A Randomized, Comparative Trial of a Potassium-Competitive Acid Blocker (X842) and Lansoprazole for the Treatment of Patients With Erosive Esophagitis

Siying Zhu, MD[1,*], Muzhou Han, MASc[1,*], Ye Zong, MD[1], Fandong Meng, MD[1], Qi Liu, MD[2], Biguang Tuo, MD[3], Zhenyu Zhang, MD[4], Qizhi Wang, MD[5], Xiaowei Liu, MD[6], Song He, MD[7], Yanbo Zhen, MD[8], Dong Shao, MD[9], Shenglan Wang, MD[10], Baohong Xu, MD[11], Xing Li, MD[12], Haitao Tang, MD[13], Yangde Miu, MD[14], Chengxia Liu, MD[15], Jiuye Hu, MD[16], Pingsheng Hu, PhD[17], Jin Xiu, MS[17], Ming Lu, MS[17], Yongdong Wu, MD[1] and Shutian Zhang, MD[1]

INTRODUCTION: **X842 is a new type of gastric acid-suppressing agent with a rapid onset of action and a long duration of effect. We aim to investigate the efficacy and safety of different doses of X842 vs lansoprazole in the treatment of patients with erosive esophagitis (EE).**

METHODS: **This phase 2 study included 90 patients with EE (Los Angeles grades A–D) who were randomized (1:1:1) to receive oral low-dose X842 (50 mg/d, n = 31), high-dose X842 (100 mg/d, n = 31), or lansoprazole (30 mg/d, n = 30) for 4 weeks. The main efficacy end point was the EE healing rate, which was the proportion of patients who achieved endoscopic healing after 4 weeks of treatment.**

RESULTS: **For intention-to-treat analysis, the EE healing rates at 4 weeks were 93.6% (29/31), 79.3% (23/29), and 80.0% (24/30) for the X842 50 mg, the X842 100 mg, and the lansoprazole 30 mg groups. For per-protocol analysis, the EE healing rates at 4 weeks were 93.6% (29/31), 80.8% (21/26), and 82.1% (23/28) in the 3 groups, respectively. The EE healing rate did not significantly differ among the 3 groups in either the intention-to-treat ($P = 0.2351$) or per-protocol ($P = 0.3320$) analysis. The incidence of drug-related treatment-emergent adverse events did not differ among groups. No severe drug-related treatment-emergent adverse events occurred in the X842 group.**

DISCUSSION: **Our findings confirmed that X842 had efficacy and a favorable safety profile similar to those of lansoprazole. Therefore, X842, a novel potassium-competitive acid blocker, is expected to become a promising therapeutic agent for EE.**

KEYWORDS: erosive esophagitis; X842; potassium-competitive acid blocker; lansoprazole

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B276; http://links.lww.com/CTG/B277

Clinical and Translational Gastroenterology 2025;16:e00803. https://doi.org/10.14309/ctg.0000000000000803

[1]Department of Gastroenterology, National Clinical Research Center for Digestive Diseases, Beijing Digestive Disease Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China; [2]Department of Gastroenterology, Affiliated Hospital of Guizhou Medical University, Guiyang, China; [3]Department of Gastroenterology, Affiliated Hospital of Zunyi Medical University, Zunyi, China; [4]Department of Gastroenterology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China; [5]Department of Gastroenterology, the First Affiliated Hospital of Bengbu Medical College, Bengbu, China; [6]Department of Gastroenterology, Xiangya Hospital, Central South University, Changsha, China; [7]Department of Gastroenterology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China; [8]Department of Gastroenterology, Jinan Central Hospital, Jinan, China; [9]Department of Gastroenterology, The First People's Hospital of Changzhou, Changzhou, China; [10]Department of Gastroenterology, Digestive Disease Institute, Tongji Hospital, Tongi, University School of Medicine, Shanghai, China; [11]Department of Gastroenterology, Beijing Luhe Hospital, Capital Medical University, Beijing, China; [12]Department of Gastroenterology, Affiliated PingXiang Hospital, Southern Medical University, Pingxiang, China; [13]Department of Gastroenterology, Liuan People's Hospital, Liuan, China; [14]Department of Gastroenterology, Taizhou Municipal Hospital, Taizhou, China; [15]Department of Gastroenterology and Hepatology, Binzhou Medical University Hospital, Binzhou, China; [16]Department of Gastroenterology, Affiliated Hospital of Xiangnan University, Chenzhou, China; [17]Jiangsu Sinorda Biomedicine Co., Ltd., Taicang, China.
Correspondence: Yongdong Wu, MD. E-mail: wuyongdong2018@sina.com. Shutian Zhang, MD. E-mail: zhangshutian@ccmu.edu.cn.
*Siying Zhu and Muzhou Han contributed equally to this work and share first authorship.
Received July 26, 2024; accepted December 4, 2024; published online January 21, 2025

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition in which abnormal reflux of gastric contents into the esophagus causes pathological symptoms and complications (1). It is classified into erosive esophagitis (EE) with esophageal mucosal injuries and nonerosive reflux disease with symptoms alone (2). In adults, the overall prevalence of GERD has been high and has been increasing since 1995 throughout the world (3–5). In general, heartburn and regurgitation are considered the characteristic symptoms of EE, which is the phenotypic presentation of GERD (6). This condition not only has a substantial impact on health-related quality of life but also places a large economic burden on social medical resources. Healing EE and controlling GERD-related symptoms are important goals of disease management (7).

Gastric acid inhibition is the most effective measure for treating EE (8). Since 1980s, the most commonly prescribed gastric acid secretion-inhibitory drugs have been proton-pump inhibitors (PPIs) (9). However, these drugs can only be activated under acidic conditions in the stomach and are greatly affected by gastric emptying (10,11). The serum half-life of single-release PPIs is extremely short (12), and the onset of efficacy is slow (13). Efficacy markedly differs between individuals because of the diversity of metabolic enzyme phenotypes in the population (14). Owing to the above limitations of PPIs, potassium-competitive acid blockers (P-CABs) with different mechanisms of action and better pharmacokinetic properties have become a new research focus. P-CABs are reversible, competitive antagonists of hydrogen-potassium adenosine triphosphatase that inhibit gastric acid secretion by reversing K-competitive ionic binding (15). P-CABs are currently widely believed to likely have significant effect on the therapeutic landscape of GERD in the coming decade. However, there are few P-CABs approved for clinical use worldwide (16–20).

X842 is a new generation P-CAB. It is orally converted to the active metabolite AZD0865 (Linaprazan) (Figure 1), the pharmacology and toxicology of which have been well characterized *in vitro* and *in vivo* (21,22). Phase 1 clinical trials involving X842 have been completed in both China and Europe. This study was a phase 2 clinical trial designed to evaluate whether X842 is noninferior to lansoprazole regarding efficacy and safety in the treatment of patients with EE. A further objective of the study was to determine whether the appropriate dose of X842 for EE healing and safety is 50 mg or 100 mg.

METHODS

Study design

This was a multicenter, randomized, double-blind, double-simulation, parallel-group, and active-controlled comparison study designed to evaluate the efficacy, safety, and dose-effect relationship of X842 capsules at different dosages for the treatment of EE in comparison with lansoprazole. The study was conducted at 15 sites in China between January 2019 and December 2020. The protocol was approved by the Institutional Review Board of each study site (SND-X842-201). The study was conducted in accordance with Good Clinical Practice and in strict compliance with the ethical guidelines of the Declaration of Helsinki for human medical research. This trial was registered at ClinicalTrials.gov with the identifier NCT04531475.

Participants

Male or female patients aged between 18 and 75 years with endoscopically diagnosed EE from Los Angeles (LA) Grades A to D were eligible for inclusion in this study. The patients with LA grade A were included in no more than 60% of the total study population. The main exclusion criteria included receiving X842 capsules or other P-CAB drugs in previous clinical trials. All detailed inclusion and exclusion criteria are listed in Table S1 (http://links.lww.com/CTG/B276). All patients fully understood the contents of the study, participated in the trial voluntarily, and signed the informed consent forms.

Randomization and masking

This study adopted the method of stratified block randomization and used the Interactive Web Response System to complete the

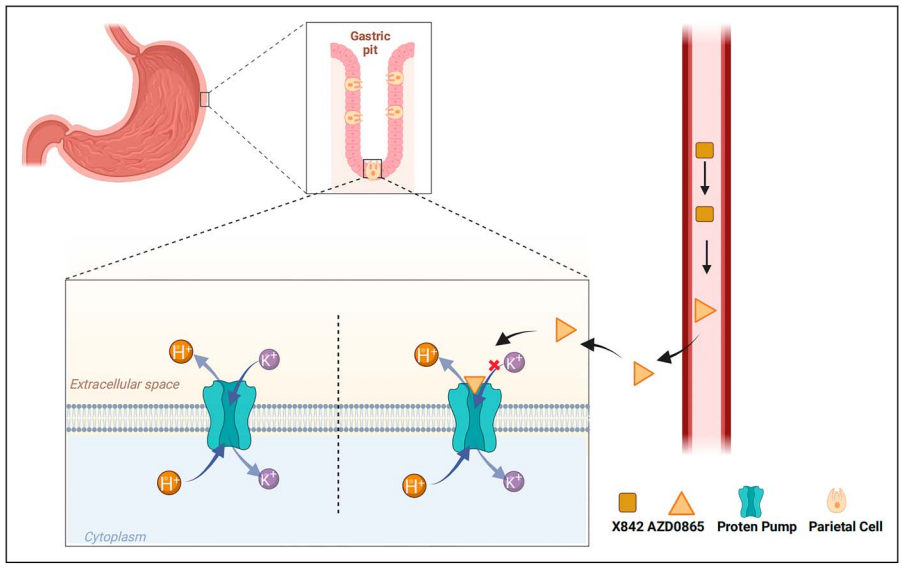

Figure 1. Mechanism of X842. After oral administration, X842 can be converted to the active metabolite linaprazan (AZD0865) by enzymes present in the bloodstream. On aggregation in the mural cell acid-excreting tubules, it reversibly inhibits the H+-K+-ATPase on the gastric mural cells in a potassium-ion-competitive manner, which, in turn, inhibits gastric acid secretion.

random allocation of patients and experimental drugs, with 30 patients in each group. The stratification factor was based on the LA grade of endoscopic esophagitis. After screening patients, researchers at each center logged on to the Interactive Web Response System to obtain subject random numbers and drug codes, and dispensed experimental drugs based on the drug codes. We use double-blind and double-simulation techniques. The physical appearance, shape, specification, and dosage of the test drug and comparator as well as the placebo were generally similar. After database locking and confirmation of statistical analysis plan, the first unblinding was performed to determine which of Group A, B, or C the case belongs to. After the finalization of the statistical analysis report, the second unblinding was conducted to determine what Group A, B, and C actually were.

Study procedures

A total of 4 visits were scheduled during the study: at the start of the screening period (visit 1), at the start of the treatment phase after randomization (visit 2), 2 weeks (visit 3) after treatment, and 4 weeks (visit 4) after treatment. During the screening period (−14 days to 0 days), demographic and other baseline characteristics of the patients were collected and recorded. After completing the relevant laboratory tests and endoscopic examinations at screening, patients were randomly assigned to the X842 50 mg group, X842 100 mg group, or lansoprazole 30 mg group for 4 weeks of treatment. All patients maintained daily diaries to record erosive esophageal symptoms. Treatment-emergent adverse events (TEAEs) and treatment compliance were also assessed and recorded. At the second week after treatment, routine blood examination, blood biochemistry, urinalysis, and electrocardiogram were performed. Laboratory tests, serum gastrin, and electronic gastroscopy were evaluated at week 4 or at the time of early withdrawal. The gastroesophageal reflux disease questionnaire (Gerd-Q) was used to assess symptoms at baseline, week 2, and week 4.

Evaluation criteria

The primary end point was the EE healing rate, defined as the proportion of patients with endoscopically confirmed healing of the EE after 4 weeks of treatment. The secondary pharmacodynamic end points were as follows: (i) the proportion of patients whose EE LA grade decreased by ≥1, as confirmed by endoscopy after 4 weeks of treatment; (ii) the changes in the Gerd-Q score after 2 and 4 weeks of treatment compared with the baseline; (iii) after 2 and 4 weeks of treatment, the proportion of patients whose heartburn symptoms disappeared and the proportion of patients whose acid reflux symptoms disappeared; (iv) the disappearance time of a single symptom of heartburn and acid regurgitation; and (v) the changes in serum gastrin after 4 weeks of treatment compared with the baseline. Safety assessment indicators included vital signs, physical examination, routine blood tests, blood biochemistry, routine urine tests, and electrocardiogram. Adverse events were classified according to severity, outcome, and relationship to the investigational drug.

Sample size and statistical analysis

The sample size was determined according to the primary end point. Based on previous studies, the sample size was estimated, assuming that the complete healing rate of mucosal breaks was 84% at week 4 after treatment with X842 and 30 mg lansoprazole. According to this threshold parameter, the sample size was at least 29 patients per treatment group using the following conditions: noninferiority margin of 0.21, a 1-sided significance level of 5%, 80% statistical power, and 1:1:1 randomization.

Primary and secondary efficacy end points were analyzed using the intention-to-treat (ITT, defined as patients who received at least one dose of study medication after randomization according to the intention-to-treat principle) analysis and the per-protocol (PP, defined as patients with an evaluable primary end point who were randomized to study treatment, completed study treatment, and had no major protocol deviation) analysis. The safety end point was analyzed using the safety set, defined as registered patients who received the study medication at least once.

Continuous variables are described by the mean, median, SD, maximum, and minimum. Categorical variables are summarized as frequencies and percentages. The Clopper-Pearson method was used to calculate 95% confidence intervals (CIs), and the Cochran-Mantel-Haenszel test was used for differences among groups. The time to symptom resolution was measured using the Kaplan-Meier method. A significant difference was set at $P < 0.05$. All the statistical analyses were performed with SAS release 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Study subjects

A total of 118 patients were screened, and 90 patients met the study entry criteria and were randomized to 3 treatment arms: X842 50 mg/d (n = 31), X842 100 mg/d (n = 29), and lansoprazole 30 mg/d (n = 30). All enrolled patients (n = 90) were treated with the respective drugs according to the protocol and were included in the ITT analysis and safety set. A total of 88 patients (97.8%) completed the 4-week, double-blind treatment phase (one patient assigned to the X842 100 mg/d group was withdrawn due to adverse events; one patient assigned to the lansoprazole 30 mg/d group withdrew consent). Among this population, 85 patients (31 in the 50 mg/d X842 group, 26 in the 100 mg/d X842 group, and 28 in the 30 mg/d lansoprazole group) had no major protocol deviation and were included in the PP analysis (Figure 2).

The baseline clinicopathological characteristics of the patients are depicted in Table 1. No significant differences in baseline characteristics were observed among the treatment groups.

Efficacy analysis

The primary end point. ITT analysis revealed that the EE healing rates at 4 weeks were 93.6% (29/31; 95% CI: 78.6%–99.2%), 79.3% (23/29; 95% CI: 60.3%–92.0%), and 80.0% (24/30; 95% CI: 61.4%–92.3%) for the 50 mg X842 group, the 100 mg X842 group, and the 30 mg lansoprazole group, respectively. No significant differences were observed among the 3 groups ($P = 0.2351$). In the PP analysis, the EE healing rates at 4 weeks were 93.6% (29/31; 95% CI: 78.6%–99.2%), 80.8% (21/26; 95% CI: 60.7%–93.5%), and 82.1% (23/28; 95% CI: 63.1%–93.9%) in the X842 50 mg, X842 100 mg, and lansoprazole groups, respectively. The PP analysis also revealed no significant difference in the EE healing rates at 4 weeks among the 3 groups ($P = 0.3320$) (Figure 3).

The secondary end points. Regarding the proportion of patients with a ≥1 grade reduction in EE LA after 4 weeks of treatment, the proportions of patients in the low-dose X842 group, high-dose X842 group, and lansoprazole group were 100.0% (31/31; 95% CI: 88.8%–100.0%), 96.55% (28/29; 95% CI: 82.2%–99.9%), and

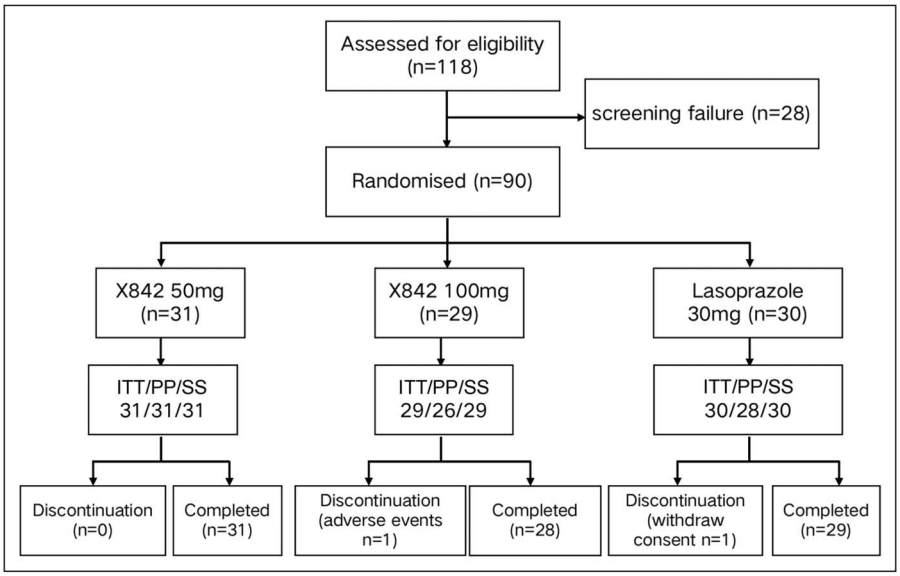

Figure 2. Flow diagram showing progression through. ITT, intention-to-treat analysis; PP, per-protocol analysis; SS, safety analysis set.

96.7% (29/30; 95% CI: 82.8%–99.9%), respectively, and no significant difference was identified among the 3 groups (P = 0.5429). The results of the PP analysis were consistent with those of the ITT (P = 0.2725).

The changes in the Gerd-Q scores from baseline at weeks 2 and 4 of treatment are presented in Table 2. After 2 and 4 weeks of treatment, the symptom scores and total Gerd-Q scores were significantly lower in all 3 groups than at baseline. However, there was no statistically significant difference in the decrease in the Gerd-Q score among the 3 groups according to either the ITT analysis or the PP analysis.

Regarding symptom relief, 62.5%, 83.3%, and 71.4% of the patients in the X842 50 mg, X842 100 mg, and lansoprazole groups, respectively, reported that their heartburn symptoms had disappeared at week 2 (P = 0.9550). At week 4, the percentages of patients who experienced heartburn symptom resolution were 68.8%, 83.3%, and 76.2%, respectively (Figure 4) (P = 0.6217). At week 2, 78.6%, 69.2%, and 57.9% of the patients reported resolution of acid regurgitation, respectively (P = 0.7968). At week 4, 78.6%, 92.3%, and 63.2% of the patients reported resolution of acid regurgitation, respectively (P = 0.5103). The relief of heartburn and acid regurgitation was similar in the 3 treatment groups after 2 and 4 weeks of treatment, irrespective of the severity at baseline (Figure 5). For the X842 50 mg, X842 100 mg, and lansoprazole groups, the median duration of heartburn disappearance was 1 day, 1 day, and 9 days, respectively, whereas the median duration of heartburn disappearance was 1 day, 1 day, and 11 days, respectively. However, the difference between any 2 groups was not statistically significant (P = 0.2379).

After 4 weeks of treatment, the serum gastrin levels increased in the X842 low-dose group, X842 high-dose group, and lansoprazole group by 0.731 ± 24.066 pg/mL, 14.043 ± 26.607 pg/mL, and 9.973 ± 20.017 pg/mL, respectively, compared with their initial values. No significant differences were found among the 3 groups (P = 0.0906). The serum gastrin levels of all patients in the X842 low-dose group and lansoprazole group were within the normal range (28.1–106.5 pg/mL) at week 4. However, the serum gastrin levels of 14.3% (4/29) of the patients in the high-dose group exceeded the upper limit of the normal value.

Subgroup analysis of efficacy. In patients with baseline LA classification B/C/D, ITT analysis showed that EE healing rates with X842 50 mg were tended to be higher than the other 2 groups at week 4 (X842 50 mg vs X842 100 mg vs lansoprazole = 100.0% [14/14] vs 81.8% [9/11] vs 84.6% [11/13], P = 0.089). However, the difference has not yet reached a statistically significant

Table 1. Demographic information and baseline characteristics

	X842 50 mg group (N = 31)	X842 100 mg group (N = 29)	Lansoprazole group (N = 30)	*P* value
Age, mean (SD), yr	47.42 (13.18)	47.93 (11.61)	46.97 (13.78)	0.9597
Gender (male/female)	25/6	27/2	23/7	0.2110
Height, mean (SD), cm	167.29 (7.00)	169.60 (6.11)	166.77 (6.64)	0.2205
Weight, mean (SD), kg	69.56 (10.41)	72.03 (9.08)	66.63 (9.60)	0.1082
Baseline LA grade (A, B, C, D)	14/14/3/0	11/15/3/0	13/14/3/0	0.8713
Gerd-Q scores, mean (SD)	7.55 (2.25)	7.03 (2.65)	7.80 (3.18)	0.5470
Serum gastrin, mean (SD), pg/mL	57.141 (17.251)	57.818 (19.073)	55.725 (15.724)	0.8942

Gerd-Q, gastroesophageal reflux disease questionnaire; LA, Los Angeles; N, number of patients.

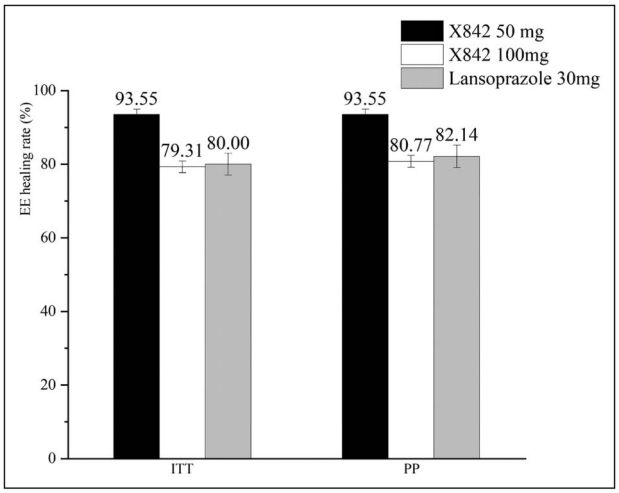

Figure 3. EE healing rate during the 4-week treatment period in the X842 50 mg group, the X842 100 mg group, and the lansoprazole group. EE, erosive esophagitis; ITT, intention-to-treat analysis; PP, per-protocol analysis.

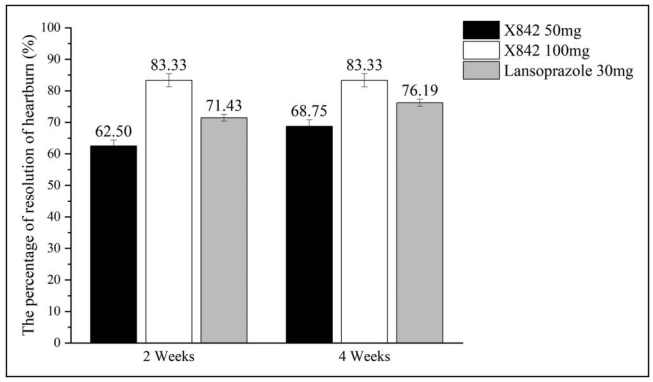

Figure 4. The percentage of resolution of heartburn during the 2-week and 4-week treatment in the X842 50 mg group, the X842 100 mg group, and the lansoprazole group.

difference. In patients with baseline LA classification A, EE healing rates at week 4 were comparable between 3 groups (X842 50 mg vs X842 100 mg vs lansoprazole = 88.2% [15/17] vs 77.8% [14/18] vs 76.5% [13/17], $P = 0.898$). PP analysis demonstrated similar results as ITT analysis.

Safety analysis

Among the 90 patients, 97 TEAEs were reported in 53 patients (Table 3). The percentages of drug-related TEAEs were 19.4% (6/31, 8 events) in the 50 mg X842 group, 34.5% (10/29, 16 events) in the 100 mg X842 group, and 36.7% (11/30, 15 events) in the 30 mg lansoprazole group. One serious TEAE was reported in the 50 mg X842 group, and one was reported in the 30 mg lansoprazole group; however, none were causally related to the study drug treatment. No deaths occurred during the entire study. The most common TEAE in all 3 groups classified by system organ class was gastrointestinal disorders; the incidence rates were 19.4% (6/31) for 50 mg X842, 24.1% (7/29) for 100 mg X842, and 20.0% (6/30) for 30 mg lansoprazole. The details of the drug-related TEAEs are listed in Table S2 (http://links.lww.com/CTG/B277). The incidence of any TEAEs did not differ among the 50 mg X842 group, the 100 mg X842 group, or the 30 mg lansoprazole group.

DISCUSSION

This work was the first randomized, double-blind, controlled phase 2 study that evaluated the efficacy and safety of X842 in EE patients. It revealed that EE healing rates at 4 weeks were statistically similar between the lansoprazole group (30 mg q.d.) and both the X842 groups (50 and 100 mg q.d). Patients in the low-dose X842 group tended to heal faster than patients in the lansoprazole group. Similarly, the proportion of patients who experienced acid regurgitation or heartburn relief during the 2 and 4 weeks of treatment did not significantly differ between the X842 and lansoprazole treatment groups. Our findings suggest that X842 has potential as a new option for the treatment of EE in the clinical setting.

Table 2. Distribution of changes in Gerd-Q score from baseline at week 2 and 4

	X842 50 mg group (N = 31)	X842 100 mg group (N = 29)	Lansoprazole group (N = 30)	*P* value
Total Gerd-Q score change				
Week 2 after treatment—baseline, mean (SD)	−1.6 (2.4)	−1.3 (3.4)	−1.0 (3.4)	0.7424
Week 4 after treatment—baseline, mean (SD)	−0.9 (2.3)	−1.2 (3.4)	−1.1 (3.0)	0.9468
Positive symptom score change				
Week 2 after treatment—baseline, mean (SD)	−1.7 (1.9)	−1.5 (2.3)	−1.4 (1.9)	0.8525
Week 4 after treatment—baseline, mean (SD)	−1.5 (2.1)	−1.6 (2.1)	−2.1 (1.9)	0.4295
Negative symptom score change				
Week 2 after treatment—baseline, mean (SD)	0.8 (1.5)	0.7 (1.9)	1.0 (2.3)	0.8206
Week 4 after treatment—baseline, mean (SD)	1.2 (1.8)	0.8 (2.0)	1.7 (1.9)	0.2244
Positive impact score change				
Week 2 after treatment—baseline, mean (SD)	−0.7 (1.0)	−0.4 (0.7)	−0.5 (0.9)	0.5109
Week 4 after treatment—baseline, mean (SD)	−0.6 (1.1)	−0.4 (0.9)	−0.7 (1.0)	0.5151

Gerd-Q, gastroesophageal reflux disease questionnaire; N, number of patients.

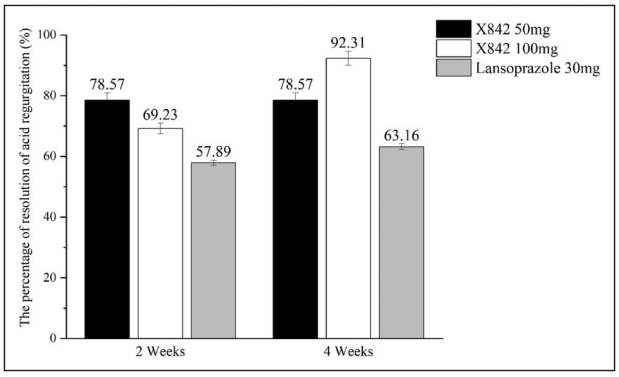

Figure 5. The percentage of resolution of acid regurgitation during the 2-week and 4-week treatment in the X842 50 mg group, the X842 100 mg group, and the lansoprazole group.

P-CABs are emerging as novel treatments of acid-related disorders. Previous studies have shown that P-CAB-based triple therapy is more effective than PPI-based triple therapy as a first-line *H. pylori* eradication treatment (23). Daisuke Asaoka et al identified the potential of P-CAB as a new therapeutic agent for GERD (24). Several types of P-CABs have been developed to date. Revaprazan (YH-1885) was the first P-CAB used in clinical practice. However, the acid suppression effect of revaprazan was not superior to that of conventional PPIs. The pH $>$ 4 holding time of the dose of revaprazan (200 mg) selected for clinical use was less than 12 hours (25), which was similar or even inferior to the value reported for conventional PPIs. The second P-CAB in clinical use is vonoprazan fumarate (TAK-438). Compared with conventional PPIs, it has become the most widely used P-CAB due to its rapid onset and longer duration of action, sustained acid inhibition independent of CYP2C19, and stronger acid inhibition. A number of multicenter clinical trials evaluating the efficacy and safety of vonoprazan in GERD therapy have been conducted. The endoscopic healing rate of vonoprazan-induced erosive esophagitis at 8 weeks after the administration of vonoprazan at a dose of 20 mg once daily was 92.4%–99.0% (26–28), which was not inferior to that of lansoprazole. Tegoprazan (CJ-12420) was approved for the treatment of EE by the Ministry of Food and Drug Safety of South Korea in July 2018. A randomized, double-blind, placebo-controlled phase I clinical trial showed that tegoprazan was well tolerated and exhibited rapid and potent gastric acid suppression (29). Once daily tegoprazan 50 or 100 mg showed noninferior efficacy to esomeprazole 40 mg in healing EE (30). Fexuprazan (DWP-14012) and keverprazan (KFP-H008) are the latest P-CABs developed and approved for marketing. One phase III clinical trial of fexuprazan for treating EE showed a esophageal mucosal healing rate of 99.1% at week 8, and fexuprazan was well tolerated. In addition, fexuprazan resulted in faster and better resolution of moderate-to-severe symptoms than esomeprazole (31). Another phase III multicenter study demonstrated the noninferior efficacy of keverprazan to lansoprazole in treating EE (32). Our results will greatly advance the acid inhibition revolution and promote the commercialization of X842 as a new type of P-CAB in Asia.

Symptom relief is another, perhaps more important, end point in GERD treatment. A previous randomized controlled trial from Japan indicated that complete sustained heartburn relief was achieved sooner with vonoprazan than with lansoprazole (33). In our study, patients in the 2 X842 groups had earlier resolution of acid regurgitation and heartburn than those in the lansoprazole group, although the difference has not yet reached statistical significance. Currently, the degree of reflux reduction or acid suppression needed to produce a clinically significant improvement in GERD symptoms is unclear. The evaluation of treatment response in patients with GERD warrants more comprehensive symptom assessment than simply quantifying acid regurgitation or heartburn. Therefore, our study also compared the changes in the Gerd-Q score after treatment among the 3 groups of patients. Encouragingly, the reduction in the Gerd-Q score was similar across the 3 groups, providing strong evidence for the effectiveness of X842.

The safety of P-CAB is a point of concern in clinical practice. In this study, all therapies were well tolerated, and the incidences

Table 3. Summary of treatment-emergent adverse events (TEAEs) (SS)

	X842 50 mg group (N = 31)			X842 100 mg group (N = 29)			Lansoprazole group (N = 30)			
	Time of cases	Number of cases	Incidence rate (%)	Time of cases	Number of cases	Incidence rate (%)	Time of cases	Number of cases	Incidence rate (%)	*P* value
TEAEs	28	16	51.6	34	18	62.1	35	19	63.3	0.6171
Drug-related TEAEs	8	6	19.4	16	10	34.5	15	11	36.7	0.2640
Severe TEAEs	1	1	3.2	0	0	0.0	1	1	3.3	1.0000
Drug-related severe TEAEs	0	0	0.0	0	0	0.0	0	0	0.0	1.0000
Serious TEAEs	0	0	0.0	1	1	3.5	1	1	3.3	0.5433
Drug-related serious TEAEs	0	0	0.0	1	1	3.5	1	1	3.3	0.5433
TEAEs leading to exit	0	0	0.0	1	1	3.5	0	0	0.0	0.3222
Drug-related TEAEs leading to exit	0	0	0.0	1	1	3.5	0	0	0.0	0.3222
TEAEs leading to death	0	0	0.0	0	0	0.0	0	0	0.0	1.0000

N, number of patients; SS, safe analysis set; TEAEs, treatment-emergent adverse events.

of drug-related TEAEs were similar between the X842 group (both doses) and the lansoprazole group. No serious drug-related adverse events occurred in the 2 X842 groups. Similar to SCH28080, the ancestor of P-CABs in the early 1980s (34), X842 still has the classical imidazopyridine structure, which can be combined with the E2 or E2-P structure of the proton-pump and can exert acid inhibition without activation of the proton pump. X842 can be quickly metabolized into the active metabolite linaprazan (AZD0865) *in vivo* without obvious hepatotoxicity. Furthermore, a number of previous studies have reported that P-CABs inevitably induce hypergastrinemia in patients treated with vonoprazan (27,35) due to its sulfopyrrole structure, which has a high pKa. Careful monitoring for endocrine cell hyperplasia and potential development of endocrine cell tumors may be necessary when continuous use of vonoprazan is needed. Reassuringly, patients receiving X842 not only exhibited ideal acid suppression but also did not exhibit extreme increases in serum gastrin levels in our study. Indeed, patients in the X842 low-dose group all had serum gastrin levels within the normal range.

Our study was subject to several limitations. First, the study was conducted only at Chinese institutions, and the number of patients was small. A larger-scale, multinational confirmatory trial will be needed to generalize the findings to a broader spectrum of populations, and increasing the sample size might be powered to obtain a significant difference. Second, the number of patients with high-grade esophagitis was relatively small in this study. Although the reflux burden is relatively low in Asian countries, with high-grade esophagitis accounting for 1%–13% of esophagitis (36–38), the therapeutic efficacy of X842 in high-grade esophagitis deserves to be continued to be explored in subsequent trials, which have great clinical significance. Third, *H. pylori* status was not evaluated in this study, which might have an impact on the EE grade and the state of esophageal mucosal healing. In addition, only short-term effects were evaluated, and EE patients did not receive maintenance treatment in this study. The efficacy and safety of X842, in the long run, need to be clarified. Despite these limitations, the results of this study could facilitate the clinical application of P-CABs and expand the choice of clinical acid-suppressing drugs, as well as provide a basis for the clinical use and dosage selection of X842.

In summary, this comparative study demonstrated that X842 had efficacy and a favorable safety profile similar to those of lansoprazole. Therefore, X842, a novel P-CAB, is expected to become a promising therapeutic agent for EE. The encouraging results provided in this study support further investigation of the full therapeutic potential of X842 in patients with GERD. X842 is highly likely to become an important drug for the treatment of GERD in the future and is even expected to have a potential role as a first-line therapy.

CONFLICTS OF INTEREST

Guarantor of the article: Yongdong Wu, MD.

Specific author contributions: Y.W., S.Z., and S.Z. designed the study. S.Z., M.H., Y.Z., F.M., and other authors were involved in patient enrolment and performing the study. S.Z. and M.H. analyzed the data and interpreted the results. M.H. wrote the manuscript. S.Z. was involved in the drafting of the manuscript and critical revision of the manuscript. All authors approved the final version of the manuscript.

Financial support: This work was funded by Jiangsu Sinorda Biomedicine Co., Ltd., and was partially financially supported by a grant from the National Natural Science Foundation of China [grant number 81600432].

Potential competing interests: None to report.

IRB approval statement: The study protocol was approved by the State Food and Drug Administration and was approved by the ethics committee of each study site. URL: https://clinicaltrials.gov/study/NCT04531475.

Trial identification number: NCT04531475.

ACKNOWLEDGEMENTS

We acknowledge the investigators and patients who participated in this study. We acknowledge Jiangsu Sinorda Biomedicine Co., Ltd., for providing the investigational drug (X842).

Study Highlights

WHAT IS KNOWN

- ✓ Gastric acid inhibition is pivotal for the successful treatment of erosive esophagitis.
- ✓ Both potassium-competitive acid blockers and proton-pump inhibitors have potent acid inhibition effects.

WHAT IS NEW HERE

- ✓ X842 (a novel potassium-competitive acid blockers) was noninferior to lansoprazole for erosive esophagitis healing with a good safety profile.
- ✓ There was no statistically significant difference in the efficacy of X842 50 mg once daily dose and X842 100 mg once daily dose in erosive esophagitis.

REFERENCES

1. Vakil N, van Zanten SV, Kahrilas P, et al., Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. Am J Gastroenterol 2006;101(8):1900–43.
2. Iwakiri K, Fujiwara Y, Manabe N, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2021. J Gastroenterol 2022;57(4):267–85.
3. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: A systematic review. Gut 2014;63(6):871–80.
4. Ness-Jensen E, Lindam A, Lagergren J, et al. Changes in prevalence, incidence and spontaneous loss of gastro-oesophageal reflux symptoms: A prospective population-based cohort study, the HUNT study. Gut 2012;61(10):1390–7.
5. Eusebi LH, Ratnakumaran R, Yuan Y, et al. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: A meta-analysis. Gut 2018;67(3):430–40.
6. Fass R, Boeckxstaens GE, El-Serag H, et al. Gastro-oesophageal reflux disease. Nat Rev Dis Primers 2021;7(1):55.
7. Moraes-Filho JP, Pedroso M, Quigley EM; PAMES Study Group. Randomised clinical trial: Daily pantoprazole magnesium 40 mg vs. esomeprazole 40 mg for gastro-oesophageal reflux disease, assessed by endoscopy and symptoms. Aliment Pharmacol Ther 2014;39(1):47–56.
8. Iwakiri K, Kinoshita Y, Habu Y, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. J Gastroenterol 2016;51(8):751–67.
9. Boeckxstaens G, El-Serag HB, Smout AJ, et al. Symptomatic reflux disease: The present, the past and the future. Gut 2014;63(7):1185–93.
10. Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: Understanding the complications and risks. Nat Rev Gastroenterol Hepatol 2017;14(12):697–710.
11. Strand DS, Kim D, Peura DA. 25 Years of proton pump inhibitors: A comprehensive review. Gut Liver 2017;11(1):27–37.

12. Morelli G, Chen H, Rossiter G, et al. An open-label, parallel, multiple-dose study comparing the pharmacokinetics and gastric acid suppression of rabeprazole extended-release with esomeprazole 40 mg and rabeprazole delayed-release 20 mg in healthy volunteers. Aliment Pharmacol Ther 2011;33(7):845–54.
13. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease[published correction appears in *Am J Gastroenterol*. 2013 Oct;108(10):1672]. Am J Gastroenterol 2013;108(3):308–29.
14. Shahabi P, Siest G, Meyer UA, et al. Human cytochrome P450 epoxygenases: Variability in expression and role in inflammation-related disorders. Pharmacol Ther 2014;144(2):134–61.
15. Kagawa T, Iwamuro M, Ishikawa S, et al. Vonoprazan prevents bleeding from endoscopic submucosal dissection-induced gastric ulcers. Aliment Pharmacol Ther 2016;44(6):583–91.
16. Lee HA, Lee KR, Jang SB, et al. A physiologically-based pharmacokinetic model adequately predicted the human pharmacokinetic profiles of YH4808, a novel K^+-competitive acid blocker. Eur J Pharm Sci 2019;130:1–10.
17. Garnock-Jones KP. Vonoprazan: First global approval. Drugs 2015;75(4): 439–43.
18. Takahashi N, Take Y. Tegoprazan, a novel potassium-competitive acid blocker to control gastric acid secretion and motility. J Pharmacol Exp Ther 2018;364(2):275–86.
19. Ramani A, Merchant A, Cash BD. Review of the clinical development of fexuprazan for gastroesophageal reflux-related disease. Eur J Clin Pharmacol 2023;79(8):1023–9.
20. Kang C. Keverprazan hydrochloride: First approval. Drugs 2023;83(7): 639–43.
21. Gedda K, Briving C, Svensson K, et al. Mechanism of action of AZD0865, a K+-competitive inhibitor of gastric H+,K+-ATPase. Biochem Pharmacol 2007;73(2):198–205.
22. Dent J, Kahrilas PJ, Hatlebakk J, et al. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. Am J Gastroenterol 2008;103(1):20–6.
23. Suzuki S, Gotoda T, Kusano C, et al. The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-Day PPI-based low-dose clarithromycin triple therapy. Am J Gastroenterol 2016;111(7):949–56.
24. Asaoka D, Nagahara A, Hojo M, et al. Efficacy of a potassium-competitive acid blocker for improving symptoms in patients with reflux esophagitis, non-erosive reflux disease, and functional dyspepsia. Biomed Rep 2017;6(2):175–80.
25. Kim HK, Park SH, Cheung DY, et al. Clinical trial: Inhibitory effect of revaprazan on gastric acid secretion in healthy male subjects. J Gastroenterol Hepatol 2010;25(10):1618–25.
26. Ashida K, Sakurai Y, Nishimura A, et al. Randomised clinical trial: A dose-ranging study of vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the treatment of erosive oesophagitis. Aliment Pharmacol Ther 2015;42(6):685–95.
27. Ashida K, Sakurai Y, Hori T, et al. Randomised clinical trial: Vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. Aliment Pharmacol Ther 2016;43(2): 240–51.
28. 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(2):224–30.
29. Han S, Choi HY, Kim YH, et al. Randomised clinical trial: Safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple oral doses of tegoprazan (CJ-12420), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther 2019;50(7):751–9.
30. 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(7):864–72.
31. Lee KN, Lee OY, Chun HJ, et al. Randomized controlled trial to evaluate the efficacy and safety of fexuprazan compared with esomeprazole in erosive esophagitis. World J Gastroenterol 2022;28(44):6294–309.
32. Chen S, Liu D, Chen H, et al. The efficacy and safety of keverprazan, a novel potassium-competitive acid blocker, in treating erosive oesophagitis: A phase III, randomised, double-blind multicentre study. Aliment Pharmacol Ther 2022;55(12):1524–33.
33. 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(2):140–6.
34. Ene MD, Khan-Daneshmend T, Roberts CJ. A study of the inhibitory effects of SCH 28080 on gastric secretion in man. Br J Pharmacol 1982; 76(3):389–91.
35. Iwakiri K, Sakurai Y, Shiino M, et al. A randomized, double-blind study to evaluate the acid-inhibitory effect of vonoprazan (20 mg and 40 mg) in patients with proton-pump inhibitor-resistant erosive esophagitis. Therap Adv Gastroenterol 2017;10(6):439–51.
36. Jung HK, Tae CH, Song KH, et al. 2020 Seoul consensus on the diagnosis and management of gastroesophageal reflux disease. J Neurogastroenterol Motil 2021;27(4):453–81.
37. Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. J Gastroenterol 2009;44(6):518–34.
38. Zhang M, Tan N, Li Y, et al. Esophageal physiologic profiles within erosive esophagitis in China: Predominantly low-grade esophagitis with low reflux burden. Neurogastroenterol Motil 2019;31(12):e13702.