# Vonoprazan-based quadruple therapy is non-inferior to esomeprazole-based quadruple therapy for *Helicobacter pylori* eradication: A multicenter, double-blind, randomized, phase 3 study

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**Abstract**

**Background:** Owing to the high prevalence of antibiotic resistance in *Helicobacter pylori* (*H. pylori*) in China, bismuth-containing quadruple therapies have been recommended for *H. pylori* eradication. This study compared the efficacy and safety of quadruple regimens containing vonoprazan *vs*. esomeprazole for *H. pylori* eradication in a patient population in China.

**Methods:** This was a phase 3, multicenter, randomized, double-blind study. Patients with confirmed *H. pylori* infection were randomized 1:1 to receive quadruple therapy for 14 days: amoxicillin 1000 mg and clarithromycin 500 mg after meals, bismuth potassium citrate 600 mg before meals, plus either vonoprazan 20 mg or esomeprazole 20 mg before meals, all twice daily. The primary outcome was the eradication rate of *H. pylori*, evaluated using a $^{13}$C urea breath test at 4 weeks after treatment. The non-inferiority margin was at 10%.

**Results:** The study included 510 patients, 506 of whom completed the follow-up assessment. The primary analysis revealed eradication rates of 86.8% (210/242) and 86.7% (208/240) for vonoprazan and esomeprazole therapy, respectively (treatment difference: 0.1%; 95% confidence interval [CI]: −5.95, 6.17; non-inferiority $P = 0.0009$). Per-protocol analysis showed eradication rates of 87.4% for vonoprazan and 86.3% for esomeprazole (treatment difference: 1.2%; 95% CI: −5.03, 7.36; non-inferiority $P = 0.0004$). Vonoprazan and esomeprazole were well tolerated, with similar safety profiles.

**Conclusion:** Vonoprazan was found to be well-tolerated and non-inferior to esomeprazole for eradicating *H. pylori* in patients from China.

**Trial registration:** ClinicalTrials.gov, NCT04198363.

**Keywords:** Vonoprazan; Esomeprazole; *Helicobacter pylori*; quadruple therapy; Phase 3; China

## Introduction

*Helicobacter pylori* (*H. pylori*) is the most common bacterial infection of the gastric mucosa, affecting 44.3–60.3% of the global population.[1] In Chinese mainland, a prevalence of approximately 44.0% has been reported, with an estimated 589 million individuals being infected.[2] *H. pylori* infection is a major cause of chronic gastritis, peptic ulcers, gastric adenocarcinoma, gastric mucosa-associated lymphoid tissue lymphoma, and other gastrointestinal diseases.[3] Therefore, the Kyoto Global Consensus Report and the Fifth Chinese National Consensus Report both recommend eradication therapy for *H. pylori* infection.[4,5]

The standard triple therapy used in conventional *H. pylori* eradication combines a proton-pump inhibitor (PPI) with amoxicillin and either clarithromycin, levofloxacin, or metronidazole. In China, microbial drug resistance rates have been reported to be 20–50% for clarithromycin, 20–50% for levofloxacin, and 40–70% for metronidazole.[5,6] As a result, the rate of *H. pylori* eradication with standard triple therapy has declined to <80%.[7–9]

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Considering the high prevalence of antibiotic resistance, bismuth-containing quadruple therapy has been recommended in China since the Fourth Chinese National Consensus Report (2012) and maintained throughout the Fifth Chinese National Consensus Report as empirical therapy.[5] The recommendation is supported by the 30–40% improvement in *H. pylori* eradication rates observed when bismuth was added to triple therapy in regions with a high prevalence of clarithromycin resistance.[5] Other studies have also shown that bismuth-based quadruple therapy has higher eradication rates than triple therapy.[10–13] In a nationwide, multicenter, cross-sectional questionnaire survey, 88.0% of respondents were prescribed a bismuth-containing quadruple regimen as the initial eradication treatment.[14]

Vonoprazan is a novel potassium-competitive acid blocker that has more potent and sustained acid-inhibitory effects than traditional PPIs. Vonoprazan 20 mg twice daily (b.i.d) results in a median intragastric pH of 6.5 compared with 6.2 with esomeprazole 20 mg b.i.d, after 7 days in healthy volunteers.[15] A previous meta-analysis reported three randomized controlled trials (RCTs) in Japan that included patients with *H. pylori* infection ($n$ = 897) who received vonoprazan-based triple therapy ($n$ = 456; 20 mg vonoprazan, 750 mg amoxicillin, and 200 mg or 400 mg clarithromycin, b.i.d for 7 days) or PPI-based triple therapy ($n$ = 441; standard dose of PPI instead of vonoprazan). In all three RCTs, the successful eradication of *H. pylori* was confirmed using urea breath tests (UBT) at least 4 weeks after the completion of treatment. The results showed that, as a first-line regimen, vonoprazan-based triple therapy had a higher eradication rate than PPI-based triple therapy (intention-to-treat analysis: pooled eradication rates, 91.4% *vs*. 74.8%; odds ratio [OR], 3.68; 95% confidence interval [CI]: 1.87–7.26; $P$ <0.05).[16] Triple-based therapy for *H. pylori* eradication is recommended in Japan because of low antibiotic resistance;[17] however, in China, quadruple therapy is recommended for *H. pylori* eradication.[5]

Esomeprazole, a second-generation PPI with greater eradication than first-generation PPIs (82.3% *vs*. 77.6%),[18] is effective for *H. pylori* eradication in combination with antibiotics.[19] The present study aimed to assess the efficacy and safety of a quadruple regimen with vonoprazan *vs*. esomeprazole for *H. pylori* eradication in a patient population in Chinese mainland.

## Methods

### Study design

This multicenter, randomized, double-blind, phase 3 study was conducted at 29 sites in China from April 2020 to November 2021 (NCT04198363). The 29 sites were listed as the Supplementary File 1, http://links.lww.com/CM9/C268. Patients with confirmed *H. pylori* infection were randomized using an interactive web-response system (IWRS) into permuted blocks, which allocated a randomly ordered but equal number of patients into each block with a length of four to receive quadruple therapy for 14 days. In the study, vonoprazan 20 mg and esomeprazole 20 mg were overencapsulated and identical in appearance. Investigator or their designee accessed the IWRS system to randomize eligible participants. Then the IWRS provided a medication identification number of the study drug to be dispensed for the participant based on the randomization schedule generated by a randomization personnel who was independent of the study conduct. The study was conducted with competitive recruitment at all sites, with blinding to the investigators and patients. The treatment included amoxicillin 1000 mg and clarithromycin 500 mg after meals, bismuth potassium citrate 600 mg (equivalent to bismuth 220 mg) before meals, and either vonoprazan 20 mg or esomeprazole 20 mg before meals, all administered b.i.d [Figure 1], as recommended by latest Chinese National Clinical Practice Guideline on the Management of *H. pylori* Infection.[5] During the treatment period, the patients were monitored for compliance. Good compliance was defined as taking at least 90% of the study drug by pill counting. Patients were instructed to bring study medication containers or unused medications to the sites on day 15 or early-termination visits. Compliance checks were conducted by the investigators or their designees through a review of the returned medications.

Each patient underwent a bacterial resistance test for clarithromycin using a biopsy specimen from the antrum and another from the gastric body. The resistance breakpoint based on minimum inhibitory concentration was >2 μg/mL for clarithromycin. All randomized patients were followed up using a post-study carbon-13 ($^{13}$C) UBT to ascertain

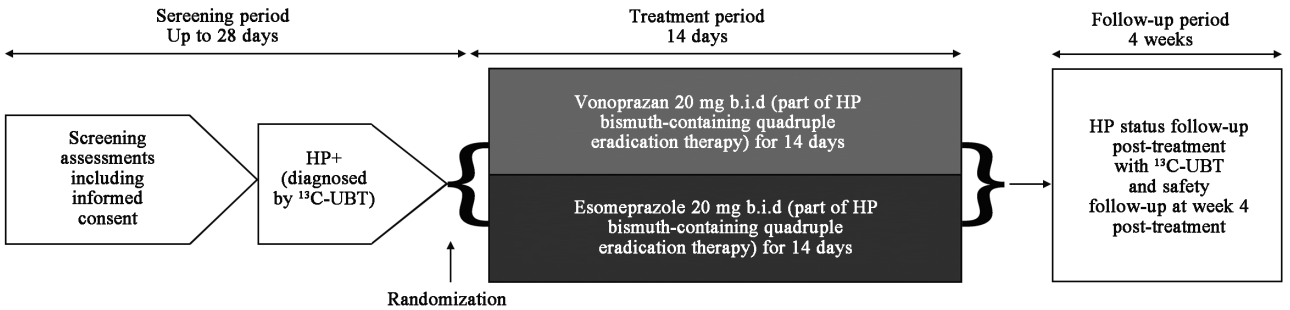


**Figure 1:** Overview of the phase 3, multicenter, randomized, double-blind study design to compare the efficacy and safety of quadruple regimens containing vonoprazan *vs*. esomeprazole for *HP* eradication. $^{13}$C-UBT: Carbon-13 urea breath test; b.i.d: Twice daily; HP: *Helicobacter pylori*; HP+: HP positive.

*H. pylori* eradication status and evaluate safety. In China, the UBT is the most investigated and recommended non-invasive test for high-accuracy *H. pylori* detection.[5]

This study was conducted in compliance with the applicable laws and regulations, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the *Declaration of Helsinki*. The protocol was approved by independent ethics committees/institutional review boards of Peking University Third Hospital (No. 2019-025-02) and all other sites, and all patients provided written informed consent prior to the conduct of any study-related procedures.

### Study population

Eligible patients were aged ≥18 years, with *H. pylori* infection confirmed by carbon-13 urea breath test ($^{13}$C-UBT) at the start of the study, and required *H. pylori* eradication based on the physician's judgment and per recommendations of the Chinese Society of Gastroenterology regarding indications for *H. pylori* eradication.[5] This study included both the patients who were treatment-naïve and those who previously received PPIs and antibiotics. The investigator performed a benefit-risk assessment to determine the eligibility of the patient's participation in this study. Patients who met any of the following criteria were excluded: (1) those with a history of hypersensitivity or allergic reactions to the investigational drugs; (2) patients who had received gastric surgery; (3) patients with a history of alcohol or illicit drug abuse; (4) those diagnosed with Zollinger–Ellison syndrome or gastric acid hypersecretion; (5) patients who had been diagnosed with malignancy or received treatment for malignancy within the 5 years preceding the screening visit; (6) patients who had used non-study-related PPIs, histamine type 2 receptor antagonists, or any other medication that may interfere with $^{13}$C-UBT within 14 days before the $^{13}$C-UBT at screening; (7) patients who had taken any antibiotics within 30 days prior to the $^{13}$C-UBT at screening.

### Study endpoints

The primary endpoint was the proportion of *H. pylori*-positive patients who achieved successful *H. pylori* eradication, as determined using $^{13}$C-UBT at week 4 post-treatment (28–35 days after last dose) with bismuth-containing quadruple therapy with vonoprazan *vs*. esomeprazole, both administered twice daily. The secondary endpoint was the proportion of clarithromycin-resistant *H. pylori*-positive patients who achieved successful *H. pylori* eradication, as determined using $^{13}$C-UBT at week 4 post-treatment.

The safety assessments included adverse events (AEs) coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 23.0) which was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), clinical laboratory tests, vital signs, 12-lead electrocardiogram, and physical examinations. An AE was defined as any untoward medical occurrence in a clinical investigation participant who was administered a drug; it does not necessarily have to have a causal relationship with this treatment.[20,21] The relationship of each AE to the study drug was assessed by the investigator as treatment-related AE or not-related AE. A treatment-related AE was defined as an AE that followed a reasonable temporal sequence from the administration of a drug (including the course after withdrawal of the drug), for which possible involvement of the drug could not be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications, and concurrent treatments, may also be responsible.

### Statistical analysis

This study used a switching strategy to evaluate the non-inferiority of vonoprazan to esomeprazole first and then to evaluate superiority only if non-inferiority was established. An interim analysis was performed by an independent statistical analysis center after approximately 50% of the initially planned sample size had been assessed for the primary endpoint. Potential options after the interim analysis were (1) early stopping for efficacy, (2) study continuation without any sample size modification, or (3) study continuation with a sample size increase based on conditional powers for the primary endpoint.

This adaptive sample size re-estimation design with an initial sample size of 425 and a maximum sample size of 510 patients provided over 90% power by the Farrington and Manning test[22] for the non-inferiority, with a non-inferiority margin of 10%, assuming *H. pylori* eradication rates were 90% for both vonoprazan and esomeprazole. According to the switching strategy, the superiority of vonoprazan to esomeprazole was to be evaluated using a score test if and only if the non-inferiority test achieved statistical significance at either the interim analysis or the final analysis. The design also provided approximately 80% power for the superiority test when the eradication rates were 95% for vonoprazan and 87% for esomeprazole. The powers of the non-inferiority and superiority tests under this design were evaluated by simulation, taking into consideration the interim analysis with a potential early stop for efficacy and the potential adaptation of the initial sample size.

The overall significance level was controlled at a one-sided 2.5% using the closed testing procedure for multiple testing of non-inferiority and superiority; the O'Brien–Fleming $\alpha$ spending function (critical value of 2.96259 and 1.96860 for interim and final analysis, respectively) for the potential early stop for efficacy; and the Cui–Hung–Wang approach, which is a linear combination of the two-stage weighted Farrington and Manning tests for non-inferiority and score test for superiority, for sample size re-estimation. The full analysis set was defined as all randomized patients who received at least one dose of the study drug, according to the original randomization. Missing data imputation was not done in the efficacy analyses unless otherwise specified. Patients who received at least one dose of the study drug were included in the safety analysis set. The primary efficacy endpoint was also analyzed in the sensitivity analysis using the per-protocol

set, which included patients from the full analysis set whose primary endpoints were evaluable and had no major protocol deviations (PDs).

Two additional sensitivity analyses were conducted to evaluate the impact of a full analysis set of patients whose *H. pylori* eradication status was missing at week 4 post-treatment or was not within the pre-specified time window. Efficacy analyses were also conducted to evaluate the eradication status at week 4 post-treatment for patients who were clarithromycin-resistant at baseline.

For binary endpoints, frequency distributions, proportions, and two-sided 95% Clopper–Pearson exact CIs were calculated for each treatment group. The proportion difference between treatment groups and its two-sided 95% Wald CI were also provided. The primary endpoint was also assessed in patient subgroups by age (<65 years or ≥65 years), sex, resistance to clarithromycin (yes/no), body mass index (BMI), or smoking. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## Results

### Patient enrollment and baseline characteristics

A total of 794 patients were assessed for eligibility; 510 were positive for *H. pylori* and were randomly assigned to the vonoprazan group ($n$ = 256) or the esomeprazole group ($n$ = 254). All 510 randomized patients were included in the full analysis and safety sets. Overall, 482 of 510 patients (vonoprazan: 242; esomeprazole: 240) were included in the primary analysis, and 457 of 510 (vonoprazan: 231; esomeprazole: 226) were included in the per-protocol analysis [Figure 2]. Eleven patients in the vonoprazan group and 14 patients in the esomeprazole group were excluded from the per-protocol analysis due to major PDs [Figure 2]. Most patients (99.2%; 506/510) completed follow-up assessment [Supplementary Figure 1, http://links.lww.com/CM9/C268]. Additional information regarding the analysis sets is provided in Supplementary Table 1, http://links.lww.com/CM9/C268.

The baseline demographics were well-balanced between the treatment groups [Table 1]. Overall mean age was 38.9 (standard deviation [SD]: 12.2) years, and 61.8% (315/510 patients) were female participants. Most patients (88.2%) were non-smokers, had never consumed alcohol (81.2%), or did not consume caffeine (92.9%). Clarithromycin-resistant strains were reported in 42.4% (28/66) of patients in the vonoprazan group and 31.8% (21/66) in the esomeprazole group. The most common concurrent medical condition was gastrointestinal disorders. Treatment adherence was similar between the treatment groups at 99.1% with vonoprazan and 98.8% with esomeprazole.

### H. pylori eradication rates

Vonoprazan was non-inferior to esomeprazole for *H. pylori* eradication at week 4 post-treatment in patients with *H. pylori* infection [Figure 3]. *H. pylori* eradication,

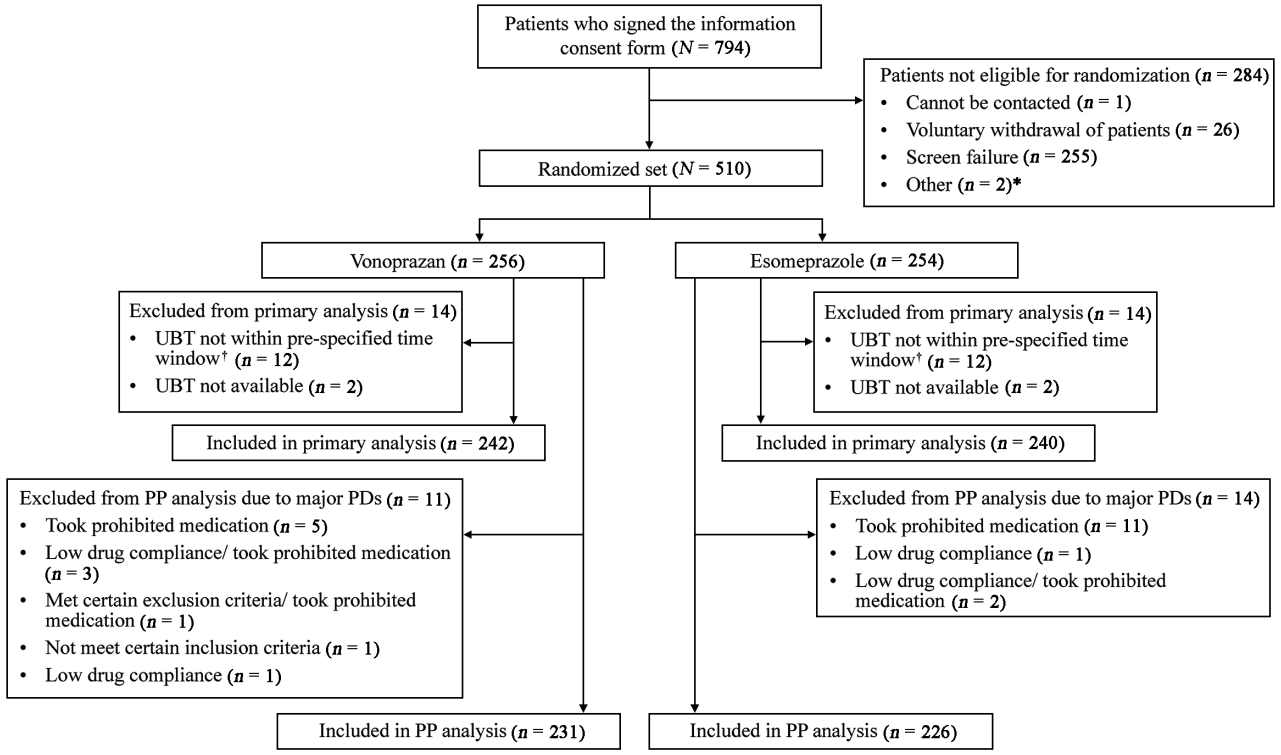


**Figure 2:** Flow chart of patient disposition in this study comparing the efficacy and safety of quadruple regimens containing vonoprazan *vs.* esomeprazole for HP eradication. *Two patients were not randomized as the quota for enrolment was full. It was not classified into any of the prespecified reasons, including AE, PD, lost to follow up, voluntary withdrawal by participant, meeting exclusion criteria, and not meeting inclusion criteria, etc. †28–35 days after the last dose. AE: Adverse event; HP: *Helicobacter pylori*; PD: Protocol deviation; PP: Per protocol; UBT: Urea breath test.

**Table 1: Demographic and baseline characteristics (randomized set) of patients with *H. pylori* treated with vonoprazan or esomeprazole.**

| Characteristics | Vonoprazan 20 mg ($n = 256$) | Esomeprazole 20 mg ($n = 254$) | Total ($N = 510$) |
|---|---|---|---|
| Age (years) | 39.5 ± 12.3 | 38.3 ± 12.1 | 38.9 ± 12.2 |
| Sex | | | |
| Male | 105 (41.0) | 90 (35.4) | 195 (38.2) |
| Female | 151 (59.0) | 164 (64.6) | 315 (61.8) |
| BMI* (kg/m$^2$) | 22.7 ± 2.9 | 22.6 ± 2.7 | 22.6 ± 2.8 |
| Smoking status | | | |
| Never smoked | 222 (86.7) | 228 (89.8) | 450 (88.2) |
| Current smoker | 21 (8.2) | 20 (7.9) | 41 (8.0) |
| Former smoker | 13 (5.1) | 6 (2.4) | 19 (3.7) |
| Alcohol use | | | |
| Every day | 2 (0.8) | 1 (0.4) | 3 (0.6) |
| Couple of days per week | 14 (5.5) | 8 (3.1) | 22 (4.3) |
| Couple of days per month | 36 (14.1) | 27 (10.6) | 63 (12.4) |
| Never | 199 (77.7) | 215 (84.6) | 414 (81.2) |
| Former drinker | 5 (2.0) | 3 (1.2) | 8 (1.6) |
| Caffeine consumption | | | |
| Yes | 21 (8.2) | 15 (5.9) | 36 (7.1) |
| No | 235 (91.8) | 239 (94.1) | 474 (92.9) |
| Patients with any reported medical history | 98 (38.3) | 102 (40.2) | 200 (39.2) |
| Patients with concurrent medical conditions | 225 (87.9) | 231 (90.9) | 456 (89.4) |
| Most common concurrent medical condition† | | | |
| Chronic gastritis | 120 (46.9) | 137 (53.9) | 257 (50.4) |
| Gastritis erosive | 62 (24.2) | 45 (17.7) | 107 (21.0) |
| Gastritis | 22 (8.6) | 26 (10.2) | 48 (9.4) |
| Duodenitis | 18 (7.0) | 12 (4.7) | 30 (5.9) |
| Hyperlipidaemia | 23 (9.0) | 16 (6.3) | 39 (7.6) |
| Hypertension | 20 (7.8) | 19 (7.5) | 39 (7.6) |
| Hepatic steatosis | 12 (4.7) | 15 (5.9) | 27 (5.3) |

Values were shown as mean ± SD, or *n* (%). *For BMI, vonoprazan ($n = 253$) and esomeprazole ($n = 249$) were considered. †Present in ≥5% of patients in total. BMI: Body mass index; *H. pylori*: *Helicobacter pylori*; SD: Standard deviation.

assessed by $^{13}$C-UBT at week 4 post-treatment, was achieved in 86.8% (210/242) of the vonoprazan group and 86.7% (208/240) of the esomeprazole group in the primary analysis (treatment difference, 0.1%; 95% CI: −5.95, 6.17; non-inferiority $P = 0.0009$) [Figure 3]. Superiority, assessed using the score test, was not demonstrated ($P = 0.5147$). Eradication rates in the per-protocol analysis were 87.4% (202/231) in the vonoprazan group and 86.3% (195/226) in the esomeprazole group (treatment difference, 1.2%; 95% CI: −5.03, 7.36; non-inferiority $P = 0.0004$) [Figure 3].

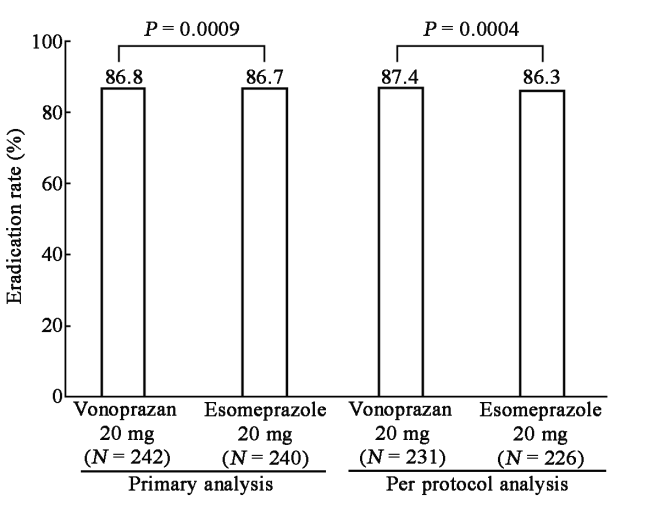


**Figure 3:** The *H. pylori* eradication rates with vonoprazan therapy and esomeprazole therapy. The *P*-values for the non-inferiority of vonoprazan therapy compared with esomeprazole therapy are provided. The differences in the eradication rates between these two therapies (vonoprazan *vs.* esomeprazole) were 0.1% (95% Wald CI: −5.95, 6.17) in the full analysis set and 1.2% (95% Wald CI: −5.03, 7.36) in the per-protocol analysis. CI: Confidence interval; *H. pylori* : *Helicobacter pylori*.

From the full analysis set, 28 patients were excluded from the primary analysis due to the missing of $^{13}$C-UBT results ($n = 4$) or $^{13}$C-UBT having been done outside the time window pre-specified in the protocol ($n = 24$), with 14 patients excluded in each group. The first sensitivity analysis of the primary endpoint used all available post-baseline $^{13}$C-UBT results, irrespective of test timing, but excluded patients whose post-baseline *H. pylori* eradication status was missing ($n = 2$ per treatment group). The resulting *H. pylori* eradication rates were 86.2% (219/254) and 86.1% (217/252) in the vonoprazan and esomeprazole groups, respectively (treatment difference, 0.1%; 95% CI: −5.91, 6.13). The second sensitivity analysis of the primary endpoint used all available post-baseline $^{13}$C-UBT results and treated patients with missing post-baseline *H. pylori*

eradication status as failure (i.e., non-responder imputation). In this analysis, the *H. pylori* eradication rates were 85.5% (219/256) in the vonoprazan group and 85.4% (217/254) in the esomeprazole group (treatment difference, 0.1%; 95% CI: −6.00, 6.23). These results were close to those seen in the primary analysis.

The eradication rates of vonoprazan therapy and esomeprazole therapy in patients with clarithromycin-resistant *H. pylori* at baseline were 78.6% and 88.9%, respectively (treatment difference, −10.3%; 95% CI: −31.34, 10.70%) [Table 2].

### Subgroup analysis

The results of the subgroup analysis showed that *H. pylori* eradication was unaffected by age, BMI, smoking classification, or sex [Table 2].

### Safety

The overall incidence of treatment-emergent adverse events (TEAEs) was comparable between treatment groups [Table 3]. In the vonoprazan group, 69.1% of patients reported ≥1 TEAE; in the esomeprazole group, 61.4%. The most common TEAE was dysgeusia, reported in 32.4% and 29.1% of patients in the vonoprazan and esomeprazole groups, respectively. At least one study-drug-related TEAE was reported by 63.3% and 53.1% of patients in the vonoprazan and esomeprazole groups, respectively. The TEAEs were mostly mild or moderate in severity. Severe AEs were reported in 1.2% ($n$ = 3) and 0.8% ($n$ = 2) of patients in the vonoprazan and esomeprazole groups, respectively; severe TEAEs in the esomeprazole group (drug eruption and enteritis infectious) were assessed by the investigator to be related to the study treatment.

The rates of serious adverse events (SAEs) were similar between the treatment groups: 1.2% ($n$ = 3) in the vonoprazan group and 2.0% ($n$ = 5) in the esomeprazole group [Table 3]. One SAE (supraventricular arrhythmia) in the vonoprazan group and two SAEs (enteritis infectious and drug eruption) in the esomeprazole group were considered to be related to the study drug.

No clinically significant changes occurred in the laboratory, electrocardiogram, vital sign, or physical examination data. Six patients (five from the vonoprazan group and one from the esomeprazole group) had elevated alanine aminotransferase levels that were more than three times as high as the upper limit of normal, and all were reported to be TEAEs related to all four components of quadruple therapy. The levels decreased to the normal range during follow-up.

## Discussion

The increasing antibiotic resistance of *H. pylori* is a cause of great concern in China and requires modification of therapeutic regimens.[5] Several studies and literature reviews have investigated the status and trends of *H. pylori* resistance in China and found that in the past decade, the highest prevalence of resistance was observed for metronidazole, followed by clarithromycin and levofloxacin, to which resistance rates are gradually increasing over time.[5] The eradication rate of *H. pylori* has rapidly declined to <80%, owing to the emergence of antibiotic resistance.[23] Hence, bismuth quadruple therapy is recommended as first-line therapy for *H. pylori* eradication in China.[24] Studies have confirmed an 85–95% eradication rate with bismuth-containing quadruple therapy.[25–28]

In this phase 3 randomized study of patients with *H. pylori* infection in China, the analysis of the primary efficacy endpoint in the full analysis set showed that the

**Table 2: Subgroup analyses of successful *H. pylori* eradication, as determined using $^{13}$C-UBT at week 4 post treatment (full analysis set), *n/N* (%).**

| Subgroups | Vonoprazan | Esomeprazole | Difference, % (95% CI)* |
|---|---|---|---|
| Age | | | |
| <65 years | 203/233 (87.1) | 202/234 (86.3) | 0.8 (−5.4, 7.0) |
| ≥65 years | 7/9 (77.8) | 6/6 (100) | −22.2 (−49.4, 4.9) |
| Sex | | | |
| Male | 83/99 (83.8) | 68/81 (84.0) | −0.1 (−10.9, 10.7) |
| Female | 127/143 (88.8) | 140/159 (88.1) | 0.8 (−6.5, 8.0) |
| Clarithromycin resistance† | | | |
| Yes | 22/28 (78.6) | 16/18 (88.9) | −10.3 (−31.3, 10.7) |
| No | 35/37 (94.6) | 40/43 (93.0) | 1.6 (−9.0, 12.1) |
| BMI | | | |
| <18.5 kg/m$^2$ | 10/12 (83.3) | 11/11 (100) | −16.7 (−37.8, 4.4) |
| ≥18.5 to <25.0 kg/m$^2$ | 156/175 (89.1) | 157/181 (86.7) | 2.4 (−4.4, 9.2) |
| ≥25.0 kg/m$^2$ | 43/53 (81.1) | 37/45 (82.2) | −1.1 (−16.4, 14.3) |
| Smoking classification | | | |
| Never smoked | 184/211 (87.2) | 186/216 (86.1) | 1.1 (−5.4, 7.5) |
| Current smoker | 15/19 (78.9) | 16/18 (88.9) | −9.9 (−33.3, 13.4) |
| Ex-smoker | 11/12 (91.7) | 6/6 (100) | −8.3 (−24.0, 7.3) |

*Two-sided Wald CI. †Antibiotic resistance at baseline in patients for whom baseline susceptibility was recorded. BMI: Body mass index; $^{13}$C-UBT: Carbon-13 urea breath test; CI: Confidence interval; *H. pylori*: *Helicobacter pylori*.

**Table 3: Overview of treatment-emergent AEs of patients with *H. pylori* treated with vonoprazan or esomeprazole (safety-analysis set).**

| Categories | Vonoprazan 20 mg ($n = 256$) | Esomeprazole 20 mg ($n = 254$) | Fisher's exact test *P*-values |
|---|---|---|---|
| Any TEAE | 177 (69.1) | 156 (61.4) | 0.0771 |
| Related to study drugs | 162 (63.3) | 135 (53.1) | 0.0247 |
| Severity | | | |
| Mild | 164 (64.1) | 143 (56.3) | |
| Moderate* | 10 (3.9) | 11 (4.3) | 1.0000 |
| Severe | 3 (1.2) | 2 (0.8) | 1.0000 |
| TEAEs leading to study drug discontinuation | 6 (2.3) | 7 (2.8) | 0.7872 |
| SAEs | 3 (1.2) | 5 (2.0) | 0.5031 |
| Related to study drugs | 1 (0.4) | 2 (0.8) | 0.6228 |
| Leading to study drug discontinuation | 0 | 2 (0.8) | 0.2476 |
| Deaths | 0 | 0 | – |
| TEAEs reported by ≥5% of patients in any treatment group | | | |
| Feces discolored | 13 (5.1) | 8 (3.1) | 0.3733 |
| Hepatic function abnormal | 17 (6.6) | 9 (3.5) | 0.1577 |
| Protein urine present | 18 (7.0) | 15 (5.9) | 0.7195 |
| Dysgeusia | 83 (32.4) | 74 (29.1) | 0.4437 |

Values are *n* (%). Percentages are based on the total number of patients in the safety set for each treatment group that experienced the event. A patient with multiple occurrences of TEAE was counted once for the TEAE with the maximum intensity. *P-value denotes the test for moderate/severe TEAEs (13/256 *vs*. 13/254). AEs: Adverse events; *H. pylori*: *Helicobacter pylori*; SAE: Serious adverse event; TEAE: Treatment-emergent adverse event. –: Not applicable.

*H. pylori* eradication rates at week 4 post-treatment with vonoprazan-based quadruple therapy were non-inferior to those achieved with esomeprazole-based quadruple therapy (86.8% *vs*. 86.7%, respectively; $P = 0.0009$). These results were supported in sensitivity analysis with the per-protocol set or using different missing data handling methods. Another recent study among Asian patients with *H. pylori* infection also demonstrated that vonoprazan quadruple therapy was non-inferior to lansoprazole quadruple therapy, with eradication rates of 91.5% and 86.8%, respectively.[29] A retrospective study was performed in China and included 340 patients (propensity score-matched) who achieved *H. pylori* eradication using vonoprazan *vs*. PPI in clarithromycin-based bismuth-containing quadruple therapy; both groups achieved comparable eradication rates (88.8% *vs*. 87.6%) in the intention-to-treat analysis, and 94.1% *vs*. 91.1% in the per-protocol analysis.[30] Recently, an RCT by Lu *et al*[31] showed that vonoprazan was as effective as esomeprazole in 2-week quadruple therapy as a first-line treatment in the Chinese population, with the eradication rates for the two therapies were 94.9% (87.4–98.6%) and 93.6% (85.7–97.9%) in the intention-to-treat analysis, respectively. Their findings aligned with our research results, reinforcing the notion that vonoprazan, when compared with esomeprazole and other PPIs, exhibits non-inferiority in terms of quadruple therapy. It is worth noting that the study by Lu *et al*[31] reported relatively high eradication rates for both treatment arms. One distinction is the choice of antibiotics. Those authors used amoxicillin and furazolidone whereas we used different antibiotics in our study. Given that antibiotics play a pivotal role in quadruple therapy, this variation could influence the rate of eradication. Furthermore, the single-center nature of their study differs from our multicenter approach, potentially reflecting regional variations in antibiotic resistance patterns. Therefore, tailoring antibiotic combinations according to regional antibiotic sensitivity profiles becomes imperative for achieving successful eradication.

The efficacy of vonoprazan-based triple or dual therapy for eradicating *H. pylori* has been reported previously in studies from Japan.[17,32–34] Indeed, vonoprazan demonstrated non-inferiority *vs*. lansoprazole in eradicating *H. pylori* (92.6% *vs*. 75.9%, respectively) as a component of first-line triple therapy with amoxicillin and clarithromycin in Japanese patients with a history of gastric or duodenal ulcer.[32] Another study reported that dual therapy with vonoprazan plus amoxicillin was as effective as vonoprazan-based triple therapy for *H. pylori* eradication (92.9% *vs*. 91.9%, respectively; $P = 0.728$).[17] Two meta-analyses showed that vonoprazan-based regimens were superior in eradicating *H. pylori*, including clarithromycin-resistant strains, compared with conventional PPI-based regimens.[33,34] Another retrospective, open-label, single-center study in Japan involving 874 patients with *H. pylori* infection showed that the first-line eradication rate with a vonoprazan regimen was significantly higher (84.6% [377/443]) than the rate with an esomeprazole regimen (79.1% [341/431]; $P = 0.021$).[35] A recent phase 3 randomized trial among treatment-naïve adults from the United States and Europe who had *H. pylori* infection ($n = 1046$) reported eradication rates using vonoprazan-based triple therapy, vonoprazan-based dual therapy, and lansoprazole-based triple therapy at 84.7%, 78.5%, and 78.8%, respectively.[36] These studies collectively show that vonoprazan-based regimens are non-inferior to PPI-based triple therapy, both in the overall study populations and in the subsets with clarithromycin-resistant strains.

The achievement of sufficient inhibition of gastric acid secretion is a key factor in eradicating *H. pylori*

infection.[15] *H. pylori* enters the replicative phase of its replication cycle when intragastric pH is almost neutral (pH 6–7), so it is more sensitive to antibiotics at this pH range. Vonoprazan, with its fast onset of action and long-acting gastric acid inhibition, is considered to provide an optimal environment for antimicrobials to exert their effect. In a study with 28 healthy Japanese volunteers who had different *CYP2C19* genotypes (7 *CYP2C19* poor metabolizers, 11 intermediate metabolizers, and 10 rapid metabolizers), vonoprazan 20 mg b.i.d inhibited acid secretion irrespective of *CYP2C19* genotype more potently than esomeprazole 20 mg b.i.d with pH 6 holding time ratios of 85% and 69%, respectively.[15]

The safety and tolerability results reported in this study for vonoprazan are consistent with previous findings, with no new safety signals identified. Vonoprazan had a similar safety profile to that of esomeprazole and was well-tolerated when used as a constituent of quadruple therapy for *H. pylori* eradication. A separate randomized, double-blind, parallel-group study showed similar systemic exposures to bismuth between vonoprazan- and lansoprazole-containing quadruple therapies.[37]

This study has certain limitations. First, the resistance of *H. pylori* to clarithromycin was only present in a small proportion of patients in each group ($n = 46$); therefore, it is difficult to draw conclusions about the efficacy of vonoprazan *vs*. esomeprazole for clarithromycin-resistant *H. pylori*. Second, the baseline characteristics in the present study did not include the proportion of patients with *H. pylori* infection who were naïve to or received previous eradication therapy, including the number of rounds of previous therapy. Therefore, the efficacy of vonoprazan compared with esomeprazole cannot be analyzed in these subgroups of patients. Considering that patients who experience treatment failure or reinfection after eradication of *H. pylori* may develop antibiotic resistance, it may contribute to lower eradication success rates observed in the present study compared with studies that only included patients naïve to eradication therapy.

In conclusion, vonoprazan-based quadruple therapy was effective and well-tolerated in eradicating *H. pylori*. The eradication rates achieved with vonoprazan-based quadruple therapy were non-inferior compared with esomeprazole-based quadruple therapy. The safety profile of vonoprazan was comparable to that of esomeprazole, and treatment with vonoprazan was well tolerated. These findings suggest that vonoprazan may offer an effective treatment alternative to PPIs for *H. pylori* eradication.

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### Conflicts of interest

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### Data availability

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual patient data supporting the results reported in this article, will be made available within 3 months of initial requests to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Proposals should be directed to Liqun Gu (liqun.gu@takeda.com). Data requestors will need to sign a data access agreement.

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