Vonoprazan Triple and Dual Therapy for *Helicobacter pylori* Infection in the United States and Europe: Randomized Clinical Trial

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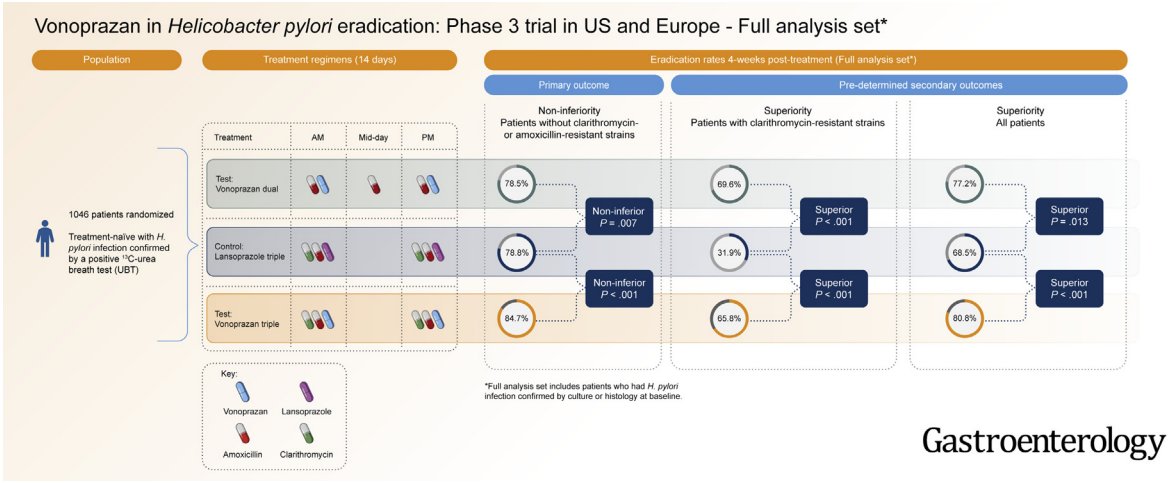

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BACKGROUND & AIMS: Novel, effective treatments for *Helicobacter pylori* infection are needed. This study evaluated the efficacy of vonoprazan, a potassium-competitive acid blocker, vs standard treatment on *H pylori* eradication in the United States and Europe. **METHODS:** In a randomized, controlled, phase 3 trial, treatment-naïve adults with *H pylori* infection were randomized 1:1:1 to open-label vonoprazan dual therapy (20 mg vonoprazan twice daily; 1 g amoxicillin 3 times daily), or double-blind triple therapy twice a day (vonoprazan 20 mg or lansoprazole 30 mg; amoxicillin 1 g; clarithromycin 500 mg) for 14 days. The primary outcome was noninferiority in eradication rates in patients without clarithromycin- and amoxicillin-resistant strains (noninferiority margin = 10%). Secondary outcomes assessed superiority in eradication rates in clarithromycin-resistant infections, and in all patients. **RESULTS:** A total of 1046 patients were randomized. Primary outcome eradication rates (nonresistant strains): vonoprazan triple therapy 84.7%, dual therapy 78.5%, vs lansoprazole triple therapy 78.8% (both noninferior; difference 5.9%; 95% confidence interval [CI], −0.8 to 12.6; $P < .001$; difference –0.3%; 95% CI, −7.4 to 6.8; $P = .007$, respectively). Eradication rates in clarithromycin-resistant infections: vonoprazan triple therapy 65.8%, dual therapy 69.6%, vs lansoprazole triple therapy 31.9% (both superior; difference 33.9%; 95% CI, 17.7–48.1; $P < .001$; difference 37.7%; 95% CI, 20.5–52.6; $P < .001$, respectively). In all patients, vonoprazan triple and dual therapy were superior to lansoprazole triple therapy (80.8% and 77.2%, respectively, vs 68.5%, difference 12.3%; 95% CI, 5.7–18.8; $P < .001$; difference 8.7%; 95% CI, 1.9–15.4; $P = .013$). Overall frequency of treatment-emergent adverse events was similar between vonoprazan and lansoprazole regimens ($P > .05$). **CONCLUSION:** Both vonoprazan-based regimens were superior to proton pump inhibitor–based triple therapy in clarithromycin-resistant strains and in the overall study population. ClinicalTrials.gov; NCT04167670.

Keywords: *Helicobacter pylori*; Vonoprazan; Antimicrobial Resistance; PPI.

Helicobacter pylori is a leading cause of peptic ulcer, gastric adenocarcinoma, and gastric mucosa–associated lymphoid tissue lymphoma.[1] Guidelines recommend *H pylori* eradication whenever identified.[1,2]

For several decades and across many countries, including the United States, the treatment landscape for *H pylori* infection has been dominated by proton pump inhibitor (PPI)-based triple therapy, comprising a PPI, clarithromycin, and amoxicillin or metronidazole.[1,2] Eradication rates with PPI-based triple therapy have dropped below 80% in Europe and the United States,[2–4] mainly attributed to rising rates of clarithromycin resistance.[3] Hence, there is a pressing need to optimize management. *H pylori* susceptibility to antibiotics is influenced by intragastric pH, which can modify their stability and activity, and affect the replication status of *H pylori*.[5] Some antibiotics require active *H pylori* replication for optimal antimicrobial activity.[6] Therefore, sustained control of intragastric pH may improve *H pylori* eradication rates.[6,7]

Vonoprazan is a potassium-competitive acid blocker, currently approved for the treatment of *H pylori* infection and other acid-related diseases in several countries, including Japan. It increases intragastric pH rapidly and potently and maintains it to a greater degree than PPIs; this has been associated with higher *H pylori* eradication rates.[8] Vonoprazan could therefore enhance *H pylori* therapy by optimizing gastric acid suppression and antimicrobial activity. Hitherto, clinical experience with vonoprazan-based eradication regimens has been limited to East Asian countries. In meta-analyses of Asian trials, the triple combination of vonoprazan, amoxicillin, and clarithromycin was associated with significantly higher eradication rates than PPI-based triple therapy,[9] including in patients with clarithromycin-resistant strains ($P < .001$).[10] Furthermore, in Japan, the dual combination of vonoprazan and amoxicillin produced eradication rates that were similar to vonoprazan-based triple therapy,[11–13] justifying its further evaluation.[14]

Here, we report data from the first phase 3 clinical trial from the United States and Europe to compare the efficacy and adverse events of vonoprazan triple and dual therapy with PPI-based triple therapy for the eradication of *H pylori*.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

This was a U.S. and European phase 3 study investigating the efficacy of regimens containing vonoprazan, an investigational potassium-competitive acid blocker, compared with lansoprazole for *Helicobacter pylori* infection eradication.

NEW FINDINGS

Based on the study results, vonoprazan regimens (dual [amoxicillin] and triple [amoxicillin and clarithromycin]) provide potential alternatives to standard proton pump inhibitor–triple therapy. More than 20% of strains were clarithromycin-resistant.

LIMITATIONS

This study was performed in treatment-naïve patients from across the United States and Europe. However, geographic distribution was not equal, limiting applicability of the results to some patient groups.

IMPACT

These results suggest that vonoprazan triple and dual therapies present efficacious alternatives to standard triple therapy for the eradication of *Helicobacter pylori* infection.

Methods

Trial Conduct and Oversight

This was a multicenter, randomized, clinical trial conducted at multiple sites in the United States and Europe. The institutional review boards at participating institutions approved the protocol, which was in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent before study entry.

Data were collected by the investigators, analyzed by statisticians who were funded by the sponsor, and interpreted by the authors, including employees of the sponsor. All authors had access to the study data and reviewed and approved the final manuscript.

At the outbreak of the Coronavirus Disease 2019 (COVID-19) pandemic, the study was paused completely for 6 weeks. Study resumption proceeded according to local health guidelines.

Patients

Eligible patients were ≥18 years old and had at least 1 of the following clinical conditions: dyspepsia; a recent/new diagnosis of nonbleeding peptic ulcer; history of peptic ulcer not previously treated for *H pylori* infection; or requirement for long-term, nonsteroidal, anti-inflammatory drug treatment at a stable dose. They were treatment-naïve and had *H pylori* infection confirmed with a positive ^{13}C-urea breath test (UBT) (BreathTek; Otsuka America Pharmaceutical, Inc, Rockville, MD).

At screening, all patients underwent endoscopic gastric mucosal biopsy. Two biopsy samples (greater curve of the antrum and lesser curve of the body) were taken for culture and antimicrobial susceptibility testing. One sample each from the greater and lesser curve of the antrum and the greater and lesser curve of the body was taken for histopathologic evaluation for the presence of *H pylori*. Positive *H pylori* status

Abbreviations used in this paper: **CI, confidence interval; COVID-19, Coronavirus Disease 2019; FDA, Food and Drug Administration; PP, per-protocol; PPI, proton pump inhibitor; PPp, per protocol-primary; TEAE, treatment-emergent adverse event; UBT, urea breath test.**

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confirmed by histology or culture was required to be included in the efficacy analyses sets. Patients with gastric cancer, gastric or duodenal ulcer with current or recent bleeding, or clinically significant gastrointestinal bleeding within 4 weeks of randomization were excluded from enrollment. Full details of the criteria for patient selection are provided in the Supplementary Appendix.

Randomization and Interventions

At trial initiation, patients were randomly assigned 1:1:1 to receive open-label vonoprazan dual therapy (vonoprazan 20 mg twice daily and amoxicillin 1 g 3 times daily), or double-blind triple therapy with either vonoprazan 20 mg twice daily, or lansoprazole 30 mg twice daily, each given with amoxicillin 1 g twice daily, and clarithromycin 500 mg twice daily for 14 days. Patients took their treatment with water 30 minutes before meals. In accordance with Good Manufacturing Practice Guidance, amoxicillin must be handled in dedicated facilities to prevent cross-contamination. For this study, it was not possible to identify a supplier with dedicated facilities that could handle amoxicillin. Therefore, it was not possible to carry out blinding of amoxicillin for the dual therapy group. Patients were randomized using a central, password-protected, web-based randomization system. The randomization used a block size of 6. There were no stratification factors.

Trial Assessments

Demographic characteristics, relevant medical history, and pertinent clinical conditions were obtained at the screening visit. Data on vital signs and laboratory assessments were collected at randomization and at the end of week 2. Treatment-emergent adverse events (TEAEs) and concomitant medication use were recorded. Adverse events were summarized for patients who received at least 1 dose of study drug.

Primary outcome. *H pylori* status was assessed by ^{13}C-UBT at week 6 (4 weeks after the last dose of study drugs). ^{13}C-UBT results that were obtained between 27 and 141 days after the last dose were allowed for the full analysis set because of the operational challenges with visit scheduling because of the COVID-19 pandemic. In accordance with treatment guidelines,[1,2] PPIs or antimicrobials were not permitted in the 2 weeks or 30 days, respectively, before the baseline ^{13}C-UBT, and were not permitted again until after the test-of-cure ^{13}C-UBT (unless as part of the allocated study treatment). Patients who remained *H pylori*–positive underwent follow-up endoscopy with repeat antimicrobial susceptibility testing for clarithromycin, amoxicillin, and metronidazole, and were then treated per local standard of care. The primary endpoint was the proportion of patients with strains that were not resistant to clarithromycin or amoxicillin with successful *H pylori* eradication. The nonresistant analysis population was recommended by the Food and Drug Administration (FDA), and this endpoint was assessed for noninferiority of vonoprazan regimens compared with lansoprazole triple therapy.

Secondary outcomes. Predetermined secondary endpoints were the proportion of patients with *H pylori* eradication among those with clarithromycin-resistant strains at baseline, and the proportion of all patients with *H pylori* eradication. These endpoints were assessed for the superiority of vonoprazan regimens compared with lansoprazole triple therapy.

Sample Size Calculation

Sample size was calculated based on the primary endpoint. Assuming an eradication rate for the primary endpoint of 90% for all therapies,[15] 260 patients without a clarithromycin- or amoxicillin-resistant strain per treatment group would provide >90% power to achieve noninferiority with a noninferiority margin of 10%.[16] Assuming 20% of patients would have clarithromycin-resistant strains at baseline,[17] 975 patients were required for enrollment.

We conducted this as a noninferiority study because the comparator group given was a standard, approved treatment that is commonly prescribed in the United States and Europe.[18–20] A noninferiority margin of 10% was chosen to ensure preservation of the clinically important incremental contribution of lansoprazole to the effectiveness of clarithromycin and amoxicillin in *H pylori* eradication. Historically, when lansoprazole was added to amoxicillin and clarithromycin, and to amoxicillin alone, the incremental contributions to improvement in eradication rates were 32% and 75%, respectively, over amoxicillin and clarithromycin alone and amoxicillin alone (ie, without a PPI).[21,22] Therefore, a 10% noninferiority margin would ensure at least 67% of the incremental treatment effect when lansoprazole was added to amoxicillin/clarithromycin and at least 86% of the incremental treatment effect when added to amoxicillin alone. Therefore, if vonoprazan triple and dual therapies were within the 10% noninferiority margin, this would demonstrate that adding vonoprazan retains a similar incremental benefit to lansoprazole over using the antibiotics alone.

Statistical Analysis

Efficacy analyses were performed primarily using the full analysis set that comprised participants who had *H pylori* infection at baseline documented by both ^{13}C-UBT and biopsy (either by histologic analysis or culture). Despite a specificity of 89.7% for the ^{13}C-UBT,[23] confirmation of *H pylori* infection by both breath test and biopsy was required for the full analysis set based on FDA guidance for the design of *H pylori* studies and to increase certainty of infection. The inclusion criteria required a positive ^{13}C-UBT, the results of which were available at the time of randomization. Because of the required processing time for testing, the biopsy-based *H pylori* test results (culture and histology) were not available at the time of randomization. Some randomized patients had negative *H pylori* biopsy results and were thus excluded from the full analysis set and efficacy analyses. The primary endpoint analysis to test for noninferiority was performed on the full analysis set (primary), which comprised only full analysis set participants with strains that were not resistant to amoxicillin or clarithromycin. The secondary endpoint analyses for superiority were performed on full analysis set participants with clarithromycin-resistant strains and on all full analysis set participants.

Analyses were conducted in a hierarchical order for each comparison (vonoprazan dual therapy vs lansoprazole triple therapy and vonoprazan triple therapy vs lansoprazole triple therapy). The first was noninferiority for the primary endpoint, followed by superiority in patients with clarithromycin-resistant strains, followed by superiority in all patients.

The type 1 error was controlled at an overall α level of 0.05 using hierarchical testing of the primary and secondary

endpoints and weighted Bonferroni for the regimen comparisons. An α level of 0.04 was initially assigned to vonoprazan triple therapy, and an α level of 0.01 was initially assigned to vonoprazan dual therapy. Endpoints were tested in the prespecified sequential order described previously. If all endpoints (noninferiority for primary endpoint and superiority for secondary endpoints) were significant for a therapy, the α could be passed to the other therapy, if needed. Therefore, endpoints for the other therapy could have been re-tested at the 0.05 level in hierarchical order. All testing for noninferiority and superiority was reported as 2-sided at α.

A point estimate and 2-sided 95% confidence interval (CI) of the difference in eradication rates between each of the 2 vonoprazan groups and the lansoprazole group was calculated via the Miettinen and Nurminen method for the primary and secondary endpoints.[24] Noninferiority for the primary endpoint was assessed with a Farrington and Manning test with a noninferiority margin of 10%. Superiority of the secondary endpoints in the full analysis set (all patients) and patients with clarithromycin-resistant strains was assessed via the Farrington and Manning test of the null hypothesis difference $\leq$0 vs the alternative hypothesis difference >0. For each noninferiority comparison of the primary endpoint yielding statistical significance, an exploratory analysis assessed superiority via the Farrington and Manning test of the null hypothesis difference $\leq$0 vs the alternative hypothesis difference >0. Patients without a post-baseline ^{13}C-UBT result were considered treatment failures as prespecified in the study protocol.

Evaluation of the primary and secondary endpoints was repeated in the per-protocol (PP) set, defined as all patients who had taken $\geq$75% of each study drug, had a documented ^{13}C-UBT performed within the visit window to test outcome (between 28 and 56 days after the end of treatment, consistent with the FDA guidance for *H pylori* studies), and had not received any other antimicrobial within 7 days, or PPI or high-dose H_2-receptor antagonist within 14 days of the first day of treatment until the test-of-cure assessment at week 6 (unless given for treatment failure).

Statistical analyses were performed using SAS for Windows, version 9.4 (SAS Institute, Cary, NC).

Results

Patient Disposition and Characteristics

Enrollment occurred between December 10, 2019, and January 14, 2021, at 103 sites in the United States, the United Kingdom, Bulgaria, the Czech Republic, Hungary, and Poland. A total of 1046 of 3385 patients screened for eligibility were randomized; 349 to vonoprazan triple therapy, 349 to vonoprazan dual therapy, and 348 to lansoprazole triple therapy (Figure 1). Final follow-up was completed on March 18, 2021.

Of patients randomized, 4.5% (47 of 1046) did not complete the study, including 7 who did not receive study drug (Figure 1). The full analysis set included 94.8% (992 of 1046) of randomized patients. Patients were excluded from the full analysis set if *H pylori* infection was not documented by biopsy and ^{13}C-UBT. Biopsy results were not available at the time of randomization and 4.9% (51 of 1046) of randomized patients were excluded from the full analysis set because of lack of confirmation of infection by biopsy. Fifty-three (5.3%) of 992 patients in the full analysis set had breath tests taken outside of the 28- to 56-day window, over a range of 27 to 141 days. Baseline characteristics of patients in the full analysis set were comparable among groups (Table 1). Reasons for exclusion from the PP set were not receiving a test-of-cure ^{13}C-UBT within the required window (71 of 1046; 6.8%), and <75% compliance with study drugs (92 of 1046; 8.8%).

Primary Endpoint: Noninferiority in Patients Without Clarithromycin- or Amoxicillin-Resistant Strains

Vonoprazan triple and dual regimens met the primary endpoint of noninferiority to lansoprazole triple therapy in the full analysis set (primary). Vonoprazan triple therapy eradicated *H pylori* in 84.7% (222 of 262) of patients vs 78.8% (201 of 255) for lansoprazole triple therapy (difference 5.9%; 95% CI, −0.8 to 12.6; noninferiority $P < .001$; Figure 2). Vonoprazan dual therapy eradicated *H pylori* in 78.5% (208 of 265) of patients (difference to lansoprazole triple therapy –0.3%; 95% CI, −7.4 to 6.8; noninferiority $P = .007$; Figure 2). Noninferiority was maintained in the PP primary (PPp) population: 90.4% (198 of 219) for vonoprazan triple therapy and 81.2% (177 of 218) for vonoprazan dual therapy, vs 82.1% (174 of 212) for lansoprazole (difference 8.3%; 95% CI, 1.9–15.0; $P < .001$; −0.9%; 95% CI, −8.3 to 6.5; $P = .016$, respectively). Eradication rates in the United States and Europe for triple therapy were 79.6% (86 of 108) and 88.3% (136 of 154), respectively. For vonoprazan dual therapy, corresponding rates were 76.1% (86 of 113) and 80.3% (122 of 152), respectively. For lansoprazole triple therapy, these were 78.4% (80 of 102) and 79.1% (121 of 153), respectively.

For the primary endpoint, approximately 5% of patients had missing data imputed, including 14 patients in each vonoprazan group and 10 in the lansoprazole group with missing ^{13}C-UBT results who were included in the analysis as "not eradicated." In a prespecified exploratory analysis, vonoprazan triple therapy produced higher eradication rates than lansoprazole triple therapy in the PPp population ($P = .012$).

Secondary Endpoints

Superiority in patients with clarithromycin-resistant strains. Vonoprazan triple therapy eradicated *H pylori* in 65.8% of patients (48 of 73) with clarithromycin-resistant strains in the full analysis set compared with 31.9% (23 of 72) on lansoprazole triple therapy (difference 33.9%; 95% CI, 17.7–48.1; $P < .001$; Figure 3). PP eradication rates were 67.2% (39 of 58) and 29.0% (18 of 62), respectively (difference 38.2%; 95% CI, 20.6–53.4; $P < .001$). Vonoprazan dual therapy eradicated clarithromycin-resistant *H pylori* infection in 69.6% of patients (39 of 56) compared with 31.9% (23 of 72) with lansoprazole triple therapy (difference 37.7%; 95% CI, 20.5–52.6; $P < .001$; Figure 3). The eradication rate with vonoprazan dual

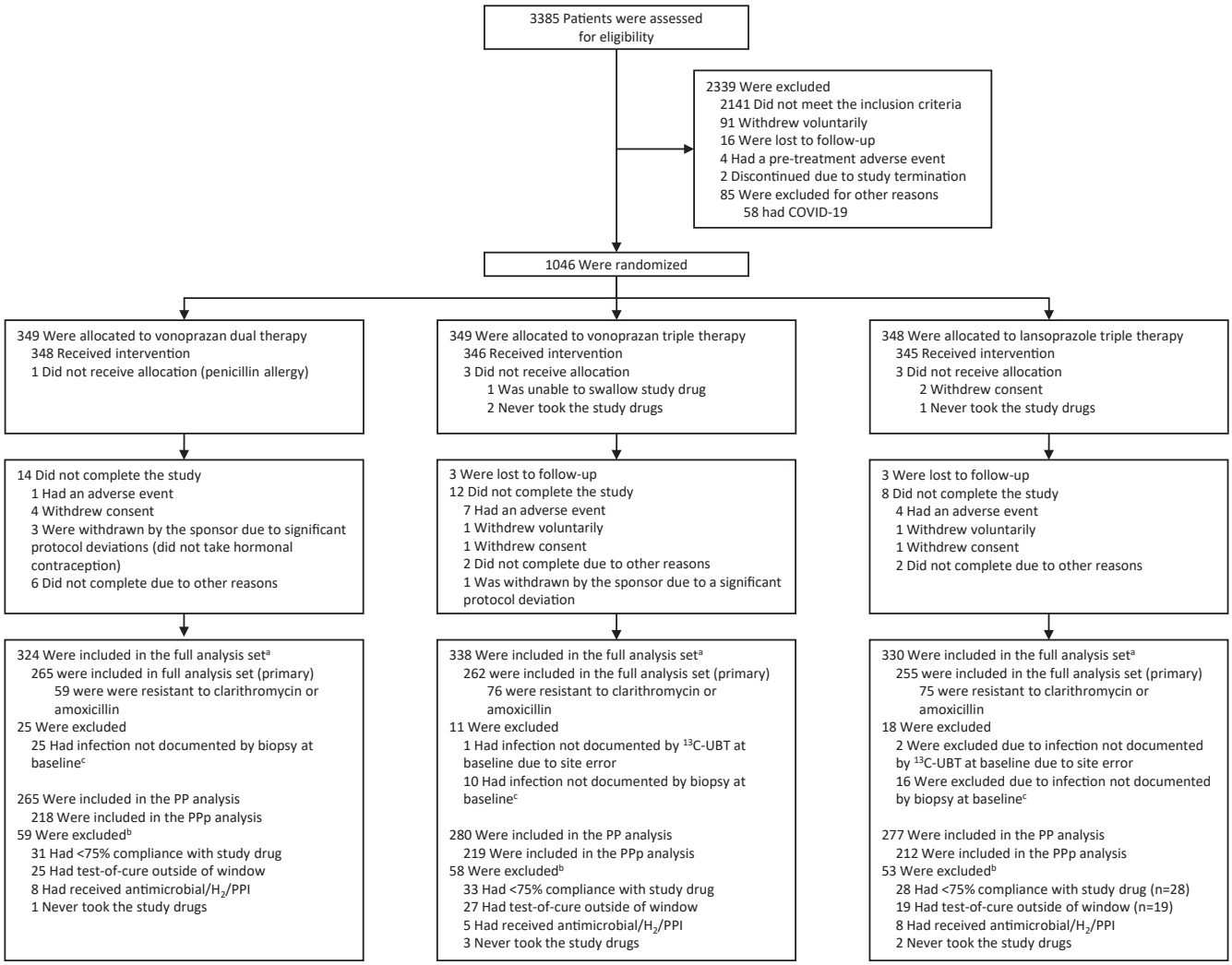

Figure 1. Study enrollment and treatments after randomization. The full analysis set included all randomized patients who had *H pylori* infection confirmed by ^{13}C-UBT and biopsy (either histology and/or culture) at baseline. The PP set included all patients who had taken ≥75% of each study drug; had a documented ^{13}C-UBT performed within the visit window to test outcome; and had not received any other antimicrobial within 7 days, or PPI or high-dose H_2-receptor antagonist within 14 days of day 1 to the test-of-cure assessment at week 6 (unless given for treatment failure). The primary sets were patients in these groups with *H pylori* strains that were not resistant to clarithromycin and amoxicillin at baseline. [a]Patients without test-of-cure ^{13}C-UBT, including those lost to follow-up or not completing the study, were counted as eradication failures. [b]Some patients were excluded from the PP for more than one reason. [c]Because of the time delay in obtaining culture and histology results, patients were randomized based on positive ^{13}C-UBT and then excluded from analysis after randomization if both culture and histology results were negative for *H pylori.*

therapy in the PP population was 79.5% (35 of 44); on lansoprazole triple therapy it was 29.0% (18 of 62; difference 50.5%; 95% CI, 32.3–65.0; $P < .001$).

Superiority in all patients. In the full analysis set, the eradication rate with vonoprazan triple therapy was 80.8% (273 of 338), compared with 68.5% (226 of 330) with lansoprazole triple therapy (difference 12.3%; 95% CI, 5.7–18.8; $P < .001$; Figure 3). PP eradication rates were 85.7% (240 of 280) and 70.0% (194 of 277), respectively (difference 15.7%; 95% CI, 8.9–22.5; $P < .001$). In the full analysis set, vonoprazan dual therapy eradicated *H pylori* in 77.2% of patients (250 of 324) compared with 68.5% (226 of 330) with lansoprazole triple therapy (difference 8.7%; 95% CI, 1.9–15.4; $P = .013$; Figure 3); in the PP population, eradication rates were 81.1% (215 of 265) and 70.0% (194 of 277), respectively (difference 11.1%; 95% CI, 3.9–18.2; $P = .003$).

Adverse Event Profile

The adverse event analysis set comprised 1039 patients (excluding 7 randomized patients who did not receive study drug), of whom 694 received vonoprazan-based regimens. TEAEs were reported in 34.1% (118 of 346) and 29.9% (104 of 348) of vonoprazan triple and dual therapy groups, respectively, and by 34.5% (119 of 345) in the lansoprazole triple therapy group (Table 2). The most common TEAEs (>2% of patients in any treatment group)

Table 1. Baseline Characteristics and Demographics (Full Analysis Set)

	Vonoprazan dual therapy[a] (n = 324)	Vonoprazan triple therapy (n = 338)	Lansoprazole triple therapy (n = 330)
Age, y, mean (SD)	51.8 (13.6)	50.6 (13.9)	51.8 (13.5)
Sex, n (%)			
Male	128 (39.5)	118 (34.9)	125 (37.9)
Female	196 (60.5)	220 (65.1)	205 (62.1)
Race, n (%)[b]			
American Indian or Alaska Native	0 (0.0)	1 (0.3)	1 (0.3)
Asian	3 (0.9)	6 (1.8)	6 (1.8)
Black or African American	21 (6.5)	29 (8.6)	22 (6.7)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0.0)	0 (0.0)
White	294 (90.7)	298 (88.2)	297 (90.0)
Other	3 (0.9)	1 (0.3)	3 (0.9)
Ethnicity, n (%)[c]			
Hispanic or Latino	86 (26.5)	94 (27.8)	80 (24.2)
BMI, median (Q1, Q3)	28.7 (25.0, 32.8)	29.1 (25.7, 32.9)	28.9 (25.7, 32.2)
Region, n (%)			
United States	134 (41.4)	144 (42.6)	134 (40.6)
Europe	190 (58.6)	194 (57.4)	196 (59.4)
Clinical condition, n (%)			
Dyspepsia[d]	312 (96.3)	334 (98.8)	326 (98.8)
Recent/new diagnosis of peptic ulcer[e]	8 (2.5)	5 (1.5)	8 (2.4)
History of peptic ulcer not treated for *H pylori* infection	6 (1.9)	10 (3.0)	9 (2.7)
Long-term NSAID requirement	5 (1.5)	11 (3.3)	12 (3.6)
Antibiotic resistance (n = 907)[f]	n=293	n=308	n=306
Clarithromycin-resistant	56 (19.1)	73 (23.7)	72 (23.5)
Amoxicillin-resistant	3 (1.0)	5 (1.6)	3 (1.0)
Metronidazole-resistant	197 (67.2)	213 (69.2)	218 (71.2)
Prior medications history (within 30 d before enrollment)			
Antibiotics	0	1 (0.3)	0
PPIs	33 (10.2)	33 (9.8)	39 (11.8)

BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.
[a]One patient randomized to the vonoprazan dual therapy group did not take study medication, as it was discovered that the patient had a penicillin allergy. Based on the definition of the full analysis set (primary), this patient was included in the analysis as "not eradicated" despite not having taken any of the study medication.
[b]Race was unknown for 2 (0.6%), 3 (0.9%), and 1 (0.3%) patient(s) in the vonoprazan dual therapy, vonoprazan triple therapy, and lansoprazole triple therapy groups, respectively.
[c]Ethnicity was unknown for 3 (0.9%) and 1 (0.3%) patient(s) in the vonoprazan dual therapy and triple therapy groups, respectively.
[d]Includes patients reporting dyspepsia lasting ≥2 weeks and/or a confirmed diagnosis of functional dyspepsia.
[e]Nonbleeding.
[f]Minimum inhibitory concentration resistance breakpoints were as follows: clarithromycin ≥1 μg/mL (Système International conversion factor: 1.708), amoxicillin >0.125 μg/mL, and metronidazole >8 μg/mL. Patients without antimicrobial susceptibility testing results were classed as not resistant to clarithromycin and amoxicillin for the purposes of the primary analysis. Analysis confined to patients with susceptibility testing results showed similar eradication rates to the primary analysis (see Supplementary Information). Some patients had strains that were resistant to more than 1 antibiotic, including 2 patients in the vonoprazan triple therapy group with resistance to both amoxicillin and clarithromycin.

are listed in Table 2. Serious TEAEs occurred in 1.7% (6 of 346), 1.4% (5 of 348), and 0.9% (3 of 345), and TEAE-related discontinuations occurred in 2.3% (8 of 346), 0.9% (3 of 348), and 1.2% (4 of 345) of patients in the vonoprazan triple, vonoprazan dual, and lansoprazole triple therapy groups, respectively (Table 2). Overall, 3 deaths occurred: 2 due to COVID-19 (1 patient each on lansoprazole triple therapy and vonoprazan triple therapy), and 1 fatal, sudden cardiac arrest (patient on vonoprazan triple therapy; Table 2).

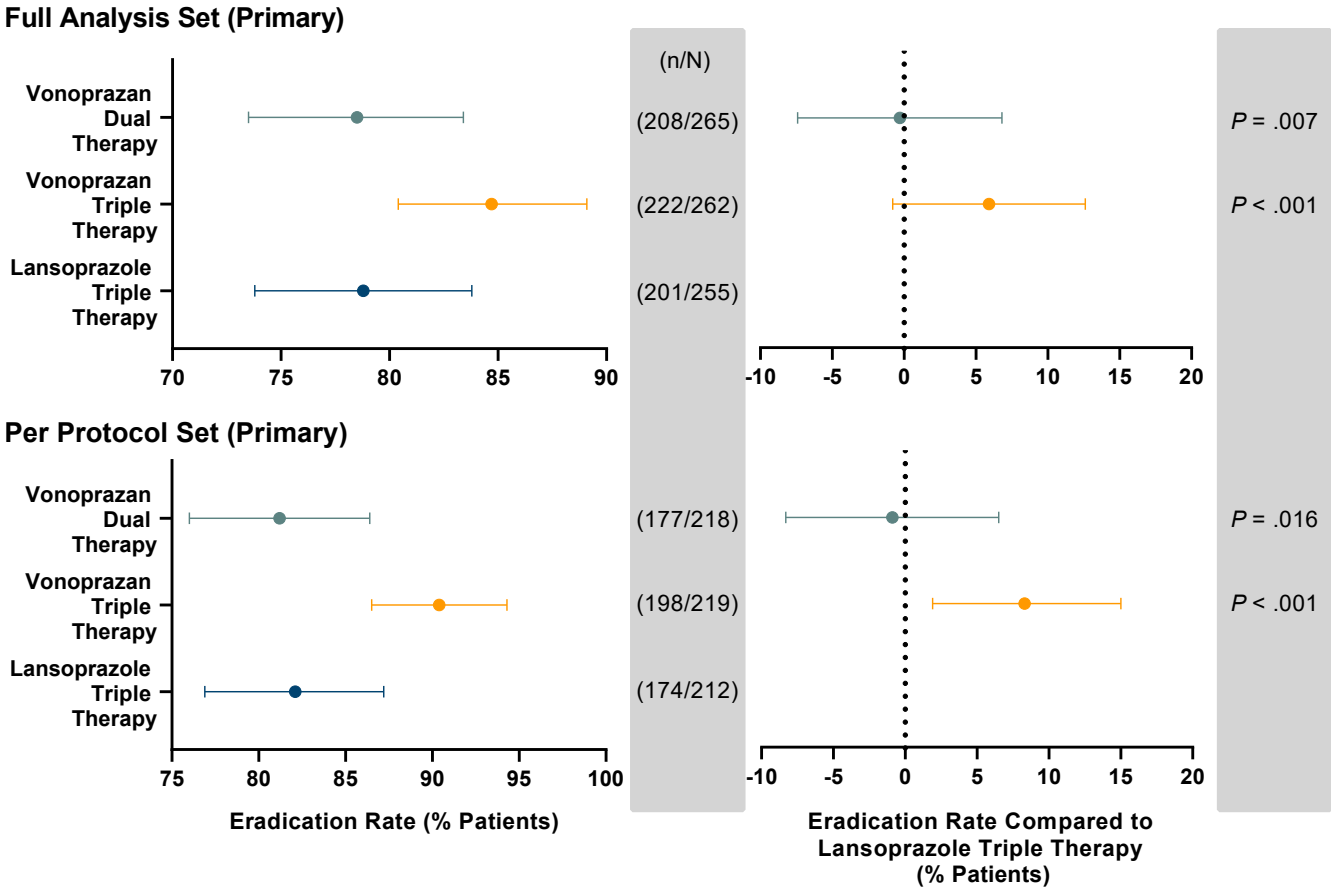

Figure 2. Primary outcome efficacy assessment. Eradication of *H pylori* infection was determined by ^{13}C-UBT 4 weeks after treatment. Eradication rates for the study regimens in strains without resistance to clarithromycin and amoxicillin in both the full analysis set (primary) and PPp analysis sets are shown on the *left*. The *right-hand side* shows the difference in eradication rate between the respective vonoprazan arm and the lansoprazole triple therapy arm. Error bars denote 95% CIs. *P* values denote significance of the noninferiority comparison. Vonoprazan triple and dual therapy were noninferior to lansoprazole triple therapy. In exploratory analyses, the eradication rate was greater with vonoprazan triple therapy ($P = .012$ [per protocol (primary)]) compared with lansoprazole triple therapy.

Discussion

Among patients from the United States and Europe, vonoprazan-based triple and dual regimens were noninferior to lansoprazole-based triple therapy for eradication of *H pylori* strains not resistant to clarithromycin and amoxicillin. In secondary analyses, vonoprazan triple and dual regimens achieved significantly higher eradication rates in the subgroup with clarithromycin-resistant strains and in the overall study population. This randomized clinical trial of 1046 patients provides the first assessment of vonoprazan-based triple and dual therapy in patients from the United States and Europe. These findings support consideration of vonoprazan-based regimens for the treatment of *H pylori* infection.

Recent *H pylori* management guidelines suggest that PPI-clarithromycin–based triple regimens should be used only in patients without prior macrolide use who live in regions where clarithromycin resistance prevalence is known to be <15%.[1,2] This is driven by concerns about clarithromycin resistance and its detrimental effect on efficacy.[2,15] Clarithromycin resistance was present in 22.2% of strains from U.S. and European participants who provided gastric mucosal biopsies for culture (Table 1). This is consistent with a recent study that showed that 17.4% of 345 U.S. isolates were clarithromycin-resistant.[25] The significantly lower eradication rates with lansoprazole triple therapy in patients with clarithromycin-resistant strains (31.9%) and in the overall study population (68.5%) indicate that PPI-clarithromycin–based triple therapy is suboptimal and should no longer be used empirically in the United States and Europe. Furthermore, eradication was successful in only 78.8% of patients (201 of 255) without clarithromycin-resistant strains, suggesting that more effective alternatives, or alternatives that allow for less unnecessary antibiotic use, should be sought. However, a recent survey showed that 53% of U.S. gastroenterologists still commonly prescribed this regimen, often without knowledge of prevailing clarithromycin resistance rates or antimicrobial sensitivity testing results. Analysis of U.S. electronic medical records indicates that 49.6% of treatment-naïve patients receive this regimen.[18,19] In a recent report from the European *H pylori* registry, Hp-EuReg, one of the most

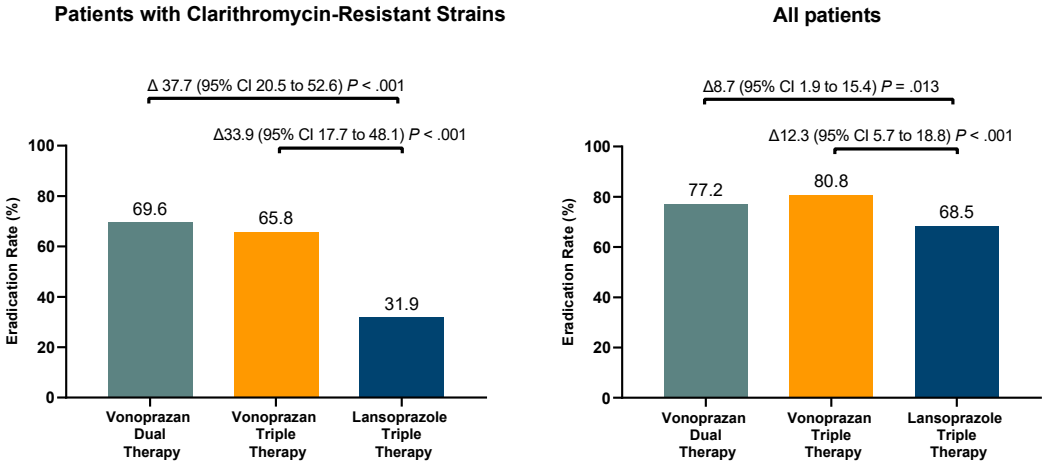

Figure 3. Secondary outcomes efficacy assessments. Eradication of *H pylori* infection was determined by ^{13}C-UBT 4 weeks after treatment. Eradication rates for the study regimens in clarithromycin-resistant strains in the full analysis set are shown in the *left* panel. The *right* panel shows eradication rates in all patients in the full analysis set. *P* values denote significance of the superiority comparison. Vonoprazan triple and dual therapy were superior to lansoprazole triple therapy in patients with clarithromycin-resistant strains and all patients.

commonly reported treatment mistakes was prescribing what was referred to as "standard triple therapy" where it is ineffective.[20]

Although a cure rate of 90% or higher, as seen in Japanese trials with vonoprazan-based regimens, would be desirable, none of the regimens in this trial reached that

Table 2. Overview of Treatment-Emergent Adverse Events

Patients, n (%)	Vonoprazan dual therapy (n = 348)	Vonoprazan triple therapy (n = 346)	Lansoprazole triple therapy (n = 345)
Deaths	0	2 (0.6)	1 (0.3)
Serious TEAEs[a]	5 (1.4)	6 (1.7)	3 (0.9)
Treatment discontinuations due to TEAEs[b]	3 (0.9)	8 (2.3)	4 (1.2)
TEAEs	104 (29.9)	118 (34.1)	119 (34.5)
Most common (≥2%)			
Abdominal pain upper	5 (1.4)	4 (1.2)	7 (2.0)
SARS-CoV-2 infection	7 (2.0)	4 (1.2)	6 (1.7)
Diarrhea	18 (5.2)[c]	14 (4.0)[c]	33 (9.6)
Nausea	6 (1.7)	6 (1.7)	9 (2.6)
Dysgeusia	2 (0.6)[c]	15 (4.3)	21 (6.1)
Headache	5 (1.4)	9 (2.6)	5 (1.4)
Hypertension	3 (0.9)	7 (2.0)	3 (0.9)
Mycotic vulvovaginal infection	3 (0.9)	8 (2.3)[c]	1 (0.3)
Nasopharyngitis	7 (2.0)	1 (0.3)	3 (0.9)
Vomiting	2 (0.6)	1 (0.3)[c]	7 (2.0)
Severe	2 (0.6)	5 (1.4)	2 (0.6)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]All individual adverse events by preferred term were reported once each in the vonoprazan dual therapy group (atrial fibrillation, cholecystitis, COVID-19 infection, lower limb fracture, metastatic lung cancer, and upper abdominal pain), vonoprazan triple therapy group (cardiac arrest, coronary artery occlusion, COVID-19 infection, duodenal polyp, jaw fracture, and spinal pain) and lansoprazole triple therapy group (acute cholecystitis, peripheral ischemia, and viral pneumonia).
[b]All individual adverse events by preferred term were reported once each in the vonoprazan dual therapy group (nausea, rash papular, and rash pruritic), and lansoprazole triple therapy group (diarrhea, dizziness, stomatitis, upper abdominal pain, and vomiting); most were reported once each in the vonoprazan triple therapy group (drug hypersensitivity, dyspepsia, hematochezia, mouth hemorrhage, and tongue discomfort), and both diarrhea and hypertension were each reported twice. Sum of individual adverse events by preferred term may not equal the overall population because 1 patient may have experienced more than 1 adverse event.
[c]$P < .05$ vs lansoprazole triple therapy

threshold. Furthermore, these results demonstrate that vonoprazan triple and dual regimens may be considered as part of a wider approach to optimize *H pylori* management in the United States and Europe. First, in recent practice in the United States, eradication rates of 90% or greater have been unattainable. In a nonrandomized study from Brown University (Providence, RI), 14-day bismuth quadruple therapy with tetracycline (rather than doxycycline) was the single most effective treatment, but only achieved a cure rate of 87%.[26] Therefore, this arbitrary threshold of 90% does not readily apply to current clinical practice. Second, we have demonstrated that replacing a PPI with vonoprazan in triple therapy boosted eradication rates when compared with a traditional PPI-based triple therapy. Vonoprazan produces more profound and durable suppression of gastric acidity than PPIs,[8] and most antibiotics currently used to treat *H pylori* infection require active bacterial replication, which is enhanced by raising intragastric pH.[27,28] Moreover, amoxicillin and, to a lesser degree, clarithromycin, are de-stabilized in an acidic environment.[5,28] Further clinical trials would be needed to compare the efficacy of vonoprazan-based regimens with other regimens. In addition to potentially optimized antibiotic activity through greater acid suppression, other possible ways to improve *H pylori* management include increasing pretreatment susceptibility testing,[29,30] which, at the current time, is not widely used in the United States[2,29] or many parts of Europe.[4] Traditional methods for determining antimicrobial susceptibility from culture of biopsy samples are invasive, time-consuming, and difficult to scale.[31] Newer molecular techniques that are becoming available include antimicrobial susceptibility testing on tissue or stool samples.[31,32] Stool testing has the potential to provide more rapid results noninvasively.[31]

These results from the United States and Europe support previous Japanese studies that reported higher eradication rates with vonoprazan-based regimens than PPI-clarithromycin–based triple therapy. Vonoprazan triple therapy was successful in up to 96% of patients in these Japanese studies, including up to 83% with clarithromycin-resistant strains, vs 70% to 77% of patients who received PPI-based triple therapy.[33–35] A recent network meta-analysis that ranked multiple first-line treatment regimens reported that vonoprazan triple therapy was associated with higher eradication rates than PPI-clarithromycin–based triple therapy (odds ratio 3.80), and was associated with the highest comparative effectiveness ranking of all the first-line regimens that were assessed.[36] In studies of vonoprazan dual therapy in Japan, eradication rates were as high as 93% and were similar to those with vonoprazan triple therapy.[11–13] Furthermore, in a meta-analysis, vonoprazan dual therapy was associated with improved eradication rates compared with triple regimens containing a PPI and clarithromycin or rifabutin, and had comparable efficacy to bismuth-based quadruple therapy, despite having fewer antimicrobials.[37]

Differences in the results observed in this study and those from Japan could be partly attributed to differing prevalence of cytochrome P450 2C19 (*CYP2C19*) mutations between populations.[38] Although lansoprazole is primarily metabolized by CYP2C19, vonoprazan is metabolized by multiple other enzymes including CYP3A4/5.[39,40] Polymorphisms related to slow CYP2C19 metabolism, which have been linked to higher eradication rates with some PPI-containing regimens, are more prevalent in Asian than White populations.[41,42] Because there are no clinically significant differences in vonoprazan pharmacokinetics between Asian and non-Asian populations, it is unlikely that any differences between results from this study and the Japanese studies are attributable to race alone.[43,44] Different treatment compliance rates between these studies may also have contributed to differences in outcomes. One Japanese study reported 98% compliance with triple therapy; in another, 97% of patients in the vonoprazan group took all medication.[33,34] In several Japanese studies, the numbers of patients in the intention-to-treat and PP populations were very similar, indicating high compliance with all study requirements.[13,33] In the study reported here, 94.2% of patients had >75% compliance as assessed by pill count, which may overestimate compliance. Furthermore, patients without a test-of-cure visit were classed as having failed eradication. Another potential explanation could be differences in body weight between study populations; patients in Japanese studies generally had a lower body mass index (<25) than in this study (median 29). Increased body surface area has been associated with a reduction in eradication rates with vonoprazan dual therapy.[45]

In the entire study population and in study participants with clarithromycin-resistant strains of *H pylori*, the observed eradication rates were significantly higher with vonoprazan than lansoprazole, consistent with the proposition that the more profound suppression of intragastric acidity seen with vonoprazan compared with PPIs improves antibiotic effectiveness. Nevertheless, participants with clarithromycin-resistant strains of *H pylori* fared poorly with all regimens, suggesting that in patients with clarithromycin-resistant organisms or living in areas with very high clarithromycin resistance, multiple drug regimens without clarithromycin may be necessary. Optimizing current regimens offers the potential to increase eradication rates and reduce additional antibiotic usage, thereby promoting and improving antimicrobial stewardship. Although vonoprazan triple therapy had the highest eradication rate and a greater therapeutic gain over lansoprazole triple therapy, it still included 2 antibiotics. Vonoprazan dual therapy, which contains only 1 antibiotic, also had significantly higher cure rates than lansoprazole triple therapy in those with clarithromycin-resistant strains and among all patients, albeit with a lower eradication rate than seen with vonoprazan triple therapy among all patients. Further studies to optimize the efficacy of dual therapy would be of interest, to evaluate whether a dual regimen with more frequent or higher amoxicillin dosing may provide higher eradication rates.

All regimens were generally well tolerated. Most TEAEs were mild to moderate in severity. Serious TEAEs were uncommon (1.3% of the overall population) and none was considered related to study drugs.

Limitations

This study has several limitations. First, the study population comprised treatment-naïve patients, limiting any generalizability to those who had previously been treated. Second, vonoprazan dual therapy was open-label and distinguishable from triple therapy because of its different dosing schedule. Possible influences on study outcomes are unclear. Compliance and completion rates were similar among the 3 groups, and the primary efficacy endpoint was objective, thereby limiting any potential bias. Third, although this was a multicenter study, sites were not evenly distributed geographically across the United States and included only 5 European countries, thus limiting generalizability to other geographic regions. Fourth, 103 different sites participated in the study, many contributing only a small number of patients. The data were not adjusted for biases associated with multiple sites. Nevertheless, this is still the most robust dataset for these treatment regimens in the United States and Europe.

Conclusions

Among patients from the United States and Europe, vonoprazan-based triple and dual regimens were noninferior to lansoprazole-based triple therapy for eradication of *H pylori* strains not resistant to clarithromycin and amoxicillin. In predetermined secondary analyses, vonoprazan triple and dual regimens were superior to lansoprazole-based triple therapy in patients with clarithromycin-resistant strains and in the overall study population. The findings support consideration of vonoprazan-based regimens in the treatment of *H pylori* infection in the United States and Europe.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2022.05.055.

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Conflict of Interest
These authors disclose the following: William D. Chey reported being a board member of the American College of Gastroenterology, GI on Demand, International Foundation of Functional GI Disorders, and the Rome Foundation; compensation as a consultant from AbbVie, Alfasigma, Allakos, Alnylam, Bayer, BioAmerica, Cosmo, Intrinsic Medicine, Ironwood Pharmaceuticals, QOL Medical, Nestle, Phathom Pharmaceuticals, RedHill Biopharma, Salix/Valeant, Takeda, Urovant, and Vibrant; grant/research support from BioAmerica, Commonwealth Diagnostics International, QOL Medical, Salix, and Vibrant; stock/stock options in GI on Demand, and Modify Health; and patents relating to methods and kits for identifying food sensitivities and intolerances, digital manometry, and a rectal expulsion device. Francis Mégraud reported receiving compensation for his role as an advisory committee member for Phathom Pharmaceuticals. Loren Laine reported compensation as a consultant for Phathom Pharmaceuticals. Barbara J. Hunt reported employment with Phathom Pharmaceuticals. Colin W. Howden reported compensation as a consultant and advisory board/committee member for Phathom Pharmaceuticals and RedHill Biopharma; consultancy fees from Allakos, Clexio, EndoStim, Ironwood, and ISOThrive; and speakers' bureau fees from Alnylam, RedHill Biopharma, Sanofi/Genzyme, and Alfasigma. Luis J. López discloses no conflicts.

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