Reviewer's report

Title: Effect of febuxostat to prevent reduced renal function in patients with hyperuricemia complicated by chronic kidney disease stage 3: study protocol for a multicenter randomized controlled study

Version: 3 Date: 13 November 2013

Reviewer: Jacques Lacroix

Reviewer's report:

MAJOR COMPULSARY REVISIONS

ABSTRACT

• 3rd line: “…supporting a cause-effect relationship” rather than “…to indicate the association”. NOT DONE.
• Section Methods/design, 3rd line: stage 3 rather than stage 3) (delete “)”). OK
• Section Methods/design, 6th line: “arthritis, who present” rather than “arthritis and present”). NOT DONE
• 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

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

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
• 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
• 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
• Blinding, page 11, 1st paragraph. – Please, write, “will” rather than “should” all over the paragraph. NOT DONE
• 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
• 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….” NOT DONE.
criteria, should be consecutively enrolled” (fill rather than fall). NOT DONE

• 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

• 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.

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

• 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

• 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

• 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”.

MINOR ESSENTIAL REVISIONS (not for publication).

• Reference 13. – The volume is missing. NOT DONE

• Reference 27. – The title must be in bold characters. NOT DONE

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.