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: 1 Date: 28 August 2013

Reviewer: Jacques Lacroix

Reviewer’s report:

Manuscript entitled “The 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” by Tatsuo Hosaya et al

Submitted to the journal “TRIALS”

Manuscript number: 130129101103208

SUMMARY. – In this research protocol, Hosaya et al describe an on-going multicentre double-blind randomized controlled trial (RCT) that they named FEATHER (FEbuxostat versus placebo rAndomized controlled Trial regarding reduced renal function in patients with Hyperuricemia complicated by chRonic kidney disease stage 3). The RCT will be conducted in 67 Japanese sites; 400 adults with hyperuricemia (serum uric acid: 7.1 to 10.0 mg/dL) and chronic kidney disease stage 3, but without gouty arthritis, will be randomized to receive febuxostat or a placebo. The dose of febuxostat will be increased progressively from one 10 mg tablet per day to one 40 mg tablet 9 weeks after randomization. The dose of placebo will also be increased in order to keep the study blinded. Patients will be monitored up to 108 weeks after time zero. The primary outcome measure is estimated glomerular filtration rate (eGFR). It is expected that renal function, as measured by eGFR, will improve and that the serum level of uric acid will decrease.

MAJOR COMPULSARY REVISIONS

TITLE

The title in the manuscript is presently: “The 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”. I suggest changing it to: “The effect of febuxostat to prevent reduced renal function deterioration in patients with hyperuricemia complicated by chronic kidney disease stage 3: study protocol for a multicenter randomized controlled study”.

BACKGROUND

• 3rd paragraph, last line. – The authors wrote “we consider it important to clarify
the clinical relevance of conducting pharmacotherapy for cohorts...”. I do not understand that sentence.

• 3rd paragraph. – By “pharmacotherapy”, are the authors meaning “pharmacodynamics and/or pharmacokinetics”?

METHODOLOGY
• Blinding, 5th line. – I do not understand the sentence “Furthermore, changes in SUA concentration under blinding should be addressed...”.
• Randomization. – I do not understand what is meant by “assignment method”; are you talking about stratification? If this is the case, it means that there are six strata (site, age, gender, serum level of uric acid, proteinuria and complication of diabetes. This is a lot of strata...!
• Statistical methods and sample size.
• 1st paragraph, last line: I do not understand at all the sentence “Multiplicity will be considered for these tests”.

DISCUSSION
• The discussion of the medical literature can be improved. For example, there should be some RCTs done in USA since the FDA approved febuxostat; these RCTs should be discussed. It might be a good idea to provide more information on the mechanisms of action of febuxostat and on its side effects.
• Strengths and limitations of the trial can be better discussed.

ETHICS
• Proof of ethics approval: OK.

FUNDING
• Proof of funding: OK.

MINOR ESSENTIAL REVISIONS (not for publication).
• General suggestions.
• The quality of the English must be improved: some sentences are difficult to understand and some of them are meaningless.

References.
• Reference 5. – The word “Community” in the title is capitalized; is this right or wrong?

DISCRETIONARY REVISIONS.
• None.

CONCLUSION OF THE REVIEWER.
• The rationale is strong: hyperuricemia is indeed a cause of kidney failure and there is evidence that febuxostat, a non purine xanthine oxidase inhibitor, can
decrease significantly the blood level of uric acid.
• The study is relevant: the prevalence of hyperuricemia in Japanese male adults is 21.5%!
• The hypothesis makes sense: administration of febuxostat to hyperuricemic patients already with chronic kidney failure will slow down or stop the progression of the kidney failure.
• The research question is clear: in adults with hyperuricemia and kidney failure (stage 3), can febuxostat improve glomerular filtration rate and decrease the serum level of uric acid?
• The design of the study is very good and should bring out data that will answer the research question.

The science detailed in this paper is good. However, the issues that I raised must be addressed by the authors and the English must be improved before this manuscript can be considered ready for publication by the journal TRIALS.

DECLARATION OF CONFLICT OF INTEREST
I declare that I have no competing interests.

REVIEWER
NAME: Jacques Lacroix, professor
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Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

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

Declaration of competing interests:

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