


ORIGINAL ARTICLE

Evaluation of safety and pharmacokinetics of bismuth-containing quadruple therapy with either vonoprazan or lansoprazole for *Helicobacter pylori* eradication

Ki Young Huh¹ | Hyewon Chung² | Yu Kyong Kim³ | SeungHwan Lee¹ |
Siddharth Bhatia⁴ | Yohei Takanami⁵ | Ryou Nakaya⁵ | Kyung-Sang Yu¹ 

¹Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea

²Department of Clinical Pharmacology and Toxicology, Korea University Guro Hospital, Seoul, Republic of Korea

³Department of Clinical Pharmacology and Therapeutics, Chungbuk National University Hospital, Chungcheongbuk-do, Republic of Korea

⁴Takeda Pharmaceuticals International Co., Cambridge, MA, USA

⁵Takeda Pharmaceutical Company Limited, Osaka, Japan

Correspondence

Kyung-Sang Yu, Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: ksyu@snu.ac.kr

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Aims: *Helicobacter pylori* (Hp) eradication plays a key role in the treatment and prevention of peptic ulcer diseases. Increasing clarithromycin resistance in Hp necessitates more effective treatments for eradication, such as bismuth-containing quadruple therapy. We aimed to compare the safety and pharmacokinetics (PK) of bismuth between vonoprazan- and lansoprazole-containing quadruple therapy in Hp-positive subjects.

Methods: In this randomised, double-blind, parallel-group study, Hp-positive subjects were randomised to receive vonoprazan- or lansoprazole-containing quadruple therapy. Each subject received vonoprazan 20 mg or lansoprazole 30 mg combined with bismuth 220 mg, clarithromycin 500 mg and amoxicillin 1000 mg twice daily for 14 days. Blood sampling and urine collection for bismuth PK were conducted pre-dose and up to 12 hours postdose at steady-state. The PK parameters of bismuth were derived using a noncompartmental method and compared between treatments. An exploratory breath test for Hp was conducted at screening and at the follow-up visit on day 42. Safety was assessed by adverse event monitoring, physical examinations, vital signs, 12-lead electrocardiograms and clinical laboratory tests.

Results: A total of 30 subjects were randomised and 26 subjects completed the study (12 in the vonoprazan group and 14 in the lansoprazole group). The systemic exposure of bismuth in the 2 treatments was comparable (~5% difference). All subjects turned negative for Hp at the follow-up visit. No significant difference in safety profiles was noted between the 2 treatments.

Conclusion: The systemic exposure of bismuth was similar between vonoprazan- and lansoprazole-containing quadruple therapy. Vonoprazan-containing quadruple therapy was safe and well tolerated.

KEYWORDS

bismuth, drug interaction, *Helicobacter pylori*, quadruple therapy, vonoprazan

The authors confirm that the Principal Investigator for this paper is Kyung-Sang Yu and that he had direct clinical responsibility for patients.

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1 | INTRODUCTION

Helicobacter pylori (Hp) infection is 1 of the most well-established risk factors for acid-related disorders¹ as well as gastric adenocarcinomas.^{2,3} The prevalence of Hp infection remains high: even European regions, which reported relatively lower prevalence, reached a prevalence of approximately 39.8% during 2000–2016.⁴ Although the prevalence is variable across regions, approximately 4.3 billion people are estimated to be Hp positive globally.⁴

Hp eradication plays a key role in the treatment and prevention of peptic ulcer diseases.¹ The standard first-line therapy for Hp eradication is triple therapy comprising a **proton-pump** inhibitor (PPI), **amoxicillin** and **clarithromycin**.⁵ However, the Hp eradication rate with triple therapy is significantly reduced in clarithromycin-resistant Hp.⁶ Recent guidelines on Hp treatment recommend that the Hp eradication regimen should be chosen based on the clarithromycin resistance rate.^{7,8}

The prevalence of clarithromycin-resistant Hp has been increasing, requiring more effective treatments, such as bismuth-containing quadruple therapy.⁹ In China, where the clarithromycin resistance rate is almost 37%, quadruple therapy has been adopted as the main empirical treatment for Hp eradication: amoxicillin 1000 mg twice daily (b.i.d.) and clarithromycin 500 mg b.i.d. (after meal) with a standard dose of a PPI and bismuth 220 mg b.i.d. (before meal).^{10,11}

Potassium-competitive acid blockers (P-CABs) offer another effective option, and have received attention owing to their superior acid-inhibitory potential compared to PPIs.¹² **Vonoprazan** is a novel P-CAB indicated for acid-related disorders.¹³ Vonoprazan maintains a higher intragastric pH for a significantly longer duration over a whole day compared with PPIs.^{14,15} It is predominantly metabolised by **cytochrome P450 (CYP) 3A4** and is not affected by CYP2C19 polymorphism, unlike PPIs.¹³

Recent studies have shown a higher Hp eradication rate with vonoprazan than with PPIs for clarithromycin-resistant Hp.^{16,17} Hp eradication was also successful with vonoprazan-containing triple therapy after failure of PPI-containing triple therapy.¹⁸ Currently, Hp treatment guidelines in Japan recommend both P-CABs and PPIs as acid-inhibitory agents.¹⁹ Standard Hp eradication treatment guidelines in Japan recommend a 7-day triple therapy regimen with either a PPI or a P-CAB combined with amoxicillin 750 mg, clarithromycin 200 mg and metronidazole 250 mg.¹⁹

Although vonoprazan is expected to improve Hp eradication rates when included in quadruple therapy,¹⁰ the drug interactions of vonoprazan in bismuth-containing quadruple therapy have not yet been studied. In particular, the pharmacokinetics (PK) of bismuth in vonoprazan-containing quadruple therapy needs to be investigated owing to the pH-dependent absorption of bismuth.²⁰ Therefore, this study aimed to compare the safety and PK of bismuth between vonoprazan- and **lansoprazole**-containing quadruple therapy in Hp-positive subjects.

2 | METHODS

2.1 | Study subjects

Korean subjects aged 18–60 years with a body mass index (BMI) of 18–30 kg/m² were enrolled in the study. Subjects were required to

What is already known about this subject

- Eradication of *Helicobacter pylori* (Hp) plays a key role in the treatment and prevention of peptic ulcer diseases.
- Hp eradication rate with the standard triple therapy, a combination of proton-pump inhibitor, amoxicillin and clarithromycin, is significantly reduced in clarithromycin-resistant Hp.
- Recent studies have shown a higher Hp eradication rate with vonoprazan than with proton-pump inhibitors for clarithromycin-resistant Hp.

What this study adds

- Vonoprazan-containing quadruple therapy was safe and well tolerated.
- The systemic exposure of bismuth was comparable between vonoprazan- and lansoprazole-containing quadruple therapy.
- Vonoprazan-containing quadruple therapy demonstrated comparable Hp eradication rate to lansoprazole-containing counterpart in the urea breath test.

be positive for Hp (not necessarily to be Hp treatment-naïve) on the basis of the urea breath test at the screening visit. Subjects were examined to exclude clinically significant abnormalities by means of a medical interview, physical examinations, vital signs, 12-lead electrocardiograms and clinical laboratory tests. Subjects with a history of gastroesophageal reflux disease, symptomatic gastroesophageal reflux disease, erosive oesophagitis, duodenal ulcer, gastric ulcer, dyspepsia, Barrett's oesophagus or Zollinger–Ellison syndrome were excluded.

Written informed consent was obtained from the subjects prior to any study-related procedures. The study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea, and the Ministry of Food and Drug Safety (*ClinicalTrials.gov* registration no.: NCT02892409). The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2 | Study design

This was a randomised, double-blind, parallel-group study. Eligible subjects were randomised to receive vonoprazan or lansoprazole treatment; each subject received quadruple therapy consisting of amoxicillin 1000 mg b.i.d., clarithromycin 500 mg b.i.d. (after meal) and bismuth 220 mg b.i.d. combined with either vonoprazan 20 mg b.i.d. or lansoprazole 30 mg b.i.d. (before meal) for 14 days (Figure 1). CYP2C19 genotyping was conducted at baseline.

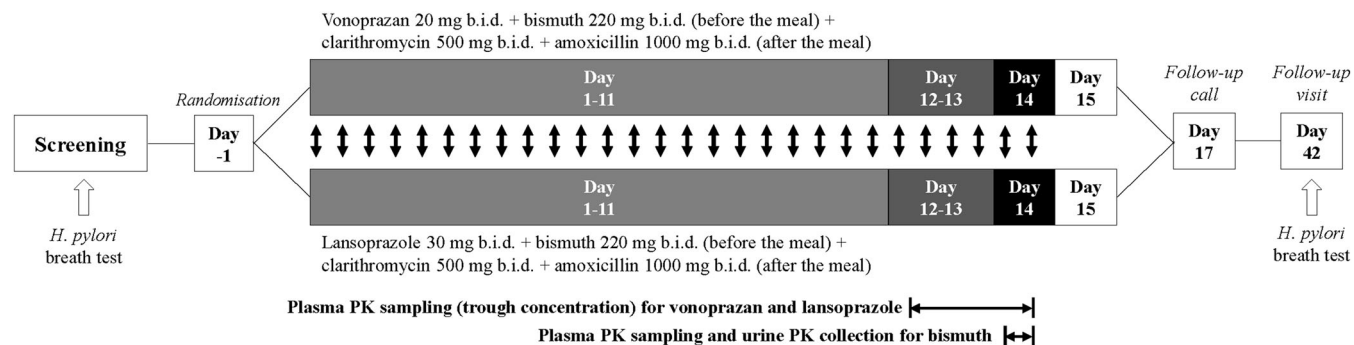


FIGURE 1 Schematic presentation of the study design. b.i.d., twice daily; *H. pylori*, *Helicobacter pylori*; PK, pharmacokinetics

Blood PK sampling for vonoprazan and lansoprazole was conducted predose for every dose administered from day 12 to day 14 to assess steady-state achievement. Plasma concentrations of vonoprazan and lansoprazole were determined by validated high-performance liquid chromatography with tandem mass spectrometry. The lower limit of quantification was 0.1 µg/L for vonoprazan and 5 µg/L for lansoprazole.

Blood PK sampling for bismuth was conducted predose and 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours after the morning dose at steady state (on day 14). Urine samples for bismuth PK were collected from predose to 12 hours after the morning dose at steady state. Plasma and urine concentrations of bismuth were determined by validated inductively coupled plasma mass spectrometry. The lower limit of quantification was 0.2 µg/L for plasma bismuth and 5 µg/L for urine bismuth.

2.3 | PK assessment

Steady-state achievement for vonoprazan and lansoprazole was graphically evaluated with trough plasma concentrations from day 12 to day 14. Steady-state PK parameters of bismuth were derived using a noncompartmental method. The maximum observed plasma concentration (C_{max}) at steady state and the time to first occurrence of C_{max} (t_{max}) were directly determined from the observed values. The area under the plasma concentration–time curve during a dosing interval (AUC_{τ}) was calculated by the linear trapezoidal method. The terminal disposition phase rate constant (λ_z) was calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration–time curve during the terminal phase. The terminal disposition half-life ($t_{1/2z}$) and apparent clearance (CL/F) were calculated as $\ln(2)/\lambda_z$ and dose/ AUC_{τ} after multiple dosing, respectively. The apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F) was calculated as $(CL/F)/\lambda_z$. The fraction of drug excreted unchanged in urine (f_e) was calculated as the amount of drug excreted in urine during a dosing interval (Ae_{τ}) divided by the dose multiplied by 100 to obtain a percentage. Renal clearance (CL_R) was calculated as Ae_{τ}/AUC_{τ} .

2.4 | Hp test

Hp infection was evaluated by the ^{13}C -urea breath test (Helifinder, Medichems, Seoul, Korea). The breath test was conducted at screening and at the follow-up visit on day 42. The proportion of subjects who turned negative for Hp was compared between the vonoprazan- and lansoprazole-containing quadruple therapy groups.

2.5 | Safety assessment

Safety was assessed by adverse event (AE) monitoring performed by investigators' questionnaire and subjects' report, physical examinations, vital signs, 12-lead electrocardiograms, and clinical laboratory tests. Subjects were discharged from the study unit on day 15 and were required to contact the study site for a follow-up call on day 17.

2.6 | Statistical analysis

To compare the systemic exposure of bismuth in vonoprazan- and lansoprazole-containing quadruple therapy, steady-state C_{max} and AUC_{τ} were evaluated using analysis of variance (ANOVA) with the term for treatment. Geometric mean ratios and 2-sided 90% confidence intervals for steady-state C_{max} and AUC_{τ} between treatments were calculated. Sample size was not primarily based on statistical considerations but set to significantly detect a 50% difference for C_{max} and AUC_{τ} of bismuth with 40% coefficient of variation considering the reported coefficient of variation of bismuth (~32%).²¹ All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.²²

3 | RESULTS

3.1 | Subject disposition

Overall, 30 subjects were randomised and received the study medication at least once (safety analysis set). A total of 26 subjects (12 in the vonoprazan group and 14 in the lansoprazole group) completed the study (PK analysis set). Four subjects discontinued the study:

TABLE 1 Demographics and baseline characteristics

	Vonoprazan (n = 15)	Lansoprazole (n = 15)
Age (y), mean \pm sd	32.8 \pm 6.9	33.3 \pm 8.6
Sex, n (%)		
Male	14 (93.3)	14 (93.3)
Female	1 (6.7)	1 (6.7)
Height (cm), mean \pm sd	173.7 \pm 5.0	168.9 \pm 5.1
Weight (kg), mean \pm sd	72.4 \pm 5.0	66.1 \pm 8.4
Body mass index (kg/m ²), mean \pm sd	24.0 \pm 1.8	23.1 \pm 2.3
CYP2C19 phenotype, n (%) ^a		
Normal metaboliser (*1/*1)	5 (33.3)	6 (40.0)
Intermediate metaboliser (*1/*2, *1/*3)	9 (60.0)	8 (53.3)
Poor metaboliser	1 (6.7)	0

sd, standard deviation; CYP, cytochrome P450.

Vonoprazan and lansoprazole represent the treatment groups comprising vonoprazan 20 mg twice daily (b.i.d.) or lansoprazole 30 mg b.i.d., respectively, coadministered with bismuth 220 mg b.i.d., clarithromycin 500 mg b.i.d. and amoxicillin 1000 mg b.i.d.

^aCYP2C19 phenotypes are annotated according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines.²³

The CYP2C19 phenotype for 1 subject in the lansoprazole group was not identified.

1 subject due to AEs in the vonoprazan group; and 3 subjects (two in the vonoprazan group and 1 in the lansoprazole group) due to withdrawal of consent. Demographics and baseline characteristics of the enrolled subjects were similar between the 2 treatment groups (Table 1).

3.2 | PK

The mean trough plasma concentrations of vonoprazan and lansoprazole showed that the steady state was reached on day 14 of treatment (Figure S1). Plasma concentration–time profiles of bismuth in quadruple therapy with either vonoprazan or lansoprazole were comparable (Table 2, Figure 2). Bismuth was rapidly absorbed with a median t_{\max} of 0.75 hours in both treatment groups. The mean terminal disposition half-life of bismuth was 13.2 and 11.6 hours in the vonoprazan and lansoprazole groups, respectively. The geometric mean ratio and 90% confidence interval for the C_{\max} and AUC_{τ} of bismuth (vonoprazan to lansoprazole) were estimated as 1.05 (0.72–1.54) and 0.94 (0.71–1.23), respectively. No remarkable differences in f_e and CL_R were noted between the vonoprazan and lansoprazole groups.

3.3 | Hp test

All subjects included in the analysis (12 in the vonoprazan group and 14 in the lansoprazole group) turned negative for Hp on the basis of the breath test at the follow-up visit.

3.4 | Safety

During the study, 8 subjects experienced 20 treatment-emergent AEs (TEAEs) in the vonoprazan group and 10 subjects experienced

TABLE 2 Summary pharmacokinetic parameters of bismuth at steady state

	Vonoprazan (n = 12)	Lansoprazole (n = 14)	Geometric mean ratio ^a (90% confidence interval)
t_{\max} (h), median [range]	0.75 [0.48–0.97]	0.75 [0.25–0.97]	
C_{\max} (ng/mL), mean \pm sd	28.1 \pm 11.7	30.1 \pm 24.6	1.05 (0.72–1.54)
AUC_{τ} (h ng/mL), mean \pm sd	103.0 \pm 37.5	111.1 \pm 45.0	0.94 (0.71–1.23)
$t_{1/2z}$ (h), mean \pm sd	13.2 \pm 7.0	11.6 \pm 5.1	
CL/F (L/h), mean \pm sd	2468 \pm 1063	2324 \pm 1015	
V_z/F (L), mean \pm sd	50 880 \pm 41 172	39 710 \pm 25 232	
f_e (%), mean \pm sd ^b	0.2 \pm 0.1	0.2 \pm 0.1	
CL_R (L/h), mean \pm sd ^b	4.9 \pm 1.2	5.0 \pm 1.5	

sd, standard deviation, AUC_{τ} , area under the plasma concentration–time curve during a dosing interval; C_{\max} , maximum observed plasma concentration at steady state; CL/F, apparent clearance; CL_R , renal clearance; f_e , fraction of drug excreted unchanged in the urine; t_{\max} , time of the first occurrence of C_{\max} ; V_z/F , apparent volume of distribution.

Vonoprazan and lansoprazole represent the treatment groups comprising vonoprazan 20 mg twice daily (b.i.d.) or lansoprazole 30 mg b.i.d., respectively, coadministered with bismuth 220 mg b.i.d., clarithromycin 500 mg b.i.d. and amoxicillin 1000 mg b.i.d.

^aVonoprazan to lansoprazole.

^bOne subject was excluded from the analysis of urine pharmacokinetic parameters (f_e , CL_R) due to an inadequate sample.

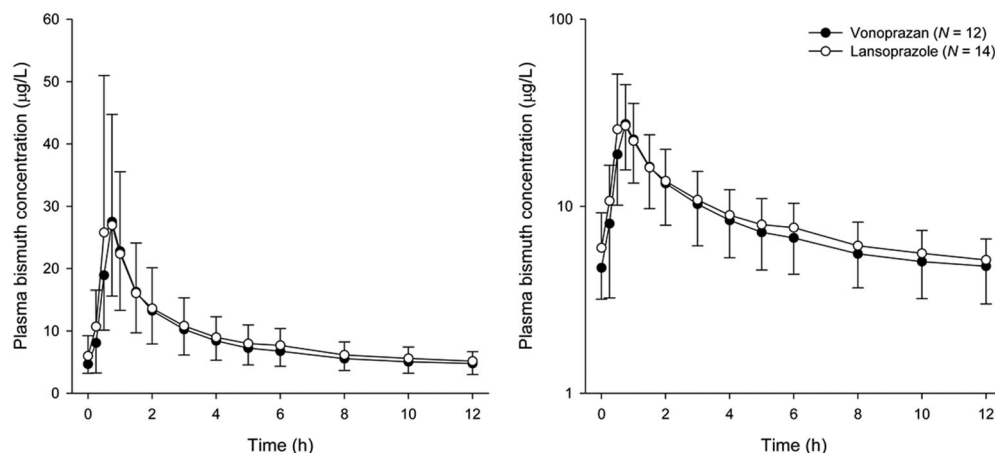


FIGURE 2 Mean plasma bismuth concentration vs. time profile at steady state (left: linear scale; right: semilogarithmic scale). Vonoprazan and lansoprazole represent the treatment groups comprising vonoprazan 20 mg twice daily (b.i.d.) or lansoprazole 30 mg b.i.d., respectively, coadministered with bismuth 220 mg b.i.d., clarithromycin 500 mg b.i.d. and amoxicillin 1000 mg b.i.d. Error bars denote standard deviation

17 TEAEs in the lansoprazole group. One subject in the vonoprazan group experienced moderate palpitations and chest discomfort that led to study discontinuation. The subject was diagnosed with hyperthyroidism, which was determined not related to the study medication. Other TEAEs were mild in severity and recovered without sequelae. No serious AEs or deaths were reported in the study.

Of the TEAEs, 5 subjects experienced 13 adverse drug reactions (ADRs) in the vonoprazan group and 6 subjects experienced 9 ADRs in the lansoprazole group. Gastrointestinal disorders were the most frequent ADRs; 3 subjects in the vonoprazan group and 4 subjects in the lansoprazole group reported gastrointestinal ADRs. The gastrointestinal ADRs included discoloured faeces, diarrhoea, dyspepsia and gastro-oesophageal reflux disease. Dermatological ADRs (i.e. hyperhidrosis and rash) were more frequently reported in the vonoprazan group than in the lansoprazole group. In contrast, dysgeusia was more frequently reported in the lansoprazole group (Table 3).

4 | DISCUSSION

In previous clinical trial in healthy subjects, vonoprazan showed stronger acid inhibition than lansoprazole.^{15,24} The median 6-hour intragastric pH of 4.30 after a single oral dose of vonoprazan was higher than that of 2.65 after a single oral dose of lansoprazole.^{15,24} Furthermore, vonoprazan could maintain increased gastric pH levels over a whole day.²⁵ As absorption of bismuth is dependent on intragastric pH,²⁰ it is possible that vonoprazan might have increased the systemic exposure of bismuth greater than lansoprazole. However, this finding has not been investigated in clinical trials.

We found that the systemic exposure of bismuth was similar after vonoprazan- and lansoprazole-containing quadruple therapy. The C_{max} or AUC_{τ} was not significantly different between the 2 therapies. Bismuth is supposed to induce encephalopathy when excessively exposed, although the relationship is not statistically clear.²⁶ The safety margin of plasma bismuth concentration is up to 50 ng/mL.²⁷ As the average concentration of bismuth (AUC_{τ} divided by 12 h) was <10 ng/mL, the systemic exposure of bismuth in vonoprazan-containing quadruple therapy is not expected to have toxic potential.²⁶

TABLE 3 Summary of adverse drug reactions (ADRs)

	Vonoprazan (n = 15)	Lansoprazole (n = 15)
Total ADRs	5 (13)	6 (9)
Cardiac disorders	1 (2)	0
Palpitations	1 (2)	0
Gastrointestinal disorders	3 (3)	4 (4)
Faeces discoloured	1 (1)	2 (2)
Diarrhoea	1 (1)	1 (1)
Dyspepsia	1 (1)	0
Gastro-oesophageal reflux disease	0	1 (1)
General disorders and administration site conditions	2 (2)	0
Feeling hot	1 (1)	0
Chest discomfort	1 (1)	0
Investigations	0	1 (1)
Neutrophil count decreased	0	1 (1)
Nervous system disorders	1 (1)	3 (3)
Dysgeusia	0	3 (3)
Headache	1 (1)	0
Reproductive system and breast disorders	1 (1)	0
Menstruation irregular	1 (1)	0
Skin and subcutaneous tissue disorders	4 (4)	1 (1)
Hyperhidrosis	3 (3)	1 (1)
Rash	1 (1)	0

Notes: ADRs are presented by systemic organ class (**bold**) and preferred term. The number of subjects (the number of adverse events) are presented. Vonoprazan and lansoprazole represent the treatment groups comprising vonoprazan 20 mg twice daily (b.i.d.) or lansoprazole 30 mg b.i.d., respectively, coadministered with bismuth 220 mg b.i.d., clarithromycin 500 mg b.i.d. and amoxicillin 1000 mg b.i.d.

The current regimen for vonoprazan-containing triple therapy comprises amoxicillin and clarithromycin.¹⁹ Amoxicillin did not show significant drug interactions in the triple therapy.²⁸ In contrast,

clarithromycin is a strong CYP3A4 enzyme inhibitor,²⁹ which increased the systemic exposure of vonoprazan by a factor of 1.8.²⁸ However, the drug interaction between clarithromycin and vonoprazan was not considered clinically significant in terms of safety and efficacy.²⁸ Well-established practices for vonoprazan-containing triple therapy in Japan also support the absence of clinical significance of this drug interaction.¹⁹ Accordingly, the expected drug interaction among vonoprazan, amoxicillin and clarithromycin in quadruple therapy would be similar to that observed in triple therapy.

By contrast, bismuth is mainly eliminated through renal and biliary excretion.²⁰ Thus, bismuth is not expected to be majorly affected by amoxicillin or clarithromycin. The effect of bismuth on other antimicrobials is not still clear, but clinical evidence of its additive effectiveness in triple therapy suggests a lack of significant interaction.³⁰ Therefore, the drug interaction potential among components in vonoprazan-containing quadruple therapy would not be clinically significant.

Several studies suggested that ingestion of food could be considered to prevent local gastric irritation.³¹ Although bioavailability of bismuth was significantly reduced,³¹ eradication rate was not impaired (~90%).^{31,32} Regarding the effect of food, the systemic exposure of vonoprazan was unaffected,³³ contrary to 27% decrease of lansoprazole,³⁴ which could provide more stable acid inhibition. The effect of food on the efficacy of P-CAB or PPI-containing quadruple therapy needs to be investigated.

The safety and tolerability results were comparable between vonoprazan- and lansoprazole-containing quadruple therapies. In a prior multicentre trial, patients who received PPI-containing quadruple therapies frequently reported darkened stool, nausea, dizziness and vomiting, which were similarly observed in our study.³⁵ Considering the sample size, the overall prevalence of AE (37%) was comparable to the previous estimate of 46–67%.^{35,36}

Increasing treatment failure with conventional triple therapy due to clarithromycin-resistant *Hp* necessitates more effective treatment options.^{5,37} Possible options include use of more potent acid inhibitors¹⁶ or addition of bismuth.³⁸ The results of our study suggested that vonoprazan-containing quadruple therapy would exhibit comparable efficacy to the lansoprazole counterpart, while tolerable. Further studies regarding the efficacy of the vonoprazan-containing quadruple therapy in larger population will be required, especially in the patients with the clarithromycin-resistant *Hp*.

Our study had some limitations. The small sample size and controlled patient population could limit the generalizability of the results. Absence of antimicrobial testing and intragastric acidity evaluation also restricts the interpretation of the results. Nonetheless, the PK results were sufficient to evaluate the interactions in the quadruple therapies. Furthermore, the results of urea breath tests implied that the treatments were adequate.

In conclusion, the systemic exposure of bismuth was comparable between vonoprazan- and lansoprazole-containing quadruple therapy. Vonoprazan-containing quadruple therapy was safe and well tolerated.

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CONTRIBUTORS

H.C. and K.S.Y. contributed to the study concept and design; H.C., Y.K.K., S.H.L. and K.S.Y. contributed to acquisition of data; K.Y.H., S.B., Y.T., R.N. and K.S.Y. contributed to the data analysis; K.Y.H., H.C., Y.K.K., S.H.L., S.B. and K.S.Y. contributed to the data interpretation. All authors participated in the manuscript revision for important intellectual content and the final approval of the manuscript. All authors agreed to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTERESTS

Siddharth Bhatia is an employee of Takeda Pharmaceuticals International Co. Yohei Takanami is an employee of Takeda Pharmaceutical Company Limited. Ryou Nakaya is an employee of Takeda Pharmaceutical Company Limited. Ki Young Huh, Hyewon Chung, Yu Kyong Kim, SeungHwan Lee and Kyung-Sang Yu have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual subject data supporting the results reported in this article, will be made available within 3 months from initial requests, to researchers who provide a methodologically sound proposal. The data will be provided after deidentification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization. Proposal should be directed to Yuuichi Sakurai at yuuichi.sakurai@takeda.com. Data requestors will need to sign a data access agreement.

ORCID

Kyung-Sang Yu  <https://orcid.org/0000-0003-0921-7225>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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