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Randomised clinical trial: tegoprazan, a novel potassium-competitive acid blocker, or lansoprazole in the treatment of gastric ulcer

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Summary

Background: Tegoprazan is a novel potassium-competitive acid blocker for the treatment of acid-related disorders.

Aims: To assess whether tegoprazan is non-inferior to lansoprazole in terms of efficacy and safety in patients with gastric ulcers.

Methods: In this phase 3, double-blind, active control, multicentre study, 306 gastric ulcer patients were randomised to one of three treatment groups: tegoprazan 50 mg, tegoprazan 100 mg and lansoprazole 30 mg once daily for 4 or 8 weeks. The primary endpoint was the cumulative proportion of patients with healed ulcers confirmed by endoscopy up to 8 weeks from treatment initiation. Symptoms and safety were assessed.

Results: In the full analysis set, the cumulative healing rates at week 8 were 94.8% (91/96) for the tegoprazan 50 mg, 95.0% (94/99) for the tegoprazan 100 mg and 95.7% (89/93) for the lansoprazole 30 mg groups. At week 4, the respective healing rates were 90.6% (87/96), 91.9% (91/99), and 89.2% (83/93). In per protocol analysis, 4-week healing rates were 95.4% (84/88), 94.6% (88/93) and 92.9% (79/85) for tegoprazan 50 mg, tegoprazan 100 mg and lansoprazole 30 mg, respectively. Both doses of tegoprazan were non-inferior to lansoprazole in ulcer healing at 4 and 8 weeks. The incidence of drug-related treatment-emergent adverse events did not differ among groups. The increase in serum gastrin concentration was not higher in tegoprazan-treated patients than in lansoprazole-treated patients.

Conclusions: Tegoprazan 50 or 100 mg were not inferior to lansoprazole 30 mg once daily in the treatment of gastric ulcers.

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The complete list of authors' affiliation are listed in Appendix 1.

1 | INTRODUCTION

Proton pump inhibitors (PPIs) are used widely for the treatment of acid-related diseases, and their therapeutic effects are considered to be satisfactory,[1] although some inadequacies must be addressed. First, PPIs have a relatively short plasma half-life (60-90 minutes), and taking PPIs twice a day may be insufficient for inhibiting gastric acid reflux at night. Second, PPIs are prodrugs that are activated under acid-secreting conditions, and the effects of PPIs can be affected by food intake. Third, a rapid response cannot be achieved because of the slow onset of the PPI effect and the time needed to achieve maximum efficacy.[2-4] Potassium-competitive acid blockers (P-CABs) comprise a new class of drugs that exhibit rapid and effective anti-secretory activity by competitively and reversibly binding to H^+/K^+-ATPase in parietal cells.[5] Unlike conventional PPIs, P-CABs can immediately inhibit proton pumps without gastric acid activation, even in the absence of food intake, and therefore provide a fast onset of action and full effect from the first dose.[6,7] Vonoprazan, which is available P-CAB in Japan, has a more potent acid-inhibitory effect.[8] It is superior to PPIs for the first-line treatment for *Helicobacter pylori* eradication,[9] and is not inferior to PPIs for the treatment of gastroesophageal reflux disease (GERD),[10] gastric ulcers (GUs) or duodenal ulcers.[11-13]

Tegoprazan is a novel P-CAB, originally developed by a RaQualia Pharma Inc HK inno.N Corporation which has the exclusive right, has completely developed and commercialised tegoprazan as a treatment for acid-related disorders. Tegoprazan was approved as a treatment for gastroesophageal reflux disease, gastric ulcer and *H. pylori* eradication in South Korea from July 2018. Tegoprazan showed rapid response from the time of initial administration, and sustained acid suppression are demonstrated in the several experimental and clinical studies.[14] Tegoprazan shows dose-dependent pH >4 holding time and a rapid and sustained acid suppressive effect compared with esomeprazole in healthy male volunteers.[15] Its effects on intragastric pH >4 holding time at day 1 and day 7 are similar to vonoprazan.[16] The superior ulcer healing effect of tegoprazan compared with esomeprazole was recently shown in a rat peptic ulcer model.[17] Tegoprazan at doses of 50 and 100 mg is not inferior to esomeprazole 40 mg for healing endoscopic esophagitis has been reported.[18]

The present study was a phase 3 clinical trial that was designed to evaluate whether tegoprazan is non-inferior in efficacy and safety to lansoprazole in treating patients with GUs. Another aim of this trial was to determine whether the proper dose of tegoprazan for healing GUs and safety is 50 mg or 100 mg.

2 | MATERIALS AND METHODS

2.1 | Study design

This phase 3 study was a multicentre study involving 33 investigators in 33 centres in South Korea. The study was a randomised, double-blind, active-controlled, comparative study designed to assess the non-inferiority of tegoprazan 50 and 100 mg to lansoprazole 30 mg q.d. for 4 or 8 weeks in patients with GU. The protocol for this study was approved by the institutional review boards at each institute according to the Declaration of Helsinki and the International Congress on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice guidelines. The study was registered with ClinicalTrials.gov under the number NCT02761512 (Study title: Study to Evaluate the Safety and Efficacy of CJ-12420 in Patients with Gastric Ulcer).

2.2 | Study population

Patients who met all of the following criteria were eligible to enter the study: men or women aged 20-75 years living in South Korea and being an outpatient who had been diagnosed with one or more active GUs measuring ≥3 mm to ≤30 mm of A1 or A2 stage according to the Sakita-Miwa classification obtained with open biopsy forceps during upper gastrointestinal (GI) endoscopy within 14 days before the initiation of the study treatment.

Patients with any one of the following conditions were ineligible to enter the study: Zollinger-Ellison syndrome; GI bleeding; oesophageal stricture; ulcer stenosis; pyloric stenosis; oesophageal gastric varices; Barrett's oesophagus measuring >3 cm; intractable ulcer; digestive ulcer perforation or malignancy on upper GI endoscopy; clinically significant hepatic, renal, cardiovascular, respiratory, endocrine or central nervous system disorder; history of malignancy or psychiatric disorder; pregnant or nursing mother; history of allergy to any of the study drugs or their related compounds; clinically significant liver disease or renal disease; using anti-psychotics, anti-depressants, or anxiolytics; using a PPI, H_2-blocker, prokinetic agent, or antacid within 14 days before screening; or persistent daily use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin during the study period.

2.3 | Study protocol

2.3.1 | Randomisation, treatment and follow-up

Clinical Development Division, HK inno.N Corp., Seoul, Korea, carried out centralised randomisation and allocation to tegoprazan 50, 100 mg or lansoprazole 30 mg group at a 1:1:1 ratio. All randomisation information was securely stored and could be accessed by authorised personnel only. A double-dummy method, using matching tegoprazan 50 mg, tegoprazan 100 mg, lansoprazole 30 mg and placebo tablets, was employed to ensure that the study was double blinded with key codes kept off site by an external data manager. All medications were provided in sealed boxes and supplied by the medication supervisor to ensure blinded allocation. Study patients were instructed to take two tablets and one capsule, one of tegoprazan 50, 100 mg or lansoprazole 30 mg and two placebos once daily before eating breakfast. Treatment was completed after 4 weeks or 8 weeks if not healed.

At the start of the screening period, patient demographics and other baseline characteristics were recorded, including medical history, medication history, vital signs, physical examination, clinical laboratory tests, pregnancy test, electrocardiogram test and Helicobacter pylori test were performed. At week 4 or 8, vital signs, physical examination, clinical laboratory tests and pregnancy test were performed. Additionally, adverse events, concomitant medication and treatment compliance were checked. Endoscopy was performed at screening, week 4 or 8. The follow-up period began when healing of the GU was endoscopically confirmed (ie the white ulcer coating was not visible) or at week 8. Patients whose GU had healed by week 4 had a follow-up visit for safety assessment 2 weeks later (visit 3-1). Those not achieving GU healing at week 4 received another batch of drugs and continued the treatment for an additional 4 weeks. For these patients, endoscopic assessment was conducted at week 8, and the final follow-up visit for safety assessment was performed 2 weeks later (visit 4-1). Symptoms were assessed using the Nepean Dyspepsia Index - Korean version (NDI-K), which was completed on the first visit before the treatment period and repeated at visits 3, 3-1 or 4, 4-1. Patient diary entries were also recorded. Serum gastrin was collected at visit 2, visit 3 and visit 3-1 for 4 weeks or at visit 2, visit 4 and visit 4-1 for 8 weeks under fasting conditions.

Helicobacter pylori infection status was checked using one of silver stains, CLO test and urea breath test prior to study enrolment. *Helicobacter* infection status was notified to all of subject at time of screening. All subjects who were positive for *Helicobacter* were treated using standard triple therapy (lansoprazole 30 mg b.i.d + amoxicillin 1 g b.i.d + clarithromycin 500 mg b.i.d for 7 days) after last follow-up. *H. pylori* eradication and follow-up urea breath test were done in clinical practice.

2.3.2 | Outcome parameters used to assess efficacy

The primary efficacy endpoint was set as the cumulative healing rate of GUs at week 8 as assessed by upper GI endoscopy. Following the Sakita-Miwa classification, healing was defined as the disappearance of all ulcers with a white coating or healing of the mucosal defect (S1 or S2 stage). The secondary efficacy endpoints were as follows: (a) healing rate of GUs, also classified according to the Sakita-Miwa classification at week 4; (b) healing rate of GUs according to *H. pylori* infections status; (c) change in ulcer size; and (d) improvement of GI symptoms.

2.3.3 | Safety assessment

Safety was evaluated through physical examination, electrocardiography, vital signs (blood pressure, heart rate and body temperature), laboratory test results (haematology, blood chemistry, blood coagulation and urinalysis) and incidence of treatment-emergent adverse events (TEAEs). A TEAE was defined as an adverse event (AE) occurring after the participant received a study drug. TEAEs were categorised by severity and relativity and compared between treatment groups. All TEAEs including AEs, adverse drug reactions and serious AEs were coded by system organ class and preferred term using MedDRA, and compared between treatment groups. Additional safety assessments were conducted at the discretion of the investigators.

2.4 | Statistical analysis

Hypothesis testing was conducted by setting the primary efficacy endpoint as the cumulative GU healing rate at week 8. The union-intersection test was used with the Hochberg method to adjust for multiple comparisons and to control for a family-wise type I error, which was set at 0.025 (one-sided). A power of >90% was assumed for detecting non-inferiority as shown by the difference in the percentages of patients with healed GUs between the treatment groups, with a non-inferiority margin of 8.54% at the lower limit of 95% confidence intervals (CIs).

Sample size was determined according to the primary endpoint. For sample size calculation, the cumulative healing rate after 8 weeks of treatment was assumed as 96.8% for both tegoprazan and lansoprazole, and a sample size of 102 patients (considering a 20% dropout rate) per treatment group was calculated, giving a total sample size of 306 patients.

Efficacy assessments were performed primarily using the per-protocol set (PPS) and complementarily using the full analysis set (FAS). The safety assessments were performed on the safety set. The FAS included all patients who were randomised to the study treatment and who received ≥1 dose of a study drug and who had at least one valid efficacy assessment. The PPS included all patients in the FAS with an evaluable primary endpoint who were randomised to a study treatment, completed their study treatment and had no major protocol deviation. The safety population included all patients who received ≥1 dose of a study drug.

All statistical analyses were done using SAS® (version 9.3; Windows) in accordance with the statistical analysis plan. For continuous variables, the values are expressed as number of participants, mean, standard deviation, median, minimum and maximum. For categorical variables, the values are presented as frequency and percentage. Demographic and other baseline characteristics, GU characteristics and serum gastrin concentrations were compared between treatment groups. The percentages of patients with healed GUs and GI symptoms were analysed by calculating frequencies, point estimates and two-sided 95% CIs for each treatment group.

3 | RESULTS

3.1 | Patient characteristics and demographics

Among the 376 patients with GUs who were screened, 51 were ineligible based on the inclusion/exclusion criteria, 18 withdrew their consent and 1 was a foreigner. These patients were considered as screening failures, and the remaining 306 patients were randomised

in a 1:1:1 ratio to one of the three treatment arms: tegoprazan 50 mg, tegoprazan 100 mg or lansoprazole 30 mg. Among the 306 randomised patients, 28 (9.2%) were discontinued from the study because of voluntary withdrawal (n = 8, 28.6%), inclusion/exclusion criteria violation (n = 6, 21.4%), the use of contraindicated drugs (n = 5, 17.9%), AEs (n = 5, 17.9%), follow-up loss (n = 2, 7.1%) or investigator discretion (n = 2, 7.1%). The patients' characteristics are summarised in Figure 1 and the details of the patients' demographics and baseline characteristics are summarised in Table 1. No significant differences in demographic characteristics between treatment groups were observed. Most patients were not using NSAIDs or low-dose aspirin at the time of enrolment. Most patients had a single GU and the most common size of the ulcers was <10 mm.

3.2 | Efficacy analysis

3.2.1 | The primary efficacy endpoints

In the PPS population, the percentages of patients with healed GUs over the 8-week treatment period were 100% in the tegoprazan 50 mg group, 97.85% in the tegoprazan 100 mg group and 100% in the lansoprazole 30 mg group. The percentage difference between tegoprazan 100 mg and lansoprazole 30 mg in PPS analysis was <8.54% (95% CI −7.66 to 2.43, P = 0.0137), which confirmed the non-inferiority of tegoprazan 50 mg and 100 mg compared with lansoprazole 30 mg. At week 4, the healing rates were 95.45% (84/88, P = 0.0038 vs lansoprazole 30 mg) for tegoprazan 50 mg, 94.62% (88/93, P = 0.0024 vs lansoprazole 30 mg) for tegoprazan 100 mg and 92.94% (79/85) for lansoprazole 30 mg, the percentage differences between each dose of tegoprazan and lansoprazole 30 mg showed both dose of tegoprazan were not inferior to lansoprazole (Table 2).

These findings were supported by the secondary analyses in the FAS. In the FAS analysis, the cumulative healing rates at week 8 were 94.79% (91/96), 94.95% (94/99) and 95.70% (89/93) and the respective healing rates at week 4 were 90.63% (87/96), 91.92% (91/99) and 89.25% (83/93) in tegoprazan 50, 100 mg and lansoprazole groups. The differences between the tegoprazan group (both doses) and the lansoprazole group were significant (P < 0.025) at both time points, for both analysis sets according to the Hochberg method, it confirmed the non-inferiority of tegoprazan to lansoprazole.

Secondary endpoint analyses showed similar healing rates between *pylori* subgroup and both treatment of tegoprazan and lansoprazole had positive effects on gastrointestinal symptoms. Both doses of tegoprazan were non-inferior to lansoprazole 30 mg in *H. pylori*-positive patients at 4- and 8-week ulcer healing. In *H. pylori*-positive patients, the 4-week healing rates were 96.15% (50/52) for tegoprazan 50 mg, 98.33% (59/60) for tegoprazan 100 mg and 92.98% (53/57) for lansoprazole 30 mg. The 8-week cumulative healing rates were 100% in all of three groups. In the *H. pylori*-negative patients, the 4-week healing rates were 94.44% (34/36) for tegoprazan 50 mg, 87.88% (29/33) for tegoprazan 100 mg and 92.86% (26/28) for lansoprazole 30 mg. The 8-week healing rates were 100% (36/36) for tegoprazan 50 mg, 93.94% (31/33), for tegoprazan 100 mg, and 100%(28/28) for lansoprazole 30 mg.

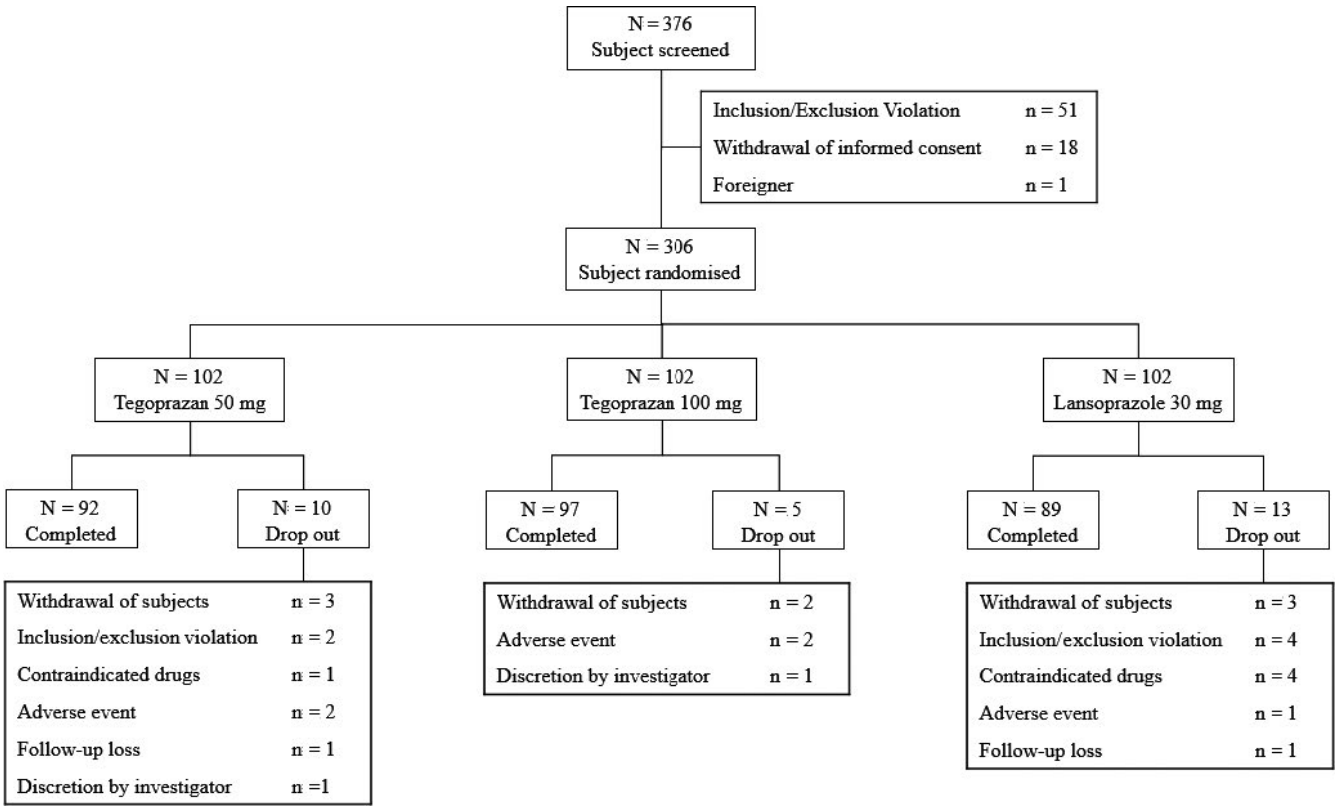

FIGURE 1 Disposition of Subjects

TABLE 1 Patient demographics and baseline characteristics (per protocol set)

	Tegoprazan 50 mg (N = 88)	Tegoprazan 100 mg (N = 93)	Lansoprazole 30 mg (N = 85)
Age (y)	53.39	54.11	54.22
Gender			
Male	58 (65.91)	61(65.59)	47(55.29)
Female	30 (34.09)	32 (34.41)	38 (44.71)
Height (cm)	166.82	166.27	165.22
Weight (kg)	66.77	67.18	65.80
Smoking; yes	36 (40.91)	33 (35.48)	30 (35.29)
Alcohol; yes	42 (47.73)	39 (41.94)	38 (44.71)
NSAID/ASA	2(2.27)	4(4.30)	3(3.53)
Helicobacter pylori positive	52 (59.09)	60 (64.52)	57 (67.06)
Current ulcers; number			
Single	74 (84.09)	73 (78.49)	73 (85.88)
Multiple	14 (15.91)	20 (21.51)	12 (14.12)
Current ulcer; size			
3-5 mm	23 (20.54)	27 (21.95)	29 (26.85)
5-10 mm	60 (53.57)	60 (48.78)	47 (43.52)
10-20 mm	25(22.32)	28 (22.76)	25(23.15)
20-30 mm	4 (3.57)	8 (6.5)	7 (6.48)

3.3 | Safety analysis

Safety analysis was performed in 304 patients who received ≥1 dose of a study drug and had ≥1 safety assessment in this clinical trial. Among the 304 patients, 113 cases of TEAEs were reported by 66 patients (Table 3). Drug-related TEAEs accounted for 9.80% (10/102, 17 events) in the tegoprazan 50 mg group, 13.73% (14/102, 18 events) in the tegoprazan 100 mg group, and 12.00% (12/100, 19 events) in the lansoprazole 30 mg group. Four cases of serious TEAEs were reported in the tegoprazan 50 mg group, two in the tegoprazan 100 mg group and one in the lansoprazole 30 mg group; however, none of these were causally related to treatment with the study drug (Table 3). The most common drug-related TEAE in all treatment groups classified by system organ class was GI disorders; the incidence rates were 4.90% (5/102) for tegoprazan 50 mg, 6.86% (7/102) for tegoprazan 100 mg, and 4.00% (4/100) for lansoprazole 30 mg. Diarrhoea (2.94%) in tegoprazan 50 mg and abdominal discomfort (2%) and blood gastrin increased (2%) in lansoprazole 30 mg were the most frequently reported drug-related TEAEs (Table 4). The incidence of any TEAE did not differ between the tegoprazan 50 and 100 mg treatment groups.

3.4 | Serum gastrin concentration

The baseline serum gastrin concentrations were 54.84 ± 59.26 pg/mL, 55.63 ± 46.40 pg/mL, and 70.92 ± 107.08 pg/mL for the tegoprazan 50 mg, tegoprazan 100 mg and lansoprazole 30 mg groups respectively (Figure 2). The final serum gastrin concentrations at week 4 or 8 were 85.52 ± 77.97 pg/mL, 119.54 ± 94.05 pg/mL and 121.75 ± 114.84 pg/mL. The change in serum gastrin concentration did not differ significantly between the tegoprazan and lansoprazole groups. Serum gastrin concentrations increased after treatment in all three treatment groups, but these returned to their baseline levels after completion of the treatment period. No significant changes in serum gastrin concentration were observed between groups during the study period (Figure 2).

4 | DISCUSSION

The present study was designed to evaluate whether tegoprazan is non-inferior to lansoprazole in terms of the efficacy and safety in patients with GUs. At week 8, the cumulative endoscopic healing rates of GUs were 100% in the tegoprazan 50 mg group, 97.85% in the tegoprazan 100 mg group and 100% in the lansoprazole 30 mg group. At week 4, the respective endoscopic healing rates were 95.45%, 94.62% and 92.94%. These results demonstrate the non-inferiority of both tegoprazan 50 and 100 mg compared with lansoprazole 30 mg in terms of endoscopic healing rates. Our study showed similar results to vonoprazan. A previous study reported that vonoprazan produced non- inferior healing rates for gastric and duodenal ulcers in *H. pylori*-positive patients at 8 weeks. In the PPS analysis, the ulcer healing rates were 93.5% in the vonoprazan group and 93.8% in the lansoprazole group.[11]

One aim of our study was to determine the proper dose of tegoprazan for GU healing. The PPS and FAS analyses showed similar healing rates for the two doses of tegoprazan (50 and 100 mg) at

TABLE 2 Endoscopic healing rate (%) of gastric ulcer up to 4 and 8 weeks

	Tegoprazan 50 mg	Tegoprazan 100 mg	Lansoprazole 30 mg
At 8 wks;			
Per protocol set	N = 88	N = 93	N = 85
Number(%) of healed patients	88 (100.00)	91 (97.85)	85 (100.00)
Difference from lansoprazole with 95% CI[d]		(−7.66, 2.43)[b]	
P value[a]	—	0.0137	
Full analysis set	N = 96	N = 99	N = 93
Number(%) of healed patients	91 (94.79)	94 (94.95)	89 (95.70)
Difference from lansoprazole with 95% CI[d]	(−7.98, 6.09)[b]	(−7.69, 6.31)[b]	
P value[a]	0.0177	0.0146	
At 4 wks;			
Per protocol set	N = 88	N = 93	N = 85
Number(%) of healed patients	84 (95.45)	88 (94.62)	79 (92.94)
Difference from lansoprazole with 95% CI[d]	(−5.18, 10.77)[b]	(−5.44, 8.80)[c]	
P value[a]	0.0038	0.0024	
Full analysis set	N = 96	N = 99	N = 93
Number(%) of healed patients	87 (90.63)	91 (91.92)	83 (89.25)
Difference from lansoprazole with 95% CI[d]	(−7.20, 9.96)[c]	(−5.60, 10.95)[c]	
P value[a]	0.0117	0.0040	

Note: Non-inferiority margin −8.54%.

[a]Non-inferiority test.

[b]Exact unconditional confidence interval.

[c]Wald confidence interval.

[d]According to Hochberg method, significant level for the test of tegoprazon and lansoprazole is 0.025 (one sided).

TABLE 3 Summary of treatment-emergent adverse events (TEAEs)

	Tegoprazan 50 mg (N = 102)	Tegoprazan 100 mg (N = 102)	Lansoprazole 30 mg (N = 100)
	N (%)	N (%)	N (%)
TEAE	18 (17.65)	23 (22.55)	25 (25.00)
95% CI, *P* value[a]	[0.10-0.25], 0.2018	[0.14, 0.31], 0.6824	[0.17, 0.33]
Drug-related TEAE	10 (9.80)	14 (13.73)	12 (12.00)
95% CI, *P* value[a]	[0.04, 0.06], 0.6164	[0.07, 0.20], 0.7143	[0.06, 0.18]
Serious TEAE	3 (2.94)	2 (1.96)	1 (1.00)
95% CI, *P* value[a]	[0.00, 0.06], 0.6213	[0.00, 0.05], 1.0000	[0.00, 0.03]

[a]χ^2 or Fisher's exact test.

4 and 8 weeks. The increase in serum gastrin concentration, and safety profiles were similar in both groups. Tegoprazan 50 mg would be effective as 100 mg in GU healing. In a phase 3 dose-ranging study of erosive esophagitis to compare tegoprazan with esomeprazole, the percentage of patients with erosive esophagitis and cumulative healing rates at week 8 did not differ between the tegoprazan 50 mg and tegoprazan 100 mg groups.[18] It is generally accepted that suppressing gastric acid secretion enhances treatment of acid-related disorders, with better efficacy achieved when intragastric pH >4 is sustained for as long of a duration as possible.[19-21] There has not been the direct comparison data of intragastric pH >4 holding time between tegoprazan and lansoprazole. The previous pharmacodynamic study showed pH >4 holding time over 24 hours increased in a dose-dependent manner after a single dose of 50-400 mg of tegoprazan.[15] The pH 4 > holding time in multiple dosing of tegoprazan 50 mg is 54.2%-68.2%, and

TABLE 4 Drug-related treatment-emergent adverse events (TEAEs) reported in the treatment group

	Tegoprazan 50 mg (N = 102)	Tegoprazan 100 mg (N = 102)	Lansoprazole 30 mg (N = 100)
	N (%)	N (%)	N (%)
Gastrointestinal disorders	5 (4.90)	7 (6.86)	4 (4.00)
Diarrhoea	3 (2.94)	2 (1.96)	0 (0.00)
Upper abdominal pain	0 (0.00)	1 (0.98)	0 (0.00)
Constipation	0 (0.00)	1 (0.98)	0 (0.00)
Dyspepsia	1 (0.98)	1 (0.98)	0 (0.00)
Abdominal discomfort	0 (0.00)	0 (0.00)	2 (2.00)
Investigations	2 (1.96)	2 (1.96)	3 (3.00)
Serum gastrin increased	1 (0.98)	0 (0.00)	2 (2.00)
Alanine aminotransferase increased	1 (0.98)	1 (0.98)	0 (0.00)
Aspartate aminotransferase increased	0 (0.00)	1 (0.98)	1 (1.00)
Blood bilirubin increased	0 (0.00)	1 (0.98)	0 (0.00)
Gamma-glutamyltransferase increased	1 (0.98)	0 (0.00)	0 (0.00)
Blood triglycerides increased	1 (0.98)	0 (0.00)	0 (0.00)
Headache	1 (0.98)	0 (0.00)	1 (1.00)
Chest discomfort or pain	2 (1.96)	0 (0.00)	1 (1.00)

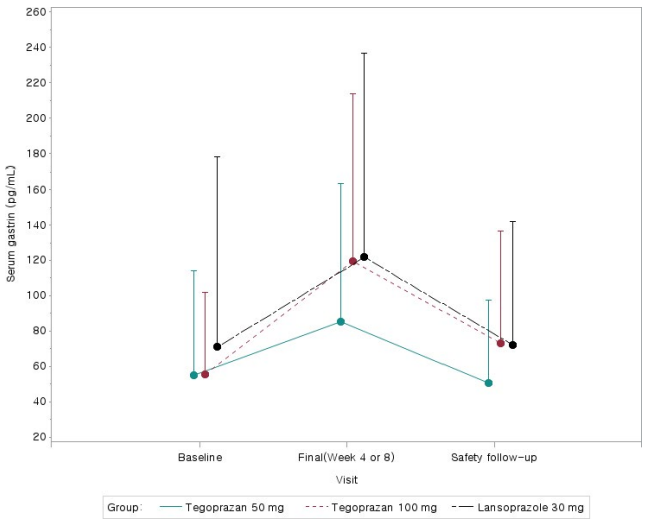

FIGURE 2 Gastrin levels from baseline (pg/mL) during treatment and follow-up periods (safety set)

66.55% of tegoprazan 100 mg in healthy males. Because two doses of tegoprazan showed similar ulcer healing rates, acid suppressive effect of tegoprazan seems satisfactory even in dose of 50 mg.

Tegoprazan showed better efficacy in *H. pylori* positive patients. In patients with *H. pylori* infection, the both doses of tegoprazan were not inferior to lansoprazole 30 mg. The 8-week healing rates were 100% in all of three groups. Subgroup analyses of *H. pylori*-negative patients showed the healing rate of tegoprazan 100 mg was not inferior, whereas tegoprazan 50 mg was not non-inferior to the lansoprazole. A previous study reported that vonoprazan also produced non- inferior healing rates to lansoprazole for gastric and duodenal ulcers in *H. pylori*-positive patients at 8 weeks.[12]

We also analysed the incidence rates of symptoms of epigastric pain, abdominal distension, nausea, heartburn and anorexia. The symptoms had resolved by the last study visit in >90% of patients in all three treatment groups. This finding shows the additional benefit to those patients who had both peptic ulcer disease and associated symptoms.

Tegoprazan was generally well tolerated. The incidence of TEAEs did not differ significantly between groups, and no serious drug-related AEs were reported throughout the study. The safety and tolerability profiles were similar to those of lansoprazole. Most TEAEs were mild in severity, and few drug-related TEAEs were reported. Moreover, the magnitude of the increase in serum gastrin concentration did not differ significantly between groups, and the serum gastrin concentration returned to the baseline levels after the patients completed their treatment. Additionally, vonoprazan increased serum gastrin levels more than lansoprazole in GU study.[11] But changes of serum gastrin levels were comparable among tegoprazan and lansoprazole groups in this study.

This is the study to compare tegoprazan and lansoprazole, or to compare P-CABs and PPIs in the GU healing. The healing effect did not differ between the tegoprazan doses of 50 and 100 mg. The healing rate at 8 weeks was nearly 100%. The strengths of this study include the randomised, double-blind, double-dummy, multisite design, the large sample size and the focus on a Korean population. One limitation of our study is that, given the study design, we could examine only the non-inferiority and not the superiority

of tegoprazan compared with lansoprazole. In conclusion, we have shown that tegoprazan at doses of 50 and 100 mg was non-inferior to lansoprazole 30 mg and had a favourable safety profile in patients with GUs.

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Author contributions: All authors were involved in patients' enrollment, performing the study, acquisition of data and interpretation of study results. Prof, Myung-Gyu Choi was involved in the study design, drafting of the manuscript and critical revision of the manuscript. DrYu Kyung Cho wrote the manuscript, all authors approved the final version of the manuscript, including the authorship list.

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