Author's response to reviews

Title: Onset of Efficacy and Tolerability Following the Initiation Dosing of Long-Acting Paliperidone Palmitate: Post-Hoc Analyses of a Randomized, Double-Blind Clinical Trial

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Author's response to reviews: see over
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Miss Angelina Ilievska MSc
on behalf of Dr Deanna L Kelly

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Onset of Efficacy and Tolerability Following the Initiation Dosing of Long-Acting Paliperidone Palmitate: Post-Hoc Analyses of a Randomized, Double-Blind Clinical Trial. Cynthia A Bossie, Jennifer K Sliwa, Yi-Wen Ma, Dong-Jing Fu and Larry Alphs

Dear Miss Ilievska:

Thank you for the interest in our manuscript for your journal BMC Psychiatry. Per your request, we have uploaded both a highlighted version of the manuscript as well as a Clean Revision on the journal website. We have addressed each of the reviewers’ comments in the revision and have enclosed a point-by-point response to each of their concerns below (including places in the document that the revisions were made).

We appreciate your review of this manuscript and look forward to your response.

Sincerely,

Cynthia A. Bossie, PhD
Ortho-McNeil Janssen Scientific Affairs, LLC
Director, CNS Medical Affairs
Major Revisions
1. Please determine the composite incidence of any EPS symptom. Although there was a low incidence of individual events, an overall estimate of any EPS symptoms would be useful in evaluating overall tolerability.
   
   **Author Response:** As requested, we have added these data for Days 1 to 7 and Days 8 to 36 (see pages 11 and 12).

   Also, add information on changes in the rate of use of anti-EPS medication, if no changes, please state that.
   
   **Author Response:** As requested, we have added more specific information on the use of anti-EPS medications prior to baseline (Patient Disposition and Characteristics section, page 8) as well as during Days 1 to 7 and Days 8 to 36 (see pages 11 and 12). The Methods now describe that prior antiparkinsonian medications were to be washed our prior to baseline, but were allowed during the study at the discretion of the investigator for EPS (page 6).

2. Add information on any serious adverse events that may have occurred or state that none occurred.
   
   **Author Response:** As requested, we have added these data under Adverse Events, see pages 10 and 11.

Minor Revisions
1. Add a sentence to the Design section on page 5 that summarizes the exclusion criteria for the original study.
   
   **Author Response:** As requested, we have added a sentence summarizing the key exclusion criteria of the primary study, see page 5.

2. There is an extra period in the second from the last sentence on page 6.
   
   **Author Response:** Removed.

3. Anxiety appears to be dose related. Please mention this in the results or discussion section.
   
   **Author Response:** The percentages of patients reporting anxiety in each arm as reported on page 11,-12 and Figure 4 were: 2.5% with placebo, 3.9% with PP 234/39, 3.1% with PP 234/156 and 3.1% with PP 234/234. This does not appear to be a dose-related effect, and no comment has been added. Please advise if something else is required.

Discretionary Revisions
1. The lead sentence in paragraph 1, page 5 starting with "An early... is duplicative. The idea was already clearly stated earlier in the background section.
   
   **Author Response:** We prefer to leave this statement in as a lead-in to the study rationale.

   Perhaps add a sentence in this same paragraph clarifying the benefit of deltoid injection (e.g. better absorption) over gluteal (e.g. less pain).
Author Response: In response, we have added statements to the background section for clarification, see page 4.

2. A composite for any sexual disorder events might also be illuminating but a 36 day time period is probably too short to evaluate the effect of hyperprolactemia.
Author Response: We agree that a 36 day time period is probably too short, but have reported this information on pages 11 and 12.

3. On page 8 in the discussion on baseline use of concomitant medications (e.g., benzodiazepines) an overall rate of use is reported. Was there a difference at baseline between placebo and treatment groups in rate of use?
Author Response: The rates of use were similar and we have added these data to the manuscript (see Patient Characteristics, see page 8).

4. While investigators must decide on "treatment-relatedness" when making a decision to withdraw treatment in the face of an adverse event for an individual patient, this is not a reliable assessment for evidence based decision-making and should not be reported.
Author Response: We agree that it is difficult to assess treatment-relatedness to adverse events. As requested, we have removed that information from the description of the adverse events on pages 10 and 12.

Dr. Schooler’s Comments and Responses

Major compulsory revisions.
1. This article provides additional information of interest to the article that was published on 2010 in the Journal of Clinical Psychopharmacology. From my perspective, it is important that the new article provide clear additional information and not repeat material that has already been presented in the published literature. Therefore, figures which have already been published should be cited rather than repeated.
Author Response: The figures submitted are original to this manuscript and have not been previously published. While there is some similarity between Figure 2 of this post-hoc analysis and Figure 1 in the primary manuscript, the presentation in our figure reflects the current objective to study the effects specifically associated with the Day 1 and Day 8 initiation doses. Since all subjects randomized to paliperidone palmitate received 234 on day 1, the data for the paliperidone palmitate arms are pooled for Days 1 to 7. Since subjects then received their assigned dose on Day 8, results are then shown for each arm for Days 8 to 36. In the primary publication, findings are presented for each paliperidone palmitate arm from baseline.

2. The authors state that this article will focus on the dose regimen of 234 -initiation dose followed by 156 at day 8. Since the data were drawn from a study that assessed three randomized doses on day 8, this article should also reflect the full design rather than focusing on what is the labeled recommendation. By doing the latter, the impression is conveyed that the article is meant to support a marketing recommendation rather than provide balanced scientific information. Thus, for example, in Table 2 it is inappropriate to highlight the Day 8 156 column. The conclusion should not focus on this dosing regimen. I would rely on the authors to review the MS to insure that other details of the article that emphasize the 156 dose are addressed.
Author Response: While a primary objective here was to answer commonly asked clinician questions regarding the initiation doses that were approved by the US FDA, we do agree that all dose data are
important. We present data for the other dose arms in the manuscript in the Results (see pages 10, 11 and 12, Tables and Figures) with all doses discussed in the discussion (see pages 12-15). To address the reviewer’s concern and minimize emphasis on one dose arm, we removed the banding highlighting the 156 mg arm from Table 2 as well as from Figure 1. We have also included information on other doses in the abstract (see pages 2 and 3) and manuscript conclusion (page 15).

3. In keeping with this goal, it is critical that data regarding adverse events be presented separately for the three doses. Thus, Figure 4 presents merged information for all doses compared to placebo. What would be extremely valuable would be to present these data for the 3 day 8 doses.

Author Response: We agree with the reviewer that data for all dose arms should be presented. While the data were originally presented only in the text, in response, we are now adding panels C and D to Figure 4 to clearly depict these data for all three dose arms.

4. Once data are presented regarding dose and adverse events as well as change in focus from 234 to 156 to a dosage comparison, the discussion will probably require modification as well.

Author Response: The Discussion includes commentary on the results across doses for both onset of efficacy and tolerability (pages 12 to 15), as well as in the conclusion (page 15).

Note to journal: After the addition of data in the text for each dose arm in response to the reviewers, we decided there was a need to simplify the naming of these dose arms so that “234 mg Day 1” is not continually repeated. Therefore, when data are presented for days 8-36, the paliperidone palmitate groups are named as the 39 mg Day 8 group, 156 mg Day 8 group, or 234 mg Day 8 group.