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Original Article

Efficacy and Safety of Fexuprazan in Patients with Acute or Chronic Gastritis

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Background/Aims: Fexuprazan is a novel potassium-competitive acid blocker that could be of benefit to patients with gastric mucosal injury. The aim of this study was to assess the 2-week efficacy and safety of fexuprazan in patients with acute or chronic gastritis.

Methods: In this study, 327 patients with acute or chronic gastritis who had one or more gastric erosions on endoscopy and subjective symptoms were randomized into three groups receiving fexuprazan 20 mg once a day (q.d.), fexuprazan 10 mg twice a day (b.i.d.), or placebo for 2 weeks. The posttreatment assessments were the primary endpoint (erosion improvement rate), secondary endpoints (cure rates of erosion and edema and improvement rates of redness, hemorrhage, and subjective symptoms), and drug-related adverse events.

Results: Among the patients, 57.8% (59/102), 65.7% (67/102), and 40.6% (39/96) showed erosion improvement 2 weeks after receiving fexuprazan 20 mg q.d., fexuprazan 10 mg b.i.d., and placebo, respectively. Both fexuprazan 20 mg q.d. and 10 mg b.i.d. showed superior efficacy to the placebo ($p=0.017$ and $p<0.001$, respectively). Likewise, both fexuprazan 20 mg q.d. and 10 mg b.i.d. also showed higher erosion healing rates than the placebo ($p=0.033$ and $p=0.010$, respectively). No difference was noted in the edema healing rate and the improvement rates for redness, hemorrhage, and subjective symptoms between the fexuprazan and placebo groups. No significant difference was noted in the incidence of adverse drug reactions.

Conclusions: Fexuprazan 20 mg q.d. and 10 mg b.i.d. for 2 weeks showed therapeutic efficacy superior to that of placebo in patients with acute or chronic gastritis (ClinicalTrials.gov identifier NCT04341454). **(Gut Liver, Published online February 15, 2023)**

Key Words: Fexuprazan; Gastritis; Phase III clinical trial; Potassium-competitive acid blocker

INTRODUCTION

Gastritis is one of the most common clinically diagnosed diseases in the world, especially in Korea. It refers to the histologic infiltration of inflammatory cells in the gastric mucosa. However, endoscopic findings, such as erosion, edema, redness, and hemorrhage, are frequently labeled as gastritis in the clinical setting despite the relatively poor correlation between these endoscopic features and histologic gastritis.[1] Specifically, erosion as a distinct mucosal defect is observed during acute gastritis and the acute exacerbation of chronic gastritis.[1] Since the prevalence of gastritis has been gradually increasing in Korea,[2] the need for effective gastritis therapies has been also increasing.

Currently, gastritis has no established treatment. The treatment mainly involves the control of the symptoms and the improvement of gastric lesions. Therefore, empirical treatment is mostly done with drugs that suppress gastric acid secretion, modulate gastrointestinal motility, or protect the gastric mucosa.[3] In clinical practice, acid-reducing agents, such as H_2-receptor antagonists and proton pump inhibitors (PPIs), are commonly used with a satisfactory effect in controlling gastritis symptoms. However, a few studies have reported the effects of H_2-receptor antagonists and PPIs in the endoscopic improvement of acute and chronic gastritis.[4]

The recently developed potassium-competitive acid blockers (P-CABs) inhibit H^+, K^+-ATPase by reversible potassium-competitive ionic binding without acid activation and have a relatively longer half-life than PPIs.[5] P-CABs (e.g., vonoprazan and tegoprazan) have shown therapeutic effects similar to those of PPIs in patients with peptic ulcer and reflux esophagitis.[6-9] Fexuprazan (Daewoong Pharmaceutical Co., Ltd., Seoul, Korea) is a novel P-CAB and it was found to inhibit gastric acid secretion equal to or greater than vonoprazan in a pre-clinical study.[10] Fexuprazan has favorable pharmacokinetics and pharmacodynamics, such as rapid action (a median Tmax of 1.75 to 3.5 hours), long elimination half-life (approximately 9 hours), and no significant influence by medication time (before meals vs after meal) in healthy subjects.[10] Furthermore, it shows sufficient inhibition of gastric acid secretion from a single administration and the duration of its action is sustained during the night. Additionally, it has antiulcer effects in reflux esophagitis and indomethacin-induced gastric injury models.[10] Therefore, we conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study to assess the efficacy and safety of fexuprazan for 2 weeks in patients with acute or chronic gastritis.

MATERIALS AND METHODS

1. Study population

This study was a multicenter (24 medical centers), randomized, double-blind, placebo-controlled, phase III clinical trial conducted in Korea from May 2020 to August 2021. We enrolled symptomatic patients aged 19 to 75 years with acute or chronic gastritis who had one or more gastric erosions on baseline esophagogastroduodenoscopy (EGD) and one or more subjective symptoms requiring medical treatment. The exclusion criteria comprised patients with the following conditions: (1) peptic ulcer in the active or healing stage; (2) reflux esophagitis, long-segment Barrett's oesophagus (≥3 cm), gastroesophageal varices, or esophageal stenosis; (3) inflammatory bowel disease, primary esophageal motility disorder, or pancreatitis; (4) history of a gastrointestinal surgery, such as an operation to inhibit gastric acid secretion, and an esophagogastric surgery; (5) Zollinger–Ellison syndrome or pyloric obstruction; (6) significant hepatic, renal, neurologic, cardiovascular, pulmonary, endocrine, haemato-oncologic, or urologic impairment; (7) cardiovascular or cerebrovascular event within 24 weeks; (8) systemic bleeding tendency, coagulation disorder, or thrombotic disorder; (9) history of malignancy within 5 years; (10) clinically significant psychiatric disorder; (11) drug or alcohol abuse within 1 year; (12) known hypersensitivity to P-CABs; (13) acquired immunodeficiency syndrome or viral hepatitis B or C; (14) previous use of any H_2-receptor antagonists, PPIs, P-CABs, gastrin receptor antagonists, antacids, prostaglandin analogues, anticholinergic drugs (muscarinic receptor antagonists), or gastric mucosal protective agents within 2 weeks of the investigational product administration; (15) currently taking corticosteroids, nonsteroidal anti-inflammatory drugs, aspirin, anti-thrombotic agents, bisphosphonates, antispasmodics, prokinetics, iron supplements, serotonin re-uptake inhibitors, or herbal medicines within 2 weeks of the investigational product administration and during the study period; (16) abnormal laboratory test values upon screening (blood urea nitrogen, serum creatinine, total bilirubin, alanine aminotransferase, and aspartate aminotransferase >2× the upper limit of normal); (17) pregnancy or lactation; and (18) nonuse of contraception during childbearing age.

This trial was conducted following the principles of Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of each of the 24 participating institutions (IRB number: 2020-02-032). Written informed consent was obtained from all the participants upon enrolment. This trial was registered as a standard, randomized clinical trial

(ClinicalTrials.gov: NCT04341454).

2. Randomization

The participants underwent electrocardiography, blood, urinalysis, and EGD screening tests. Based on the screening test results, the eligible patients were randomized into three equal groups wherein they were given fexuprazan 20 mg once a day (q.d.), fexuprazan 10 mg twice a day (b.i.d.), or a placebo for 2 weeks. Therefore, the investigational drugs were orally administered twice daily (two tablets in the morning and one tablet in the evening), while maintaining an interval of 12 hours without regard to meals, for a total of 2 weeks. This study was assigned by central enrolment and randomized by an interactive web response system. The participants were stratified by gastritis status (acute or chronic) as classified by their EGD findings. On EGD, acute gastritis was defined as the presence of mucosal edema, redness, and hemorrhage, whereas chronic gastritis was defined as the presence of atrophy and metaplasia.[11] *Helicobacter pylori* infection was examined using at least one of the following methods: histology, rapid urease test, and urea breath test.

This study was conducted in a double-blind manner. During allocation, the participants were assigned numbers, which were used by investigators to describe the investigational products provided by clinical trial pharmacists to the participants. To maintain the double-blind study design throughout the treatment period, the investigational drugs were administered in a double-dummy manner. Each patient visited the treating hospital for a follow-up EGD 2 weeks after initiating the medication. Compliance was determined by the number of remaining tablets per drug type at the follow-up visit.

3. Study assessments

1) Efficacy

Each patient underwent an EGD before and 2 weeks after treatment initiation. Based on the EGD results, gastric erosion was scored from 1 to 4 (1: no visible erosion; 2: one or two erosions; 3: three to five erosions; 4: more than five erosions).[3,12] The primary efficacy endpoint was the improvement rate of erosions, defined as the percentage of the patients with an erosion score improved by 50% or more (e.g., 4→2, 4→1, 3→1, or 2→1) at the follow-up EGD 2 weeks after treatment initiation. Before the start of the clinical trial, the principal investigators from the participating institutions discussed how to assess endoscopic findings, especially erosion. To ensure a unified assessment, all the EGD examinations were recorded and evaluated by the principal investigators, who re-confirmed the data in cases wherein the sub-investigators conducted the EGD. Since accurately assessing the presence of gastric erosions at screening EGD was essential to derive reliable study results, the screening EGD images were re-evaluated by independent investigators who did not participate in this study.

The secondary efficacy endpoints were the healing rates of erosion and edema, the improvement rates of redness and hemorrhage, and the improvement rate of subjective symptoms 2 weeks after treatment initiation. Edema was scored 1–2; redness, 1–4; and hemorrhage, 1–5.[12,13] The healing of erosion and edema was defined as the disappearance of erosion and edema, and the improvement of redness and hemorrhage was defined as a ≥50% reduction in their initial scores at the follow-up EGD 2 weeks after treatment initiation. The subjective symptoms were self-reported and consisted of epigastric pain, heartburn, epigastric discomfort, early satiety, postprandial fullness, intragastric pooling, upper abdominal bloating, nausea, vomiting, and excessive belching.[14,15] The intensity of symptoms was scored from 0 to 4 (0: no problem, 1: mild problem, 2: moderate problem, 3: severe problem, and 4: very severe problem). The frequency of symptoms was scored from 0 to 4 (0: absent, 1: one to two days per week, 2: three to four days per week, 3: five to six days per week, and 4: every day). The symptom scores were obtained through the sum of the intensity and frequency scores of the ten symptoms, with a maximum score of 80. The improvement of subjective symptoms was defined as a ≥50% reduction in the initial gastritis symptom scores. In addition, the improvement rate of erosions according to the *H. pylori* infection status (positive or negative) and gastritis status (acute or chronic) was also investigated as exploratory endpoints.

2) Safety

Safety assessments included adverse events (AEs) and adverse drug reactions (ADRs), including any gastrointestinal symptoms and abnormalities in the electrocardiography, laboratory findings, or vital signs. All AEs reported during the study, regardless of their relationship with the investigational product, were recorded in detail in terms of the date of onset, duration, seriousness, severity, required treatment modification, causal relationship with the study medication, and outcome. ADRs were defined as AEs for which a causal relationship could not be ruled out. AEs and ADRs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 and classified using System Organ Class and Preferred Term.

4. Sample size and statistical analysis

Based on previous studies,[4,16-18] we estimated the sample

size by assuming that the efficacy rates of placebo and acid-reducing agents, such as revaprazan and ranitidine, for the gastric erosions determined by EGD were 40.0% and 65.2%, respectively. Based on these threshold parameters, the total sample size calculated was 327 divided into 109 participants per group, with a power of 90% at a two-sided significance level of 0.025 and a dropout rate of 15%.

The patient data were subjected to three types of analyses: safety set, full-analysis set (FAS), and per-protocol set (PPS). Efficacy assessments were primarily analyzed through the FAS, which included all the participants who had data on the primary efficacy evaluation parameters after treatment with the investigational products. After examination by the independent investigators, those found to have no erosion on baseline EGD were excluded from the FAS analysis because the primary efficacy endpoint was the improvement rate of erosions based on the number of erosions detected on EGD. The safety set analysis, from which safety data were principally based, included all data from randomly assigned participants who took at least one dose of the investigational products after randomization and had at least one safety assessment follow-up. The PPS analysis was focused on the participants from the FAS analysis with data indicating that they had completed the clinical trial according to the protocol.

Efficacy parameters were presented as frequency and proportion (with a 95% confidence interval [CI]) in each group. To compare the placebo group and each of the fexuprazan groups, the common risk difference between the two treatment groups (the fexuprazan group excluding the placebo group) and p-value were presented using the Cochran–Mantel–Haenszel method with a stratification factor (acute or chronic gastritis on baseline EGD) adjusted. The Hochberg's step-up procedure was used to adjust the significance level for multiple comparisons. Statistical analyses of other parameters were performed using the one-way analysis of variance or Kruskal-Wallis test for continuous data and the chi-square or Fisher exact test for categorical data. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a p-value <0.05 was considered statistically significant.

RESULTS

1. Allocation of the patients

Of the 615 participants enrolled in the study, 288 were ineligible based on the inclusion/exclusion criteria. A total of 327 eligible patients were randomized into the three treatment groups: fexuprazan 20 mg q.d. (n=110), fexuprazan 10 mg b.i.d. (n=108), and the placebo (n=109). Two patients assigned to the fexuprazan 20 mg q.d. and placebo groups withdrew consent before taking the investigational product and were excluded from the safety set analysis. Additionally, 25 patients were excluded from the FAS analysis due to the absence of primary efficacy results (n=11) and erosion on baseline EGD upon the independent review (n=14). Therefore, 300 patients (fexuprazan 20 mg q.d., n=102; fexuprazan 10 mg b.i.d., n=102; placebo, n=96) were included in the FAS analysis. Before performing the PPS analysis, ten patients were excluded because of protocol violation (n=9) and prohibited drug intake (n=1). Consequently, the data for 290 patients (fexuprazan 20 mg q.d., n=95; fexuprazan 10 mg b.i.d., n=102; placebo, n=93)

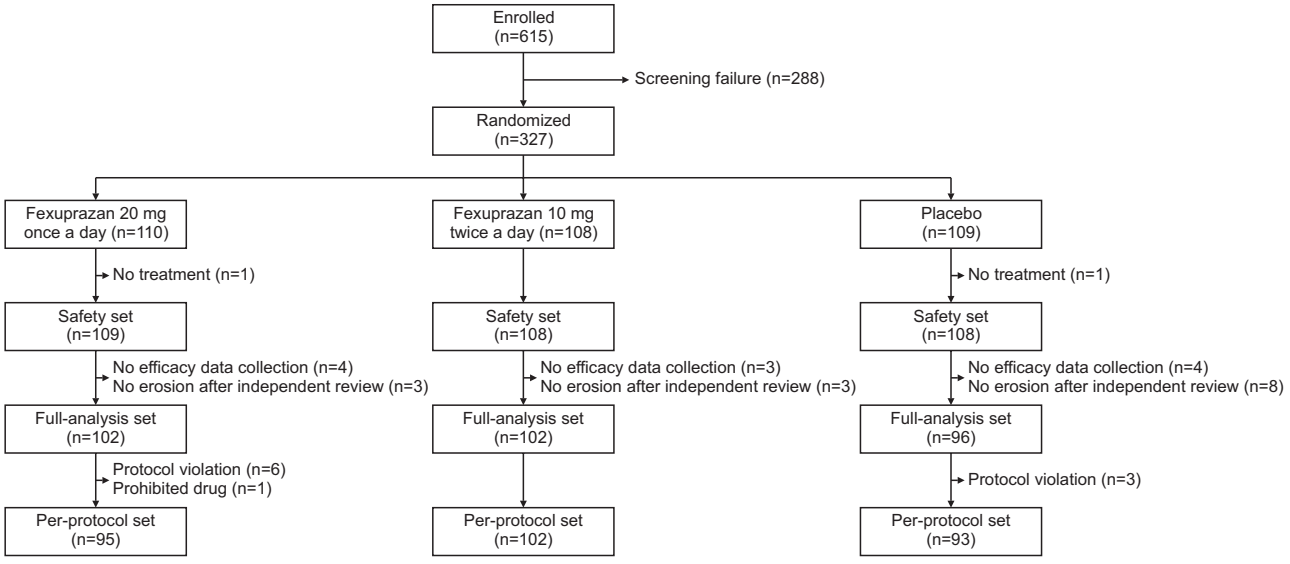

Fig. 1. Flowchart of patient progression through the study.

were used in the PPS analysis. Fig. 1 presents the flowchart of patient progression through the study.

2. Demographics and clinical characteristics

Table 1 shows the demographic and clinical characteristics of the patients in the three groups. No differences were noted among the three groups in terms of age, sex, body mass index, alcohol consumption, *H. pylori* infection, gastritis status, and subjective symptom scores (Table 1). The proportion of smokers was significantly higher in the fexuprazan 20 mg q.d. group than that of the other groups. The baseline endoscopic findings (erosion, edema, redness, and hemorrhage) of the patients were comparable among the three groups (Table 2).

3. Drug compliance

Drug compliance rates throughout the treatment period were 96.8%, 97.9%, and 98.2% in the fexuprazan 20 mg q.d., fexuprazan 10 mg b.i.d., and placebo groups, respectively; the drug compliance rate did not differ among the three groups (p=0.952).

4. Primary efficacy assessment

Based on the FAS analysis, the erosion improvement rates 2 weeks after treatment initiation were 57.8% (59/102), 65.7% (67/102), and 40.6% (39/96) with the use of fexuprazan 20 mg q.d., fexuprazan 10 mg b.i.d., and the placebo, respectively (Table 3). The common risk differences between each fexuprazan group and the placebo group were 17.0% (95% CI, 3.3% to 30.6%) and 25.1% (95% CI, 11.7% to 38.6%) for the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups, respectively. Both the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups had erosion improvement rates significantly higher than that of the placebo group (p=0.017 and p<0.001, respectively) (Fig. 2). In the PPS analysis, the erosion improvement rates 2 weeks after treatment initiation were 58.9% (59/95), 65.7% (67/102), and 40.9% (38/93) with the use of fexuprazan 20 mg q.d., fexuprazan 10 mg b.i.d., and the placebo, respectively. The common risk differences between each fexuprazan group and the placebo group were 17.9% (95% CI, 3.9% to 31.9%) and 24.9% (95% CI, 11.3% to 38.5%) for the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups, respectively. Both the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups had erosion improvement rates significantly higher than that of the placebo group (p=0.014 and p<0.001, respectively). Based on the results of the FAS and PPS analyses, fexuprazan was superior to the placebo in improving gastric erosions.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Participants (Full-Analysis Set)

Characteristic	Fexuprazan		Placebo (n=96)	p-value
	20 mg once a day (n=102)	10 mg twice a day (n=102)		
Age, yr	44.4±13.8	46.4±13.3	47.2±13.8	0.293
Sex				0.324
Male	37 (36.3)	36 (35.3)	43 (44.8)	
Female	65 (63.7)	66 (64.7)	53 (55.2)	
Body mass index, kg/m^2	23.7±3.0	23.7±3.2	24.3±3.7	0.570
Smoking status				0.037
Non-smoker	77 (75.5)	79 (77.5)	70 (72.9)	
Smoker	23 (22.6)	12 (11.8)	16 (16.7)	
Ex-smoker	2 (2.0)	11 (10.8)	10 (10.4)	
Alcohol consumption				0.957
Non-drinker	29 (28.4)	29 (28.4)	28 (29.2)	
Drinker	59 (57.8)	59 (57.8)	58 (60.4)	
Ex-drinker	14 (13.7)	14 (13.7)	10 (10.4)	
Helicobacter pylori infection*				0.868
Positive	24 (24.0)	22 (21.6)	20 (21.1)	
Negative	76 (76.0)	80 (78.4)	75 (78.9)	
Gastritis status				0.655
Acute gastritis	72 (70.6)	66 (64.7)	66 (68.8)	
Chronic gastritis	30 (29.4)	36 (35.3)	30 (31.3)	
Symptom score				
Total	18.8±11.9	20.5±13.1	16.6±11.8	0.103
Severity	9.2±5.7	10.3±6.9	8.2±5.8	0.105
Frequency	9.7±6.5	10.2±6.5	8.4±6.2	0.117

Data are presented as mean±SD or number (%).
*Test for *H. pylori* infection was not performed in two patients from the fexuprazan 20 mg once a day group and one patient from the placebo group.

Table 2. Baseline Endoscopic Findings in the Study Participants (Full-Analysis Set)

Endoscopic finding	Fexuprazan		Placebo (n=96)	p-value
	20 mg once a day (n=102)	10 mg twice a day (n=102)		
Erosion score				0.220
1 (no erosion)	0	0	0	
2 (1–2 erosions)	58 (56.9)	58 (56.9)	53 (55.2)	
3 (3–5 erosions)	34 (33.3)	25 (24.5)	33 (34.4)	
4 (≥6 erosions)	10 (9.8)	19 (18.6)	10 (10.4)	
Edema score				0.571
1 (none)	75 (73.5)	72 (70.6)	64 (66.7)	
2 (present)	27 (26.5)	30 (29.4)	32 (33.3)	
Redness score				0.155
1 (none)	46 (45.1)	48 (47.1)	34 (35.4)	
2 (mild)	48 (47.1)	39 (38.2)	55 (57.3)	
3 (moderate)	6 (5.9)	11 (10.8)	6 (6.3)	
4 (severe)	2 (2.0)	4 (3.9)	1 (4.0)	
Hemorrhage score				0.355
1 (none)	73 (71.6)	85 (83.3)	78 (81.3)	
2 (1 hemorrhagic lesion)	10 (9.8)	9 (8.8)	5 (5.2)	
3 (2–5 hemorrhagic lesions)	14 (13.7)	6 (5.9)	8 (8.3)	
4 (6–10 hemorrhagic lesions)	4 (3.9)	1 (1.0)	4 (4.2)	
5 (>10 hemorrhagic lesions)	1 (1.0)	1 (1.0)	1 (1.0)	

Data are presented as number (%).

Table 3. Primary Efficacy Assessment: Erosion Improvement Rates

	Fexuprazan		Placebo
	20 mg once a day	10 mg twice a day	
Full-analysis set			
No. of patients	102	102	96
Erosion improvement rate, No. (%)	59 (57.8)	67 (65.7)	39 (40.6)
Common risk difference (95% CI)	17.0 (3.3–30.6)	25.1 (11.7–38.6)	
p-value*	0.017	<0.001	
Per-protocol set			
No. of patients	95	102	93
Erosion improvement rate, No. (%)	56 (58.9)	67 (65.7)	38 (40.9)
Common risk difference (95% CI)	17.9 (3.9–31.9)	24.9 (11.3–38.5)	
p-value*	0.014	<0.001	

CI, confidence interval.
*Compared with the placebo group.

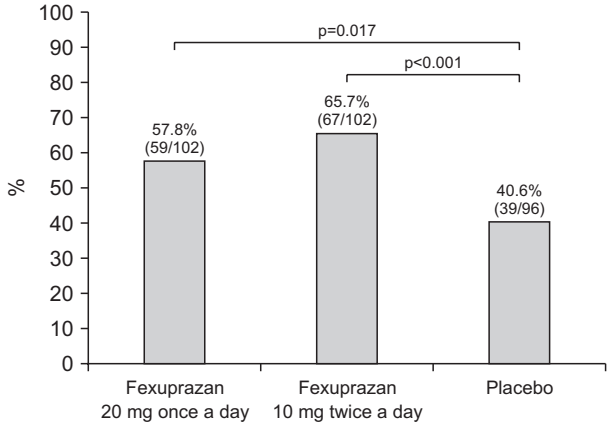

Fig. 2. Erosion improvement rate according to the full participant analysis set.

5. Secondary efficacy assessment

The erosion healing rates 2 weeks after treatment initiation were 54.9% (56/102), 57.8% (59/102), and 39.6% (38/96) with the use of fexuprazan 20 mg q.d., fexuprazan 10 mg b.i.d., and the placebo, respectively (Table 4). The common risk differences between each fexuprazan group and the placebo group were 15.0% (95% CI, 1.35% to 28.7%) and 18.4% (95% CI, 4.73% to 32.1%) for the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups, respectively. Both the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups had erosion healing rates significantly higher than that of the placebo group (p=0.033 and p=0.010, respectively).

The healing rate of edema and the improvement rates of redness and hemorrhage in the fexuprazan 20 mg q.d. and

Table 4. Secondary Efficacy Assessment: Analysis of Other Endoscopic Findings and Subjective Symptoms (Full-Analysis Set)

	Fexuprazan		Placebo
	20 mg once a day	10 mg twice a day	
Erosion healing	56/102 (54.9)*	59/102 (57.8)†	38/96 (39.6)
Edema healing	20/27 (74.1)	22/30 (73.3)	22/32 (68.8)
Redness improvement	29/56 (51.8)	26/54 (48.1)	31/62 (50.0)
Hemorrhage improvement	24/29 (82.8)	16/17 (94.1)	14/18 (77.8)
Symptom improvement	63/102 (61.8)	69/102 (67.6)	68/96 (70.8)

Data are presented as number (%).
*p=0.033 compared with the placebo group; †p=0.010 compared with the placebo group.

Table 5. Incidence of Adverse Drug Reactions (Safety Set)

	Fexuprazan		Placebo (n=108)	p-value
	20 mg once a day (n=109)	10 mg twice a day (n=108)		
Gastrointestinal disorders	2 (1.8) [3]	1 (0.9) [2]	2 (1.9) [2]	
Abdominal distension	0	1 (0.9) [1]	0	
Abdominal pain	1 (0.9) [1]	1 (0.9) [1]	0	
Bowel habit change	1 (0.9) [1]	0	0	
Diarrhea	0	0	2 (1.9) [2]	
Dyspepsia	1 (0.9) [1]	0	0	
Nervous system disorders	2 (1.8) [2]	0	0	
Headache	1 (0.9) [1]	0	0	
Somnolence	1 (0.9) [1]	0	0	
Renal and urinary disorders	1 (0.9) [1]	0	0	
Urinary calculus	1 (0.9) [1]	0	0	
Laboratory abnormalities	0	2 (1.9) [2]	0	
Liver enzyme elevation	0	1 (0.9) [1]	0	
Leukopenia	0	1 (0.9) [1]	0	
Total	4 (3.7) [6]	3 (2.8) [4]	2 (1.9) [2]	0.912

Data are presented as number (%) [case].

10 mg b.i.d. groups did not differ from that of the placebo group (74.1% and 73.3% vs 68.8%, p=0.649 and p=0.783; 51.8% and 48.1% vs 50.0%, p=0.810 and p=0.915; and 82.8% and 94.1% vs 77.8%, p=0.700 and p=0.228, respectively). The improvement rates of subjective symptoms in the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups did not differ from that of the placebo group (61.8% and 67.6% vs 70.8%, p=0.182 and p=0.636, respectively).

Subgroup analyses were performed on the status of *H. pylori* infection and gastritis. In patients without *H. pylori* infection, both the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups had erosion improvement rates significantly higher than that of the placebo group (57.9% [44/76] and 61.3% [49/80] vs 41.3% [31/75], p=0.045 and p=0.014, respectively). In patients with *H. pylori* infection, only the fexuprazan 10 mg b.i.d. group had an erosion improvement rate significantly higher than that of the placebo group (81.8% [18/22] vs 40.0% (8/20), p=0.007). In patients with acute gastritis, both the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups had erosion improvement rates significantly higher than that of the placebo group (63.9% [46/72] and 65.2% [43/66] vs 42.4% [28/66], p=0.012 and p=0.009, respectively). In patients with chronic gastritis, only the fexuprazan 10 mg b.i.d. group had an erosion improvement rate significantly higher than that of the placebo group (66.7% [24/36] vs 36.7% (11/30), p=0.015).

6. Safety

During the study period, nine patients in the fexuprazan 20 mg q.d. group (8.3%, 11 cases), nine patients in the fexuprazan 10 mg b.i.d. group (8.3%, 15 cases), and five patients in the placebo group (4.6%, 6 cases) reported AEs. Among them, four from the fexuprazan 20 mg q.d. group (3.7%, 6 cases), three from the fexuprazan 10 mg b.i.d. group (2.8%, 4 cases), and two from the placebo group (1.9%, 2 cases) were confirmed to have ADRs (Table 5), with gastrointestinal disorders being the most common. The occurrence of AEs and ADRs did not significantly vary among the three groups (p=0.479 and p=0.912, respectively). There were no reports of serious AEs and/or

ADRs leading to drug discontinuation.

DISCUSSION

This was the first randomized, double-blind, controlled phase III study that evaluated the effectiveness of fexuprazan, a novel P-CAB, in patients with acute or chronic gastritis. Two weeks of treatment with fexuprazan 20 mg q.d. and 10 mg b.i.d. was superior to the placebo, significantly improving erosions in patients with acute or chronic gastritis. In addition, no difference was noted in the reported ADRs between the fexuprazan and placebo groups.

In 2021, fexuprazan was approved for the treatment of reflux esophagitis in Korea. The drug exhibited rapid acid inhibition with long-lasting effect;[10] the median time to reach maximum drug concentration ranged from 1.8 to 3.5 hours, and the half-life was approximately 9 hours. The mean gastric pH–time profile of the participants showed that fexuprazan 40 mg had an acid inhibitory potential similar to that of esomeprazole 40 mg.[10] In addition, the high-fat diet given before fexuprazan administration did not cause clinically significant effects on the pharmacokinetics and pharmacodynamics of fexuprazan.[10] Therefore, fexuprazan may likely have at least a therapeutic effect in acid-related diseases, such as gastroesophageal reflux disease and peptic ulcer disease, similar to that of the PPIs. It can be administered regardless of food intake, similar to other P-CABs. Considering gastric erosion as a mucosal injury is less severe than gastric ulcer, we selected 20 mg instead of 40 mg as a total dose of fexuprazan in the present study.

Fexuprazan 20 mg q.d. and 10 mg b.i.d. achieved erosion improvement and healing rates significantly higher than that of the placebo. The erosion improvement rates in the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups were 57.8% and 65.7%, respectively. These results are consistent with the erosion improvement rates after using ranitidine 150 mg b.i.d. (60.5%) and another P-CAB, revaprazan 100 mg q.d. (55.6%).[4] However, the erosion improvement rate from using fexuprazan 20 mg was slightly lower than that of revaprazan 200 mg q.d. (79.9%).[4] This could be explained by our study design, wherein we selected a total fexuprazan dose of 20 mg, a half dose of fexuprazan (40 mg) that has a potency similar to that of esomeprazole 40 mg or revaprazan 200 mg.

Using fexuprazan 20 mg q.d. resulted in an erosion improvement rate higher than that of the placebo only in patients without *H. pylori* infection; however, using fexuprazan 10 mg b.i.d. resulted in an erosion improvement rate significantly higher than that of the placebo, irrespective of *H. pylori* infection. Specifically, the erosion improvement rate was higher in patients with *H. pylori* infection than in patients without *H. pylori* infection (81.8% vs 61.3%). These results are consistent with that of a previous study wherein the erosion improvement rate was higher in patients with *H. pylori* infection than in those without *H. pylori* infection within the revaprazan group.[4] Although *in vitro* studies showed that revaprazan has anti-inflammatory and gastroprotective properties in *H. pylori*-infected gastric mucosa,[19,20] further studies about the similar properties of fexuprazan in *H. pylori*-infected gastric mucosa are needed to explain the high erosion improvement rate among patients with *H. pylori* infection in this study.

We also analyzed the erosion improvement rate according to gastritis status. In patients with acute gastritis, the erosion improvement rates in the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups were 63.9% and 65.2%, respectively, which were significantly higher than that in the placebo group. In patients with chronic gastritis, the erosion improvement rates in the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups were 43.3% and 66.7%, respectively; only fexuprazan 10 mg b.i.d. was superior to the placebo. These results suggest that frequent administration of fexuprazan might be required to treat erosions in patients with chronic gastritis.

The improvement rates of subjective symptoms in the fexuprazan 20 mg q.d. and 10 mg b.i.d. groups were 61.8% and 67.6%, respectively, which was consistent with the results of a previous study about revaprazan 200 mg (66.7%).[4] However, no significant difference was noted in the improvement rates of subjective symptoms between the fexuprazan and placebo groups. A recent network meta-analysis about drugs for functional dyspepsia showed that standard-dose PPIs are superior to a placebo, especially when the treatment duration was ≥8 weeks and the trial was conducted in the West.[21] However, in the present study, the treatment duration was only 2 weeks; most patients had mild symptoms, and the sample size was calculated based on the endoscopic findings. These could explain why no difference was noted in the improvement rates of subjective symptoms between the fexuprazan and placebo groups. Further, well-designed, prospective, multicenter studies are mandatory to investigate the efficacy of fexuprazan in patients with functional dyspepsia.

According to the safety analysis, no significant differences in the incidence of ADRs between the fexuprazan and placebo groups were noted (3.7%, 2.8%, and 1.9% for fexuprazan 20 mg q.d., 10 mg b.i.d., and the placebo, respectively). Moreover, no serious ADRs were reported throughout the study, confirming a safety profile for the oral administration of fexuprazan. Hepatoxicity is an im-

portant obstacle to the clinical use of P-CABs. The first clinically used P-CAB in the world, revaprazan, is effective in treating gastritis and peptic ulcer disease but is not currently used in most countries except India due to hepatotoxicity.[22] Based on the miR-122, liver enzyme and total bilirubin test results, the potential hepatotoxicity of fexuprazan in healthy male participants was not higher than that of the placebo.[10] In the present study, mild liver enzyme elevation was observed in only one patient who took fexuprazan 10 mg b.i.d.

This study had several limitations. First, the included participants consisted of only Koreans; thus, the generalizability of the study results is limited to one ethnicity. However, a recent study showed that the pharmacokinetics and pharmacodynamics of fexuprazan were similar in healthy participants of different ethnicities (Korean, Japanese, and Caucasian).[23] Therefore, fexuprazan would have similar efficacy in people of other ethnicities. Second, to investigate the effect of fexuprazan, we included the following endoscopic findings of gastritis: erosion, edema, redness, and hemorrhage, with erosion as the main endoscopic finding analyzed. However, the inter-observer agreement for the endoscopic findings of gastritis is poor.[1] As such, the principal investigators discussed how to assess the endoscopic findings before the start of the clinical trial. In addition, all the EGD data were evaluated by the principal investigators, and the screening EGD images were re-evaluated by independent investigators who did not participate in this study; this process could have reduced the inter-observer variability to some degree.

In conclusion, this study demonstrated that the novel P-CAB, fexuprazan 20 mg q.d. and 10 mg b.i.d. for 2 weeks resulted in an efficacy statistically superior to that of the placebo in improving gastric erosions in patients with acute or chronic gastritis. With its good efficacy and safety profile, fexuprazan will be another promising option to treat gastritis.

CONFLICTS OF INTEREST

O.Y.L. was a member of outside directors at the Daewoong Co., Ltd. from March 24, 2018, to November 2, 2021. G.H.K. and Y.C.L. are editorial board members of the Journal but were 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.

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AUTHOR CONTRIBUTIONS

Study concept and design: O.Y.L. Acquisition of data in each institute: G.H.K., M.G.C., J.I.K., S.T.L., H.J.C., K.L.L., S.C.C., J.Y.J., Y.C.L., J.G.K., K.B.K., K.N.S., C.I.S., S.K.K., S.G.K., J.S.J., N.K., H.Y.J., H.P., K.C.H., K.J.L., S.J.H., O.Y.L. Data analysis and interpretation: G.H.K., S.B., J.J.H. Drafting of the manuscript: G.H.K. Approval of final manuscript: all authors.

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REFERENCES

1. Laine L, Cohen H, Sloane R, Marin-Sorensen M, Weinstein WM. Interobserver agreement and predictive value of endoscopic findings for H. pylori and gastritis in normal volun-

teers. Gastrointest Endosc 1995;42:420-423.
2. Park HK, Kim N, Lee SW, et al. The distribution of endoscopic gastritis in 25,536 heath check-up subjects in Korea. Korean J Helicobacter Up Gastrointest Res 2012;12:237-243.
3. Kim GH, Lee HL, Joo MK, et al. Efficacy and safety of rebamipide versus its new formulation, AD-203, in patients with erosive gastritis: a randomized, double-blind, active control, noninferiority, multicenter, phase 3 study. Gut Liver 2021;15:841-850.
4. Choi MG, Park SH, Kim SK, et al. Phase III clinical trial of revaprazan (Revanex®) for gastritis. Korean J Gastrointest Endosc 2006;33:212-219.
5. Sunwoo J, Ji SC, Oh J, et al. Pharmacodynamics of tegoprazan and revaprazan after single and multiple oral doses in healthy subjects. Aliment Pharmacol Ther 2020;52:1640-1647.
6. Oshima T, Arai E, Taki M, et al. Randomised clinical trial: vonoprazan versus lansoprazole for the initial relief of heartburn in patients with erosive oesophagitis. Aliment Pharmacol Ther 2019;49:140-146.
7. Xiao Y, Zhang S, Dai N, et al. Phase III, randomised, double-blind, multicentre study to evaluate the efficacy and safety of vonoprazan compared with lansoprazole in Asian patients with erosive oesophagitis. Gut 2020;69:224-230.
8. Lee KJ, Son BK, Kim GH, et al. Randomised phase 3 trial: tegoprazan, a novel potassium-competitive acid blocker, vs. esomeprazole in patients with erosive oesophagitis. Aliment Pharmacol Ther 2019;49:864-872.
9. Miwa H, Uedo N, Watari J, et al. Randomised clinical trial: efficacy and safety of vonoprazan vs. lansoprazole in patients with gastric or duodenal ulcers: results from two phase 3, non-inferiority randomised controlled trials. Aliment Pharmacol Ther 2017;45:240-252.
10. Sunwoo J, Oh J, Moon SJ, et al. Safety, tolerability, pharmacodynamics and pharmacokinetics of DWP14012, a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther 2018;48:206-218.
11. Kayaçetin S, Güreşçi S. What is gastritis? What is gastropathy? How is it classified? Turk J Gastroenterol 2014;25:233-247.
12. Choi YJ, Lee DH, Choi MG, et al. Evaluation of the efficacy and safety of DA-9601 versus its new formulation, DA-5204, in patients with gastritis: phase III, randomized, double-blind, non-inferiority study. J Korean Med Sci 2017;32:1807-1813.
13. Shim KN, Kim JI, Kim N, et al. The efficacy and safety of irsogladine maleate in nonsteroidal anti-inflammatory drug or aspirin-induced peptic ulcer and gastritis. Korean J Intern Med 2019;34:1008-1021.
14. Jeong JJ, Choi MG, Choi H, et al. Single blinded, randomized, active drug comparative, multi-center study to evaluate the therapeutic efficacy of gliptide (R) tab (sulglycotide 200 mg) in gastritis patients; phase IV study. Korean J Gastrointest Endosc 2007;35:125-132.
15. Adam B, Liebregts T, Saadat-Gilani K, Vinson B, Holtmann G. Validation of the gastrointestinal symptom score for the assessment of symptoms in patients with functional dyspepsia. Aliment Pharmacol Ther 2005;22:357-363.
16. Kim SH, An BO. DA-9601, Gastrointestinal agent from Artemisiae herba extract. Sejong: Ministry of Health and Welfare, 2001.
17. Min DS. Development of botanical new drug for gastritis. Sejong: Ministry of Health and Welfare, 2012.
18. Baek HI, Kim SW, Ha KC, et al. Effectiveness of Hizikia fusiformis extract on erosive gastritis: a 4-week, randomized, double-blind and placebo-controlled trial. Int J Pharmacol 2015;11:719-725.
19. Yeo M, Kwak M, Chung IS, et al. Pharmacologic actions of proton pump inhibitors and acid pump antagonists; implication in the treatment of Helicobacter pylori-associated gastric diseases. Korean J Helicobacter Up Gastrointest Res 2005;5:113-123.
20. Lee JS, Cho JY, Song H, Kim EH, Hahm KB. Revaprazan, a novel acid pump antagonist, exerts anti-inflammatory action against Helicobacter pylori-induced COX-2 expression by inactivating Akt signaling. J Clin Biochem Nutr 2012;51:77-83.
21. Ford AC, Moayyedi P, Black CJ, et al. Systematic review and network meta-analysis: efficacy of drugs for functional dyspepsia. Aliment Pharmacol Ther 2021;53:8-21.
22. Oshima T, Miwa H. Potent potassium-competitive acid blockers: a new era for the treatment of acid-related diseases. J Neurogastroenterol Motil 2018;24:334-344.
23. Hwang JG, Jeon I, Park SA, et al. Pharmacodynamics and pharmacokinetics of DWP14012 (fexuprazan) in healthy subjects with different ethnicities. Aliment Pharmacol Ther 2020;52:1648-1657.