronodular clusters of at least 5 cells or micronodular clusters ≤ 150 μm in greatest dimension.

Populations for analysis. The primary analysis population was the modified intent-to-treat data set: all subjects randomized who had documented erosive esophagitis at baseline in the healing phase or documented healing of erosive esophagitis at baseline in the maintenance phase and received ≥ 1 doses of the study medication. Given that the primary analyses for the healing and maintenance phase of the study were noninferiority comparisons, we also prespecified a per-protocol population for these analyses of the primary end points. Per-protocol population criteria included the following: subject received assigned study medication, was compliant with treatment, did not take PPI or histamine$_2$-receptor antagonist, had endoscopy performed by week 8 in the healing phase and week 24 in the maintenance phase, and had no other major protocol deviation (1 subject had a major deviation: bariatric surgery during maintenance phase). The safety set included all randomized subjects who received ≥ 1 doses of the study medication.

Missing data. The statistical analysis plan agreed to with regulatory authorities originally prespecified that patients with missing postbaseline endoscopy would be considered as non-responders for efficacy analyses. However, modification due to

Figure 1. Testing hierarchy shows fixed sequence of analyses used for primary and secondary efficacy end points in healing and maintenance phases. *The hypothesis testing of the primary end point of the maintenance phase was adjusted using Hochberg's multiple comparisons method to control the overall 0.05 level of significance to test the noninferiority of each dose group of vonoprazan to lansoprazole. The comparisons to lansoprazole, 15 mg, for the secondary efficacy end points were performed using this fixed-sequence testing procedure only after noninferiority was declared for both vonoprazan dose groups in the primary efficacy analysis.

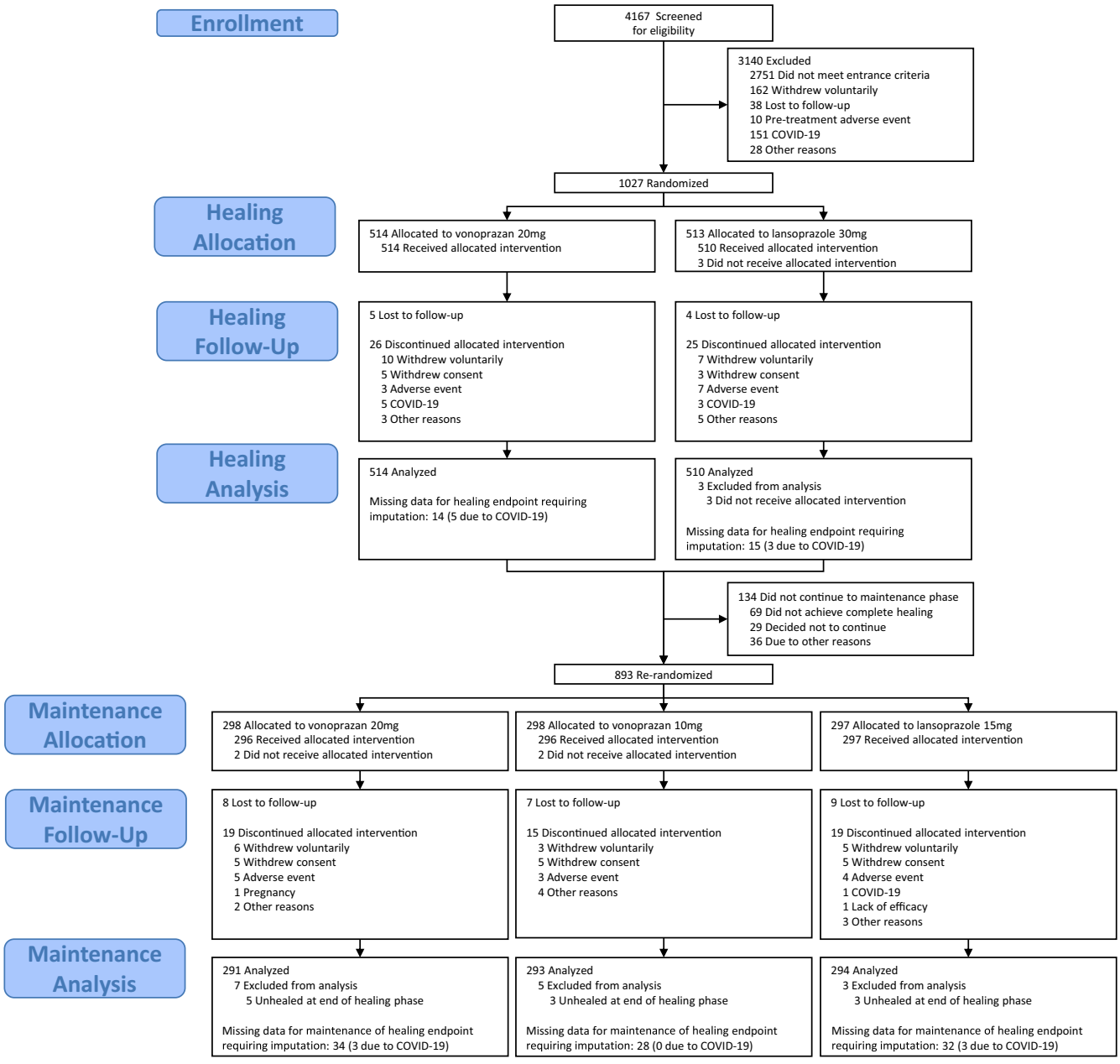


Figure 2. Flow diagram showing progression of patients through the study.

the potential impact of COVID-19 was incorporated into the study after the advent of the pandemic. Based on US Food and Drug Administration feedback, the statistical analysis plan was adjusted to impute missing data for subjects without a postbaseline endoscopy at a visit due to COVID-19–related reasons using a missing-at-random assumption using logistic regression with treatment effect and LA Grade as predictor variables. Subjects with missing endoscopy results not due to the COVID-19 pandemic were still imputed as nonresponders. Sensitivity analyses were conducted for the primary end points, with several imputation methods, including the most conservative method in which patients with missing data in the lansoprazole group were assumed to be healed and those in the vonoprazan group assumed to be not healed (Supplementary Table 1).

Subgroup analysis. The primary end points for both phases were analyzed for the multiple predefined subgroups (Supplementary Figure 1). The secondary end point, percentage of 24-hour heartburn-free days, also was analyzed separately for LA Grade A/B and C/D.

Results

From November 2019 to November 2020, 1027 subjects were randomized in the healing phase, and 893 with healing were randomized into the maintenance phase (Figure 2). Baseline characteristics are summarized in Table 1. LA Grade C/D esophagitis was present in 351 of the healing-phase subjects (34.3%).

Table 1. Selected Baseline Characteristics of Treatment Groups

Characteristics	Healing phase		Maintenance phase		
	Vonoprazan, 20 mg (n = 514)	Lansoprazole, 30 mg (n = 510)	Vonoprazan, 20 mg (n = 291)	Vonoprazan, 10 mg (n = 293)	Lansoprazole, 15 mg (n = 294)
Age, mean (SD), *y*	51.0 (13.4)	51.7 (14.1)	51.0 (14.5)	52.3 (13.8)	51.0 (13.0)
Female sex	256 (49.8)	287 (56.3)	146 (50.2)	159 (54.3)	171 (58.2)
Geographic region					
US	325 (63.2)	316 (62.0)	159 (54.6)	178 (60.8)	195 (66.3)
Europe	189 (36.8)	194 (38.0)	132 (45.4)	115 (39.2)	99 (33.7)
Race					
White	474 (92.2)	455 (89.2)	269 (92.4)	267 (91.1)	265 (90.1)
Black	23 (4.5)	41 (8.0)	17 (5.8)	15 (5.1)	20 (6.8)
Asian	7 (1.4)	6 (1.2)	3 (1.0)	4 (1.4)	3 (1.0)
Other/unknown	10 (1.9)	8 (1.6)	2 (0.7)	7 (2.4)	6 (2.0)
Latin American ethnicity	62 (12.1)	58 (11.4)	33 (11.3)	31 (10.6)	31 (10.5)
BMI, mean (SD), kg/m^2	30.8 (6.0)	31.5 (6.6)	31.0 (6.7)	31.6 (6.8)	31.1 (6.1)
Current smoker	77 (15.0)	70 (13.7)	38 (13.1)	39 (13.3)	42 (14.3)
Any alcohol use	313 (60.9)	315 (61.8)	187 (64.3)	183 (62.5)	180 (61.2)
PPI use	163 (31.7)	164 (32.2)	86 (29.6)	94 (32.1)	94 (32.0)
Cytochrome P450 2C19 status					
Extensive metabolizer	411 (80.0)	402 (78.8)	238 (81.8)	245 (83.6)	242 (82.3)
Poor metabolizer	9 (1.8)	9 (1.8)	6 (2.1)	4 (1.4)	6 (2.0)
Missing	94 (18.3)	99 (19.4)	47 (16.2)	44 (15.0)	46 (15.6)
Baseline erosive esophagitis					
LA Grade A	168 (32.7)	184 (36.1)	106 (36.4)	110 (37.5)	101 (34.4)
LA Grade B	169 (32.9)	152 (29.8)	93 (32.0)	88 (30.0)	97 (33.0)
LA Grade C	154 (30.0)	156 (30.6)	81 (27.8)	86 (29.4)	92 (31.3)
LA Grade D	23 (4.5)	18 (3.5)	11 (3.8)	9 (3.1)	4 (1.4)
Mean heartburn severity score (0-4)[a]	1.3 (0.8–2.0)	1.3 (0.6–1.9)	1.2 (0.7–1.8)	1.3 (0.6–1.9)	1.3 (0.6–2.0)
Days with heartburn	7 (5–7)	6 (4–7)	6 (4–7)	6 (4–7)	6 (4–7)
Serum gastrin ≥200 pg/mL	6 (1.2)	8 (1.6)	5 (1.7)	2 (0.7)	5 (1.7)
Serum gastrin, mean (SD), *pg/mL*	29.8 (45.6)	32.3 (62.8)	124.8 (158.6)	125.0 (147.7)	117.5 (121.4)

NOTE. Data are presented as n (%) or median (interquartile range), unless indicated otherwise.
SD, standard deviation.
[a]Mean severity of heartburn was calculated for each patient using the highest severity of heartburn (daytime or nighttime) recorded for each of the 7 days before treatment initiation. The median of the mean severities across the treatment group is presented.

Noncompliance was 14 (2.7%) and 23 (4.5%) for vonoprazan and lansoprazole in the healing phase, respectively, and 11 (3.7%), 6 (2.0%), and 14 (4.7%) for vonoprazan, 20 mg, vonoprazan, 10 mg, and lansoprazole, respectively, in the maintenance phase. The numbers of subjects with missing data for healing and maintenance of healing end points due to lack of postbaseline endoscopy are shown in the "Analysis" boxes of Figure 2.

Healing Phase

The primary analysis of healing by week 8 showed vonoprazan was noninferior to lansoprazole: 92.9% vs 84.6% (difference, 8.3%; 95% CI, 4.5%–12.2%, $P < .0001$) (Table 2), with noninferiority maintained in sensitivity analyses with differing imputation methods (Supplementary Table 1). Analysis in the per-protocol population yielded similar findings for healing with vonoprazan (n = 488) vs lansoprazole (n = 474): 94.7% vs 86.6% (difference, 8.1%; 95% CI, 4.1%–11.9%; $P < .0001$ for noninferiority). Vonoprazan was also superior on the predefined exploratory analysis (Table 2). Treatment effect was generally comparable across different subgroup analyses, with greater treatment effect in LA Grade C/D, as discussed below (Supplementary Figure 1).

Table 2. Primary and Secondary Efficacy End Points in Predefined Fixed-Sequence Analyses for Healing Phase

Efficacy end point	Vonoprazan, 20 mg (n = 514)	Lansoprazole, 30 mg (n = 510)	Difference (95% CI)
Healing by week 8, %	92.9	84.6	8.3 (4.5–12.2)[a,b]
24-hour heartburn-free days, mean (SD), %	66.8 (34.6)	64.1 (35.5)	2.7 (−1.6 to 7.0)[c]
Healing at week 2 in LA Grade C/D, %[d]	70.2	52.6	17.6 (7.4–27.4)[e]
Onset of sustained resolution of heartburn by day 3, n (%)	177 (34.4)	164 (32.2)	2.3 (−3.5 to 8.0)
Healing by week 8 in LA Grade C/D, %[d,f]	91.7	72.0	19.6 (11.8–27.6)
Healing at week 2, %[f]	74.3	68.2	6.1 (0.5–11.6)

SD, standard deviation.
[a]Noninferiority established in primary analysis (noninferiority margin was 10%, which required lower bound of 95% CI to be $> -10\%$; P for noninferiority $<.0001$).
[b]$P < .0001$ for superiority in predefined exploratory analysis performed after noninferiority established in primary analysis.
[c]Noninferiority established in predefined fixed-sequence analysis of secondary end point (noninferiority margin was 15%, which required lower bound of 95% CI to be $> -15\%$).
[d]Number for LA Grade C/D end points was 177 for vonoprazan and 174 for lansoprazole.
[e]$P = .0008$ for superiority in predefined fixed-sequence analysis of the secondary end point.
[f]Hypothesis testing was not performed because prior end point (sustained heartburn resolution) did not show superiority in fixed-sequence analysis.

Secondary end points assessed in fixed-sequence analyses revealed vonoprazan was noninferior to lansoprazole in mean 24-hour heartburn-free days (−1.6% lower 95% CI bound of difference higher than the noninferiority bound of −15%), was superior in healing at week 2 for LA Grade C/D esophagitis (70.2% vs 52.6%, $P = .0008$), and was not superior in sustained resolution of heartburn by day 3 (34.4% vs 32.2%; $P = .44$). Descriptive analyses for the remaining secondary end points showed higher rates of healing with vonoprazan than with lansoprazole at week 2 (difference, 6.1%; 95% CI, 0.5%–11.6%) and in LA Grade C/D esophagitis by week 8 (difference, 19.6%; 95% CI, 11.8%–27.6%). Post hoc analysis revealed healing by week 8 for LA Grade A/B esophagitis of 93.5% for vonoprazan and 91.2% for lansoprazole (difference, 2.3%; 95% CI, −1.8% to 6.4%).

Predefined exploratory analysis of distributions of percentage of heartburn-free days did not show superiority of vonoprazan. Medians were 81.3% for vonoprazan and 78.3% for lansoprazole and were similar for the 2 treatment groups

Table 3. Primary and Secondary Efficacy End Points in Predefined Fixed-Sequence Analyses for Maintenance Phase

Efficacy end point	Vonoprazan, 20 mg(n = 291)	Vonoprazan, 10 mg(n = 293)	Lansoprazole, 15 mg(n = 294)	Difference (95% CI) vonoprazan, 20 mg, vs lansoprazole, 15 mg	Difference (95% CI) vonoprazan, 10 mg, vs lansoprazole 15 mg
Healing maintained, %	80.7	79.2	72.0	8.7 (1.8–15.5)[a,b]	7.2 (0.2–14.1)[a,b]
Healing maintained in LA Grade C/D, %[c]	77.2	74.7	61.5	15.7 (2.5–28.4)[d]	13.3 (0.02–26.1)[d]
24-hour heartburn-free days, mean (SD), %	80.6 (30.0)	80.9 (28.6)	78.6 (27.5)	2.0 (−2.6 to 6.7)[e]	2.3 (−2.3 to 6.8)[e]

SD, standard deviation.
[a]Noninferiority established in primary analyses (noninferiority margin was 10%, which required lower bound of 95% CI to be $> -10\%$; P for noninferiority $<.0001$).
[b]P values for superiority were .014 for 20 mg and .044 for 10 mg in predefined fixed-sequence analyses performed after noninferiority established in primary analyses.
[c]Number for LA Grade C/D end point was 95 for vonoprazan, 10 mg, 92 for vonoprazan, 20 mg, and 96 for lansoprazole.
[d]P values for superiority were .020 for 20 mg and .049 for 10 mg in predefined fixed-sequence analyses of secondary end point.
[e]Noninferiority established in predefined fixed-sequence analyses of secondary end point (noninferiority margin was 15%, which required lower bound of 95% CI to be $> -15\%$).

in LA Grade A/B (75.0% vs 76.5%) but higher with vonoprazan in LA Grade C/D esophagitis (87.5% vs 80.0%).

Maintenance Phase

The primary analysis of maintenance of healing at week 24 showed both doses of vonoprazan were noninferior to lansoprazole (vonoprazan, 20 mg, 80.7%; vonoprazan, 10 mg, 79.2%; lansoprazole, 72.0%; $P < .0001$ for both comparisons) (Table 3), with noninferiority maintained in sensitivity analyses with differing imputation methods (Supplementary Table 1). Analysis in the per-protocol population also documented noninferiority, with maintenance of healing of 90.7% with vonoprazan, 20 mg (n = 246), 89.2% with vonoprazan, 10 mg (n = 259), and 79.7% for lansoprazole (n = 251) (difference vs vonoprazan, 20 mg, 11.0%; 95% CI, 4.8%–17.3%, $P < .0001$; vs vonoprazan, 10 mg, 9.5%; 95% CI, 3.3%–15.9%; $P < .0001$). Treatment effect was generally comparable across different subgroup analyses (Supplementary Figure 1).

Fixed-sequence analyses of secondary end points showed both doses of vonoprazan were superior to lansoprazole for maintenance of healing in LA Grade C/D esophagitis (vonoprazan, 20 mg, 77.2% [$P = .020$]; vonoprazan, 10 mg, 74.7% [$P = .049$]; lansoprazole, 61.5%) and in all grades of esophagitis combined, and were noninferior to lansoprazole in 24-hour heartburn-free days (Table 3). Post hoc analysis revealed maintenance of healing for LA Grade A/B esophagitis of 82.3% for vonoprazan, 20 mg, 81.3% for vonoprazan, 10 mg, and 77.1% for lansoprazole (difference vs 20 mg, 5.3%; 95% CI, −2.7% to 13.2%; difference vs 10 mg, 4.3%; 95% CI, −3.8% to 12.3%).

Predefined exploratory analysis showed higher distributions of percentage of heartburn-free days for vonoprazan. Medians were 95.2% for vonoprazan, 20 mg; 94.6% for vonoprazan, 10 mg; and 89.3% for lansoprazole ($P = .002$ and $P = .026$ vs 20 mg and 10 mg), with similar findings in LA Grade A/B (vonoprazan, 20 mg, 94.3%; vonoprazan, 10 mg, 94.0%; and lansoprazole, 87.8%) and LA Grade C/D patients (vonoprazan, 20 mg, 97.6%; vonoprazan, 10 mg, 95.4%; and lansoprazole, 90.5%).

Safety and Tolerability

The proportion of subjects with adverse events in the safety population is provided in Table 4. The most common adverse event reported in the healing phase was diarrhea and in the maintenance phase was COVID-19. Two subjects died of COVID-19 during the maintenance phase in the vonoprazan, 20 mg, group.

Serum gastrin rose with vonoprazan to a greater extent than with lansoprazole (Table 4). Four weeks after the end of maintenance therapy, serum gastrin dropped to 77.0 pg/mL (vonoprazan, 20 mg), 65.9 pg/mL (vonoprazan, 10 mg), and 59.7 pg/mL (lansoprazole).

Comparison of gastric biopsy specimens from endoscopies at baseline and at the end of the maintenance phase showed net changes of 1, −3, and, −3 in the number of patients with gastric atrophy in the vonoprazan, 20 mg, vonoprazan, 10 mg, and lansoprazole groups, and net changes of −2, −3, and 2 in the number of patients with gastric intestinal metaplasia (Supplementary Tables 2 and 3). The changes from baseline for neuroendocrine cell proliferation percentages (CD56, chromogranin, and synaptophysin) were virtually nil and

Table 4. Safety and Tolerability of Treatment Groups in Patients Receiving at Least 1 Dose of Study Medication

	Healing phase		Maintenance phase		
Variable	Vonoprazan, 20 mg (n = 514)	Lansoprazole, 30 mg (n = 510)	Vonoprazan, 20 mg (n = 296)	Vonoprazan, 10 mg (n = 296)	Lansoprazole, 15 mg (n = 297)
Adverse events	155 (30.2)	149 (29.2)	167 (56.4)	160 (54.1)	150 (50.5)
Severe adverse events	2 (0.4)	4 (0.8)	17 (5.7)	8 (2.7)	8 (2.7)
Serious adverse events	3 (0.6)	3 (0.6)	14 (4.7)	10 (3.4)	7 (2.4)
Adverse event leading to treatment discontinuation	5 (1.0)	11 (2.2)	8 (2.7)	2 (0.7)	2 (0.7)
COVID-19	11 (2.1)	9 (1.8)	30 (10.1)	18 (6.1)	20 (6.7)
Clostridium difficile infection	0	0	0	0	0
Bone fracture	1 (0.2)	0	4 (1.4)	2 (0.7)	1 (0.3)
ALT or AST >3× upper limit of normal	2 (0.4)	1 (0.2)	1 (0.3)	3 (1.0)	6 (2.0)
Serum gastrin, mean (SD), *pg/mL*	158.3 (143.6)	64.1 (68.6)	223.0 (216.6)	166.0 (189.8)	74.1 (96.1)
Serum gastrin >500 pg/mL	22 (4.3)	7 (1.4)	47 (15.9)	33 (11.1)	4 (1.3)

NOTE. Data are presented as n (%) unless indicated otherwise.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.

similar across all 3 maintenance treatment arms (Supplementary Tables 4–6). The net increase in subjects with ECL cell hyperplasia was slightly higher with vonoprazan, 20 mg (13 of 263 [4.9%]) than with vonoprazan, 10 mg (6 of 266 [2.3%]), and lansoprazole, 15 mg (3 of 260 [1.2%]) (Supplementary Table 7). No evidence of neoplasia was identified over the course of the study.

Discussion

This double-blind randomized trial confirmed its primary hypotheses that vonoprazan was noninferior to lansoprazole for healing and maintenance of healing of erosive esophagitis. Furthermore, vonoprazan achieved higher rates of healing and maintenance of healing than lansoprazole, with the differences seen primarily in those with more severe esophagitis (LA Grades C and D). The differences in healing rates were seen after 2 weeks of therapy and maintained throughout the study.

This is the first study to compare a PCAB and a PPI for erosive esophagitis in a Western population. The differences between vonoprazan and lansoprazole in healing tended to be greater in our study than in prior studies from Asia. The 8-week healing rates for vonoprazan, 20 mg, vs lansoprazole, 30 mg, in 3 much smaller Asian randomized trials were 92.4% vs 91.3%,[19] 99.0% vs 95.5%,[18] and 96.5% vs 95.5%,[17] compared with our results of 92.9% vs 84.6%, despite comparable proportions with LA Grade C or D esophagitis.

Higher efficacy for PPIs might be expected in Asian studies. First, poor metabolizers of cytochrome P450 2C19, which is much more common in Asian than Western populations (16%–17% in the Asian studies[17,18] vs 2% in our trial), have greater acid inhibition with PPIs but not PCABs.[15] Second, patients with *H pylori* infection were excluded from our study, but not the Asian studies cited. PPIs have greater efficacy in individuals with vs those without *H pylori* infection.[26,27]

A prior randomized trial from Japan found maintenance of healing at 24 weeks with vonoprazan, 20 mg, vonoprazan, 10 mg, and lansoprazole, 15 mg, to be 98%, 95%, and 83%,[22] respectively, compared with our rates of 81%, 79%, and 72%, respectively. Reasons for the lower rates of maintenance of healing in all groups in our study are uncertain but might include a higher proportion with LA Grade C or D esophagitis in our study (32% vs 20%), exclusion of *H pylori* infection in our trial, differences in handling missing data, higher BMI in our study (30 kg/m^2 vs 25 kg/m^2), poorer medication compliance in Western populations over 24 weeks, and greater parietal cell mass and lower prevalence of chronic atrophic gastritis in Western populations.[28]

The impact of more potent acid inhibition with vonoprazan was seen predominantly in those with more severe esophagitis (LA Grades C or D). An 18% absolute difference in healing was seen in this group at 2 weeks, and the difference in healing was maintained to a similar degree at 8 weeks (20%) and after 24 weeks of maintenance therapy (13%–16%). This confirms the importance of maximizing acid inhibition in healing and preventing recurrence of more severe erosive esophagitis.[7,18,22,23]

The number of median heartburn-free days was not superior with vonoprazan in the healing phase and was only 5% to 6% greater with vonoprazan in the maintenance phase. The fact that results for heartburn relief did not mirror results for healing of erosive esophagitis is not surprising. Prior studies demonstrate that doubling the dose of PPI has limited impact on symptom relief.[23,29-31] Thus, greater increases in intragastric acid inhibition will not necessarily fully translate into better heartburn control.

The potential impact of more potent inhibition of gastric acid with long-term administration of vonoprazan also needs to be considered. The hormone gastrin is a growth factor that can stimulate the proliferation of ECL cells, gastric stem cells, and Barrett's metaplastic cells.[32,33] Suppression of gastric acid secretion can induce hypergastrinemia, a feature that has previously raised concern that chronic PPI use might result in ECL cell hyperplasia, neuroendocrine tumors, gastric cancer, and Barrett's-related esophageal adenocarcinoma. A systematic review concluded that long-term PPI therapy is indeed associated with ECL cell hyperplasia but not with an increased risk for neuroendocrine tumors or gastric cancers.[34]

Furthermore, the Aspirin and Esomeprazole Chemoprevention in Barrett's Metaplasia Trial (AspECT), which monitored 2557 patients with Barrett's esophagus randomized to high-dose PPI (40 mg of esomeprazole twice daily) or an approved maintenance dose of PPI (20 mg of esomeprazole once daily)—with or without aspirin—for a median of 8.9 years, found a reduction in a composite end point of high-grade dysplasia, esophageal adenocarcinoma, and death with high-dose vs low-dose PPI.[35]

Thus, early concerns that chronic PPI use would result in malignancy have not been substantiated. The long-term use of PPIs has been associated with an increased risk of gastric fundic gland polyps, presumably due to hypergastrinemia,[36] although these polyps typically have virtually no malignant potential.[37] Data on fundic gland polyps were not collected as part of our protocol. Because PCABs such as vonoprazan also induce hypergastrinemia, any PPI effects caused by hypergastrinemia are expected to be associated with PCABs as well.

As expected, serum gastrin in our study increased to a greater extent with vonoprazan than lansoprazole, with 16% of those taking 20 mg exceeding 500 pg/mL at the end of maintenance therapy. After discontinuation of vonoprazan, gastrin levels dropped by ~60% to 65% within 4 weeks. The duration of our study was too short to adequately evaluate the risk of long-term PCAB use on the development of neoplasia and other histologic outcomes. Changes in gastric histology and in neuroendocrine cell proliferation were negligible and comparable among treatment groups. We observed a possible trend to a small net increase of 2.6% to 3.7% in the proportion of subjects with ECL cell hyperplasia at the end of maintenance therapy with vonoprazan, 20 mg, compared with lower-dose vonoprazan and lansoprazole, 15 mg. Neoplasia was not identified in any subject. Whether the more potent acid inhibition and higher levels of gastrin seen with PCABs induce additional

histologic or clinical effect with long-term administration as compared with PPIs requires further study.

Strengths of this study relate to study design: a large multicenter double-blind randomized trial with blinded central adjudication of erosive esophagitis rather than a local site investigator's assessment used to determine eligibility and endoscopic outcomes. Most prior erosive esophagitis studies have not mandated blinded central readings of endoscopic photographs for both study entry eligibility and response to treatment.

Limitations of our trial are those related to study population and generalizability. Our study population was primarily a White European and US population, limiting our ability to generalize results to other groups. Our study is not generalizable to patients with *H pylori* infection. Given that PPIs may have greater efficacy in individuals with *H pylori* infection,[26,27] smaller differences potentially may have occurred with inclusion of subjects positive for *H pylori* infection. In addition, our results cannot be generalized to all patients presenting with GERD-like symptoms. Patients with symptoms such as heartburn but without erosive esophagitis represent a more heterogeneous group with less consistent response to gastric acid inhibition.

Conclusions

Vonoprazan was noninferior and superior to the PPI lansoprazole in healing and maintenance of healing of erosive esophagitis in patients negative for *H pylori* infection from the US and Europe. Furthermore, differences in favor of vonoprazan were greater in patients with LA Grade C/D esophagitis than in those with LA Grade A/B esophagitis. Our prespecified analyses indicated superiority for vonoprazan in patients with LA Grade C/D esophagitis, while post hoc analyses did not establish superiority in those with LA Grade A/B esophagitis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2022.09.041.

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Conflicts of interest
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Data Availability
Individual participant data will not be shared.