Author's response to reviews

Title: Phase IV non-inferiority trials and additional claims of benefit

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

As required, below are our responses to the queries of the reviewer. Our responses are in font 
Times New Roman. Given the queries and our responses, we found it unnecessary to do any 
changes on our previously revised paper.

We hope you will find our responses adequate and that our paper suitable for publication.

Authors’ reply   1012486587804563- R1 - Phase IV non-inferiority trials and additional 
claims of benefit

Reviewer 1: Jörg Zinserling

I comment on the authors’ responses referenced by the original numbers:

1. No additional comment.

2. No additional comment.

3. The methods section is improved by the revision of the wording of the referenced 
paragraph in the methods section. The use of ICH E9 terminology is appreciated. The clear 
link of a hypothesis or objective to an additional claim in the wording is helpful.

We thank the reviewer for these comments.

4. The authors did specify better what they mean by an “additional claim” in the response to 
comment 3. Together with the change in the methods section (cf.response to 3.), the small 
change of wording in the introduction makes things clearer. Although I think that additional 
claims on the safety profile could be difficult to show in case of rare adverse events, I can 
clearly accept the way the authors did the analysis and presented the results. The wording in 
the methods sections “existence of a priori objective/hypothesis pertaining to the additional 
claim” is considered comprehensible.

We thank the reviewer for the comments.

5. In my opinion it is helpful to include the additional reference on the article in the 
discussion. A way forward would indeed be adding an objective to show superiority for a 
relevant endpoint to the objective to show non-inferiority for another endpoint of interest. 
The concern of my original comment was that phase IV trials could be described as 
superiority trials in PUBMED and the (subordinate) non-inferiority objective may not have
been mentioned in the abstract. These studies are then consequently not included in the analysis presented by the authors, which is acceptable, but could be mentioned briefly in the discussion.

6. I think comment 6 was a bit difficult to understand. The size of the sample of articles is a limitation of the presented study. As I was not sure how the editor and other reviewers would assess this aspect, comment 6 was more meant as a proposal to include trials that are not explicitly non-inferiority trials if a major revision with additional analyses would have deemed necessary (cf. comment 5).

In our previously revised version, we added the said reference. Please refer to reference #14.

We appreciate the reviewer’s concern that phase IV trials could be described as superiority trials in PUBMED and the (subordinate) non-inferiority objective may not have been mentioned in the abstract. However, a trial was referred as superiority or non-inferiority based on its primary objective and not on its secondary/subordinate objective, so we did not believe that we have missed phase IV NI trials with our search strategy. To include trials that are not explicitly stated as NI trials, in our opinion, would be extremely difficult. Our analysis was done based on published reports of NI trials in PUBMED. We did not include trials database, such as the clinicaltrials.gov, since data included in such database are not suitable for our in-depth analysis (for example data on NI margin and how it was determined as missing from the database).

Additional analyses as suggested by the reviewer might be feasible if we limit our analysis on certain therapeutic area or drugs, where we can carefully assess the method used in those trials. Nevertheless, in order to do that, we would need a complete trial protocol and report which might be difficult to obtain from public domains.

7. No additional comment.

We are hoping for the editor’s positive decision on our paper.

For the co-authors,

Rosemarie Bernabe