Reviewer's report

**Title:** A randomized, placebo-controlled trial to determine the course of aminotransferase elevation during prolonged acetaminophen administration

**Version:** 2  
**Date:** 14 April 2014

**Reviewer:** Raja Venkatasubramanian

**Reviewer's report:**

The authors have described the results from their large randomized placebo-controlled study to investigate the course of alanine aminotransferase (ALT) elevation during prolonged acetaminophen administration. The ALT elevation was monitored as a biomarker for suspected liver injury. This manuscript summarized the course of ALT variation with time in subjects in the Acetaminophen OR Placebo arm of the study. Overall the study is a very interesting one and the results it yields would be interesting for the clinical Pharmacology / Toxicology community. These results will be of interest to the hepatic injury research community and also to some extent to a broader audience given the recent actions by FDA.

However, I found the method and results section to be too long and I believe can be reorganized in the interest of shortening. Also, I believe the abstract can be improved in terms of lessons learnt from the study (conclusions). I have recommended some changes in the comments and would look forward to the authors response.

**Major Compulsory Revisions**

**Choice of outcome:**

The authors claim that the primary aim of their study is to describe the “course of ALT elevation” following acetaminophen dosing. The author’s choice of the outcome (which I admit is a little less clear to me) was the proportion of subjects with resolved ALT levels on their respective last day in the trial. Characterizing the ALT levels on a specific pre-chosen day (e.g. day 16) would serve the purpose of “describing the course of ALT elevation” better. What was the rationale for this choice?

**Comparison with Placebo:**

Abstract

There is no mention of the comparison made with the placebo arm in this study. The authors need to contrast the findings in the placebo and treatment arms.


It seems that the whole paragraph is about the difference in ALT increase in the placebo group with different study designs. I am not sure about the relevance of this to the manuscript. This is a very important issue, and further highlights the
lack of sufficient comparison of ALT profiles between placebo and acetaminophen arms in the current manuscript.

Abstract: Conclusions

The conclusions is simplistic and descriptive. It can be improved upon to summarize the specific conclusions. Drawing specific implications for the hepatic injury biomarker community would enhance it further.

Minor Essential Revisions

Abstract: What does “resolution of ALT levels” mean?
Clearly describing “resolution” would make this manuscript more reader-friendly.

Please highlight the relevance of 0.015?

Please provide some details about the calculation for 95% CI. Also, it is unclear as to what the exact time for outcome is. Is it Day 16? Day 40? Last day? Also please provide the rationale for the choice.

Page 14: Line 8
I am not able to locate Table 1. I am not sure why?

Page 15: Line 11
“99.5 %; Confidence interval 0 - 3%”. This does not make sense. Please describe either 1/205 OR 204/205.

Page 16 .. Line 16-17.
In the copy of the manuscript I have Table 2 is missing. I am not sure why?

Page 16 .. Line 6-12.
Please present only one of the descriptive statistics.

Discretionary Revisions

Abstract:
It would be helpful to highlight the rationale for mentioning the highest ALT measurement without summarizing the mean / median.

Page 5; Line 4:
2000-4000 mg .. Please be consistent with units.

Page 5; Line 22.
reference before “.”

Protocol procedures and Data collection. Page 8: Line 10 ---- Page 10 Line 20. & Figure 1.
The description of the study procedures and data collection during various methods are presented in a detailed manner. However, much of the information can be better presented and visualized in Figure 1. Given the authors have Figure 1 highlighting the treatment schedule after Day 16. It would be easier if the data protocol procedures prior to Day 16 were also included in Figure 1.

Page 9: Last Paragraph (ending in Page 10):
“Finally, we conducted an exploratory analysis. ... study day 16”. This can be moved to the statistical section. The exploratory analysis is mentioned in two different places and becomes confusing to follow.

Figure 3&4
Figure 3 & 4 can be improved for used visualization by plotting data only up to day 40 as there is only one individual who exceeds this time range. Also it seems a better idea to stratify these figures into 3 categories (A) Placebo, (B) Acetaminophen subjects who met criteria on day 16. and (C) acetaminophen subjects who did not meet criteria on day 16.

Page 17.
This paragraph can be sub-titled “Safety”. In general having more subheadings will help the reader with the results section.

Line 8: Line 18
Adverse events. Please provide a brief summary of the recorded events in the manuscript or as a supplemental section.

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 declare that I have no competing interests