Author's response to reviews

Title: Adjunctive long-acting risperidone in patients with bipolar disorder who relapse frequently and have active mood symptoms

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Dr Deanna L Kelly  
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Dear Dr Kelly

We greatly appreciate the opportunity to respond to the reviewers of the manuscript, “Adjunctive long-acting risperidone in patients with bipolar disorder who relapse frequently and have active mood symptoms” (Manuscript #1977018164972285).

Responses to the reviewer comments follow; changes to the manuscript based on these comments are indicated in tracked changes.

Thank you again for your continued consideration; we hope you find the responses to the reviewers’ comments satisfactory.

Regards,

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Reviewer 1

This was a post-hoc analysis of an open-label study of 162 bipolar patients with persistent mania and/or depression that were treated for 16 weeks with risperidone long-acting injection (RLAI) as adjunctive therapy. Significant improvements in CGI-BP-S, MADRS and YMRS were noted for the population as a whole. Moreover, subjects with predominantly manic/mixed symptoms at baseline showed significant improvements on the CGI-BP-S and YMRS scales and subjects with predominantly depressive symptoms showed significant improvements on the CGI-BP-S and MADRS scales. This article deserves to be published, however we have some suggestions.

We have a few comments in order to improve the manuscript:

1. The persistent symptoms in this population could have been due to noncompliance, which may explain some of the benefits of RLAI. Did the authors measure medication compliance/plasma levels in the patients at baseline? If so, these data would be interesting to report.

Response: Since compliance is a common problem, it is certainly possible that subjects were not compliant with their prior treatments. However, plasma concentrations of medications were not assessed at baseline, so we cannot address this concern directly with our available data. We have included this as a limitation to interpreting our results in the discussion on page 14.

However, a possible indirect surrogate for subjects’ adherence to antipsychotic treatment is their compliance with concomitant oral psychotherapeutic treatments that many subjects in this trial were taking. Plasma concentrations of lithium and/or valproate were assessed at the open label endpoint (ie, double-blind baseline) and throughout the double-blind phase. We observed that plasma concentrations were essentially the same for patients at all points in the trial, suggesting that adherence to those oral therapies was generally consistent throughout the trial. Data from these subjects show that 68 subjects from our analysis met remission criteria for inclusion in the double-blind phase and of those subjects 30 (44.1%) had recorded serum levels of lithium and 31 (45.6%) had recorded serum levels of valproate. It should be noted that many subjects were dosed at relatively low dosages of these medications. Of these individuals the majority of subjects had lithium and/or valproate levels within the recommended range (lithium: 0.4-1.2 mmol/L; valproate: 50-150 µg/mL) (Table). These results suggest that subjects with therapeutic levels were likely compliant with oral medication, and subjects with subtherapeutic levels would be questionably compliant with oral medications.

We have provided this information knowing that this was a very indirect approach to understand the treatment adherence of this study population, and we believe it is too speculative to include in the body of this manuscript.
Table. Lithium and Valproate Use at the End of the Open-Label Phase (Double-Blind Baseline) for Subjects From this Analysis Who Entered the Double-Blind Maintenance Phase

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Total (N = 68)</th>
<th>Baseline Depressive (n = 24)</th>
<th>Baseline Manic/Mixed (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with recorded serum levels of Lithium Valproate</td>
<td>30 (44.1)</td>
<td>11 (45.8)</td>
<td>19 (43.2)</td>
</tr>
<tr>
<td></td>
<td>31(45.6)</td>
<td>10 (41.7)</td>
<td>21(47.7)</td>
</tr>
<tr>
<td>Subjects with doses within recommended range*</td>
<td>25 (83.3)</td>
<td>8 (72.7)</td>
<td>17 (89.5)</td>
</tr>
<tr>
<td>Lithium Valproate</td>
<td>28 (90.3)</td>
<td>9 (90.0)</td>
<td>19 (90.5)</td>
</tr>
<tr>
<td>Subjects with doses above recommended range*</td>
<td>3 (10.0)</td>
<td>2 (18.2)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Lithium Valproate</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Subjects with doses below recommended range*</td>
<td>2 (6.7)</td>
<td>5 (50.0)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Lithium Valproate</td>
<td>3 (9.7)</td>
<td>1 (10.0)</td>
<td>2 (9.5)</td>
</tr>
</tbody>
</table>

*Percentages derived from subjects who had recorded serum levels of lithium and/or valproate.
Recommended dose levels: lithium: 0.4-1.2 mmol/L; valproate: 50-150 µg/mL.

2. The authors state that “subjects were receiving therapeutic plasma levels of RLAT by the week 4” (pg.14). Were plasma levels of risperidone obtained to confirm this statement?

**Response:** Plasma concentrations of RLAl were not obtained in this study. The purpose of this statement was to highlight that although patients received oral risperidone for the 3 weeks of the study, by week 4 therapeutic levels of risperidone would be present from RLAI based on its release profile (RISPERDAL® CONSTA® [prescribing information]. Titusville, NJ: Janssen; 2010.). We have modified the statement on page 14 in order to clarify this point.

We also performed an additional analysis to support this statement. We evaluated the percentage of patients who received a both the initial and week 2 injections of RLAl and found that no one has missed their injection.

3. The purpose of this study was, in part, to compare the effectiveness of RLAl for bipolar patients with predominantly manic symptoms, relative to those with predominantly depressive symptoms. Interestingly, it seems that at week 4,
patients with depressive symptoms were showing more remission than patients with manic symptoms, whereas this was the opposite at LOCF endpoint. However, no statistical analyses were performed on these data. Were the differences statistically significant? Could the differences be related to rising plasma levels of risperidone? If these questions are uneasy to answer, the authors might modify the limitations section.

**Response:** Although the graph suggests there may be a more rapid onset of effect for depressive symptoms, we do not feel a between-group comparison is valid. There are substantial between-group differences in baseline demographics, baseline disease characteristics, symptomatology, and the scales used to measure symptoms. While these data may generate hypotheses, we would not use them to draw a conclusion on the timing of improvement of symptom domains among different sub populations. We have added this to the discussion on page 14.

**Reviewer 2**

**Introduction**

1. The introduction took a long time to explain what the paper was about. A lot of the information in the introduction is really trivial. I would start off right from the very beginning to discuss non-compliance, although this could be handled more succinctly in one or two sentences, moving on to the role of depot medication specifically. The introduction should then state an overview of what the present study is. In my opinion, the most useful way to think about the scientific hypothesis of the present analysis would be to identify predictors or of whether or not depot risperidone will (A) improve patients and (B) establish stability. In other words, in which type of bipolar disease is depot risperidone useful? Undoubtedly, some of the improvement may be a consequence of receiving medication and being in a clinical trial. This cannot be assessed without a placebo group. But data on open trials can be helpful in giving us some information about what may be important.

**Response:** We have shortened the introduction to improve its flow.

2. I think it is good to choose an acronym which is intuitively obvious. If you are reading fast and miss the first time it is defined, you get confused about what it stands for. I would call it depot risperidone such as DepRis.

**Response:** In order to clarify the acronym, we have replaced the term “risperidone long-acting therapy (RLAT)” with “risperidone long-acting injection (RLAI).”

**Method, Study Design**

I had to look up the original study to try to figure out just how this fit in. Since patients were started on treatment as usual, it is pertinent to examine the stage of their illness and
their state of the last acute episode and the medication use in the TAU. If they were started close to an acute episode, patients might have more room for improvement; however, some patients may have been on maintenance medication for some time, but had a history of frequent relapse. Therefore, predictors of who depot risperidone would help would be (1) near and acute episode versus not near an acute episode; (2) The type of the most recent episode (bipolar depressive, manic, or mixed); (3) The medication they were on at start (mood stabilizers, antipsychotics; mood stabilizers plus antipsychotics); (4) How depressed they were at start; and (5) whether they had mixed symptomatology; (6) whether or not they usually had psychotic manias or depressions; (7) whether they had more psychotic-like symptoms such as grandiosity; (8) number or relapses per unit time. (The absolute number of relapses is not pertinent because the older the patient is, the more time they would have had to have had relapses.) (9) frequencies of past hospitalizations. You should identify more such variables. In order to find out what the indications for depot risperidone would be (A) the outcome criteria and improvement, (B) improvement adjusted by baseline state, (C) successfully becoming stabilized. (Y/N) This is different from absolute improvement because the patient could start very psychotic and have a good deal of improvement, but never stabilize. After such analyses are done, one could then choose the most interesting findings to present. The present tables tend to give too much minor information. Your search for indications for depot risperidone and finding some would help structure the rest of the paper. It is interesting that the patients did improve considerably; but this all could be placebo effect (broadly conceived) and finding indications for the drug would make it a much more clinically useful paper. Once you have indications of varying degrees, one wants to find out to what degree of overlap between the indications, so this needs to be statistically examined as well. One has to think thoroughly how to handle the so-called “law on initial value” (the baseline where the patient started) because a patient with an elevated level on a given scale has more room for improvement.

**Response:** The original study was designed to look at the maintenance of effect with RLAI added to treatment as usual in stable bipolar subjects. The purpose of the current analysis was to examine and characterize the clinical, symptomatic, and functional outcomes in subgroups of symptomatic patients who exhibited prominent manic or depressive symptoms at study entry. We believe these are distinct and relevant subgroups of patients and treatment outcomes in these groups would be of interest to clinicians. The reviewer’s suggestions of examining predictors of remission are interesting, and we are currently planning such analyses. However, this is a different question and beyond the scope of our current manuscript. We do appreciate the many useful suggestions and will certainly consider them in the context of the next analyses and a subsequent manuscript.