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Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects - a randomised open-label cross-over study

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SUMMARY

Background
Proton pump inhibitors (PPIs) are widely used for the treatment of acid-related diseases. Vonoprazan is a member of a new class of acid suppressants; potassium-competitive acid blockers. Vonoprazan may thus be an alternative to PPIs.

Aim
To evaluate efficacy, rapidity and duration of acid-inhibitory effects of vonoprazan vs. two control PPIs, esomeprazole and rabeprazole, in 20 healthy Japanese adult male volunteers with CYP2C19 extensive metaboliser genotype.

Methods
In this randomised, open-label, two-period cross-over study, vonoprazan 20 mg and esomeprazole 20 mg (Study V vs. E) or rabeprazole 10 mg (Study V vs. R) were orally administered daily for 7 days. Primary pharmacodynamic endpoint was gastric pH over 24 h measured as percentage of time pH ≥3, ≥4 and ≥5 (pH holding time ratios; HTRs) and mean gastric pH.

Results
Acid-inhibitory effect (pH4 HTR) of vonoprazan was significantly greater than that of esomeprazole or rabeprazole on both Days 1 and 7; Day 7 difference in pH4 HTR for vonoprazan vs. esomeprazole was 24.6% [95% confidence interval (CI): 16.2–33.1] and for vonoprazan vs. rabeprazole 28.8% [95% CI: 17.2–40.4]. The Day 1 to Day 7 ratio of 24-h pH4 HTRs was >0.8 for vonoprazan, compared with 0.370 for esomeprazole and 0.393 for rabeprazole. Vonoprazan was generally well tolerated. One vonoprazan subject withdrew due to a rash which resolved after discontinuation.

Conclusions
This study demonstrated a more rapid and sustained acid-inhibitory effect of vonoprazan 20 mg vs. esomeprazole 20 mg or rabeprazole 10 mg. Therefore, vonoprazan may be a potentially new treatment for acid-related diseases.

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INTRODUCTION

Proton pump inhibitors (PPIs) are widely used globally for the treatment of acid-related diseases such as gastro-oesophageal reflux disease (GERD), gastric and duodenal ulcers and as a component of eradication therapy for *Helicobacter pylori*.[1–4] Although highly effective in these indications, conventional PPIs have some characteristics which mean that they are not the ideal therapy for all patients. PPIs are prodrugs that require acid secretion for conversion into active sulfenamide intermediates which interact with cysteine residues on gastric H^+, K^+-ATPase (proton pump), the enzyme that catalyses the final step in the gastric acid secretion pathway.[5] The onset of effect is slow and cumulative because several doses are required to inhibit newly synthesised proton pumps and achieve maximal acid-inhibition.[5, 6] Even when taken twice daily, conventional PPIs are not exposed to proton pumps synthesised at night due to their relatively short plasma half-life (60–90 min); this can result in continuing symptoms and damage to the oesophagus or stomach in some patients.[7] In addition, the acid-inhibitory effects of PPIs may vary because of polymorphism of the main enzyme responsible for their metabolism: cytochrome P450 (CYP) 2C19. Specifically, plasma PPI concentrations and gastric pH have been shown to be lower in extensive vs. poor metabolisers.[8] This may be particularly relevant in Asia where approximately 80% of the population has the extensive metaboliser genotype.[6] CYP2C19 polymorphism may influence the response of some patients to dual or triple therapy for *H. pylori* eradication, because a gastric pH >5 is important for the activity of many antibacterial agents.[9, 10] Lastly, the high affinity of (especially) omeprazole for CYP2C19 carries potential for drug-drug interactions with substances either activated or metabolised (e.g. clopidogrel) by this enzyme.[11, 12]

Potassium-competitive acid blockers (P-CABs) are a new class of gastric acid suppressant agents.[13] Similar to PPIs, P-CABs inhibit gastric H^+, K^+-ATPase but, unlike PPIs, P-CABs inhibit the enzyme in a K^+-competitive and reversible manner.[13] Vonoprazan is a novel member of this class that was discovered and developed by Takeda Pharmaceutical Company Ltd., Japan.[7, 14] Vonoprazan has a potent and long-lasting anti-secretory effect on H^+, K^+-ATPase on account of its high accumulation and slow clearance from gastric tissue.[14, 15] As its inhibitory effect on gastric acid secretion is unaffected by the acid secretory state, the timing of vonoprazan administration is mealtime independent.[16]

In a phase I study in healthy male volunteers, single doses of vonoprazan 1–120 mg produced a rapid and profound dose-related suppression of 24-h gastric acid secretion and were well tolerated;[17] the effects were maintained during multiple dosing of vonoprazan (10–40 mg) over 7 days.[18] Vonoprazan has an elimination half-life of up to 9 h and its pharmacokinetics after single or multiple increasing doses of 10–40 mg for 7 days were shown to be unaffected by CYP2C19 genotype.[17, 18] A phase II dose-ranging study compared vonoprazan 5–40 mg once daily with lansoprazole 30 mg once daily over an 8-week period in patients with endoscopically confirmed erosive oesophagitis.[19] At doses ≥5 mg, vonoprazan produced healing rates comparable to that of lansoprazole and was well tolerated. At doses of 20 mg and 40 mg, healing rates at week 4 with vonoprazan for Los Angeles Grade C/D erosive oesophagitis were 100% and 96%, respectively, compared with 87% for lansoprazole. The 20 mg dose provided the optimal balance between efficacy and tolerability.

To date, no studies have compared directly the acid-inhibitory effects of vonoprazan and PPIs. The objective of this study was, therefore, to compare the acid-inhibitory effect of multiple oral doses of vonoprazan 20 mg with that of two control PPIs, esomeprazole 20 mg or rabeprazole 10 mg, in healthy Japanese adult male subjects with the CYP2C19 extensive metaboliser genotype.

SUBJECTS AND METHODS

Study design

This study was a randomised, open-label, two-period, crossover study (ClinicalTrials.gov identifier NCT02037477) that examined the acid-inhibitory effects of vonoprazan compared with esomeprazole (Study V vs. E) or rabeprazole (Study V vs. R). Each study group comprised two treatment sequences (Figure 1). The study was conducted during February and March 2014 at Medical Co. LTA Hakata Clinic in Fukuoka, Japan.

The study was approved by the Institutional Review Board at the Medical Co. LTA Hakata Clinic and was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and Japanese regulatory requirements. All subjects provided written informed consent.

SUBJECTS

Healthy Japanese adult male volunteers were eligible for inclusion in the study if they were aged 20–45 years,

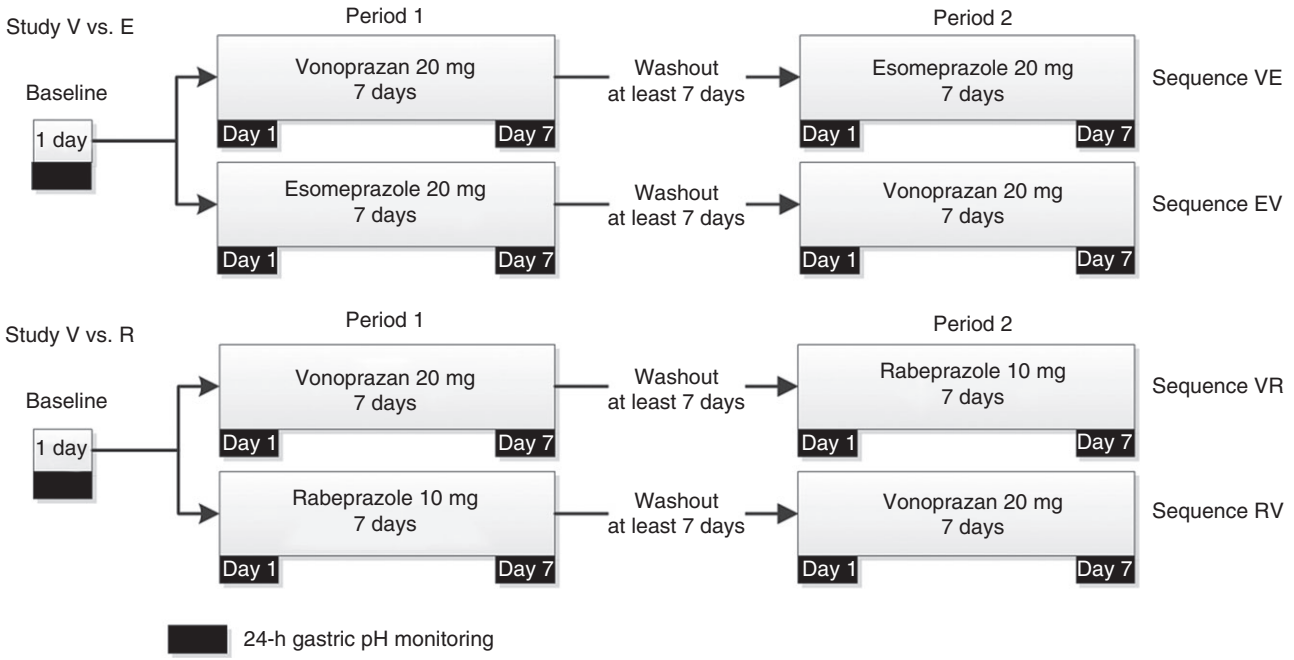

Figure 1 | Study design: treatment sequences and periods for Study V vs. E and Study V vs. R. A minimum 7-day washout period was set between administration periods to minimise any drug carry-over effect. Seven days after the last dose in Period 2, follow-up tests were conducted.

weighed ≥50.0 kg, had a body mass index (BMI) ≥18.5 kg/m^2 and <25.0 kg/m^2, had a CYP2C19 extensive metaboliser (**1/*1, *1/*2, *1/*3*) genotype, and tested negative for *H. pylori* antibody at screening.

Subjects were excluded if they had: previously received vonoprazan; undergone previous vagotomy or resection of the upper gastrointestinal tract; hypoacidity or anacidity; a history of acid-related diseases (erosive oesophagitis, gastric ulcer, duodenal ulcer, non-erosive gastro-oesophageal reflux disease, Barrett's oesophagus or Zollinger-Ellison syndrome); undergone treatment for *H. pylori* eradication within 6 months before the first dose of study medication; received any investigational compound within 16 weeks before the first dose of study medication; poor peripheral venous access; any uncontrolled, clinically significant abnormality which may impact the study results; a history of drug or alcohol abuse within 5 years before the first dose of study medication; or a history of cancer.

Subjects were not permitted to take prescription medications, vitamin supplements, nutrient supplements, Chinese herbs or over-the-counter drugs from 28 days before each administration period until follow-up examination or to consume any foods or beverages containing grapefruit, Seville orange, alcohol or caffeine from 72 h before each administration period until check-out.

Randomisation

Thirty-five candidates were determined to be eligible at screening and, after check-in examinations, 20 candidates (10 in each study group) were selected as study subjects. Subjects were randomly and equally allocated to the two treatment sequences within each study group based on CYP2C19 extensive metaboliser genotype (homozygous [**1/*1*] or heterozygous [**1/*2, *1/*3*]) in the ascending order of subject identification number in accordance with the allocation table generated by a designated statistician.

Interventions

Subjects were required to fast for ≥10-h overnight before each administration period. During the first 7-day period, subjects in Study V vs. E received vonoprazan 20 mg (Sequence VE) or esomeprazole 20 mg (Nexium capsule; AstraZeneca K.K., Osaka, Japan) (Sequence EV) each day. Similarly, subjects in Study V vs. R received vonoprazan 20 mg (Sequence VR) or rabeprazole 10 mg (Pariet; Eisai Co., Ltd., Tokyo, Japan) (Sequence RV). A minimum 7-day washout period was set between administration periods to minimise any drug carry-over effect. After the washout period, subjects in Sequences VE and EV were crossed over to receive esomeprazole 20 mg or vonoprazan 20 mg, respectively, and subjects in

Sequences VR and RV were crossed over to receive rabeprazole 10 mg or vonoprazan 20 mg, respectively (Figure 1). All study drugs were administered orally with 150 mL water under fasting conditions (Days 1 and 7) or 1 h before breakfast (Days 2–6).

Doses of esomeprazole 20 mg and rabeprazole 10 mg were selected based on the approved standard doses for treatment of reflux oesophagitis in Japan. The 20 mg dose of vonoprazan was chosen based on the clinical data observed in a phase II erosive oesophagitis healing study.[19]

Study protocol and evaluation criteria

Subjects were admitted to the study site at baseline and remained on site throughout both administration periods except for the washout period. Subjects returned to the study site 7 days after the last dose in Period 2 for follow-up tests to confirm the absence of abnormalities. At baseline, demographical and clinical characteristics including age, height, weight, *H. pylori* antibody test, CYP2C19 genotype test, smoking status and consumption of alcohol and caffeine were checked.

Subjects underwent 24-h gastric pH monitoring at baseline (from Day-2 to Day-1 before the start of study medication in Period 1), and on Days 1 and 7 in each administration period (Periods 1 and 2; Figure 1). A total of five sessions of 24-h gastric pH monitoring were conducted during the course of the study. Subjects' gastric pH was monitored for at least 24 h beginning at the same time of day as study drug administration (as a rule, 9:00 AM). A catheter-guided pH measuring device, calibrated using standard pH 4 and pH 7 solutions, was placed in the stomach transnasally under X-ray guidance. The device consisted of a portable pH monitor (PH-101ZG; Chemical Instruments, Tokyo, Japan) and a glass pH electrode (CM-181; Chemical Instruments, Tokyo, Japan).

The primary pharmacodynamic endpoint was the gastric pH over 24 h measured as percentage of time pH $\geq$3, $\geq$4 and $\geq$5 (pH holding time ratios; HTRs) and mean gastric pH.

Safety endpoints were adverse events, treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram (ECG) findings and clinical laboratory test values.

Statistical analysis

The planned number of subjects for evaluation of the pharmacodynamic effect was 10 per study group (five per sequence), or 20 in total. Previous clinical studies in Japanese have documented mean 24-h pH 4 HTRs of 83.4% after 7 days of vonoprazan at 20 mg,[18] 62.4% after 5 days esomeprazole at 20 mg,[20] and 60.5% and 55.1% after 5 days rabeprazole at 10 mg in subjects with CYP2C19 hetero-extensive and homo-extensive metaboliser genotypes, respectively.[21] In this study, the 24-h pH 4 HTR on Day 7 was assumed to be 80% for subjects receiving vonoprazan 20 mg and 65% for subjects receiving esomeprazole 20 mg. Assuming that the coefficient of variation was 20% for both treatments, and that the correlation coefficient between periods was 0.5, the power to detect the difference in the study was at least 80% with a sample size of 5 per sequence.

The pharmacodynamic analysis set comprised subjects who received study medication and completed study protocol procedures without serious violation. The safety analysis set comprised all subjects who received study medication.

Demographics and other baseline characteristics were summarised using descriptive statistics for all continuous variables and frequencies for all categorical variables. For vital signs, ECG findings and clinical laboratory test values, descriptive statistics were used to summarise continuous variables and their changes from baseline by study medication. For categorical variables (i.e. normal or abnormal findings or qualitative clinical laboratory tests), shift tables summarising changes from baseline to each post-baseline evaluation were presented for each study medication.

Time courses of gastric pH, averaged over successive 10-min periods during 24-h gastric pH monitoring at baseline and on Days 1 and 7 were plotted for each study medication in each study group. For pH 3, 4 and 5 HTRs and mean gastric pH on Days 1 and 7, the point estimate of the difference in changes from baseline between study medications (vonoprazan − esomeprazole and vonoprazan − rabeprazole) was calculated with a 2-sided 95% confidence interval (CI), using an analysis of variance (ANOVA) with study medication, sequence and period as fixed effects and subject as a random effect.

TEAEs were coded using the Medical Dictionary for Regulatory Activities (version 16.0). In each study group, the incidences of all TEAEs, drug-related TEAEs, TEAEs leading to study drug discontinuation and serious adverse events were summarised by Preferred Term. All TEAEs and drug-related TEAEs were summarised similarly by severity.

Data analyses and tabulations of descriptive and inferential statistics were performed using SAS release 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Subject disposition

A total of 56 subjects signed the informed consent form and 20 received the study drug. The most frequent reasons for subjects not receiving study drug were 'did not meet inclusion criteria' (n = 16) or 'sample size sufficient' (n = 12). One subject in Study V vs. R withdrew from the study before administration of study drug on Day 5 of Period 2 due to a rash that occurred after administration of vonoprazan. A total of 19 subjects completed the study.

In Study V vs. E, all 10 subjects were included in both the pharmacodynamic and safety analysis sets. In Study V vs. R, three subjects were excluded from the pharmacodynamic analysis set: two subjects in Sequence VR for 'administration of excluded medication' and 'deviation concerning diet and beverages', respectively, and one subject in Sequence RV for 'missing gastric pH monitoring due to withdrawal'. All 10 subjects in Study V vs. R were included in the safety analysis set.

There were no meaningful differences in baseline demographical and clinical characteristics according to treatment sequence for each study group in the pharmacodynamic analysis set, except for age in Study V vs. E (Table 1), where the mean age was 34 years in Sequence VE and 24 years in Sequence EV.

Pharmacodynamic effects

Time course of gastric pH over 24 h. The time courses of gastric pH, averaged over successive 10-min periods, over 24 h at baseline, on Days 1 and 7 indicate that gastric pH tended to be higher after administration of vonoprazan than after administration of esomeprazole or rabeprazole (Figures 2 and 3). This difference was noticeable 2 h after administration of study drugs and the trend continued until Day 7. Gastric pH over 24 h tended to be lower on Day 1 compared with Day 7 after administration of esomeprazole or rabeprazole. In contrast, after administration of vonoprazan, gastric pH over 24 h was similar and mostly above 4 on Days 1 and 7 except for the initial 4 or 5 h on Day 1.

Gastric pH 3, 4 and 5 HTRs. For all study drugs, the mean 24-h pH 4 HTRs were lowest at baseline and highest on Day 7 (Tables 2 and 3). On Day 1, the mean (s.d.) 24-h pH 4 HTRs for Study V vs. E were 71.4% (17.0%) for vonoprazan and 23.9% (16.9%) for esomeprazole. On Day 7, the pH 4 HTRs were 85.8% (14.7%) for vonoprazan and 61.2% (17.1%) for esomeprazole. The difference in pH 4 HTR between vonoprazan and esomeprazole was 47.5% [95% confidence interval (CI): 35.5–59.4] on Day 1 and 24.6% [95% CI: 16.2–33.1] on Day 7 (Table 2). Similarly, on Day 1, the mean (s.d.) 24-h pH 4 HTRs for Study V vs. R were 84.2% (12.4%) for vonoprazan and 26.3% (13.4%) for rabeprazole. On Day 7, the pH 4 HTRs were 93.8% (7.3%) for vonoprazan and 65.1% (14.2%) for rabeprazole. The difference in pH 4 HTR between vonoprazan and rabeprazole was 58.2% [95% CI: 43.6–72.9] on Day 1 and 28.8% [95% CI: 17.2–40.4] on Day 7 (Table 3).

A greater acid-inhibitory effect of vonoprazan compared with both esomeprazole and rabeprazole was observed. The means of 0–24 h, 0–12 h (daytime) and 12–24 h (night-time) pH 4 HTRs on Days 1 and 7 were higher after administration of vonoprazan than after administration of esomeprazole (Table 2) or rabeprazole (Table 3). In addition, the Day 1 to Day 7 ratios of 24-h pH 4 HTRs were higher for vonoprazan than they were

Table 1 | Baseline demographical and clinical characteristics of subjects in Study V vs. E and Study V vs. R: pharmacodynamic analysis sets

	Study V vs. E		Study V vs. R	
	Sequence VE (n = 5)	Sequence EV (n = 5)	Sequence VR (n = 3)	Sequence RV (n = 4)
Age, years	34.0 ± 6.93	23.8 ± 5.17	20.3 ± 0.58	26.3 ± 5.50
Height, cm	172.0 ± 7.75	173.0 ± 6.52	172.0 ± 5.00	169.8 ± 5.56
Weight, kg	64.1 ± 8.93	64.1 ± 9.81	60.5 ± 3.27	59.6 ± 5.08
BMI, kg/m^2	21.6 ± 1.67	21.3 ± 1.84	20.4 ± 0.25	20.7 ± 1.06
CYP2C19 genotype, n (%)				
Homozygous EM	2 (40.0)	3 (60.0)	2 (66.7)	1 (25.0)
Heterozygous EM	3 (60.0)	2 (40.0)	1 (33.3)	3 (75.0)

BMI, body mass index; CYP, cytochrome P450; EM, extensive metaboliser; Sequence VE, vonoprazan → esomeprazole; Sequence EV, esomeprazole → vonoprazan; Sequence VR, vonoprazan → rabeprazole; Sequence RV, rabeprazole → vonoprazan

Data are expressed as mean ± s.d. or as n (%) of subjects

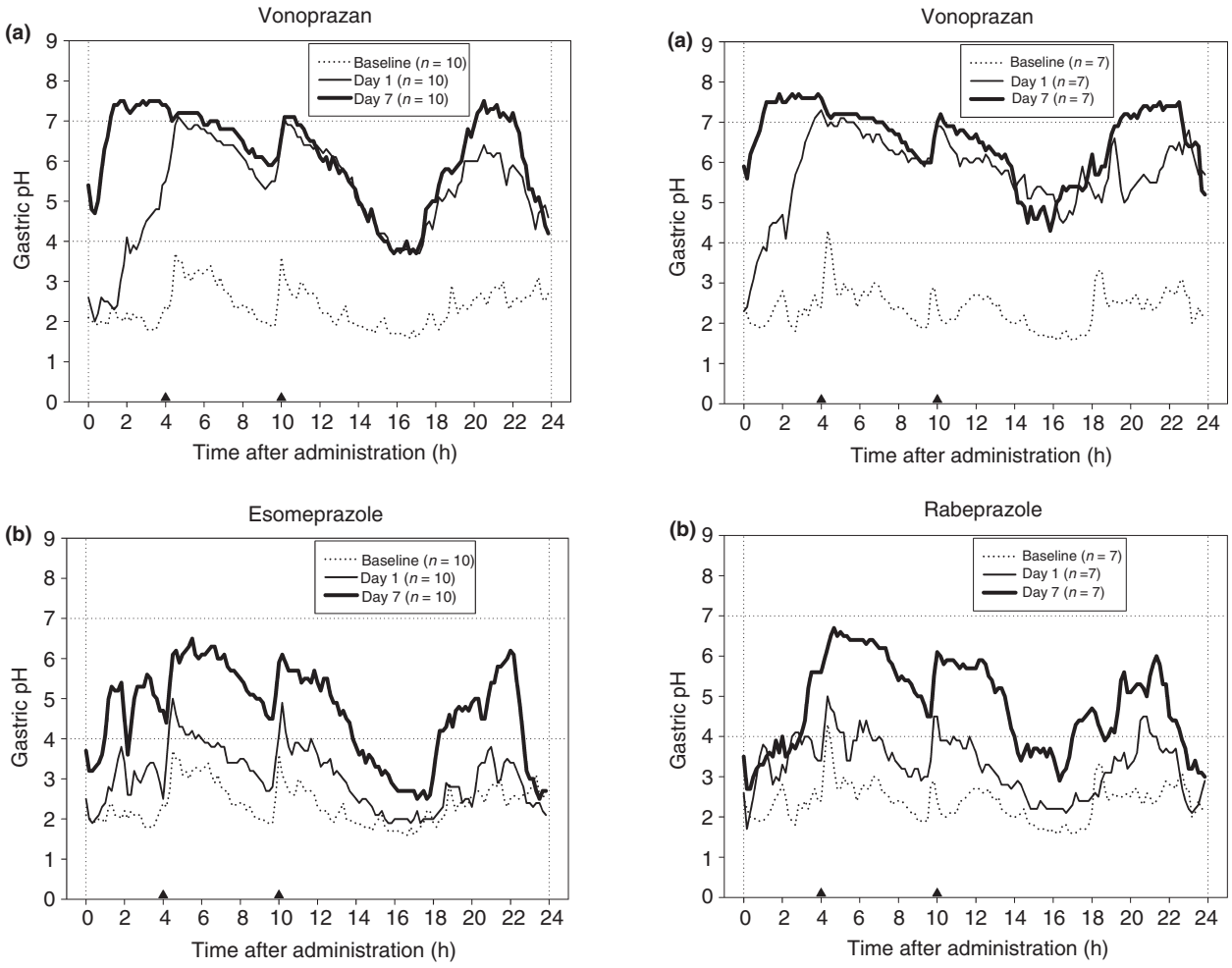

Figure 2 | Time courses of gastric pH over 24 h for (a) vonoprazan and (b) esomeprazole at baseline, on Days 1 and 7 for Study V vs. E: pharmacodynamic analysis set (n = 10). The pH data from Day-2 to Day-1 were used as baseline data for both treatments. All study drugs were administered at time 0 (as a rule, 9:00 AM) on Days 1–7. The triangles indicate the timing of meals. Subjects were given identical meals at these time points.

Figure 3 | Time courses of gastric pH over 24 h for (a) vonoprazan and (b) rabeprazole at baseline, on Days 1 and 7 for Study V vs. R: pharmacodynamic analysis set (n = 7). The pH data from Day-2 to Day-1 were used as baseline data for both treatments. All study drugs were administered at time 0 (as a rule, 9:00 AM) on Days 1–7. The triangles indicate the timing of meals. Subjects were given identical meals at these time points.

for esomeprazole or rabeprazole (Table 4). A greater acid-inhibitory effect of vonoprazan was also observed in the individual subject measurements of 24-h pH 4 HTR (Figures 4 and 5). Similar trends were observed with respect to pH 3 and pH 5 HTRs (Tables S1 and S2).

Results from ANOVA of changes from baseline confirmed the greater acid-inhibitory effect of vonoprazan compared with both esomeprazole and rabeprazole. Increases from baseline in 0–24 h, 0–12 h and 12–24 h pH 4 HTRs were significantly greater on both Days 1 and 7 after administration of vonoprazan than after administration of esomeprazole (Table 2) or rabeprazole (Table 3). In each instance, the lower limit of the 95% CI of the difference exceeded 0, indicating that the differences between vonoprazan and esomeprazole or rabeprazole were statistically significant, although no adjustments for multiplicity were applied.

Mean gastric pH. The mean 0–24 h, 0–12 h and 12–24 h mean gastric pH on Days 1 and 7 was higher after administration of vonoprazan than after administration of esomeprazole (Table S3) or rabeprazole (Table S4). The

Table 2 | pH 4 HTRs (mean ± s.d.) and differences (95% CIs) between vonoprazan and esomeprazole for Study V vs. E: pharmacodynamic analysis set (n = 10)

Variable	Visit	Treatment	Mean ± s.d.*	Difference (95% CIs)
0–24 h pH 4 HTR (%)	Baseline†	Vonoprazan	10.6 ± 7.4	
		Esomeprazole	10.6 ± 7.4	
	Day 1	Vonoprazan	71.4 ± 17.0	47.5 (35.5–59.4)
		Esomeprazole	23.9 ± 16.9	
	Day 7	Vonoprazan	85.8 ± 14.7	24.6 (16.2–33.1)
		Esomeprazole	61.2 ± 17.1	
0–12 h pH 4 HTR (%)‡	Baseline†	Vonoprazan	13.0 ± 11.1	
		Esomeprazole	13.0 ± 11.1	
	Day 1	Vonoprazan	74.8 ± 9.7	39.9 (22.0–57.9)
		Esomeprazole	34.9 ± 24.6	
	Day 7	Vonoprazan	96.5 ± 4.4	18.8 (7.8–29.8)
		Esomeprazole	77.6 ± 17.3	
12–24 h pH 4 HTR (%)§	Baseline†	Vonoprazan	8.2 ± 13.7	
		Esomeprazole	8.2 ± 13.7	
	Day 1	Vonoprazan	67.9 ± 28.3	54.9 (36.3–73.6)
		Esomeprazole	12.9 ± 10.9	
	Day 7	Vonoprazan	75.2 ± 26.4	30.4 (16.2–44.6)
		Esomeprazole	44.8 ± 17.3	

pH 4 HTR, percentage of time pH ≥4; CI, confidence interval; s.d., standard deviation

* The 0–12 h means are based on daytime pH values, while 12–24 h means are based on night-time pH values.

† The pH data from Day-2 to Day-1 were used as baseline data for both treatments.

‡ The 0–12 h period was defined as the first 12-h period from 0 h to 12 h after the dose.

§ The 12–24 h period was defined as the second 12-h period from 12 h to 24 h after the dose.

mean 0–24 h mean gastric pH was 5.2 vs. 3.0 on Day 1 and 6.1 vs. 4.7 on Day 7 for vonoprazan vs. esomeprazole, and was 5.8 vs. 3.3 on Day 1 and 6.5 vs. 4.8 on Day 7 for vonoprazan vs. rabeprazole. The ANOVA of changes from baseline in 24-h mean gastric pH indicated that increases were significantly greater on Days 1 and 7 after administration of vonoprazan than after administration of esomeprazole (Table S3) or rabeprazole (Table S4). Again, the lower limit of the 95% CI of the difference exceeded 0, indicating that the differences between vonoprazan and esomeprazole or rabeprazole were statistically significant, although no adjustments for multiplicity were applied.

Safety. No serious adverse events were reported during the study. There were no TEAEs reported in Study V vs. E. In Study V vs. R, two TEAEs were reported in one subject after administration of rabeprazole and three TEAEs were reported in three subjects after administration of vonoprazan (Table 5). An episode of rash that occurred after administration of vonoprazan was considered to be drug-related and the subject discontinued the study drug; the rash was moderate in intensity and resolved. All other TEAEs were mild in intensity.

No significant changes were observed during the study in values for serum chemistry, haematology or urinalysis. After administration of vonoprazan, esomeprazole and rabeprazole, pepsinogen I and II levels increased from baseline (Table S5). After administration of vonoprazan and rabeprazole, mean serum gastrin concentrations also increased from baseline (Table S5). The increases in serum gastrin and pepsinogen I and II levels, although greater after administration of vonoprazan than esomeprazole or rabeprazole, were not considered to be clinically significant. No abnormalities were observed in vital signs or ECG findings during the study.

DISCUSSION

The results of this randomised open-label, two-period, cross-over study indicate that the acid-inhibitory effect of vonoprazan was greater than that of esomeprazole or rabeprazole. Acid-inhibition was evident after the first administration of vonoprazan and was sustained over 24 h during 7 days of treatment. The Day 1 to Day 7 ratio of 24-h pH 4 HTRs was >0.8 for vonoprazan, compared with 0.370 for esomeprazole and 0.393 for rabeprazole. In addition, the mean 0–24 h, 0–12 h and 12–24 h mean gastric pH on Days 1 and 7 was higher

Table 3 | pH 4 HTRs (mean ± s.d.) and differences (95% CIs) between vonoprazan and rabeprazole for Study V vs. R: pharmacodynamic analysis set (n = 7)

Variable	Visit	Treatment	Mean ± s.d.*	Difference (95% CIs)
0–24 h pH 4 HTR (%)	Baseline†	Vonoprazan	8.9 ± 6.5	
		Rabeprazole	8.9 ± 6.5	
	Day 1	Vonoprazan	84.2 ± 12.4	58.2 (43.6–72.9)
		Rabeprazole	26.3 ± 13.4	
	Day 7	Vonoprazan	93.8 ± 7.3	28.8 (17.2–40.4)
		Rabeprazole	65.1 ± 14.2	
0–12 h pH 4 HTR (%)‡	Baseline†	Vonoprazan	8.0 ± 5.7	
		Rabeprazole	8.0 ± 5.7	
	Day 1	Vonoprazan	84.0 ± 7.8	47.4 (24.2–70.5)
		Rabeprazole	37.3 ± 20.4	
	Day 7	Vonoprazan	98.8 ± 3.0	22.7 (13.9–31.5)
		Rabeprazole	76.1 ± 9.6	
12–24 h pH 4 HTR (%)§	Baseline†	Vonoprazan	9.8 ± 14.1	
		Rabeprazole	9.8 ± 14.1	
	Day 1	Vonoprazan	84.3 ± 20.3	69.1 (50.5–87.7)
		Rabeprazole	15.3 ± 13.3	
	Day 7	Vonoprazan	88.8 ± 14.4	34.9 (13.2–56.6)
		Rabeprazole	54.1 ± 25.3	

pH 4 HTR, percentage of time pH ≥4; CI, confidence interval; s.d., standard deviation

* The 0–12 h means are based on daytime pH values, while 12–24 h means are based on night-time pH values.

† The pH data from Day-2 to Day-1 were used as baseline data for both treatments.

‡ The 0–12 h period was defined as the first 12-h period from 0 h to 12 h after the dose.

§ The 12–24 h period was defined as the second 12-h period from 12 h to 24 h after the dose.

Table 4 | Day 1 to Day 7 Ratios of 0−24 h pH 4 HTRs: mean ± s.d.: pharmacodynamic analysis sets

Treatment	n	Ratio
Vonoprazan	10	0.825 ± 0.075
Esomeprazole	10	0.370 ± 0.239
Vonoprazan	7	0.897 ± 0.109
Rabeprazole	7	0.393 ± 0.158

pH 4 HTR, percentage of time pH ≥4; s.d., standard deviation

after administration of vonoprazan than after administration of esomeprazole or rabeprazole. Taken together, these results suggest that vonoprazan has a rapid, sustained and potentially more potent acid-inhibitory effect compared with esomeprazole and rabeprazole in healthy Japanese adult male subjects with the CYP2C19 extensive metaboliser genotype.

The results from this study, compared with previously published data, show similar acid-supression profiles for esomeprazole 20 mg and rabeprazole 10 mg in healthy subjects who are extensive metabolisers.[20, 22–24] Previous studies have shown that there is a delay in achievement of steady-state levels of acid-reduction with both esomeprazole 20 mg and rabeprazole 10 mg.[20, 22–24] In contrast to esomeprazole and rabeprazole, vonoprazan reached steady-state levels by Day 1 and the levels of acid-reduction were maintained until Day 7 in this study.

Patients receiving therapeutic doses of conventional PPIs similar to the doses used in this study may experience inadequate acid-inhibition during the night[25, 26] commonly called nocturnal acid breakthrough and defined as the occurrence of gastric pH <4 for more than 1 h. These episodes may interfere with the resolution of GERD symptoms, and thus inhibition of acid regurgitation during the night is considered important for the relief of symptoms. Nocturnal acid breakthrough was observed with esomeprazole and rabeprazole in this study. Although 24-h gastric pH profiles indicated that patients taking vonoprazan may experience nocturnal acid breakthrough (Figures 2 and 3), the differences in mean 12–24 h pH 4 HTRs between vonoprazan and esomeprazole or rabeprazole were >30%, demonstrating that the duration was approximately 4 h longer compared with the control PPIs. Likewise, *H. pylori* eradication depends critically on maintenance of a near neutral gastric pH throughout the entire day.[5] In this study, the

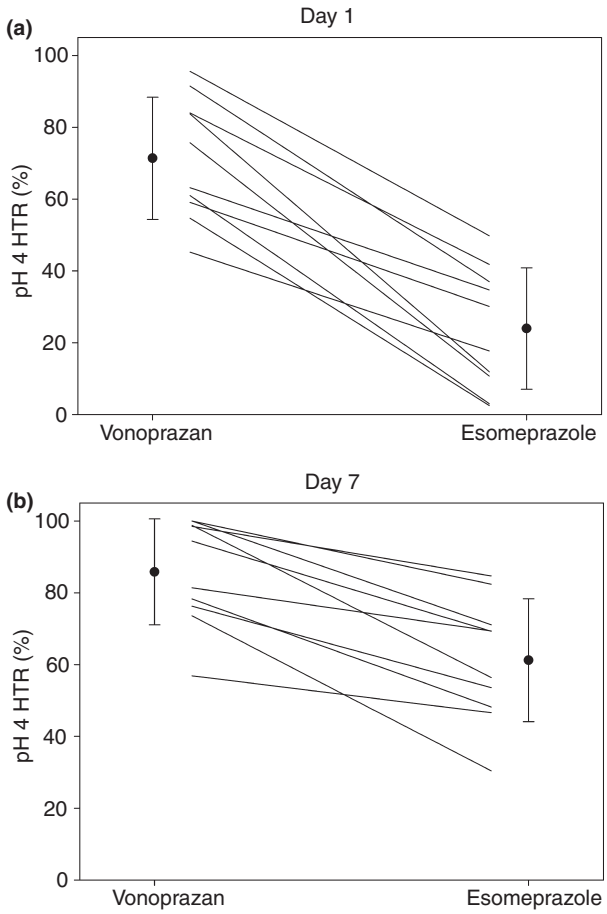

Figure 4 | Comparison in the individual subject measurements of 0–24 h pH 4 HTRs on (a) Day 1 and (b) Day 7 for Study V vs. E: pharmacodynamic analysis set (n = 10). Mean ± s.d. 0–24 h pH 4 HTRs for vonoprazan and esomeprazole were also provided. pH 4 HTR, percentage of time pH ≥4; s.d., standard deviation.

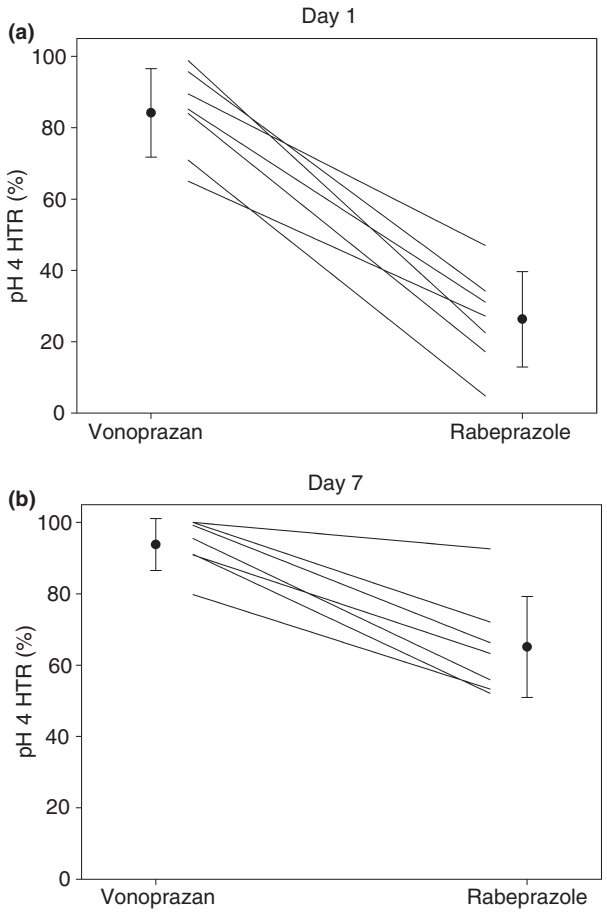

Figure 5 | Comparison in the individual subject measurements of 0–24 h pH 4 HTRs on (a) Day 1 and (b) Day 7 for Study V vs. R: pharmacodynamic analysis set (n = 7). Mean ± s.d. 0–24 h pH 4 HTRs for vonoprazan and rabeprazole were also provided. pH 4 HTR, percentage of time pH ≥4; s.d., standard deviation.

mean 0–24 h mean gastric pH was 5.2 vs. 3.0 on Day 1 and 6.1 vs. 4.7 on Day 7 for vonoprazan vs. esomeprazole and was 5.8 vs. 3.3 on Day 1 and 6.5 vs. 4.8 on Day 7 for vonoprazan vs. rabeprazole. This data suggests that vonoprazan could be a useful alternative to PPIs in combination with antibiotics for the eradication of *H. pylori*.

Due to polymorphisms in the CYP2C19 affecting the metabolism of some PPIs, plasma concentrations and gastric pH of PPIs are lower in extensive compared with poor metaboliser genotypes.[25] In patients with an extensive metaboliser genotype the effect of PPIs may be less than optimal. The results of this study indicate that vonoprazan has an acid-inhibitory effect in individuals with a CYP2C19 extensive metaboliser genotype.

Vonoprazan was well tolerated in this study. No TEAEs were reported by subjects in Study V vs. E. One subject in Study V vs. R discontinued the study drug after developing a rash which was considered to be vonoprazan-related; the rash was moderate in intensity and resolved upon discontinuation of vonoprazan. No safety signals were identified during treatment with vonoprazan in healthy male volunteers for 7 days.

The strengths of this study were the randomised, two-period, cross-over design and eligibility criteria which controlled subject enrolment. Subjects were confined to the study site during each administration period and controls were in place for diet, fluid intake and activity level. The study design included a washout period of at least 7 days between administration periods to minimise any carry-over

Table 5 | Treatment-emergent adverse events (TEAEs) reported during exposure to vonoprazan or rabeprazole for Study V vs. R*: safety analysis set (n = 10)

	Vonoprazan (n = 10)		Rabeprazole (n = 10)	
	Events	Subjects	Events	Subjects
Any TEAE	3	3	2	1
Any drug-related TEAE	1	1	0	0
Any TEAE leading to study drug discontinuation	1	1	0	0
Any serious adverse event	0	0	0	0
Deaths	0	0	0	0
TEAE by preferred term†,‡				
Nausea	0		1	
Pyrexia	1		0	
Rash	1§		0	
Vomiting	1		0	

* No TEAEs were reported in Study V vs. E.

† Data are expressed as number of subjects.

‡ MedDRA version 16.0.

§ Drug-related TEAE leading to study drug discontinuation.

effect of study medication. Also, the active treatment (vonoprazan) was evaluated against two active comparator PPIs (esomeprazole and rabeprazole).

Limitations of the study included the fact that it was not blinded and was conducted in confined Japanese healthy male volunteers, thus limiting the ability to generalise the results. However, the use of a cross-over design in which subjects acted as their own controls and the ability to eliminate many confounding factors (e.g. concurrent medication, noncompliance) and to control for other factors (e.g. diet, smoking, exercise) increased the power of detecting a significant difference in the acid-inhibitory effects of multiple doses of vonoprazan vs. esomeprazole and rabeprazole with fewer subjects. For uniformity, the study included only CYP2C19 extensive metabolisers and conclusions are therefore limited to this population. However, this is the dominant metaboliser type both in Japanese and Caucasian populations.[27] It is likely that the age differences between treatment sequences in Study V vs. E, were compensated for by the cross-over design and are not expected to have had any influence on the results.

In this randomised, open-label, two-period, cross-over study in healthy Japanese adult male volunteers with the CYP2C19 extensive metaboliser genotype, the onset of acid-inhibitory effect of vonoprazan was more rapid than that of esomeprazole and rabeprazole. In addition, pH 4 HTRs were higher after treatment with vonoprazan compared with the other two drugs. No safety signals were identified during the 7-day treatment with vonoprazan. The findings of this study suggest that vonoprazan through its enhanced pharmacodynamic profile may be a possible treatment for acid-related diseases in patients with a CYP2C19 extensive metaboliser genotype.

AUTHORSHIP

Guarantor of the article: Yuuichi Sakurai.

Author contributions: Yuuichi Sakurai, Yuuya Mori, Akira Nishimura and Emiko Komura were involved in the study concept and design. Hiroyuki Okamoto was involved in the statistical analysis. Masanari Shiramoto conducted the study. Yuuichi Sakurai, Yuuya Mori, Akira Nishimura, Emiko Komura and Takahiro Araki were involved in the interpretation of study results, and in the drafting and critical revision of the manuscript.

All authors contributed to writing of the manuscript and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. pH 3 and pH 5 HTRs (mean ± s.d.) for Study V vs. E: pharmacodynamics analysis set (n = 10).

Table S2. pH 3 and pH 5 HTRs (mean ± s.d.) for Study V vs. R: pharmacodynamics analysis set (n = 7).

Table S3. Mean gastric pH on Days 1 and 7 (mean ± s.d.) and differences (95% CIs) between vonoprazan and esomeprazole for Study V vs. E: pharmacodynamic analysis set (n = 10).

Table S4. Mean gastric pH on Days 1 and 7 (mean ± s.d.) and differences (95% CIs) between vonoprazan and rabeprazole for Study V vs. R: pharmacodynamic analysis set (n = 7).

Table S5. Serum gastrin, pepsinogen I, and pepsinogen II levels before administration of study drug and at Day 8 for Study V vs. E and Study V vs. R: safety analysis sets.

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