Reviewer's report

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

Version: 3 Date: 15 December 2012

Reviewer: Gerd K Rosenkranz

Reviewer's report:

Minor essential revisions:

1. The authors correctly state that any NI trial should be able to demonstrate some additional benefit of the experimental treatment over some reference treatment above and beyond being not less efficacious than the reference in terms of a primary efficacy endpoint, otherwise the new treatment would mainly provide a contingency in case a patient cannot tolerate the reference treatment. Besides the important aspect of clinical relevance, aiming for demonstrating a benefit of the new treatment on endpoints other than the primary can help to relieve some of the criticism raised against NI trials like no direct evidence of assay sensitivity (see Temple and Ellenberg, 2000).

2. The authors mention that they randomly selected 300 of 669 articles “based on pragmatic consideration rather than formal sample size calculations”. Was 300 the amount of articles that could be processed within some time frame? What are the implications of this selection for the results of the paper?

3. The authors classify studies as pharmaceutical industry sponsored or non-pharmaceutical industry sponsored according to whether industry was actively involved in writing the protocol, monitoring, analysis or reporting or not. In case a trial was funded by industry without further involvement, it was also classified as non-industry sponsored. This is considered misleading since funding constitutes one way of sponsoring. For the sake of clarity the authors should consider a classification according to industry-initiated (including funding and further involvement), non-industry initiated but industry funded, and non-industry sponsored trials.

4. It is recommended to avoid the terminology of a “formal” statistical analysis throughout since there might be nothing like an “informal” analysis. The terms “descriptive” versus “confirmatory” should be more appropriate. Likewise the authors should be mindful about the meanings of “efficacy” and “effectiveness”.

5. In 73% of the trials was non-inferiority concluded. Was additional benefit only investigated in these trials or also in those where non-inferiority could not be confirmed? It would also be interesting to know what analysis population was used for the NI analysis and whether the NI margin was reasonably justified.

6. Only one trial performed a sample size calculation for the claimed additional benefit. Rosenkranz (1997) is another industry-initiated one.

7. The authors mention the concept of “comparative effectiveness” which is becoming more relevant in the assessment of new treatments. This approach is
complemented by the introduction of patient reported outcomes (PROs). PROs let the patients speak about what they consider a benefit as compared to what the caregivers consider and provide a tool to measure additional benefit. The inclusion of PROs early on in the development process is strongly supported by health authorities, for example by the Food and Drug Administration.

8. The terminology “establish clinically relevant differences” is ambiguous. It could mean to demonstrate a superior effect in an endpoint other than the one in which NI was established. It could also mean provide evidence for a relevant difference in addition to a statistically significant result which provides evidence for some difference. The authors are asked for checking the document to achieve clarity where applicable.

9. The authors raise ethical concerns about trials that only demonstrate non-inferiority in regard to existing treatment without the intention to demonstrate additional benefits. They should consider the following in this context. First, a treatment which is not worse that an existing one is doing no harm. At least in indications with a medical need and a small number of effective treatments, an additional treatment option may still be worthwhile even if it cannot be proven to be better than existing ones in some important variables. It provides the treating physician with an alternative in case existing treatment is not tolerated by an individual patient. Second, in many situations combinations of drugs with similar efficacy may prove more efficient in combination but have to prove efficacy on their own. Third, newly developed treatments are usually more expensive than existing ones (in particular when the latter have become generic). The prospect that payers may not be willing to pay additional money for the same value is a substantial hurdle to develop new medicines without consideration (and confirmation) of additional benefit.


References:

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
The reviewer is employee of Novartis Pharma AG, Basel, Switzerland, and owns shares of this company.