Author's response to reviews

Title: Efficacy and safety of olanzapine for treatment of patients with bipolar depression: Japanese subpopulation analysis of a randomized, double-blind, placebo-controlled study

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Author's response to reviews: see over
Dear Mr. Chua:

Thank you for the review and comments on the manuscript MS: 1456915597806235, entitled “Efficacy and safety of olanzapine for treatment of patients with bipolar depression: Japanese subpopulation analysis of a randomized, double-blind, placebo-controlled study”. We have revised the manuscript according to the reviewer’s recommendations and included a point-by-point explanation of the changes that were made (below). We feel that these changes have resulted in an improved submission.

Thank you for considering our revised manuscript for publication in BMC Psychiatry. Should you have further questions, do not hesitate to contact me.

Kind regards,

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Reviewer #1

Major Compulsory Revisions
Introduction
(1) The rationale of this additional analysis seems weak, which should be further emphasized. Otherwise, this would be regarded as another boring post-hoc analysis paper.

The rationale for this analysis has been strengthened and reads as follows (pages 6-7):

Prior to 2012, there were no medication options with well-established evidence approved in Japan for treatment of bipolar depression. Though compelling data existed for treatment of bipolar depression in Western populations, it was unclear whether these findings would hold true for a cohort of Japanese patients. The olanzapine monotherapy trial described above included a large cohort of Japanese patients and, to our knowledge, was the first double-blind, placebo-
controlled trial to do so. Based on the results of this trial, Japan became the first country in the world to approve olanzapine monotherapy for treatment of bipolar depression. Though olanzapine monotherapy has been used for the treatment of this condition in Japan, limited data have been published. Therefore, we analyzed efficacy and safety data from Japanese patients who were enrolled in the larger study described above, so that clinicians who care for Japanese patients will have a more comprehensive understanding of its treatment profile in this population.

Methods:
(2) Mention to MMRM should be included here.

In the statistics section, the following change has been made (page 10):

As a sensitivity analysis, observed-case ANOVA and mixed-effects model repeated measures (MMRM) were used to assess changes in MADRS total score.

Discussion:
(3) The paragraph that begins with “Of note,” is not necessary. This is not based on the results of this study.

The paragraph that the reviewer has identified has been removed.

(4) Statistically significant differences in outcome measures were found between OLZ and PLB; however, the differences are numerically minor. Please fairly discuss clinical relevance of those statistically significant but minor differences.

New text regarding this point has been added as the 3rd paragraph of the Discussion (page 16) and reads as follows:

Although statistically significant differences in outcome measures were found between olanzapine and placebo, the differences were numerically small. In addition, the effect size demonstrated by olanzapine monotherapy in this population was modest. Although this could be indicative of a modest effect of the active drug, it may also have been influenced by a relatively strong placebo response. Increased placebo response is a phenomenon which has been noted in different areas of psychopharmacology in recent years.25,26 Also, it is important to appreciate that bipolar disorder is particularly difficult to manage, and very few treatments have regulatory approval for treatment of bipolar depression. Therefore, even a modest effect size may be of clinical relevance to patients, although treatment-emergent adverse events need to be taken into consideration as well.

(5) The paragraph that begins with “The results in the Japanese population...” should be removed. This is not based on the results of this study.

The paragraph that the reviewer has identified has been removed.

Reviewer #2

The authors reported the efficacy and tolerability of olanzapine in the treatment in
Japanese patients with bipolar depression. This manuscript was written well and I have no more comment to the authors. That’s all. Thank you very much.

Comments from the Editor:

1. Name of the ethics board that approved the study

Please document within the methods section of your manuscript the specific name of the organization that granted ethical approval to your study going ahead.

Ethics: Research involving human subjects (including human material or human data) that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html). A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

The protocol was approved at multiple individual study sites. The statement regarding ethical approval of the study protocol has been amended as shown below (page 8), and a list of protocol approval sites has been added at the end of the manuscript (page 19).

The study was approved by the relevant institutional ethics committee at each center and was conducted in compliance with the Declaration of Helsinki. Names of the specific review boards can be found in the Ethics Approval section at the end of this manuscript.

Ethics Approvals

Ethics committees at the following sites provided ethical approval for the study:
Institutional Review Board Yamaguchi University Hospital; Aino Clinic Institutional Review Board; Suzuki Internal & Circulatory Medical Clinic IRB; Himorogi Psychiatric Institute Institutional Review Board; Medical Corporation Cattleyakai Dr. Mano Medical Clinic Institutional Review Board; Kawaguchi Clinic Institutional Review Board; Medical Corporation Seikokai New Medical Research System Clinic Institutional Review Board; Institutional Review Board of CNS Yakurikenkyukai; Seimou Hospital Institutional Review Board; The Institutional Review Board, the University of Tokyo Hospital; Institutional review board of Nippon Medical School Hospital; Aichi Medical Association Institutional Review Board; Institutional Review Board of Fujita Health University Hospital; Institutional Review Board, Nippon Medical School Chiba Hokusoh Hospital; Mitsui Memorial Hospital Institutional Review Board; Japanese Red Cross Medical Center Institutional Review Board; and the Institutional Review Board of Ome Municipal General Hospital.

2. Copyediting:
After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.

We advise you to seek the assistance of a fluent English speaking colleague, or to have a professional
editing service correct your language. Please ensure that particular attention is paid to the abstract.

For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/info/authors/authorfaqs#12

The manuscript has been reviewed by a native English-speaker and adjustments have been made throughout.