Author’s response to reviews

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

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We thank the Editor and reviewers for their comments and consideration of this manuscript. Please find a point-by-point response to the concerns raised by Reviewer 2/3 below, which primarily related to the safety profile of hookworm infection, and public health concerns of optional deworming.

Reviewer’s comment
The authors have clearly attended to all the comments made by previous reviewers. They have provided justification for optional anthelmintic treatment after the end of the study. However, in view of the ethical issues surrounding this type of study, it will be good that the participants are very much aware of the implication of having hookworm infection during the duration of the study.

Response
The participant information sheet that is provided to all potential participants prior to consent and enrolment details the implications of having hookworm infection during the course of the study, and
beyond. We agree with the reviewer that this is of obvious and critical importance and was already covered in detail within the existing text from our most recent submission (page 13, lines 296-308).

Reviewer’s comment
Authors should emphasize that anthelmintic treatment after the study is mandatory. Therefore, offering the optional anthelmintic treatment is not acceptable as the study participants can become a source of contamination which lead to the establishment of Necator Americanus in Australia.

Response
With respect to the possibility that hookworm disease will be established in Australia if deworming is optional, this risk is negligible (or zero). Critically, the parasite eggs that are shed in the faeces require 7-10 days in the external environment to hatch and become infective larvae. Hence, in a country like Australia with excellent sanitation facilities, the participant uses a toilet and the eggs are not able to develop, hence there is zero risk of transmission. We hope that this clarifies with the reviewer how our study will not be a source of contamination of the Australian environment. We have extended Section 3.3.1 to address these issues (page 12, lines 275-278).

Reviewer’s comment
Inoculation of 20-40 third stage larvae are enough to establish a serious hookworm disease in any non-exposed human. I surprised this protocol was approved.

Response
Our research team has lead 4 other clinical trials involving Necator americanus infections in Australia and New Zealand, which have necessitated ethical review and approval by six separate committees (Princess Alexandra Hospital, Prince Charles Hospital, Townsville Hospital, James Cook University, Queensland Institute of Medical Research and Christchurch Hospital). In each of these trials, the respective human ethics committees are satisfied with the many years of expertise of our research team in participant care and safety monitoring. Therefore there is substantial precedent for us undertaking this trial with doses of 20-40 larvae, which we have published to be safe and well-tolerated in people who are otherwise healthy and maintain adequate nutrition. This important point is clarified in new text on page 5, lines 120-121 and page 11 lines 257-258.

In the rare event that a participant demonstrates an adverse event relating to hookworm infection, the participant is immediately administered deworming medication that clears the infection. The fact that we can deliver low doses of these worms and rapidly cure the infection if adverse events occur is the primary reason why we and others (in UK, The Netherlands, USA and New Zealand) have been able to conduct these clinical hookworm challenge studies.

We hope that this additional information has reassured the reviewer that there is substantial precedent in the nature of this trial and in the safety of challenging healthy participants with low doses of hookworm to advance research into potential cures for diseases (such as autoimmune or metabolic diseases) or for hookworm vaccine development.

Reviewer’s comment
The author should revise the protocol to make it mandatory for all study participants receive anthelmintic treatment. The option of keeping the helminths is not acceptable, even if the trial is successful. "

Response
Our research team has a 14-year published track record in performing these hookworm challenge trials in Australia, with an excellent record of safety and tolerability of the treatment. In each of these studies, deworming has been optional and in the overwhelming majority of cases, the participant elects to keep their worms (despite us providing them with the medication). We are acutely aware of the hookworm life cycle and the importance of educating our participants of the requirement to use appropriate sanitation methods, which is now described on page 12, lines 275-278.

We hope that this reassures the reviewer, editor and readers of the article that the health and safety of participants and the community will not be compromised by this study.