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Randomised clinical trial: comparison of tegoprazan and lansoprazole as maintenance therapy for healed mild erosive oesophagitis

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SUMMARY

Background: Tegoprazan is a novel potassium-competitive acid blocker used to treat acid-related disorders.

Aim: To compare tegoprazan 25 mg with lansoprazole 15 mg as maintenance therapy in healed erosive oesophagitis (EE)

Methods: In this phase 3, double-blind, multi-centre study, patients with endoscopically confirmed healed EE were randomised 1:1 to receive tegoprazan 25 mg or lansoprazole 15 mg once daily for up to 24 weeks. The primary efficacy endpoint was the endoscopic remission rate after 24 weeks. The secondary efficacy endpoint was the endoscopic remission rate after 12 weeks. Safety endpoints included adverse events, clinical laboratory results and serum gastrin and pepsinogen I/II levels.

Results: We randomised patients to tegoprazan 25 mg ($n = 174$) or lansoprazole 15 mg ($n = 177$). Most had mild EE (Los Angeles (LA) grade A: 57.3%, LA grade B: 37.3%). The endoscopic remission rate after 24 weeks was 90.6% with tegoprazan and 89.5% with lansoprazole. Tegoprazan was not inferior to lansoprazole for maintaining endoscopic remission at 24 weeks and 12 weeks. In subgroup analysis, tegoprazan 25 mg showed no significant difference in maintenance rate according to LA grade ($p = 0.47$). The maintenance effect of tegoprazan was consistent in CYP2C19 extensive metabolisers ($p = 0.76$). Increases in serum gastrin were not higher in tegoprazan-treated than lansoprazole-treated patients.

Conclusions: Tegoprazan 25 mg was non-inferior to lansoprazole 15 mg in maintenance of healing of mild EE. In this study, tegoprazan had a similar safety profile to lansoprazole.

1 | INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a common gastrointestinal disorder resulting from reflux of gastric acid into the oesophagus. Treatment goals of GERD consist of relieving symptoms, healing EE and preventing recurrences and complications that directly affect the quality of life of patients.[1] Proton pump inhibitors (PPIs) have been the first-line treatment for GERD. They are indicated for initial treatment and relapse.[1] Their therapeutic effects are associated with the holding time of intragastric pH above 4, which is important for the healing and maintenance treatment of severe EE with Los Angeles (LA) grade C and D.[2] However, PPIs have several limitations. First, they have a slow onset of action without completely suppressing acid production, leading to night-time acid breakthrough. Second, the efficacy of PPIs is influenced by cytochrome P450 CYP2C19 genetic polymorphism. Third, they are unstable in acidic conditions. In addition, many studies have revealed various safety concerns with PPIs. However, the majority of these studies were retrospective. In addition, they lacked sufficient evidence to establish causal relationships. Therefore, there are many unmet needs of using PPIs for the treatment of GERD.[3,4] A potassium-competitive acid blocker (P-CAB) can potently and reversibly inhibit gastric H^+/K^+-ATPase. P-CAB exhibits a faster onset of action and prolonged inhibition of gastric acid secretion, making it advantageous over PPIs for the treatment of EE.[4,5] Tegoprazan, a potent and highly selective P-CAB, exhibits a rapid onset of action within 1 h and a sustained holding of intragastric pH above 4 after single or multiple administration.[6,7] Tegoprazan 50 mg or 100 mg shows non-inferior efficacy to esomeprazole 40 mg in EE patients after 8 weeks of treatment.[8] Furthermore, tegoprazan 50 mg and 100 mg are non-inferior to lansoprazole 30 mg for the treatment of patients with gastric ulcer and superior to placebo for the treatment of non-erosive reflux disease.[9,10] Tegoprazan has been approved as a treatment for GERD, gastric ulcer and *H. pylori* infection in South Korea and for EE in China.

A step-down dose of PPIs is recommended as a long-term maintenance therapy to prevent the relapse of EE. Maintenance therapy with lansoprazole 15 mg and 30 mg for 6 months can prevent the relapse of EE in up to 81% and 93% of patients, respectively, with maintenance rates sustained after 6 months of treatment.[11] Moreover, vonoprazan

10 mg, another actively used P-CAB drug, shows non-inferior efficacy and similar safety compared to lansoprazole 15 mg after maintenance therapy in preventing relapse.[12] Therefore, this phase 3 randomised controlled trial (RCT) was designed to evaluate whether tegoprazan 25 mg, a half dose of the marketed dose, was non-inferior in efficacy and safety to lansoprazole 15 mg. The secondary goal was to evaluate the proportion of patients with symptomatic non-relapse at 24 weeks.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multi-centre, randomised, double-blind, actively controlled, phase 3 study designed to assess the non-inferiority of tegoprazan 25 mg to lansoprazole 15 mg as maintenance therapy in Korean patients with healed EE. The study protocol was reviewed and approved by the Institutional Review Boards of 33 institutes. This study was performed in accordance with the Declaration of Helsinki and the International Congress on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use for Good Clinical Practice guidelines. Written informed consent was obtained from all subjects prior to any study-related procedure. This study was registered at ClinicalTrials.gov (identifier number: NCT04022096; Study title: Study to confirm the safety and efficacy of tegoprazan in patients with healed erosive oesophagitis).

2.2 | Study population

Participants aged 20–75 years with endoscopically confirmed healed EE were considered eligible for inclusion in this study. Patients with any of the following conditions were excluded: Zollinger–Ellison syndrome, gastrointestinal (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, pregnancy or nursing mother, history of allergy to any of the aforementioned drugs or their related compounds, use of antipsychotics, antidepressants, or anxiolytics, use of a PPI, H_2-blocker, prokinetic agent, or antacid within 14 days before screening, or persistent 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

During the screening period, endoscopy was performed to evaluate the presence and severity of EE based on the Los Angeles Classification System. Following 4 or 8 weeks of treatment with either PPIs (esomeprazole, lansoprazole, dexlansoprazole, pantoprazole or rabeprazole) or tegoprazan, endoscopy confirmed that EE was healed. Patients with endoscopically confirmed healed EE were randomised to receive tegoprazan 25 mg or lansoprazole 15 mg at a 1:1 ratio using an interactive web response system of the central registration system. Patients received tegoprazan 25 mg or lansoprazole 15 mg once daily 30 minutes before breakfast. The treatment was completed after 24 weeks (Figure 1).

2.3.2 | Outcome parameters used to assess efficacy

The primary efficacy endpoint was the endoscopic remission rate following 24 weeks of maintenance therapy. The secondary efficacy endpoint was endoscopic remission rate following 12 weeks of maintenance therapy. Additional efficacy endpoints included evaluation of the proportion of patients without symptomatic heartburn and acid reflux, days without symptoms at 4, 12 and 24 weeks, and baseline-adjusted gastro-oesophageal reflux disease health-related quality of life (GERD-HRQL) scores at 4, 12 and 24 weeks. The GERD-HRQL scale has 11 items focusing on heartburn symptoms, dysphagia, effects of medications and health condition of patients. Each item was scored from 0 to 5, with a higher score indicating a poorer quality of life.

2.3.3 | Safety and tolerability assessment

Safety was evaluated through physical examination, electrocardiography, vital signs (blood pressure, heart rate and body temperature), laboratory explorations (haematology, blood chemistry, blood coagulation and urinalysis), serum gastrin, pepsinogen I and II, vitamin B12, folate, iron and magnesium levels, and incidence of treatment-emergent adverse events (TEAEs). A TEAE was defined as an adverse event (AE) that occurred after the participant received the study drug(s). All TEAEs including AEs, adverse drug reactions

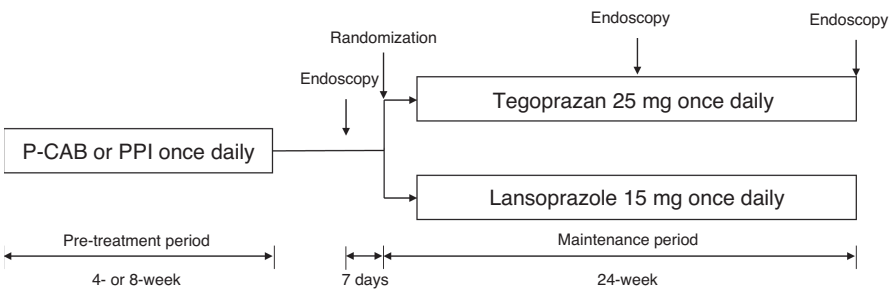

FIGURE 1 Scheme of clinical trial.

and serious AEs were recorded using the Medical Dictionary for Regulatory Activities version 24.0. TEAEs were categorised according to system organ class and compared between treatment groups. Additional safety assessments were conducted at the discretion of investigators.

2.3.4 | Statistical analysis

Hypothesis testing was conducted by setting the primary efficacy endpoint to be endoscopic remission rate at week 24. The sample size was determined based on primary endpoint. For sample size calculation, the endoscopic remission rate at week 24 was assumed to be 88.4% for tegoprazan and 83.2% for lansoprazole, with a non-inferiority margin of −10% and a power of 90% at a significance level of 0.025. Therefore, the sample size was 318 subjects (159 patients per treatment group) considering a dropout rate of 30%.

Efficacy assessments were performed primarily using a per-protocol set (PPS) and secondarily using a full analysis set (FAS). Safety assessments were performed using a safety analysis set (SAS). FAS included all patients randomised to the study treatment group who received at least one dose of the study drug. PPS included all patients who had an evaluable primary endpoint. They were randomised to a study treatment group and completed their study treatment. Among them, subjects with major protocol violation, randomisation error, use of drugs prohibited by the study and lower compliance rate were excluded from the PPS. The safety analysis set included all patients who received at least one dose of the study drug and one safety analysis. The non-inferiority of tegoprazan versus lansoprazole in the endoscopic remission rate at 24 weeks was declared if the lower bound of two-sided 95% confidence interval (CI) for the difference between the two arms was greater than the non-inferiority margin of −10%.

All statistical analyses were performed using SAS® (version 9.4; Windows) in accordance with the analysis plan. Continuous variables are expressed as number of participants, mean, standard deviation, median, minimum and maximum values. Categorical variables are presented as frequencies and percentages. All statistical tests were performed at a significance level of two-sided 5% unless otherwise specified in the protocol.

3 | RESULTS

3.1 | Study subjects

Among 398 patients with endoscopically healed EE who were screened, 47 were excluded due to violation of inclusion/exclusion criteria ($n = 38$), withdrawal of consent ($n = 7$) and others ($n = 2$). The remaining 351 patients with endoscopically healed EE after 4 or 8 weeks of administration of a PPI or P-CAB were randomised to either tegoprazan 25 mg ($n = 174$) or lansoprazole 15 mg ($n = 177$) as maintenance therapy at a 1:1 ratio. After randomisation, 57 patients discontinued this study due to withdrawal of informed consent ($n = 45$), inclusion/exclusion criteria violation ($n = 7$), use of contraindicated drugs ($n = 2$), investigator discretion ($n = 2$) and investigator's judgement of AE ($n = 1$). The disposition of subjects is summarised in Figure 2. Their demographics and baseline characteristics are summarised in Table 1. There was no significant difference in baseline characteristics of participants between treatment groups. Most patients had mild EE (LA grade A: 57.3%; LA grade B: 37.3%) in both groups. LA grade C or D esophagitis accounted for only 5.3% of all patients (FAS population).

3.2 | Efficacy

In the PPS population, the endoscopic remission rate after 24 weeks was 90.6% for the tegoprazan 25 mg group and 89.5% for the lansoprazole 15 mg group. The difference in

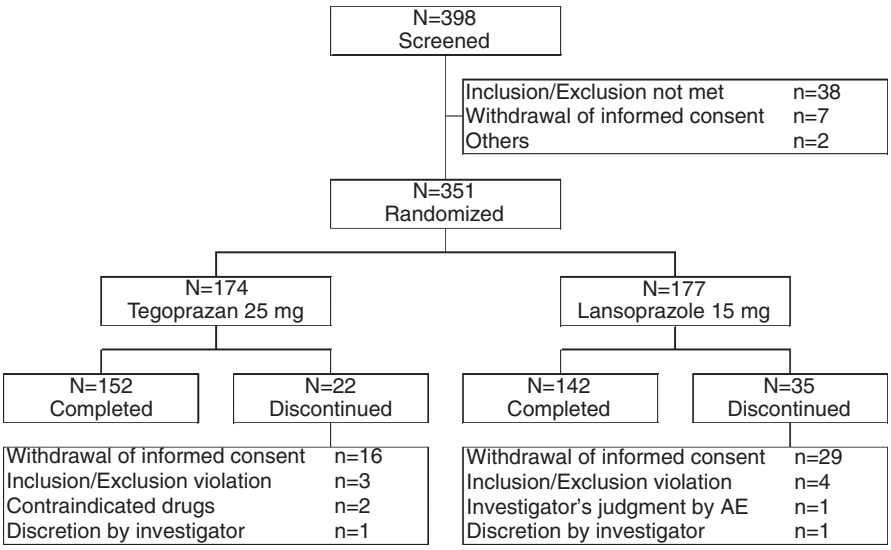

FIGURE 2 Randomisation protocol and patient disposition.

endoscopic remission rate after 24 weeks between tegoprazan 25 mg and lansoprazole 15 mg was <10.0% (95% CI: −6.2 to 8.3; $p = 0.0014$), confirming the non-inferiority of tegoprazan 25 mg to lansoprazole 15 mg. In the FAS population, the endoscopic remission rate after 24 weeks was 86.4% for the tegoprazan 25 mg group and 84.1% for the lansoprazole 15 mg group. The difference in endoscopic remission rate after 24 weeks was <10.0% (95% CI: −5.7 to 10.2; $p = 0.0013$) in the FAS population, also confirming the non-inferiority of tegoprazan 25 mg to lansoprazole 15 mg.

In the PPS population, the endoscopic remission rate after 12 weeks was 92.8% for the tegoprazan 25 mg group and 96.0% for the lansoprazole 15 mg group. The difference in these rates between tegoprazan 25 mg and lansoprazole 15 mg was <10.0% (95% CI: −8.8 to 2.3; $p = 0.0082$). Tegoprazan 25 mg (92.9%) was also shown to be non-inferior to lansoprazole 15 mg (96.0%) in the FAS population (95% CI: −8.3 to 2.0, $p = 0.0045$). Endoscopic remission rates after 24 weeks and 12 weeks in PPS and FAS populations are illustrated in Table 2. There was no significant difference in the percentage of subjects or days without major symptom at 24 weeks between tegoprazan and lansoprazole. in the 4, 12 and 24 weeks.

A subgroup analysis was conducted for endoscopic remission rate after 24 weeks of treatment according to the severity of the disease (LA grade), CYP2C19 genotype and *H. pylori* infection status. In the FAS population, the maintenance rate in the lansoprazole group was significantly decreased if EE was severe ($p = 0.0048$). However, in the tegoprazan group, the maintenance rate was not significantly decreased if EE was severe ($p = 0.4707$). Tegoprazan showed consistent endoscopic remission rate irrespective of CYP2C19 genotype ($p = 0.7637$)

TABLE 1 Demographic information and baseline characteristics (full analysis set)

	Tegoprazan 25 mg (N = 154)	Lansoprazole 15 mg (N = 151)
Age (years)	55.40 ± 12.10	55.99 ± 13.40
Gender, *n* (%)		
Male	114 (74.03)	110 (72.85)
Female	40 (25.97)	41 (27.15)
Height (cm)	167.50 ± 9.27	166.64 ± 8.48
Weight (kg)	72.03 ± 12.73	70.17 ± 10.99
Smoking; Yes	31 (20.13)	30 (19.87)
Drinking; Yes	58 (37.66)	62 (41.06)
H. pylori; Positive	33 (21.43)	38 (25.33)[a]
LA grade		
A	88 (57.14)	86 (56.95)
B	58 (37.66)	55 (36.42)
C	8 (5.19)	9 (5.96)
D	0 (0.00)	1 (0.66)

Note: Data expressed as mean ± standard deviation or number of subjects with percentages in parentheses, LA; Los Angeles.

[a]One subject in lansoprazole 15 mg was excluded due to missing result of *H. pylori* test.

TABLE 2 Endoscopic remission rate after maintenance therapy

	Tegoprazan 25 mg	Lansoprazole 15 mg
24-week (primary endpoint)		
Per protocol set		
Endoscopic remission rate of healed patients	90.6 (125/138)	89.5 (111/124)
Difference and 95% CI, *p*-value	1.1 (−6.2, 8.3), 0.0014	
Full analysis set		
Endoscopic remission rate of healed patients	86.4 (133/154)	84.1 (127/151)
Difference and 95% CI, *p*-value	2.3 (−5.7, 10.2), 0.0013	
12-week (secondary endpoint)		
Per protocol set		
Endoscopic remission rate of healed patients	92.8 (128/138)	96.0 (119/124)
Difference and 95% CI, *p*-value	−3.2 (−8.8, 2.3), 0.0082	
Full analysis set		
Endoscopic remission rate of healed patients	92.9 (143/154)	96.0 (145/151)
Difference and 95% CI, *p*-value	−3.2 (−8.3, 2.0), 0.0045	

Note: Data expressed as percentages with number of subjects in parentheses, CI; Confidence interval, non-inferiority margin −10%.

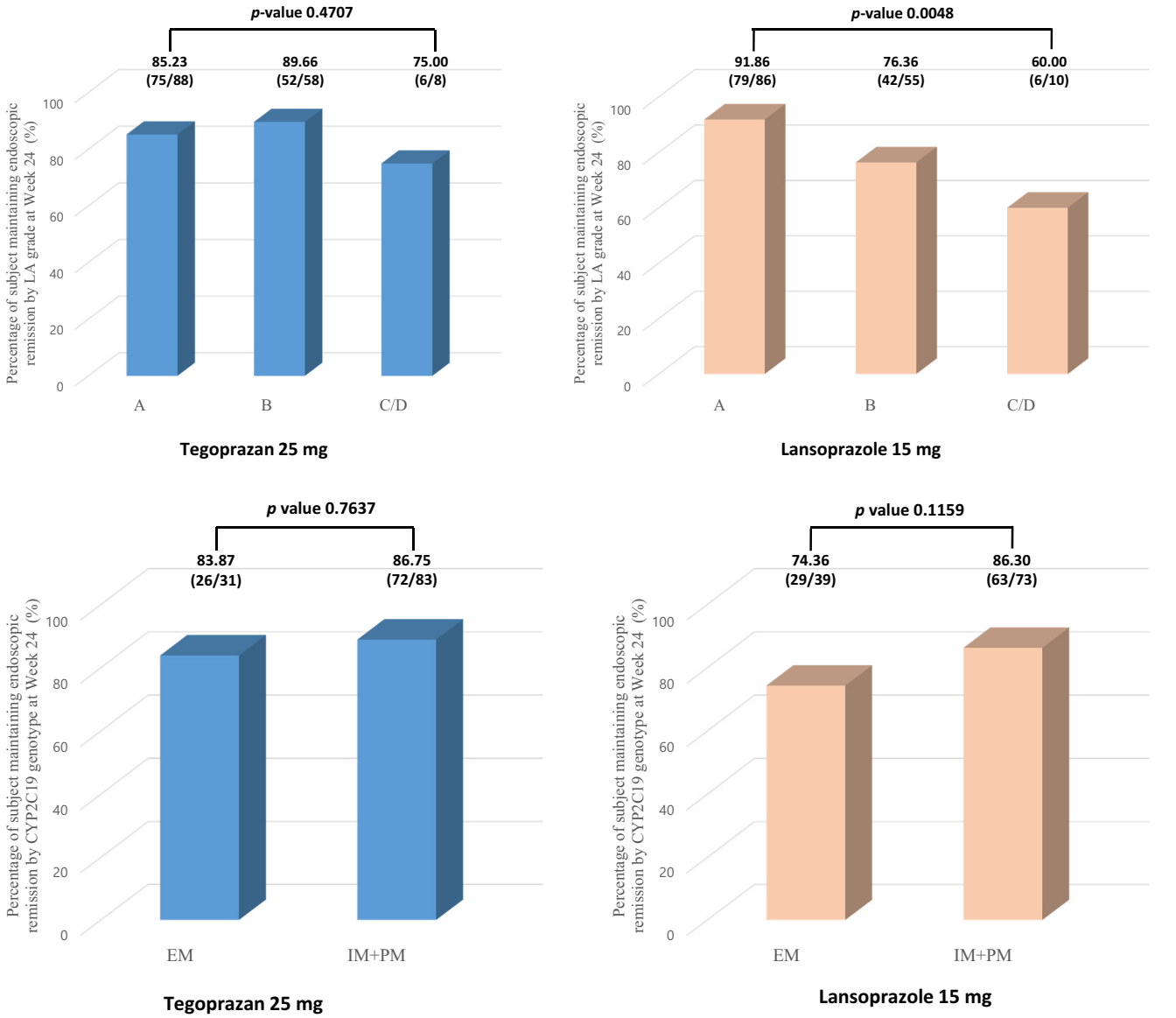

FIGURE 3 Subgroup analysis: maintenance rate according to (1) disease severity and (2) CYP2C19 genotypes (full analysis set).

(Figure 3). There was no difference in the maintenance rate between the two groups according to *Helicobacter* infection status.

3.3 | Safety

Safety analysis was performed for 347 patients who received at least one dose of the study drug and underwent at least one safety assessment in this study (Table 3). A total of 173 cases of TEAEs were reported by 115 participants. Incidence rates of TEAEs were similar between treatment groups ($p = 0.0573$): 28.3% (49/173 patients, 68 cases) for tegoprazan 25 mg and 37.9% (66/174 patients, 105 cases) for lansoprazole 15 mg. Drug-related TEAEs were less frequent in the tegoprazan 25 mg group (12.7%, 22/173 patients) than in the lansoprazole 15 mg group (21.3%, 37/174 patients) ($p = 0.0341$). The most common TEAE classified by system organ class was GI disorder: 11.6% (20/173 patients) in the tegoprazan 25 mg group and 12.6% (22/174) in the lansoprazole 15 mg group. All serious TEAEs in the tegoprazan 25 mg group (1.2%, 2 /173 patients) were considered unrelated to the study medication as judged by the investigators. There was no case of TEAE-related withdrawal of tegoprazan.

There was no clinically significant increase of mean serum level of gastrin, pepsinogen I, or pepsinogen II concentration in the tegoprazan 25 mg group after maintenance therapy. During the study period, one case of drug-related hypergastrinaemia with lansoprazole 15 mg treatment and two cases of drug-related hypergastrinaemia with tegoprazan 25 mg treatment were reported. Mean levels of vitamin B12, folate, magnesium and iron in the two treatment groups were comparable after maintenance therapy with respect to

TABLE 3 Treatment-emergent adverse events (TEAE) during maintenance therapy

	Tegoprazan 25 mg (N = 173)		Lansoprazole 15 mg (N = 174)		
	n (%)	[F]	n (%)	[F]	p-value[a]
TEAE	49 (28.3)	68	66 (37.9),	105	0.0573
Drug-related TEAE	22 (12.7)	30	37 (21.3)	56	0.0341
Serious TEAE	2 (1.2)	2	10 (5.7)	10	0.0193
Death	0 (0.0)	0	0 (0.0)	0	
TEAE (preferred term)					
Gastritis erosive	6 (3.5)	6	3 (1.7)	3	
Chronic gastritis	4 (2.3)	5	1 (0.6)	1	
Gastric polyps	4 (2.3)	4	3 (1.7)	3	
Diarrhoea	2 (1.2)	2	6 (3.4)	7	
Abdominal pain	1 (0.6)	1	2 (1.1)	3	
Dyspepsia	1 (0.6)	1	2 (1.1)	2	
Dizziness	3 (1.7)	3	2 (1.1)	2	
Headache	2 (1.2)	2	2 (1.1)	2	
Nasopharyngitis	3 (1.7)	3	4 (2.3)	4	
Blood creatine phosphokinase increased	3 (1.7)	3	2 (1.1)	2	
Alanine aminotransferase increased	1 (0.6)	1	2 (1.1)	2	
Blood gastrin increased	0 (0.0)	0	2 (1.1)	2	
Gamma-glutamyltransferase increased	0 (0.0)	0	2 (1.1)	2	
Cough	2 (1.2)	2	0 (0.0)	0	
Dysuria	0 (0.0)	0	2 (1.1)	2	

Abbreviation: F, Frequency.

[a]Chi-square test.

baseline. No clinically significant changes in vital signs or ECG findings were observed during the study period.

4 | DISCUSSION

This study was designed to determine the effect of long-term acid suppression with tegoprazan 25 mg or lansoprazole 15 mg on the maintenance of endoscopic remission in patients with healed EE. Tegoprazan 25 mg was not inferior to Lansoprazole 15 mg to maintain endoscopic remission after 24 weeks and 12 weeks treatment in mild EE. Tegoprazan 50 mg is the recommended dose to heal EE. In previous studies, the % Time pH > 4 at 7 days of repeated administration of Tegoprazan 25 mg was confirmed to be 56.6%, which was similar to the previously reported % Time pH > 4 at 20 mg of esomeprazole and 15 mg of lansoprazole. Therefore, 25 mg of tegoprazan was determined as maintenance dose of GERD. This is the 1st clinical study using half-dose tegoprazan and the only study to evaluate maintenance efficacy of P-CAB other than vonoprazan.

PPIs have a low healing rate in severe EE patients (LA grade C/D) after 8-week treatments.[13] Maintenance rates of endoscopic remission after healing following PPI treatment have been shown to be markedly lower in patients with more severe (LA grades C/D) versus milder disease.[14] LA grade C or D severe EE is rare in South Korea.[15,16] Therefore, most of enrolled patients had mild LA A and B EE. In mild EE, tegoprazan and lansoprazole maintenance showed compatible endoscopic remission rates. However, since the proportion of patients with LA C and D was small, it was difficult to apply conclusions of this study to a full range of EE. In the subgroup analysis, the maintenance rate of tegoprazan was not significantly decreased in those with LA grade B or more whereas the maintenance rate of lansoprazole was decreased. Since LA C/D EE was a minority, differences between the two treatment groups would mainly occur in the LA B group. The sustained effect of tegoprazan in LA B moderate EE suggests that it is clinically useful.

Therapeutic efficacies of PPIs are influenced by polymorphic genotypes of CYP2C19 because most PPIs are metabolised by CYP2C19. Tegoprazan 25 mg demonstrated similar endoscopic remission rates regardless of CYP2C19 genotypes ($p = 0.7637$). This was due to different major metabolic pathways of tegoprazan and lansoprazole (CYP3A4 vs. CYP2C19).[5] This means that the effect of

tegoprazan is less individual-specific and predictable. It will have less interaction with other drugs metabolised by CYP2C19 or clopidogrel.

A few studies have reported long-term data of gastrin level of P-CABs. In this study, mean levels of serum gastrin at baseline prior to maintenance therapy were 91.27 pg/mL and 102.20 pg/mL in tegoprazan 25 mg and lansoprazole 15 mg groups respectively. After a PPI or P-CAB was administered for 4 weeks or 8 weeks to treat EE before randomisation, levels defined at baseline were expected to be elevated, although all were within the normal range. After 24 weeks of maintenance therapy, gastrin and pepsinogen I/II levels were lower at the last visit than those at baseline in the tegoprazan group. Although tegoprazan and lansoprazole were not directly compared, gastrin elevation of tegoprazan 25 mg was less than that of lansoprazole 15 mg. In studies reported so far, hypergastrinaemia was associated with long-term study of vonoprazan.[17] This has prompted an ongoing long-term study, the VISION study, of vonoprazan in patients with EE to re-evaluate its safety profile since 2016. Hypergastrinaemia in tegoprazan-treated patients is expected to be significantly less common than that in vonoprazan-treated patients, although further long-term studies are recommended to evaluate the risk of hypergastrinaemia, including serum gastrin monitoring and histopathologic studies on gastric mucosa in patients on long-term low-dose P-CAB treatment.

Overall, tegoprazan was well tolerated during the 24-week maintenance period. The TEAE profile of tegoprazan was similar to that of lansoprazole. In particular, consistent with other phase 3 studies, we observed fewer liver-related TEAEs of tegoprazan in this long-term study which was a possible concern in earlier P-CABs.[8–10,18] Furthermore, there was no newly identified safety signal for tegoprazan.

This study has several limitations. First, it was difficult to extend our results to the global scale as we included only Korean patients. Moreover, the proportion of patients with severe EE (LA grades C and D) at baseline endoscopic characterisation or CYP2C19 EMs was small in this study. Further studies with larger sample sizes are needed to compare endoscopic remission rates of tegoprazan versus PPI according to the severity of EE and polymorphic genotypes of CYP2C19 after maintenance therapy.

In conclusion, tegoprazan 25 mg was non-inferior to lansoprazole 15 mg as maintenance therapy in patients with healed mild EE. Tegoprazan 25 mg could be administered for a long period without risking gastrin elevation or nutritional deficiency. A step-down dose of Tegoprazan 25 mg once daily can be used for maintenance treatment of mild degree EE, showing symptom improvement effect and safety over a long term.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs

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REFERENCES

1. Chapelle N, Ben Ghezala I, Barkun A, Bardou M. The pharmacotherapeutic management of gastroesophageal reflux disease (GERD). Expert Opin Pharmacother. 2021;22(2):219–27. https://doi.org/10.1080/14656566.2020.1817385
2. Bell NJ, Burget D, Howden CW, Wilkinson J, Hunt RH. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. Digestion. 1992;51(Suppl 1):59–67. https://doi.org/10.1159/000200917
3. Strand DS, Kim D, Peura DA. 25 years of proton pump inhibitors: a comprehensive review. Gut Liver. 2017;11(1):27–37. https://doi.org/10.5009/gnl15502
4. Oshima T, Miwa H. Potent potassium-competitive acid blockers: a new era for the treatment of acid-related diseases. J Neurogastroenterol Motil. 2018;24(3):334–44. https://doi.org/10.5056/jnm18029
5. Mori H, Suzuki H. Role of acid suppression in acid-related diseases: proton pump inhibitor and potassium-competitive acid blocker. J Neurogastroenterol Motil. 2019;25(1):6–14. https://doi.org/10.5056/jnm18139
6. Han S, Choi HY, Kim YH, Nam JY, Kim B, Song GS, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple oral doses of tegoprazan (CJ-12420), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther. 2019;50(7):751–9. https://doi.org/10.1111/apt.15438
7. Sunwoo J, Ji SC, Oh J, Ban MS, Nam JY, Kim B, et al. Pharmacodynamics of tegoprazan and revaprazan after single and multiple oral doses in healthy subjects. Aliment Pharmacol Ther. 12. 2020;52(11–12):1640–7. https://doi.org/10.1111/apt.16121
8. Lee KJ, Son BK, Kim GH, Jung HK, Jung HY, Chung IK, et al. Randomised phase 3 trial: tegoprazan, a novel potassium-competitive acid blocker, vs. esomeprazole in patients with erosive oesophagitis. Aliment Pharmacol Ther. 2019;49(7):864–72. https://doi.org/10.1111/apt.15185
9. Cho YK, Choi MG, Choi SC, Lee KM, Kim TO, Park SH, et al. Randomised clinical trial: tegoprazan, a novel potassium-competitive acid blocker, or lansoprazole in the treatment of gastric ulcer. Aliment Pharmacol Ther. 2020;52(5):789–97. https://doi.org/10.1111/apt.15865
10. Kim SH, Cho KB, Chun HJ, Lee SW, Kwon JG, Lee DH, et al. Randomised clinical trial: comparison of tegoprazan and placebo in non-erosive reflux disease. Aliment Pharmacol Ther. 2021;54(4):402–11. https://doi.org/10.1111/apt.16477
11. Freston JW, Jackson RL, Huang B, Ballard ED. Lansoprazole for maintenance of remission of erosive oesophagitis. Drugs. 2002;62(8):1173–84. https://doi.org/10.2165/00003495-200262080-00004
12. Ashida K, Iwakiri K, Hiramatsu N, Sakurai Y, Hori T, Kudou K, et al. Maintenance for healed erosive esophagitis: phase III comparison of vonoprazan with lansoprazole. World J Gastroenterol. 2018;24(14):1550–61. https://doi.org/10.3748/wjg.v24.i14.1550
13. Mizuno H, Matsuhashi N, Sakaguchi M, Inoue S, Nakada K, Higuchi K, et al. Recent effectiveness of proton pump inhibitors for severe reflux esophagitis: the first multicenter prospective study in Japan. J Clin Biochem Nutr. 2015;57(3):233–8. https://doi.org/10.3164/jcbn.14-144
14. Higuchi K, Joh T, Nakada K, Haruma K. Is proton pump inhibitor therapy for reflux esophagitis sufficient?: a large real-world survey of Japanese patients. Intern Med. 2013;52(13):1447–54. https://doi.org/10.2169/internalmedicine.52.0349
15. Kim BJ, Cheon WS, Oh HC, Kim JW, Park JD, Kim JG. Prevalence and risk factor of erosive esophagitis observed in Korean National Cancer Screening Program. J Korean Med Sci. 2011;26(5):642–6. https://doi.org/10.3346/jkms.2011.26.5.642
16. Song JH, Chung SJ, Lee JH, Kim YH, Chang DK, Son HJ, et al. Relationship between gastroesophageal reflux symptoms and dietary factors in Korea. J Neurogastroenterol Motil. 2011;17(1):54–60. https://doi.org/10.5056/jnm.2011.17.1.54
17. Kojima Y, Takeuchi T, Sanomura M, Higashino K, Kojima K, Fukumoto K, et al. Does the novel potassium-competitive acid blocker vonoprazan cause more hypergastrinemia than conventional proton pump inhibitors? A multicenter prospective cross-sectional study. Digestion. 2018;97(1):70–5. https://doi.org/10.1159/000484217
18. Rawla P, Sunkara T, Ofosu A, Gaduputi V. Potassium-competitive acid blockers—are they the next generation of proton pump inhibitors? World J Gastrointest Pharmacol Ther. 2018;9(7):63–8. https://doi.org/10.4292/wjgpt.v9.i7.63

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