Safety and Efficacy of Long-Term Maintenance Therapy with Oral Dose of Rabeprazole 10 mg Once Daily in Japanese Patients with Reflux Esophagitis

Kazuma Fujimoto¹, Michio Hongo² and The Maintenance Study Group

Abstract

Objective The aim of this prospective clinical study was to evaluate the efficacy and safety of long-term proton pump inhibitor (PPI) treatment for two years in Japanese patients with reflux esophagitis (RE).

Methods The efficacy and safety of two-year (104-week) treatment with rabeprazole (RPZ) 10 mg were studied in patients confirmed to have been cured of RE by PPI and who required long-term maintenance therapy with PPI. We performed serial endoscopy, checked gastroesophageal reflux disease (GERD) symptoms, adverse events, laboratory values and serum gastrin. We also monitored gastric mucosal histology, atrophy and polyps.

Results The endoscopic non-relapse rate for RE was 87.3% for the 104-week period. GERD symptoms improved based on the fact that the mean change from baseline in GERD symptom score after treatment was a negative value. Treatment was safe; and atrophy was found to have developed in virtually no cases. A few new benign fundic gland or hyperplastic polyps developed throughout the study, but no ECL carcinoids were found to have developed. Serum gastrin levels tended to increase up to 24 weeks, but there were no subsequent changes thereafter up to 104 weeks.

Conclusion The results confirmed oral RPZ 10 mg to be effective for maintenance therapy in Japanese patients with RE. Although effects on the gastric mucosa were not ruled out, long-term use of RPZ was confirmed to be safe overall.

Key words: rabeprazole, reflux esophagitis

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Introduction

Reflux esophagitis (RE) is a major complication of gastroesophageal reflux disease (GERD), which defined as “a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications” (1), leading to inflammation of the esophageal mucosa. It has also long been known that RE tends to recur even after drug therapy (2). Maintenance therapy with proton pump inhibitors (PPIs), which have potent gastric acid-suppressing action, is recommended for those recurrent RE patients (3, 4). Although trailing behind the Western countries, PPI maintenance therapy was approved in Japan in 2000. Maintenance therapy requires continuous long-term administration, but there have been no reports of prospective clinical studies on the efficacy and safety of long-term PPI treatment lasting longer than one year in Japanese patients with RE up to today.

Mucosal atrophy is a known gastric mucosal condition involved in the onset and development of gastric cancer, and Kuipers et al reported in 1996 that gastric mucosal atrophy of the gastric corpus progressed as a result of long-term PPI treatment in Helicobacter pylori (H. pylori)-positive RE patients (5). Rat toxicity studies conducted during the development of the world’s first clinical application of PPI also re-
revealed that enterochromaffin-like (ECL) cell carcinoids develop in the stomach as a result of long-term PPI administration (6). Long-standing hypergastrinemia resulting from the potent gastric acid-suppressing action of PPI is believed to be a major factor in this, because gastrin might have a trophic effect on gastric mucosal cells (7). Considering those concerns, many clinical studies involving the long-term administration of PPI for several years have been conducted in Europe and the US, confirming the absence of problems in terms of tolerability (8-11). However, collecting evidence on the safety and tolerability of long-term PPI treatment in Japanese patients with RE may be extremely important in terms of the future usability of PPI due to the high prevalence of *H. pylori* infection rate in elderly patients in Japan (12, 13), and also based on the fact that a high prevalence of RE patients are also elderly individuals (14, 15).

Considering these backgrounds, we conducted a 104-week (two-year) long-term dosing study of rabeprazole (RPZ), a type of PPI (16). In terms of efficacy, we investigated the potential efficacy to suppress RE relapse and GERD symptoms over the long term by the approved RPZ dosage of 10 mg once daily for RE maintenance therapy in Japan. We previously reported risk factors for relapsing of RE (17) and developing hyperplastic and fundic gland polyps (18) from the results of the study. In terms of safety, we focused on the influence on the gastric mucosa in view of the matters noted above. This report focused on safety and efficacy of long-term administration of RPZ.

## Materials and Methods

### Study design

This study was a multicenter (27 sites in Japan), open-label, prospective trial with the RPZ maintenance study group as described previously (17, 18). Written informed consent to participate in the study was obtained from each subject before the start of the study. Subject characteristics, including the inclusion/exclusion criteria, related to study registration were then monitored within 14 days before the start of treatment with the study drug (baseline). Subjects registered in the study were treated with the study drug for 104 weeks. The intent of each subject to continue participating in the study was confirmed before the end of the 52-week study drug treatment period. The study drug was given for the remaining 52-week period when written informed consent was again obtained. Subjects were asked to visit every 4 weeks during the study period. Table 1 presents the parameters that were checked at each visit. 

***Table 1. Study Design***

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Visit (week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
</tr>
<tr>
<td>Characteristics</td>
<td>X</td>
</tr>
<tr>
<td>GERD symptoms</td>
<td>X</td>
</tr>
<tr>
<td>Adverse events</td>
<td>X</td>
</tr>
<tr>
<td>Study medication compliance</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
</tr>
<tr>
<td>Hematology*</td>
<td>X X X X X X X X</td>
</tr>
<tr>
<td>Biochemistry*</td>
<td>X X X X X X X X</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>X X X X X</td>
</tr>
<tr>
<td>Gastric mucosal histology *</td>
<td>X X X X X</td>
</tr>
<tr>
<td>Serum gastrin*</td>
<td>X X X X X</td>
</tr>
</tbody>
</table>

* The clinical laboratory tests were performed at SRL, Inc., a central laboratory.
Treatments

RPZ 10 mg tablets were used as the study drug. The dosage and administration was one tablet taken orally once daily. Compliance was checked during each visit of every four weeks. Compliance was classified as ≥90%, <90%-≥75%, <75%-≥50% and <50%. The concomitant of other PPIs, H₂ receptor antagonists, selective muscarin receptor antagonists and prokinetics were prohibited during the study period. H. pylori eradication therapy was also prohibited.

Efficacy assessments

Maintenance of GERD symptom-free

The study investigated whether subjects remained GERD symptom-free as a result of treatment with the study drug. The frequency and severity of GERD symptoms (epigastric pain, chest pain, heartburn, acid reflux symptoms, dysphagia, nausea/vomiting) within a week before a visit day were checked and scored in interviews with each subject. Symptoms occurring ≥6 days a week were rated as 3 points, those occurring 3 to 5 days a week were rated as 2 points, those occurring 1 to 2 days a week were rated as 1 point, and the absence of symptoms was rated as 0 points. Severe symptoms significantly interfering with daily activities or sleep were rated as 3 points, moderate symptoms interfering somewhat were rated as 2 points, and mild symptoms that did not interfere were rated as 1 point. The GERD symptom score was defined as the combined scores for frequency and severity. The symptom-free rate (%) was defined as the percent of patients with 0 points throughout the study drug treatment period out of the subjects with a GERD symptom score of 0 at baseline.

Safety assessments

Gastric mucosal atrophy

The progress of gastric mucosal atrophy after the start of treatment was investigated. The expansion of gastric mucosal atrophy was endoscopically checked and was classified as C-1, C-2, C-3, O-1, O-2, or O-3 using the Kimura-Takemoto classification system (Fig. 1) (20, 21). The absence of atrophy corresponded to C-0, and the expansion of atrophy in the entire stomach corresponded to O-p. Atrophy was defined as having progressed when the classification at the end of the study had changed 1 grade or more, compared to baseline, in the direction of atrophic expansion. Classifications that were the same at the end of treatment as at baseline were handled as no change.

Gastric mucosal histology

Changes in fundic gland mucosa after the start of treatment were histologically investigated. During endoscopy, a sample of the fundic gland mucosa was taken from the greater curvature of the upper body, and the specimen was Hematoxylin-Eosin stained (HE stained), Grimelius stained (G stained), and chromogranin A immunostained (Cg A immunostained) at a central laboratory. HE staining was done to identify all fundic mucosal cells. G staining and Cg A immunostaining were also done to identify neuroendocrine cells (primarily ECL cells). The density (cells/mm²) of fundic mucosal cells, G stain-positive cells, and Cg A immunostain-positive cells were each calculated, and the density results were used to calculate the percentage of G stain-positive cells (%) and percentage of Cg A immunostain-positive cells (%) among the fundic mucosal cells.

Serum gastrin

The changes in serum gastrin after the start of treatment were investigated as previously indicated (17). The gastrin in serum samples was assayed by a central laboratory using a radioimmunoassay kit (Gastrin-RIA kit II; SRL, Tokyo, Japan) (the normal level is ≤200 pg/mL).

Adverse events

The emergence of adverse events after the start of treatment with the study drug was investigated. Adverse events were defined as clinically untoward signs, symptoms, or illness and abnormal changes in clinical laboratory results, which occurred during the study period, regardless of causal relation to the study drug. Adverse drug reactions were also defined as adverse events for which a relation to the study drug could not be ruled out. Adverse events were checked by medical examination or tests, and were recorded.

Statistical analysis

The non-relapse rate (%) and 95% confidence interval (CI) were calculated by the Kaplan-Meier method to assess
Table 2. Baseline Characteristics of the Analyzed Patients (Cited from 17 and 18 with Modification)

<table>
<thead>
<tr>
<th></th>
<th>Male (n=126)</th>
<th>Female (n=66)</th>
<th>Total (n=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±standard deviation)</td>
<td>59.6±13.1</td>
<td>69.8±10.8</td>
<td>63.1±13.2</td>
</tr>
<tr>
<td>&lt;65</td>
<td>78 (61.9)</td>
<td>16 (24.2)</td>
<td>94 (49.0)</td>
</tr>
<tr>
<td>≥65</td>
<td>48 (38.1)</td>
<td>50 (75.8)</td>
<td>98 (51.0)</td>
</tr>
<tr>
<td><em>Helicobacter pylori infection</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>79 (62.7)</td>
<td>35 (53.0)</td>
<td>114 (59.4)</td>
</tr>
<tr>
<td>positive</td>
<td>47 (37.3)</td>
<td>31 (47.0)</td>
<td>78 (40.6)</td>
</tr>
<tr>
<td>Proton pump inhibitor used before trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rabeprazole</td>
<td>65 (51.6)</td>
<td>29 (43.9)</td>
<td>94 (49.0)</td>
</tr>
<tr>
<td>lansoprazole</td>
<td>42 (33.3)</td>
<td>24 (36.4)</td>
<td>66 (34.4)</td>
</tr>
<tr>
<td>omeprazole</td>
<td>19 (15.1)</td>
<td>13 (19.7)</td>
<td>32 (16.7)</td>
</tr>
</tbody>
</table>

Note) *H. pylori* infection was examined by enzyme-linked immunosorbent assay using antigen (JHM-CAP; Scimedx Corp., Denville, NJ, USA). Serum immunoglobulin G antibodies to *H. pylori* were measured in the central research center, and enzyme immunoassay values (EVs) of ≥2.3 and <2.3 were judged to be positive and negative, respectively.

Results

Patients

Screening resulted in the registration of 194 subjects in the study, of whom 193 started treatment with the study drug. Among those subjects, 144 subjects continued the study beyond 52 weeks, and 129 subjects completed the 104-week study drug treatment period (17, 18). One subject did not take the study drug, and one subject was found not to have met the inclusion criteria after the start of treatment. The efficacy and safety of the drug were analyzed excluding these subjects. Table 2 (17, 18) shows the primary baseline patient characteristics of the 192 cases in the analysis set.

Treatment compliance

Most subjects complied with the study drug treatment, and maintained ≥90% compliance between every 4-week visit. A compliance of <50% between every 4-week visit was seen in only 2 subjects. One of these subjects withdrew from the study upon confirmation of RE relapse 24 weeks after the start of treatment with a compliance rate >50% between 20 and 24 weeks after the start of treatment. The other subject requested to withdraw from the study 4 weeks after the start of treatment and had a compliance rate >50% by the time of withdrawal.

Efficacy

Maintenance of GERD symptom-free

As indicated previously (17), the RE non-relapse rate at 24, 52, 76, and 104 weeks after the start of treatment was 94.0% (95% CI: 90.5-97.4), 91.0% (95% CI: 86.7-95.2), 89.6% (95% CI: 85.1-94.2), and 87.3% (95% CI: 82.1-92.4), respectively (Fig. 2: cited from 17 with modification). The development of GERD symptoms was analyzed in 191 cases excluding 1 subject who had visited but never been interviewed for GERD symptoms after the start of treatment. The development of GERD symptoms was analyzed in 191 cases excluding 1 subject who had visited but never been interviewed for GERD symptoms after the start of treatment. The GERD symptom score at baseline was 0 points in 151 cases (79.1%). 51.7% (95% CI: 43.4-59.9) of these subjects were symptom-free throughout the study drug treatment period. The ratios of symptom-free patients based on symptom...
Table 3. Rates of Gastroesophageal Reflux Disease Symptom-free during the Rabeprazole Treatment

<table>
<thead>
<tr>
<th>GERD symptom</th>
<th>Number of patients without symptom at baseline</th>
<th>Ratio of GERD symptom-free patients throughout the study</th>
<th>95% CI for symptom-free rate (F-Distribution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric pain</td>
<td>179</td>
<td>83.2</td>
<td>(76.9-88.4)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>188</td>
<td>90.4</td>
<td>(85.3-94.2)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>172</td>
<td>64.0</td>
<td>(56.3-71.1)</td>
</tr>
<tr>
<td>Acid regurgitation</td>
<td>169</td>
<td>74.6</td>
<td>(67.3-80.9)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>188</td>
<td>92.0</td>
<td>(87.2-95.5)</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>189</td>
<td>82.5</td>
<td>(76.4-87.7)</td>
</tr>
</tbody>
</table>

1) Patients without symptom are defined as patients whose GERD score was 0.
2) Ratio of GERD symptom-free patients throughout the study is defined as the ratio of patients whose GERD symptom score was 0 at baseline and throughout the study period.

Table 4. Relationship between the Relapse of Reflux Esophagitis and Symptoms of Gastroesophageal Reflux Disease

<table>
<thead>
<tr>
<th>Los Angeles Classification*</th>
<th>Grade A (n=14)</th>
<th>Grade B (n=5)</th>
<th>Grade C (n=1)</th>
<th>Grade D (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+), n=7; (-), n=7</td>
<td>(+), n=2; (-), n=3</td>
<td>(+), n=0; (-), n=1</td>
<td>(+), n=0; (-), n=1</td>
<td></td>
</tr>
</tbody>
</table>

Note) Los Angeles Classification (Grade A, B, C, or D) in case of the relapse of reflux esophagitis during the rabeprazole treatment; (+), there is any symptom of gastroesophageal reflux disease; (-), there is no symptom of gastroesophageal reflux disease; n, the total number of subjects.

183 types are shown in Table 3. The most frequently confirmed GERD symptom during the treatment period was heartburn, followed by acid regurgitation/reflux symptoms. Table 4 shows the presence or absence of the GERD symptoms at the time of RE relapse for patients in whom RE relapse was endoscopically confirmed. GERD symptoms of some sort were found in 9 out of 21 cases (42.9%). Analysis of the change from baseline in the GERD symptom scores of 144 evaluable subjects who had continued the study for more than 52 weeks revealed the mean change at 52, 76, and 104 weeks to be negative, confirming overall improvement of GERD symptoms during the study. Figure 3 shows the mean and standard deviation for the GERD symptom score at baseline and at 24, 52, 76, and 104 weeks after the start of treatment.

Safety

Gastric mucosal atrophy

The severity of gastric mucosal atrophy at baseline in the 192 cases of the analysis set is divided into H. pylori-positive and negative populations and is presented in Fig. 4. The expansion of gastric mucosal atrophy tended to be greater in the H. pylori-positive population compared to the negative population. The progress of gastric mucosal atrophy was analyzed in 139 evaluable subjects who had continued the study for more than 52 weeks. Gastric mucosal atrophy had progressed at the end of the study compared to baseline in 8 subjects (5.8%; 95% CI: 2.5-11.0) (Table 5). All such progress had changed by 1 grade according to the Kimura-Takemoto Classification. No particularly noteworthy patient characteristics were found in the subjects in whom atrophy had progressed. There were also subjects in whom the classification at the end of the study had changed, compared to baseline, in the direction opposite to the direction in which atrophy was supposed to expand. The number of these subjects was the same as the subjects with progressive atrophy. There was no change in 123 subjects (88.5%).

Gastric mucosal histology

Gastric mucosal histology was analyzed in 140 evaluable subjects who had continued the study for more than 52 weeks. Figure 5 shows the percent of G stain-positive cells and percent of Cg A immunostain-positive cells among the fundic mucosal cells. Analysis of the change from baseline by paired t test revealed significantly increased fluctuation in the percentage of G stain-positive cells 104 weeks after the start of treatment (p=0.006), but not significantly increased fluctuation in the percentage of Cg A immunostain-positive cells throughout the treatment period.
**Serum gastrin**

The changes in serum gastrin were analyzed in 144 evaluable subjects who had continued the study for more than 52 weeks. The mean serum gastrin level was 215.1 pg/mL at baseline, which was above the upper limit of the normal range. The mean level at 24 weeks after the start of treatment was 259.1 pg/mL. The mean change from baseline was 44.0 pg/mL (95% CI: 16.4-71.6). Paired t tests revealed a significant difference (p=0.001). However, there was virtually no change after 24 weeks following the start of treatment (Fig. 6: cited from 17 with modification).

**Adverse events**

The development of fundic gland polyps and gastric hyperplastic polyps was previously reported (18), and 8 cases noted adverse events related to other gastric protruding lesions. In addition to the previously noted adverse events related to gastric protruding lesions, 1,011 other adverse events were reported in 180 cases, among which 29 adverse drug reactions were reported in 24 cases. The most frequently reported adverse drug reaction was increased blood pressure (3 events in 3 cases), followed by elevated blood triglycerides and toxic skin eruption (2 events each in 2 cases each). Six subjects also withdrew from the study because of adverse drug reactions. These included toxic skin eruption (2 cases), urticaria (1 case), increased blood pressure (1 case), elevated blood triglycerides (1 case), and decreased white blood cell count and platelet count (1 case). All of these events were already known as adverse drug reactions to RPZ.

**Table 5.** Patients with Progressive Gastric Atrophy during Proton Pump Inhibitor Therapy

<table>
<thead>
<tr>
<th>Subject</th>
<th>Key characteristics at baseline</th>
<th>Gastric mucosal atrophy assessment (week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Gender</td>
<td>Age</td>
</tr>
<tr>
<td>1</td>
<td>Male</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>77</td>
</tr>
</tbody>
</table>
over the long term in Japanese patients with RE. Five-year long-term treatment studies on RPZ (10 mg once daily) and RPZ (20 mg once daily) have been conducted in Europe and the US, and have confirmed the effect in suppressing RE relapse (11, 22). In the European study, the effects in suppressing relapse were comparable in the two treatment groups. In the results of the US study, on the other hand, the effect in suppressing relapse was higher in the 20 mg group compared to it in the 10 mg group (p=0.005). Although the reasons for the discrepancy between the results of the two studies are unclear, differences in the H. pylori infection rate at baseline were raised as a possible reason in the discussion of the US study (23). This notion is based on the postulation (24) that the effect of PPI is more readily manifested in patients infected with H. pylori than in those who are not infected. The H. pylori infection rate was 16 to 18% in the US study which indicated that the effect in suppressing RE relapse was lower in the 10 mg group compared to the 20 mg group, whereas the H. pylori infection rate was 36 to 46% in the European study which indicated that the effect in suppressing RE relapse was about the same in the 10 mg group and 20 mg group. An investigation of the risk factors for RE relapse using the data of the present study revealed that the non-relapse rates at 104 weeks after the start of treatment in the H. pylori-positive and negative populations were 94.2% and 82.2%, respectively, suggesting that the presence of H. pylori was a factor inhibiting RE relapse as in our previous conclusion (17).

Based on the overall improvement in GERD symptoms after the start of treatment compared to baseline, RPZ (10 mg once daily) is believed to suppress GERD symptoms over the long term in maintenance therapy for Japanese patients with RE. An investigation of the relationship between RE endoscopic findings and GERD symptoms also demonstrated that about 60% of RE relapsed cases had developed no GERD symptoms at the time of RE relapse. Several reports to date have also indicated that RE endoscopic findings were not accompanied by GERD symptoms (25-35), and this trend was often found in elderly (28). It has also been reported that the percentage of severe RE is higher in the elderly than in juveniles, whereas the frequency of severe heartburn in patients with severe RE is lower in the elderly (27, 36). In this study, there were 2 cases of severe (Grades C and D according to the Los Angeles Classification) RE relapse, but these were also elderly subjects who had not developed GERD symptoms at the time of RE relapse. Their ages at baseline were 82 and 83 years, respectively.

In this study, gastric mucosal atrophy was not often found to have progressed in H. pylori-positive subjects after treatment, which did not match the report by Kuipers et al (5) in 1996 that atrophic gastritis of the gastric corpus progressed as a result of long-term PPI treatment in H. pylori-positive patients with RE. Because there was also no change in gastric mucosal atrophy in most cases throughout the study period, Japanese patients with RE are believed to be at low risk for developing gastric mucosal atrophy as a result of long-term PPI treatment with RPZ (10 mg once daily). It was furthermore confirmed that the expansion of gastric mucosal atrophy at baseline tended to be greater in the H. pylori-positive population compared to the negative population, and it therefore appeared that the development of gastric mucosal atrophy was significantly affected by H. pylori. Based on the results of studies on long-term PPI treatment reported in 2004, Kuipers et al recommended H. pylori eradication therapy for H. pylori-positive patients in need of long-term treatment with PPI (37). In those study results, two-year long-term PPI treatment of H. pylori-positive GERD patients who had undergone the recommended PPI treatment for at least 1 year revealed no progression of mucosal gastric atrophy, but moderate to severe gastritis of the
gastric corpus was confirmed to predominate in those subjects at the start of the study. Most of this gastritis had resolved by final observation in the group receiving two-year PPI long-term treatment after the eradication of *H. pylori*. Also, GERD did not worsen as a result of *H. pylori* eradication, and the PPI dose was not increased as well.

Changes in fundic gland mucosa were also examined by histology in this study, but the G staining and Cg A immunostaining which were performed in order to identify neuroendocrine cells (primarily ECL cells) did not yield similar results. Gastric mucosal histological changes in the results of the above-mentioned 5-year long-term dosing study conducted in Europe have been separately reported in detail (38). According to the results, ECL cell hyperplasia was found in a small number of cases, but no ECL cell dysplasia or tumors were found. No carcinoids were found in the present study either.

In present study, the mean serum gastrin levels at baseline were already over the upper limit of normal, but it may have been because the subjects of the study were patients who had already been using some type of PPI at baseline, as established in the inclusion criterion (ii) of this study. It has been confirmed that serum gastrin levels were also elevated in other PPI clinical studies on Japanese patients with RE (39). The mean serum gastrin level 24 weeks after the start of treatment in this study was found to be about 20% greater than at baseline, and subsequent mean levels were about the same as the mean at 24 weeks after the start of treatment, and it therefore appears that there is little risk that serum gastrin levels will continue to increase as a result of long-term treatment with RPZ (10 mg once daily) in Japanese patients with RE.

Other noteworthy safety-related parameters include the effect on thyroid function by RPZ treatment. Although the results are from rat toxicity studies, 52 weeks of oral RPZ (25 mg/kg) administration was reported to result in an increase in thyroid weight and blood thyroxine levels (40). Thyroid-stimulating hormone, free triiodothyronine, and free thyroxine were tested as part of blood biochemistry tests in this study, but the reported adverse drug reactions included only one incident of thyroid-stimulating hormone increased in one case. The increased thyroid-stimulating hormone level was also spontaneously resolved during the study. Clinical findings included no reports of thyroid-related adverse drug reactions. In view of the above, there appears to be little risk that long-term treatment of Japanese RE patients with RPZ (10 mg once daily) would lead to abnormal thyroid function.

In conclusion, the results of this two-year long-term dosing study confirmed RPZ (10 mg once daily) to be effective for maintenance therapy in Japanese patients with RE. Although effects on the gastric mucosa cannot be ruled out, the drug was also confirmed to be safe overall. This study did not include placebo controls and/or time course controls, which may warrant further exploration.

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**Appendix 1**

The members of the Maintenance Study Group contributed to the study design, and interpretation and acquisition of data.

**Members of the maintenance study group**

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