

December 9th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format entitled NERD paper (revised)-F.

**Title:** Irsogladine maleate and rabeprazole in non-erosive reflux disease – a double-blind, placebo-controlled study

**Author:** Takayoshi Suzuki, Masashi Matsushima, Aya Masui, Shingo Tsuda, Jin Imai, Jun Nakamura, Yoko Tsukune, Tetsufumi Uchida, Hiroki Yuhara, Muneki Igarashi, Jun Koike, Tetsuya Mine.

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 14668

Thank you very much for providing us with such valuable comments. We have incorporated the information requested by the reviewers and the manuscript has improved substantially.

Responses to the questions from Reviewer 02286315

1 Gastric acid measurements were not undertaken as part of this study.

2 There were no differences in relation to the pre-treatment FSSG scores between grades N and M in either group I or group P.

Group I: (grade N:  $18.1 \pm 8.7$ , grade M:  $17.5 \pm 6.8$ )

Group P: (grade N:  $17.2 \pm 7.3$ , grade M:  $18.4 \pm 7.5$ )

3 We do not completely understand why the effects of IM were limited to patients with NERD grade N; however, our speculation regarding this is described within the third and fourth paragraphs of the Discussion.

4 The units for height, weight, and BMI have been added to Table 1.

5 Patients who were being treated with atazanavir sulfate or pro-kinetic agents were excluded from this study. We have included treatment with atazanavir sulfate and pro-kinetic agents as exclusion criteria in the Materials and Methods section.

6 Patients were asked whether they had experienced any adverse events at the end of the study. We have added a sentence to the Materials and Methods section to convey this information.

No serious adverse events occurred, and none of the participants terminated the study because of adverse events.

We have added a sentence to the Results section to convey this information.

7 The fourth limitation of the study relates to the effects that IM metabolites or drug interactions among IM, rabeprazole, and other medicines might have had on

the results of this study.

We have added a sentence to the Discussion section to convey this information.

Responses to the questions from Reviewer 000029540

1 However, recent studies have shown that different pathophysiological mechanisms underlie the condition in patients who have reflux symptoms but have minimal endoscopic changes. On the basis of esophageal 24-h multichannel intraluminal impedance combined with pH measurements, NERD patients can be classified into three groups, as follows: (a) patients with abnormal distal esophageal acid exposure; (b) patients with normal distal esophageal acid exposure and positive symptom associations for either acid and/or non-acid reflux (hypersensitive esophagus); and (c) patients with normal distal esophageal acid exposure and negative symptom associations (functional heartburn). Furthermore, a recent meta-analysis emphasized that well-defined NERD patients, including those in the aforementioned groups (a) and (b), have responses to PPI therapy that are similar to those seen in patients with RE, and that patients with functional heartburn do not respond to PPI therapy. However, NERD that is diagnosed on the basis of endoscopic findings alone cannot exclude some patients who have functional heartburn.

We have added the above sentences to the Introduction section to convey this information required.

The main limitation of this study might relate to the fact that NERD was diagnosed on the basis of the endoscopic findings alone. An accurate and reliable definition of NERD is needed to appropriately inform the discussion about the treatment of NERD.

We have added a sentence to the Discussion section to convey this information.

2 The third limitation of the study might relate to the controversy that surrounds the diagnostic and clinical relevance of the modified Los Angeles Classification for NERD.

We have added a sentence to the Discussion section to convey this information.

3 In the fourth paragraph of the Discussion we have now explored the role of non-acid reflux, and we have cited the literature that was suggested.

Responses to the questions from Reviewer 01803905

It is very regrettable that our manuscript did not interest this reviewer very much.

Major comments

1 It is impossible to distinguish between functional heartburn and NERD on the basis of endoscopic findings alone. We have commented on this in both the Introduction and Discussion.

2 We have remarked on the controversy surrounding the diagnostic and clinical relevance of the modified Los Angeles Classification for NERD in the Discussion.

3 We do not completely understand why the effects of IM were limited to patients with NERD grade N; however, our speculation regarding this is described within the third and fourth paragraphs of the Discussion section.

4 Endoscopy was performed before the participants entered the study. None of the participants took any medications for NERD before they entered this study.

#### Minor comments

1 and 2 This study was performed in accordance with the principles laid down in the Declaration of Helsinki. The study was registered in the UMIN Clinical Trials Registry (Registry ID Number: UMIN000015731).

We have added information to the Materials and Methods section that conveys this information.

3 Patients compliance was determined by counting the remaining units of medication at the end of the four-week study period. All of the patients took more than 90% of the prescribed medications.

We have added information to the Results section that conveys this

information.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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