Author's response to reviews

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

Authors:

Danielle Coppola (DCoppol2@its.jnj.com)
Yanning Liu (yliu@prdus.jnj.com)
Srihari Gopal (SGopal2@its.jnj.com)
Bart Remmerie (BREMMERI@its.jnj.com)
Mahesh Samtani (MSamtani@its.jnj.com)
David Hough (DHough2@ITS.JNJ.com)
Isaac Nuamah (INUamah@its.jnj.com)
Ahmad Sulaiman (hatim@um.edu.my)
Gahan Pandina (GPandina@its.jnj.com)

Version: 2 Date: 10 October 2011

Author's response to reviews: see over
Dear Dr. Patel,

Re: Long-term safety, tolerability and pharmacokinetics of the highest available dose of paliperidone palmitate: a one-year open-label study in patients with schizophrenia (Manuscript ID 1067037660555337).

Thank you for your email dated August 31, 2011, informing us that our manuscript could be considered for publication in the journal *BMC Psychiatry* if we adequately address the reviewers’ comments. We also thank the reviewers for the suggestions to enhance the scientific value of this manuscript. Reviewers’ comments have been addressed and our responses to each of the comments are given below. Based on the reviewers’ comments, corrections are incorporated in the revised manuscript in blue font.

**Reviewer #1:**

**Major Revisions**

1) In the Title, and throughout the text, the expressions “long-term” and “open-label” should be avoided. A 12-month trial should not be considered long-term, since, for schizophrenia, average duration of illness and treatment is quite longer, and since steady state for long-acting injectable formulations is usually reached after months (8/9 months for PP). The use of the term “open-label” is misleading, as it is usually used for
randomized comparisons. The expression “observational” is preferable. I suggest to define the study as a phase-1 observational study.

Response:

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.

2) Since the study aim is to examine the long-term pharmacokinetics and tolerability of the highest available dose of PP, the patients who dropped out from this dosing regimen should be considered separately. Classifying patients in Treatment A and B is confusing. Actually, patients on Treatment B dropped out from Treatment A.

Response:
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). Dropouts (i.e. early withdrawals) in this trial were prospectively defined as patients who withdrew early without completion of Day 372, and not as patients who switched from Treatment A to Treatment B. All patients who completed Day 372 (regardless of treatment group) were considered as completers. Among the 26 patients in Treatment B, 4 completed the trial on 150 mg eq; 3 withdrew early while on 150 mg eq; 9 completed the trial on a flexible dose of paliperidone palmitate; and 10 withdrew early while on flexible dose.

Presenting results separately for the 104 patients (100 in Treatment A and 4 in Treatment B) who completed the study on 150 mg eq. dose of paliperidone palmitate would require extensive reanalysis of the data, and would be post-hoc, as it was not planned per protocol. This would weaken the strength of any conclusions that could be drawn.

3) Out of 212 patients, 104 (49%) completed the study receiving the 150 mg eq. dose regimen for the entire period. I believe that those subjects should form the primary analysis group and could be called “continuers” or “completers”.

Response:
Such an analysis was not planned per protocol. Of the 104 patients completing the study on 150 mg eq., only 4 patients were in Treatment B. None of these patients experienced an adverse event that was deemed by the investigator to be serious. The adverse events reported in these patients were consistent with the known safety profile of the drug, and a statement to that effect is added to the manuscript (pg 21).

4) Dropouts should be considered altogether (Treatment A discontinuers: n=86 + Treatment B discontinuers: n=13 + Treatment B flexible dose: n=9 --> n=102) and could be called “discontinuers” or “non-completers”.

**Response:**

The 9 patients who continued in the study on a flexible dose of paliperidone palmitate cannot be considered discontinuers. These patients completed Day 372 and were defined as completers, per protocol.

5) Comparisons in terms of baseline characteristics and follow-up endpoints of efficacy and tolerability between continuers and discontinuers should be performed.

**Response:**

As per protocol, from the beginning of the study, Treatment B group also included those patients who were not willing to go through extensive pharmacokinetic sampling; hence, patients in Treatment B cannot be called discontinuers. Treatment B included both completers and those who withdrew early. Thus, we would retain the comparison as it is
currently presented in the manuscript for baseline characteristics and efficacy and
tolerability endpoints.

6) The group of subjects to be included in the assessment of safety and tolerability is often
called “safety analysis set” and is often defined as those subjects who received at least
one dose of the study medication. I appreciate this approach. However, the safety
analyses should include a comparison between continuers and discontinuers as well.

**Response:**

Similar to the response above, to be consistent with the protocol, we prefer to retain the
comparison based on safety analyses as it is currently presented in the manuscript.

7) At page 12, “Pharmacokinetic analysis” please specify the number of subjects included in
the “Pharmacokinetic analysis set” (n=100?)

**Response:**

For table 4, the following footnote has been added: N refers to the number of
pharmacokinetic samples used in the calculation of the PE% and |PE|% statistics. The
5382 pharmacokinetic samples were derived from 211 patients.

For Figure 2, the following footnote has been added: Time-concentration profiles were
based on data from 212 patients
For Figure 2, the number of patients has been specified: Figure 2. Median plasma concentration-time profiles of paliperidone (data from 212 patients). Different pharmacokinetic analyses and explorations were conducted, requiring different exclusion strategies. Each pharmacokinetic-related table or graph contains information on the number of patients in the revised manuscript.

For Figure 3, the following footnote has been added: Data included are of 192 patients who received 150 mg eq. paliperidone palmitate till the time of their discontinuation.

8) I suggest to cut off the paragraphs on the Population-PK model evaluation both in the Methods and in the Results section (and Figure 2). This analysis could be the subject of a following brief report or letter.

**Response:**

The population pharmacokinetic information is necessary in the manuscript in order to answer the query on ethnicity from the other reviewer. Hence, we prefer retaining this information.

9) In the Discussion, authors should interpret their findings in light of the results of the comparisons between continuers and discontinuers, keeping in mind that the study is meant to answer one principal question: Do these preliminary results support recommendation of the proposed dosing regimen? If yes, authors should propose further exploration the advantages of the proposed dosing regimen through randomized
comparisons --> Which could be the advantages of this dosing regimen in comparison to a more flexible one?

**Response:**

This study was designed to answer a different question, which was, “What are, the long-term safety and pharmacokinetics of continued administration of the highest dose (150 mg eq.) of paliperidone palmitate?” Studies of the approved dosing regimen have been published elsewhere (Invega® sustenna® - prescribing information, revised June 2011) and hence any discussion of this dosing regimen versus the approved dosing regimen are not appropriate.

10) In this observational study, treatment with highest available dose of PP resulted safe and tolerable in the medium term (one year) in half of the sample. What the authors wrote at page 20 (lines 10-13 of the Discussion) is questionable. Results do not attest directly to the tolerability of the proposed dosing regimen in long-term therapy.

**Response:**

Refer to response given for comment no 1. The EMEA guideline supports the use of word “long-term” for a trial of 6 months duration. Hence, we prefer to retain this sentence in the manuscript.

11) The authors should thoroughly discuss the reasons for discontinuing the proposed dosing regimen. It resulted in fact practicable for only half of the included subjects and,
generally speaking, a 50% discontinuation rate is not low for a long-acting formulation in stable, young schizophrenic subjects without hypersensitivity to paliperidone or risperidone (or their excipients).

Response:
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.

12) Page 22, line 4: it is questionable to argue that, since underlying factors for glucose-related adverse events were identified, PP could not be the primary cause. Those subject had rather been excluded from the beginning.

Response:
While clinically significant laboratory abnormalities and unstable medical conditions were general criteria for exclusion based on the investigator’s judgment, the study design did not have any exclusionary parameters specific for fasting blood glucose. In this case, 4 patients with fasting blood glucose concentrations either in diabetic or prediabetic range were enrolled, and thus included.
13) At page 23, the authors wrote: “The lack of a placebo group...”. This make little sense, since no comparison was planned. The lack of an experimental (or even a quasi-experimental) design requires caution in interpreting these findings. The main problem is that a comparison (blinded or unblinded, randomized or not) was not prospectively planned and the post-hoc comparisons I suggested above cannot solve the problem.

Response:
The reviewer is correct that a placebo group was not planned. However, we feel it is still valuable to remind readers that without a placebo group with which to compare, the interpretation of the data is limited.

We have reworded the statement to read: This study did not include a placebo group; hence no background rates of TEAE incidences were available for comparison. This limits the clinical interpretation of the data (pg 24).

Minor Revisions

1) Methods, second line: #70

Response: We have corrected “70” to “≤70” in the method section of abstract (pg 3)

2) Figures 1-5 (page 38 onward) should be renumbered and captions should be included.

Response: We corrected this error in the manuscript and thank the reviewer for pointing this out.
Reviewer #2:

1) My greatest concern with the paper is that it does not go far enough to impart clinical recommendations given the extensive amount of collected data. The audience for this journal likely includes many practicing psychiatrists and even consumers who have open access. Thus, it may be advantageous to distill the findings into clinically pragmatic messages that can be utilized in day-to-day patient care. Some specific areas than can be addressed include the following:

A. Do data show any inconsistency in bioequivalence when administered in gluteal muscle as compared to deltoid muscle?

Response:

This study was not designed to assess the impact of injection sites on the paliperidone pharmacokinetics. Also, in this study, the investigators and patients had the choice to switch injection sites after the initiation regimen.

In the previously reported phase I studies (Cleton et al. 2008a and Cleton 2008b; Posters presented at American Society Clinical Pharmacology Therapeutics [ASCPT], Orlando, April, 2008), the overall exposure to paliperidone was similar after i.m. administration of paliperidone palmitate in either the deltoid or gluteus. The area under the curves (AUCs) after deltoid and gluteal injections were similar and a difference between injection sites was less pronounced for AUC than for
peak plasma concentration ($C_{\text{max}}$), indicating that the overall exposure to paliperidone is similar after i.m. administration of paliperidone palmitate in either the deltoid or gluteus. The observed difference in $C_{\text{max}}$ between injection in the deltoid or the gluteal muscle can likely be explained by the different distribution of muscle and adipose tissue between the two injection sites (Cockshott et al. *NEJM*.1982; 307[6]:356-8, Haramati et al. *Arch. Fam. Med*.1994; 3[2]:146-8), which may affect the dissolution of paliperidone palmitate and the subsequent uptake of paliperidone in the circulation at the site of injection. At the deltoid injection site, the likelihood of an injection that is truly intramuscular is higher compared with the gluteal injection site. The hypovascularity of subcutaneous adipose tissue compared with muscle tissue results in a slower uptake of paliperidone from the gluteal compared to the deltoid injection site, due to the slower dissolution of the palmitate ester at the gluteal injection site. This effect will have a greater impact at the initiation of treatment i.e. gluteal injections will delay the time taken to achieve steady state. However, after multiple injections, fluctuations in paliperidone plasma concentrations are reduced since steady state is approached, and a difference between deltoid and gluteal injections would no longer be expected.

B. Is any overlap in oral paliperidone necessary prior to solely using paliperidone palmitate? How do the data answer this question?

**Response:**
This study is not designed to address this question. However, that patients remained stable in spite of prohibition of either oral paliperidone or risperidone after day -5 suggests that oral supplementation is not required upon initiation of paliperidone palmitate therapy in symptomatically stable patients. Also, there are previous reports resulting from an extensive phase 3 development programs indicating that treatment with paliperidone palmitate does not require oral supplementation. The initiation regimen of this formulation allows immediate and gradual release of the drug (Hough et al. *Neuro-Psychopharmacology & Biological Psychiatry* 2009; 33:1022-1031 and Gopal et al. *Current Medical Research & Opinion* 2010;26[2]: 377-387).

C. There is an opportunity to look at how the results were impacted by ethnicity, given the diversity of the current study with enrollment of a large number of Asian and African-American participants. What do the data tell us about ethnicity?

**Response:**

Across studies, it has been found that body mass index (BMI) rather than ethnicity, has the most impact on the pharmacokinetics of paliperidone palmitate, but this is overcome by the recommended dosing regimen and use of appropriate needle length. As an example, in the current study Asian patients also had approximately 4% higher plasma exposure to paliperidone compared with white patients (see Additional File 1), which can be explained by the lower BMI in the
Asian population (see Additional File 2). Furthermore, the population pharmacokinetic analysis showed that race does not have an independent effect on pharmacokinetics once the difference in BMI across ethnicities is accounted (see Additional File 3).

D. It appears that 97% of steady state is achieved after 41 weeks of administration. How does this value relate to the pharmacokinetics after the first or 2nd injection? What are the clinical implications around this finding?

**Response:**

The pharmacokinetic findings of this study indicate that the paliperidone concentrations approach the steady state after the 2nd injection of paliperidone palmitate, and slowly reaches steady state after the 14th injection (Please refer table 2 of the manuscript). The first injection of paliperidone palmitate, 150 mg eq. in the deltoid muscle, increases the initial exposure to the drug and the second injection allows for rapid achievement of target plasma levels that can be further maintained by once-monthly dosing (Pandina et al. *J Clin Psychopharmacol* 2010;30:235-244).

2) The results indicate that schizophrenia (5%) and psychotic disorder (3%) were serious treatment emergent adverse events. I’m confused as to how schizophrenia is an adverse event. My understanding is that all patients were diagnosed with schizophrenia in order to enroll in the study. Perhaps it is being implied that patients are experiencing a worsening
of psychotic symptoms? In this case, are the early discontinuations due to poor symptom control?

**Response:**

As correctly stated by the reviewer, all patients enrolled in the study had a diagnosis of schizophrenia. Investigators were instructed to report any adverse event occurring during the clinical trial, and while this would not include stable symptoms of a pre-existing disease, it does include decompensation of symptoms of any underlying condition. The terms “schizophrenia” and “psychotic disorder” are indeed used to summarize the incidences of worsening of underlying schizophrenia or psychosis based on the internationally recognized standardized medical coding dictionary, the Medical Dictionary for Regulatory Affairs (MedDRA). Unfortunately, this standardized dictionary does not include a mechanism to code worsening of such disorders, and the reporters’ terms (i.e. the verbatim adverse event reports from investigators) are variably described, such that they cannot be pooled in a meaningful way without the use of a coding dictionary. A review of the verbatim terms coded to schizophrenia or psychotic disorder revealed, for example, events described as: “exacerbation of schizophrenia,” “worsening of symptoms of schizophrenia,” “deterioration of psychotic symptoms,” “psychotic symptoms relapse,” and so on. In all cases, the adverse events describe a worsening of the underlying condition.

Thus in the manuscript we have replaced “schizophrenia” with “worsening of symptoms of schizophrenia” (pg 17).
3) Please indicate how many patients had worsening in PANSS score of 20% or greater and 30% or greater.

**Response:**

Out of 204 patients, 46 in Treatment A and 5 in Treatment B had \( \geq 30\% \) of worsening of PANSS scores. Out of 204 patients, 52 in Treatment A and 6 in Treatment B had \( \geq 20\% \) of worsening of PANSS scores.

We have added the data for \( \geq 30\% \) of worsening of PANSS scores in manuscript (pg 20).

4) Were any differences observed in the side effects among the higher dose and flexible (lower) dose groups (i.e. dose related side effects)?

**Response:**

Over all incidences of treatment emergent adverse event (TEAEs) possibly related and leading to permanent stop are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Treatment A (Pali 150 mg eq. (N=186) n (%)</th>
<th>Treatment B (Pali 50-150 mg eq. (N=26) n (%)</th>
<th>Total (N=212) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>159 (85)</td>
<td>25 (96)</td>
<td>184 (87)</td>
</tr>
<tr>
<td>Possibly related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAE leading</td>
<td>116 (62)</td>
<td>20 (77)</td>
<td>136 (64)</td>
</tr>
<tr>
<td>to permanent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stop</td>
<td>22 (12)</td>
<td>5 (19)</td>
<td>27 (13)</td>
</tr>
</tbody>
</table>
Treatment-emergent adverse events were reported more frequently in patients in Treatment group B as compared to patients in Treatment group A. Among these adverse events, the most frequently reported adverse events were anxiety (Treatment A, 5.9%, Treatment B, 15.4%), akathisia (Treatment A, 7.0%, Treatment B, 23.1%), weight increased (Treatment A, 7.5%, Treatment B, 19.2%) and hyperprolactinemia (Treatment A, 4.8%, Treatment B, 11.5%).

These differences however, should be viewed with caution, as only 12% of the patients in Treatment B were included in the safety analysis set.

5) It is reported that 78% of patients had treatment-emergent abnormal prolactin levels, particularly among women. Can the authors expand upon this finding within the discussion as to the clinical implications:

A. What recommendations are being made regarding the prolactin findings? Should patients be continued on treatment despite elevated levels if asymptomatic? Should monitoring of prolactin levels occur at specific intervals?

**Response:**

There are currently no established guidelines for the monitoring of prolactin concentrations during treatment with antipsychotics. On the basis of this study, there is no information that would warrant such monitoring at regular intervals in asymptomatic patients. The potential benefits must be weighed against the risks on a case-by-case basis, and our experience to date indicates that management of
prolactin-related adverse events with dopamine agonists may be a viable option for patients who benefit from treatment with the antipsychotic.

B. How does the rate of elevated prolactin compare with oral paliperidone?

**Response:**

In this study, paliperidone palmitate showed a greater increase from baseline to endpoint in prolactin levels in women (Treatment A, increase from 23 to 101 ng/mL and Treatment B, increase from 9 to 101 ng/mL) compared with men. These findings were consistent with those reported with oral paliperidone (Karmer et al *International Journal of Neuropsychopharmacology* 2010;13:635-647), where in an increase of 20 to 124 ng/mL was reported in women. However, findings of these two studies cannot be compared due to the differences in the study design.

C. Some discussion about the potential long-term risks appears indicated. For instance, how might this affect menstruation, libido, and osteoporosis?

**Response:**

No new risks associated with prolonged exposure to paliperidone palmitate were identified on the basis of this one-year study. Any future risks would be purely speculative. In this study, one-fifth of all patients in the safety analysis set experienced at least 1 potentially prolactin-related adverse event. Women had a
higher incidence (32.8%) of potentially prolactin-related adverse events as compared to men (14.3%). Out of 212 patients, a total of 4 patients were reported with decrease in libido, 2 patients were reported with amenorrhea. No incidence of osteoarthritis was reported in this study. However, these safety outcomes cannot be extrapolated for the use of paliperidone palmitate over the period of several years.

D. Were patients specifically queried for side effects related to hyperprolactinemia?

For example, some of the side effects that might include difficulty with sexual functioning or galactorrhea may be embarrassing for patients with schizophrenia to spontaneously report and may be underestimated if they were not raised on direct questioning.

Response:

In contrast to prior double-blind clinical studies, where these values were not disclosed to the investigator in order to maintain the blind of the study medication, prolactin concentrations were periodically measured and reported to investigators throughout this study. This enabled investigators to probe the patient further for potentially prolactin-related adverse events based on clinical judgment. Nonetheless, there was no requirement in the study protocol to specifically query patients for adverse effects related to hyperprolactinemia. We have added this as one of the limitations in the manuscript (pg 25).
MINOR REVISIONS

1. The eligibility criteria in the abstract (Methods) states the PANSS total score is \( \geq 70 \). Is this a typo, as in other places it states \( \leq 70 \)?

   **Response:** We corrected this error in the manuscript and thank the reviewer for pointing this out.

2. On page 19, the prolactin concentrations among women are reported to decrease to the Day 372 timepoint. In Figure 5, although there is a gradual decrease to Day 372, at endpoint there appears to be a rise in the slope again. Please discuss what accounts for this change and how the endpoint differs from the Day 372 timepoint (are these LOCF findings?).

   **Response:**

   The findings on Day 372 were not subjected to LOCF findings; it is the visit for patients who continue to or visit at Day 372 (i.e. completers). Out of the total 212 enrolled patients, not everyone had Day 372 data, but all had endpoint data. The differences in prolactin concentrations observed on Day 372 and endpoint are attributed to the differences in the number of patients at both the timepoints. On an average, the early withdrawal patients had higher prolactin concentrations at the time of withdrawal than the completers, resulting in higher mean values at endpoint than at Day 372.
On behalf of all of the authors, I would like to thank the reviewers for their comprehensive appraisal of our manuscript and for the constructive comments and suggestions for revision.

Yours truly,

Dr. Danielle Coppola,
Johnson & Johnson Pharmaceutical Research & Development, LLC
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560
Phone: 609 730 6581
Fax: 609 730 6587
e-mail: DCoppol2@its.jnj.com