Author’s response to reviews

Title: Concomitant, sequential, and 7-day triple therapy in the first-line treatment of Helicobacter pylori infection in Korea: A study protocol for a randomized controlled trial

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Responses to the editor requests

1. Trial design and study setting. Add the framework of the design: superiority, equivalence, noninferiority, exploratory?

RESPONSE: We have clarified the framework of the study design in the revised abstract and Method section.

2. Can the author provide the formula used for the calculation of the sample size?

RESPONSE: We additionally described the formula used for the calculation of the sample size in the Method section.

3. Procedures. “Compliance with treatment will be assessed both by questioning patients”. Is it a validated questionnaire? What questions will be used?
RESPONSE: Thank you for your feedback. The questionnaire used to assess the incidence of adverse events and compliance was not validated in our study. Similar to other trials that address the efficacy and safety of H. pylori eradication regimens, adverse events and severity were scored using a 4-point scale. The Method section was corrected to reflect this information.

4. Procedures. “…Recommendations for Interventional Trials (SPIRIT) Checklist (Table 1)”. Note that you have placed the SPIRIT checklist in a supplementary table, not Table 1.

RESPONSE: This error in describing the checklist has been corrected, as follows. “The standard protocol for this study is shown in Table1.” “Recommendations for Interventional Trials (SPIRIT) Checklist (Supplementary Table)”

5. Authors should write more on interventions. Include:

RESPONSE: As you suggested, we included a discussion of the criteria for discontinuing or modifying allocated interventions, strategies to improve adherence to intervention protocols, and relevant concomitant care and interventions that are permitted or prohibited in this trial.


RESPONSE: We have described the allocation concealment mechanism in greater detail in the Method section.

7. If any, report on data monitoring committee. Alternatively, an explanation of why a DMC is not needed.

RESPONSE: We additionally described the plan for data monitoring.


RESPONSE: Thank you for your feedback. We included further details in the Method section.

Responses to the Comments of Reviewer #1

1. Is clarithromycin resistance related to race and region?

RESPONSE: Clarithromycin resistance is associated with regional variation. Also, due to regional variation in drug resistance in Korea, the reliability of results from a single center study is limited. Therefore, any determination of a treatment regimen for use in Korea requires a nationwide database that is obtained from a multicenter trial, such as in this protocol.
2. The eradication rate would be superior in the sequential or concomitant therapy groups, with a 10% difference compared to the rate for standard triple therapy (85% vs. 75%). Is the 10% difference data derived from a pilot study or other reports? please explain it.

RESPONSE: Thank you for your feedback. Several studies have demonstrated that the eradication rate of standard triple therapy is approximately 75% in Korea. The eradication rate of sequential or concomitant therapy has been reported to be more than 80%. To obtain the optimal eradication rate, an efficacy of more than 85% is needed for each treatment. Hence, we calculated the sample size to measure a 10% difference (85% vs. 75%) from the rate of eradication obtained for standard triple therapy.

3. Figure 2 show a 20% loss to follow-up, I consider that the loss to follow-up should be controlled to 10-15%, is that OK?

RESPONSE: In this study, voluntary withdrawal will be due to various adverse events. For this reason, we determined that a 20% loss to follow-up would be realistic. Indeed, many trials that have assessed the efficacy of treatment regimens for H. pylori eradication experienced a 15-20% dropout rate. (e.g., Gut Liver. 2016 Jul 15;10(4):556-61; Aliment Pharmacol Ther. 2002 Jul;16(7):1261-7; Gut Liver. 2013 Jul;7(4):406-10).

4. in Table 1, the follow-up period is 8 weeks after post-allocation, however, there are not any description and explanation for it in text.

RESPONSE: We additionally described the follow-up period following group allocation.

Responses to the Comments of Reviewer #2

1. In the methods section of the abstract, it says standard therapy will be given for 14 days. In other parts of the manuscript it says standard therapy will be given for 7 days.

RESPONSE: This was corrected.

2. The more recent European Guidelines should be included (Malfertheiner 2017 PMID: 27707777)

RESPONSE: This guideline reference was added.

3. The authors should further discuss the rationale for using 7 day standard triple therapy given that the clarithromycin resistance rate in Korea is high.
RESPONSE: Recent Korean health guidelines recommend a 7-d standard triple regimen as the first-line therapy and is the only regimen reimbursed by the Korean National Health Insurance Service. However, due to high clarithromycin resistance, the efficacy was found to be unfavorable. For this reason, this trial explores the efficacy of alternative regimens (sequential or concomitant regimen) versus standard triple therapy. This rationale was more carefully described in the revised version of the manuscript.

Responses to the Comments of Reviewer #3

1. The duration of triple drug regimen is only 7 days which is less than the recommended 10-14 days.

RESPONSE: The revised Korean revised guidelines have indicated that triple therapy, including a standard dose of PPI, 1 g of amoxicillin, and 500 mg clarithromycin twice a day for 7–14 days, is the recommended primary regimen for H. pylori eradication. However, the Korean National Health Insurance Service reimburses treatment for only a 7-day duration. For this reason, one arm of this trial included the 7-day standard triple regimen.

2. Urea breath test should be done before therapy also.

RESPONSE: Thank you for your feedback. A urea breath test has been added as part of the baseline study. However, the Korean National Health Insurance Service does not accept the UBT test as a screening test. For this reason, only the UBT cannot be used as a screening test in this trial.

We appreciate these insightful comments from the reviewers regarding our manuscript. We hope that our responses are sufficient to resolve the concerns of the reviewers. Thank you for your thorough review of our manuscript.