Reviewer's report

Title: Long-term safety, tolerability and pharmacokinetics of the highest available dose of paliperidone palmitate: a one-year open-label study in patients with schizophrenia

Version: 2 Date: 14 November 2011

Reviewer: Alberto Parabiaghi

Reviewer's report:

Dear authors,

After careful consideration of your resubmission I'm sorry to inform you that I am not going to recommend acceptance of your manuscript. In my opinion, it still needs revision before it would be suitable for publication.

As Reviewer #2 correctly pointed out, the audience for this Journal likely includes many practicing psychiatrists and even consumers. Thus, I think that the choice of words is very important and that a manuscript should avoid expressions that could give rise to misinterpretation.

You wrote: “We agree with the reviewer that schizophrenia is a life-long illness requiring treatment for long durations. However, the EMEA guidance on the clinical investigation of medicinal products in the treatment of schizophrenia (CPMP/EWP/559/95, 26th February 1998, pg 9), defines any trial of 6 months duration as long-term. Hence, we prefer to retain the word ‘long-term’ in the title and in the manuscript. Similarly, the term ‘open-label’ has been used for nonrandomized studies [Smith et al. Breast Cancer Res Treat. 2009;118(2):361-7 and Gomes et al. Clin Appl Thromb Hemost. 2011;17(1):66-9]. As this study was a systematic clinical trial, with administration of a study drug (intervention), in a population that was recruited into a controlled environment, we believe it is more correctly described as interventional and does not meet the definition of observational trial. Thus, we prefer to maintain the current descriptor.”

The EMEA guidance you mentioned (CPMP/EWP/559/95) referred to placebo-controlled randomized clinical trials. Moreover, page 9 of this document contains no specific definition of what is to be defined “long-term”.

The use of the term “open-label” is misleading, as it is usually used for randomized comparisons (with some exceptions). In my opinion, in the title and abstract (by far the “most-read” sections) the use of the expressions “long-term” and “open-label” should be avoided. Of course I don’t mean by this that you should avoid those expressions also in the text where they could be better contextualized.

You wrote: “this study was a systematic clinical trial, with administration of a study drug (intervention), in a population that was recruited into a controlled
environment, we believe it is more correctly described as interventional and does not meet the definition of observational trial. Thus, we prefer to maintain the current descriptor.”

Randomized controlled trials are often defined as “systematic clinical trials”. Thus, I think that this definition might be misleading too. Of course this was not a naturalistic study, it tried an intervention, and I understand your point of view and the fact that you prefer to call it “interventional”. However, you did control the “trial” very little (just through the exclusion criteria) and you mainly controlled the “observation”. Another suggestion might be: “prospective outcome study”.

You wrote: “Per protocol, Treatment B group was planned to include those patients who could not tolerate the high dose of paliperidone palmitate and those who were not willing to go through the extensive pharmacokinetic sampling. Thus, these patients did not drop out from the study, but entered a different treatment group as described on page 7 (methods section).”

Your “trial” comprised an intervention (highest available dose of PP) and an extensive monitoring (extensive pharmacokinetic sampling). Thus, I really cannot get how patients who could not tolerate the high dose of PP and those who were not willing to go through the extensive pharmacokinetic sampling could be considered as a “different treatment group”.

As you wrote in the text (page 6): “All patients began the study entering into Treatment A, and were allowed to switch to Treatment B (dose range 50-150 mg eq) after the first injection, at the discretion of the investigator.”

As far as I understand, 26 patients were allocated to “Treatment B” because they were discontinued from treatment A. Thus, they simply “dropped" from Treatment A.

In my opinion, to examine, under controlled environment, the medium-term tolerability of highest available dose of PP you should bring into comparison those who completed the one-year trial of fixed dose 234 mg-deltioin injection (n=104) with those who had to switch or discontinue. Otherwise, the acceptability and tolerability of the dosing regimen you propose could be highly overestimated.

I see that this would require an extensive re-analysis of the data and but I don’t think it would weaken the strength of the conclusions. The only fact that the re-analysis I prescribed was not planned per protocol does not mean that it is not suitable for the aims of the study. A very close relationship between study design and statistical analysis is essential in experimental design. In this case, however, the “trial” was not experimental and the design is, therefore, not to be considered untouchable.

You wrote:” Considering it is a long-term study, the discontinuation rate does not seem to be too high. In the CATIE study (Lieberman et al. NEJM. 2005, 353[12]:1029-23), which compares the effectiveness of first and second generation antipsychotic drugs, overall 64-82% of patients discontinued the study medication before completing 18 months of treatment. In addition, this study
tested a fixed dose of the highest dose available and therefore would have been expected to have a higher discontinuation rate than may be observed in clinical practice.”

The dramatically high discontinuation rate was among the most important and worrying findings of the CATIE trial. Thus, I don’t think it should be considered a good mean of comparison. Anyway, I think that a direct comparison with the CATIE trials is misleading. The CATIE -Phase 1- study was a 18-months double-blind RCT. Thus, its follow-up was longer and the design was truly experimental. Moreover, the antipsychotic therapy was orally administered. The 64-82% discontinuation rate in CATIE referred to a specific and peculiar definition of discontinuation. CATIE participants, in fact, were classified as discontinuers as they discontinued antipsychotic monotherapy.

Best regards

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

The Mario Negri Institute for Pharmacological Research, with whom I am affiliated, has received unrestricted funding from Bristol-Myers Squibb to run the GiSAS trial, a pragmatic RCT on aripiprazole, olanzapine and haloperidol in the long-term treatment of schizophrenia. I declare that I have no competing interests and that I have no past, current or pending financial link to any pharmaceutical company other than the research support administered for the GiSAS trial conduct.