Expert Scientific Review Report

C2203-123456-Smith-FS
Report prepared by: Bob Jones, MD

Manuscript Summary

Title:	[Drug] for [outcome] in patients with [disease]

About Your Expert Scientific Review Report

Key
- ✓ No changes necessary
- ✓ Minor revisions suggested; see the comments for more information
- ✘ Major or important revisions suggested; see the comments for more information

Please note that this report focuses on the content of your manuscript rather than the language. If you have ordered English language editing, please send your revised manuscript to us for editing.

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Title and Abstract

The title is appropriate and indicates the main message of the paper ✗
The title specifies the intervention and the primary outcome, but not the comparator or the study design. • *Please add that this was a randomized, placebo-controlled trial.*
The abstract provides a concise but complete summary of the content of the paper ✗

Several items of information are missing from the abstract.
• *Please add the following information:*
  ○ *The setting and number of centers.*
  ○ *The number of patients randomized and the number analyzed.*
  ○ *The trial registration number.*

The abstract can stand alone without reference to the main text (e.g., abbreviations and jargon clearly defined) ✓
Once the information mentioned above is added, the abstract will be able to stand alone without reference to the main text.
The abstract is understandable by a non-specialist reader ✓
No changes needed.

Introduction

The introduction provides sufficient background information for readers not in the immediate field to understand the problem/hypotheses ✗
The background information about [disease] and the disease burden are clearly described. However, the information about disease prevalence is based on references published over 20 years ago. • *Please cite more recent data when discussing the prevalence of [disease] (preferably within the last 5 years).*
The reasons for performing the study are clearly defined (e.g., the gap in the existing knowledge and the importance of the topic are clearly defined) ✗
The limitations of existing available treatments are not described, so the need for new therapeutic approaches is not clear to the reader. • *Please discuss the limitations of existing treatments to more clearly define the rationale for this study.*
The study objectives are clearly and explicitly defined ✓
No changes needed.

The objectives match the results and conclusions ✘
The objective was to investigate efficacy for [primary outcome] but results for [secondary outcomes] are presented first in the Results section, and the conclusions focus on the efficacy against [secondary outcomes] without mentioning the lack of efficacy observed against [primary outcome]. • *In the Results, please present the findings for the primary outcome before the findings for the secondary outcomes.* • *In the Conclusion section, please add your conclusion regarding the primary outcome.*

Methods/Technical Rigor

The methods used are appropriate to the aims of the study ✘
Reviewers are likely to question the use of a placebo control given the availability of treatments for [condition] that have been demonstrated to be effective. • *Please clearly justify your use of a placebo control. For example, are existing treatments unavailable in your low-resource setting?* It is unclear whether the primary analysis was intention-to-treat or per protocol. Typically, an intention-to-treat analysis would be expected for a trial of this type. • *Please clearly indicate whether the primary analysis was intention-to-treat or per protocol.*
Sufficient information is provided for a capable researcher to reproduce the experiments described ✘

Some key methodological information is missing.
• *Please add the following information:*
  ○ *The method used to generate the randomization sequence (e.g., random number table).*
  ○ *The method used to conceal allocation (e.g., sequentially numbered opaque envelopes).*
  ○ *Details of randomization (e.g., any stratification; use of permuted blocks).*
  ○ *Which patients were to be included in the primary analysis (i.e., indicate whether the planned analysis was intention-to-treat or per protocol).*
  ○ *How sample size was determined.*

No additional experiments are required to validate the results of those that were performed ✓
No changes needed.
There are no additional experiments that would greatly improve the quality of this paper ✓
No changes needed.
Appropriate references are cited where previously established methods are used ✓
• *When you add information about sample size calculation, please cite appropriate references to support your assumptions about effect size and event rate.*

Results/Statistics

The results are clearly explained and presented in an appropriate format ✓
The results are clearly presented; however, the results for the secondary outcomes are presented before those for the primary outcome. • *Please rearrange the Results section to present your findings for the primary outcome first.*
The figures and tables show essential data that could not be easily summarized in the text ✓
No changes needed.
There is no unnecessary duplication of data in the graphics and/or the text ✓
No changes needed.
The figures and tables are easy to interpret ✓
The figures and tables are generally easy to interpret; however, some minor improvements are possible: • *Please indicate in the figure captions whether error bars represent standard deviation or standard error.* • *Figure 3 has low resolution, which makes reading some of the text a little difficult. Please provide a higher resolution figure.*
There are no additional graphics that would add clarity to the text ✗
As mentioned above, it is unclear which patients were included in the analyses. • *Please provide a flow diagram to indicate the numbers of patients included/excluded at each stage and the numbers who received the allocated intervention.*
Appropriate statistical methods have been used to test the significance of the results ✗
P-values have been supplied for comparisons of the baseline characteristics of participants in the two study arms in Table 1. This is technically inappropriate – hypothesis testing evaluates the probability that differences between two groups are a result of random chance; in a randomized study, any difference between groups is *by definition* the result of random chance (see this reference for further explanation). • *Please remove the p-values from Table 1 and instead add a brief qualitative discussion of the similarity of the groups to the end of the first paragraph of the Results section.*
P-values and other indicators of statistical significance are included where necessary ✓
P-values are present in most places where they are necessary. However, they are missing from Table 3 and the final paragraph of the results. Additionally, confidence intervals are not provided for the effect estimates in the Results text. • *Please add p-values for the group comparisons in Table 3.* • *Please add 95% confidence intervals where you state effect estimates in the Results text.*

Discussion

All possible interpretations of the data are considered; there are no alternative hypotheses that are consistent with the available data ✓
No changes needed.
The findings of the study are properly described in the context of the published literature ✓
The findings are compared with the published literature, but possible reasons for discrepancies are not discussed. • *Please discuss why your findings may differ from those of Kenyon et al. For example, theirs was an observational study and therefore more prone to bias than a randomized controlled trial; and their study population was larger and had less stringent exclusion criteria for disease severity.*
The limitations of the study are discussed ✗
There are several limitations that are not currently mentioned: • *Please mention the comparatively high loss to follow-up, and the imbalance between groups in loss to follow-up, because these features have the potential to introduce bias.* • *Please mention that patients with the most severe disease classification were excluded; further investigation is needed to determine whether the intervention is effective in that population.* There is also a strength of the study that could be emphasized to balance the limitations: • *Please mention that this was a large, multi-center study.*
The conclusions of the study are supported by appropriate evidence; the claims are not exaggerated ✗
The conclusion mentions only the secondary outcomes where a statistically significant effect was detected. The overall conclusion that [drug] is an effective treatment for [disease] is exaggerated given the lack of effect on the primary outcome and does not acknowledge the limitation to the generalizability of the findings. • *Please transparently declare the finding of no effect in relation to the primary outcome before drawing conclusions about the secondary outcomes.* • *Please also mention that the effect observed for the secondary outcome was in patients with lower-severity disease.*
The conclusions address the aim of the study ✗
As mentioned above, the conclusions focus on two of the secondary outcomes. • *Please state your conclusions regarding the primary outcome before drawing conclusions about the secondary outcomes.*

Literature Cited

The literature cited is appropriate, recent and balanced ✓
Most of the cited literature is suitable. However, in the Introduction section, the literature citing the prevalence of [disease] was published over 20 years ago. • *Please cite more recent data when discussing the prevalence of [disease] (preferably within the last 5 years).*
There are no statements that are missing citations or have an insufficient number of citations, given the strength of the claim made ✓
No changes needed.

Significance and Novelty

The claims are sufficiently novel to warrant publication ✓
No changes needed.
The study represents a conceptual advance over previously published work ✓
The study does not represent a conceptual advance because other drugs of the same class have been demonstrated to be effective against the same (secondary) outcomes. However, the study is an incremental advance and warrants publication. Although your findings regarding the primary outcome are "negative", it is important to communicate this to the clinical community, particularly given that observational studies have suggested efficacy of [drug] against [primary outcome].
The study represents an incremental advance over previously published work ✓
No changes needed.

Journal Selection

The target journal (if known) is appropriate
A target journal has not yet been chosen. A suitable target would be an international journal with a moderate Impact Factor and a broad medical or cardiovascular focus. The likely target audience of this paper includes clinicians in the fields of primary care, emergency medicine and cardiovascular disease.

Summary

Major action points

- Please clearly justify the use of a placebo control.
- Please clarify which patients were included in the analysis (a flow diagram will help with this).
- Please present your findings for the primary outcome before those for the secondary outcome.
- Please discuss the additional limitations mentioned in the above report.
- Please modify your conclusions to mention the lack of effectiveness against [primary outcome] and to acknowledge the limitations regarding generalizability.

Minor action points

- Please cite more recent data when discussing the prevalence/burden of [disease] (preferably within the last 5 years).
- In the Introduction section, please discuss the limitations of existing treatments to more clearly define the rationale for this study.
- Please add the missing information detailed in the above report.
- Please remove the p-values from Table 1 and instead add a brief qualitative discussion of the similarity of the groups to the end of the first paragraph of the Results section.
- Please provide a higher resolution version of Figure 3.

How can Liwen Bianji help?

- **If you have ordered English language editing, please send your revised manuscript to us for editing.**
- If you would like more in-depth advice on appropriate journals, we offer a range of Journal Selection services.
- If you would like assistance with your abstract, we offer an Abstract Development service.