Reviewer’s report

**Title:** Mechanistic biomarkers of liver safety and benign elevations in serum aminotransferases - A study in healthy volunteer treated with cholestyramine

**Version:** 1  **Date:** 4 February 2014

**Reviewer:** Kevin Park

**Reviewer’s report:**

**Abstract**

• The abstract also does not appear to have an important conclusion – I assume they set out to find a biomarker that DOES distinguish between benign and serious rises in liver injury (according to the first line), but since they ALL go up, perhaps this concept is merely ideological?

• Is miR-122 the most sensitive biomarker measured (22-fold change) or is HMGB1 the most useful at distinguishing between benign and important biomarker elevations (only 1.7 fold different)? The authors should clearly state the most important finding of their study

**Introduction**

• The introduction is very good and sets out clearly why the study was performed: to understand the source and/or mechanism of release of clinically benign ALT levels. This could be reflected in the title and abstract.

**Results**

• There may be an association between the young women who were taking oral contraceptives. Is there any evidence that oral contraceptives exacerbate the potential of DILI in the literature with any other drugs? CYP upregulation or RXR/PXR activation?

• What form is miR-122 (or the other biomarkers) release in? microvesicles, exosomes? Evidence exists that miR-122 is released in exosomes and may explain why they rise in blood before ALT with respect to time. Could they investigate this experimentally in human hepatocytes?

• Has the mechanism cholestyramine been previously explored in human cell lines, hepatocytes etc. Could these biomarkers be applied here in a more translational approach to the problem?

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**Conclusion**

• Well written to support the data but provides more questions than answers.

A more focused conclusion on the outcome of the paper and what this means for the development of these markers to predict DILI in man and in preclinical development
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.