Author’s response to reviews

Title: Role of cerebral hypoperfusion in multiple sclerosis (ROCHIMS): study protocol for a proof-of-concept randomized controlled trial with bosentan.

Authors:

Stéphanie Hostenbach (Stephanie.Hostenbach@uzbrussel.be)
Ayla Pauwels (ayla.pauwels@vub.be)
Veronique Michiels (Veronique.Michiels@uzbrussel.be)
Hubert Raeymaekers (Hubert.Raeymaekers@uzbrussel.be)
Anne-Marie Van Binst (AnneMarie.VanBinst@uzbrussel.be)
Annick Van Merhaeghen-Wieleman (Annick.VanMerhaegenWieleman@uzbrussel.be)
Peter Van Schuerbeek (Peter.VanSchuerbeek@uzbrussel.be)
Jacques De Keyser (Jacques.dekeyser@uzbrussel.be)
Miguel D’haeseleer (miguel.dhaeseleer@uzbrussel.be)

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Author’s response to reviews:

Dear Editor,

Thank you for allowing us to revise our manuscript “Role of cerebral hypoperfusion in multiple sclerosis (ROCHIMS): study protocol for a randomized controlled trial with bosentan”.

We have taken into account all your comments and those of the reviewers.

Please find the point-by-point responses and we highlighted in yellow all changes in the manuscript.

We also included the completed SPIRIT checklist as a supplementary file, as requested.

We hope that this revised version will be approved.

Thank you in advance,
Sincerely yours,

Stéphanie Hostenbach

A. Points raised by the editor:

1. It is unclear whether it is a proof-of-concept trial or confirmatory trial.

Thank you for raising this point.

In the past, we only performed a study in MS patients with a single dose of bosentan. This showed a normalisation of the cerebral blood flow (CBF). The present study is a proof-of-concept trial investigating for the first time whether the administration of bosentan for 28 /-2 days (1) restores CBF in a sustainable way, (2) enhances cerebral white matter NAA levels in patients with RRMS, and (3) ameliorates clinical disability and hippocampal brain volume (page 4).

2. Additional information about allocation concealment and assessor blinding, sample size calculation and the planned statistical analyses.

Information about allocation concealment, assessor blinding and sample size calculation is provided on page 5 of the manuscript.

Information about the planned statistical analyses is provided on page 9-10 of the manuscript.

3. The participant timeline is not easily to understand using a figure.

The participant timeline is now displayed like a SPIRIT figure on page 6.

B. Points raised by reviewer 1:

4. There is no clear statistical analysis plan.

The statistical analysis plan is now better described on page 9-10 of the manuscript.

5. It is not well understood why the authors decided to include the clinical trial into an “proof-of-concept” design.

Please see point 1
C. Points raised by reviewer 2:

6. There are important areas in relation to the protocol description which need to be addressed in line with SPIRIT statement.

Thank you. The SPIRIT checklist is completed and added to the manuscript as an additional file.

7. There is no information about the randomisation process, allocation concealment or maintenance of blinding, as well as on safety reporting.

Additional information about these points is provided in the manuscript on page 5.

8. The sample size calculation of difficult to understand.

This is better explained in the manuscript on page 5.

9. The follow-up period is 1 month. It would be helpful to justify this length of follow-up in relation to the clinical measures. Surely, fatigue and cognition would require longer follow-up periods.

We agree but this is planned to be done in a next trial.

10. The study flowchart is unclear using a figure.

Please see point 3