AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: prevention of recurrence of peptic ulcers by rabeprazole in patients taking low-dose aspirin

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Publication data
Submitted 23 May 2014
First decision 28 May 2014
Resubmitted 9 July 2014
Resubmitted 18 July 2014
Accepted 18 July 2014
EV Pub Online 6 August 2014

This article was accepted for publication after full peer-review.

SUMMARY

Background
Few studies have evaluated the effects of rabeprazole on low-dose aspirin (LDA)-induced gastroduodenal injuries.

Aim
To conduct a randomised, double-blind, triple-dummy, active-controlled, multicentre trial, named the PLANETARIUM study, to assess the efficacy, dose–response relationship and safety of rabeprazole for peptic ulcer recurrence in Japanese patients on long-term LDA therapy.

Methods
Eligible patients had a history of endoscopically confirmed peptic ulcers and were receiving long-term LDA (81 or 100 mg/day) therapy for cardiovascular or cerebrovascular protection. Subjects were randomly segregated into three groups receiving rabeprazole 10 mg once daily (standard dose in Japan), rabeprazole 5 mg once daily, or teprenone (geranylgeranylacetone; mucosal protective agent commercially available in Japan) 50 mg three times per day as an active control. The primary endpoint was recurrence of peptic ulcers over 24 weeks.

Results
Among 472 randomised subjects, 452 subjects (n = 151, 150, 151, respectively) constituted the full analysis set. The cumulative recurrence rates of peptic ulcers over 24 weeks in the 10- and 5-mg rabeprazole groups were 1.4% and 2.8%, respectively, both of which were significantly lower than that in the teprenone group (21.7%). The cumulative occurrence rate of bleeding ulcers over 24 weeks in the teprenone group was 4.6%, while bleeding ulcers were not observed in the 10- or 5-mg rabeprazole groups. Rabeprazole was well tolerated at both doses.

Conclusion
Rabeprazole prevents the recurrence of peptic ulcers with no evidence of a major dose–response effect in subjects on low-dose aspirin therapy.

Aliment Pharmacol Ther 2014; **40**: 780–795

doi:10.1111/apt.12907

INTRODUCTION

The two main causes of peptic ulcer are *Helicobacter pylori* infection and use of medications such as low-dose aspirin (LDA) and nonsteroidal anti-inflammatory drugs (NSAIDs).[1, 2] As *H. pylori*-positive populations are decreasing in the EU, USA, Japan, etc., the occurrence of ulcers attributable to *H. pylori* is also decreasing in these countries, while drug-induced ulcers are on the rise.[3, 4] The use of aspirin as one of the key anti-thrombotic drugs for ischaemic heart disease and cerebrovascular disease is rapidly increasing.[5–7] However, erosive lesions were previously reported in approximately 40–60%, peptic ulcers in approximately 10–20%[8, 9] and gastrointestinal bleeding in approximately 1–2%[10, 11] of patients on LDA therapy, with reports of cases in which haemorrhage and perforation resulted in death. To overcome LDA-induced adverse effects, the concomitant use of proton pump inhibitors (PPI) has been recommended as a measure to prevent upper gastrointestinal mucosal injury.[12] In Japan, combination therapy of LDA with lansoprazole or esomeprazole is available, although combination therapy with rabeprazole is not yet available.

Rabeprazole exerts a rapid and potent inhibitory effect on gastric acid secretion, and has been reported to be efficacious against various acid-related diseases, with an emphasis on GERD.[13, 14] Users of LDA are primarily elderly and often have multiple diseases and take concomitant medications. Under these circumstances, PPIs with fewer drug interactions would be preferred, because the drug interaction may induce adverse effects or decrease the efficacy of the concomitantly administered drug by increasing or decreasing its plasma concentration, respectively. A recent study of the effects of PPIs on cytochrome 450 (CYP) activity assessed by the [^{13}C]-aminopyrene breath test in healthy subjects showed that omeprazole and lansoprazole at the standard doses inhibit CYP activity, while rabeprazole does not.[15] This finding is consistent with the previously known fact that rabeprazole has relatively less effects on CYP2C19 and CYP3A4.[16, 17] Thus, for example, rabeprazole provides a clinically safe combination with tacrolimus, which is metabolised by CYP2C19 and CYP3A4,[18, 19] and with clopidogrel, which is activated by CYP2C19.[20]

Rabeprazole is a promising candidate PPI for use in combination with LDA. So far, only an open-label comparative study of the preventive effects of rabeprazole on ulcer recurrence in patients on LDA therapy has been reported[21]; there are no reports of double-blind comparative studies, which have the minimum bias, or reports investigating the preventive effects of 5-mg rabeprazole (in Japan, the standard dose of rabeprazole is 10 mg).

We conducted a Phase 2/3 double-blind comparative study (PLANETARIUM study) to confirm the efficacy and safety of 5- and 10-mg rabeprazole in preventing the recurrence of gastric and duodenal ulcers in patients with a history of peptic ulcer who were on long-term LDA therapy. As an active control, we used teprenone (geranylgeranylacetone). Teprenone was first commercialised by Eisai Co., Ltd. in Japan in 1984 for curing gastric ulcer and gastritis.[22, 23] Teprenone decreased *H. pylori* density in the corpus of gastritis patients.[24] The clinical mucoprotective efficacy of teprenone against NSAID-induced gastroduodenal injury was previously reported.[25, 26] Teprenone has shown to induce heat shock protein 70 (HSP70) resulting in protection against NSAID-induced gastric lesions.[27, 28]

MATERIALS AND METHODS

The PLANETARIUM study is a Phase 2/3, randomised, parallel-group, double-blind, triple-dummy, active-controlled, multicentre study, and was conducted between July 2011 and March 2013 at 63 institutions in Japan. This study was registered at http://clinicaltrials.gov (NCT01397448). Before the start of the study, the protocol was reviewed and approved by the individual Institutional Review Boards of each institution. Written informed consent was obtained from all subjects prior to enrolment. This study was conducted in compliance with the Good Clinical Practice guidelines and ethical principles based on the Declaration of Helsinki.

Subjects

Subjects were out-patients ≥20 years old, with a history of gastric or duodenal ulcer (ulcer scar at baseline endoscopy or ulcer scar/active ulcer at prior endoscopy), taking LDA (81 or 100 mg/day) for preventing thrombosis/embolisation in patients with angina pectoris, myocardial infarction or ischaemic cerebrovascular disorders. Eligibility was determined based on the subjects' history of ulcer or the presence of an ulcer scar at baseline endoscopy, as determined by the endoscopy central review panel (panel of three endoscopy specialists: KH, MK and MF), using endoscopy photos submitted by each institution. Other inclusion criteria included stable disease condition of the patient, with no pressing need to change the dosage and administration of aspirin. Patients with the following findings on baseline endoscopy performed within 14 days before randomisation were excluded:

acute gastroduodenal mucosal lesion, gastric ulcer or duodenal ulcer, upper gastrointestinal haemorrhage, reflux oesophagitis (the modified Los Angeles Classification[29, 30] Grade A or above) or Barrett's oesophagus (columnar-lined epithelium ≥3 cm). Other exclusion criteria included: patients with a history of upper gastrointestinal surgery, patients continuously using NSAIDs or adrenocortical steroids, patients with serious diseases of the heart, brain, blood, kidneys or liver, patients with malignant tumours, and patients with a history or presence of aspirin-sensitive asthma.

Patients were eligible for study participation regardless of whether they were *H. pylori*-positive or -negative. Presence of *H. pylori* infection was determined by enzyme immunoassay using an antibody determination kit (E-Plate Eiken *H. pylori* antibody) (Eiken Chemical Co., Ltd., Tokyo, Japan). The relative sensitivity, specificity and accuracy rate between results obtained by E-Plate and those obtained by culture/histological examination/rapid urease test were 100%, 80.0% and 97.1% respectively.[31] *Helicobacter pylori* eradication therapy was prohibited during the study. At baseline, CYP2C19 genotyping information was obtained using fluorescence correlation spectroscopy [homo extensive metabolizer (EM), hetero EM, or poor metabolizer (PM)]. Anti-*H. pylori* IgG antibody and CYP2C19 genotype analyses were performed by SRL Medisearch (Tokyo, Japan).

There were no restrictions on medications used before the start of the study. During the study period, concomitant use of the following was prohibited: drugs indicated for improving ulcers or gastrointestinal symptoms (such as PPIs, except those that were used in this study, histamine H_2 receptor antagonists, prokinetics, mucosal protective agents, antacids, prostaglandin agents, or traditional Chinese herbal medications, etc.), and atazanavir sulphate and rilpivirine hydrochloride, which are contraindicated for concomitant use with rabeprazole. The concomitant use of anti-platelet drugs or anticoagulants other than LDA was permitted.

Treatment

Subjects in this 24-week clinical trial were divided into three treatment groups: the rabeprazole 10-mg (once daily) group, the rabeprazole 5-mg (once daily) group and the teprenone 150-mg (50 mg three times a day) group. Subjects who met the inclusion criteria were randomly assigned in a 1:1:1 ratio to one of the three groups, using a dynamic allocation method where the following three baseline covariates were considered prognostic: age (under 70 years old or 70 years and older), concomitant use of anti-platelet or anticoagulant medication other than LDA (positive or negative), and institution. The study medications were prepared such that the active drugs were indistinguishable in appearance from their corresponding placebo. Following a triple-dummy method, subjects in the rabeprazole 10-mg group received a rabeprazole 10-mg tablet and a rabeprazole 5-mg placebo tablet in the morning, and a teprenone-placebo capsule in the morning, afternoon and evening; subjects in the rabeprazole 5-mg group received a rabeprazole 5-mg tablet and a rabeprazole 10-mg placebo tablet in the morning, and a teprenone-placebo capsule in the morning, afternoon and evening; while subjects in the teprenone group received 10-mg and 5-mg rabeprazole placebo tablets in the morning and a teprenone capsule in the morning, afternoon and evening. Bell Medical Solutions, Inc. (Tokyo, Japan) was contracted to allocate the study medication and safeguard the key codes. EPS Corporation (Tokyo, Japan) was contracted to administer the Subject Enrollment Center. Each of these organisations is a third party entity, which maintained independence from the institutions conducting the study and the sponsor (Eisai Co., Ltd.). By having the key code stored in Bell Medical Solutions, Inc., blinding of treatment groups from all personnel involved in the study was secured until code break.

Assessments

During the study period, subjects made hospital visits every 4 weeks. Upper endoscopy was performed at the start of the study, at week 12 and at week 24 or at discontinuation. If findings suggestive of upper gastrointestinal haemorrhage or intolerable upper gastrointestinal symptoms occurred, additional upper endoscopy was performed at the discretion of the investigator. If gastric or duodenal ulcers were observed, the case was treated as a recurrence and study participation was terminated for that subject. Gastric and duodenal ulcers were rated based on the Sakita–Miwa classification as:[32] active stage (1, 2), healing stage (1, 2) or scar stage (1, 2). The Forrest classification[33] was used to assess the presence or absence of bleeding if an ulcer was observed: type I (a, b) and type II (a, b) indicating bleeding, and type III indicating no bleeding. Reflux oesophagitis was assessed according to the modified Los Angeles Classification[29, 30] as: O (without mucosal breaks) and A–D (with mucosal breaks). The modified Lanza score was used to assess the severity of gastric or duodenal mucosal injury,[34, 35] based on which gastric findings were rated from grade 0

(no erosion, no ecchymosis) to 5 (ulcer), and duodenal findings from grade 0 (no erosion, no ecchymosis) to 4 (ulcer). Every 4 weeks, a physician interviewed the subject regarding any upper gastrointestinal symptoms (epigastric pain, stomach discomfort, feeling of abdominal fullness, heartburn and nausea/queasiness), and assessed these on a 4-grade scale (none, mild, moderate and severe). Laboratory tests were conducted and vital signs were measured every 4 weeks. Serum gastrin and thyroid function tests (TSH, F-T_3, F-T_4) were performed at the start of the study, at week 12 and at week 24 or at discontinuation. Data of serum gastrin levels were masked until code break. At each visit, subjects were also surveyed for compliance with the study drugs and LDA, as well as the types of concomitant medications they were taking and for the occurrence of any adverse events.

Endpoints

The primary endpoint was cumulative recurrence rate of gastric or duodenal ulcers at week 24 (Kaplan–Meier life-table estimates). Ulcer was defined as a mucosal break measuring ≥3 mm along its longest diameter with a white coating. The size definition of ≥3 mm was also used in recent studies from 10 countries (mostly European countries),[36] USA,[37] Taiwan,[38] and Japan, Korea, and Taiwan[39] where PPI and LDA were dosed. The presence or absence of ulcer recurrence was determined by the endoscopy central review panel (panel of three endoscopy specialists: KH, MK and MF) who were blinded to the investigators' assessments, based on endoscopy photos submitted by each of the institutions. In cases of ulcer recurrence, the stage classification was assessed (healing stage 2 or above).

Secondary endpoints included cumulative incidence of bleeding ulcers at week 24 (Forrest Classification, type IIb or above), incidence of reflux oesophagitis at week 24 (Grade A or above based on the modified Los Angeles Classification), percentage of patients showing improvement/worsening of gastric and duodenal mucosal injury based on modified Lanza scores (improvement was defined as a decrease of at least 1 grade and worsening as an increase of at least 1 grade at the final assessment compared to baseline) and percentage of patients showing worsening of upper gastrointestinal symptoms (worsening was defined as an increase in severity of at least 1 grade at the final assessment compared to baseline).

Safety was evaluated based on adverse events, laboratory tests, vital signs, and the results of serum gastrin and thyroid function tests. Incidence rates were calculated for adverse events and drug-related adverse events in each treatment group.

Statistical analysis

Based on the results of studies on lansoprazole in patients with a history of ulcers,[40] it was postulated that the cumulative recurrence rate for gastric or duodenal ulcers at week 24 would be 4% in the rabeprazole 10-mg group and 17% in the teprenone group. A sample size of 122 subjects per group was estimated to be required, with a two-sided significance level of $\alpha = 0.05$ and a power of 90% (Fisher's exact test). In addition, in consideration of the quantity of data that would be lost due to ineligible subjects and early discontinuations, etc., the number of subjects required for randomisation was set at 150 per group, i.e. a total of 450 subjects in the three groups.

Efficacy analyses were primarily performed on the full analysis set (FAS), defined as all randomised subjects who received at least one dose of the study drug and showed no ulcers at baseline, and from whom the results of at least one endoscopic assessment was available. The primary endpoint was also analysed based on the per protocol set (PPS). All safety analyses were performed on the safety analysis set (SAS), defined as all randomised subjects who received at least one dose of the study drug.

For the cumulative recurrence rate of gastric or duodenal ulcers at week 24, the log-rank test was used to check superiority of each rabeprazole dose group as compared with the teprenone group. In this study, closed multiple testing procedures were used: the rabeprazole 10-mg group and teprenone group were compared in the first step, and only if a significant difference was observed, the rabeprazole 5-mg group and teprenone group were compared in the second step. The Kaplan–Meier method was used to estimate hazard ratios (+95% confidence intervals) for each rabeprazole dose group against the teprenone group. A secondary endpoint, the cumulative incidence of bleeding ulcers at week 24, was analysed in the same way. Fisher's exact test was used to compare the teprenone group and each rabeprazole dose group with respect to incidence rates of reflux oesophagitis, the percentage of subjects showing improvement/worsening of gastric and duodenal mucosal injury based on the modified Lanza score, and the percentage of subjects with worsening of upper gastrointestinal symptoms.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute., Cary, NC, USA).

P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Demographics

Four hundred and seventy-two subjects were randomised (Figure 1). There were 52 discontinuations (11%): 16 in the rabeprazole 10-mg group, 18 in the rabeprazole 5-mg group and 18 in the teprenone group. The main reasons for discontinuation were adverse events, subject choice and inadequate therapeutic effect. Four hundred and fifty-two subjects constituted the FAS for efficacy: 151 subjects in the rabeprazole 10-mg group, 150 in the rabeprazole 5-mg group and 151 in the teprenone group. The main reasons for exclusion from the FAS were lack of administration of the study drug, no evaluable endoscopic data and ineligibility to participate due to the presence of peptic ulcer at baseline. There were 431 subjects in the PPS (144, 144 and 143 subjects, respectively), and 471 subjects in the SAS (157, 156 and 158 subjects, respectively).

No major differences were observed among the treatment groups in terms of baseline characteristics (Table 1). The heterogeneities about previous drugs, the presence of *H. pylori* and eradication history were similar between the three groups. The mean compliance with study medication in each treatment group (SAS) was 99.5% in the rabeprazole 10-mg group, 99.1% in the rabeprazole 5-mg group and 96.9% in the teprenone group. There were two subjects in the rabeprazole 5-mg group and two subjects in the teprenone group with less than 75% compliance with the study medication.

Efficacy

Ulcer recurrence. The primary endpoint, the cumulative recurrence rate (number) for gastric and duodenal ulcers at week 24, was 1.4% (two subjects) in the rabeprazole 10-mg group, 2.8% (four subjects) in the rabeprazole 5-mg group and 21.7% (32 subjects) in the teprenone group (Kaplan–Meier estimates, FAS). Thus, both the rabeprazole groups demonstrated a significantly better preventive effect than the teprenone group ($P < 0.001$ for both rabeprazole groups vs. the teprenone group, log-rank test) (Figure 2). In addition, the hazard ratio with respect to the teprenone group was 0.05 in the rabeprazole 10-mg group, and 0.11 in the rabeprazole 5-mg group, indicating a risk reduction of ulcer recurrence of 95% and 89% respectively. The cumulative recurrence rate (number) for gastric or duodenal ulcers at week 24 in the PPS was 1.4% (two subjects) in the rabeprazole 10-mg group, 2.8% (four subjects) in the rabeprazole 5-mg group and 22.0% (31 subjects) in the teprenone group ($P < 0.001$ for both rabeprazole groups vs. the teprenone group, log-rank test). Thus, both FAS and PPS analyses showed that the rabeprazole groups experienced a significantly better preventive effect than the teprenone group. The ulcer conditions (site, stage classification, size, number, ulcer with or without upper gastrointestinal symptoms) at the time of recurrence are shown in Table 2.

Figure 2 shows that cumulative ulcer recurrence rates at week 12 were 0% in the rabeprazole 10-mg group, 1.3% in the rabeprazole 5-mg group and 16.6% in the teprenone group (Kaplan–Meier estimates, FAS), indicating that rabeprazole at doses of both 10 and 5 mg are significantly efficacious at week 12 compared with the teprenone group.

Cumulative incidence of bleeding ulcers. Table 2 shows Kaplan–Meier estimates of the cumulative incidence of bleeding ulcers at week 24. No cases of bleeding ulcer were seen in the rabeprazole 10- or 5-mg groups, and a significantly better preventive effect was seen in the groups receiving rabeprazole compared to the teprenone group ($P = 0.001$ for both rabeprazole groups vs. the teprenone group, log-rank test). Bleeding ulcers were observed in seven subjects in the teprenone group (Forrest classification type Ib, three subjects and type IIb, four subjects).

Erosive oesophagitis. Incidence rates of reflux oesophagitis at the end of treatment are shown in Table 2. The rabeprazole 10-mg (zero subjects) and 5-mg groups (grade A, three subjects) both demonstrated a significantly greater preventive effect compared to the teprenone group (grade A, seven subjects; grade B, six subjects). ($P < 0.001$, $P = 0.018$, for each rabeprazole group vs. the teprenone group, respectively, Fisher's exact test).

Severity scores of gastroduodenal damage. The percentage of subjects with improvement/worsening of gastric mucosal injury and duodenal mucosal injury based on the modified Lanza scores are shown in Figure 3(a). Both the rabeprazole groups demonstrated significantly greater preventive effects on worsening compared to the teprenone group ($P < 0.001$ for both rabeprazole groups vs. the teprenone group, Fisher's exact test). In addition, for gastric mucosal injury, the rabeprazole 10-mg group

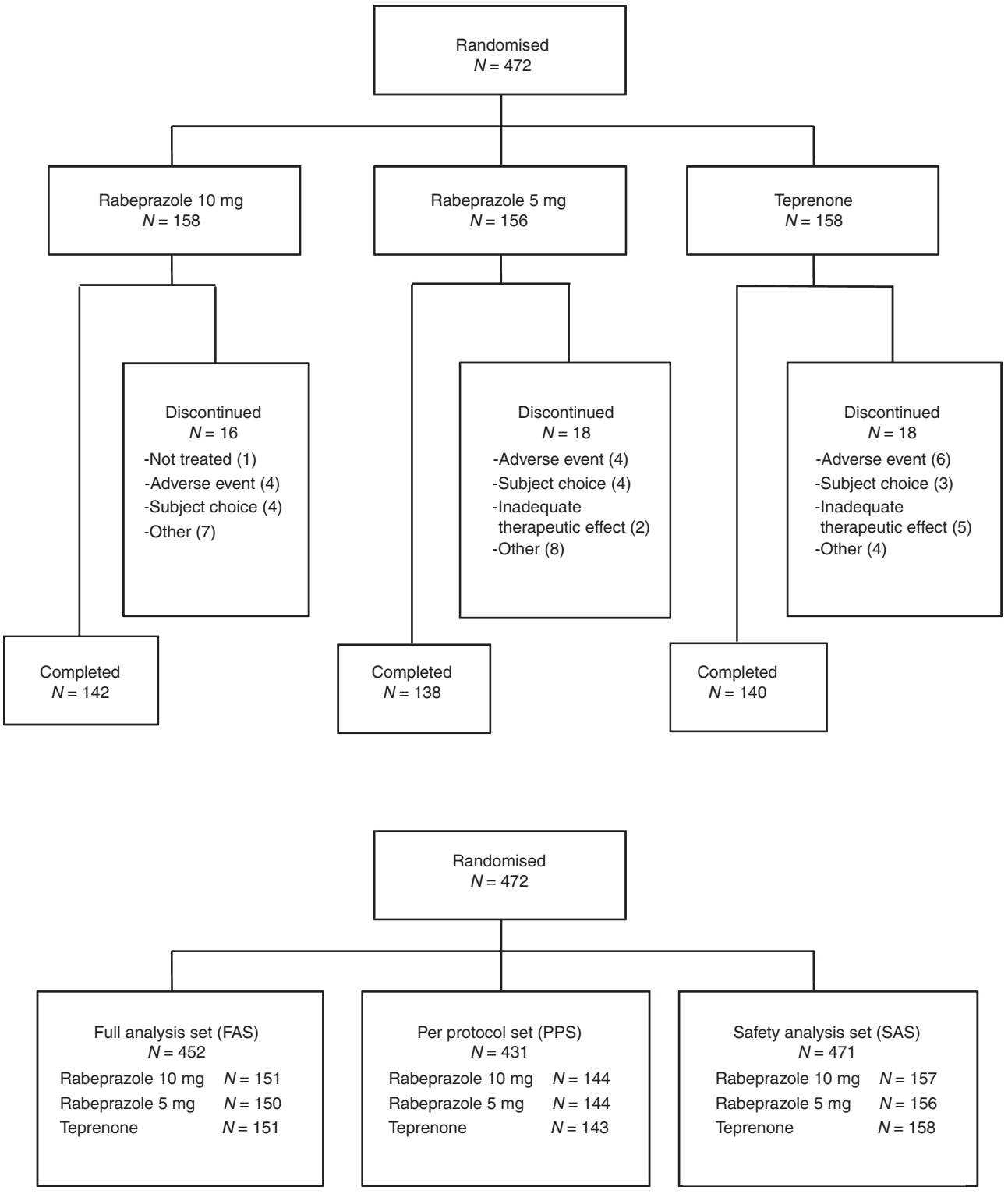

Figure 1 | Subject disposition and analysis set.

demonstrated a significantly greater improvement than the teprenone group ($P = 0.040$, Fisher's exact test). At end of treatment, the percentage of subjects with gastric mucosal injury of ≥grade 3 [presence of lesions (erosion, ecchymosis) in ≥2 regions or presence of ≥6 lesions] was 2.0% in the rabeprazole 10-mg group, 10.0% in the

Table 1 | Demographic and clinical characteristics (full analysis set)

	Rabeprazole 10 mg (n = 151)	Rabeprazole 5 mg (n = 150)	Teprenone (n = 151)
Male sex, *n* (%)	118 (78.1)	118 (78.7)	112 (74.2)
Mean age ± s.d. (years)	69.7 ± 9.6	69.2 ± 9.0	69.3 ± 7.9
Ischaemic condition*, *n* (%)			
Angina	62 (41.1)	67 (44.7)	65 (43.0)
Myocardial infarction	30 (19.9)	26 (17.3)	32 (21.2)
Ischaemic cerebrovascular disease	72 (47.7)	76 (50.7)	72 (47.7)
CABG or PTCA	49 (32.5)	51 (34.0)	46 (30.5)
Other	10 (6.6)	6 (4.0)	9 (6.0)
Aspirin dose (mg)			
81	14 (9.3)	12 (8.0)	16 (10.6)
100	137 (90.7)	138 (92.0)	135 (89.4)
Duration of aspirin use, *n* (%)			
<2 years	40 (26.5)	36 (24.0)	35 (23.2)
≥2 years	111 (73.5)	114 (76.0)	116 (76.8)
Concomitant use of anti-thrombotic drug except aspirin, *n* (%)	33 (21.9)	30 (20.0)	34 (22.5)
Helicobacter pylori status, *n* (%) (anti-*H. pylori* IgG antibodies)			
Positive	66 (43.7)	68 (45.3)	75 (49.7)
Negative (with history of eradication)	50 (33.1)	44 (29.3)	43 (28.5)
Negative (without history of eradication)	35 (23.2)	38 (25.3)	33 (21.9)
History of ulcers, *n* (%)			
Gastric	94 (62.3)	105 (70.0)	94 (62.3)
Duodenal	57 (37.7)	45 (30.0)	57 (37.7)
History of bleeding ulcers, *N* (%)			
Gastric	7 (4.6)	7 (4.7)	11 (7.3)
Duodenal	7 (4.6)	4 (2.7)	6 (4.0)
History of erosive oesophagitis, *n* (%)	18 (11.9)	26 (17.3)	22 (14.6)
Modified Lanza score ≥grade 1, *n* (%)			
Gastric	38 (25.2)	32 (21.3)	39 (25.8)
Duodenal	4 (2.6)	0 (0.0)	4 (2.6)
Pre-treatment drug for prevention of ulcer, *n* (%)			
PPIs	74 (49.0)	76 (50.7)	71 (47.0)
H_2 receptor antagonists	34 (22.5)	41 (27.3)	32 (21.2)
Mucosal protective agents	20 (13.2)	27 (18.0)	37 (24.5)
CYP2C19 genotypes, *n* (%)			
Homo EM	60 (39.7)	51 (34.0)	46 (30.5)
Hetero EM	65 (43.0)	76 (50.7)	77 (51.0)
PM	26 (17.2)	23 (15.3)	28 (18.5)
Current smoking, *n* (%)	26 (17.2)	23 (15.3)	22 (14.6)
Current alcohol consumption, *n* (%)	94 (62.3)	82 (54.7)	81 (53.6)

CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; CYP2C19, cytochrome P450 isoenzyme; EM, extensive metabolizer; PM, poor metabolizer.

* Multiple choice allowed.

rabeprazole 5-mg group and 29.1% in the teprenone group, indicating a significant difference between the rabeprazole 10-mg and 5-mg groups (P = 0.003, Fisher's exact test).

Upper gastrointestinal symptoms. Figure 3(b) shows the percentages of subjects with worsening of upper gastrointestinal symptoms. In terms of epigastric pain, stomach discomfort and heartburn, both the rabeprazole groups demonstrated a significantly greater preventive effect on worsening than the teprenone group (epigastric pain, P = 0.009 for both rabeprazole groups vs. the teprenone group; stomach discomfort, P = 0.006 and P = 0.018 for each rabeprazole group vs. the teprenone group, respectively; heartburn, $P < 0.001$ for both rabeprazole groups vs. the teprenone group, Fisher's exact method).

Subgroup analysis

Subgroup analyses were performed for the primary endpoint, cumulative recurrence rates of peptic ulcers at

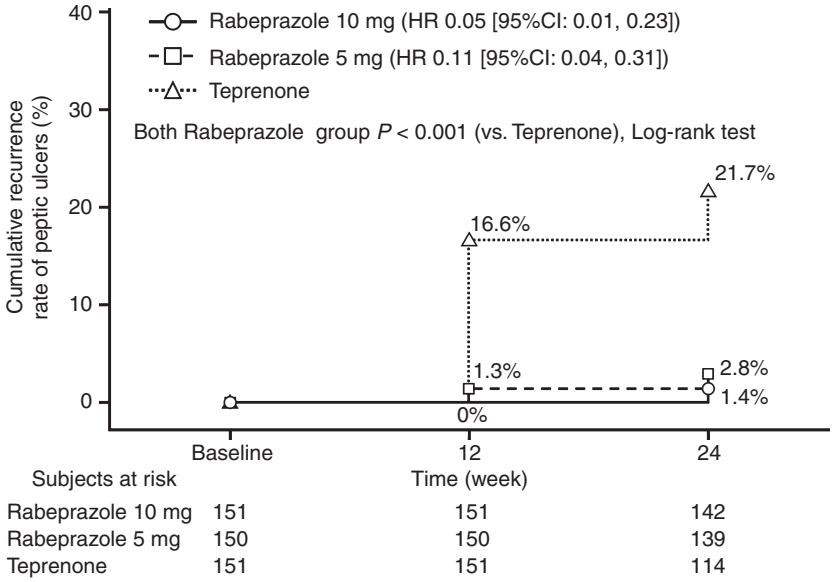

Figure 2 | Cumulative recurrence rates of peptic ulcers over 24 weeks (Kaplan–Meier estimates, FAS).

Table 2 | Endoscopic results (full analysis set)

Parameter	Rabeprazole 10 mg (n = 151)	Rabeprazole 5 mg (n = 150)	Teprenone (n = 151)	P value 10 mg vs. Teprenone 5 mg vs. Teprenone
Recurrent gastric and duodenal ulcers over 24 weeks, n	2	4	32	–
Site of ulcer, n				
Gastric	2	4	24	–
Duodenal	0	0	8	–
Grade of ulcer, n				
Healing stage	2	1	13	–
Active stage	0	3	19	–
Size of ulcer, n (mm)				
3≤ <5	1	1	17	–
5≤ <15	1	2	13	–
15≤	0	1	2	–
Number of ulcer, n				
Single	1	2	17	–
Multiple	1	2	15	–
Ulcer with or without upper gastrointestinal symptoms, n*				
With	0	0	15	–
Without	2	4	16	–
Bleeding ulcer, n (%; cumulative occurrence rate at week 24)	0 (0.0)	0 (0.0)	7 (4.6)	P = 0.001† P = 0.001†
Erosive oesophagitis, n (%; occurrence rate at end of treatment)	0 (0.0)	3 (2.0)	13 (8.6)	P < 0.001‡ P = 0.018‡

* One subject in the teprenone group did not give data of upper gastrointestinal symptoms at the time of ulcer recurrence.

† Log-rank test, significance level α = 0.05 (two sides).

‡ Fisher's exact test, significance level α = 0.05 (two sides).

week 24, based on Kaplan–Meier estimates of the FAS (Table 3). For each of the patient background factors (sex, age, LDA dose, concomitant use of anti-platelet or anticoagulant drugs except LDA, *H. pylori* infection, history of bleeding ulcers, CYP2C19 genotypes, current smoking and alcohol consumption habits), the hazard ratio for the rabeprazole groups vs. the teprenone group was either <1 or no ulcer recurrence was observed in the

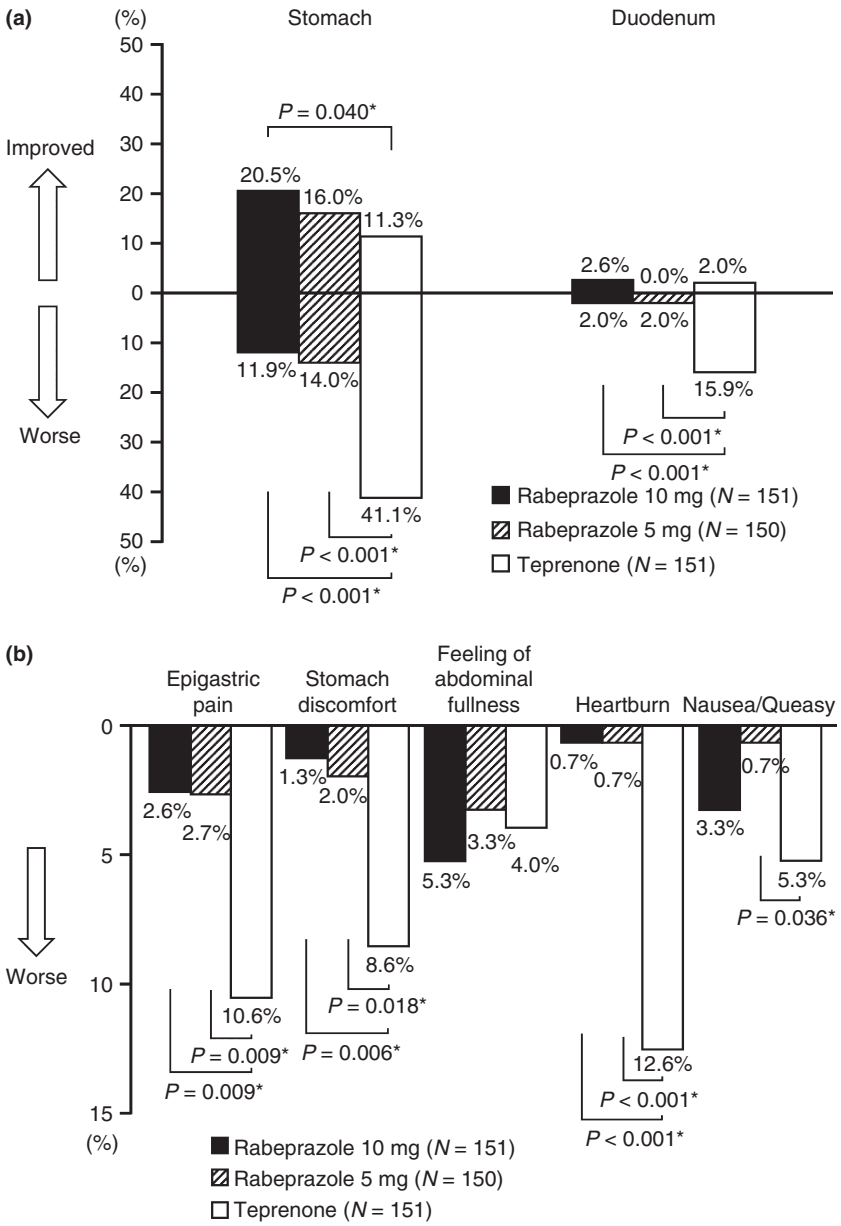

Figure 3 | Gastroduodenal damage and upper gastrointestinal symptoms (FAS). (a) Percentage of subjects with improvement/worsening of gastric mucosal injury and duodenal mucosal injury based on the modified Lanza scores at the final assessment compared to baseline. (b) Percentage of subjects with worsening of upper gastrointestinal symptoms at the final assessment compared to baseline.

rabeprazole group (in the latter case, hazard ratio was indicated as 'Not calculated'). Background factors had little impact on the superiority of the efficacy of the rabeprazole group compared with the teprenone group.

Safety

Table 4 shows a summary of the adverse events. Incidence rates of adverse events were 58.0% in the rabeprazole 10-mg group, 54.5% in the rabeprazole 5-mg group and 59.5% in the teprenone group. Incidence rates of drug-related adverse events were 8.9% in the rabeprazole 10-mg group, 4.5% in the rabeprazole 5-mg group and 10.1% in the teprenone group, indicating no clear differences among the three groups with respect to adverse events and drug-related adverse events. The most commonly occurring adverse event was nasopharyngitis in all groups.

There were no deaths during the study treatment. A serious adverse event that occurred in two or more subjects was angina pectoris (two subjects in the teprenone group). Another serious adverse event for which a causal relationship with the study drug could not be ruled out was acute cholecystitis in one patient in the rabeprazole 10-mg group. Other serious adverse events, classified into ischaemic disease, cardiac failure and cerebrovascular disorders, were observed in two subjects in the rabeprazole 10-mg group (subdural haematoma and carotid artery stenosis, one patient each), one patient in the rabeprazole 5-mg group (angina pectoris in a patient

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Table 3 | Cumulative recurrence rates of peptic ulcers over 24 weeks based on patient background (full analysis set)

Covariate classification	Events/*N* (%)			Hazard ratio (95% CI)
	Rabeprazole 10 mg (*n* = 151)	Rabeprazole 5 mg (*n* = 150)	Teprenone (*n* = 151)	10 mg vs. Teprenone 5 mg vs. Teprenone
Sex				
Men	2/118 (1.8)	3/118 (2.6)	28/112 (25.8)	0.06 (0.01, 0.24) 0.09 (0.03, 0.29)
Women	0/33 (0.0)	1/32 (3.3)	4/39 (10.3)	NC 0.29 (0.03, 2.59)
Age				
<70	1/72 (1.4)	2/73 (2.7)	18/72 (25.1)	0.05 (0.01, 0.37) 0.10 (0.02, 0.42)
≥70	1/79 (1.4)	2/77 (2.8)	14/79 (18.2)	0.06 (0.01, 0.48) 0.13 (0.03, 0.57)
Aspirin dose (mg)				
81	1/14 (7.1)	2/12 (16.7)	3/16 (19.8)	0.32 (0.03, 3.10) 0.80 (0.13, 4.80)
100	1/137 (0.8)	2/138 (1.5)	29/135 (21.9)	0.03 (0.00, 0.22) 0.06 (0.01, 0.25)
Concomitant use of anti-thrombotic drug except aspirin				
With	1/33 (3.2)	0/30 (0.0)	10/34 (30.1)	0.09 (0.01, 0.68) NC
Without	1/118 (0.9)	4/120 (3.4)	22/117 (19.2)	0.04 (0.01, 0.30) 0.16 (0.05, 0.46)
Helicobacter pylori status (Anti-*H. pylori* IgG antibodies)				
Positive	2/66 (3.1)	1/68 (1.5)	20/75 (27.3)	0.10 (0.02, 0.41) 0.05 (0.01, 0.36)
Negative	0/85 (0.0)	3/82 (3.8)	12/76 (15.8)	NC 0.21 (0.06, 0.75)
History of bleeding ulcers				
With	0/14 (0.0)	0/11 (0.0)	5/17 (29.9)	NC NC
Without	2/137 (1.6)	4/139 (3.0)	27/134 (20.6)	0.06 (0.02, 0.27) 0.13 (0.04, 0.36)
CYP2C19 genotypes				
Homo EM	1/60 (1.7)	0/51 (0.0)	14/46 (30.7)	0.05 (0.01, 0.35) NC
Hetero EM	1/65 (1.7)	3/76 (4.1)	15/77 (19.9)	0.07 (0.01, 0.52) 0.18 (0.05, 0.61)
PM	0/26 (0.0)	1/23 (4.3)	3/28 (11.0)	NC 0.40 (0.04, 3.86)
Current smoking				
With	1/26 (3.8)	0/23 (0.0)	8/22 (36.4)	0.09 (0.01, 0.69) NC
Without	1/125 (0.9)	4/127 (3.3)	24/129 (19.0)	0.04 (0.01, 0.28) 0.15 (0.05, 0.44)
Current alcohol consumption				
With	2/94 (2.2)	2/82 (2.4)	22/81 (27.7)	0.07 (0.02, 0.28) 0.08 (0.02, 0.33)
Without	0/57 (0.0)	2/68 (3.2)	10/70 (14.7)	NC 0.19 (0.04, 0.87)

NC, not calculated; CI, confidence interval.

concomitantly on clopidogrel), and three subjects in the teprenone group (angina pectoris in two subjects, one of whom was on concomitant clopidogrel, and embolic stroke in one subject). Cardiovascular adverse events did not trend disproportionately to the rabeprazole group compared to the teprenone group.

Table 4 | Adverse events (safety analysis set)

	Rabeprazole 10 mg (*n* = 157)	Rabeprazole 5 mg (*n* = 156)	Teprenone (*n* = 158)
Any adverse events, *n* (%)	91 (58.0)	85 (54.5)	94 (59.5)
Serious adverse events (SAEs), *n* (%)	6 (3.8)	10 (6.4)	10 (6.3)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Other SAEs	6 (3.8)	10 (6.4)	10 (6.3)
Adverse events leading to study drug withdrawal, *n* (%)	5 (3.2)	7 (4.5)	5 (3.2)
Treatment-related adverse events, *n* (%)	14 (8.9)	7 (4.5)	16 (10.1)
≥2 events SAEs, *n* (%)			
Angina pectoris	0 (0.0)	1 (0.6)	2 (1.3)
≥2% adverse events, *n* (%)			
Constipation	5 (3.2)	1 (0.6)	6 (3.8)
Diarrhoea	6 (3.8)	4 (2.6)	2 (1.3)
Nasopharyngitis	22 (14.0)	25 (16.0)	25 (15.8)
Pharyngitis	1 (0.6)	6 (3.8)	2 (1.3)
Upper respiratory tract infection	3 (1.9)	5 (3.2)	2 (1.3)
Contusion	0 (0.0)	4 (2.6)	3 (1.9)
Diabetes mellitus	2 (1.3)	4 (2.6)	1 (0.6)
Epistaxis	1 (0.6)	0 (0.0)	4 (2.5)
Eczema	6 (3.8)	1 (0.6)	1 (0.6)
Hypertension	5 (3.2)	0 (0.0)	3 (1.9)

DISCUSSION

The use of LDA therapy to prevent the occurrence of arterial thrombotic disease is steadily increasing. On the other hand, ill effects of LDA therapy have also been pointed out, such as the occurrence of peptic ulcer and upper gastrointestinal haemorrhage.[3, 4, 8, 9] Acid-suppressive therapy with PPIs has already been recommended in a variety of guidelines and review articles on the prevention of upper gastrointestinal mucosal injury in patients taking LDA,[12, 41] and this practice is gradually spreading to the clinical setting. However, the efficacy of rabeprazole when combined with LDA has not yet been investigated sufficiently.

In previous studies, when investigations have been conducted in populations that included patients undergoing primary prevention for peptic ulcers, incidence rates for ulcers in the placebo group have ranged from 6.2% to 7.4%,[36, 37] suggesting that there were many patients taking LDA who did not necessarily need concomitant PPIs. Consequently, in this study, which is the first double-blind comparative study of rabeprazole, we targeted secondary prevention in a population with a history of ulcers, a higher risk group. In addition, from an ethical perspective as well as from the standpoint of feasibility, it was difficult to establish a placebo as the comparator in Japan, and hence, teprenone was selected instead.

The present study results have demonstrated that rabeprazole prevents ulcer recurrence in subjects taking LDA. Moreover, statistically significant effects in comparison with the teprenone group were confirmed not just in the rabeprazole 10-mg group (standard dose in Japan), but also in the 5-mg group. In the present 24-week study, ulcer recurrence rates were 1.4% in the rabeprazole 10-mg group and 2.8% in the rabeprazole 5-mg group. The present results with rabeprazole are comparable to those with other PPIs in subjects with a history of ulcers who were both negative and positive for *H. pylori*. That is, the recurrence rate with esomeprazole 20 mg plus gefarnate 100 mg at week 24 was 1.7% (98.3% nonrecurrence rate)[39] and those with lansoprazole 15 mg at day 181 was 2.1%.[40]

As shown in the present Table 2, several subjects showed ulcer with the size of ≥5 mm when recurrence occurred; that is, one subject in the rabeprazole 10-mg group, three subjects in the rabeprazole 5-mg group and 15 subjects in the teprenone group. Endoscopy confirmed no episodes of clinically significant bleeding ulcers in either the rabeprazole 10-mg or 5-mg groups. Furthermore, no subject in the rabeprazole 10-mg and 5-mg groups showed recurrence of ulcer that was accompanied by upper gastrointestinal symptoms, but 15 subjects in the teprenone group showed it.

The present recurrence rate was 21.7% in the teprenone group, while the previously reported rates were

15.0% in the gefarnate plus placebo group[39] and 24.0% in the gefarnate group,[40] indicating that the present use of teprenone as the active control is valid.

In a previous LDA plus lansoprazole 30-mg study where the ulcer size definition of ≥5 mm was used and *H. pylori* was eradicated, the ulcer occurrence rate at month 12 was reported to be 1.6% in the lansoprazole group and 14.8% in the placebo group.[42] We consider that the larger size definition of ≥5 mm and *H. pylori* eradication would have contributed to the lower placebo value (14.8%) compared with active control values in the present and recent clinical studies (21.7%, 15.0% and 24.0%).

The improvement of secondary endpoints also demonstrated the efficacy of rabeprazole, namely, incidence rates of erosive oesophagitis, the severity scores of gastric and duodenal mucosal injury, and upper gastrointestinal symptom scores (epigastric pain, stomach discomfort and heartburn). These results are consistent with those of previous studies using rabeprazole in healthy individuals[43, 44] and those of an open-label study in patients with a history of ulcers.[21]

Overall, there were no major differences in most of the efficacy parameters between the rabeprazole 10-mg and 5-mg groups, except that the percentage of subjects with grade 3 or higher gastric mucosal injury based on Lanza scores at end of treatment was significantly lower in the 10-mg group than the 5-mg group, and the ulcer condition (grade and size), in the event of recurrence, was somewhat milder in the 10-mg group than the 5-mg group.

The results of subgroup analyses showed that in the teprenone group, there were many subjects with ulcer recurrence among populations positive for *H. pylori*, and with concomitant use of an anti-thrombotic drug and with a history of bleeding ulcers, which are reported to be general risk factors for LDA-associated ulcers,[40, 45] while ulcer recurrence in each of these population subtypes was not observed in the rabeprazole groups. Multivariate analysis showed that teprenone administration was the only risk factor for ulcer development in this study (data not shown).

Under conditions of routine clinical care, LDAs are administered for extended periods, often in patients with multiple risk factors. Further, LDA users without current or past *H. pylori* infections who develop ulcer bleeding were reported to have a very high risk of recurrent bleeding in a long-term study.[46] In routine clinical care, it is difficult to thoroughly investigate whether the patient has a history of ulcers or upper gastrointestinal haemorrhage, and the existence and type of any concomitant medication. Taking these into consideration, we believe that rabeprazole 10 mg may exert a reliable and stable prophylactic effect in all types of patients because there were only two subjects in the rabeprazole groups with ulcer recurrence in this study, and the pharmacodynamic effect (as seen with 24-h gastric pH monitoring) was better in the rabeprazole 10-mg group than the 5-mg group.[47] In fact, subgroup analyses in this study among *H. pylori*-negative subjects who require more potent inhibition of acid secretion showed that ulcer recurrence was experienced by three subjects in the rabeprazole 5-mg group, but none of the subjects in the 10-mg group.

Appropriate selection of the concomitant PPI is an important issue in elderly LDA users. Rabeprazole is less affected by CYP2C19 genotype,[15–17] and has little interaction with clopidogrel, which is often used together with LDA.[20, 48–50] It is also reported to be safe even if used concomitantly with warfarin after open-heart surgery, as it is unlikely to produce haemorrhagic complications.[51] In the present study, 20% of subjects had concomitant administration of anti-platelet agents or anticoagulants, and serious adverse events, such as ischaemic disease, cardiac failure or cerebrovascular disorders occurred in two subjects (1.3%) in the rabeprazole 10-mg group, one subject (0.6%) in the rabeprazole 5-mg group and three subjects (1.9%) in the teprenone group, indicating that use of rabeprazole did not increase the frequency or type of serious cardiovascular adverse events. There were also no deaths among the study population.

This study has the following limitations. First is the problem of the duration of treatment. In this study, to confirm the efficacy of rabeprazole vs. teprenone, the duration of treatment was set at 24 weeks. However, once LDA treatment is begun as routine clinical care, treatment may continue on a semi-permanent basis. This study did not adequately investigate if the efficacy and safety of rabeprazole can be sustained over a longer time frame. To overcome this limitation, a long-term study is currently ongoing for subjects who had not experienced ulcer recurrence at week 24, extending the duration of treatment by an additional 52 weeks (maximum duration of treatment of 76 weeks) (ClinicalTrials.gov Identifier: NCT01398410). The results of this long-term study will certainly provide additional key information. The second limitation is the problem of the subjects included. A procedure that would require *H. pylori* eradication in all *H. pylori*--

positive subjects should be considered to eliminate the effect of *H. pylori* infection on ulcer recurrence. However, because the objective was to cover all scenarios that could potentially be encountered in routine clinical care, it was decided to treat *H. pylori* infection status as irrelevant. Third, is the problem of the number of subjects. In this study, the focus was on ulcer recurrence rates, and the sample size was determined based on evidence from similarly designed studies involving other PPIs. Therefore, for evaluating efficacy in subgroup analyses and safety in terms of adverse events related to haemorrhage, etc., the power may be inadequate. Future, larger studies are needed to address these problems.

In conclusion, both rabeprazole 5 and 10 mg are efficacious in preventing ulcer recurrence in subjects with a history of ulcers currently taking LDA for cardiovascular protection. The drug is well tolerated at both these doses.

AUTHORSHIP

Guarantor of the article: Kazuma Fujimoto.

Author contributions: Ryuichi Iwakiri was involved in protocol planning, patient recruitment, data interpretation, and writing and editing the original paper. Kazuhide Higuchi, Mototsugu Kato and Mitsuhiro Fujishiro, as endoscopy specialists, were involved in protocol planning and data interpretation, and were members of the endoscopy central review panel. Toshio Watanabe and Toshihisa Takeuchi were involved in protocol planning, patient recruitment and data interpretation. Tetsuo Arakawa and Yoshikazu Kinoshita, as specialists in gastroenterology, were involved in protocol planning, implementation and overall coordination of the study, and data interpretation. Yasushi Okada and Hisao Ogawa, as cerebrovascular and cardiovascular specialists, were involved in protocol planning, implementation and overall coordination of the study and data interpretation. Masao Yamauchi, Makoto Sanomura and Hidemitsu Nakagawa contributed to patient recruitment and data interpretation. Nobuyuki Sugisaki was the sponsor's (Eisai Co., Ltd.) employee in charge of this study. Kazuma Fujimoto, as the principal investigator, had overall responsibility for the study. All authors reviewed this article and approved the final version of the manuscript. The PLANETARIUM study group contributed to acquisition of data.

ACKNOWLEDGEMENTS

The authors thank all contributing members (listed in the Appendix) and the sponsor, Japan/Asia Clinical Research Product Creation Unit of Eisai Co., Ltd., Tokyo, Japan and the project members of Mediscience Planning Inc.,Tokyo, Japan for their contribution in the study monitoring.

Declaration of personal interests: Kazuhide Higuchi has served in speaking and teaching commitments for Eisai Co., Ltd. and Daiichi Sankyo Company, Ltd. and has received scholarship grants from Eisai Co., Ltd., and Daiichi Sankyo Company, Ltd. Mototsugu Kato has served in speaking and teaching commitments for Eisai Co., Ltd., Daiichi Sankyo Company, Ltd., Takeda Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd. and AstraZeneca K.K. and has received scholarship grants from Eisai Co., Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Ltd., AstraZeneca K.K. and Astellas Pharma Inc. Mitsuhiro Fujishiro has served in speaking and teaching commitments for Eisai Co., Ltd and has received from scholarship grants from Dainippon Sumitomo Pharma Co., Ltd. Yoshikazu Kinoshita has served in speaking and teaching commitments in Eisai Co., Ltd., Daiichi Sankyo Company, Ltd., Takeda Pharmaceutical Co., Ltd. and AstraZeneca K.K. and has received research grants and scholarship grants from Eisai Co., Ltd., Daiichi Sankyo Company, Ltd., Takeda Pharmaceutical Co., Ltd. and AstraZeneca K.K. Toshio Watanabe has received from research grants from Eisai Co., Ltd. Masao Yamauchi has received from research grants from AstraZeneca K.K. Nobuyuki Sugisaki is an employee of Eisai Co., Ltd. Hisao Ogawa has served on advisory committees and review panels for Eli Lilly Japan K.K, Novartis Pharma K.K. and Pfizer Japan Inc., has served as a board membership of Takeda Pharmaceutical Co., Ltd., has received research grants from AstraZeneca K.K., Astellas Pharma Inc., Bayer Holding Ltd., Boehringer Ingelheim, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Ltd., Eisai Co., Ltd, Kowa Company, Ltd., Mitsubishi Tanabe Pharma Corporation, MSD K.K., Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., Shionogi & Co., Ltd. and Takeda Pharmaceutical Co., Ltd., and has served in speaking and teaching commitments for Pfizer Japan Inc. and Sanofi K.K. Tetsuo Arakawa has served on advisory committees and review panels for Eisai Co., Ltd, and Otsuka Pharmaceutical Co., Ltd. Kazuma Fujimoto has served on advisory committees and review panels for Eisai Co., Ltd. The following authors have nothing to declare: Ryuichi Iwakiri, Toshihisa Takeuchi, Makoto Sanomura, Hidemitsu Nakagawa and Yasushi Okada.

Declaration of funding interests: This study was funded by Eisai Co., Ltd., Tokyo, Japan. Writing support was provided by Eisai. Data management and analyses were undertaken by Eisai.

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APPENDIX 1: MEMBERS OF THE PLANETARIUM STUDY GROUP: PLANETARIUM (PREVENTION OF RECURRENT GASTRIC OR DUODENAL ULCERS CAUSED BY LOW-DOSE ASPIRIN WITH RABEPRAZOLE TREATMENT -A MULTICENTRE, RANDOMISED, PARALLEL-GROUP, DOUBLE-BLIND, COMPARATIVE TRIAL-)

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