Author's response to reviews

Title: Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: A randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety

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Author's response to reviews:

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Re: MS: 1093242025361773
Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: A randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety by Alan G Wade, Ian Ford, Gordon M Crawford, Alex McConnachie, Tali Nir, Moshe Laudon and Nava Zisapel

Dear Mr. Aulakh

Thank you for your message dated 24 June 2010 concerning our paper. We noticed that all referees found the study to be of substantial importance and are satisfied with the merit, quality and presentation of the results.

One reviewer (Mayer) still has a single outstanding concern that is related to the interpretation of the results, criticizing our stringent definition of the age cut off for
patients who are likely to respond to PRM and utility of 6SMT measurements.

We actually agree with the reviewer that the age cutoff for patients >65 years used for the primary analysis in this study, does not preclude response to PRM in younger patients. Rather, there is sufficient evidence in previous studies [21-25] for an equal or greater response to PRM in patients aged 55 and older. The age cutoff for response to PRM should thus be further explored.

Having said that, the efficacy results presented here are those obtained in the primary preplanned analysis of the study and therefore the results and discussion had to be focused on this age group. We also explain why single measurements of 6SMT, due to marked inter-individual variability are not useful to predict response.

We have addressed the reviewer’s concern in the Response to Reviewers and revised the Abstract, Discussion and Conclusion sections accordingly. We hope that the paper will be accepted to BMC Medicine in its present form.

Sincerely

Alan G Wade
Reviewer: Geert Mayer

All major points of the review have been addressed properly except for point 4 (age difference between groups). The explanation is not very satisfactory. Even though the difference of the means of age is 7 years the conclusion of the study, that the compound is effective for patients >65 years needs to be explained. In my opinion the arguments for this cut-off are not sufficient. This point needs special consideration as one might argue that younger low excretors are underrepresented and due to the study results may not have access to the compound, which they might benefit from.

We agree that the age cutoff for patients >65 years used for the primary analysis in this study, does not preclude response to PRM in younger patients. Rather, there is sufficient evidence in previous studies [21-25] for an equal or greater response to PRM in patients aged 55 and older. Having said that, the efficacy results presented here are those obtained in the primary preplanned analysis of the study and therefore the results and discussion had to be focused on this age group. The age cutoff for response to PRM should be further explored.

We thus believe that our conclusion that low melatonin production regardless of age is not useful to predict response to PRM in insomnia is well substantiated in this study. The sample size of the low melatonin group, although less than originally planned was large enough to reach 86% power, which is well within the acceptable range in clinical trials. However, between patient melatonin levels vary widely. There is also evidence that regardless of initial levels, there is a
reduction in melatonin levels with age. Thus the strong finding of age related efficacy may reflect within patient reduction in melatonin levels which is masked in the younger age groups by the wide variability in normal levels.

We have now revised the Abstract, Discussion and Conclusion sections accordingly, to clarify that the age cut off used for the primary analysis does not preclude response in younger patients and further explain why in our opinion the 6SMT measurements are not useful in the case of insomnia.