Author's response to reviews

Title: Efficacy and safety of bilateral continuous theta burst stimulation (cTBS) for the treatment of chronic tinnitus: design of a three-armed randomized controlled trial

Authors:

Carola Arfeller (carola.arfeller@ed.uni-tuebingen.de)
Reinhard Vonthein (reinhard.vonthein@imbs.uni-luebeck.de)
Stefan K Plonke (stefan.plonke@uni-tuebingen.de)
Christian Plewnia (christian.plewnia@uni-tuebingen.de)

Version: 3 Date: 21 July 2009

Author's response to reviews: see over
Dear Editors,

enclosed please find the manuscript entitled "Efficacy and safety of bilateral continuous theta burst stimulation (cTBS) for the treatment of chronic tinnitus: design of a three-armed randomized controlled trial." by C. Arfeller, R. Vonthein, S. K. Plontke, and C. Plewnia for consideration as a study protocol in TRIALS.

In this revision of the manuscript (MS#: 1079994847267764) submitted on April, 10th 2009 we have fully addressed all of the referees’ concerns as described in detail in the appendix of this cover letter.

We hope that the manuscript is now considered suitable for publication in TRIALS.

With best regards,

Christian Plewnia, MD
Reviewer's report

Title: Efficacy and safety of bilateral continuous theta burst stimulation (cTBS) for the treatment of chronic tinnitus: design of a three-armed randomized controlled trial

Version: 2 Date: 23 June 2009
Reviewer: Gordon Murray

The authors have resolved the major weakness by dropping the plan to replace subjects who do not complete the study protocol. However their response to the issue about using the Last Observation Carried Forward approach to handle missing data is not adequate.

We thank the reviewer for pointing out this issue. The LOCF approach was retracted and instead we will handle the data per protocol (PP).
We modified the protocol as follows (p. 5):

*The analysis of the efficacy measures, especially with respect to the stimulus placement, requires a concentration on patients treated per protocol (PP).*

This LOCF approach is methodologically flawed and has been superceded by far more robust statistical approaches based either on mixed models repeated measures or multiple imputation. The authors should adopt one of these approaches.

We thank the reviewer for this crucial advise and added the following sentence (p. 5):

*Missing observations are imputed using a full conditional Markov-Chain Monte Carlo method for variables with more than 75% valid values.*

In responding to comments from the other referee the authors have introduced a new problem. As this is a Phase II trial the primary analysis ought to be per-protocol. The ITT analysis should be reported as well but as a secondary analysis.

We thank the reviewer for the explanation and corrected our former manuscript (p. 5):

*An exploratory analysis of all dependent variables by the randomised treatment, i.e. the mere intention to treat (ITT), will be conducted to plan subsequent confirmatory studies.*
Reviewer's report

Title: Efficacy and safety of bilateral continuous theta burst stimulation (cTBS) for the treatment of chronic tinnitus: design of a three-armed randomized controlled trial

Version: 2 Date: 23 June 2009

Reviewer: Peter Sandercock

I agree with Gordon Murray's comment. The major weakness of substituting subjects has been dealt with. I agree the response to the comment on last observation carried forward is not appropriate.

We thank the reviewer for pointing out this issue. The LOCF approach was retracted and instead we will handle the data per protocol (PP). We modified the protocol as follows (p. 5):

*The analysis of the efficacy measures, especially with respect to the stimulus placement, requires a concentration on patients treated per protocol (PP).*

I also agree that both ITT and per-protocol analyses should be presented.

We thank the reviewer for the explanation and corrected our former manuscript (p. 5):

*An exploratory analysis of all dependent variables by the randomised treatment, i.e. the mere intention to treat (ITT), will be conducted to plan subsequent confirmatory studies.*