Author's response to reviews

Title: An open-label study examining the effect of pharmacological treatment on mannitol- and exercise-induced airway hyperresponsiveness in asthmatic children and adolescents with exercise-induced bronchoconstriction

Authors:

Salome Schafroth Toeroek (salome.schafroth@usb.ch)
Thomas Mueller (thm.mueller@gmail.com)
David Miedinger (david.miedinger@unibas.ch)
Anja Jochmann (anja.jochmann@ukbb.ch)
Ladina Joos Zellweger (ladina.joos@claraspital.ch)
Sabine Sauter (sabinesautter@yahoo.de)
Alexandra Goll (Alexandra_Goll@gmx.net)
Prashant N Chhajed (pchhajed@gmail.com)
Anne B Taegtmeyer (anne.taegtmeyer@usb.ch)
Bruno Knoepfl (bruno.knoepfl@k-j-m.ch)
Joerg D Leuppi (joerg.leuppi@ksli.ch)

Version: 4 Date: 4 July 2014

Author's response to reviews: see over
Dear Catherine Olino,

Re: 2018322704101185 “An open-label study examining the effect of pharmacological treatment on mannitol- and exercise-induced airway hyperresponsiveness in asthmatic children and adolescents with exercise-induced bronchoconstriction”

Thank you for your e-mail from 23rd June 2014. Please find the revised manuscript enclosed and the point-by-point responses below.

Reviewer 1 (Maria R Bonsignore)

1) The authors did their best to improve the manuscript, but it still raises some doubts on the role of the interventions (drug treatment, exercise) on bronchial reactivity to exercise or mannitol. Ideally, the study would need to increase the sample size since the results of MCT are actually based on half of the subjects who resulted positive at the MCT challenge.
Answer: We agree that studies which include larger numbers of subjects have greater statistical power. Clinical studies in children, however, represent particular challenges to recruitment, largely based on the fact that disease prevalence is low, they are usually managed in an out-patient setting and screening large numbers to identify study subjects is unethical. Furthermore, it would not make sense to expand the study size at this stage as the conditions would not be the same and there would be too many confounding factors which would preclude pooling the data from the original study group with an additional group.
We have addressed this limitation in the discussion (please see response to the Editors below).

2) A control group receiving only drug treatment would be very useful to understand the effects of exercise training + optimal drug treatment on EIB, and might strengthen the
results considerably.

**Answer:** Thank you for this suggestion. For the reasons already outlined above, study of a control group at this stage is, unfortunately, not possible. We have addressed this limitation in the discussion (please see response to the Editors below).

3) Minor revision: Table 1 does not report p values or significance between variables recorded in MCT+ and negative subjects.

**Answer:** Thank you. We have added the p-values to Table 1.

**Reviewer 2 (Claudia Calogero)**

The authors have properly addressed all my comments and have changed the text accordingly. I have no further comments.

**Answer:** Thank you.

**Editors’ comment:**

1) Additionally, we must ask that you include a section in which you detail and discuss the limitations of the study as were raised in the original reviews and the ones attached below. Due to the concerns raised by the reviewers, such a section must be included at the end of the discussion.

**Answer:** Thank you for this suggestion. We have added the following paragraph about the study limitations at the end of the discussion:

“Limitations of the study are its observational design, relatively small sample size and intervention period as well as the absence of a control group that underwent pharmacological treatment without concurring training. Conclusions which can be drawn from the study must therefore be made in the light of these limitations.”

2) Also given these limitations, the small sample size and the fact that the study was observational, not a randomized controlled study, we would ask that you please temper the definitive statements made in your conclusions section accordingly.

**Answer:** Thank you. We have re-written the conclusions as follows:

“Children and adolescents with asthma and exercise induced bronchoconstriction repeatedly underwent challenge tests with exercise and mannitol. A multimodal treatment concept including physical training and medical treatment with an inhaled steroid and a leukotriene inhibitor resulted in a decrease in airway hyperresponsiveness to both exercise and mannitol.”
We hope we have addressed all the comments sufficiently and that you find the manuscript suitable for publication.

As the corresponding author I confirm that the manuscript has neither been submitted nor been published elsewhere. I also confirm that all authors have read and approved the submitted version of the manuscript.

Yours sincerely,

Jörg D. Leuppi, MD PhD