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Randomised trial of acid inhibition by vonoprazan 10/20 mg once daily vs rabeprazole 10/20 mg twice daily in healthy Japanese volunteers (SAMURAI pH study)

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Summary

Background: Vonoprazan (V), a potassium-competitive acid blocker, has a more durable acid-inhibitory effect as compared with standard-dose proton pump inhibitors (PPIs) but has not been compared with 2-4 times higher daily PPI doses administered in two divided doses.

Aims: To evaluate the acid-inhibitory effect of V 10/20 mg once-daily (OD; V10/V20) vs rabeprazole (R) 10/20 mg twice-daily (BID; R20/R40) in healthy Japanese volunteers.

Methods: This multicentre, randomised, open-label, two-period, crossover study compared V10 or V20 vs R20, or V20 vs R40 using three cohorts of 10 healthy Japanese adults. Within each cohort, subjects were randomised to receive V or R for 7 days and, following a washout period ≥7 days, the other treatment for 7 days. On day 6 of each period, 24-hours multichannel gastric impedance-pH monitoring was performed. Percent times pH ≥ 3, ≥4 and ≥5 (pH 3, 4 and 5 holding time ratios [HTRs]) in 24 hours were evaluated as primary pharmacodynamic endpoints.

Results: Acid-inhibitory effect (24-hours pH 3 HTR) of V20 was greater than those of R20 (91.0% vs 65.3%; $P = .0049$) and R40 (98.5% vs 85.9%; $P = .0073$). Similar results were obtained for 24-hours pH 4 and 5 HTRs. V20 also achieved greater nocturnal pH 4 (91.5% vs 73.2%; $P = .0319$) and 5 HTRs (78.8% vs 62.2%; $P = .0325$) as compared with R40. One subject (20%) developed diarrhoea while receiving R40 which was considered treatment-related.

Conclusions: Compared with 2-4 times the standard daily dose of R, V20 exerts a more potent and durable acid-inhibitory effect. Trial identifier: UMIN000022198 (www.umin.ac.jp/ctr/index.htm).

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1 | INTRODUCTION

Gastro-esophageal reflux disease (GERD) is prevalent worldwide. According to a systematic review of population-based epidemiological studies, the range of GERD prevalence estimates was 18.1-27.8% in North America, 8.8-25.9% in Europe, 2.5-7.8% in East Asia, 8.7-33.1% in Middle East, 11.6% in Australia and 23.0% in South America. Evidence suggests an increase in GERD prevalence since 1995, particularly in North America and east Asia.[1] In Japan, the prevalence of endoscopically diagnosed GERD increased from about 1% in 1985-1987 to 7.1% in 2005.[2] GERD has a high rate of relapse and recurrence because persistent gastro-esophageal reflux causes esophageal mucosal injury and results in protracted symptoms such as heartburn, throat discomfort, and belching.

Acid inhibitors are accepted as effective treatments for GERD and among others, PPIs have proved to be most cost-effective in relieving symptoms and healing esophageal mucosal injury. Based on Grade 1 evidence from a systematic review, the Swedish Council on Health Technology Assessment has concluded that a normal PPI dose for 8 weeks is more effective than histamine H_2-receptor antagonists or other strategies in treating a reflux disorder with coexisting oesophagitis.[3] It is generally recommended to use drugs with potent acid-inhibitory activity for the management of erosive GERD because reduction in GERD symptoms and mucosal healing correlates with the number of hours that intragastric acid is suppressed to a pH > 4.0.[4] In the US and European countries, PPIs are also recommended for the management of GERD but mostly at once-daily (OD) dosages.[5-9] Initial (up to 8 weeks) and maintenance treatments with an OD PPI can achieve and maintain healing in most GERD patients but cannot in about 15% patients,[10] probably because OD morning doses of PPIs can only produce inadequate nocturnal acid inhibition due to the nocturnal gastric acid breakthrough (NAB) phenomenon. To enhance nocturnal acid inhibition, the standard or twice the standard daily dose of rabeprazole administered in two divided (morning and evening) doses was studied in Japanese patients with GERD refractory to standard-dose PPI therapy. Since the study showed favourable outcomes with the twice-daily (BID) dosage in mucosal healing and symptomatic relief,[11] rabeprazole was then approved at new BID dosages (twice and four times the standard daily dose). Evidence from a meta-analysis shows that PPIs are the most effective agents in the first-line and maintenance treatment of GERD.[12] However, PPI resistance can still occur and lead to health impairment,[13,14] suggesting the need for more potent acid-inhibitory agents.

Vonoprazan is a potassium-competitive acid blocker that has become available in Japan. It acts by different mechanisms from those of PPIs and exhibits a rapid onset of action.[15] In a crossover study involving 20 healthy Japanese male adults, vonoprazan at 20 mg/day exerted a more durable acid-inhibitory effect than esomeprazole 20 mg/day or rabeprazole 10 mg/day.[16] However, no clinical studies have compared the acid-inhibitory effect of the standard dose of vonoprazan vs twice or 4 times the standard daily dose of a PPI administered in two divided doses. Thus, we conducted a crossover study to evaluate the acid-inhibitory effect of standard-dose vonoprazan as compared with twice or four times the standard daily dose of rabeprazole in healthy Japanese adult volunteers.

2 | SUBJECTS AND METHODS

2.1 | Study design

This was a multicentre, randomised, open-label, two-period, crossover study (UMIN-CTR trial identifier: UMIN000022198) that compared the acid-inhibitory effect of vonoprazan with rabeprazole at 20 mg/day (V20) vs 20 mg/day (R20) (Cohort A), 20 mg/day (V20) vs 40 mg/day (R40) (Cohort B), and 10 mg/day (V10) vs 20 mg/day (R20) (Cohort C). Each cohort consisted of two treatment sequences (Figure 1). The study was conducted at seven Japanese institutions from February 19, 2016 until March 6, 2019. All individuals involved in the study complied with the Declaration of Helsinki and the Ethical Guidance for Medical and Health Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare). Before commencement of the study, the protocol was approved by the ethical committee of each participating institution. All subjects gave written informed consent to the study.

2.2 | Subjects

Healthy Japanese male or female adults (aged ≥ 20 years) were eligible for the study. Those who had any of the following conditions were excluded from the study: a history of acid-related disease, any previous surgery, any previous radiotherapy directed towards the upper part of the abdomen, previous treatment with vonoprazan or rabeprazole, use of any drug within 1 month of enrollment, a history of allergy to vonoprazan or rabeprazole, any systemic serious illness such as active malignancy, any abnormal finding at upper gastrointestinal endoscopy, any planned treatment for upper gastrointestinal disease, positive screening test for GERD (total score ≥ 8 on F-scale questionnaire), *Helicobacter pylori* infection, prior eradication therapy for *H pylori*, current pregnancy or breastfeeding and any other condition that disqualified the volunteer in the opinion of the investigator. For screening, candidate subjects were requested to complete the Frequency Scale for Symptoms of GERD questionnaire and to undergo serological test for *Helicobacter pylori* IgG antibody and upper gastrointestinal endoscopy.

2.3 | Randomisation and intervention

Three cohorts of 10 healthy volunteers were enrolled centrally. The subjects were randomly assigned to the six sequences in the ascending order of unique identification number. Randomisation was done by the permuted block method. During the first 7-day period (Period 1), subjects in Cohort A received orally vonoprazan

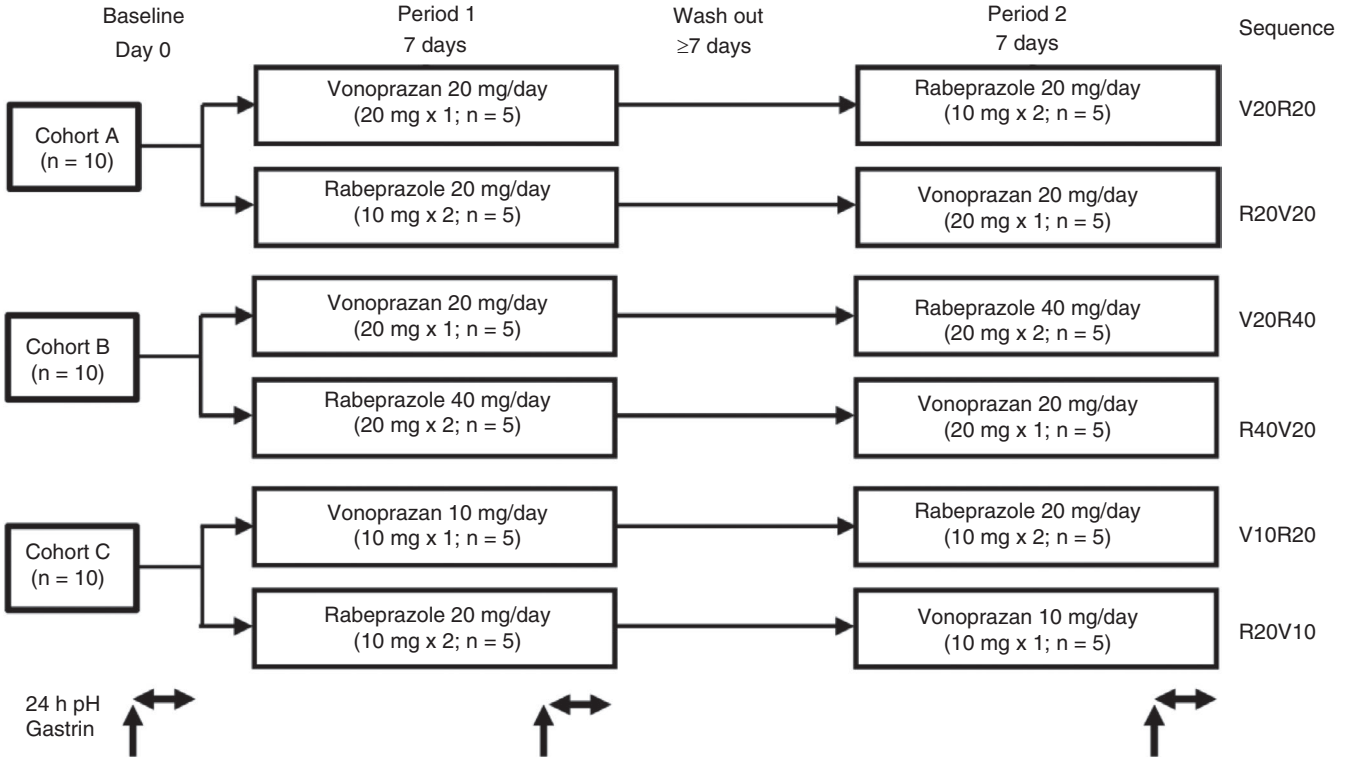

FIGURE 1 Study design. For screening, candidate subjects were requested to complete the Frequency Scale for Symptoms of GERD questionnaire and to undergo serological test for *Helicobacter pylori* IgG antibody and upper gastrointestinal endoscopy. Those with confirmed eligibility then underwent CYP2C19 genotyping and 24-h gastric impedance-pH monitoring at baseline. On Day 6 of Periods 1 and 2, 24-h gastric impedance-pH monitoring was repeated. Immediately before the start of gastric pH monitoring, blood collection was done to measure blood gastrin level at all three times

20 mg OD after breakfast (V20R20) or rabeprazole 10 mg BID after breakfast and after evening meal (R20V20). Rabeprazole was given after breakfast and after evening meal because it had no effect on meals.[17] Also, since there is no regulation on the timing of administration of vonoprazan, it was decided after breakfast. In a similar manner, subjects in Cohort B received orally vonoprazan 20 mg OD (V20R40) or rabeprazole 20 mg BID (R40V20), while subjects in Cohort C received vonoprazan 10 mg OD (V10R20) or rabeprazole 10 mg BID (R20V10). After a washout period of at least 7 days, the subjects were crossed over to receive the other treatment for 7 days (Period 2) (Figure 1). During the study period, subjects visited each research institution only when the pH meter was inserted. Subjects consumed a prescribed diet of 2000 Kcal/ day at home daily during the study. Meals at home were managed daily at 7:00 (breakfast), 13:00 (lunch) and 20:00 (evening meal). Each meal intake time was the average time of the Japanese.

2.4 | Study variables and assessments

At baseline and on day 6 of each period, subjects underwent 24-hours multichannel gastric impedance-pH monitoring and measurement of blood gastrin level. The pH meter used in all cases was SLEUTH ZepHr (Sandhill Scientific Inc [US]). Then, the intragastric electrode was placed in the lower part of the stomach using X-ray fluoroscopy. After confirming the subject's fasting status, a blood test was performed. Blood was also collected at baseline for cytochrome P450 isotype 2C19 (CYP2C19) genotyping. According to CYP2C19 genotypes, three CYP2C19 phenotypes, rapid metaboliser (RM; *1/*1), intermediate metaboliser (IM; *1/*2 or *1/*3) and poor metaboliser (PM; *2/*3 or 3*/3*), were defined. Throughout the study period, all clinical and laboratory treatment-emergent adverse events (TEAEs) were recorded and evaluated. If required, adequate follow-ups were provided to subjects with TEAEs.

3 | STATISTICAL ANALYSIS

The planned sample size was 10 per cohort, 5 per sequence. Based on the results of previous studies,[11,18,19] an absolute difference of 15% was expected in 24-hours pH 4 HTR between vonoprazan 20 mg OD and rabeprazole 10 mg BID. On the assumption that the coefficient of variation was 20% for both treatments and that the correlation coefficient between the two periods was 0.5, the planned sample size (n = 5 per sequence) would provide a power of at least 80% to show this difference at an alpha error rate of 5%.

The primary pharmacodynamic (PD) endpoints of the study were pH 3, 4 and 5 holding time ratio (HTR) in 24 hours, each calculated as percentage of the time period of pH at the specified level or higher to the entire continuous monitoring period, after treatment with vonoprazan compared with rabeprazole. Key secondary endpoints included pH 3, 4 and 5 HTRs during nighttime (a period of lying), during 2 hours before and after meals and by CYP2C19 phenotype, as well as blood gastrin level over time and overall incidence of TEAEs.

The PD analysis set was defined as consisting of all subjects that received at least one dose of the study drug and evaluable PD data. The safety analysis set was defined as consisting of all subjects that received at least one dose of the study drug. Statistical analyses of the primary endpoints were performed within each cohort without adjustments for multiple comparisons. For the treatment difference, the point estimate was calculated with its 95% confidence interval (CI) and was tested for significance using unpaired t-test to determine whether vonoprazan was superior to rabeprazole. To see if there was a carry-over effect, a sum of the changes from baseline in Period 1 and Period 2 was compared between the two treatment sequences using unpaired t-test at a two-tailed type I error rate of 0.10. If any carry-over effect was detected, the hypothesis that vonoprazan was superior to rabeprazole was rejected. Data on secondary PD variables were analysed in a similar manner. Missing data were not imputed and were left missing. All tests of significance were two-tailed and at the 0.05 level. Data from this study were aggregated and analysed by a biostatistician at a contract research organisation (EP-CRSU Co., Ltd.,).

4 | RESULTS

No subjects were withdrawn and all those enrolled completed the protocol. Demographic and baseline characteristics of the subjects are summarised in Table 1. Within each cohort, those allocated to the two treatment sequences were well-matched at baseline with respect to gender, age, body weight, blood gastrin level and CYP2C19 phenotypic distribution.

Figure 2 shows the gastric pH over time of the entire continuous monitoring period (24 hours) at baseline and after treatment with vonoprazan and rabeprazole in each cohort. After V20 and R40 treatments, there was a trend towards higher gastric pH maintained as compared with baseline. V20 was also associated with a smaller periprandial variation of gastric pH. Table 2 shows a comparison of 24-hours pH 3, 4 and 5 HTRs between the two treatments within each cohort. Significantly greater pH 3 HTR was seen after V20 vs R20 (91.0 ± 12.6% vs 65.3 ± 19.8%; P = .0049,[95%CI:10.3-41.1]) in Cohort A and vs R40 (98.5 ± 3.8% vs 85.9 ± 9.0%;P = .0073,[95%CI:4.5-20.8]) in Cohort B, with no significant difference between V10 and R20 in Cohort C. Similar results were obtained for 24-hours pH 4 and 5 HTRs. By CYP2C19 phenotype, pH 4 HTR in RMs was significantly greater after V20 compared with R20 (Cohort A), and that in IMs was significantly greater after V20 compared with R20 (Cohort A) and R40 (Cohort B). pH 5 HTRs in RMs and IMs were also significantly greater after V20 compared with R20 (Cohort A). Table 3 shows a comparison of nocturnal pH 3, 4 and 5 HTRs between the two treatments within each cohort. V20 also achieved significantly greater nocturnal gastric pH ≥ 4 (91.5 ± 9.4% vs 73.2 ± 23.9%;P = .0319,[95%CI:2.1-34.7]) and ≥ 5 HTRs (78.8 ± 25.1% vs 62.2 ± 24.7%;P = .0325,[95%CI:1.8-31.4]) as compared with R40. pH 3 HTR in 2 hours before and after evening meal was significantly greater after V20 compared with R20 (Cohort A), and pH 4 and 5 HTRs in 2 hours before and after evening meal were significantly greater after V20 compared with R20 (Cohort A) and R40 (Cohort B). There were no significant treatment differences in pH 3, 4 or 5 HTRs in 2 hours before and after breakfast.

Table 4 shows blood gastrin level measured on day 6 of each treatment in each cohort. In Cohort A, a significant carry-over effect (P = .0392) was detected, preventing between-treatment comparison. Blood gastrin level was higher after V20 compared with R40

TABLE 1 Baseline characteristics of subjects

		Cohort A		Cohort B		Cohort C	
Variables		V20R20 (n = 5)	R20V20 (n = 5)	V20R40 (n = 5)	R40V20 (n = 5)	V10R20 (n = 5)	R20V10 (n = 5)
Age, mean (SD) [years]		28.4 (7.9)	26.8 (7.5)	35.6 (4.9)	36.2 (22.1)	35.2 (24.2)	23.8 (5.8)
Gender, male n (%)		4 (80.0)	3 (60.0)	5 (100.0)	3 (60.0)	4 (80.0)	4 (80.0)
Body weight, mean (SD) [kg]		67.2 (16.9)	58.0 (9.9)	69.2 (7.0)	62.6 (13.6)	63.6 (8.4)	60.8 (8.2)
BMI, mean (SD) [kg/m^2]		24.3 (5.5)	21.1 (1.5)	24.0 (2.9)	22.9 (2.4)	22.2 (2.3)	22.0 (1.5)
Blood gastrin level, mean (SD) [pg/mL]		124.0 (94.7)	79.0 (37.8)	100.2 (24.5)	144.4 (96.3)	133.6 (135.9)	90.6 (23.5)
CYP2C19 phenotypes, n (%)	RM	3 (60.0)	2 (40.0)	0 (0.0)	1 (20.0)	3 (6.0)	3 (60.0)
	IM	2 (40.0)	3 (60.0)	4 (80.0)	4 (80.0)	1 (20.0)	2 (40.0)
	PM	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)	0 (0.0)

Abbreviations: BMI, body mass index; IM, intermediate metaboliser; PM, poor metaboliser; RM, rapid metaboliser; SD, standard deviation.

(P = .0212; Cohort B) but was not different after V10 vs R20 (Cohort C). Individual subject data (Figure 3) shows a tendency toward higher gastrin level after V20 compared with R40, especially when V20 followed R40. One subject in Cohort B had an outlier after V20. The effect on blood gastrin level was not different between V10 and R20.

One subject (20%) assigned to R20V10 sequence in Cohort C developed diarrhoea while receiving rabeprazole 20 mg/day during Period 1. This was the only TEAE and was considered treatment-related.

5 | DISCUSSION

This open-label crossover study showed that vonoprazan 20 mg/day had a more potent and durable acid-inhibitory effect as compared with rabeprazole 20 or 40 mg/day. Compared with BID treatment with rabeprazole, vonoprazan OD maintained higher gastric pH during 24 hours with a smaller periprandial variation. Vonoprazan 20 mg and 10 mg OD achieved significantly greater and comparable pH 3 HTR, respectively, as compared with rabeprazole 10 mg BID. Although nocturnal pH 3 HTR was not significantly different between vonoprazan 20 mg OD and rabeprazole 10 mg BID, nocturnal pH 4 and 5 HTRs were significantly greater with vonoprazan 20 mg OD. As compared with rabeprazole 10 mg BID, vonoprazan 20 mg OD produced a significantly greater increase in pH 4 HTR after evening meal, indicating that vonoprazan is more effective in reducing gastric acidity. In this study, vonoprazan 10 mg and V20 mg OD consistently maintained gastric pH >4 for 24 hours, suggesting that vonoprazan may have excellent clinical effects on GERD.[4] The potassium-competitive H^+K^+ATPase inhibiting activity of vonaprazan is about 350 times more potent than that of lansoprazole. In human subjects, the acid-inhibitory effect of vonaprazan is exerted at 4 hours post-dose and sustained for up to 24 hours.[13] After oral administration, vonoprazan is localised at high concentrations in secretory canaliculi in parietal cells and strictly binds to H^+K^+ATPase through firm ionic or hydrogen bonds. Its slow dissociation rate permits its prolonged retention at high density within parietal cells.[20] In rats, vonoprazan administered orally was eliminated from the blood relatively quickly but high levels of the drug were maintained in gastric tissue even at 24 hours post-dose.[21] These data suggest that prolonged retention of vonoprazan at high levels in parietal cells produces sustained acid inhibition by the drug. In the present crossover study, a washout period of 7 days was insufficient to eliminate the carry-over effect of vonoprazan on blood gastrin level in V20R20 sequence in Cohort A, which precluded between-treatment comparison in this cohort. The very high response of one subject to vonoprazan in Period 1 probably contributed to this carry-over effect. There was no carry-over effect of either treatment on gastric acidity. Vonoprazan administered even once daily exerted a sustained acid-inhibitory effect, which was at least as great as that produced by rabeprazole administered twice daily. Because of its long-lasting acid-inhibitory effect, vonoprazan has achieved an endoscopic healing rate of 95% in patients with GERD treated for 1 year and has been shown to be useful for the control of GERD.[22]

When analysed by CYP2C19 phenotype, the acid-inhibitory effect (pH 4 or 5 HTR) of vonoprazan 20 mg/day in RMs or IMs was significantly greater than that of rabeprazole 20 or 40 mg/day. Since vonoprazan is primarily metabolised by CYP3A4 isotype to inactive metabolites, its pharmacokinetic profile is little affected by CYP2C19 phenotypes.[15] This suggests that its PD effects may undergo only a small inter-individual variation, unlike with PPIs,[23] which was confirmed in the present study. However, due to the small, substantially different sample sizes of the three CYP2C19 phenotypes, the present study might be underpowered to show that the PK/PD profiles of vonoprazan are not affected by CYP2C19 phenotypes. In addition, the much lower percentage of PMs among the subjects might lead to slight underestimation of the acid-inhibitory effect of rabeprazole, which is known to be less affected by CYP2C19 phenotypes than those of other PPIs. Nevertheless, the percentages of the three phenotypes among the subjects of this study can represent a real-world setting and would not introduce a bias to the comparison of acid inhibition by vonoprazan vs rabeprazole.

In the present study, we also observed that the blood gastrin level measured on day 6 of each period was significantly higher after

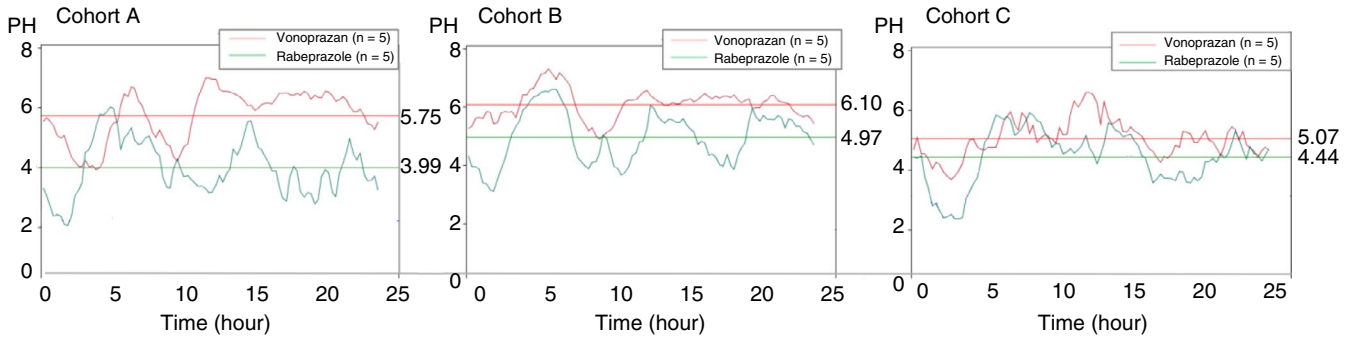

FIGURE 2 Mean gastric pH over time during the 24-h continuous monitoring period. Data are mean values of 24-h gastric pH observed at baseline and on Day 6 of Period 1 in subjects treated with V20 vs R20 (Cohort A), V20 vs R40 (Cohort B) and V10 vs R20 (Cohort C). In each graph, horizontal bars (from bottom to top) are average daily gastric pH values observed at baseline, after treatment with rabeprazole and after treatment with vonoprazan, respectively

TABLE 2 24-h pH ≥ 3, ≥4, and ≥ 5 HTRs by treatment and phenotypes[a]

	Cohort A		Cohort B		Cohort C	
24-h pH HTRs	V20	R20	V20	R40	V10	R20
pH ≥ 3 HTR						
Total, n	10	10	10	10	10	10
HTR[b]	91.0 (12.6)	65.3 (19.8)	98.5 (3.8)	85.9 (9.0)	77.5 (18.4)	75.4 (19.0)
Treatment difference[c]	25.7 (10.3 to 41.1)		12.6 (4.5 to 20.8)		2.1 (−9.3 to 13.5)	
P value	0.0049[d]		0.0073[d]		0.6830	
RM,n	5	5	1	1	6	6
HTR	87.6	54.5	100	71.5	72.5	69.2
Treatment difference[c]	33.2 (−6.7 to 73.0)		–		3.3 (−12.1 to 18.8)	
P value	0.0770		–		0.5805	
IM,n	5	5	8	8	63	3
HTR	94.7	76.8	98.2	88.1	91.8	81.1
Treatment difference[c]	17.9 (−5.0 to 40.9)		10.1 (1.5 to 18.6)		10.7 (−99.3 to 120.7)	
P value	0.0885		0.0278[d]		0.4332	
PM,n	0	0	1	1	1	1
HTR	–	–	100	82.8	67.4	96.9
Treatment difference[c]	–		–		–	
P value	–		–		–	
pH ≥ 4 HTR						
Total, n	10	10	10	10	10	10
HTR[b]	88.4 (14.9)	53.8 (21.0)	95.0 (5.9)	74.5 (12.9)	69.9 (23.1)	65.5 (23.5)
Treatment difference[c]	34.6 (18.9 to 50.4)		20.5 (10.5 to 30.6)		4.3 (−9.0 to 17.6)	
P value	0.001[d]		0.0015[d]		0.4746	
RM,n	5	5	1	1	6	6
HTR	84.9	41.4	93.2 (–)	50.4 (–)	64.1	62.0
Treatment difference[c]	43.6 (4.9 to 82.2)		–		2.1 (−14.3 to 18.5)	
P value	0.0370[d]		–		0.7403	
IM,n	5	5	8	8	3	3
HTR	92.3	67.5	95.2	78.8	87.1	66.6
Treatment difference[c]	24.8 (2.4 to 47.3)		16.4 (7.8 to 25.1)		20.5 (5.6 to 35.3)	
P value	0.0390[d]		0.0036[d]		0.0363[d]	
PM,n	0	0	1	1	1	1
HTR	–	–	95.4	64.4	58.5	89.7
Treatment difference[c]	–		–		–	
P value	–		–		–	
pH ≥ 5 HR						
Total, n	10	10	10	10	10	10
HTR[b]	80.9 (16.3)	38.1 (16.8)	81.5 (16.8)	56.5 (16.7)	58.7 (24.0)	45.7 (22.6)
Treatment difference[c]	42.7 (28.3 to 57.2)		25.0 (13.3 to 36.7)		13.0 (−2.1 to 28.0)	
P value	0.0001[d]		0.0011[d]		0.0820	
RM,n	5	5	1	1	6	6
HTR	79.9	27.5	80.6	26.8	50.8	42.8
Treatment difference[c]	52.4 (18.8 to 86.0)		–		7.9 (−2.5 to 18.4)	
P value	0.0157[d]		–		0.1031	

(Continues)

TABLE 2 (Continued)

	Cohort A		Cohort B		Cohort C	
IM,n	5	5	8	8	3	3
HTR	81.4	50.7	81.4	61.3	81.3	46.3
Treatment difference[c]	30.7 (23.4 to 38.0)		20.1 (10.6 to 29.6)		35.0 (−8.5 to 78.4)	
P value	0.0009[d]		0.0021[d]		0.0621	
PM,n	0	0	1	1	1	1
HTR	–	–	83.7	48.6	47.8	74.8
Treatment difference[c]	–		–		–	
P value	–		–		–	

Abbreviations: CI, confidence interval; HTR, holding time ratio; LSmean, least square mean; SD, standard deviation.

[a]HTRs are means of the values observed during Periods 1 and 2. No carry-over effect was observed in any treatment sequence.

[b]mean (SD) [%].

[c]LSmean (95% CI).

[d]Significant ($P < 0.05$).

vonoprazan 20 mg OD compared with rabeprazole 20 mg BID, especially in R40V20 sequence. The abnormally high gastrin value observed in one subject after vonoprazan treatment suggests the need of safety monitoring especially during maintenance therapy with the drug for GERD. After treatment with a PPI, feedback from increased gastric pH results in enhanced gastrin secretion. Hence, blood gastrin levels as high as twice to 6 times higher than the upper limit of normal (500 pg/mL, and even higher in 30% patients) have been reported in 80%-100% of patients maintained on a PPI.[24,25] In a phase I study of vonoprazan in healthy adult men, 300 pg/mL was the maximum value of blood gastrin level observed during or after 7 daily doses of 10 to 40 mg.[18] In a study of 24-week maintenance therapy with vonoprazan 10 mg OD in 60 patients with healed GERD, the mean blood gastrin level was 1059 pg/mL, while no serious adverse drug reactions occurred.[26] This value is comparable to those observed in the present and other studies of vonoprazan.[27-29] During 8 weeks of treatment with vonoprazan at 20 and 40 mg/day that followed 7 to 14 days of treatment with lansoprazole, considerable rises of blood gastrin level (maximum of 3000 and 7000 pg/mL, respectively) were reported.[29] This finding is consistent with the trend towards a greater increase of gastrin observed during treatment with vonoprazan following rabeprazole in the present study, to which extraordinary responses of some subjects to vonoprazan might be contributory. Despite the methodological differences between the two studies (treatment duration of 8 weeks vs 7 days, with or without a washout period, in patients with GERD vs healthy volunteers), one should bear in mind the potential of severe hypergastrinemia upon switch to vonoprazan in patients unresponsive to sustained PPI therapy.

There has been a concern about relationship between gastric carcinogenesis and promotion of gastrin secretion by PPIs. Gastrin has

TABLE 3 Nocturnal pH ≥ 3, ≥4, and ≥ 5 HTRs by treatment[a]

	Cohort A		Cohort B		Cohort C	
Nocturnal pH HTRs	V20 (n = 10)	R20 (n = 10)	V20 (n = 10)	R40 (n = 10)	V10 (n = 10)	R20 (n = 10)
pH ≥ 3 HTR, mean (SD) [%]	75.0 (31.2)	65.4 (22.3)	97.5 (7.1)	83.8 (21.2)	59.4 (35.1)	65.9 (22.9)
Treatment difference, LSmean (95% CI)	9.5 (−18.9 to 38.0)		13.6 (−4.5 to 31.7)		-6.5 (−34.3 to 21.3)	
P value	0.4617		0.1207		0.6038	
pH ≥ 4 HTR, mean (SD) [%]	70.7 (33.2)	59.8 (24.6)	91.5 (9.4)	73.2 (23.9)	54.0 (35.8)	57.1 (27.5)
Treatment difference, LSmean (95% CI)	11.0 (−19.3 to 41.2)		18.4 (2.1 to 34.7)		-3.1 (−29.8 to 23.6)	
P value	0.4273		0.0319[b]		0.7960	
pH ≥ 5 HTR, mean (SD) [%]	62.4 (34.1)	47.7 (17.5)	78.8 (25.1)	62.2 (24.7)	47.3 (31.1)	44.0 (22.8)
Treatment difference, LSmean (95% CI)	14.7 (−18.2 to 47.5)		16.6 (1.8 to 31.4)		3.4 (−23.3 to 30.0)	
P value	0.3327		0.0325[b]		0.7781	

Abbreviations: CI, confidence interval; HTR, holding time ratio; LSmean, least square mean; SD, standard deviation.

[a]HTRs are means of the values observed during Periods 1 and 2. No carry-over effect was observed in any treatment sequence.

[b]Significant ($P < 0.05$).

TABLE 4 Blood gastrin level measured on day 6 of each treatment in each cohort[a]

	Cohort A		Cohort B		Cohort C	
Blood gastrin levels (pg/mL)	V20 (n = 10)	R20 (n = 10)	V20 (n = 10)	R40 (n = 10)	V10 (n = 10)	R20 (n = 10)
mean (SD) [%]	464.2 (279.6)	184.8 (92.2)	491.1 (339.7)	296.7 (172.3)	278.2 (188.2)	292.2 (244.9)
carry-over effect	0.0392[b]		0.2850		0.3101	
Treatment difference, LSmean (95% CI)	–		194.4 (37.3 to 351.1)		-14.0 (–156.5 to 128.5)	
P value	–		0.0212[c]		0.8265	

Abbreviations: CI, confidence interval; LSmean, least square mean; SD, standard deviation.

[a]Blood gastrin levels are means of the values observed during Periods 1 and 2.

[b]A significant carry-over effect was detected in Cohort A, precluded between-treatment comparison in this cohort.

[c]Significant($P < 0.05$).

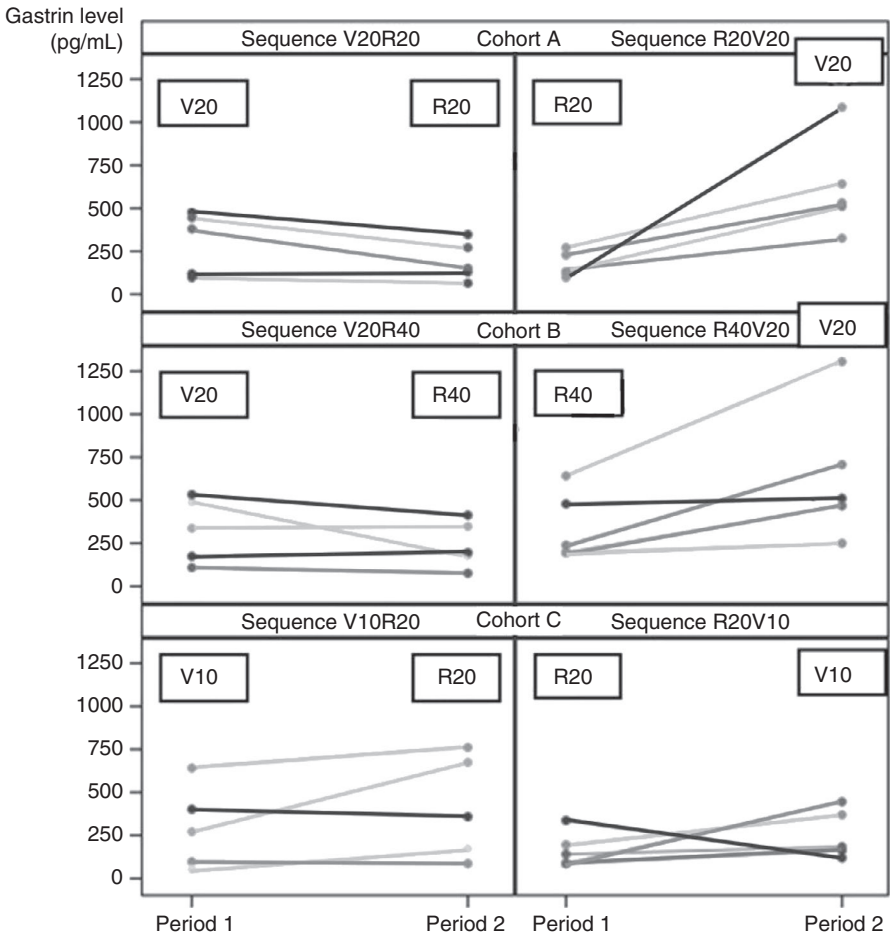

FIGURE 3 Individual blood gastrin levels measured on Day 6 of each period

been shown to have trophic effects on tissues throughout the gastrointestinal tract, including the enterochromaffin-like (ECL) cells, which are distributed throughout the oxyntic mucosa.[30-32] Long-term hypergastrinemia leads to ECL cell hyperplasia, manifested by rebound acid hypersecretion[33] and in the long-term by ECL cell-driven tumours of variable malignancies.[34] Long-term treatment with PPIs has been reported to induce altered gene expressions in gastric mucosa[35] and has been associated with increased risk of gastric carcinogenesis.[36,37] Several case reports of gastric carcinomas (including neuroendocrine tumours [NETs]) in long-term PPI users have suggested a pathogenic role of PPI-induced severe sustained hypergastrinaemia.[38-41] In contrast, a systematic literature review has shown that long-term (3-15 years') treatment with PPIs induces a moderate increase in blood gastrin level and hyperplasia of ECL cells but does not cause NETs,[42] which was supported by another study that observed no significant safety problems during 5-12 years' treatment with PPIs.[43]

No human subjects treated with vonoprazan in pre-approval clinical studies developed NETs.[15] In recent studies, vonoprazan administered at 10 or 20 mg OD for up to 1 year or even longer increased serum gastrin level but was tolerated well in patients with healed GERD or peptic ulcer.[44-46] Nonetheless, as 2- to 3-times higher serum gastrin levels were sustained in subjects treated with vonoprazan

compared with those treated with lansoprazole,[15] attention should still be paid to possible occurrence of severe hypergastrinemia that may induce NETs during vonoprazan treatment, particularly long-term treatment. Several circulating proteins have been accepted as diagnostic markers for NETs[47,48] and may be used to monitor the risk of these malignancies during long-term acid suppression by vonoprazan.

In the present study, diarrhoea in one subject was the only TEAE related to the study treatment. Both vonoprazan and rabeprazole each administered for 7 days were tolerated well.

This study had several limitations. First, this was a multicentre study; inter-centre variability might reduce the accuracy of gastric pH measurements. Second, the presence of a carry-over effect on blood gastrin level precluded valid comparison between the two treatments in terms of this variable. In the present study, there was a washout of 168 hours, which is much longer than five times the half-life of vonoprazan. However, this was insufficient to eliminate its effect on gastrin secretion, possibly due to its longer retention in the gastric wall than expected. This suggests that the effects of vonoprazan on acid and gastrin secretion may depend on its level in the gastric wall rather than its blood concentration and that its blood concentration measured alone is not a suitable marker for monitoring its toxicities.

In conclusion, vonoprazan 20 mg OD exerts a more potent and durable acid-inhibitory effect as compared with rabeprazole 10 or 20 mg BID. This PD profile of vonoprazan makes it useful as an initial treatment of GERD (reflux esophagitis) for achieving early mucosal healing. However, long-term use of vonoprazan should be noted as it is associated with sustained hypergastrinemia, which may induce NETs.

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