AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: rabeprazole improves symptoms in patients with functional dyspepsia in Japan

R. Iwakiri*[,1], K. Tominaga†[,1], K. Furuta‡[,1], M. Inamori§, T. Furuta¶, H. Masuyama**, K. Kanke††, A. Nagahara‡‡, K. Haruma§§, Y. Kinoshita‡, K. Higuchi¶¶, S. Takahashi***, M. Kusano†††, K. Iwakiri‡‡‡, M. Kato§§§, M. Hongo¶¶¶, H. Hiraishi††, S. Watanabe‡‡, H. Miwa****, Y. Naito††††, K. Fujimoto‡‡‡‡ & T. Arakawa†

*Department of Internal Medicine & Gastrointestinal Endoscopy, Saga Medical School, Saga, Japan.
†Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka, Japan.
‡Department of Gastroenterology and Hepatology, Shimane University School of Medicine, Shimane, Japan.
§Gastroenterology Division, Yokohama City University Hospital, Kanagawa, Japan.
¶Center for Clinical Research, Hamamatsu University School of Medicine, Shizuoka, Japan.
**Masuyama Gastrointestinal Clinic, Tochigi, Japan.
††Department of Gastroenterology, Dokkyo Medical University, Tochigi, Japan.
‡‡Department of Gastroenterology, Juntendo University School of Medicine, Tokyo, Japan.
§§Department of Gastroenterology, Kawasaki Medical School, Kanagawa, Japan.
¶¶Second Department of Internal Medicine, Osaka Medical College, Osaka, Japan.
***Third Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan.
†††Department of Endoscopy and Endoscopic Surgery, Gunma University Hospital, Gunma, Japan.
‡‡‡Department of Medicine, Division of Gastroenterology, Nippon Medical School, Tokyo, Japan.
§§§Division of Endoscopy, Hokkaido University Hospital, Hokkaido, Japan.
¶¶¶Department of Comprehensive Medicine and Psychosomatic Medicine, Tohoku University Hospital, Miyagi, Japan.
****Division of Upper Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan.
††††Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan.
‡‡‡‡Department of Internal Medicine, Saga Medical School, Saga, Japan.

Correspondence to:
Dr R. Iwakiri, Department of Internal Medicine & Gastrointestinal Endoscopy, Saga Medical School, 5-1-1 Nabeshima, Saga, Saga 849-8501, Japan.
E-mail: iwakiri@cc.saga-u.ac.jp

[1]These authors contributed equally to this study.

Publication data
Submitted 22 April 2013
First decision 26 April 2013
Resubmitted 17 July 2013
Accepted 18 July 2013

SUMMARY

Background
The efficacy of proton pump inhibitors (PPIs) for treating functional dyspepsia (FD) is not well established.

Aim
This study, named the SAMURAI study, aimed to assess the efficacy and dose–response relationship of rabeprazole in Japanese patients with FD in a multicentre, double-blinded, randomised, placebo-controlled trial.

Methods
Investigated FD was diagnosed using the Rome III criteria. Subjects who did not respond to 1 week of single-blind placebo treatment in a run-in period were randomly assigned to 8 weeks of double-blind treatment with rabeprazole 10 mg, 20 mg, 40 mg or placebo, once daily. Dyspeptic symptoms were assessed by a dyspepsia symptom questionnaire (7-point Likert scale) and symptom diary.

Results
Of 392 subjects entered into the run-in period, 338 were randomly assigned. Although there was no significant difference between placebo and rabeprazole groups in complete symptom relief for four major dyspeptic symptoms, the satisfactory symptom relief of rabeprazole 20 mg was significantly higher than placebo according to the dyspepsia symptom questionnaire (45.3% vs. 28.2%, $P = 0.027$) and the symptom diary assessment (48.7% vs. 30.0%, $P = 0.016$). The efficacy was not influenced by syndrome type or *Helicobacter pylori* status. No statistically significant differences in the incidence of adverse events were seen among treatment groups.

Conclusions
Rabeprazole 20 mg once daily but not 10 or 40 mg significantly provides satisfactory symptom relief for functional dyspepsia (ClinicalTrials.gov, Number NCT01089543).

Aliment Pharmacol Ther

doi:10.1111/apt.12444

INTRODUCTION

Functional dyspepsia (FD) is common worldwide, and is defined as the presence of persistent epigastric pain, epigastric burning, postprandial fullness or early satiety in the absence of evident organic disease.[1] FD has an appreciable impact on quality of life.[2] The pathogenesis of FD is complex and characterised by multiple pathophysiological mechanisms such as delayed gastric emptying, impaired gastric accommodation, hypersensitivity to gastric distension, abnormal clearance of duodenal acid or dysregulation of the central nervous system.[3] Among these, visceral hypersensitivity is recognised as an important pathophysiological mechanism and hypersensitivity to acid secretion is known to cause dyspeptic symptoms.[4] Although most patients with FD have normal acid output,[5] acid-suppressive therapies have been the mainstay of treatment. Acid-suppressing agents such as H_2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) have induced symptom relief in a proportion of FD patients in various clinical studies.[6] Several studies have shown that PPIs have greater efficacy against dyspeptic symptoms than H_2RAs or prokinetics.[7,8] In studies conducted in Europe and the United States, PPIs have generally achieved modest but clinically significant improvements in dyspeptic symptoms,[9–12] but data from Asian countries are lacking.

Rabeprazole is used widely for the treatment of reflux oesophagitis and non-erosive reflux disease.[13,14] It has been shown to have a dose-dependent antisecretory effect in Japanese healthy adult male volunteers.[15] We performed a Phase II study to assess the efficacy of rabeprazole and to evaluate the possible dose-dependent effects in the treatment of investigated FD diagnosed according to the Rome III criteria. We decided to name this trial the 'SAMURAI study' (Suppression of Acid Milieu with Rabeprazole Improving Functional Dyspepsia).

MATERIALS AND METHODS

Study design

This Phase II study was a multicentre, double-blinded, randomised, placebo-controlled trial conducted to assess the efficacy and safety of rabeprazole (10, 20 or 40 mg) administered once daily for 8 weeks to Japanese patients with investigated FD diagnosed using the Rome III criteria.[16] The study design is summarised in Figure 1.

The study was conducted at 66 sites in Japan between January 2010 and August 2011. It was performed in compliance with the ethical principles based on the Declaration of Helsinki (and subsequent revisions) and with good clinical practice. The study was approved by the institutional review boards of each participating study centre and was registered with clinicaltrials.gov (NCT01089543). All subjects provided written informed consent before enrolment in the trial.

Patient population

Patients entered into the run-in period were aged ≥20 years, had suffered one or more of the four major dyspeptic symptoms (epigastric pain, epigastric burning, early satiety and postprandial fullness) for ≥6 months, and had continually experienced dyspeptic symptoms of at least moderate severity within the last 3 months; this was assessed using a dyspepsia symptom questionnaire

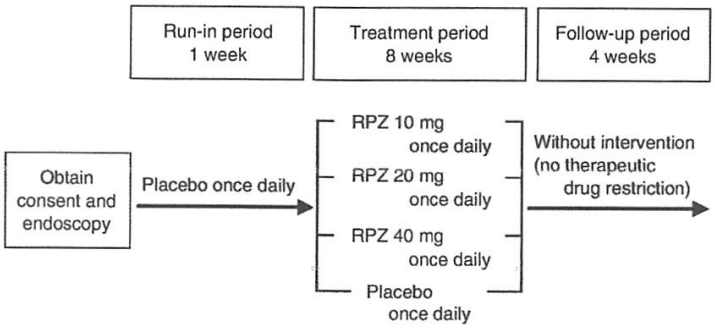

Figure 1 | Study design. The study comprised three terms. The first term was a run-in period, during which patients who were eligible for the inclusion criteria were treated with placebo for 1 week in a single-blinded manner. In the next treatment period, patients were randomly assigned to 8 weeks of double-blinded treatment with rabeprazole 10 mg, 20 mg, 40 mg or placebo, once daily. During the third follow-up period, patients were allowed to receive any treatment considered adequate by the treating physicians.

based on the Rome III criteria (see the 'Assessment' section below). Endoscopic examination was done ≤7 days before the start of the run-in period. Patients were excluded if there was any endoscopic evidence that would explain the dyspeptic symptoms, such as active gastric or duodenal ulcers, reflux oesophagitis or acute gastroduodenal mucosal lesions. Patients with a chief complaint of heartburn or regurgitation were also excluded.

Assessment

Dyspepsia symptoms were assessed using a dyspepsia symptom questionnaire and a symptom diary was designed specifically for this study with reference to previously utilised symptom scales such as the Rome III diagnostic questionnaire for adult functional gastrointestinal disorders,[17] the Global Overall Symptom Scale,[18] and the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease.[19] The dyspepsia symptom questionnaire, a self-assessment questionnaire, comprised eight questions covering eight symptoms (epigastric pain, epigastric burning, heartburn or regurgitation, early satiety, nausea, belching, postprandial fullness, epigastric bloating) assessed on a 7-point Likert scale: 1, none; 2, awareness of symptom, but can be easily ignored; 3, mild symptom and easily tolerated; 4, moderate symptom, but does not influence daily activities; 5, moderate-to-severe symptoms that occasionally limit daily activities; 6, severe symptoms that often limit daily activities; and 7, very severe symptoms often requiring rest. Patients answered the dyspepsia symptom questionnaire at each visit to obtain baseline (beginning of the run-in period), week 0, week 4, week 8 and end of follow-up scores. The symptom diary comprised four questions on major dyspeptic symptoms (epigastric pain, epigastric burning, early satiety, postprandial fullness). From bedtime on the previous day until bedtime on the current day, patients recorded each of these symptoms as being 'present' or 'absent'. The dyspepsia symptom questionnaire evaluated the severity of dyspeptic symptoms or difficulty of daily life, and the symptom diary evaluated the frequency of dyspeptic symptoms. In addition, to investigate the willingness to continuing use of the study drugs, following questionnaire was administered 'If available, do you want to continue to take this study drug after this clinical trial?' Patients provided a 'yes/no' answer to this question at the week-8 visit.

Study protocol

Patients who had scores ≥5 for at least one symptom in the four major dyspeptic symptoms according to the dyspepsia symptom questionnaire were initially enrolled into a 1-week run-in period (single-blinded administration of placebo). Only subjects who did not respond to the placebo (defined as patients who had scores ≥5 for the same symptoms on the dyspepsia symptom questionnaire, and had ≥2 days/week episodes of the same symptoms recorded in the symptom diary) were randomised to an 8-week double-blinded treatment period. All patients received three tablets once daily after breakfast in double-dummy fashion. The tablet types were as follows: A10, active rabeprazole 10 mg; P10, placebo rabeprazole 10 mg; A20, active rabeprazole 20 mg; P20, placebo rabeprazole 20 mg. Thus, the four treatment arms were as follows: placebo group (including run-in period), P10-P20-P20; rabeprazole 10 mg group, A10-P20-P20; rabeprazole 20 mg group, P10-A20-P20; and rabeprazole 40 mg group, P10-A20-A20. Patients who completed the treatment period moved on to the follow-up period, during which they were allowed to receive any treatment considered adequate by their treating physicians. Investigators and patients were blinded to the assigned treatment during the treatment period, whereas only the investigators were aware of the placebo nature of the treatment in the run-in period. Third-party organisation (Bellsystem24, Inc., Tokyo, Japan) randomly created key code of study drug (1:1:1:1), assigned the subjects to the four treatment arms and kept the code until the public key to maintain the blindness.

Endpoints

The primary endpoints were the rate of complete relief of symptoms according to the dyspepsia symptom questionnaire (defined as scores of 1 for all four major dyspeptic symptoms at week 8) and the symptom diary (defined as the absence of all four symptoms during the 7 days before week 8). Secondary endpoints were the rate of satisfactory relief of symptoms according to the dyspepsia symptom questionnaire (defined as scores of ≤2 for all four major symptoms at week 8) and the symptom diary (defined as a frequency of ≤1 day for all four major symptoms during the 7 days before week 8). The mean scores for each of individual symptoms according to the dyspepsia symptom questionnaire were evaluated at each visit basis. The time to first sustained complete relief according to the symptom diary was assessed using Kaplan–Meier plots. In this analysis, each plot represents the percentage of patients achieving sustained complete symptom relief from the day when complete symptom relief began to the last day of observation. The willingness to continuing use of the study drugs was assessed at week 8. The primary analysis

was conducted for the per protocol set, because this trial was a Phase II (dose-finding) study.

Statistical analysis

Based on previous studies, the expected difference in complete symptom relief rates between placebo and rabeprazole groups was assumed to be 15% based on a placebo response rate of 10–50%. A sample size of 80 in each group had 80%, 75% and 74% power to detect a 10% threshold difference in response rate assuming that the placebo response rate was 10%, 30% and 50% respectively.

Most statistical analyses were performed using SAS software (version 9.1 or later; SAS Institute Inc., Cary, NC, USA). All statistical tests were conducted for homogeneity of demographic characteristics among treatments ($\alpha = 0.15$) and for comparison of the efficacy and safety between placebo and each rabeprazole group ($\alpha = 0.05$) unless specified.

To assess efficacy, primary endpoints were compared using the chi-squared test. There was no adjustment for multiplicity in comparisons between placebo and each rabeprazole group. The secondary endpoints and the rates of the willingness to continuing use of the study drugs were analysed by the same method as for the primary endpoint. Each symptom was assessed by a 7-point Likert scale and mean scores for each of eight dyspeptic symptoms were calculated respectively. The time to first sustained complete relief according to the symptom diary was assessed using the Kaplan–Meier method and compared using the generalised Wilcoxon test to assess the onset and duration of the effects of rabeprazole.

For the safety assessment, the incidences of adverse events and adverse drug reactions were summarised by treatment and compared using the chi-squared test.

RESULTS

Demographics

Three hundred and ninety-two patients entered the run-in period, and 338 were randomised into the 8-week, double-blinded treatment period. The participation of the remaining 54 patients was discontinued before randomisation for the reasons shown in Figure 2. Forty-two patients (10.7%) showed a response to placebo during the run-in period. Among the randomised patients ($n = 338$), 326 patients completed the randomisation period and entered the follow-up period, and 321 patients completed the follow-up period. No significant difference in demographic characteristics was observed between the four treatment groups ($P < 0.15$; Table 1).

Efficacy analysis

Scores for each dyspeptic symptom according to the dyspepsia symptom questionnaire. The mean (±standard deviation) scores for each dyspeptic symptom (epigastric pain, epigastric burning, heartburn or regurgitation, early satiety, nausea, belching, postprandial fullness, epigastric bloating), total four major dyspeptic symptoms and total eight dyspeptic symptoms at each visit are shown in Table 2. All scores from week 0 to week 8 indicated improvements over time including placebo group.

Complete symptom relief and satisfactory symptom relief for all four major dyspeptic symptoms (epigastric pain, epigastric burning, early satiety, postprandial fullness). Complete symptom relief rates based on the dyspepsia symptom questionnaire were 17.9% (14/78), 22.4% (17/76), 29.3% (22/75) and 27.0% (20/74) for the placebo and rabeprazole 10, 20 and 40 mg groups respectively (Figure 3a, open columns). As in complete symptom relief rates, rabeprazole 20 mg treatment exhibited a better response compared with the placebo group ($P = 0.097$, chi-squared test). Rates of satisfactory symptom relief according to the dyspepsia symptom questionnaire were 28.2% (22/78), 42.1% (32/76), 45.3% (34/75) and 39.2% (29/74) respectively (Figure 3a, closed columns). A significant difference in satisfactory relief was seen between the rabeprazole 20 mg group and placebo group ($P = 0.027$, chi-squared test). Similar results were observed for complete relief and satisfactory relief according to the symptom diary between the rabeprazole 20 mg group and placebo group (28.9% vs. 17.5%, $P = 0.089$; 48.7% vs. 30.0%, $P = 0.016$) (Figure 3b). No significant differences were observed between the placebo group and the rabeprazole 10 or 40 mg group. The time to first sustained complete relief according to the symptom diary is shown in Figure 4. The rabeprazole 20 mg group had a significantly greater response rate than the placebo group throughout the examined period ($P = 0.044$, generalised Wilcoxon test). The rates of the willingness to continuing use of the study drugs were 59.0% (46/78), 72.4% (55/76), 85.3% (64/75) and 64.9% (48/74) in the placebo and rabeprazole 10, 20 and 40 mg groups respectively. A significant difference was identified between the placebo and rabeprazole 20 mg group ($P = 0.0002$, chi-squared test).

Subpopulation analysis based on subject background. Although syndrome type [i.e. epigastric pain

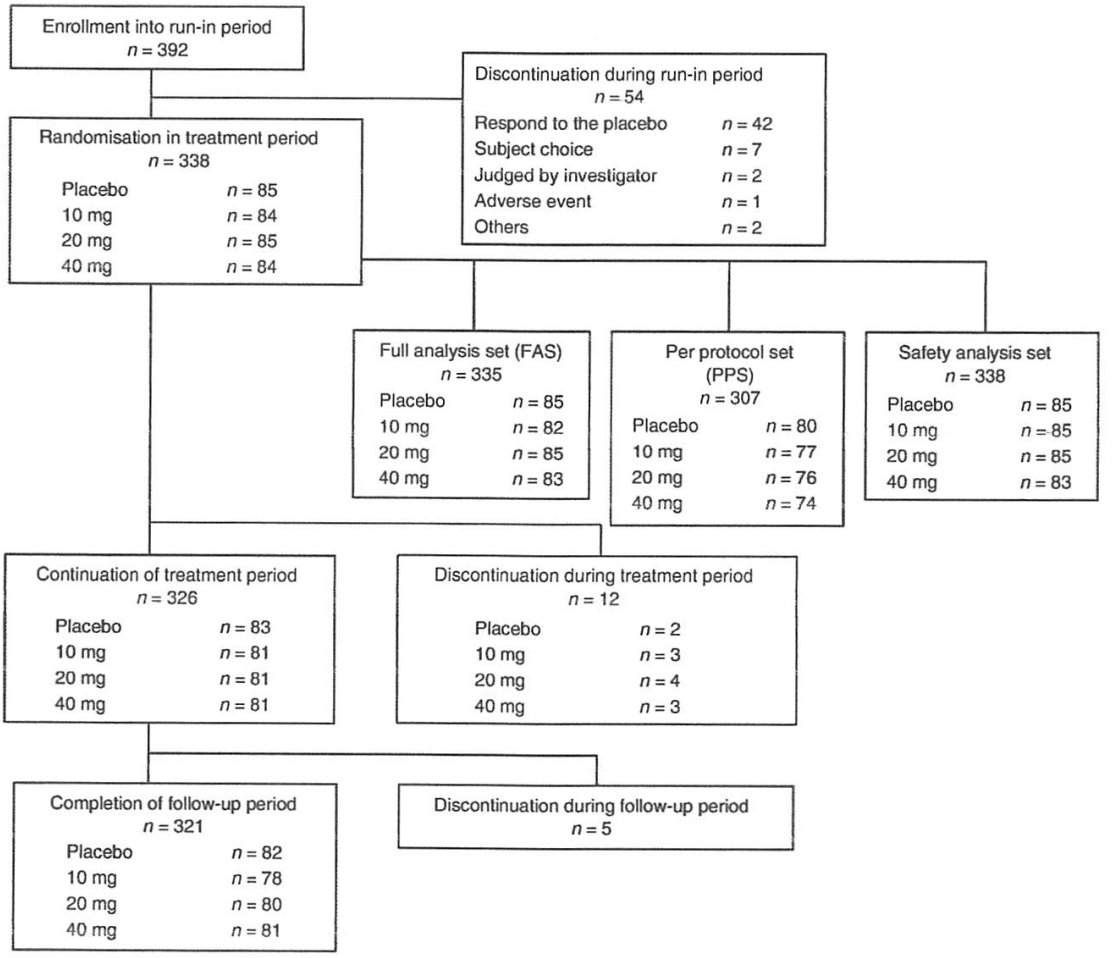

Figure 2 | Patient flow chart. Three hundred and ninety-two patients entered the run-in period, and 338 were randomised into the double-blinded treatment period.

syndrome (EPS) or postprandial distress syndrome (PDS)] and *Helicobacter pylori* status are very important subject background factors for FD, these characteristics did not significantly influence the efficacy of rabeprazole. No difference in the efficacy of rabeprazole was apparent between EPS and PDS (Figure 5a). Conversely, the efficacy of rabeprazole 10 and 20 mg tended to increase in *H. pylori*-positive patients compared with those of *H. pylori*-negative patients, except for those in the rabeprazole 40 mg group (Figure 5b).

Safety analysis

Among the 338 patients in the safety analysis set, the incidences of adverse events were 42.4%, 42.4%, 42.4% and 45.8% in the placebo and rabeprazole 10, 20 and 40 mg groups respectively. The incidences of adverse drug reactions were 10.6%, 5.9%, 9.4% and 7.2% respectively. No significant differences in these incidences were apparent between groups (data not shown). Adverse events with incidences of >3% were nasopharyngitis (4.7%), back pain (4.7%) and pharyngitis (3.5%) in the placebo group; nasopharyngitis (11.8%), diarrhoea (3.5%), blood triglycerides increased (3.5%), back pain (3.5%) and headache (3.5%) in the 10 mg group; nasopharyngitis (8.2%), diarrhoea (3.5%), gastroenteritis (3.5%) and headache (3.5%) in the 20 mg group; and nasopharyngitis (18.1%) and stomatitis (3.6%) in the 40 mg group.

Table 1 | Demographic characteristics of patients with functional dyspepsia enrolled in the study (per protocol set)

Category	Placebo (n = 80)	Rabeprazole 10 mg (n = 77)	Rabeprazole 20 mg (n = 76)	Rabeprazole 40 mg (n = 74)
Sex = Male, *n* (%)	36 (45.0)	34 (44.2)	36 (47.4)	27 (36.5)
Mean age (year)	45.8	46.9	50.2	46.4
Mean body weight (kg)	57.3	57.6	58.8	55.9
Mean BMI (kg/m^2)	21.6	21.8	22.1	21.5
Duration ≥1 year, *n* (%)	61 (76.3)	60 (77.9)	65 (85.5)	57 (77.0)
Positive anti-*Helicobacter pylori* IgG antibody, *n* (%)	14 (17.5)	14 (18.2)	23 (30.3)	20 (27.0)
Present heartburn or regurgitation, *n* (%)	45 (56.3)	45 (58.4)	45 (59.2)	41 (55.4)
Syndrome type, *n* (%)				
EPS	39 (48.8)	36 (46.8)	36 (47.4)	37 (50.0)
PDS	61 (76.3)	60 (77.9)	58 (76.3)	55 (74.3)
EPS > PDS	19 (23.8)	17 (22.1)	18 (23.7)	19 (25.7)
PDS > EPS	41 (51.3)	41 (53.2)	40 (52.6)	37 (50.0)
EPS = PDS	20 (25.0)	19 (24.7)	18 (23.7)	18 (24.3)

EPS, epigastric pain syndrome; PDS, postprandial distress syndrome.

DISCUSSION

This study has demonstrated, for the first time, the efficacy of a PPI in investigated FD patients in an Asian country, as previously shown in Europe and the United States.[9–12] One report from Asia showed negative responses to lansoprazole with respect to placebo in patients with FD.[20] In this earlier study, almost one-half of the subjects had mild dyspepsia. In contrast, in this study, the severity of the symptoms of the FD patients entered into the treatment period was relatively high because patients with mild symptoms (defined as scores of ≤4 for all four major symptoms according to the dyspepsia symptom questionnaire) were likely to drop out at the placebo run-in period.

This study incorporated a single-blinded run-in period to eliminate two 'reassuring effects' biases. The first may arise from a patient's sense of reassurance after he or she is notified of the absence of worrisome endoscopic findings (e.g. gastric or duodenal ulcer, gastric cancer) at the start of the run-in period[12, 20]; the second arises from the patient's expectation of receiving cutting-edge medical care. Both effects may render symptom relief irrelevant to treatment with rabeprazole, and we judged that the efficacy of this drug could be more accurately evaluated in their absence. Using a single-blind run-in period, as in this study, the magnitude of placebo effect might be minimised and the effects of rabeprazole might be observed more clearly.

We also assessed the dose dependence of the efficacy of rabeprazole in patients with FD, and found that a double dose (20 mg once daily) may be superior to the standard dose (10 mg once daily). In previous studies, no dose dependence was observed.[10, 12, 21] These conflicting results might be attributed to differences in patient selection and study design. In this study, diagnosis of FD was based on a questionnaire derived from the Rome III criteria. Moreover, because of the placebo run-in period, the magnitude of placebo response was considered to be minimised and the dose–response relationship with standard and double doses was easier to detect.

The low efficacy of rabeprazole 40 mg relative to 20 mg observed in this study was considered to be caused by the multifactorial pathophysiology of FD and the lower acid secretion of patients in Asian countries relative to those in Europe and the United States.[22, 23] As noted previously, various mechanisms may contribute to dyspeptic symptoms, including several factors not related to acid suppression.[3] Hence, strong acid suppression may not necessarily elicit benefit in patients with symptoms partially involving acid. Indeed, according to the results of this study, the efficacy of rabeprazole 40 mg tended to be limited compared with that of 10 or

Table 2 | Mean scores for each of eight dyspeptic symptoms, total four major dyspeptic symptoms and total eight symptoms according to the dyspepsia symptom questionnaire (per protocol set)

		Placebo	10 mg	20 mg	40 mg
Epigastric pain	Week 0	3.9 ± 1.8 (80)	3.5 ± 1.8 (77)	3.7 ± 1.7 (76)	4.0 ± 1.6 (74)
	Week 4	2.5 ± 1.6 (79)	2.3 ± 1.5 (77)	2.4 ± 1.4 (76)	2.7 ± 1.6 (74)
	Week 8	2.2 ± 1.4 (78)	2.0 ± 1.3 (76)	1.9 ± 1.2 (75)	2.1 ± 1.3 (74)
	Follow-up	1.9 ± 1.2 (76)	2.0 ± 1.2 (75)	2.0 ± 1.2 (76)	2.2 ± 1.4 (74)
Epigastric burning	Week 0	2.5 ± 1.8 (80)	2.5 ± 1.7 (77)	2.8 ± 1.9 (76)	2.5 ± 1.8 (74)
	Week 4	1.7 ± 1.2 (79)	1.6 ± 1.1 (77)	1.6 ± 1.2 (76)	2.0 ± 1.6 (74)
	Week 8	1.6 ± 1.0 (78)	1.3 ± 0.9 (76)	1.3 ± 0.8 (75)	1.7 ± 1.2 (74)
	Follow-up	1.5 ± 1.0 (76)	1.5 ± 1.0 (75)	1.5 ± 0.8 (76)	1.7 ± 1.2 (74)
Heartburn or regurgitation	Week 0	2.2 ± 1.2 (80)	2.2 ± 1.3 (77)	2.3 ± 1.3 (76)	2.1 ± 1.2 (74)
	Week 4	1.9 ± 1.1 (79)	1.8 ± 1.0 (77)	1.7 ± 0.9 (76)	1.9 ± 1.2 (74)
	Week 8	1.6 ± 0.8 (78)	1.5 ± 0.9 (76)	1.5 ± 0.8 (75)	1.6 ± 0.9 (74)
	Follow-up	1.8 ± 1.1 (76)	1.6 ± 1.0 (75)	1.6 ± 0.9 (76)	1.8 ± 1.2 (74)
Early satiety	Week 0	3.3 ± 2.0 (80)	3.5 ± 1.9 (77)	3.5 ± 2.0 (76)	3.1 ± 1.8 (74)
	Week 4	2.3 ± 1.5 (79)	2.3 ± 1.4 (77)	2.3 ± 1.4 (76)	2.3 ± 1.7 (74)
	Week 8	1.8 ± 1.2 (78)	1.9 ± 1.3 (76)	1.7 ± 1.2 (75)	1.8 ± 1.2 (74)
	Follow-up	2.0 ± 1.3 (76)	1.9 ± 1.1 (75)	1.8 ± 1.2 (76)	2.0 ± 1.3 (74)
Nausea	Week 0	2.4 ± 1.5 (80)	2.2 ± 1.6 (77)	2.1 ± 1.3 (76)	2.3 ± 1.5 (74)
	Week 4	1.7 ± 1.2 (79)	1.5 ± 1.0 (77)	1.7 ± 1.2 (76)	2.1 ± 1.4 (74)
	Week 8	1.6 ± 1.2 (78)	1.4 ± 0.9 (76)	1.5 ± 1.0 (76)	1.6 ± 1.0 (74)
	Follow-up	1.5 ± 0.8 (76)	1.5 ± 0.9 (75)	1.6 ± 1.0 (76)	1.9 ± 1.4 (74)
Belching	Week 0	2.6 ± 1.5 (80)	2.6 ± 1.5 (77)	2.3 ± 1.2 (76)	2.7 ± 1.5 (74)
	Week 4	2.0 ± 1.3 (79)	1.9 ± 1.2 (76)	1.8 ± 1.1 (76)	2.1 ± 1.2 (74)
	Week 8	1.8 ± 1.1 (78)	1.4 ± 0.9 (76)	1.4 ± 0.9 (75)	1.9 ± 1.0 (74)
	Follow-up	1.6 ± 0.9 (76)	1.7 ± 1.2 (75)	1.5 ± 0.7 (76)	1.7 ± 0.8 (74)
Postprandial fullness	Week 0	4.6 ± 1.4 (80)	4.6 ± 1.4 (77)	4.6 ± 1.3 (76)	4.6 ± 1.5 (74)
	Week 4	2.8 ± 1.5 (79)	3.0 ± 1.6 (77)	2.8 ± 1.5 (76)	2.9 ± 1.7 (74)
	Week 8	2.4 ± 1.3 (78)	2.5 ± 1.5 (76)	2.1 ± 1.3 (75)	2.5 ± 1.4 (74)
	Follow-up	2.2 ± 1.1 (76)	2.5 ± 1.4 (75)	2.4 ± 1.3 (76)	2.2 ± 1.3 (74)
Epigastric bloating	Week 0	3.5 ± 1.7 (80)	3.3 ± 1.6 (77)	3.3 ± 1.4 (76)	3.2 ± 1.7 (74)
	Week 4	2.4 ± 1.4 (79)	2.5 ± 1.4 (77)	2.3 ± 1.4 (76)	2.5 ± 1.8 (74)
	Week 8	2.1 ± 1.3 (78)	1.9 ± 1.3 (76)	1.8 ± 1.1 (75)	2.1 ± 1.3 (74)
	Follow-up	2.1 ± 1.3 (76)	2.0 ± 1.4 (75)	1.9 ± 1.1 (76)	1.8 ± 1.2 (74)
Total four major dyspeptic symptoms	Week 0	14.2 ± 3.9 (80)	14.1 ± 3.7 (77)	14.7 ± 3.8 (76)	14.2 ± 3.6 (74)
	Week 4	9.2 ± 3.7 (79)	9.2 ± 3.8 (77)	9.0 ± 3.9 (76)	9.9 ± 5.0 (74)
	Week 8	8.1 ± 3.6 (78)	7.8 ± 3.6 (76)	7.2 ± 3.2 (75)	8.0 ± 4.1 (74)
	Follow-up	7.6 ± 3.4 (76)	7.9 ± 3.4 (75)	7.7 ± 3.2 (76)	8.1 ± 4.4 (74)
Total eight dyspeptic symptoms	Week 0	24.8 ± 6.7 (80)	24.4 ± 6.8 (77)	24.7 ± 6.2 (76)	24.5 ± 6.8 (74)
	Week 4	17.2 ± 6.9 (79)	16.8 ± 6.0 (77)	16.5 ± 6.5 (76)	18.6 ± 8.9 (74)
	Week 8	15.1 ± 6.5 (78)	14.1 ± 6.2 (76)	13.3 ± 5.7 (75)	15.2 ± 6.9 (74)
	Follow-up	14.6 ± 6.1 (76)	14.7 ± 6.4 (75)	14.3 ± 5.7 (76)	15.3 ± 7.6 (74)

Mean ± standard deviation (*n*).

20 mg in *H. pylori*-positive patients, in whom acid secretion is considered to be lower than in *H. pylori*-negative patients. Conversely, rabeprazole 40 mg had the most effect on complete symptom relief in *H. pylori*-negative patients (Figure 5b). Therefore, it is difficult to conclude if the strong acid suppression achieved by 40 mg of rabeprazole might be because of too high a dose in Japanese patients. In addition, omeprazole has been reported to cause delayed gastric emptying in a dose-dependent manner in mice,[24] so the excessive acid suppression induced by 40 mg of rabeprazole may negatively influence dyspeptic symptoms. The finding that patients with gastric achlorhydria showed impaired gastric motility may be supportive of this notion.[25] Furthermore, elevation of intra-gastric pH due to excessive acid suppression inhibits the activation of pepsin, a digestive enzyme required to process protein-containing food.[26] Therefore, undigested foods may pass from the stomach into the small intestine, leading to overload of the digestive tract and induction of dyspeptic symptoms. In fact, incidences

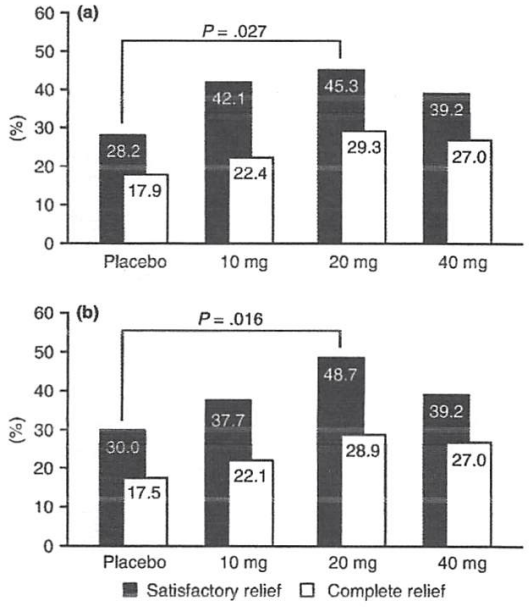

Figure 3 | Primary and secondary endpoints at week 8 (per protocol set). Complete symptom relief rate and satisfactory symptom relief rate for all four major dyspeptic symptoms (epigastric pain, epigastric burning, early satiety, postprandial fullness) according to the dyspepsia symptom questionnaire (a) and the symptom diary (b) were assessed at week 8. Open columns represent complete symptom relief; closed columns represent satisfactory relief. (a) rabeprazole 20 mg vs. placebo, $P = 0.027$; (b) rabeprazole 20 mg vs. placebo, $P = 0.016$ respectively.

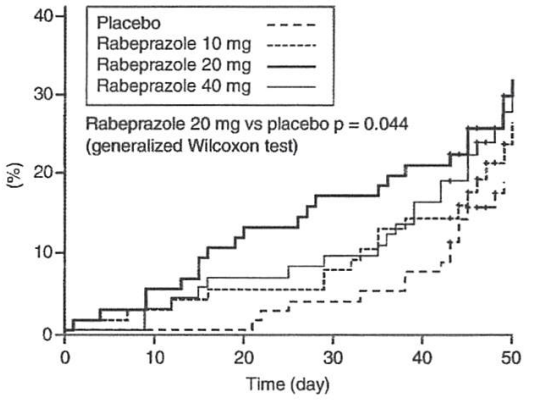

Figure 4 | Time to first sustained complete relief; Kaplan–Meier plots (per protocol set). The time to first sustained complete relief for all four major dyspeptic symptoms (epigastric pain, epigastric burning, early satiety, postprandial fullness) according to the symptom diary was assessed using Kaplan–Meier plots; to assess the speed and sustainability of the effects of placebo (*dashed line*), rabeprazole 10 mg (*dotted line*), 20 mg (*thick line*) or 40 mg (*thin line*) once daily for FD. In this figure, each plot represents the percentage of patients achieving sustained complete symptom relief from the day when complete symptom relief began to the last day of observation.

of gastrointestinal disorders (adverse events) suspicious for the association with motility disorders were higher in rabeprazole 40 mg group (14.5%) compared with placebo (7.1%), 10 mg (7.1%) and 20 mg group (7.1%). These data may affect the low efficacy of 40 mg group. Considering these findings, the lack of an effect of the higher rabeprazole dose may be due to the negative effects, but not its saturation or ceiling effects for patients with FD. However, we think that much consideration must be given to the efficacy of the rabeprazole 40 mg group from the results of this study alone and it is not possible to simply conclude about the efficacy of the 40 mg group so far. We believe that at least some patients with FD require acid suppression therapy and that appropriate inhibition of gastric acid is needed while avoiding excessive inhibition of gastric acid to achieve optimal outcomes in patients with FD. Further study will be needed to elucidate this problem.

In clinical studies using Rome I or II criteria, the efficacy of PPIs has been limited in patients with dysmotility-like conditions.[12,21] However, the results of this study showed that the response in PDS patients has the same tendency as that in EPS patients (Figure 5a). The reason remains unclear; however, differences between PDS diagnosed according to the Rome III criteria and dysmotility-like FD conditions diagnosed according to previous definitions may be relevant. Nevertheless, gastric acid plays an important part in the generation of dysmotility symptoms such as feelings of 'heaviness' in the stomach and satiety through gastric and/or duodenal hypersensitivity,[27] and the results of this study may reflect these perceptions, which are consistent with recent evidence.

Although the results of this study did not show good rates of complete symptom relief after 8 week in the rabeprazole groups, the time to first sustained complete relief for all four major dyspeptic symptoms according to the symptom diary showed that 20 mg group was significantly higher than placebo group (Figure 4). Complete symptom relief after 8 week is evaluated at a specific point in time, whereas the time to first sustained complete relief is evaluated over an entire

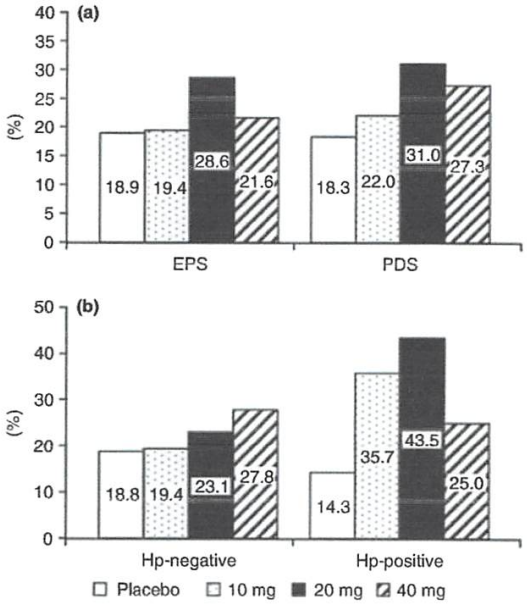

Figure 5 | Complete symptom relief rate for all four major dyspeptic symptoms (epigastric pain, epigastric burning, early satiety, postprandial fullness) according to the dyspepsia symptom questionnaire at week 8 for each syndrome type (a) and in *Helicobacter pylori*-positive and -negative patients (b) (per protocol set). Epigastric pain syndrome (EPS) was defined as EPS-dominant type [EPS > postprandial distress syndrome (PDS)] or EPS/PDS-equal type (EPS = PDS) in the patient's background. PDS was defined as PDS-dominant type (PDS > EPS) or EPS/PDS-equal type. No difference in the efficacy of rabeprazole was apparent between patients with EPS and those with PDS for placebo (*open columns*), rabeprazole 10 mg (*dotted columns*), 20 mg (*closed columns*) or 40 mg (*hatched columns*) once daily (a). The efficacy of rabeprazole tended to increase in *H. pylori*-positive patients, except for those in the rabeprazole 40 mg group (b).

period. Therefore, the efficacy of rabeprazole 20 mg for FD may be indicated throughout the entire period. The rates of the willingness to continuing use of rabeprazole 20 mg also provided more potent efficacy compared with placebo. Although this assessment may not really mean the patient impression, its therapeutic gain (approximately 25%) in rabeprazole 20 mg group may suggest the impact of rabeprazole.

This study had limitations. We could not ascertain the efficacy of rabeprazole for FD at the primary endpoint (complete symptom relief). The facts of neither significant difference in the primary endpoint nor dose–response relationship could be due (at least in part) to the small sample size (about 80 subjects per group). A larger scale study is needed in the future to examine and identify the definite efficacy of rabeprazole in a dose-dependent manner because clinical drug interventional studies using large sample sizes generally have greater power to detect a statistically significant difference when compared with smaller studies. Although this study has shown that the 20 mg dose of rabeprazole gives satisfactory relief of symptoms, it remains uncertain as to whether 20 mg is the only recommended dose for FD, and the complete relief of symptoms is not really appropriate as the primary outcome parameter. However, considering the difficulty for complete elimination of the disease-based symptoms even by PPI therapy in FD patients, satisfactory relief may be considered as the initial stage goal of FD treatment. If further studies are conducted, it may be a candidate to choose another primary endpoint such as overall treatment efficacy along with satisfactory symptom relief rates. The dyspepsia symptom questionnaire that we used as scale to evaluate the efficacy of rabeprazole was not validated. However, the definitions of complete symptom relief and satisfactory symptom relief were very strict, so we think our data were very reliable. In addition, in 'Asian consensus report on functional dyspepsia' reported by Miwa *et al.*,[28] it is recommended that *H. pylori* eradication therapy be pursued first when positive *H. pylori* is identified; therefore in future, a large-scale clinical trials should be performed including only FD patients who are negative for *H. pylori*.

In conclusion, rabeprazole 20 mg once daily but not 10 or 40 mg significantly provides satisfactory symptom relief for FD. However, the number of cases per group is low, and we believe that no definite conclusion can be stated regarding dose–response relationship. Determination of the optimal dose will be an important topic for further study.

AUTHORSHIP

Guarantor of the article: Ryuichi Iwakiri.

Author contributions: Ryuichi Iwakiri, Kazunari Tominaga, Yoshikazu Kinoshita, Kazuma Fujimoto and Tetsuo Arakawa contributed to the study concept and design, interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

Kenji Furuta contributed to drafting of the manuscript and critical revision of the manuscript for important intellectual content.

Masahiko Inamori, Takahisa Furuta, Hironori Masuyama, Kazunari Kanke, Akihito Nagahara, Katsuhiko Iwakiri, Hideyuki Hiraishi, Sumio Watanabe, Hiroto Miwa and Yuji Naito contributed to critical revision of the manuscript for important intellectual content.

Ken Haruma, Kazuhide Higuchi, Shin'ichi Takahashi, Motoyasu Kusano, Mototsugu Kato and Michio Hongo contributed to the study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENTS

Declaration of personal interests: Takahisa Furuta has received research grants from Astellas Pharma Inc., AstraZeneca, Daiichi-Sankyo, Eisai Co., Ltd., Mitsubishi Tanabe Pharma, Takeda Pharmaceutical Co., Ltd., Tsumura, Otsuka Pharmaceutical Co., Ltd. and Zeria Pharmaceutical Co., Ltd. Hironori Masuyama has received research grants from Eisai Co., Ltd. and Takeda Pharmaceutical Co., Ltd. Yoshikazu Kinoshita has served in speaking and teaching commitments for AstraZeneca Pharmaceuticals, Takeda Pharmaceutical Co., Ltd., Astellas Pharma Inc., Eisai Co., Ltd., Taiho and Daiichi-Sankyo. Motoyasu Kusano has served in speaking and teaching commitments for AstraZeneca Pharmaceuticals and Eisai Co., Ltd. Mototsugu Kato has served in speaking and teaching commitments for Eisai Co., Ltd. and Takeda Pharmaceutical Co., Ltd. Michio Hongo has served as a consultant for Astellas Pharma Inc., Zeria Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eisai Co., Ltd., AstraZeneca Pharmaceuticals, Sucampo Pharmaceuticals and Abbott Japan.

Hideyuki Hiraishi has received research grants from Ajinomoto, Eisai Co., Ltd. and MSD.

Sumio Watanabe has received research grants from AstraZeneca, Daiichi-Sankyo, Eisai Co., Ltd. and Takeda Pharmaceutical Co., Ltd. Hiroto Miwa has received lecture fees from AstraZeneca, Daiichi-Sankyo and has received research grants from AstraZeneca, Daiichi-Sankyo, Takeda Pharmaceutical Co., Ltd., Chugai and Yakult. Yuji Naito has received research grants from Takeda Pharmaceutical Co., Ltd. and Otsuka Pharmaceutical Co., Ltd. Kazuma Fujimoto has served on advisory committees and review panels for Eisai Co., Ltd. and AstraZeneca.

Tetsuo Arakawa has served on advisory committees and review panels for Eisai Co., Ltd. and Otsuka Pharmaceutical Co., Ltd. The following people have nothing to declare: Ryuichi Iwakiri, Kazunari Tominaga, Kenji Furuta, Masahiko Inamori, Kazunari Kanke, Akihito Nagahara, Ken Haruma, Kazuhide Higuchi, Shin'ichi Takahashi and Katsuhiko Iwakiri.

The authors thank all contributing members (listed in the Appendix). The authors also thank Mr. M. Munesue, Mr. R. Nishiki and the project members at Eisai Co., Ltd.

Declaration of funding interests: This study was funded by Eisai Co., Ltd.

REFERENCES

1. Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999; **45**(Suppl. 2): II37–42
2. Aro P, Talley NJ, Agréus L, *et al.* Functional dyspepsia impairs quality of life in the adult population. *Aliment Pharmacol Ther* 2011; **33**: 1215–24.
3. Tack J, Kindt S. Pathogenesis and therapy for idiopathic dyspepsia. *Curr Gastroenterol Rep* 2005; **7**: 437–44.
4. Sarnelli G, Vandenberghe J, Tack J. Visceral hypersensitivity in functional disorders of the upper gastrointestinal tract. *Dig Liver Dis* 2004; **36**: 371–6.
5. Nyrén O, Adami HO, Gustavsson S, Lindgren PG, Lööf L, Nyberg A. The epigastric distress syndrome. A possible disease entity identified by history and endoscopy in patients with nonulcer dyspepsia. *J Clin Gastroenterol* 1987; **9**: 303–9.
6. Moayyedi P, Soo S, Deeks J, *et al.* Systematic review: antacids, H2-receptor antagonists, prokinetics, bismuth and sucralfate therapy for non-ulcer dyspepsia. *Aliment Pharmacol Ther* 2003; **17**: 1215–27.
7. Sakurai K, Nagahara A, Inoue K, *et al.* Efficacy of omeprazole, famotidine, mosapride and teprenone in patients with upper gastrointestinal symptoms: an omeprazole-controlled randomized study (J-FOCUS). *BMC Gastroenterol* 2012; **12**: 42.
8. Veldhuyzen van Zanten SJ, Chiba N, Armstrong D, *et al.* A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in *Helicobacter pylori* negative, primary care patients with dyspepsia: the CADET-HN Study. *Am J Gastroenterol* 2005; **100**: 1477–88.
9. Blum AL, Arnold R, Stolte M, Fischer M, Koelz HR. Short course acid suppressive treatment for patients with functional dyspepsia: results depend on *Helicobacter pylori* status. The Frosch Study Group. *Gut* 2000; **47**: 473–80.
10. Peura DA, Kovacs TO, Metz DC, Siepman N, Pilmer BL, Talley NJ. Lansoprazole in the treatment of functional dyspepsia: two double-blind, randomized, placebo-controlled trials. *Am J Med* 2004; **116**: 740–8.
11. van Zanten SV, Armstrong D, Chiba N, *et al.* Esomeprazole 40 mg once a day in patients with functional dyspepsia: the randomized, placebo-controlled

"ENTER" trial. *Am J Gastroenterol* 2006; **101**: 2096–106.
12. Talley NJ, Meineche-Schmidt V, Paré P, *et al.* Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). *Aliment Pharmacol Ther* 1998; **12**: 1055–65.
13. Kinoshita Y, Hongo M; Japan TWICE Study Group. Efficacy of twice-daily rabeprazole for reflux esophagitis patients refractory to standard once-daily administration of PPI: the Japan-based TWICE study. *Am J Gastroenterol* 2012; **107**: 522–30.
14. Kinoshita Y, Ashida K, Hongo M; Japan Rabeprazole Study Group for NERD. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2011; **33**: 213–24.
15. Hayato S, Hasegawa S, Hojo S, *et al.* Dose-response relationships of rabeprazole 5, 10, 20, and 40 mg once daily on suppression of gastric acid secretion through the night in healthy Japanese individuals with different CYP2C19 genotypes. *Eur J Clin Pharmacol* 2012; **68**: 579–88.
16. Tack J, Talley NJ, Camilleri M, *et al.* Functional gastroduodenal disorders. *Gastroenterology* 2006; **130**: 1466–79.
17. Thompson WG, Drossman DA, Talley NJ, *et al.* Rome III Diagnostic Questionnaire for the Adult Functional GI disorders (including Alram Question) and Scoring Algorism. In: Drossman DA, ed. *ROME III. The Functional Gastrointestinal Disorders*, 3rd ed. McLean, VA: Degnon Associates, Inc, 2006; 917–51.
18. Veldhuyzen van Zanten SJ, Chiba N, Armstrong D, *et al.* Validation of a 7-point Global Overall Symptom scale to measure the severity of dyspepsia symptoms in clinical trials. *Aliment Pharmacol Ther* 2006; **23**: 521–9.
19. Kusano M, Shimoyama Y, Sugimoto S, *et al.* Development and evaluation of FSSG: frequency scale for the symptoms of GERD. *J Gastroenterol* 2004; **39**: 888–91.
20. Wong WM, Wong BC, Hung WK, *et al.* Double blind, randomised, placebo controlled study of four weeks of lansoprazole for the treatment of functional dyspepsia in Chinese patients. *Gut* 2002; **51**: 502–6.
21. Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis. *Gastroenterology* 2004; **127**: 1329–37.
22. Kinoshita Y, Kawanami C, Kishi K, Nakata H, Seino Y, Chiba T. *Helicobacter pylori* independent chronological change in gastric acid secretion in the Japanese. *Gut* 1997; **41**: 452–8.
23. Iijima K, Ohara S, Koike T, Sekine H, Shimosegawa T. Gastric acid secretion of normal Japanese subjects in relation to *Helicobacter pylori* infection, aging, and gender. *Scand J Gastroenterol* 2004; **39**: 709–16.
24. Sanaka M, Yamamoto T, Kuyama Y. Effects of proton pump inhibitors on gastric emptying: a systematic review. *Dig Dis Sci* 2010; **55**: 2431–40.
25. Tosetti C, Stanghellini V, Tucci A, *et al.* Gastric emptying and dyspeptic symptoms in patients with nonautoimmune fundic atrophic gastritis. *Dig Dis Sci* 2000; **45**: 252–7.
26. Kerrigan DD, Mangnall YF, Read NW, Johnson AG. Influence of acid-pepsin secretion on gastric emptying of solids in humans: studies with cimetidine. *Gut* 1991; **32**: 1295–7.
27. Miwa H, Nakajima K, Yamaguchi K, *et al.* Generation of dyspeptic symptoms by direct acid infusion into the stomach of healthy Japanese subjects. *Aliment Pharmacol Ther* 2007; **26**: 257–64.
28. Miwa H, Ghoshal UC, Fock KM, *et al.* Asian consensus report on functional dyspepsia. *J Gastroenterol Hepatol* 2012; **27**: 626–41.

APPENDIX

MEMBER SITES IN THE SAMURAI STUDY

Mototsugu Kato from Hokkaido University Hospital, Sapporo, Japan; Takeshi Hagiwara from Sapporo-Kosei General Hospital, Sapporo, Japan; Mineo Kudo from Sapporo Hokuyu Hospital, Sapporo, Japan; Toshiharu Chikama from Chikama Gastro-Intestinal & Internal Medicine Clinic, Sapporo, Japan; Shinya Mitsui from Teine Keijinkai Clinic, Sapporo, Japan; Kazuyoshi Yamashita from Japanese Red Cross Sendai Hospital, Sendai, Japan; Hiromitsu Watanabe from Aramaki Nabe Clinic, Sendai, Japan; Masafumi Komatsu from Akita City Hospital, Akita, Japan; Harufumi Oizumi from Oizumi Gastrointestinal Medical Clinic, Yamagata, Japan; Koichi Taya from Taya Clinic, Tsuchiura, Japan; Kazunari Kanke from Dokkyo Medical University, Tochigi, Japan; Hironori Masuyama from Masuyama Gastrointestinal Clinic, Ohtawara, Japan; Motoyasu Kusano, Osamu Kawamura and Yasuyuki Shimoyama from Gunma University Hospital, Maebashi, Japan; Tomohiro Tada from Tada Tomohiro Gastroenterology & Proctology Clinic, Saitama, Japan; Keiji Ogura from Tokyo Metropolitan Police Hospital, Tokyo, Japan; Akihito Nagahara from Juntendo University School of Medicine, Tokyo, Japan; Katsuhiko Iwakiri from Nippon Medical School, Tokyo, Japan; Katsutoshi Yoshida from Jiai Hospital, Tokyo, Japan; Jun Miwa from Toshiba General Hospital, Tokyo, Japan; Kengo Tokunaga from Kyorin University School of Medicine, Mitaka, Japan; Toshiomi Kusano from Shinjuku-Kaijo Building Clinic, Tokyo, Japan; Kenzo Matsumura from Matsumura Gastroenterology Clinic, Tokyo, Japan; Ryuji Yasumura from Yebisu Gardenplace Clinic, Tokyo, Japan; Tomofumi Murakami from Shimokitazawa Tomo Clinic, Tokyo, Japan; Masae Banno from Banno Clinic, Tokyo, Japan; Masahiko Inamori from Yokohama City University Hospital, Yokohama, Japan; Kuniharu Akita from Gifu Central Hospital, Gifu, Japan; Takahisa Furuta from Hamamatsu University School of Medicine, Hamamatsu, Japan; Kei Matsuki from Matsuki GI Clinic, Sizuoka, Japan; Yasuhiko Maruyama from Fujieda Municipal General Hospital, Fujie-

da, Japan; Takafumi Ando from Nagoya University Graduate School of Medicine, Nagoya, Japan; Takeshi Kamiya from Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; Shigeki Koyama from Kusatsu General Hospital, Kusatsu, Japan; Hitoshi Hayashi from Hayashi Katagihara Clinic, Kyoto, Japan; Kenjiro Yasuda from Kyoto Second Red Cross Hospital, Kyoto, Japan; Yuji Naito from Kyoto Prefectural University of Medicine, Kyoto, Japan; Norimasa Yoshida from Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan; Keiichi Kiriya from Hirakata Kohsai Hospital, Hirakata, Japan; Eiji Umegaki from Osaka Medical College, Takatsuki, Japan; Tsukasa Itabashi and Makoto Sanomura from Hokusetsu General Hospital, Takatsuki, Japan; Masahiro Sakaguchi from Moriguchi Keijinkai Hospital, Moriguchi, Japan; Kazunari Tominaga from Osaka City University Graduate School of Medicine, Osaka, Japan; Shujiro Yazumi from the Tazuke Kofukai Medical Research Institute Kitano Hospital, Osaka, Japan; Kiyoshi Ashida from Saiseikai Nakatsu Hospital, Osaka, Japan; Kenji Sugimoto from Sugimoto Kenji Clinic, Suita, Japan; Hiroto Miwa from Hyogo College of Medicine, Nishinomiya, Japan; Yasushi Sano from Sano Hospital, Kobe, Japan; Kenji Furuta from Shimane University Faculty of Medicine, Izumo, Japan; Hirofumi Fujishiro from Shimane Prefectural Central Hospital, Izumo, Japan; Akira Tari from Hiroshima Red Cross Hospital & Atomic-Bomb Survivors Hospital, Hiroshima, Japan; Tomoki Inaba from Kagawa Prefectural Central Hospital, Takamatsu, Japan; Shuuji Inoue from National Hospital Organization Kochi Hospital, Kochi, Japan; Nobutoshi Kuniyoshi from Kuniyoshi Hospital, Kochi, Japan; Takayuki Matsumoto from Kyushu University, Fukuoka, Japan; Hideyuki Nomura from Shin-Kokura Hospital, Kitakyushu, Japan; Takemi Noda from Kasumigaoka Clinic, Fukuoka, Japan; Toru Umezu from Umezu Clinic, Chikushino, Japan; Ryuichi Iwakiri from Saga Medical School, Saga, Japan; Takahiro Noda from Karatsu Red Cross Hospital, Karatsu, Japan; Yutaka Sasaki from Kumamoto University, Kumamoto, Japan; Hiroshi Morinaga from Morinaga Ueno Clinic, Kumamoto, Japan; Kazunari Murakami from Oita University, Yuhu, Japan; Hisanori Abe from Arita GI Hospital, Oita, Japan; Shojiro Yamamoto from University of Miyazaki, Miyazaki, Japan; Akio Inui from Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan; Fukunori Kinjo from University Hospital of the Ryukyus, Okinawa, Japan.