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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 79101

Title: Randomized controlled trial to evaluate the efficacy and safety of fexuprazan compared with esomeprazole in erosive esophagitis

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03352142
Position: Editorial Board
Academic degree: PhD
Professional title: Full Professor, Statistician
Reviewer's Country/Territory: Iran
Author's Country/Territory: South Korea

Manuscript submission date: 2022-09-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-09 06:04

Reviewer performed review: 2022-09-19 08:46

Review time: 10 Days and 2 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Authors investigated comparative efficacy of fexuprazan to esomeprazole and establish its efficacy and safety in patients with erosive esophagitis (EE) The following points should be addressed First it is not correct approach to randomize and odd numbers of people in two groups it is highly recommended groups with equal number at randomization stage! The following results are not correct, when the efficacy rate is equal unto two groups the difference 0.89% is not correct. (99.1% (106/107) vs 99.1% (110/111)) with a difference of 0.89% (95% confidence interval, -0.86 to 2.64). How about the previous studies about the efficacy and safety of fexuprazan, please explain with more details. Which method of randomization (simple, block…) was used, please declare it. How about the random or regime assignment concealment? Which rate of compliance was considered in current study? Matters such as "EE (LA Classification Grades A to D) " and so on needs relevant references. More important: who about the inclusion and exclusion criteria? All variables you have reported them in results section should be introduced in methods section appropriately. My mean is those variable you reported them in table 1,…. The noninferiority margin 0.1 (your mean is 10% you wrote in it as 10% in results section) and type one error rate 2.5% and power 90% needs more sample size than 130 per group?! Please present the data about the validity and reliability RDQ and GERD - HRQL with relevant reference particularly in your country. Results and Statistical analysis needs major revisions and your results should be based on new relevant statistical analyses; please get sophisticated consults from Biostatistician. How about the data presentation for continuous and categorical data? How about the normality evaluation data for continuous data? Which statistical tests

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you used for comparing variables in table 1? Please declare them in this section and footnote in below table. Which statistical test you used for evaluating changes in serum gastrin levels in each group and between groups (Repeated measures ANOVA is needed with relevant and sound presentation of results) . please refer the matters under heading Healing rate of EE (first paragraph) to figure 3. What is LL? (Lower limit), also present relevant p-value for the both and second paragraph. Data presented in Supplementary tables 1-4 need p-value and you should clarify which tests are they based. Table 2 should be based on repeated measures ANOVA or GEE with relevant presentation (p for time, intervention and interaction of time and intervention. Table 4 needs p-value for compared data.

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Reviewer's code: 05329158
Position: Peer Reviewer
Academic degree: MD

Professional title: Research Assistant

Reviewer's Country/Territory: Iran

Author's Country/Territory: South Korea

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-23 03:56

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Review time: 6 Days and 10 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Dear editor-in-chief: It is my pleasure to be selected as one of the reviewer of the manuscript named "Phase III, Randomized, Double-Blind, Multicenter, Active-controlled, Parallel-Group, Therapeutic Confirmatory Study to Evaluate the Efficacy and Safety of Fexuprazan Compared with Esomeprazole in Patients with Erosive Esophagitis". In this randomized clinical trial, Lee et al. found Fexuprazan was as effective as Esomeprazole in healing erosive esophagitis. By the way, there are some major and minor comments which might be helpful for improving the quality of the article. - Although it is obvious, please write the full names of LA, IP, AIDS and LL for the first time in the manuscript. Then the authors can freely use the abbreviations. - It is better not to use drug prescription orders like "QD" in scientific paper. Please change it to once daily or other similar terms. - Please write the full name of abbreviations in figure 1. - In figure 2, please put the exclusion reasons from FAS in parenthesis. In this current format, it is misleading. - In table 1, please report P-values with similar decimals. The last row P-value has four digits, but the others have three digits. On the other hand, other P-values in other tables and texts are reported with four digits of decimals. - The healing rate difference reported at 8 weeks in abstract and figure 3 are not the same as results section. of 0.89% (95% CI, -0.86 to 2.64) vs. 0.9% (95% CI, -0.9−2.6). - It is better to report erosive esophagitis healing rate difference at 4 weeks in abstract section. - The authors found Fexuprazan effects rapidly observed after 4 weeks and the difference was similar compared to Esomeprazole. Thus, it might be possible to suggest a relative shorter treatment period for erosive esophagitis instead of 8 weeks of therapy. Although it needs further support, it could be promising. Please consider this point and expand it

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further in discussion. - Please write full names of "fexu" and "esome" in results section. - "Hp +" and "hp –" are quite misleading, especially when no abbreviations is previously determined. Please kindly edit this point. - Total H.Pylori positive patients was 51 subjects (table 1), but in results it was reported as 43 (17 + 26). These controversial calculations have been also seen in H.Pylori negative as well as EM and PM subjects. Please clarify this issue and correct it accordingly. - In table 1, EM and PM differed significantly according to intervention and control groups (P= 0.007), but there is not any explanation in results section. Please report it. - Please briefly report the results of proportions of symptom-free days in the first 7 days and through the 8 weeks (supplementary tables 3 and 4) in results section. - It is not any comparison with reported P-values in table 2. In this current manner, a deduction cannot be made regarding the presence/absence of any difference between intervention and control groups or even within each group from the baseline. - It seems evaluation of GERD-HRQL questionnaire (table 3) was not done on all participants. It is better to report the probable reasons in results. Also if all participants were not assessed through RDQ, it is better to consider this issue and report the subjects being evaluated in table 2. - In the last paragraph of "symptom response" section, the authors assessed symptoms relief in patients with moderate-to-severe symptoms and reported relevant percentages in the text. Also, they mentioned the supplementary tables. However, it should be noted that in supplementary table 5, the variables were assessed for total population (n= 218), NOT just for patients with moderate-to severe symptoms (n= 128 based on calculation in table 1). It is better to add relevant tables for these groups of patients and also report these variables based on total population. - Which one is corrects? TEAE or TEAR? Both of these terms were used in the text and tables. Please select one of them. Otherwise, usage of these two indices is confusing. Also, please explain the definition of TEAE/TEAR. - In just supplementary tables 5 and 6, Fexuprazan is written as its generic

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name (DWP 14012). Please use one common name. - Although the manuscript has been edited by editorial agencies, it has still some minor issues needed to be corrected. For instance, "moderate events" has been written two times consecutively in results (safety section). - The authors used RDQ to assess severity of symptoms, but there is not any relevant references cited to this questionnaire. Also, there is not any explanation regarding the scoring system of this questionnaire. Please add them. - Moreover, the authors stated "Symptom severity in the daytime and at night were classified as none, mild, moderate, severe, or very severe". However, it seems none of the patients were in "none", "mild" and "very severe" groups (based on table 1). It is better to report this explanation in results section to avoid confusion. - In table 1, the summation of H.Pylori, CYP2C19 (EM and PM) are not compatible with the total number of intervention and control groups. Please clarify this inconsistency. - Despite the authors assessed ADR, no definition was provided in the main text. Also, there is not any information regarding this outcome in table 4. - For appropriate comparison of TEAEs between groups, P-values are necessary. Please add them in table 4 or just mention those with significant difference between intervention and control groups, if applicable. - The authors stated "some statistically significant changes were observed in laboratory tests and vital signs". Please briefly mention them in the text. - The item "n" is supplementary tables 3, 4 and 6 are redundant, because the main outcome in these tables is days, not participant numbers. - There is a major statistical issue in supplementary table 6 in "Proportion of Symptom-Free of Chronic Cough" variable. The median is equal to maximum which is statistically impossible. Re-analysis of the outcomes is highly recommended. Regards