Reviewer's report

Title: Long-term Effects of high-doSe pitavaStatin on Diabetogenicity in comparison with atorvastatin in patients with Metabolic syndrome (LESS-DM): study protocol for a randomized controlled trial

Version: 0 **Date:** 16 Aug 2017

Reviewer: Cyril Mamotte

Reviewer's report:

There is a dearth of information, and more particularly of trials that properly assess the potential diabetogenic effects of statins. As such this paper, focusing on subjects with the metabolic syndrome (MetS)- but who are not (yet) diabetic, and comparing the diabetogenic effects of pitavastatin and atorvastatin should be of great interest.

The paper is well written, and easy to follow. The primary end point is the change in haemoglobin A1c (HbA1c). Secondary end points include changes in various metabolic parameters associated with MetS (e.g. CRP, insulin, adiponectin), vascular changes (e.g. carotid ultrasound, echocardiography), and clinical events -new onset diabetes and cardiovascular disease.

There is however some scope for improvement.

1. The authors do discuss meta-analyses that have examined the diabetogenic effects of statins. They should also specifically discuss the lack of clinical trials that address this problem

2. Subjects/participants to the study. A) there is a wide age range; do the authors have any evidence that this is suitable- the effects may depend on age, and subgroup analyses looking at smaller age ranges would reduce statistical power. A greater number of subjects would be preferable. . B) There is little information on where/how the subjects will be recruited from- is it through advertising, from hospital/university clinics.

3. Laboratory Investigations. There should be more information on sample collection and analysis. Will the measurements be conducted in an accredited diagnostic laboratory. Given the central role of HbA1C, and the potential lack of statistical power (given the small sample size), how well does the assay perform in the investigator's hands/lab. How will samples be processed or stored. Is there a previous paper by the authors that they can refer to? Are the samples fasting samples? Will they analysed as patients present, or as a batch?

4. Finally, the authors concede that their small sample size limits their ability to detect new onset diabetes (NOD) or cardiovascular (CVD) events- and that this will be compensated by use of imaging surrogate end-point- but this strategy while understandable for the CVD is not relevant to NOD.

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