Gut and Liver
https://doi.org/10.5009/gnl250019
pISSN 1976-2283 eISSN 2005-1212

Original Article

Comparing the Efficacy and Safety of Fexuprazan and Lansoprazole for the Prevention of Nonsteroidal Anti-Inflammatory Drug-Induced Peptic Ulcer

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See editorial on page 631.

Article Info
Received January 8, 2025
Revised May 9, 2025
Accepted May 12, 2025
Published online June 26, 2025

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Background/Aims: To compare the efficacy and safety of fexuprazan and lansoprazole for preventing peptic ulcers (PUs) induced by nonsteroidal anti-inflammatory drugs (NSAIDs).
Methods: This multicenter, double-blind, randomized, active-controlled study was conducted across 32 hospitals in South Korea. Patients with musculoskeletal disease requiring long-term treatment with celecoxib, naproxen, or meloxicam were randomized to receive either fexuprazan 20 mg/day (n=212) or lansoprazole 15 mg/day (n=211) for 24 weeks. The primary endpoint was the occurrence of PUs, which were confirmed via esophagogastroduodenoscopy (EGD), with a non-inferiority margin of 8.3%. Only ulcers that developed during the treatment period were examined in the analysis. The occurrence of gastroduodenal bleeding was also monitored via EGD, and symptoms were assessed by using the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM). Adverse events were recorded during the study.
Results: The incidence rate of EGD-confirmed PUs at week 24 was 1.16% in the fexuprazan group and 2.76% in the lansoprazole group, with a between-group difference of –1.64% (95% confidence interval, –4.52% to 1.25%), demonstrating non-inferiority. No patients presented with gastroduodenal bleeding. No significant between-group differences were found in the PAGI-SYM scores (least-square mean difference in the total score at week 24, –0.42; 95% confidence interval, –2.48 to 1.64; p=0.69). There were low rates of adverse drug reactions in the fexuprazan and lansoprazole groups (8.57% vs 4.78%, respectively p=0.12).
Conclusions: Given its non-inferiority to lansoprazole and similar safety profile, fexuprazan is a promising alternative for the prevention of NSAID-induced PUs (ClinicalTrials.gov identifier NCT04784910). **(Gut Liver, 2025;19:685-695)**

Key Words: Fexuprazan; Peptic ulcer; Nonsteroidal anti-inflammatory drugs; Phase III clinical trial

INTRODUCTION

Peptic ulcer (PU), typically occurring within the stomach or the duodenum, is a common disease with a lifetime prevalence of 5% to 10% in the general population and an annual incidence rate of 0.1% to 0.3%.[1] Prolonged treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), introduced commonly in chronic diseases, is an established risk factor for PU development.[2] According to the literature, upper gastrointestinal events associated with the use of non-selective NSAIDs may occur in 2.7% to 4.5% of patients, and 1% to 1.5% of them may present with major complications, such as bleeding or perforation.[3-6] Established risk factors for NSAID-induced PUs and related complications include old age, a history of PU, administration of high-dose NSAIDs, and co-administration of aspirin, antiplatelet agent, or steroid.[7] NSAID-induced PUs appear to be widespread in ageing populations, such as the South Korean population.[8,9]

According to currently published guidelines, patients receiving long-term NSAID therapy should also receive low-dose proton pump inhibitors (PPIs) to prevent NSAID-induced PUs and complications thereof.[7,10-12] However, the effectiveness of PPIs can be limited by several factors, such as slow onset of action, reduced acid-inhibiting activity when administered after meal and problems in controlling nocturnal acid breakthrough.[13] Moreover, prolonged PPI therapy can be associated with some serious adverse events, including fractures and gastrointestinal infections with *Clostridium difficile*, and even lead to gastric carcinogenesis.[14-22]

Potassium-competitive acid blockers (P-CABs) are a novel class of gastric acid-reducing agents inhibiting H^+, K^+-ATPase through reversible potassium-competitive ionic binding without acid activation. P-CABs have a longer half-life than PPIs and produce acid-inhibiting effect regardless of medication time (after meal vs before meal).[23] Fexuprazan is a novel P-CAB developed by Daewoong Pharmaceutical Co., Ltd. (Seoul, Korea). Pharmacokinetic and pharmacodynamic characteristics of the drug, such as rapid action, long elimination half-life, and high effectiveness, similar to or greater than other P-CABs, were documented regardless of medication time and sustained throughout the night.[24]

Current guidelines recommend P-CABs for managing esophagitis and *Helicobacter pylori* eradication therapy.[25-27] The efficacy and safety of P-CABs were also confirmed in managing NSAID-induced PUs and artificial ulcers after endoscopic submucosal dissection.[28,29] Given their pharmacokinetic and pharmacodynamic characteristics mentioned in the paragraph above, P-CABs also appear to be an attractive alternative to PPIs in preventing NSAID-induced PUs. However, to the best of our knowledge, the problem in question has been the subject of only one published study.[30]

The aim of this double-blind, randomized study was to verify the efficacy and safety of fexuprazan (20 mg/day) in the prevention of NSAID-induced PUs, using a PPI, lansoprazole (15 mg/day), as an active comparator.

MATERIALS AND METHODS

1. Study population

This was a multicenter, double-blind, randomized, active-controlled study. The target population was defined as patients diagnosed with a musculoskeletal disease requiring treatment for at least 24 weeks with one of three NSAIDs: celecoxib, naproxen, or meloxicam. Celecoxib was chosen as it was the most commonly prescribed NSAID.[31] Naproxen and meloxicam were included to represent other classes of NSAIDs having a higher risk of developing gastrointestinal complications than that of celecoxib (Supplementary Table 1). Eligibility criteria included: age ≥19 years, at least one risk factor for ulcer development, among the following: documented history of PU confirmed via esophagogastroduodenoscopy (EGD); age ≥60 years; use of low-dose (≤325 mg/day) aspirin; or use of corticosteroid, an equivalent of 10 mg/day (or 20 mg/every other day) of prednisone. No active or healing-stage lesions, according to the Sakita and Miwa classification system, should have been present at screening.[32] Patients with esophageal varices, Barrett's esophagus (greater than 3 cm), esophageal dysplasia, esophageal stricture, ulcer stricture, acute gastrointestinal bleeding, inflammatory bowel disease, *H. pylori* infection confirmed at screening, Zollinger-Ellison syndrome, primary esophageal motility disorders, pyloric obstruction, or pancreatitis were excluded. Also, patients with a history of gastric or duodenal surgery (e.g., acid-reducing surgery, gastrectomy, gastric mucosal resection) or total small bowel resection were excluded. A complete list of exclusion criteria is provided in Supplementary Table 2.

Eligible patients were randomized to receive either oral fexuprazan 20 mg/day or lansoprazole 15 mg/day for 24 weeks. A stratified block randomization was performed using an interactive web response system, with NSAID type (celecoxib, naproxen, or meloxicam) and the number of risk factors for ulcer development (≤2 or ≥3) as stratification factors. A double-dummy method was used by providing each patient with one bottle of the randomized active drug and another containing a matching placebo.

Patients were instructed to take one capsule and one tablet from each bottle together once a day, preferably before a meal at regular times. Follow-up visits were made at weeks 4, 12, and 24. The randomized treatment was continued till week 24 or until PU was confirmed by EGD, whichever occurred first. In the latter case, the end-of-treatment (EOT) visit was made at the time of PU finding through EGD. Otherwise, all EOT visits were carried out at week 24 or at the time of the patient's withdrawal. Two weeks after the EOT visit, a safety follow-up visit was made for all patients, defined as an end-of-study visit.

2. Ethics

The study was conducted according to the ethical standards of the Helsinki Declaration and the regulations of the Ministry of Food and Drug Safety of Korea. The study protocol was approved by the Ministry of Food and Drug Safety and the institutional review boards of each study center (Supplementary Table 3). A written informed consent was obtained from each patient before initiating study-related procedures. The study information was registered in the public registry (NCT04784910 at ClinicalTrials.gov).

3. Procedures and study outcomes

EGD was performed by the investigator at screening and at weeks 12 and 24. The primary endpoint was the occurrence rate of EGD-confirmed PU at week 24. PU lesions were defined as any active, healing, or newly developed scarring-stage lesions, classified according to the Sakita and Miwa system.[32] Scarring-stage lesions (S1 or S2) present at screening were not included in the primary endpoint unless new PU lesions—regardless of stage—were identified in those patients at week 24. A secondary endpoint was an occurrence rate of gastric or duodenal bleeding confirmed by EGD at week 24. The variables used for the primary and secondary endpoints were also assessed at week 12 and included as exploratory endpoints. Other exploratory assessments included changes in the total score and each symptom score of the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM), a proportion of patients whose gastrointestinal symptoms resolved, and a proportion of patients with newly developed gastrointestinal symptoms. Also, the occurrence of gastrointestinal bleeding of unknown origin, which was a composite endpoint of bleeding signs, was defined as one of the following: hemoglobin reduction ≥2.0 g/dL from baseline, hematocrit reduction ≥10%, or presence of melena or hematochezia. Subgroup analyses were performed for the occurrence of PU depending on the number of risk factors (≤2 or ≥3). The safety of the study treatment was assessed based on the adverse events, laboratory results, including blood gastrin level, physical examination, vital signs, and electrocardiogram. Any adverse event that occurred after the administration of the study drug was defined as treatment-emergent adverse event (TEAE). TEAEs were classified as mild in intensity if they caused minimal discomfort that did not interfere with the subject's normal daily functional activities and were easily tolerable for the subject, moderate if they caused significant discomfort that interfered with the subject's normal daily functional activities, and severe if they caused inability to perform the subject's normal daily functional activities.

4. Statistical analysis

A sample size of 145 per group was required to test the non-inferiority of fexuprazan to lansoprazole at a one-sided significance level of 2.5% with a power of 80%, considering the assumed event rate of 6.8% in both groups and a non-inferiority margin of 8.3%.[30,33] Assuming a drop-out rate of 30%, a total of 416 patients were targeted for enrolment. The efficacy analysis was done following the intention-to-treat principle and primarily based on the full-analysis set (FAS), consisting of randomized patients who received both the study treatment and an NSAID at least once and had an available EGD evaluation record after the randomization. For the primary endpoint, a sensitivity analysis was carried out using a subset of FAS comprising patients with at least one or more risk factors of PU. Another subset of FAS, comprising patients who completed the end-of-study visit, was defined as the per-protocol set and used for a supplementary efficacy analysis. Patients who received at least one dose of the study treatment were included in the safety analysis. To compare the occurrence rates of PU or gastroduodenal bleeding between the two study groups, a common risk difference was calculated using the Cochran-Mantel-Haenszel method, adjusted for the randomization stratification factors, presented with the two-sided 95% confidence interval (CI) for the common risk difference (fexuprazan–lansoprazole). If the upper end of the 95% CI of the common risk difference in the occurrence of PU was less than 8.3%, a non-inferiority of fexuprazan to lansoprazole was declared. In the case of FAS analysis, if an endoscopic examination result at 24 weeks was missing, the missing value was replaced with the last available result obtained at or after week 12 only for those who had a study treatment adherence of 80% or higher and had taken an NSAID for at least 12 weeks. No missing data imputation was made for other variables. Changes in the PAGI-SYM scores were analyzed using the analysis of covariance, in which the randomization stratification factors were treated

as covariates, and the between-group difference was presented with the least-square mean difference, its 95% CI, and p-value. Other data were summarized with descriptive statistics. For continuous variables, between-group differences were tested using the two-sample t test or Wilcoxon rank-sum test, and within-group differences using the paired t test or Wilcoxon signed-rank test. For categorical variables, between-group differences were tested using the chi-square test or Fisher exact test. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. All statistical analyses were two-tailed tests with a significance level of 5%, performed using the Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

1. Patients

Of the 677 patients screened, 423 were randomized to the fexuprazan group (n=212) or the lansoprazole group (n=211) (Fig. 1). Patients' demographics and baseline characteristics were generally well balanced between the two groups (Table 1). More than 10% of the study population (18.40% and 13.74%) experienced previous PU, based on the medical history or ulcer scars confirmed through EGD at baseline. Limited proportions of patients (5.66% and 7.11%) were concomitantly treated with low-dose aspirin, whereas over one-third (35.38% and 36.02%) received concomitant corticosteroid therapy.

2. Efficacy

At week 24, no active-stage ulcer lesions were identified via EGD in either of the groups. Two patients in the fexuprazan group and three patients in the lansoprazole group had healing-stage lesions at week 24 (Supplementary Fig. 1). Additionally, two patients in the lansoprazole group had newly identified scarring lesions. Accordingly, the occurrence rate of EGD-confirmed PU at week 24, was 1.16% (2/172) in the fexuprazan group and 2.76% (5/181)

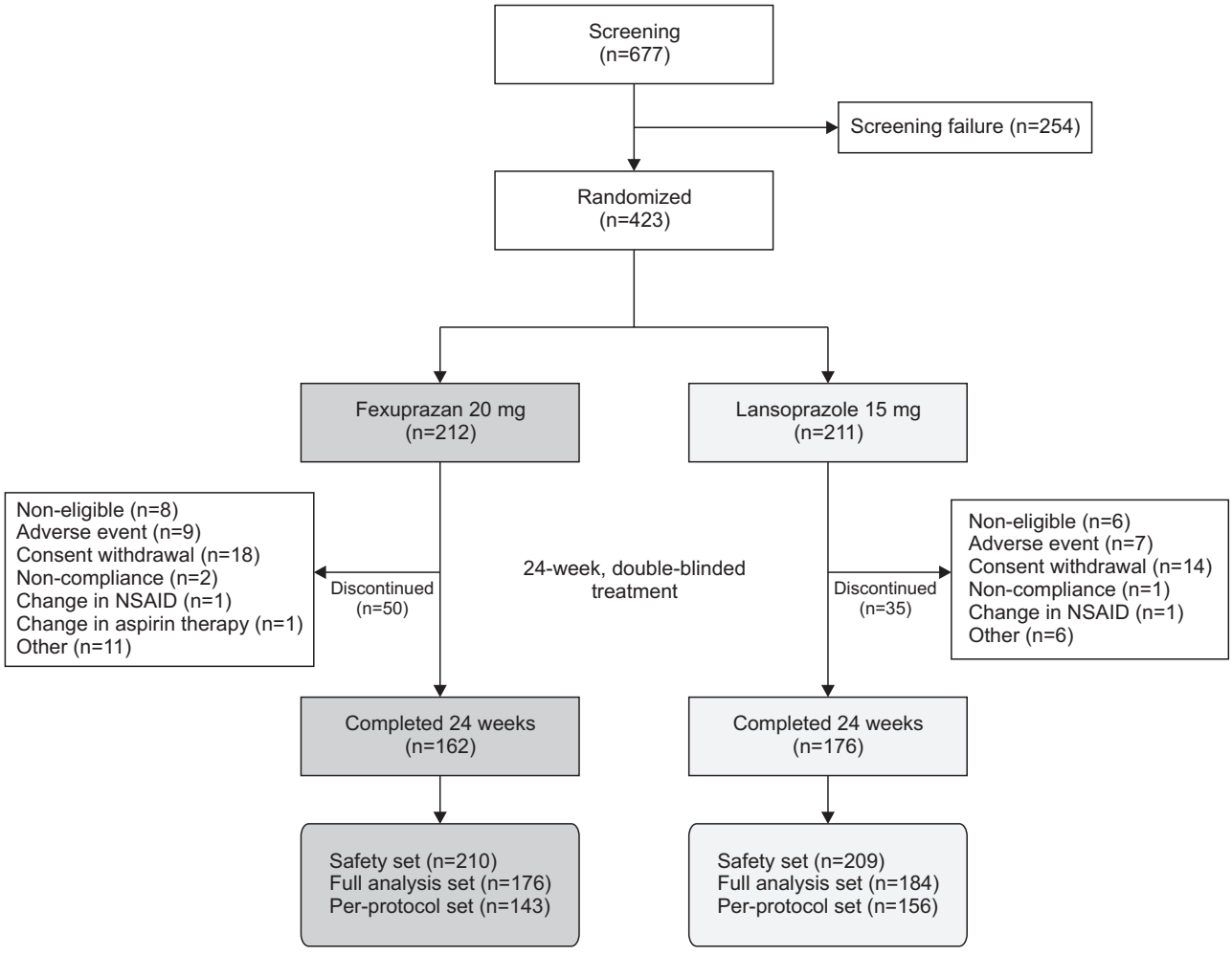

Fig. 1. Distribution of patients. NSAID, nonsteroidal anti-inflammatory drug.

Table 1. Baseline Patient Characteristics

Characteristic	Fexuprazan 20 mg (n=212)	Lansoprazole 15 mg (n=211)
Age, yr	60.89±10.91	61.36±9.60
Female sex	158 (74.53)	161 (76.30)
Alcohol use		
Never	131 (61.79)	123 (58.29)
Current	56 (26.42)	69 (32.70)
Former	25 (11.79)	19 (9.00)
Tobacco use		
Never	168 (79.25)	171 (81.04)
Current	18 (8.49)	19 (9.00)
Former	26 (12.26)	21 (9.95)
BMI, kg/m^2	24.29±3.52	24.43±3.43
Target disease*		
Rheumatoid arthritis	94 (44.34)	87 (41.23)
Osteoarthritis	91 (42.92)	94 (44.55)
Ankylosing spondylitis	24 (11.32)	22 (10.43)
Others	30 (14.15)	21 (9.95)
Duration of disease, mo	59.37 (13.24–118.18)	49.97 (12.16–97.58)
No. of risk factors for ulcer development		
0	0	3 (1.42)
1	156 (73.58)	158 (74.88)
2	49 (23.11)	43 (20.38)
3	7 (3.30)	7 (3.32)
4	0	0
History of peptic ulcer of EGD-confirmed ulcer scar (grade S1 or S2)	39 (18.40)	29 (13.74)
History of peptic ulcer	18 (8.49)	12 (5.69)
EGD-confirmed ulcer scar (grade S1 or S2)	29 (13.68)	23 (10.90)
Concomitant use of low-dose aspirin	12 (5.66)	15 (7.11)
Concomitant use of corticosteroids	75 (35.38)	76 (36.02)

Data are presented as mean±SD, number (%), or median (interquartile range). All randomized patients were included in the analyses of demographic characteristics and baseline clinical characteristics.
BMI, body mass index; EGD, esophagogastroduodenoscopy.
*A total percentage in each group may exceed 100%, as multiple counts were allowed if a patient had more than one target disease.

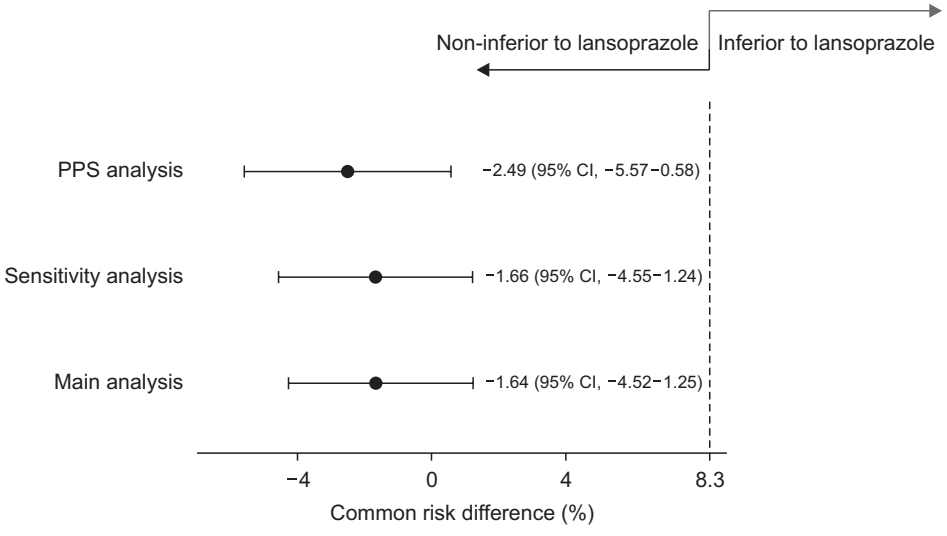

Fig. 2. Common risk difference in the incidence of esophagogastroduodenoscopy-confirmed peptic ulcer for 24 weeks of treatment. The main analysis and sensitivity analysis were carried out using a full-analysis set. PPS, per-protocol set; CI, confidence interval.

in the lansoprazole group, based on which a common risk difference was calculated at –1.64% (95% CI, –4.52% to 1.25%) (Fig. 2). As the upper bound of the 95% CI was less than the predefined margin (8.3%), the non-inferiority of fexuprazan to lansoprazole was demonstrated. The same findings, with no significant difference in PU develop-

ment between the two groups, were confirmed in the per-protocol set and sensitivity analyses (Fig. 2).

No patients from either of the groups had gastroduodenal bleeding confirmed via EGD at 24 weeks of treatment.

The adjusted mean change in the PAGI-SYM total score was –2.22 in the fexuprazan group and –2.23 in the lanso-

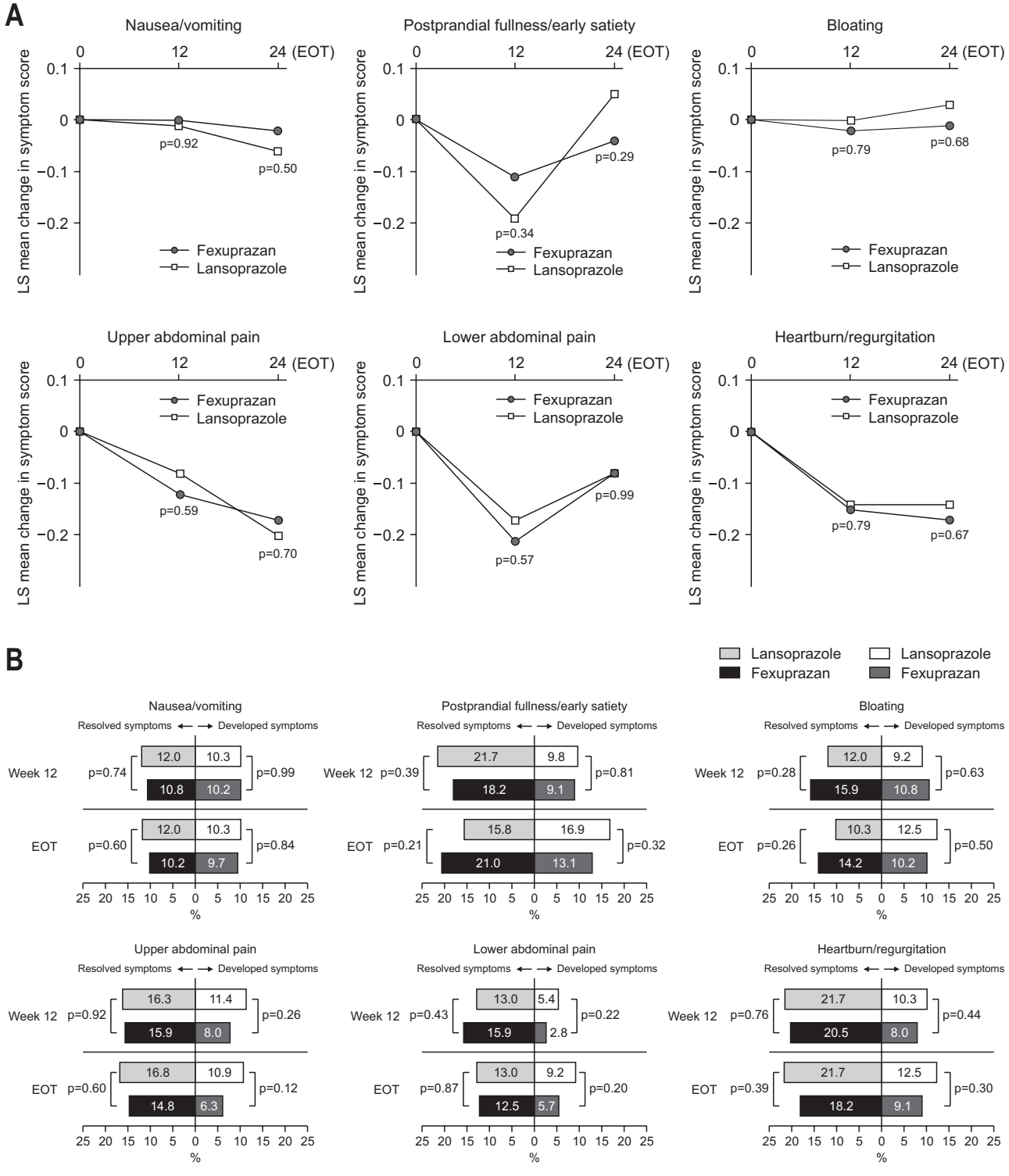

Fig. 3. Patient-reported symptoms based on the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM). (A) Least-square (LS) mean changes in symptom scores. (B) Proportion of patients with resolution or development of symptoms based on changes in symptom scores. The bars on the right side of each graph represent the proportions of patients whose PAGI-SYM symptom score increased by at least 1 from 0 at baseline, whereas the bars on the left side represent the proportions of patients whose PAGI-SYM symptom score changed to 0 from positive numbers at baseline. EOT, end-of-treatment.

prazole group at week 12 (least-square mean difference, 0.02; 95% CI, –1.94 to 1.97; p=0.98), and –1.93 and –1.51, respectively, at the EOT (least-square mean difference, –0.42; 95% CI, –2.48 to 1.64; p=0.69), with no significant difference between the groups.

In addition, no significant between-group difference was found in the change of each gastrointestinal symptom score (Fig. 3A). Among the symptom domains, a trend of a decrease in the symptom score for the upper abdominal pain and heartburn/regurgitation domains was pronounced in both groups. The proportions of patients who experienced resolution of fullness/early satiety, upper or lower abdominal pain, and heartburn/regurgitation were higher than those who experienced the development of new symptoms that were not present at baseline (Fig. 3B).

In a subgroup of patients with ≤2 risk factors of PU (170 and 177 patients in the fexuprazan and lansoprazole groups, respectively), no significant between-group difference was detected in the proportion of patients who developed PU (1.20% vs 2.87%: common risk difference, –1.70%; 95% CI, –4.70 to 1.29; p=0.27) (Table 2). In a subgroup of patients with ≥3 risk factors for PU (n=6 in fexuprazan group and n=7 in lansoprazole group), none developed PU by 24 weeks of the treatment period.

No significant between-group difference was detected in the proportion of patients with gastrointestinal bleeding of unknown origin at week 24 (1.23% vs 0.00%: common risk difference, 1.22%; 95% CI, –0.47 to 2.91; p=0.15). Gastrointestinal bleeding of unknown origin was demonstrated solely due to the decrease in hemoglobin ≥2.0 g/dL. No patients had hematocrit decrease ≥10% or melena/hematochezia.

Table 2. Proportion of Patients Who Developed Peptic Ulcer by Week 24: Subgroup Analyses

Risk factors for ulcer development (≤2 or ≥3)	Fexuprazan 20 mg (n=176)	Lansoprazole 15 mg (n=184)
Risk factors for ulcer development ≤2	170	177
Percentage (95% CI)	1.20 (0.15 to 4.28)	2.87 (0.94 to 6.58)
Common risk difference (95% CI)	–1.70 (–4.70 to 1.29)	
p-value	0.27	
Risk factors for ulcer development ≥3	6	7
Percentage (95% CI)	0 (0 to 70.76)	0 (0 to 84.19)
Common risk difference (95% CI)	-	

Table 3. Summary of Safety Results

Safety results	Fexuprazan 20 mg (n=210)	Lansoprazole 15 mg (n=209)	*p*-value
TEAE			0.25
No. of patients (%)	71 (33.81)	82 (39.23)	
No. of events	128	157	
95% CI	27.41–40.21	32.61–45.85	
ADR			0.12
No. of patients (%)	18 (8.57)	10 (4.78)	
No. of events	27	14	
95% CI	4.79–12.36	1.89–7.68	
Serious TEAE			0.24
No. of patients (%)	8 (3.81)	4 (1.91)	
No. of events	12	4	
95% CI	1.22–6.40	0.06–3.77	
Serious ADR			-
No. of patients (%)	0	0	
No. of events	0	0	
95% CI	0–1.74	0–1.75	
TEAE leading to treatment discontinuation			0.62
No. of patients (%)	9 (4.29)	7 (3.35)	
No. of events	11	9	
95% CI	1.55–7.03	0.91–5.79	
ADR leading to treatment discontinuation			0.69
No. of patients (%)	4 (1.90)	2 (0.96)	
No. of events	6	4	
95% CI	0.52–4.80	0.12–3.41	

TEAE, treatment-emergent adverse event; CI, confidence interval; ADR, adverse drug reaction.

A limited number of patients (46 in the fexuprazan group and 39 in the lansoprazole group) were examined with EGD at week 12, and none of those patients had PU or gastroduodenal bleeding detected by EGD at week 12.

3. Safety

The incidence rate of TEAEs was similar between the two groups (33.81% vs 39.23%, p=0.25). Adverse drug reactions (ADRs) occurred at a low rate (8.57% vs 4.78%, p=0.12) (Table 3). The majority of the TEAEs were mild or moderate in intensity. Specifically, the number of mild, moderate, and severe events in the fexuprazan group was 95, 32, and 1, respectively, versus 132, 24, and 1, respectively, in the lansoprazole group. The most common ADR was gastrointestinal related, constituting 16 out of 27 ADR in the fexuprazan group and nine out of 14 ADR in the lansoprazole group (Supplementary Table 4). None of the serious TEAE was study treatment-related, and no deaths occurred during the study. No significant between-group difference was found in the blood level of gastrin at baseline or changes in the variable at any point of the study. All clinically relevant abnormalities in laboratory results (including hypergastrinemia), physical assessment, vital signs, or electrocardiography readings were reported as TEAE.

DISCUSSION

In the present study, fexuprazan (20 mg/day) demonstrated non-inferior efficacy to lansoprazole (15 mg/day) in preventing EGD-confirmed peptic ulcers (PUs) over a 24-week observation period in patients taking NSAIDs and having at least one risk factor for PU development, including a history of previous PUs. Additionally, no significant differences were found between fexuprazan and lansoprazole regarding subjective patient symptoms determined by PAGI-SYM score changes. The overall safety profile of fexuprazan appeared satisfactory, not significantly different from that of lansoprazole. These findings point to fexuprazan as an alternative to lansoprazole in the prevention of NSAID-induced PUs.

In the present study, EGD-confirmed PUs were observed in 1.16% and 2.76% of patients from the fexuprazan and lansoprazole groups, respectively. These percentages are similar to those reported in a previous phase 3 randomized study verifying the efficacy of another P-CAB, vonoprazan (10 mg/day or 20 mg/day), against lansoprazole (15 mg/day).[30] In this previous study, the only one analyzing the efficacy of a P-CAB in the prevention of NSAID-induced PUs, the proportions of patients with endoscopically confirmed recurrent PUs during a 24-week observation period were 3.3%, 3.4%, and 5.5% for vonoprazan 10 mg/day, 20 mg/day and lansoprazole 15 mg/day, respectively.[30] However, it should be noted that, unlike the previous study, the present study included a proportion of patients with no history of peptic ulcers but with associated risk factors. Nevertheless, our findings are consistent with the results of the previous phase 3 study.[30] Importantly, the occurrence of PUs throughout a 24-week period of the present study was low regardless of the treatment group, which suggests that both fexuprazan 20 mg/day and lansoprazole 15 mg/day effectively prevented ulcer formation. Notably, the results of the extension part of the previously mentioned study of vonoprazan also suggest that P-CABs might be even more effective than lansoprazole in preventing NSAID-induced PUs if administered for an extended time. Specifically, the study demonstrated that at each evaluation time point from week 12 through week 104, the proportions of patients with recurrent PUs were lower, albeit insignificantly, with vonoprazan 10 mg/day or 20 mg/day than with lansoprazole 15 mg/day.[30]

The present study included too small a proportion of patients with ≥3 risk factors for PU, and none of them developed PUs during the observation period. Therefore, it cannot be conclusively determined whether the preventive effect of fexuprazan is consistent regardless of patients' risk profiles. However, the outcome of the previously mentioned study of vonoprazan (10 mg/day or 20 mg/day) was not affected by the number of PU risk factors in a given patient.[30] Thus, one may infer that P-CABs effectively prevent NSAID-induced PUs in both high- and low-risk patients.

The lack of occurrence in the secondary endpoint (gastroduodenal bleeding confirmed via EGD) in either group precluded the analysis of this endpoint in the present study. However, it should be emphasized that in a previous phase 3 randomized study comparing vonoprazan (10 mg/day or 20 mg/day) to lansoprazole (15 mg/day) in the secondary prevention of low-dose aspirin-associated PUs, gastroduodenal bleeding occurred significantly more often in the lansoprazole arm than in both vonoprazan arms.[34] In the same study, vonoprazan (10 mg/day or 20 mg/day) appeared to be superior to lansoprazole (15 mg/day) in preventing gastroduodenal bleeding in patients receiving oral antithrombotic drugs on top of low-dose aspirin therapy.[34] Lower, albeit not significantly, gastroduodenal bleeding rates in both vonoprazan arms were also documented in the previously mentioned study comparing this P-CAB with lansoprazole in the prevention of recurrent PUs during long-term NSAID therapy.[30] Based on these findings, one might conclude that P-CABs are at least non-inferior to lansoprazole in the secondary prevention of gastroduodenal bleeding during prolonged NSAID treatment.

Although P-CABs are not currently authorized for the prevention of PUs,[28] the results of the present study imply that these drugs could also be applied in the prevention of NSAID-induced PUs. This notion is also supported by the presence of some specific pharmacokinetic characteristics of P-CABs, such as longer half-life and the occurrence of the acid-inhibiting effect regardless of medication time, that make them superior to PPIs.[23]

The present study demonstrated the non-inferiority of fexuprazan to lansoprazole not only in terms of objective clinical indices but also with regard to the subjective well-being of patients determined based on PAGI-SYM score changes. This observation is also clinically meaningful as improved patient satisfaction with treatment is an established determinant of better compliance.[35]

Fexuprazan was tolerated well by the study patients, and its safety profile did not differ considerably from that of lansoprazole. This observation is consistent with the results of both previously mentioned randomized studies analyzing the efficacy and safety of vonoprazan (10 mg/day and 20 mg/day) in the secondary prevention of NSAID-induced PUs and low-dose aspirin-associated PUs, respectively.[30,34] Importantly, specific adverse events that, according to literature, might be associated with PPI therapy, were either sporadic (fractures, one per treatment group) or absent (gastrointestinal infections with *C. difficile*).[19-22] This observation is consistent with the results of the previously mentioned phase 3 randomized study comparing vonoprazan (10 mg/day or 20 mg/day) to lansoprazole (15 mg/day) in the secondary prevention of low-dose aspirin-associated PUs.[34] According to the literature, the loss of acidity caused by PPIs promotes the proliferation of bacteria, including *C. difficile*, in previously sterile stomach.[21] In turn, decreased intestinal absorption of calcium associated with reduced acidity, resulting in negative calcium balance, secondary hyperparathyroidism and enhanced bone loss, is postulated as a plausible biological mechanism of increased fracture risk in chronic PPI users.[36] It is currently unclear whether the mechanisms mentioned above are involved in the case of P-CAB therapy, but the results of our present study justify research in this matter.

Regarding the strengths of the study, we included a large group of patients, and all participants from the fexuprazan group presented with at least one risk factor for PU development. Given the large sample size and its homogeneity in terms of risk profiles, the low incidence of PU in the fexuprazan group and the lack of complications, such as bleeding, should by no means be considered a limitation in the evaluation of the drug's value in PU prevention.

In conclusion, given its non-inferiority to lansoprazole (15 mg/day) and similar safety profile, fexuprazan (20 mg/day) appears to be a promising alternative to the latter drug in preventing NSAID-induced PUs.

CONFLICTS OF INTEREST

Y.C.L. 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.

H.L., M.P., J.H., and S.B. are employees of Daewoong Pharmaceutical Co., Ltd. The remaining authors declare no conflicts of interest relevant to this article.

ACKNOWLEDGEMENTS

This study was sponsored by Daewoong Pharmaceutical Co., Ltd. (Seoul, Korea).

AUTHOR CONTRIBUTIONS

Study concept and design: C.K.L., K.D.C. Acquisition of data in each institute: C.K.L., S.H., J.H.J., S.H.L., S.J.H., S.H.K., G.Y.A., J.H.J., J.W.H., Y.J.H., J.K.P., H.S.K., S.W.L., Y.B.P., M.J.L., Y.S.K., J.S.S., C.B.C., S.H.K., I.A.C., K.D.C., T.H.L., Y.S.C., Y.C.L., K.S.K. Data analysis and interpretation: H.L., M.P., J.H., S.B. Drafting of the manuscript: C.K.L., S.H. Critical revision of the manuscript for important intellectual content: all authors. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl250019.

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