Reviewer’s report

Title: Safety and Tolerability of Experimental Hookworm Infection in Humans with Metabolic Disease: Study Protocol for a Phase 1b Randomised Controlled Clinical Trial

Version: 0 Date: 13 Apr 2019

Reviewer: Bruno Guigas

Reviewer's report:

In this concise and well-written manuscript, Merone et al. detail the study protocol of a phase 1b clinical trial aiming to investigate the safety and tolerability of human-controlled hookworm infection for metabolic syndrome. This is a timely and exciting new approach intended to translate to humans what has been suggested by both epidemiological and pre-clinical studies, i.e. that helminth infection might improve metabolic homeostasis in obese/insulin-resistant subjects by promoting either type 2 immune response and/or modulating gut microbiota composition. I have only few minor comments that do not need to be systematically implemented in the manuscript.

Minor comments
Page 4, ref [4]: Please replace by relevant recent literature reviewing the concept of obesity-induced chronic low-grade inflammation (or meta-inflammation), e.g. PMID: 21233852, 26553134, 28179656.

Page 5: A reference to the recent study reporting that helminth infection promote colonization resistance via type 2 immunity might be added to illustrate the possible immune-mediated modulation of gut microbiota by the parasite (PMID:27080105)

Page 6, line 20: "obese young". Taken into that you'll include subjects between 18 and 50 year-old, I'm not sure that you should keep the term "young" here…(although debatable when being close to reach this canonical age!)

Page 8: the criteria for defining dyslipidemia (see for example ESC/EAS Guidelines for the Management of Dyslipidaemias, Eur Heart J. 2016) and abnormal liver function (ALAT/ASAT levels ?) should be better specified. Of note, blood glucose level 2-hour post glucose challenge (>140 mg/dL and <199 mg/dL being considered as pre-diabetics) is usually a more stable criteria for MetS than HOMA-IR (quite high day-to-day intra-individual variations, increasing the risk of having a significant number of pre-screened eligible subjects not confirming this criteria at the day of baseline visit).

Page 10: It is unclear how the safety will be checked during the first 6 months, the period during which the most significant side effects might occur. Do the participants only contact the investigators when sometimes unexpected happen or is there any pro-active communication between them during the first weeks ? What would be the frequency for filling the structured questionnaires during the first 6 month (page 12) ? It would definitely be important to carefully monitor the adverse effects/quality of life
during the first weeks/months post-infection

Page 11: The information relative to the source and L3 preparation are rather sparse. Is there any quality control step before inoculation?

Page 11: What happens if unexpected pregnancy occurs during the trial?

Page 17: "systemic immune system"; please rephrase

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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