Author's response to reviews

Title: The effect of febuxostat to prevent a further reduction in renal function of patients with hyperuricemia who have never had gout and are complicated by chronic kidney disease stage 3: study protocol for a multicenter randomized controlled study

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Author's response to reviews: see over
Professor Doug Altman  
Editor-in-Chief, Trials  

December 10, 2013  

Re: Submission of the re-revised manuscript (manuscript No.: 1011386667103203)  

Dear Professor Altman:  

I highly appreciate your kind e-mail dated November 19, 2013, which included valuable suggestions from Reviewer 1.  

I carefully read the suggestions and prepared the replies on a comment-by-comment basis. I highlighted the modifications/corrections that I made green to facilitate verification by you and the reviewer.  

To explicitly describe the intervention of Public Health Research Foundation in the present study as described in the documents submitted to the editorial office of TRIALS, furthermore, I modified the sentences of the “Acknowledgments” Section as follows: “The research fund for the FEATHER study was provided to Comprehensive Support Project for Clinical Research of Lifestyle-Related Disease of Public Health Research Foundation by Teijin Pharma Limited.”  

I do expect you and the reviewer find the present re-revised manuscript finally acceptable for publication in you journal.  

Sincerely,  

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Reviewer 1’ comments

MAJOR COMPULSORY REVISIONS

ABSTRACT

• 3rd line: “…supporting a cause-effect relationship” rather than “…to indicate the association”. NOT DONE.
Reply: I modified the sentence as per your valuable suggestion.

• Section Methods/design, 3rd line: stage 3 rather than stage 3) (delete “)”). OK
Reply: I appreciate your valuable comment and would ask you to note that there is a preceding left parenthesis “(” in the first line of this section. Therefore, I would prefer to leave a subsequent right parenthesis “)”) in the sentence.

• Section Methods/design, 6th line: “arthritis, who present” rather than “arthritis and present”). NOT DONE
Reply: I modified the sentences as per your kind suggestion as follows: “… who have hyperuricemia without gouty arthritis, who present CKD stage 3, and whose SUA concentration is 7.1-10.0 mg/dL.”

• Section Methods/design, 7th line: “…to either the febuxostat or the control group” rather than “…to either of the febuxostat and the control group”. NOT DONE
Reply: I modified the sentences as per your valuable suggestion.

BACKGROUND

• 1st paragraph, 3rd line. – The authors wrote “the prevalence of the disease is 30% in the former cohort of patients…”. I do not understand that sentence. What disease? What “former cohort”? NOT ADDRESSED
Reply: I am sorry for ambiguous expressions. I intended to mean “hyperuricemia” with “the disease” and “patients in their thirties” with “the former cohort of patients.” I modified the sentences as per your kind suggestion as follows: the prevalence of hyperuricemia is 30% in patients in their thirties.
METHODS/DESIGN

• Study design and study organization. – The expression “the roles, e.g., the…” is found in 3 sentences that I do not understand. NOT ADDRESSED

Reply: I intend to mean “such as, for example” with “e.g.” In response to your insightful suggestion, I modified the expression as follows in three sentences: “the roles, including …, and other tasks.” Furthermore, I consider it necessary to explicitly describe the concrete roles of three committees because of the nature of “protocol study.”

• Patients, page 10, 2nd line. – “…who never had gout, who contracted CKD stage 3a or 3b, who…” rather than “…who have never had gout and are complicated by CKD stage 3a or 3b who…”. NOT DONE, BUT NOT A BIG DEAL.

Reply: I appreciate your kind suggestions but would prefer to leave the expressions unchanged because of the following arguments: 1) Since our article deals with a protocol, we need to cover patients who were, are, and will be enrolled in the study. Therefore, we need to ensure that each patient be enrolled who has never had gout at the time of enrollment—reference time point. Hence, I prefer to express the sentence in the “present perfect form”, not in the “past sentence form.”; and 2) We consider CKD not as an “independent disease” but a “complication” in relation to the presence of “hyperuricemia.” Therefore, I would prefer to leave the expression “are complicated by CKD” unchanged.

• Study treatment, 1st line. – “…assigned to the febuxostat or the control group” rather than “assigned to either of the febuxostat and control groups”. NOT DONE

Reply: I modified the sentence as per your kind suggestion.

• Blinding, page 11, 1st paragraph. – Please, write, “will” rather than “should” all over the paragraph. NOT DONE

Reply: I modified the expression “should” in the paragraph as per your kind suggestion.

• Blinding, page 11, 4th line. – “…in an attempt to keep blinded the allocation” rather than “…in an attempt to ensure the blindness of the allocation”. NOT DONE

Reply: I modified the expression as per your kind suggestion.
• Randomization, page 12, 1st line. – “…who do not fill any exclusion criteria, are consecutively enrolled…” rather than “…who do not fall under any exclusion criteria, should be consecutively enrolled” (fill rather than fall). NOT DONE
Reply: I appreciate your kind suggestions and would prefer to address these points as follows: I intended to mean “correspond, fall into” with “fall under.” The protocol states that patients falling under any exclusion criterion should be excluded from enrolment. Therefore, we prefer to modify the sentence to “…who do not fall under any exclusion criterion, are consecutively enrolled…”.

• Endpoints, 2nd paragraph, 4th line. – “…of patients who developed SUA concentration ≤ 6.0 mg/dL” rather than “…of patients who achieved an SUA concentration of 6.0 mg/dL or below”. NOT DONE
Reply: I appreciate your comment and would modify the sentence as follows to facilitate the comprehension of readers: “… of patients whose SUA concentration became ≤ 6.0 mg/dL.”

• Statistical methods and sample size, 1st paragraph, last line. – I do not understand at all the sentence “The problem of statistical multiplicity should be avoided when conducting these statistical analysis”. Are you talking about the problem of multiple comparisons? If this is the case, please, write this down more clearly, and tell us how you will address this problem. In the past, statisticians used the Bonferroni adjustment to address the problem of multiple comparisons; however, this approach is not advocated anymore (Perneger TV. What's wrong with Bonferroni adjustments. BMJ 1998;316(7139):1236-8). Presently, the approach that is advocated by most statisticians is to decrease the number of statistical tests as much as possible. NO CHANGE WERE MADE.
Reply: I am sorry for the still ambiguous sentences and highly appreciate your valuable suggestions and information. You rightfully understand what we intend to express. In response to your valuable suggestions, I quitted using the concept of “the problem of statistical multiplicity” and extensively modified the sentences as follows: “The statistical analysis of the primary endpoint should be made to demonstrate the superiority of febuxostat to placebo. The linear regression line will be fitted to the longitudinal data of the eGFR for each patient. In patients with CKD stage 3, the intergroup difference in the eGFR slope should be compared between the febuxostat group and the control group according to Student’s t-test (analysis of variance), with the stratified adjustment of stages 3a and 3b. Subgroup analysis by stage 3a and 3b should be conducted to check the heterogeneity of the effect size.” This is a protocol study article, and the
study is currently ongoing. Since the proportions of patients with stages 3a and 3b are not
determined at the present, the details of the statistical procedures to address the issue of multiple
comparisons will be determined in the statistics analysis plan in the future.

DISCUSSION

· Page 15, 1st paragraph, 12th line. – “In Western countries, pharmacotherapy for asymptomatic
hyperuricemia is not proactively recommended” rather than “Neither in western countries,
pharmacotherapy for asymptomatic hyperuricemia is proactively recommended” (I hope that I
understand correctly the sentence).
    NOT DONE
    Reply: I modified the sentences as per your valuable suggestion.

· Page 17, 3rd paragraph, 1st line. – “…controlled trials published before approval of febuxostat
by the Food…” rather than “controlled trials before approval by the Food…”. NOT DONE
    Reply: I modified the sentences as per your valuable suggestion.

· Page 17, 3rd paragraph, 4th line. – “…40 mg daily showed a significantly more potent
urate-lowering effect than…” rather than “40 mg daily showed the significantly more potent
urate-lowering effect than…”. NOT DONE
    Reply: I modified the sentence as per your valuable suggestions.

· Page 18, last paragraph. – I suggest moving the paragraph on study limitations before the
paragraph on the conclusion. Moreover, I do not understand the last two sentences of this
paragraph: “Furthermore, patients who participate in a double-blind, randomized,
placebo-controlled clinical study have understanding of medicine and clinical studies. Hence,
selection bias cannot be ruled out.”
    Reply: I moved the sentences on study limitations just before the paragraph of the conclusion in
response to your valuable suggestion. By the last two sentences, we intended to mean “Under a
beneficial medical insurance system in Japan—the universal healthcare insurance system,
furthermore, patients who are willing to participate in a double-blind, randomized,
placebo-controlled clinical study are represented by a particular population of patients with
asymptomatic hyperuricemia complicated by stage 3 CKD. Under the universal healthcare
insurance system, namely, participants in the present placebo-controlled randomized controlled
study can be considered highly motivated by a distinct physician-patient relationship and for
noble spirits for medical progress. In this sense, selection bias cannot be ruled out.” Therefore, I
reflected these sentences in the re-revised manuscript.
To explicitly describe the intervention of Public Health Research Foundation in the present study as described in the documents submitted to the editorial office of TRIALS, furthermore, I modified the sentences of the “Acknowledgments” Section as follows: “The research fund for the FEATHER study was provided to Comprehensive Support Project for Clinical Research of Lifestyle-Related Disease (CSP-LD) of Public Health Research Foundation by Teijin Pharma Limited.”

MINOR ESSENTIAL REVISIONS (not for publication).

· Reference 13. – The volume is missing. NOTDONE
Reply: I replaced “suppl 2” with the volume number “32” for Reference 13 as per your kind suggestion.

· Reference 27. – The title must be in bold characters. NOT DONE
Reply: I expressed the title in bold characters as per your kind suggestion.

DISCRETIONARY REVISIONS.
· None.

CONCLUSION OF THE REVIEWER.
This manuscript is greatly improved. However, I still believe that the issues that I raised above must be addressed by the authors before this manuscript can be considered ready for publication by the journal TRIALS.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.