

**Comments on
CPMP Points to Consider on the Clinical Investigation of Medicinal
Products for the Treatment of Neuropathic Pain
(CPMP/EWP/252/03, Draft, 26 February 2004)**

German Region of the International Biometric Society

Comments:

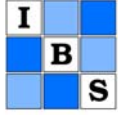
1. Target population

(page 3, Introduction, 3rd paragraph, 3rd sentence and page 7, III.2, 6th paragraph and page 7, III.2 10th paragraph)

Some clarification in the recommendations concerning the target population that should be studied in clinical trials is desired.

In the introduction it is stated “As different disease processes could generate similar pain mechanisms we can expect that the efficacy data from a studied treatment can be extrapolated to clinical situations with different causal factors” indicating that an investigation restricted to specific disease settings is sufficient. This seems to be a contradiction to chapter “Target population” on page 7, stating “Studies conducted in only one pain model can only support an indication restricted to the specific condition”.

On page 7 the chapter “Methodological considerations before initiation of the study” says “Efficacy should be studied in a homogenous population”. This seems to be a contradiction to some statements in the section “Target population” (same page, above), e.g. “Models with mixed pain origins (...) could be considered in non-pivotal supportive studies.” (first paragraph of this section, last sentence), or “For the claim 'peripheral neuropathic pain', the efficacy of the tested drug should be shown in more than one model of peripheral neuropathic



pain (...), ...” (second paragraph, second sentence). Are “non-pivotal supportive studies” no efficacy trials? Are several trials in different populations necessary to claim the indication “peripheral neuropathic pain”?

2. Primary efficacy endpoint in confirmatory trials
(page 5, II., 4th and 5th paragraph)

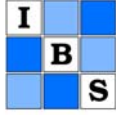
It should be clarified whether one primary endpoint or two primary endpoints are required. The wording “Primary endpoint may be based upon the McGill Pain Questionnaire (MPQ)...” and “It is recommended also to define responders, ...” could be somewhat misleading. What is the role of the responder analyses and which outcomes with respect to the response variable are considered as successful? If two primary endpoints are required, multiplicity and efficiency issues should be considered.

3. Measurement scale of differences in pain scores
(page 5, II. 5th paragraph, and page 7, III.2, Methodological considerations before initiation of the study, 2nd paragraph)

There seems to be a contradiction in the choice of the measurement scale of differences in pain scores used for analysis.

Page 5 says “It is recommended also to define responders e.g. subjects with a 50% reduction in pain score as compared to baseline ...”, indicating that relative differences are relevant.

Page 7 says “The clinically relevant threshold should be discussed and predefined in the study protocol, e.g. how many points of improvement in the assessment scales would be considered a clinically relevant difference between active treatment and placebo at the end of the study”, indicating that absolute differences are relevant. It is not clear, whether it is expected that, in addition to statistical significance, the point estimate of the treatment effect lies above the defined threshold to call the study successful. If this additional success criterion is expected to be fulfilled in the analysis, it should also be taken into account when planning the sample size.



4. Specific comments on wording

- Page 3, 4th paragraph, 2nd sentence:
“Neuropathic pain has been shown to be therapy resistant ...” instead of “Treatment of neuropathic pain has been shown to be therapy resistant ...”.
- Page 5, 2nd sentence from below: “appropriate”
- Page 8, (a) 3rd paragraph last sentence, and (b) 5th paragraph
(b) is a repetition of (a).
- Page 9, (a) 5th paragraph, and (b) 6th paragraph
(b) is a repetition of (a). Skip (a).
- Capitalization of titles is not uniform throughout the document.