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6 February 2018

Dear Professor Ma

RE: World Journal of Gastroenterology Manuscript NO. 36567 – Maintenance for healed erosive esophagitis: Phase III comparison of vonoprazan with lansoprazole

On behalf of all the authors, I would like to thank you for your provisional acceptance of our manuscript for publication in the *World Journal of Gastroenterology*. My co-authors and I would also like to thank the peer reviewers for their insightful queries and suggestions, and detail below a point-by-point response to each of these, together with descriptions of the revisions made to the manuscript to address the comments.

In addition to the amendments made to the manuscript in direct response to the peer reviewers' comments, please note that we have: revised the list of participating study centers and principal investigators, and the conflict-of-interest statement, on the manuscript's title page; amended the *Treatment, randomization, and blinding* section at the top of page 11 to provide more detailed information; on page 13, added the name of the biostatistician who reviewed and approved the statistical methods to that of the individual who carried out the

data analyses; and added the study's start and end dates to page 14. All changes made to the original submission draft have been tracked for your consideration.

We hope that the manuscript, as revised, meets with your approval, and look forward to hearing from you again when a final decision has been reached.

Yours sincerely

Kiyoshi Ashida, on behalf of the manuscript authors

Reviewers' comments to authors

Reviewer 00073423

This is well designed and performed randomized clinical study. I have just a few minor comments: 1. It remains unclear if the Helicobacter positive patients were enrolled? If yes, was there any difference in recurrence rates according HP status? 2. It would be informative if the authors could stratify the results according age, gender, smoking status and H.pylori status as mentioned above? 3. It is curious why the authors state the Non-Inferiority? Could it not be better to conclude that both doses of Vonoprazan are superior to lanzoprazole? 4. Is it possible to show the p values in the Table 5 5. I just could speculate if the Table 5 and Figure 2 adds something important to the manuscript. In the discussion authors recognize that the duration of the study is too short to assess the clinically significant histopathological changes

Authors' response

1. and 2. As shown in Table 1, Helicobacter-positive patients were enrolled into the study. EE recurrence rates did, indeed, differ according to HP status, and we would like to thank the reviewer for raising this question. In response to this, and to the reviewer's comment regarding stratification by age, gender, smoking status, and *H. pylori* status, we have added the results of all the subgroup analyses mentioned to Table 3, and have rewritten the final paragraph of the *Efficacy* subsection under the Results subheading (first paragraph of page 15) to read as follows: "*Subgroup analyses were conducted on the EE recurrence rates*

during the 24-week maintenance period according to age, sex, smoking classification, disease severity, extent of CYP2C19 metabolism, and H. pylori infection status. Post-hoc analyses confirmed that the differences in recurrence rates following treatment with vonoprazan 10 mg or 20 mg versus lansoprazole 15 mg were significant among patients who were: aged <65 years; of either sex; never smokers; had any LA classification grade; CYP2C19 extensive metabolizers; or H. pylori-negative (Table 3)."

3. The reason that we describe the results in terms of non-inferiority, rather than superiority, is that the primary objective of the study was to verify the non-inferiority of vonoprazan to lansoprazole, not to demonstrate superiority. Superiority was confirmed by post-hoc analysis.

4. Unfortunately, we did not perform statistical comparisons of the histopathology data, and are therefore unable to add P values to Table 5.

5. Although the duration of the study was too short to enable us to assess whether clinically significant changes would occur in the gastric mucosa in the long term, and this information is not central to the aims of the manuscript, my co-authors and I feel that our data may still be of interest to readers. We would therefore like to leave Table 5 and Figure 2 in place for reference for future studies.

Reviewer 02440966

This is a prospective, randiomized, multi-center study for comparing vonoprazan with lansoprazole as maintenance therapy in healed erosive esophagitis (EE). The authors concluded that vonoprazan 10 and 20 mg are not inferior to lansoprazole 15 mg as maintenance therapy for patients with healed EE. These results will give readers a good information on a kind of future treatment option for maintence therapy of GERD. There are minor issues to be considered. (1) In the Result section of Abstract, the p-value is not correct compared with the main results. (2) The authors described that they performed full-thckness biospy during endoscopy. Of course, I understand that this means full-mucosal layer biopsy. However, this is hard to understand for general readers. (3) The frequency of nasopharyngitis as a whole is not 4.1%, more than 13%, according to the frequency of nasopharyngitis in each group. (3) The setence for abnormal liver function (this is an imporant potential advere events of vonoprazan) is hard to understand. (4) Why are p-values of many parameters not-applicable in Table 2?

Authors' response

(1) My co-authors and I would like to thank the reviewer for pointing out this error on our part, which we have corrected by revising sentence 3 is the Results section of the Abstract to read as follows: "*In a post-hoc analysis, EE recurrence at Week 24 was significantly reduced with vonoprazan at both the 10 mg and the 20 mg dose vs lansoprazole 15 mg (5.1% vs 16.8%, P = 0.0002, and 2.0% vs 16.8%, P < 0.0001, respectively); by contrast, the EE recurrence rate did not differ significantly between the two doses of vonoprazan (P = 0.1090).*"

(2) This is a valid point, and we are again grateful to the reviewer for making it. For clarity, we have amended sentence 7 under the Procedures subheading on page 11 to read: "*All biopsy specimens were full mucosal layer samples taken from the greater curvature of the upper gastric corpus during endoscopic procedures.*"

(3) We have corrected this error by changing the relevant percentage in line 6 beneath the *Safety* subheading on page 15 from 4.1 to 14.7. The sentence now reads as follows: "*Nasopharyngitis was the most commonly reported TEAE in each treatment group (13.9%, 16.8%, and 13.2%, respectively; 14.7% of patients overall).*"

(3) The information on abnormal liver function tests has now been rewritten and expanded in response to the first comment from Reviewer 03024603, as detailed fully below.

(4) As the aim of the study was to show that vonoprazan is non-inferior to lansoprazole, there is no non-inferiority P value for the comparison of vonoprazan 10 mg versus vonoprazan 20 mg. Additionally, the post-hoc analysis was performed for the primary endpoint only, not for the secondary endpoint; consequently, Fisher exact test P values were not calculated for the Week 12 comparisons.

Reviewer 03024603

I revised the manuscript entitled "Maintenance for healed erosive esophagitis: Phase III comparison of vonoprazan with lansoprazole" The study is interesting and the manuscript is well written. The data provided gives information about maintenance therapy option for GERD. I have few comments 1- The authors mentioned "abnormal liver function", this should be discussed in details including type and severity of the abnormal liver function. 2- Authors should clearly mention whether the Helicobacter positive patients were included in the study or not? And why?

Authors' response

1 – My co-authors and I agree that more information should be provided in relation to the incidences of abnormal liver function test and hepatic function during the study, and are extremely grateful to the reviewer for pointing out this oversight on our part. Accordingly, we have added brief descriptions of each of the cases under the *Safety* subheading on page 15 of the revised manuscript. Thus, beginning on line 10 of that section, the text now reads as follows: "*Very few serious TEAEs were reported with lansoprazole 15 mg, vonoprazan 10 mg, or vonoprazan 20 mg (4, 5, and 4 TEAEs, respectively); of the TEAEs reported, one case of atrial fibrillation and abnormal liver function test (elevated ALT and AST [303 U/L and 228 U/L, respectively]) in the vonoprazan 20 mg group were considered to be possibly related to the study drug. The abnormal liver function test was reported in a patient with a prior history of alcoholic hepatic steatosis, and led to his premature withdrawal from the study. As no specific cause was identified, a possible causal relationship with the study drug could not be ruled out.*

With regard to SIAEs, one case each of abnormal liver function test (elevated ALT [179 IU/L] and AST [209 IU/L] owing to fenofibrate treatment for dyslipidemia) and elevated ALT (137 IU/L], which was not associated with any symptoms and was considered possibly related to the study medication) were reported in the lansoprazole 15 mg group, while two cases of abnormal liver function test were reported in the vonoprazan 10 mg group (elevated ALT [467 IU/L] and AST [571 IU/L] in one patient, which were considered possibly related to the study medication; and elevated ALT [326 IU/L] and AST [127 IU/L] that occurred in a patient with concurrent hepatic steatosis and were considered unrelated to the study drug). In the vonoprazan 20 mg group, elevated ALT (86 IU/L) and AST (47 IU/L) were reported at the final study visit in a patient with concurrent hyperlipidemia and hepatic steatosis. Having completed the study, the patient began to receive lansoprazole as maintenance treatment for EE. Four weeks after the patient had completed the study, a further ALT elevation (139 IU/L) was reported, which qualified as a SIAE. Two days later, dark urine and itching were reported. The patient's condition remained unresolved 2 months later but, owing to the invasive nature of blood sampling, the investigator decided that further follow-up was unnecessary, and that the patient should receive routine medical care and further treatment as required. As the initial ALT and AST elevations had occurred during the maintenance period of the study, the possibility of a causal relationship with the study medication could not be ruled out. Also in the vonoprazan 20 mg group, elevated ALT (138 IU/L, which was considered to have been caused by pre-existing hepatic steatosis) was reported in one patient, and two cases of abnormal liver function test were noted; the first in a patient with ALT elevated to 161 IU/L following the consumption of a large quantity of alcohol, and the second being the case that is described above as a serious TEAE. All the SIAEs were

considered resolved or resolving, with the exception of the case of abnormal hepatic function in the vonoprazan 20 mg group. This patient was followed up with routine medical care and treated as required."

2 – Table 1 already shows that patients who were positive for Helicobacter *pylori* were included in each of the three study groups. We have therefore not made any changes to the manuscript to address this particular query. As EE occurs in both Helicobacter pylori-positive and -negative patients, we chose not to exclude patients on the basis of Helicobacter pylori status.

Reviewer 00503535

In this clinical study, the authors compared vonoprazan 10 and 20 mg vs lansoprazole 15 mg as maintenance therapy in healed erosive esophagitis (EE), and confirmed the non-inferiority of vonoprazan 10 and 20 mg to lansoprazole 15 mg. In particular, vonoprazan was found to be highly effective among CYP2C19 extensive metabolizers and patients with baseline EE of LA Classification grade C or D. The safety profile of vonoprazan at the administered doses was similar to that of lansoprazole 15 mg. The study was well performed and the article is precisely written and very interesting. The reviewer's only one question was as follow; as shown in Figure 2, the mean levels of serum gastrin, pepsinogen I, and pepsinogen II significantly increased in vonoprazan 10 and 20 mg compared with lansoprazole 15 mg after the start of maintenance therapy. However, clinically significant effects on the gastric mucosa were observed. What were these increases resulted from? Please discuss it.

Authors' response

My co-authors and I would like to thank the reviewer for raising this important question. The observed increases in serum gastrin, pepsinogen I, and pepsinogen II in all treatment groups were likely a negative feedback effect caused by the increase in intragastric pH that resulted from treatment with lansoprazole or vonoprazan. To clarify this for readers, we have now added the following as a new sentence on lines 6−9 of page 19 of the manuscript: *"This, as well as the observed increases in pepsinogen I and II, were likely a negative feedback effect caused by the increase in intragastric pH that resulted from treatment with lansoprazole or vonoprazan."*

Reviewer 01557050

Dr. Ashida, et al. investigated ‘Maintenance for healed erosive esophagitis: Phase III comparison of vonoprazan with lansoprazole’. The article is informative and well-presented. The reviewer has a minor comment. Comments 1. In Table 3, it is hard to understand the line of Erosive esophagitis grade and CYP2C19 genotype. Please prepare a horizontal line. For example, LA Grade C/D 13.2% (5/38) might be one line bottom.

Authors’ response

As requested by the reviewer, we have reformatted Table 3 to clearly differentiate the EE grade from the CYP2C19 genotype data.