Author's response to reviews

Title: African American Patients With Gout: Efficacy and Safety of Febuxostat vs Allopurinol

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Version: 3 Date: 16 December 2011

Author's response to reviews: see over
Dear Dr. Patel,

On behalf of my colleagues, I am pleased to submit a revised version of our manuscript “African American Patients With Gout: Efficacy and Safety of Febuxostat vs Allopurinol” for consideration of publication in *BMC Musculoskeletal Disorders*.

We are encouraged by the favorable reviews received and very much appreciate the opportunity to address reviewer comments. Our responses to each reviewer comment are provided below and appropriate, corresponding changes to the manuscript have been tracked.

Thank you for your time and consideration.

Sincerely,

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**Reviewer's report**

**Title:** African American Patients With Gout: Efficacy and Safety of Febuxostat vs Allopurinol  
**Version:** 2  
**Date:** 28 September 2011  
**Reviewer:** Edward Roddy

**Reviewer's report:**
This paper describes the comparative efficacy and safety of febuxostat and allopurinol for the treatment of gout in African Americans and Caucasians, presenting data from an already published RCT. Differential response to urate-lowering therapies is of great interest and relevance clinically. The report is well-written and easy to follow, largely complying with guidelines for reporting of randomised controlled trials.

Major Compulsory Revisions
1) I appreciate that the main trial in which this analysis is nested has already been published, however, in certain places the reader is referred to the report of the main trial when a brief description of key methodological features would enhance the methods section. This is particularly of relevance in two places:

   a) Pg 5 - the authors state that "....inclusion and exclusion criteria have been previously described" and then that "Exclusion criteria included, but were not limited to...". The authors should describe full inclusion and exclusion criteria here.

   **Response:** We have provided full exclusion criteria as provided in the primary manuscript in the methods on page 5.

b) Pg 6, Statistical analysis - I appreciate that the authors do not wish to replicate the full details of the main trial analysis here but more detail is required than that given for the reader to fully understand what analyses were undertaken.

   **Response:** We have provided additional details regarding statistical analyses used to compare efficacy between the treatment groups in the Methods on pages 6 and 7.

2) Methods, page 6 - All subjects received prophylaxis with naproxen or colchicine. What about individuals in whom these were contra-indicated or not previously tolerated?

   **Response:** In our expanded description of exclusion criteria on pages 5 and 6, we have noted that individuals with known hypersensitivity to colchicine, naproxen, or any NSAID were excluded. Approximately 0.6% (n=13) of the total CONFIRMS cohort received other prophylactic medications (Celebrex, Indocin, indomethacin, nabumetone, or prednisone) presumably due to contraindications. We do not have a breakdown by race for this.

3) Discussion, page 13 - the authors report greater efficacy of febuxostat 40mg in African American subjects compared to Caucasians but no difference between these groups for febuxostat 80mg or allopurinol. One possible explanation for this not offered by the authors is compliance. Compliance overall was lower in African Americans than Caucasians. Was compliance between racial groups the same for the three interventions? Furthermore, although described in the statistical analysis section, the p-value for the difference in primary outcome between racial groups for those taking febuxostat 40mg is not presented until the discussion (first line, page 14) whereas it belongs in the results section.

   **Response:** You raise a valid point. Compliance (≥90%) for African American subjects in the febuxostat 40 mg, febuxostat 80 mg, and allopurinol treatment groups was 66.3%, 76.9%, and 74.6%, respectively, while it was 82.4%, 82.2%, and 81.6%, respectively, for Caucasian subjects. This has been added to the results on page 8. We have also added the following statements to the discussion on 13-14 to address this, "One plausible explanation for this
observed difference may be the noted difference in compliance with treatment. Caucasian subjects in the febuxostat 40 mg group had a considerably higher compliance rate (82.4%) than their African American counterparts (66.3%). This difference is greater than those observed in the other 2 treatment groups.”

We have also added a statement regarding the statistical significance of this difference in the results on page 9.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I received a small honorarium from Ipsen, the manufacturers of febuxostat, following attendance at an educational meeting in February 2008.

Reviewer's report
Title: African American Patients With Gout: Efficacy and Safety of Febuxostat vs Allopurinol
Version: 2 Date: 26 October 2011
Reviewer: Francisca Sivera

Reviewer's report:

MINOR ESSENTIAL REVISIONS
1. Please state explicitly in the last paragraph of the Background Section if the subgroup analysis was pre-planned or post-hoc.

Response: This was a post-hoc analysis. We have added that clarification on page 5.

2. Please consider summarising the data presented in paragraphs 3 and 4 of the Discussion. They provide evidence of the relationship between incident hypertension and hyperuricemia and cardiovascular mortality and sUA respectively; however they are not directly related to the study results but rather provide a wider justification for the use of ULT on African-American gouty patients. Even though relevant, the discussion is too lengthy for this aim.

Response: We have summarized the information presented in these 2 paragraphs and combined into 1 paragraph.

DISCRETIONARY REVISIONS
1. Background section, paragraph 2. Consider changing the next to last sentence to "Long-term management of gout focuses on achieving and maintaining...". It should be stressed that lowering uric acid in order to clear the deposits of MSU is the primary goal of gout treatment.

Response: Thank you for pointing this out. We have modified this statement, on page 4, to read as follows – "Long-term management of chronic gout with ULT focuses on achieving and maintaining sUA in a sub-saturating range (<6.0 mg/dL) with the goal of dissolving monosodium urate crystals and decreasing the body pool of uric acid."

MINOR ISSUES NOT FOR PUBLICATION
1. In the first paragraph, Background section please consider changing "however" for another link such as moreover, furthermore... ("Moreover, when they are treated they are less likely to receive...")

Response: We have made the suggested change.

2. Consider removing "and" from the next sentence in the Background Section "Furthermore, African Americans typically present with higher rates..."

Response: With all due respect, both uses of “and” in that sentence are grammatically correct.

3. In the first paragraph of the Results Section please consider improving readability. Some examples are:

- delete primary before reason for discontinuation

Response: We have left the descriptor “primary” in these statements because subjects/investigators may have provided multiple reasons for discontinuation, but when doing so, had to identify which was the primary, or main, reason. The values would change if we included a reason that could also have been listed as a secondary or tertiary reason for discontinuation

- change lost to follow-up to loss to follow-up

Response: “lost to follow-up” is how this reason for discontinuation was reported in the clinical study report.

Level of interest: An article of limited interest
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.