Reviewer’s report

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

Version: 4  Date: 26 February 2013

Reviewer: Jörg Zinserling

Reviewer’s report:

A) The authors provide a point-by-point reply for the comments by the reviewers. The revised manuscript was clearly improved by the revisions done by the authors as proposed by the reviewers.

B) The limitation of the size and index date of the sample of trials the authors selected for their analysis remains. Nevertheless, I can agree with the authors that the main message of the analysis by the authors, “the importance of showing additional benefits in Phase IV NI trials” (response to comment 9) would not substantially change with a larger or more current sample. Following my original comment, I think that the limitations are adequately addressed and the discussion of limitations was improved in the revised manuscript. More precise terminology is used now for some aspects (comment 3 and 4). Presentation of results was improved in response to reviewers’ comments (comments 10 and 12). In my opinion no essential revisions are mandatory.

C) Discretionary Revisions

A short addition could be made according to comment 5 below.

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.
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.
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).

7. No additional comment.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.