Gut and Liver
https://doi.org/10.5009/gnl250334
pISSN 1976-2283 eISSN 2005-1212

Original Article

Randomized, Double-Blind, Active-Controlled, Parallel, Phase 3 Clinical Trial for Evaluating the Efficacy and Safety of Zastaprazan in Patients with Gastric Ulcers

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Article Info

Received July 9, 2025
Revised October 21, 2025
Accepted November 11, 2026

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Background/Aims: Zastaprazan (JP-1366) is a novel potassium-competitive acid blocker with a fast onset and prolonged duration. This study aimed to assess the efficacy and safety of zastaprazan versus lansoprazole in patients with gastric ulcers.

Methods: A total of 329 subjects with confirmed gastric ulcers participated in a phase 3, multicenter, randomized, double-blind, active-controlled clinical study. Subjects were randomized to receive zastaprazan 20 mg or lansoprazole 30 mg once daily up to 8 weeks. The primary endpoint was the cumulative healing rate of gastric ulcers as confirmed by upper gastrointestinal endoscopy at 8 weeks in patients. Secondary endpoints included ulcer healing rate, symptom recovery, quality of life changes, and safety assessment results.

Results: In the per-protocol set, the cumulative healing rate at 8 weeks was 100.00% (146/146) for zastaprazan 20 mg and 97.06% (132/136) for lansoprazole 30 mg, while at week 4, the healing rates were 93.84% (137/146) and 91.91% (125/136), respectively. Zastaprazan was noninferior to lansoprazole in ulcer healing, while the incidence of adverse events was comparable between groups. Gastrin levels increased during the treatment and declined after the treatment in both groups.

Conclusions: An 8-week therapy involving zastaprazan 20 mg demonstrated noninferiority to lansoprazole 30 mg in the cumulative rate of healing of gastric ulcers at 8 weeks, and the two demonstrated similar safety profiles. (ClinicalTrials.gov identifier NCT05448001) **(Gut Liver, Published online January 16, 2026)**

Key Words: Stomach ulcer; Zastaprazan; Potassium-competitive; Lansoprazole

INTRODUCTION

Peptic ulcer disease (PUD) is characterized by lesions that penetrate the muscularis mucosa of the gastric epithelium, resulting from damage caused by gastric acid or pepsin. Based on the ulcer's location, PUD is classified as either a gastric ulcer (GU) or a duodenal ulcer. If left untreated, PUD can lead to serious complications such as acute gastrointestinal (GI) bleeding or perforation.[1] In 2019, the global prevalence of PUD reached approximately 8.09 million, marking a 25.82% increase compared to 1990.[2] *Helicobacter pylori* infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are the primary risk factors for PUD development. According to a meta-analysis, compared to individuals who were *H. pylori*-negative and did not use NSAIDs, *H. pylori* infection increased the risk of PUD by 18.1-fold, while NSAIDs increased the risk of PUD by 19.4-fold. Furthermore, indi-

viduals with both *H. pylori* infection and NSAID use had a 61.1-fold higher risk of developing PUD.[3] Since the 2000s, there also has been an increase in idiopathic peptic ulcers, which occur in the absence of known risk factors such as *H. pylori* and NSAID use.[4]

The treatment of GU is most effective when it reduces gastric mucosal damage caused by excessive acid. Multiple studies have demonstrated that maintaining a gastric pH above 4 for prolonged periods enhances the ulcer healing rate.[5] Proton pump inhibitors (PPIs), such as lansoprazole and esomeprazole, are widely utilized in the management of acid-related disorders, including GU, duodenal ulcer, NSAID-induced ulcers, gastroesophageal reflux disease, and in the treatment of *H. pylori* infections.[6] PPIs are administered as pro-drugs that are activated in the acidic environment of the stomach, where the active drug then irreversibly binds H^+/K^+-ATPase on parietal cells, thereby inhibiting acid secretion.[7] Although PPIs are generally effective in treating acid-related disorders, they have several limitations. For instance, it takes 3 to 5 days of continuous administration to reach maximum efficacy, making rapid symptom relief difficult. In addition, their short half-life prevents them from inhibiting newly synthesized H^+/K^+-ATPase, resulting in insufficient suppression of nocturnal acid secretion (nocturnal acid breakthrough). Furthermore, since PPIs are activated in an acidic environment, food intake may negatively impact their effectiveness.[8,9] Consequently, 15% to 30% of patients with acid-related disorders continue to experience symptoms despite PPI treatment.[10]

Zastaprazan [azetidin-1-yl(8-(2,6-dimethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-yl)methanone-2-hydroxypropane-1,2,3-tricarboxylate] is a potassium-competitive acid blocker (P-CAB) developed by Onconic Therapeutics to address the limitations of PPIs. Unlike PPIs, P-CABs inhibit acid secretion by reversibly binding to the H^+/K^+-ATPase and are administered as active drugs, allowing them to be taken irrespective of food intake while providing an immediate effect from the first dose.[11] Zastaprazan rapidly suppresses acid secretion within approximately 1 hour after administration and, due to its long half-life, effectively controls nocturnal acid secretion.[12] After 7 days of 20 mg daily dosing, % time with gastric pH >4 over 24 hours was 85.2%, compared to 47.0% (lansoprazole 30 mg), 83.4% (vonoprazan 20 mg), 68.2% (tegoprazan 50 mg), and 55.7% (fexuprazan 40 mg).[13-16]

Unlike PPIs, zastaprazan is unaffected by CYP2C19 genotype, minimizing efficacy variability due to genetic differences.[17,18] It demonstrated non-inferiority to esomeprazole in a phase 3 trial for erosive esophagitis (and received Korean approval for erosive esophagitis treatment in April 2024.[19,20] Zastaprazan has also shown significant efficacy in GU animal models.[21] Based on these findings, this phase 3 trial was conducted to evaluate the safety and efficacy of zastaprazan versus lansoprazole in GU patients, aiming to confirm non-inferiority.

MATERIALS AND METHODS

This randomized, double-blind, parallel-group, multicenter study was conducted at 39 sites in Korea from September 2022 to July 2024 to evaluate the non-inferiority of zastaprazan versus lansoprazole in treating GU. The study was approved by institutional review boards at all participating centers, adhered to ethical guidelines, and was registered on ClinicalTrials.gov (NCT05448001, title: Clinical Trial to Evaluate the Efficacy and Safety of JP-1366 in Patients with Gastric Ulcer). All procedures followed the Declaration of Helsinki and its amendments or equivalent ethical standards.

1. Study design and treatment

Adult patients provided written informed consent prior to enrollment and subsequently underwent a screening test, including upper GI endoscopy. Following screening, eligible participants were randomly assigned in a 1:1 ratio to receive either 20 mg of zastaprazan or 30 mg of lansoprazole. Based on the assigned group, the investigational drug was administered orally once daily for 4 weeks. Participants who demonstrated ulcer healing on upper GI endoscopy at week 4 discontinued the investigational drug. Conversely, participants whose ulcers were not healed at week 4 continued to receive the investigational drug for an additional 4 weeks, with a maximum treatment duration of 8 weeks.

2. Study subjects

Eligible participants for this clinical trial were adults aged 19 years or older who provided written informed consent, underwent upper GI endoscopy within 14 days prior to visit 2 confirming at least one GU (3–30 mm in size, classified as A1 or A2 under the Sakita-Miwa system), and were able to understand study information and voluntarily agree to participate.

Patients with any of the following conditions were excluded from the study: a history of acid-suppressive surgery, esophageal or gastric surgery, or total small bowel resection; Zollinger-Ellison syndrome; gastric acid hypersecretion; hypersensitivity to P-CAB, PPI, or benzimidazole compounds; galactose intolerance or genetic defects in carbohydrate digestion or absorption; GI malignancies;

malignancies within the past 5 years; substance or alcohol abuse within the past year; clinically significant psychiatric disorders; thrombotic conditions; or abnormal electrocardiogram (ECG) findings. Patients with active GI disorders, warning signs suggestive of GI malignancy (e.g., dysphagia, anemia, weight loss), pancreatitis, inflammatory bowel disease, or malignancy detected during upper GI endoscopy were also ineligible. Laboratory abnormalities, including elevated total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or gamma-glutamyl transferase levels exceeding twice the upper limit of normal, or an estimated glomerular filtration rate below 70 mL/min/1.73 m^2, led to exclusion.

Pregnant or nursing individuals, as well as participants unwilling to use effective contraception during the study period, were not eligible. Furthermore, participants who had received *H. pylori* eradication therapy within 4 weeks prior to enrollment were excluded. To minimize potential confounding effects on ulcer healing and bleeding risk, the use of medications that could interfere with efficacy evaluation was prohibited. These included acid-suppressive agents, gastric mucosal protectants, antacids, P-CABs, GI motility regulators, NSAIDs, low-dose aspirin, other antithrombotic agents (e.g., clopidogrel), antipsychotics, and certain antivirals. The use of NSAIDs, low-dose aspirin, and other antithrombotic agents was strictly prohibited from 1 week prior to the baseline endoscopic examination until the end of treatment, and therefore no patients received or continued these agents during the study period.

The full analysis set (FAS) included all randomized patients who received at least one dose of the investigational product and underwent upper GI endoscopy at both baseline and at least once post-baseline. In accordance with the intention-to-treat principle, patients were analyzed in their originally randomized treatment group, even if they inadvertently received the incorrect study medication.

The per-protocol set (PPS) was defined as a subset of the FAS without major protocol deviations. Major protocol deviations leading to exclusion from the PPS were determined at a blinded data review meeting prior to database lock and included: absence of endoscopic confirmation of ulcer healing at week 4 (+5 days) and/or week 8 (+5 days); violation of inclusion/exclusion criteria affecting efficacy evaluation; use of prohibited concomitant medications that could affect efficacy; non-compliance with study medication (<80% or >120%); randomization errors; dispensing or dosing errors of the investigational product; and any other significant protocol violation deemed to affect efficacy assessment.

3. Study protocol

This clinical trial was conducted as a double-blind study, utilizing block randomization to assign participants to treatment groups in a 1:1 ratio at each study site. A statistician who was not directly involved in the study generated randomization codes using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA). The randomization manager provided the randomization codes to the packaging personnel before the trial began. The packaging personnel then packaged and labeled the investigational drugs according to the assigned codes and distributed them to the study sites before the trial commenced.

Participants who met the inclusion and exclusion criteria were randomized into the treatment groups sequentially via an Interactive Web Response System according to the randomization codes. To ensure scientific validity, a double-blind, placebo-controlled design was employed, using identical formulations and appearances for the investigational drug and placebo, making them indistinguishable during the treatment period.

At the beginning of the screening period, patient demographics and baseline characteristics were recorded, including medical history, medication history, vital signs, physical examinations, clinical laboratory tests, pregnancy tests, ECGs, and *H. pylori* tests. The presence of *H. pylori* infection was primarily assessed by the ^{13}C-urea breath test, with valid results obtained within 14 days prior to visit 2 or invasive diagnostic methods (e.g., rapid urease test or histology) accepted as substitutes. At weeks 4 and 8, vital signs, physical examinations, clinical laboratory tests, and pregnancy tests were repeated. Additionally, adverse events (AEs), concomitant medication usage, and treatment compliance were assessed. Concomitant medications were defined as any drugs taken in addition to the investigational product during the treatment period. Approximately 14% to 16% of patients in each group received at least one concomitant medication, most commonly agents classified under Alimentary Tract and Metabolism. In accordance with the study protocol, the use of acid suppressants and gastric mucosal protective agents other than the investigational product was strictly prohibited from 2 weeks prior to screening until the end of treatment, as such agents could potentially confound efficacy assessment. Medications given after the end of treatment were not considered protocol violations. Endoscopic evaluations were conducted at baseline (screening), week 4, and week 8.

The follow-up period lasted 2 weeks and commenced once the healing of GU was confirmed via endoscopy, indicated by the absence of a visible white ulcer coating. Patients whose GU had healed by week 4 (visit 3) underwent a follow-up safety assessment 2 weeks later (visit 3-1).

Patients whose GU had not healed by week 4 received an additional course of treatment for 4 weeks. For these patients, endoscopic evaluations were performed at week 8 (visit 4), followed by a final safety assessment 2 weeks later (visit 4-1).

GI symptoms and quality of life were assessed using the Nepean Dyspepsia Index-Korean version (NDI-K) and the 5-level EQ-5D version (EQ-5D-5L) questionnaire, respectively. These assessments were completed prior to the initiation of treatment and repeated during visits 3, 3-1, 4, and 4-1. Additionally, patient diaries were maintained throughout the study. For serum gastrin analysis, fasting blood samples were collected during the 4-week treatment period at visits 2, 3, and 3-1, or during the 8-week treatment period at visits 4 and 4-1.

4. Outcome parameters used to assess efficacy

The primary efficacy endpoint of the clinical trial was the cumulative healing rate of GUs at week 8, as assessed by upper GI endoscopy. Healing was defined, per the Sakita-Miwa classification, as the complete disappearance of ulcers with a white coating or the healing of mucosal defects (S1 or S2 stage). Secondary endpoints included (1) the healing rate of GUs at week 4, classified by the Sakita-Miwa criteria; (2) healing rates stratified by *H. pylori* infection status; (3) changes in ulcer size; and (4) improvements in GI symptoms.

At each scheduled visit, upper GI endoscopy was performed, and ulcer status was evaluated. Endoscopic procedures followed the Clinical Trial Imaging Guideline developed by the Asan Medical Center Clinical Trial Imaging Core (Protocol No. JP-1366-303, Version 2.0, 18-SEP-2023). Ulcer size was measured with biopsy forceps, and the longest diameter of the mucosal defect was recorded.

At baseline, week 4, and week 8, GI symptoms were assessed using the NDI-K, adapted with the original author's approval and validated in Korean. The NDI-K consists of sections evaluating symptom scores, quality of life, and weighting factors. The symptom section assessed 15 GI symptoms, including upper abdominal pain, discomfort, burning, cramps, and bloating, among others. Each symptom was rated based on frequency (0–4), intensity (0–5), and level of distress (0–4), with a combined score ranging from 0 to 13 per symptom. Total symptom scores were calculated by summing the scores of all 15 symptoms, and both individual and total scores were analyzed.

Quality of life was evaluated at baseline, week 4, and week 8 using the EQ-5D-5L, a standardized measure developed in Europe for assessing health status across clinical trials. The EQ-5D-5L assesses five dimensions of health: motor skills, self-care, daily activities, pain/discomfort, and anxiety/depression. Participants rated their health in each dimension on a 5-point scale and provided an overall health evaluation using a visual analog scale ranging from 0 (worst health) to 100 (best health). These scores were used to quantify participants' overall health-related quality of life.

5. Safety assessment

Safety assessments encompassed physical examinations,

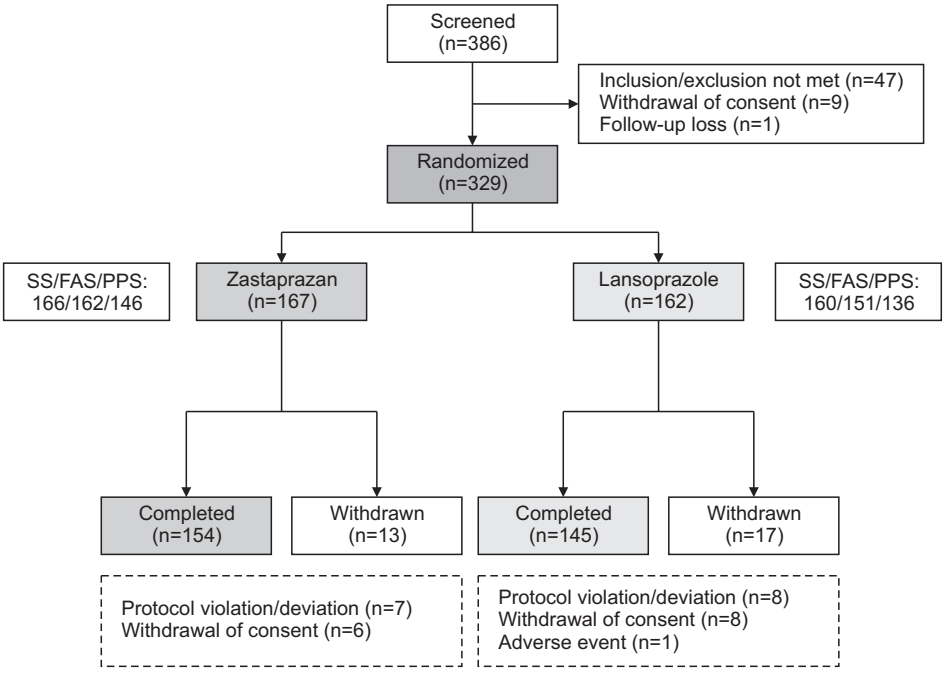

Fig. 1. Flow diagram showing disposition of subjects. SS, safety set; FAS, full analysis set; PPS, per-protocol analysis set.

Table 1. Demographics and Baseline Characteristics

Characteristics	Zastaprazan 20 mg (n=167)	Lansoprazole 30 mg (n=162)
Age, mean±SD, yr	59.6±11.59	57.4±12.45
Sex, No. (%)		
Male	96 (57.49)*	73 (45.06)
Female	71 (42.51)*	89 (54.94)
Height, mean (range), cm	164.67 (147.0–188.0)	163.14 (142.0–184.0)
Weight, mean (range), kg	64.81 (41.9–93.6)	64.63 (37.3–96.0)
BMI, mean±SD, kg/m^2	23.83±3.10	24.14±3.40
Alcohol consumption (current), No. (%)	82 (49.10)	82 (50.62)
Smoking (current), No. (%)	44 (26.35)	31 (19.14)
Caffeine consumption, No. (%)		
<2 units/day	96 (57.49)	92 (56.79)
2–3 units/day	40 (23.95)	38 (23.46)
>3 units/day	12 (7.19)	19 (11.73)
Unknown	19 (11.38)	13 (8.02)
Duration of gastric ulcer history, median (range), day	9 (1–6,534)	9 (1–8,583)
NSAID or low-dose aspirin use, No. (%)	10 (5.99)	7 (4.32)
NSAID	6 (60.00)	6 (85.71)
Aspirin	4 (40.00)	1 (14.29)
Helicobacter pylori infection, No. (%)†	58 (35.80)	50 (33.11)
The number of ulcers, No. (%)†		
Single	118 (72.84)	108 (71.52)
Multiple	44 (27.16)	43 (28.48)
Current ulcer (size), No. (%)		
3 to <5 mm	33 (19.76)	37 (22.84)
5 to <10 mm	80 (47.90)	86 (53.09)
10 to <20 mm	46 (27.54)	30 (18.52)
20 to <30 mm	7 (4.19)	8 (4.94)
≥30 mm	1 (0.60)	1 (0.62)

BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug.
*p-value <0.05, zastaprazan vs lansoprazole, Fisher exact test; †Values were calculated based on the zastaprazan group (n=162) and the lansoprazole group (n=151).

Table 2. Healing Rates (%) of Gastric Ulcer

Treatment	Healed, No. (%)	Difference (Z-L)	95% CI	p-value
Week 8 PPS				
Zastaprazan 20 mg (n=146)	146 (100.00)	2.94	–2.17 to 8.05	0.0529
Lansoprazole 30 mg (n=136)	132 (97.06)			
Week 8 FAS				
Zastaprazan 20 mg (n=162)	153 (94.44)	–0.22	–5.89 to 5.44	1.0000
Lansoprazole 30 mg (n=151)*	142 (94.67)			
Week 4 PPS				
Zastaprazan 20 mg (n=146)	137 (93.84)	1.92	–4.37 to 8.57	0.6441
Lansoprazole 30 mg (n=136)	125 (91.91)			
Week 4 FAS				
Zastaprazan 20 mg (n=162)	143 (88.27)	–1.52	–8.87 to 5.78	0.7184
Lansoprazole 30 mg (n=147)	132 (89.80)			

Difference Z–L, difference of between zastaprazan and lansoprazole; CI, confidence interval; PPS, per-protocol set; FAS, full analysis set.
*One patient in the lansoprazole FAS group was excluded from the analysis due to visit window deviation.

ECGs, evaluations of vital signs (blood pressure, heart rate, and body temperature), laboratory tests (hematology, blood chemistry, coagulation, and urinalysis), and the incidence of treatment-emergent AEs (TEAEs). TEAEs are AEs that either newly arise or worsen in severity or frequency following the administration of the study drug. All TEAEs, adverse drug reactions (ADRs), and serious AEs (SAEs) were coded by the Medical Dictionary for Regulatory Activities (MedDRA, version 27.0) and summarized in accordance with system organ class and preferred term.

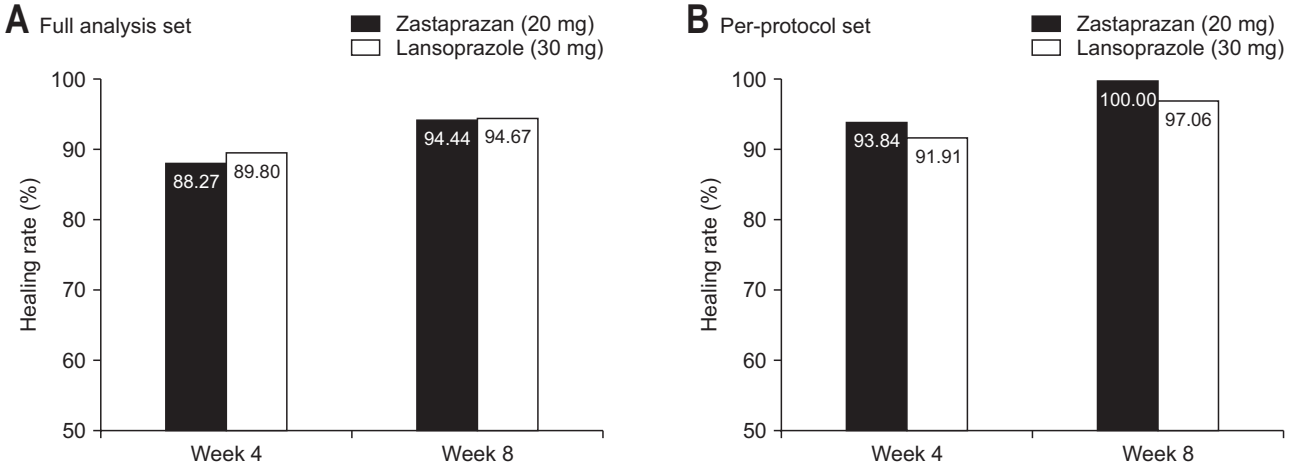

Fig. 2. Endoscopic gastric ulcer healing rates during the 4- and 8-week treatment: (A) full analysis set and (B) per-protocol set.

Table 3. Ulcer Size at Baseline, Week 4 and Week 8

Ulcer size	Zastaprazan 20 mg			Lansoprazole 30 mg		
	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
FAS (n)	162	162	11	151	147	11
Ulcer size, mm	7.9±4.7	0.6±2.3***	0.5±1.5***	7.4±5.0	0.9±3.4***	2.5±4.6*
Percent change, %		–94.1	–90.9		–93.3	–83.3
PPS (n)	146	146	9	136	136	11
Ulcer size, mm	7.7±4.6	0.3±1.2***	0.0***	7.3±4.9	0.6±2.7***	2.5±4.6*
Percent change, %		–97.4	–100.0		–95.0	–83.3

FAS, full analysis set; PPS, per-protocol set.
*p-value <0.05 vs baseline; ***p-value <0.001 vs baseline. No significant differences were observed in ulcer size between zastaprazan and lansoprazole groups.4

Table 4. EQ-5D-5L (Quality of Life) Index Scores at Baseline, Week 4 and Week 8

Index	Zastaprazan 20 mg			Lansoprazole 30 mg		
	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
FAS (n)	162	162	11	151	151	11
EQ-5D-5L score	0.91±0.10	0.97±0.07***	0.98±0.08*	0.91±0.10	0.96±0.07***	0.92±0.10*
PPS (n)	146	146	9	136	136	11
EQ-5D-5L score	0.91±0.09	0.97±0.07***	1.00*	0.91±0.10	0.96±0.07***	0.92±0.10*

The EQ-5D-5L is a standardized instrument that evaluates health status across five dimensions—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—with a 5-point scale.
FAS, full analysis set; PPS, per-protocol set.
*p<0.05 vs baseline, ***p<0.001 vs baseline. No significant differences were observed in the EQ-5D-5L index score between the zastaprazan and lansoprazole groups.

6. Statistical analysis

This clinical trial evaluated the efficacy of zastaprazan 20 mg versus lansoprazole 30 mg in patients with GU, with the primary objective of demonstrating non-inferiority based on the cumulative ulcer healing rate at week 8 as assessed by endoscopy. The non-inferiority margin (δ) was predefined as –8%, with a one-sided significance level of 2.5% and a statistical power of 80%.

To establish the assumed control rate, previous randomized controlled trials of lansoprazole 30 mg in GU patients were reviewed, which reported 8-week cumulative healing rates of 95.7%, 93.8%, and 98.6%.[22-24] A random-effects meta-analysis of these data yielded a pooled estimate of 95.84%, which was adopted as the expected healing rate for the control group. The same expected rate was assumed for the experimental group under the null hypothesis of non-inferiority (H0: $Pt - Pc \leq -\delta$; H1: $Pt - Pc > -\delta$, where Pt and Pc represent the healing rates of the zastaprazan and

Table 5. VAS (Health Status) Scores at Baseline, Week 4 and Week 8

Score	Zastaprazan 20 mg			Lansoprazole 30 mg		
	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
FAS (n)	162	161	11	151	146	11
VAS	78.5±14.0	85.6±10.7***	85.2±8.2*	77.4±15.6	85.4±11.2***	85.3±14.6*
PPS (n)	146	146	9	136	136	11
VAS	79.1±13.7	86.5±9.7***	85.0±8.7	77.8±15.6	85.5±11.5***	85.3±14.6*

The visual analog scale (VAS) is a self-reported measure of overall health status, scored from 0 (worst health) to 100 (best health), and was used to quantify health-related quality of life.
FAS, full analysis set; PPS, per-protocol set.
*p<0.05 vs baseline; ***p<0.001 vs baseline. No significant differences were observed in the VAS score between the zastaprazan and lansoprazole groups.

Table 6. NDI-K (Gastrointestinal Symptoms Questionnaire) Scores at Baseline, Week 4 and Week 8

Score	Zastaprazan 20 mg			Lansoprazole 30 mg		
	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
FAS (n)	162	161	11	151	146	11
NDI-K	26.1±25.8	7.6±13.9***	1.2±2.9**	26.7±29.4	8.2±14.5***	8.2±12.0**
PPS (n)	146	146	9	136	136	11
NDI-K	24.9±25.9	6.5±10.5***	1.4±3.1**	27.6±29.3	8.5±14.9***	8.2±12.0**

The Nepean Dyspepsia Index-Korean version (NDI-K) is a validated tool for assessing gastrointestinal symptoms, quality of life, and symptom burden in Korean patients with dyspepsia.
FAS, full analysis set; PPS, per-protocol set.
*p<0.05 vs baseline; **p<0.01 vs baseline. No significant differences were observed in the NDI-K scores between the zastaprazan group and lansoprazole group.

lansoprazole groups, respectively).

The sample size was calculated using the Farrington–Manning method for two-group non-inferiority testing of proportions, with equal allocation (1:1 ratio). The minimum required size was 131 patients per group. To allow for an anticipated dropout rate of 20%, the final target enrollment was increased to 164 patients per group, resulting in a total of 328 patients. The sample size calculation was performed using PASS 2013 (NCSS, LLC, Kaysville, UT, USA).

The primary endpoint was the cumulative healing rate at week 8, analyzed using the Farrington and Manning method to compute 95% two-sided (97.5% one-sided) CIs. Zastaprazan was considered noninferior if the lower confidence interval (CI) limit exceeded –8%. Secondary endpoints included the week 4 healing rate, analyzed using Fisher exact test. Subgroup analyses by *H. pylori* status used Fisher's exact and Cochran–Mantel–Haenszel tests. Cumulative healing through week 8 was also assessed.

Changes in GI symptoms (NDI-K), quality of life (EQ-5D-5L), and ulcer size were analyzed using descriptive statistics and analysis of covariance, adjusting for baseline values. Ulcer count changes were compared using Fisher exact test. Statistical significance was set at $p<0.05$. Analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Of 386 patients screened, 57 were excluded due to failure to meet the inclusion/exclusion criteria, withdrawal of consent, or loss to follow-up (Fig. 1). A total of 329 patients were subsequently randomized in a 1:1 ratio to receive either zastaprazan 20 mg (n=167) or lansoprazole 30 mg (n=162). Of these, 30 patients (9.1%) discontinued the study due to protocol violations or deviations (n=15), voluntary withdrawal (n=14), or AEs (n=1).

Baseline characteristics (Table 1) showed a statistically significant difference in sex distribution between groups (p=0.0242). However, the proportions of male and female participants were broadly comparable (zastaprazan: 57.49% male, 42.51% female; lansoprazole: 45.06% male, 54.94% female). Most participants were not current users of NSAIDs or low-dose aspirin, and the majority presented with a single GU (zastaprazan: 72.84%, lansoprazole: 71.52%). *H. pylori* infection was identified in 35.80% of patients in the zastaprazan group and 33.11% in the lansoprazole group. The most common ulcer size was 5–10 mm, observed in 47.90% of the zastaprazan group and 53.09% of the lansoprazole group.

Table 7. Summary of Treatment-Emergent Adverse Events

TEAEs	Zastaprazan 20 mg (n=166)		Lansoprazole 30 mg (n=160)	
	No. (%)	Events	No. (%)	Events
TEAEs	22 (13.25)	27	17 (10.63)	24
ADRs	7 (4.22)	9	8 (5.00)	9
SADRs	0	0	0	0
SAE	0	0	1 (0.63)	1
Death	0	0	0	0
TEAE leading to withdrawal	0	0	1 (0.63)	1
ADRs				
Gastrointestinal disorders	5 (3.01)	7	2 (1.25)	3
Dyspepsia	3 (1.81)	3	0	0
Abdominal pain	0	0	2 (1.25)	2
Eructation	1 (0.60)	1	1 (0.63)	1
Abdominal pain upper	1 (0.60)	1	0	0
Gingival swelling	1 (0.60)	1	0	0
Nausea	1 (0.60)	1	0	0
Infections	0	0	1 (0.63)	1
COVID-19	0	0	1 (0.63)	1
Musculoskeletal and connective tissue disorders	0	0	1 (0.63)	1
Arthralgia	0	0	1 (0.63)	1
Nervous system disorders	0	0	3 (1.88)	3
Dizziness	0	0	2 (1.25)	2
Lumbar radiculopathy	0	0	1 (0.63)	1
Respiratory, thoracic and mediastinal disorders	2 (1.20)	2	0	0
Cough	1 (0.60)	1	0	0
Vocal cord thickening	1 (0.60)	1	0	0
Skin and subcutaneous tissue disorders	0	0	1 (0.63)	1
Pruritus	0	0	1 (0.63)	1

TEAEs, treatment-emergent adverse events; ADR, adverse drug reaction; SADRs, serious adverse drug reactions; SAE, serious adverse event; COVID-19, coronavirus disease 2019.
No significant differences were observed in SAEs, AEs leading to discontinuation or death between the zastaprazan and lansoprazole groups.

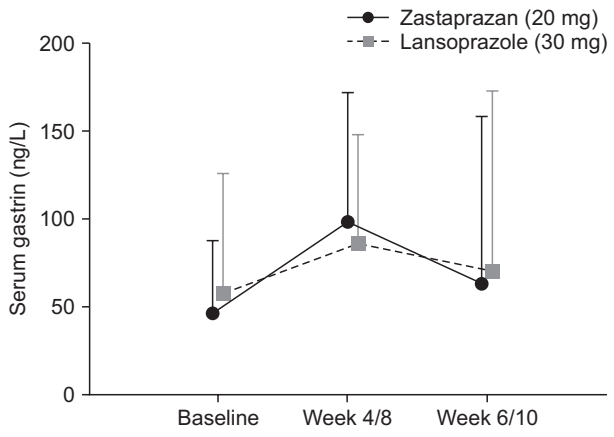

Fig. 3. Serum gastrin concentrations from baseline (ng/L) during treatment and follow-up periods (week 6 or week 10). Each bar shows the standard deviation.

1. Efficacy

Table 2 summarizes the GU healing rates. At week 8 in the PPS population, the cumulative healing rate was 100% with zastaprazan and 97.06% with lansoprazole (difference, 2.94%; 95% CI, –2.17 to 8.05; p=0.0529), demonstrating non-inferiority since the lower bound of the CI exceeded –8% (Fig. 2). In the FAS population, healing rates were 94.44% and 94.67%, respectively (difference, –0.22%; 95% CI, –5.89 to 5.44 p=1.0000). At week 4, healing rates in the PPS were 93.84% and 91.91% (difference, 1.92%; 95% CI, –4.37 to 8.57; p=0.6441), and in the FAS were 88.27% and 89.80% (difference, –1.52%; 95% CI, –8.87 to 5.78; p=0.7184). No statistically significant differences were observed at any time point. Subgroup analysis according to *H. pylori* status showed similarly high and comparable healing rates (Supplementary Table 1).

Ulcer size was assessed at baseline, week 4, and week 8 to evaluate the efficacy. In the FAS, the mean ulcer size significantly decreased from 7.9±4.7 mm to 0.6±2.3 mm (p<0.001) at week 4 and 0.5±1.5 mm (p<0.001) at week 8 in the zastaprazan group, while in the lansoprazole group, it decreased from 7.4±5.0 mm to 0.9±3.4 mm (p<0.001) at week 4 and 2.5±4.6 mm (p<0.05) at week 8. Similar results were observed in the PPS, with ulcer size in the zastaprazan group decreasing to 0.3±1.2 mm (p<0.001) at week 4 and 0.0 mm (p<0.001) at week 8. While both treatments significantly reduced ulcer size, intergroup differences were not statistically significant (Table 3).

2. Symptom response

Both treatment groups showed improved EQ-5D-5L and visual analog scale scores over 8 weeks, with significant within-group increases from baseline at weeks 4 and 8 (Tables 4 and 5). However, no statistically significant differences were observed between groups in either the FAS or PPS, indicating comparable quality-of-life improvements. Sub-dimension analysis (Supplementary Table 2) showed consistent improvements in motor skills, self-care, daily activities, and pain/discomfort, with increasing proportions of patients reaching level 1 over time in both groups. No significant intergroup differences were noted for these domains. However, at week 4, the anxiety/depression domain showed a significant difference (p=0.032), with more patients at level 1 in the zastaprazan group (94.41%) than in the lansoprazole group (89.04%).

NDI-K scores were analyzed to evaluate the severity of GI symptoms (Table 6). By weeks 4 and 8, both treatments showed significant reductions from baseline, demonstrating overall symptom relief. However, the differences between the two groups were not statistically significant in either the FAS or PPS, indicating comparable efficacy in

symptom alleviation across both treatment groups.

3. Safety

Among the 326 subjects included in the safety set, 39 subjects reported 51 AEs. The overall incidence of TEAEs was 11.96% (39/326), with a rate of 13.25% (22/166) in the zastaprazan group and 10.63% (17/160) in the lansoprazole group (Table 7). ADRs were observed in 4.22% (7/166) of subjects in the zastaprazan group and 5.00% (8/160) in the lansoprazole group, with no notable difference between the groups. No serious ADRs were reported in either treatment group. Additionally, no SAEs were observed in the zastaprazan group, whereas one case (0.63%) of SAE was reported in the lansoprazole group. Similarly, TEAEs leading to treatment withdrawal were reported in one subject (0.63%) in the lansoprazole group. Among ADRs, GI disorders were the most frequently reported, occurring in 3.01% (5/166) of the zastaprazan group and 1.25% (2/160) of the lansoprazole group. The most common GI event in the zastaprazan group was dyspepsia (1.81%), whereas the most frequently reported event in the lansoprazole group was abdominal pain (1.25%). Nervous system disorders were observed in 1.88% (3/160) of the lansoprazole group, encompassing dizziness (1.25%) and lumbar radiculopathy (0.63%). Additionally, single cases of COVID-19 (0.63%), arthralgia (0.63%), and pruritus (0.63%) were exclusively reported in the lansoprazole group. No significant changes in vital signs, ECG findings, or laboratory tests including liver function tests (aspartate aminotransferase and alanine aminotransferase) were observed during the study period.

Serum gastrin levels increased from baseline to the end of the treatment period in both the zastaprazan group (46.5±40.8 to 98.4±74.4 ng/L) and the lansoprazole group (57.6±69.1 to 85.9±62.3 ng/L). Although serum gastrin levels increased in both groups after treatment, they gradually returned to baseline following the completion of the treatment period (Fig. 3).

DISCUSSION

This study evaluated the cumulative healing rates of GU between zastaprazan and lansoprazole, demonstrating comparable efficacy across all time points and analysis sets. At week 8, the PPS analysis showed a cumulative healing rate of 100% for zastaprazan and 97.06% for lansoprazole, demonstrating the non-inferiority of both groups. In the FAS analysis at week 8, the cumulative healing rates were nearly identical (94.44% for zastaprazan vs 94.67% for lansoprazole). Similar trends were observed at week 4, where no statistically significant differences were noted in either the PPS or FAS. Subgroup analysis further confirmed consistent healing rates across *H. pylori* subgroups. These findings support the non-inferiority of zastaprazan to lansoprazole. Similarly, the vonoprazan has previously shown non-inferiority to lansoprazole, with 8-week cumulative healing rates of 95.0% in *H. pylori*-positive and 84.4% in *H. pylori*-negative patients in FAS analysis.[23]

The 8-week cumulative healing rate in the PPS analysis highlights zastaprazan's strong efficacy in GU treatment, aligning with expectations based on previous clinical findings. In a previous phase 3 trial in patients with erosive esophagitis, the PPS analysis similarly reported a 100% healing rate at week 8.[19] Furthermore, phase 1 pharmacokinetic and pharmacodynamic studies showed that zastaprazan maintained gastric pH above 4 for 85.2% of a 24-hour period after 7 days of dosing, while the single-dose study demonstrated rapid absorption within approximately 1 hour and a half-life of 8.63 hours.[12] Given that maintaining gastric pH above 3 is known to enhance ulcer healing,[25] these results support zastaprazan's clinical efficacy in GU treatment.

Beyond mucosal healing, patient-reported outcomes provide additional insights into treatment benefits. Although not a primary endpoint, some early improvements in GI symptoms observed in this study may have contributed to perceived emotional well-being. This is consistent with prior evidence demonstrating that effective acid suppression and rapid symptom relief are associated with enhanced quality of life and psychological outcomes in patients with PUD.[25,26] While these findings should be interpreted with caution, they suggest that the symptomatic benefits of zastaprazan may extend to broader aspects of patient well-being, an area that warrants further investigation.

The most commonly reported drug-related AEs with P-CABs were mild-to-moderate GI issues, such as diarrhea and elevated liver enzyme levels. For vonoprazan, GI symptoms—including abdominal pain, discomfort, constipation, diarrhea, and vomiting—were frequently observed, along with infections such as nasopharyngitis, bronchitis, and esophageal candidiasis, with an overall drug-related AE incidence of 6.6%.[23] Similarly, tegoprazan at doses of 50 mg or 100 mg had a drug-related AE incidence of 9.80% to 13.73%, with diarrhea, dyspepsia, and elevated liver enzyme levels being the most reported events.[22] In the current study, ADRs were observed in 4.22% of patients, demonstrating a comparable safety profile.

From the perspective of hepatic toxicity, a comprehensive analysis was conducted to evaluate changes in aspartate aminotransferase and alanine aminotransferase levels during the treatment period in a total of 463 patients en-

rolled across three clinical trials. The results demonstrated no clinically significant alterations in hepatic transaminase levels in any patient, with all values consistently remaining within the normal reference range throughout the treatment period (Supplementary Table 3). Zastaprazan, based on an imidazopyridine backbone and optimized for proton pump targeting, exhibited a favorable hepatic safety profile in good laboratory practice-compliant toxicology studies. While earlier imidazopyridine-based P-CABs like SCH28080 and AZD0865 (linaprazan) were discontinued due to hepatotoxicity, recent findings suggest liver toxicity is more influenced by peripheral group modifications than by the core structure.[11,27,28] For instance, zolpidem, which also contains an imidazopyridine backbone, has no reported remarkable hepatotoxicity, whereas alpidem was withdrawn from the market due to liver toxicity.[29] Similarly, the development of linaprazan glurate, a derivative of linaprazan with structural modifications to address hepatotoxicity, highlights the role of peripheral functional groups in modulating toxicity profiles.[30,31] Zastaprazan, now marketed in South Korea as JAQBO, has shown no hepatotoxic events in post-marketing surveillance, further supporting its hepatic safety.

This study has several limitations. First, most participants had relatively small GUs, which may limit the generalizability of the findings to patients with larger or more complicated lesions. Second, the follow-up period was short, preventing evaluation of long-term outcomes. Third, the baseline imbalance in sex, although unlikely to have influenced efficacy, may represent a potential source of bias. Fourth, multiple secondary endpoints were analyzed without statistical adjustment, increasing the risk of type I error. Furthermore, the relatively low prevalence of *H. pylori* infection (<35%) and NSAID/ASA use (approximately 5%) suggests that other factors—such as smoking, alcohol consumption, or idiopathic ulcers—may have contributed to disease development in this population. Although the ^{13}C-urea breath test is generally highly accurate, reliance on a single assessment and incomplete data on prior eradication therapy mean that some underestimation of *H. pylori* infection cannot be ruled out. Nevertheless, these caveats do not diminish the principal finding that zastaprazan demonstrated robust efficacy and safety in the treatment of GUs. They underscore the need for future studies with larger, more diverse populations and longer follow-up to further validate and extend these results.

In conclusion, this phase 3 trial demonstrated that zastaprazan 20 mg was noninferior to lansoprazole 30 mg in the treatment of GUs, with comparable healing rates and a favorable safety profile. These findings establish zastaprazan as an effective and safe therapeutic option within the class of P-CABs, supporting its clinical use as an alternative to conventional PPIs.

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CONFLICTS OF INTEREST

Hyesoo Kwon, Jun Kim, and John Kim are employees of Onconic Therapeutics Inc. G.H.K. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported. All remaining authors declare no conflicts of interest in this work.

ACKNOWLEDGEMENTS

We are grateful to the investigator for their co-participation in this clinical trial and providing valuable data.

AUTHOR CONTRIBUTIONS

Study concept and design: K.S.P., H.S.K., J.H.O., W.C.C., S.C.C., S.H.L., T.H.K., D.Y.C., G.H.B., S.M.K., H.K.L.,J.S.M., C.W.C., C.S., H.K. (37th author), J.K. (38th author), J.K. (39th author). Data acquisition: K.O.K., B.W.K., H.K.J., D.J., S.S.K., M.I.P., J.Y.L., G.K., H.S.M., H.C., K.N.S., W.G.S., C.H.P., T.K., S.J., H.K. (30th author). Data analysis and interpretation: K.S.P., H.S.K., J.H.O., W.C.C., S.C.C., S.H.L., T.H.K., D.Y.C., G.H.B., S.M.K., H.K.L., J.S.M., C.W.C., C.S., S.R.J., K.L., Y.K.C., S.C.P., J.C., C.H. Drafting of the manuscript: H.K. (37th), J.K. (38th), J.K. (39th). Critical revision of the manuscript for important intellectual content: K.S.P., H.S.K., J.H.O., W.C.C., S.C.C., S.H.L., T.H.K., D.Y.C., G.H.B., S.M.K., H.K.L., J.S.M., C.W.C., C.S., H.K. (37th), J.K. (38th), J.K. (39th) Statistical analysis: S.R.J., K.L., Y.K.C., S.C.P., J.C., C.H. Administrative, technical, or material support: K.O.K., B.-W. K., H.K.J., D.J., S.S.K., M.I.P., J.Y.L., G.K., H.S.M., H.C., K.N.S., W.G.S., C.H.P., T.K., S.J. Study supervision: J.J.P., H.K. (37th), J.K. (38th), J.K. (39th) Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl250334.

DATA AVAILABILITY STATEMENT

Data analyzed in this study are available from the corresponding author upon reasonable request.

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