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Efficacy and Safety Profile of Z-215 (Azeloprazole Sodium), a Proton Pump Inhibitor, Compared with Rabeprazole Sodium in Patients with Reflux Esophagitis: A Phase II, Multicenter, Randomized, Double-Blind, Comparative Study

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ABSTRACT

Background: The metabolism of many proton pump inhibitors is influenced by CYP2C19 genotype, which is a limitation of their use.
Objectives: To determine the efficacy and safety profile of Z-215 (azeloprazole sodium) as initial treatment for reflux esophagitis (RE), dose response, and optimal dose compared with rabeprazole sodium (RPZ).
Methods: We conducted an exploratory, multicenter, randomized, double-blind, parallel-group study in Japan. Patients with RE aged ≥20 years were enrolled and randomly assigned to receive 10, 20, or 40 mg Z-215 or 10 mg RPZ (1:1:1:1), and orally administered the respective drug for 8 weeks. The primary efficacy end point was the endoscopic healing rate after 8 weeks of treatment (at Week 8). We also assessed the effects of CYP2C19 genotype. Safety end points were the incidence of adverse events and adverse drug reactions.
Results: Five hundred three patients received the study drugs (10 mg Z-215: 125 patients, 20 mg Z-215: 126 patients, 40 mg Z-215: 126 patients, and 10 mg RPZ: 126 patients). The endoscopic healing rate at Week 8 was above 95% in all groups (10 mg Z-215: 95.2%, 20 mg Z-215: 96.8%, 40 mg Z-215: 95.2%, and 10 mg RPZ: 96.8%). The endoscopic healing rate and serum gastrin levels of the Z-215 groups were not influenced by CYP2C19 genotype. In patients with Grade C/D, the endoscopic healing rate at Week 4 was slightly higher in the 40-mg Z-215 group compared with the other groups. Incidences of adverse events/adverse drug reactions did not markedly differ between the Z-215 and 10-mg RPZ groups.
Conclusions: Z-215 was as effective and well tolerated as 10 mg RPZ in the treatment of RE in this selected population. CYP2C19 genotype status may not influence the efficacy and safety of Z-215. There were no clear dose–response effects between Z-215 doses in the endoscopic healing of RE. These findings suggest that Z-215 may be 1 option for the initial treatment of RE. ClinicalTrials.gov identifier: NCT 02463643.

Introduction

Proton pump inhibitors (PPIs), which irreversibly bind to proton pumps in parietal cells to potently suppress gastric acid secretion, are first-line drugs for acid-related diseases, such as gastroesophageal reflux disease (GERD).[1,2] Reflux esophagitis (RE), a type of GERD, is accompanied by esophageal mucosal injury, and some patients exhibit troublesome symptoms such as heartburn

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and acid reflux. In Japan, the number of patients with GERD has increased due to factors such as increasing gastric acid secretion resulting from changes in dietary habits and lower *Helicobacter pylori* infection rates.[3,4] PPIs do not sufficiently suppress gastric acid secretion in all patients. One factor responsible for the difference in efficacy is CYP2C19 genotype.[2,5,6] Most existing PPIs are predominantly metabolized by CYP2C19, which is known to have low enzyme activity due to genetic polymorphisms.[2,6–8] For this reason, differences in plasma drug concentration and suppression of gastric acid secretion are observed between extensive metabolizers (EMs) and poor metabolizers (PMs), which have high and low metabolic activity, respectively. Because the proportion of PMs is high, especially throughout Asia, including Japan, CYP2C19 genotype is a major determinant of differences in drug efficacy.[8,9] Further, combination therapy with PPIs may be difficult due to drug–drug interactions, especially if the other drug is metabolized by CYP2C19.[2,6–8]

Z-215 (azeloprazole sodium; also known as E3710)[10] is an orally administered PPI that is primarily metabolized by CYP3A4[11] and is unaffected by CYP2C19 genotype. In nonclinical studies, a single intraduodenal dose of Z-215 into the gastric fistula of dogs inhibited histamine-induced gastric acid secretion more than twice as potently as esomeprazole (EPZ).[10] Previous clinical studies have confirmed the safety profile and tolerability of Z-215 up to 540 mg in a single dose study to healthy subjects and up to 180 mg in a multiple dose study to patients with *H. pylori*-negative symptomatic GERD (unpublished findings). In another study, repeated administration of 10, 20, and 40 mg Z-215 to healthy Japanese men showed that the intragastric pH ≥4 holding time ratio (HTR) was dose-dependent. In addition, pH ≥4 HTR on the fifth day of administration was approximately 8% higher in the 40-mg Z-215 group than in the 10-mg rabeprazole sodium (RPZ) group (40 mg Z-215: 72.4%, 10 mg RPZ: 64.4%). Furthermore, the pH ≥4 HTR of Z-215 was not influenced by CYP2C19 genotype.[12] Because PPIs that are not influenced by CYP2C19 genotype are rare, Z-215 represents a new type of initial treatment option that is efficacious and safe for all patients.

Here, to better understand the pharmacologic characteristics of Z-215, we conducted a Phase II clinical study to determine its efficacy, safety profile in initial treatment for RE, as well as dose response, and optimal dose. In addition, to identify differences in efficacy and safety by CYP2C19 genotype status, we included RE patients of all CYP2C19 genotypes. RPZ at 10 mg/day was used for comparison.

Methods

Study design

This was an exploratory, multicenter, randomized, double-blind, active drug control, parallel-group study conducted at 48 sites in Japan. All sites were considered and approved as suitable for participation by the institutional review board before the start of the study. This study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice guidelines. Written informed consent was obtained from all patients before study initiation. The study sponsor paid all study drug expenses, as well as all examination and diagnostic imaging expenses within the study period. The patients and their insurance paid for the remaining medical expenses under Japanese health insurance.

Participants

Eligible patients were recruited from June 2015 to March 2016. Adult RE patients assessed as Grade A through D according to the modified Los Angeles classification[13] and aged 20 years or older at the time that written informed consent was obtained were enrolled in this study. We ensured that at least 20% of the sample size was composed of patients with Grade C/D. The major exclusion criteria were as follows: presence of coexisting or previous history of eosinophilic esophagitis, systemic scleroderma, esophageal varices, esophageal stricture, long-segment Barrett's esophagus, or high-grade dysplasia; presence of upper gastrointestinal bleeding, gastric ulcer, or duodenal ulcer within 28 days before the screening period; presence of excessive gastric acid secretion such as due to Zollinger-Ellison syndrome; presence of a history of esophagus, stomach, or duodenal surgery; receipt of any PPI within 14 days before the screening period; receipt of any drugs for RE within 7 days before the screening period; PPI resistance; presence of severe disease; history of allergy to PPIs; undergoing treatment for a malignant tumor or follow-up duration ≤5 years before the screening period; and pregnancy or nursing.

Control group

For the control group, RPZ at 10 mg/day was used. RPZ[14] is a PPI used globally to treat acid-related diseases and has low susceptibility to CYP2C19 genetic polymorphisms.[15] The standard dose of RPZ for initial treatment of RE in Japan is 10 mg/day.[16]

Randomization, blinding, and intervention

Patients who were judged to be eligible during the screening period (baseline: maximum 3 weeks) were randomly assigned to 10, 20, or 40 mg Z-215 and 10 mg RPZ (Eisai, Tokyo, Japan) groups such that the ratio of patients was 1:1:1:1. The patients were dynamically and stochastically assigned to their groups using central registration. The allocation factors were treatment history for RE (with or without) and modified Los Angeles classification (Grade A/B or Grade C/D) assessed by the investigator at baseline. Dynamic allocation was first performed according to the number of patients assigned to each group in each site followed sequentially by each of the above allocation factors until all patients were grouped. Information on the allocation factors was transmitted from each site to the registration center using a preset algorithm.

Patients were orally administered the study drugs once a day within about 30 minutes after breakfast for 8 weeks. The study drugs were prepared such that the Z-215 10-mg capsule, Z-215 20-mg capsule, and Z-215 placebo capsule were indistinguishable in appearance from each other. This was because the Z-215 10-mg and 20-mg capsules contain different amounts of active ingredient but have the same size and appearance, and the 10-mg RPZ tablet was indistinguishable in appearance from the RPZ placebo tablet. Following the double-dummy method, patients in the 10-mg Z-215 group were administered a Z-215 10-mg capsule, a Z-215 placebo capsule, and an RPZ placebo tablet; patients in the 20-mg Z-215 group were administered a Z-215 20-mg capsule, a Z-215 placebo capsule, and an RPZ placebo tablet; patients in the 40-mg Z-215 group were administered 2 Z-215 20-mg capsules and an RPZ placebo tablet; and patients in the 10-mg RPZ group were administered 2 Z-215 placebo capsules and a 10-mg RPZ tablet. Concomitant medicines are frequently taken after meals; the study drugs were taken together with these after breakfast to ensure high compliance. Compliance was assessed using diaries recorded by each patient and by counting the number of study drugs returned. The participating sites, patients, sponsors, and members of the Independent Adjudication Committee (IAC) were blinded to the administration information and gastrin levels of all patients. Information regarding administration group and serum gastrin level was secured by the allocation manager and the central laboratory, respectively, until the key codes were broken.

Patients visited the study site at baseline, 2 weeks after the initiation of treatment (Week 2), and at Week 4 and Week 8. Endoscopy was performed at baseline, Week 4, and Week 8. Patients whose mucosal break had healed (Grade N/M; that is, absence of mucosal breaks) at Week 4 were permitted to terminate the study at that time. Laboratory tests (eg, hematology, biochemistry, qualitative urine, serum gastrin, and thyroid function) were performed at each visit by the central laboratory (SRL Inc, Tokyo, Japan). CYP2C19 genotype and *H. pylori* antibody blood tests were performed at baseline by the same central laboratory. Because all tests were performed by the same central laboratory, quality control was also performed by this laboratory.

During the study period, drugs for RE and symptom improvement, CYP3A4 inhibitor/inducers, and bisphosphonate drugs were prohibited. However, patients who were diagnosed with Grade C/D in the past and who showed during the screening period that they could not tolerate going without treatment due to severe symptoms were allowed to take antacids until 4 days before the administration of the study drug. Surgery for RE that could influence function of the lower esophageal sphincter and/or gastric acid secretion was also prohibited.

Efficacy outcome

The primary efficacy end point was endoscopic healing rate as assessed by the investigator at Week 8. Endoscopic healing was defined as Grade N/M. The secondary efficacy end points were the endoscopic healing rate assessed by the investigator and IAC at Week 4 and that assessed by the IAC at Week 8. The IAC consisted of 3 experts in this disease field who were not affiliated with the study site and were blinded to the background, administration group, and modified Los Angeles classification grade assessed by the investigator. The IAC assessed the modified Los Angeles classification grade using endoscopic photographs. In addition, patient symptoms were evaluated using the modified frequency scale for the symptoms of GERD (FSSG) at baseline, Week 2, Week 4, and Week 8.[17]

Safety outcome

The safety end points were defined as the incidence rate of adverse events (AEs) and adverse drug reactions (ADRs) throughout the study period. Serum gastrin levels were also measured as a safety end point at each visit.

Statistical analysis

Each group consisted of 120 patients, with 480 patients in total. Because this was an exploratory study to determine the efficacy and safety of various doses of Z-215 compared with 10-mg RPZ, sample size was not determined by a statistical method. For safety profile evaluation, we used the safety analysis set (SAF), which included all administered patients except those without Good Clinical Practice compliance or safety data. For efficacy evaluation, we used the full analysis set (FAS), which included all patients included in the SAF, except those who had no efficacy evaluation data and those who did not have RE at baseline after administration of 1 of the test drugs. All statistical analyses were performed using SAS release 9.3 (SAS Institute Inc, Cary, NC).

The primary efficacy end point was determined by calculating the number of cumulative patients showing endoscopic healing assessed by the investigator at Week 8 or earlier as a proportion of the number of patients in the FAS. For the secondary efficacy end points, assessments of the endoscopic healing rate by the investigator and IAC at Week 4 and by the IAC at Week 8 were conducted using the same method as for the primary efficacy end point. Calculation of the endoscopic healing rate by the IAC excluded patients who were assessed as modified Los Angeles classification Grade N/M at baseline by the IAC. The endoscopic healing rate at Week 8, as categorized by the modified Los Angeles classification grade at baseline (assessed by the investigator and IAC) and by CYP2C19 genotype, were analyzed using the same method as for the primary efficacy end point. Furthermore, as an ad hoc analysis, the endoscopic healing rate at Week 4 categorized by modified Los Angeles classification grade at baseline (assessed by the investigator and IAC) and by CYP2C19 genotype were analyzed after key code breaking.

For the modified FSSG, the total score from 14 questions was calculated and the mean and 95% CI were calculated for each group and observation period. The exact 95% CI was used to calculate the 95% CI of the modified FSSG total score. The modified FSSG total score of patients who were healed at Week 4 were not included in the evaluation at Week 8. The improvement rate of the modified FSSG total score was calculated as follows: (Baseline total score – Score at Week 2, Week 4, or Week 8) / Baseline total score × 100 (%). The number and proportion of patients with improvement rates ≥75% and ≥50% were also calculated.

To assess the effects of CYP2C19 genotype, serum gastrin levels were categorized by CYP2C19 genotype using ad hoc analysis after key code breaking.

Results

Analysis set and demographic characteristics

Among 562 patients who gave informed consent, 42 patients were excluded according to the inclusion or exclusion criteria, and 17 patients declined to participate, leaving 503 patients who were randomly assigned to the study drug groups (**Figure 1**). The major reason that some participants have for declining to participate before randomization was opposition to participation in the study by family members. No patients were excluded from the SAF or FAS. According to the investigator's assessment at baseline (**Table 1**), patients with modified Los Angeles classification Grade A/B and C/D comprised approximately 75% and 25% of the enrolled patients, respectively. Homozygous EM and heterozygous EM patients comprised approximately 30% and 50% of each of the 10-mg and 40-mg Z-215 and 10-mg RPZ groups, respectively. The proportion of patients with heterozygous EM was 43.7% in the 20-mg Z-215 group. The proportion of PM patients was 26.2% in the 20-mg Z-215 group, which was higher than that in the other groups, where PM patients comprised approximately 15% of participants. There were no notable differences in baseline demographic characteristics among the groups. Only 1 patient in each of the 20-mg Z-215 and 10-mg RPZ groups showed remarkably low compliance rates (66.7% and 63.6%, respectively); both were withdrawn from the study.

Efficacy outcome measures

Endoscopic healing rate of RE

The endoscopic healing rate assessed by the investigator at Week 8 for the 10-, 20-, and 40-mg Z-215 and 10-mg RPZ groups was 95.2%, 96.8%, 95.2%, and 96.8%, respectively, being notably higher than 95% in all groups (**Table 2**). No statistically significant differences were observed among the Z-215 dose groups. In addition, the endoscopic healing rate assessed by the IAC at Week 8 for the 10-, 20-, and 40-mg Z-215 and 10-mg RPZ groups was 96.7%, 98.4%, 98.4%, and 96.8%, respectively, similarly reaching above 95% in all groups, with no statistically significant difference among Z-215 dose groups (data not shown).

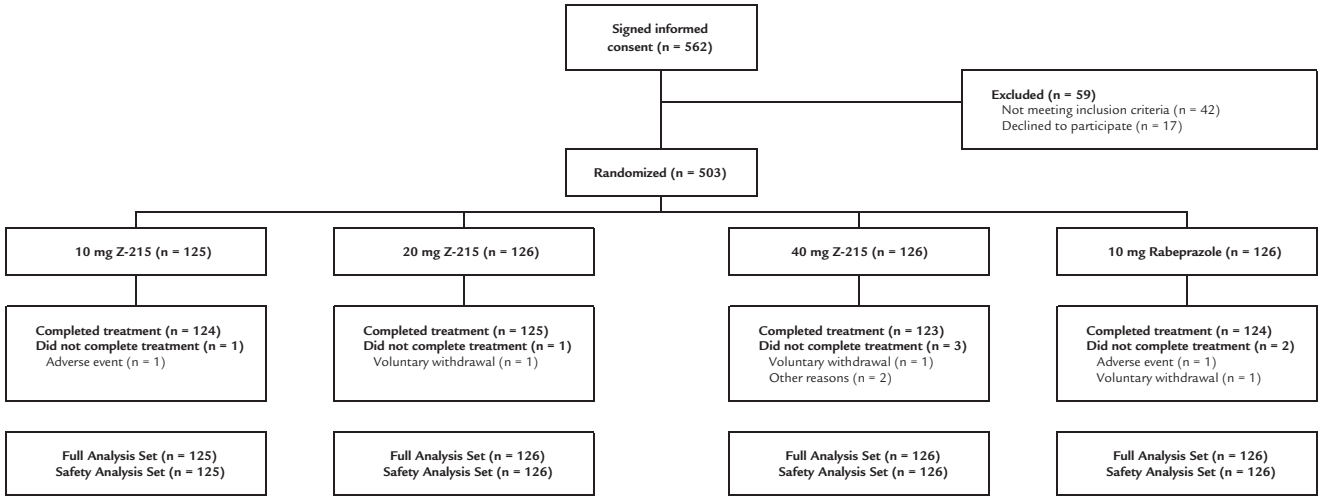


Figure 1. Patient flow chart.

The endoscopic healing rate as assessed by the investigator at Week 4 was highest in the 40-mg Z-215 group, and most patients in all groups were endoscopically healed at Week 4 (Table 2). Similarly, the endoscopic healing rate as assessed by the IAC at Week 4 was also highest in the 40-mg Z-215 group (data not shown).

Efficacy outcome measures in the subgroup analyses

Endoscopic healing rate categorized by the modified Los Angeles classification of RE at baseline

Table 3 shows the endoscopic healing rate assessed by the investigator categorized by the modified Los Angeles classification (assessed by the investigator) at baseline. The endoscopic healing rate assessed by the investigator was lower in patients with Grade C/D compared with those with Grade A/B in all groups. Similarly, the endoscopic healing rate assessed by the IAC was lower in patients with Grade C/D compared with those with Grade A/B, except for the 20-mg Z-215 group (Table 4). The results of the ad hoc analysis of endoscopic healing rate at Week 4 categorized by the modified Los Angeles classification at baseline are summarized in Table 3 and Table 4. The endoscopic healing rate assessed by the investigator for patients with Grade A/B was more than 90% for all groups. In contrast, only patients with Grade C/D in the 40-mg Z-215 group showed an endoscopic healing rate of more than 90%. Similarly, only patients with Grade C/D in the 40-mg Z-215 group

Table 1
Patient demographic characteristics (randomized participants).

Characteristic	10 mg Z-215 (n = 125)	20 mg Z-215 (n = 126)	40 mg Z-215 (n = 126)	10 mg Rabeprazole (n = 126)
Sex				
Male	101 (80.8)	90 (71.4)	105 (83.3)	101 (80.2)
Female	24 (19.2)	36 (28.6)	21 (16.7)	25 (19.8)
Age (y)	55.4 (12.7)	57.4 (12.5)	53.7 (13.4)	56.0 (12.1)
Weight (kg)	70.65 (12.59)	67.64 (12.49)	69.73 (14.50)	68.85 (11.56)
Body mass index	25.43 (3.35)	24.80 (3.49)	24.95 (3.93)	24.97 (3.49)
Treatment history of RE				
No	60 (48.0)	61 (48.4)	60 (47.6)	62 (49.2)
Yes	65 (52.0)	65 (51.6)	66 (52.4)	64 (50.8)
Helicobacter pylori status				
Negative ($<$ 10 U/mL)	118 (94.4)	113 (89.7)	111 (88.1)	111 (88.1)
Positive ($\geq$ 10 U/mL)	7 (5.6)	13 (10.3)	15 (11.9)	15 (11.9)
Esophageal hiatal hernia				
No	40 (32.0)	36 (28.6)	36 (28.6)	36 (28.6)
Yes	85 (68.0)	90 (71.4)	90 (71.4)	90 (71.4)
CYP2C19 genotype				
Homo EM	43 (34.4)	38 (30.2)	42 (33.3)	40 (31.7)
Hetero EM	66 (52.8)	55 (43.7)	64 (50.8)	64 (50.8)
PM	16 (12.8)	33 (26.2)	20 (15.9)	22 (17.5)
Baseline modified Los Angeles grade (assessed by investigator)				
A/B	93 (74.4)	94 (74.6)	94 (74.6)	94 (74.6)
C/D	32 (25.6)	32 (25.4)	32 (25.4)	32 (25.4)
Baseline modified Los Angeles grade (assessed by IAC)				
N/M	2 (1.6)	4 (3.2)	2 (1.6)	2 (1.6)
A/B	94 (75.2)	96 (76.2)	96 (76.2)	98 (77.8)
C/D	29 (23.2)	26 (20.6)	28 (22.2)	26 (20.6)
Baseline modified FSSG total score	10.9 (9.5)	12.7 (8.6)	10.2 (8.4)	10.7 (9.6)

Data for age, weight, body mass index, and Baseline modified FSSG total score are presented as mean (SD). All other values are presented as n (%).
FSSG = frequency scale for the symptoms of gastroesophageal reflux disease; homo EM = homozygous extensive metabolizers; hetero EM = heterozygous extensive metabolizers; IAC = Independent Adjudication Committee; PM = poor metabolizers.

Table 2
Endoscopic healing rate assessed by the investigator at Week 4 and Week 8 (full analysis set).

Time	10 mg Z-215		20 mg Z-215		40 mg Z-215		10 mg Rabeprazole	
	Healed patients*/all patients†	%	Healed patients*/all patients†	%	Healed patients*/all patients†	%	Healed patients*/all patients†	%
Week 4	112/124‡	90.3	113/126	89.7	116/125‡	92.8	113/126	89.7
Week 8	118/124‡	95.2	122/126	96.8	119/125‡	95.2	122/126	96.8

* The number of cumulative patients assessed as Grade N/M by the investigator at each evaluation point or earlier.
† All patients except those from the target analysis group with missing values.
‡ One patient was excluded from the full analysis set because of missing endoscopic data during the treatment period.

showed an endoscopic healing rate of more than 90% at Week 4 according to the IAC (Table 4).

Endoscopic healing rate of RE categorized by CYP2C19 genotype

To assess the effects of CYP2C19 genotype, we examined the endoscopic healing rate assessed by the investigator at Week 8 according to CYP2C19 genotype (eg, homozygous EM and heterozygous EM and PM) (Table 5). The endoscopic healing rate was not dependent on CYP2C19 genotype in any group. Similarly, the endoscopic healing rate assessed by the IAC at Week 8 was not dependent on CYP2C19 genotype in any group (data not shown).

Subjective symptoms

The mean modified FSSG total score decreased with time in all groups (Table 6). In particular, mean scores at Week 2 decreased to less than half of the respective mean scores at baseline in the 20-mg and 40-mg Z-215 and 10-mg RPZ groups. In addition, the 40-mg Z-215 group had the lowest modified FSSG total score among all groups at Week 2, Week 4, and Week 8. The number of patients showing ≥75% and ≥50% improvement in the modified FSSG total score increased with time in all groups. In addition, within each Z-215 group for a given time point, the number of patients showing ≥75% and ≥50% improvement in total score tended to increase in a dose-dependent manner (Table 6).

Safety measures

A summary of AEs and ADRs is shown in Table 7. There was no dose-dependent increase in AEs or ADRs in the 10-, 20-, and 40-mg Z-215 dose groups, and there was no remarkable difference in the incidence rate of AEs or ADRs between the Z-215 and 10-mg RPZ groups. The AEs that occurred in ≥2% of patients in at least 1 group were cystitis, influenza, nasopharyngitis, dehydration, constipation, eczema, increased blood thyroid stimulating hormone, and increased gamma-glutamyltransferase levels. Nasopharyngitis was the most frequent AE, occurring in 21 patients across all groups, and was considered unlikely to have been caused by the study drugs. No fatal or life-threatening AEs were observed. However, 2 serious AEs were observed: unstable angina in the 10-mg Z-215 group and gastric cancer in the 40-mg Z-215 group, both of which were considered unlikely by the investigators to be caused by the study drugs. ADRs that occurred in ≥1% of patients in at least 1 group were constipation, loose stools, eczema, and increased blood thyroid stimulating hormone levels. No severe ADRs were observed.

Serum gastrin levels

Changes in serum gastrin levels (reference range: < 200 pg/mL) are shown in Table 8. Serum gastrin levels increased in all groups following drug administration. There was no remarkable difference in serum gastrin levels between the Z-215 and 10-mg RPZ groups at the final observation point. To assess the effects of CYP2C19 genotype, serum gastrin levels were examined according to CYP2C19 genotype using ad hoc analysis as shown in Figure 2. Z-215 groups showed almost no change in serum gastrin levels among CYP2C19 genotypes at the final observation point. In contrast, in the 10-mg RPZ group, the serum gastrin level of PM patients tended to be higher than that of homozygous EMs and heterozygous EMs at the final observation point.

Discussion

Based on the endoscopic healing rates assessed by the investigator and IAC at Week 4 and Week 8, our data suggest that the 3 doses of Z-215 (10, 20, and 40 mg) were just as effective for the initial treatment of RE in this selected population as the 10-mg dose of RPZ. In particular, the endoscopic healing rate in Grade C/D patients suggests that 40 mg Z-215 may be the most effective treatment for RE, although no clear dose-dependency was observed among Z-215 doses. Furthermore, Z-215 administration resulted in high endoscopic healing rates for RE regardless of CYP2C19 genotype. In addition, the efficacy of Z-215 for subjective symptoms increased with time.

Table 3
Endoscopic healing rate assessed by the investigator at Week 4 and Week 8 categorized by the modified Los Angeles classification grade at baseline (full analysis set) (assessed by the investigator).

Time	Baseline	10 mg Z-215		20 mg Z-215		40 mg Z-215		10 mg Rabeprazole	
		Healed patients*/all patients†	%	Healed patients*/all patients†	%	Healed patients*/all patients†	%	Healed patients*/all patients†	%
Week 4‡	A/B	85/93	91.4	85/94	90.4	87/93§	93.5	85/94	90.4
	C/D	27/31§	87.1	28/32	87.5	29/32	90.6	28/32	87.5
Week 8	A/B	90/93	96.8	93/94	98.9	90/93§	96.8	92/94	97.9
	C/D	28/31§	90.3	29/32	90.6	29/32	90.6	30/32	93.8

* The number of cumulative patients assessed as Grade N/M by the investigator at each evaluation point or earlier.
† All patients except those from the target analysis group with missing values.
‡ Calculated as ad hoc analysis.
§ One patient was excluded from the full analysis set because of missing endoscopic data during the treatment period.

Table 4
Endoscopic healing rate assessed by the Independent Adjudication Committee (IAC) at Week 4 and Week 8 categorized by the modified Los Angeles classification grade at baseline (full analysis set) (assessed by the IAC).

Time	Baseline	10 mg Z-215		20 mg Z-215		40 mg Z-215		10 mg Rabeprazole	
		Healed patients*/all patients†	%	Healed patients*/all patients†	%	Healed patients*/all patients†	%	Healed patients*/all patients†	%
Week 4‡	A/B	92/94	97.9	92/96	95.8	94/95§	98.9	96/98	98.0
	C/D	23/28§	82.1	22/26	84.6	27/28	96.4	22/26	84.6
Week 8	A/B	93/94	98.9	94/96	97.9	94/95§	98.9	96/98	98.0
	C/D	25/28§	89.3	26/26	100.0	27/28	96.4	24/26	92.3

* The number of cumulative patients assessed as Grade N/M by the IAC at each evaluation point or earlier.
† All patients except those from the target analysis group with missing values.
‡ Calculated as ad hoc analysis.
§ One patient was excluded from the full analysis set because of missing endoscopic data during the treatment period.

Table 5
Endoscopic healing rate assessed by investigator at Week 8 categorized by CYP2C19 genotype (full analysis set).

	10 mg Z-215		20 mg Z-215		40 mg Z-215		10 mg Rabeprazole	
	Healed patients*/all patients†	%	Healed patients*/all patients†	%	Healed patients*/all patients†	%	Healed patients*/all patients†	%
Homo EM	40/43	93.0	38/38	100.0	41/41‡	100.0	39/40	97.5
Hetero EM	63/66	95.5	53/55	96.4	60/64	93.8	62/64	96.9
PM	15/15‡	100.0	31/33	93.9	18/20	90.0	21/22	95.5

homo EM = homozygous extensive metabolizers; hetero EM = heterozygous extensive metabolizers; PM = poor metabolizers.
* The number of cumulative patients assessed as Grade N/M by the investigator at Week 8.
† All patients except those from the target analysis group with missing values.
‡ One patient was excluded from the full analysis set because of missing endoscopic data during the treatment period.

In a previous pharmacodynamic and pharmacokinetic (PK/PD) parameters study, repeated oral administration of 10, 20, and 40 mg Z-215 to healthy Japanese adult men showed that Z-215 suppressed gastric acid secretion (based on pH ≥4 HTR) in a dose-dependent manner.[12] In addition, 20 mg Z-215 and 10 mg RPZ showed comparable gastric acid secretion suppression. However, in this study, we did not observed a clear dose-dependent response in the endoscopic healing rate at Week 8 assessed by either the investigator or IAC among the 3 doses of Z-215 (10, 20, and 40 mg). Although the endoscopic healing rate assessed by the investigator and IAC at Week 4 was higher in the 40-mg Z-215 group than in the other groups, the difference was slight. The endoscopic healing rate assessed by the investigator and IAC in Grade C/D patients in the 40-mg Z-215 group was also higher than in the other groups, but the number of patients in this subgroup was small, as was the observed difference. Further, the Z-215

Table 6
Modified frequency scale for the symptoms of gastroesophageal reflux disease score and improvement (full analysis set).

Group	Visit	Score			Improvement				
		n*	Mean	95% CI	n‡	Improvement rate† ≥75%		Improvement rate† ≥50%	
						n	%¶	n	%¶
10 mg Z-215	Baseline	125	10.9	9.3–12.6	–	–	–	–	–
	Week 2	124‖	6.0	4.7–7.3	116‖	39	33.6	65	56.0
	Week 4	124‖	3.7	2.7–4.6	116‖	58	50.0	95	81.9
	Week 8§	12	2.6	0.9–4.3	12	7	58.3	11	91.7
20 mg Z-215	Baseline	126	12.7	11.2–14.1	–	–	–	–	–
	Week 2	126	5.6	4.6–6.6	120	43	35.8	71	59.2
	Week 4	125	3.4	2.6–4.1	119	72	60.5	97	81.5
	Week 8§	12	2.8	0.3–5.2	12	10	83.3	11	91.7
40 mg Z-215	Baseline	126	10.2	8.8–11.7	–	–	–	–	–
	Week 2	126	4.3	3.4–5.3	118	43	36.4	73	61.9
	Week 4	125	2.4	1.6–3.2	117	81	69.2	97	82.9
	Week 8§	7	1.1	0.2–2.1	7	6	85.7	7	100.0
10 mg Rabeprazole	Baseline	126	10.7	9.0–12.3	–	–	–	–	–
	Week 2	126	5.0	3.9–6.0	114	41	36.0	69	60.5
	Week 4	124	2.6	2.0–3.2	112	71	63.4	94	83.9
	Week 8§	13	2.3	0.4–4.2	11	8	72.7	11	100.0

* All patients except those from the target analysis group with missing values.
† Improvement rate (%) = (Baseline score – Score at each treatment period) / Baseline score × 100.
‡ All patients except those whose total score was "0" throughout the study.
§ Patients who were assessed as "healed" at Week 4 were not included in the Week 8 calculation.
‖ One patient was excluded from full analysis set because of missing score data during the treatment period.
¶ Proportion of patients with improvement.

Table 7
Summary of adverse events (AEs) and adverse drug reactions (ADRs) (safety analysis set).

	10 mg Z-215 (n = 125)	20 mg Z-215 (n = 126)	40 mg Z-215 (n = 126)	10 mg Rabeprazole (n = 126)
AE[*,†]	37 (29.6)	26 (20.6)	31 (24.6)	36 (28.6)
Cystitis	3 (2.4)	1 (0.8)	0 (0.0)	0 (0.0)
Influenza	3 (2.4)	1 (0.8)	1 (0.8)	2 (1.6)
Nasopharyngitis	7 (5.6)	4 (3.2)	6 (4.8)	4 (3.2)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.4)
Constipation	0 (0.0)	4 (3.2)	0 (0.0)	1 (0.8)
Eczema	2 (1.6)	0 (0.0)	1 (0.8)	3 (2.4)
Blood thyroid stimulating hormone increased	3 (2.4)	2 (1.6)	2 (1.6)	1 (0.8)
Gamma-glutamyl transferase increased	0 (0.0)	1 (0.8)	3 (2.4)	2 (1.6)
ADR[*,†]	6 (4.8)	10 (7.9)	8 (6.3)	7 (5.6)
Constipation	0 (0.0)	4 (3.2)	0 (0.0)	0 (0.0)
Feces soft	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Blood thyroid stimulating hormone increased	2 (1.6)	2 (1.6)	1 (0.8)	0 (0.0)

Data are presented as n (%).
[*] Event term based on MedDRA/J version 19.0.
[†] AEs that occurred in ≥2% of patients in at least 1 group and ADR that occurred in ≥1% of patients in at least 1 group are listed.

groups showed improvements in subjective symptoms with time, according to the modified FSSG total score. In this selected population, the modified FSSG total score throughout the treatment period was lowest in the 40-mg Z-215 group. Therefore, the 40 mg Z-215 regimen may be the most effective for early resolution of RE symptoms. Although these results suggest that 40 mg Z-215 may show stronger efficacy for RE than the 10 mg or 20 mg doses, no clear dose-dependent response was observed.

To clarify the dose–response relationship among Z-215 groups, some limitations observed in this study need to be overcome. First, other studies that tested standard doses of PPIs reported that 80% to 90% of RE patients showed healing of mucosal breaks and maintenance of remission.[18] However, the endoscopic healing rate of RE in all groups in this study was higher than that observed in other studies. Therefore, it is possible that many patients with easily healed RE were enrolled in our study, and that they would have healed regardless of the strength of the study drugs. In addition, from the endoscopic healing rate categorized by the modified Los Angeles classification at baseline, Grade C/D patients tended to have a lower endoscopic healing rate than Grade A/B patients, as assessed by both the investigator and IAC. This indicates that the mucosal breaks in severe RE patients were difficult to heal. Therefore, increasing the proportion of severe RE patients (Grade C/D patients) at baseline may change the endoscopic healing rate with Z-215 dose. Second, according to clinical practice guidelines for GERD, PPIs should be administered for 8 weeks as an initial treatment.[2] However, our results indicate a high healing rate of 89.7% to 92.8% assessed by the investigator in all groups at Week 4. Therefore, it would be informative to evaluate the healing rate at an earlier time point to confirm the dose response.

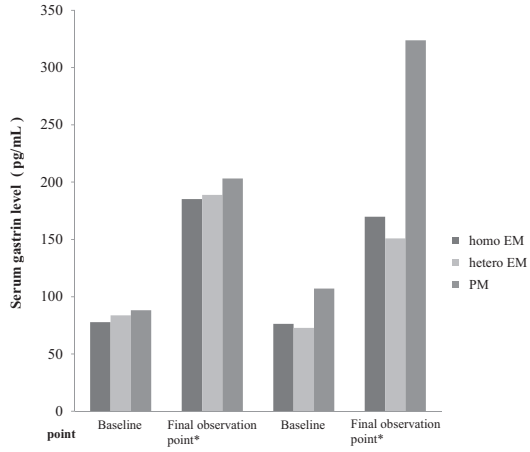
The ratio of the 3 CYP2C19 genotypes in this study was almost the same as that reported in the Japanese population (homozygous EM:heterozygous EM:PM = 3:5:2).[19] There were no differences in the effect of Z-215 among CYP2C19 genotypes, which is consistent with the results of a previous PK/PD parameters study of Z-215.[12] However, we also showed that CYP2C19 genotype does not influence the efficacy of 10 mg RPZ, which is different from the results of the previous PK/PD parameters study.[12] On the other hand, whereas serum gastrin levels in the Z-215 groups were not influenced by CYP2C19 genotype, those in the 10-mg RPZ group were, which is consistent with the PK/PD parameters study.[12] Therefore, we found that the influence of CYP2C19 genotype on the RPZ-induced endoscopic healing rate of RE differed from that on serum gastrin levels. This may be explained by the fact that RPZ is less susceptible to CYP2C19 genetic polymorphisms compared with other PPIs.[15] That is, the effect of RPZ on gastric acid suppression is only slightly influenced by CYP2C19 genotype. Because the amount of gastrin secretion depends on the amount of gastric acid secretion, the influence of CYP2C19 genotype on serum gastrin levels was evident, although it may have been small. On the other hand, the slight difference in gastric acid suppression due to CYP2C19 genotype was not reflected in the healing of mucosal breaks. In contrast, neither the endoscopic healing rate nor serum gastrin levels in the Z-215 groups were influenced by CYP2C19 genotype, indicating that the contribution of CYP2C19 to Z-215 metabolism is smaller than that for RPZ.

In a previous randomized, double-blind study for EPZ (initial treatment for RE), the endoscopic healing rates after 8 weeks were 84.1%, 93.5%, and 93.1% in the 40-mg/day EPZ group, 82.0%, 90.6%, and 87.5% in the 20-mg/day EPZ group, and 84.3%, 89.4%, and

Table 8
Change in serum gastrin levels (safety analysis set).

Time point	10 mg Z-215		20 mg Z-215		40 mg Z-215		10 mg Rabeprazole	
	n	Mean (SD) (pg/mL)	n	Mean (SD) (pg/mL)	n	Mean (SD) (pg/mL)	n	Mean (SD) (pg/mL)
Baseline	125	81.5 (54.9)	125[*]	82.5 (54.3)	126	84.0 (65.6)	126	80.0 (55.0)
Week 2	124[*]	179.2 (164.4)	126	222.3 (193.5)	126	239.6 (234.6)	126	177.1 (137.3)
Week 4	124[*]	171.5 (135.2)	125	196.7 (146.3)	125	198.4 (131.9)	124	187.0 (145.9)
Week 8[†]	12	271.8 (256.4)	12	258.6 (192.2)	7	184.9 (105.7)	13	180.8 (109.2)
Final observation point[‡]	124[*]	172.8 (141.0)	126	200.0 (148.4)	126	197.5 (132.2)	126	187.1 (144.1)

[*] One patient was excluded from the safety analysis set because of missing data.
[†] Patients who were assessed as "healed" at Week 4 were not included in the Week 8 calculation.
[‡] Latest point in treatment period.



		Z-215 groups		RPZ 10 mg	
		Baseline	Final observation point*	Baseline	Final observation point*
N	homo EM	123	123	40	40
	hetero EM	185	185	64	64
	PM	68	68	22	22
SD	homo EM	54.7	148.9	42.2	92.0
	hetero EM	58.5	131.6	34.3	100.3
	PM	64.6	151.2	101.1	231.3

RPZ, rabeprazole solium; homo EM, homzygous extensive metabolizers; hetero EM, hetero zygous extensive metabolizers; PM, Poor metabolizers; N, number of subjects; SD' standard deviation.
*Latest point in treatment period.

Figure 2. Serum gastrin levels categorized by CYP2C19 genotype.

88.5% in the 20-mg/day OPZ group for homozygous EM, and heterozygous EM and PM patients, respectively. This result indicates that the mucosal healing rate in homozygous EM patients is markedly lower than that in other CYP2C19 genotypes.[20]

We found no dose-dependent increase in AE or ADR incidence rates in the 10-, 20-, and 40-mg Z-215 dose groups. Further, there was no remarkable difference in AE or ADR incidence rates between the Z-215 and 10-mg RPZ groups. Therefore, the safety profile of 10, 20, and 40 mg Z-215 was comparable to that of 10 mg RPZ. In addition, serum gastrin levels were not markedly different between the Z-215 and 10-mg RPZ groups at the final observation point. Therefore, 10, 20, and 40 mg Z-215 showed a comparable safety profile to 10 mg RPZ following administration for 8 weeks.

We examined the efficacy and safety profile of Z-215 for RE as an initial treatment. Because Z-215 may be used not only as an initial treatment but also as continuous maintenance therapy for RE, its efficacy in maintenance therapy and safety profile during long-term administration, including changes in serum gastrin levels, should be evaluated.

Conclusions

RE healing rate following Z-215 at 10, 20, and 40 mg once daily was equivalent to that obtained with 10 mg RPZ once daily. Other studies are needed to precisely evaluate appropriate doses of Z-215 for patients with severe RE. The safety profile of Z-215 was comparable with that of 10 mg RPZ. CYP2C19 genotype status may not influence the efficacy and safety of Z-215. These findings suggest that Z-215 may be a useful drug for the initial treatment of RE.

Conflicts of interest statement

Funding for this study was provided by Zeria Pharmaceutical Co Ltd, Tokyo, Japan. The study sponsor was involved in the study design, data collection, data analysis, and preparation of the manuscript. M. Kusano owns the copyright for the modified frequency scale for the symptoms of gastroesophageal reflux disease and the copyright fee was funded by Zeria Pharmaceutical Co Ltd. M. Fujishiro received manuscript fees from Zeria Pharmaceutical Co Ltd. Y. Kinoshita, K. Haruma, M. Kusano, K. Iwakiri, and M. Fujishiro received consulting fees from Zeria Pharmaceutical Co Ltd during the study period. N. Tachikawa is an employee of Zeria Pharmaceutical Co Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Y. Kinoshita, M. Kusano, K. Iwakiri, M. Fujishiro, N. Tachikawa, and K. Haruma participated in the study planning and interpretation of the study results. Y. Kinoshita served as the coordinating investigator; K. Haruma served as the medical advisor; and M. Kusoan, K. Iwakiri, and M. Fujishiro served as the independent adjudication committee.

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