Author's response to reviews

Title: Efficacy of Two Once-Daily Methylphenidate Formulations Compared Across Dose Levels at Different Times of the Day: Preliminary Indications from a Secondary Analysis of the COMACS Study Data

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Author's response to reviews: see over
Re: Efficacy of Two Once-Daily Methylphenidate Formulations Compared Across Dose Levels at Different Times of the Day: Preliminary Indications from a Secondary Analysis of the COMACS Study Data
[manuscript ID # 1409676503377467]

To the Editor:

On behalf Drs. Sonuga-Barke, Swanson, Coghill and Hatch, I am pleased to resubmit to BMC Psychiatry the above manuscript. We have made changes to the manuscript as requested by the reviewers, and these are outlined in the table below. Please note that Dr. Roeyers’ and Banaschewski’s comments were considered discretionary. Also, our response to Dr. Wilson and Springer’s comments were based on Matt Hodgkinson’s summary/interpretation of their comments.

As mentioned in the original submission, all research was the responsibility of the authors, who have participated in the concept and design, analysis and/or interpretation of data, and/or drafting or revising of the manuscripts and approved the manuscript as submitted.

We hope that you find the revised manuscript worthy of publication in your journal.

Sincerely,

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<table>
<thead>
<tr>
<th>Reviewer Comment</th>
<th>Response/Action taken</th>
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<tbody>
<tr>
<td><strong>Dr. Herbert Roeyers</strong></td>
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<tr>
<td>1. p. 7 second paragraph: Is this speculation on the part of the authors? Or is there research to support this statement?</td>
<td>This is speculation on our part. We have modified the sentence to reflect this fact.</td>
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<tr>
<td>2. p.11, bottom: Can the authors explain in more detail why they combined the Attention and Deportment Scales of the SKAMP?</td>
<td>Since the pattern of effects are generally the same (highly correlated), we combined Attention and Deportment scores primarily for ease of presentation. We modified the text slightly on the bottom of page 11/top of page 12 to clarify. Please note that total SKAMP scores were consistent with the results presented in the original paper by Swanson et al.</td>
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<td>3. p.12: The authors should mention here that the placebo response for the same time period is the covariate</td>
<td>We believe some confusion arose due to the fact that the Abstract indicated that the placebo response for the same time period was used as the covariate, yet the Methods section indicated that the children’s active drug SKAMP scores were adjusted to take account of their behavior on placebo using a weighted combined SKAMP score for all observation periods. The text in the Abstract was incorrect and we have modified the text therein to be in line with the Methods section of the manuscript. We have modified the text in the Discussion on the bottom of page 17 as well to indicate that we used a placebo response across all time periods as the covariate.</td>
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<td>4. p 13. line 2; typo: effects</td>
<td>Done</td>
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<td><strong>Dr. Tobias Banaschewski</strong></td>
<td></td>
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<td>1. The placebo superiority immediately after dosing should be explained in this paper, as well.</td>
<td>We do not feel that a discussion of the placebo response immediately after dosing is critical to this paper. We have added a sentence in the Results section directing the reader to Swanson et al/ for a full discussion of the potential reasons behind this observation.</td>
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<td>2. The number of subjects in each condition should be mentioned.</td>
<td>The number of patients included in each analysis was added to the Results section.</td>
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<td>3. Effect sizes of the differences at time points should be given. I agree that the reader might calculate those from the results in Table 2</td>
<td>Since, as indicated by the reviewer, the reader might calculate these from Table 2, no changes were made.</td>
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<tr>
<td>4. For the statistical analysis, a weighted combined SKAMP score determined by PCA over all observation points was used. It might be helpful to state which SKAMP scores loaded to which degree on this score</td>
<td>We have modified page 12 to indicate that the weighting used was “similar for each observation period”.</td>
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</table>

**Drs John T. Wilson and Margaret Springer**

1. "We would add that plasma levels of MPH should be assessed and the appropriate PK/PD model developed from the population under study. Random assignment and plasma level data would substantiate (or not) concepts advocated by Swanson et. al. 2004 and by Sonuga-Barke et. al."

   **Matt Hodgkinson**: This revision should be to the Discussion section of the manuscript.

   We acknowledge that plasma levels were not determined in children and have modified the text throughout the manuscript to reflect the fact that the plasma concentration vs. time data alluded to was generated in adults. However, we have added information to the Introduction section of the manuscript indicating that plasma profiles have been reported to be qualitatively similar between adults and children and that the children plasma concentration vs. time profile for Metadate CD is similar to that obtained in adults. Please see page 6 of the manuscript.

   We agree that random assignment and plasma level data would substantiate the initial COMACS study conclusions and this post hoc analysis and have indicated so in the Discussion just prior to Conclusion. Please see page 19.

2. "The Methods section of the paper is a synopsis of the description by Swanson et al 2004, and is subject to the study design limitations already discussed. (Extensive review of statistical concepts and programs requires attention of an expert statistician.)"

   **Matt Hodgkinson**: You should consult a statistician to confirm the use of statistics within the manuscript.

   Please note that we have consulted additional statisticians who have confirmed that the methodology used was appropriate. No change was made to the manuscript.
3. "Greater efficacy for the mid and high dose CON (36 and 54 mg) at 7.5 hr and 7.5 and 12 hr, respectively, is deemed expected on the basis of PK profiles. This comment is difficult to interpret since no plasma levels were done, and since, according to Table 1, the amount of ER MPH is similar for CON and MCD."

**Matt Hodgkinson:** You should consider revising this prediction.

| As indicated above for Comment #1 we acknowledge that plasma levels were not obtained in children in the COMACS study. We altered the relevant text to reflect that this comment was based on expected plasma concentration vs time profiles in children. A discussion of how differences in dissolution of the ER MPH in the formulations makes MCD more front-loaded and CON more back-loaded is provided in the paragraph before this text thereby providing an additional background for this comment. |

4. "A prediction that appeared in Figure 1 was that low and mid doses of CON gave effects equivalent to mid and high doses of MCD at 12 hr post dose. Early period enhanced efficacy of MCD at these doses appears consistent with a higher IR MPH component for this formulation. The authors should again consult Figure 1 in the paper by Gonzales et al 2002 for the MPH plasma level profile from MCD and CON as such data impact bioavailability and time course release characteristics for the formulations."

**Matt Hodgkinson:** Please check the article by Gonzales et al 2002 again.

| No change made. Both Dr. Hatch and Dr. DeCory are co-authors of the Gonzalez manuscript and are aware of how the formulation characteristics of Metadate CD and Concerta affect the bioavailability and time course release characteristics of Metadate CD and Concerta. Please see page 6 of the Introduction and page 16 of the Discussion for a description of these differences. |

5. "A problem with descriptions throughout the paper is use of the term "PK" when dose or dissolution characteristics are the parameters in question. Plasma levels of MPH and a PK profile were not determined in these children. A lack of such data, it would seem, leads to difficulty with interpretation of unfulfilled predictions." Please avoid referring to plasma levels of MPH or PK profiles when they have not been determined. Discuss the predictions with care in light of the fact that plasma levels were not determined.

| Again, we acknowledge that the PK data referred to in the manuscript was obtained in adults. We have revised the manuscript to ensure that when we mention PK profiles in reference to the COMACS PD data, that these are “predicted” or “expected” profiles. In addition, as mentioned above, we have added text to the Discussion prior to the Conclusion indicating that a study with random assignment and plasma level data would substantiate the initial COMACS study conclusions as well as this post-hoc analysis. |
6. "It is important that care be exercised in extrapolation of adult data to children, application of theoretical PK/PD models, estimation of drug bioavailability without plasma level-time course profiles in the subject population, formulation dissolution characteristics or metabolic clearance that may be affected by dose, and for assumptions about response-concentration relationships in those with different severity of illness."

Please see comments #1, #3, #5.


Also, plasma concentration vs. time curves generated in children for Metadate CD were generated in children with ADHD and are similar to those generated in healthy adults (see Metadate CD package insert or Wigal, Sanchez, DeCory, D'Imperio, Swanson.  *J Appl Res* 2003, 3(1):1-18).

Finally, the PD data obtained in the COMACS study suggests a close correlation between expected/predicted plasma concentration vs. time profiles and efficacy, thus indirectly validating the extrapolations made. We have added text to the Discussion section indicating that a study with random assignment and plasma level data is needed to further validate the initial COMACS study as well as this ensuing post-hoc analysis.