Author’s response to reviews

Title: The efficacy and safety of Shenzhu Guanxin Recipe Granules for treatment of patients with coronary artery disease: protocol for a double-blind, randomized controlled trial

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Author’s response to reviews:

RE: TRLS-D-19-00162, entitled “The efficacy and safety of Shenzhu Guanxin Recipe Granules for treatment of patients with coronary artery disease: protocol for a double-blind, randomized controlled trial“

Dear Editor,

We would first like to thank you and the reviewers for your kind letter and professional advice concerning our article (Manuscript No. TRLS-D-19-00162). The following advice was valuable and helpful in improving our article. All authors have seriously discussed the review and opinions on the article and based on these reviews, we have modified our manuscript to meet the requirements of your journal. In this revised version of the manuscript, changes to our manuscript are presented in red text. Point-by-point responses to the reviewers are listed below.
Reviewer reports:

Thank you for your revision and providing some clarifications for your protocol and its novelty. The present protocol can be a leading article for this intervention (SGR), so you'd better provide definite rationale for your sample size calculation.

You have not provided any reference for your pilot study. We have asked you provide a reference for your pilot study and a rationale for 10% clinical significance. However, you have only mentioned statistical rationale for your hypothesis that 10% decrease in CCS can be clinically significant (a coverage probability of 90% for the confidence interval in the case of bioequivalence studies has become the accepted standard when evaluating whether the average values of the pharmacokinetic parameters of two formulations are sufficiently close).

1- It is better to omit the following sentence, since you have not added any reference for your pilot study (as you have provided statistical rationale instead a reference for pilot study):

"The calculation of sample size was undertaken based on the results of our pilot study."

Response:

Thank you very much for your advice. Because the preliminary study only recruited 50 patients, and the endpoints mainly included CCS (coronary artery calcification score), the design of pilot study is relatively simple. Consequently, we haven't published any relevant articles.

It is kind of you remind me to omit the following sentence: "The calculation of sample size was undertaken based on the results of our pilot study”, we had already omitted it, thank you!

2- Add you statistical rationale for sample size calculation in the main text as follows:

"Firstly, the reason that we consider 10% decrease as the clinically significant effect size is because a coverage probability of 90% for the confidence interval in the case of bioequivalence studies has become the accepted standard when evaluating whether the average values of the pharmacokinetic parameters of two formulations are sufficiently close (Ref. 1 in your revision letter). Thus, the 95% CI of the difference in the group means within the interval of -10 to +10% was defined as clinical equivalence in the current study."
Response:

Thank you for your advice, we had added statistical rationale for sample size calculation in the main text according to your advice, which are presented on page 5, lines 14-28. The amendments are as follows:

Firstly, we hypothesized that the expected difference in the primary outcome (coronary artery calcification score) between the SGR group and placebo group was estimated to be 10%. The reason that we considered 10% decrease as the clinically significant effect size was because a coverage probability of 90% for the confidence interval in the case of bioequivalence studies had become the accepted standard when evaluating whether the average values of the pharmacokinetic parameters of two formulations were sufficiently close. Thus, the 95% CI of the difference in the group means within the interval of -10 to +10% was defined as clinical equivalence in the current study. Secondly, to calculate the sample size, we employed the “pwr.t.test” function in R package “pwr” (R package version 1.2-2. https://CRAN.R-project.org/package=pwr) [20]. As an example, say we want to be able to detect a difference of at least 6.2 in the mean CCS (about 10% decreases in CCS) with a common standard deviation of the two groups to be 10. Therefore our effect size is 6.2/10 = 0.62 according to Cohen (1988) [21]. For a desired power of 80%, Type I error tolerance of 0.05, and a hypothesized effect size of 0.62, we should sample at least 84 participants per group, i.e., a total of 168 participants. If assuming there will be a dropout rate of 15% within 6 months, then 194 participants can eventually be recruited.