Author’s response to reviews

Title: Antiviral Treatment Perspective against Borna disease virus 1 infection in Major Depression: A Double-Blind Placebo-Controlled Randomized Clinical Trial

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Author’s response to reviews:

Authors’ response to statistical reviewer 3:

At first, the authors would like to thank statistical reviewer 3 for his favourable general comments, reviewing the study as well-designed, well analysed including statistics, and well-written.

Secondly, we are particularly grateful for his questions which include very useful suggestions and comments to further improve the manuscript.

Point-by-point consideration (in the order they have been mentioned):

1. Original line 154-155, change to dose up to 300 mg during follow-up

We agree, this should be explained. With respect to the length of the post-trial optional treatment offer of 12 months, the amantadine dose needed an individual adjustment to 2-4 mg daily per kilogram (kg) body weight (BW). In practice, patients between 50 kg and 75 kg BW could stay with amantadine doses of 100-200 mg daily, but patients with more than 75 kg BW were offered to switch to 150-300 mg daily.

Revised manuscript, methods: We inserted a paragraph under “Patients” explaining this point (new lines 157-160).
2. Original line 221, Antigen definition, CAG, PAG

We agree, the term CAG has not been defined properly. CAG stands for antigens extracted from PBMCs. In contrast to PBMCs, blood plasma is the by far dominating source for BDV-1 antigens. Therefore, final statistical evaluations on antigen values only considered plasma antigen (PAG).

Revised manuscript, methods: For better clarity, we omitted the term CAG under “Detection methods” (new lines 222-223).

3. Original line 298: SPSS software version

Revised manuscript, methods: We inserted the version, finally used to complete statistics at the end of “Statistical analysis” (new lines 301-302).

4. Original line 745: Abbreviations

Revised manuscript, abbreviations: The abbreviation now reads “AB, antibodies;” (new line 768). The now omitted term “BDV” was superfluous, indeed.

5. Cross-over design and patients’ information.

Yes, the patients were kept informed of all study details of which the cross-over design was an important part. Cross-over guaranteed that all patients eventually received amantadine, regardless of which group the patients have been randomly assigned to.

Revised manuscript, methods: For improved clarity, we inserted a sentence under “Study design” emphasizing that cross-over was a legitimate ethical request in view of previously beneficial open trials (new lines 133-134). Under “Patients” we included a sentence that patients were informed on cross-over (new line 141).


7. Additional Table with separated amantadine and placebo groups, Period II
Both comments touched related issues and were answered together. We are particularly grateful to reviewer 3 for requesting more information on whether and to which extent amantadine treatment in Period I would impact on the placebo treatment in Period II. We agree completely that addressing this issue associated with cross-over would fill a gap and would improve the manuscript.

Detailed analysis of individual responders of either groups in each period revealed that amantadine treatment in Period I had an unexpectedly strong impact on the placebo effect in Period II. Of amantadine responders in Period I, 69.2% (9/13) maintained response in placebo Period II. Thus, with respect to the whole Group A, even 80% (12/15) were responders after cross-over at week 14. This was double as high as the primary placebo response of Group P in Period I (35.3%).

We agree that a possible carry-over effect could be expected to be related to amantadine (point 6). However, the magnitude of doubled placebo responders after cross-over could be more likely explained by sustained anti-depressive and antiviral efficacy of amantadine rather than by carry-over effects. Thus, the question 6 and 7 raised by reviewer 3 added support to the sustainability argumentation in the manuscript.

The cross-over design could also confirm that the placebo patients of Period I (Group P) responded significantly different to amantadine in Period II (35.3% vs. 68.8%), and even reached 92.9% response after 12 months post-study optional treatment.

The requested additional Table and above issues were inserted and discussed in the revised manuscript as indicated below.

Revised manuscript, different sections:

The new Table has been added in the revised manuscript as Additional file 3: Table S1. Overall clinical response. The following Additional files were renumbered accordingly (new lines 760-765) and this corrected throughout the text.

In Results, under “Clinical outcomes”, the paragraph describing response rates of all patients in Period II were completed with data of the Follow-up period (new lines 328-331). Afterwards, the findings related to the new Table S1 were described in a new paragraph (new lines 332-340). In Discussion, under “Clinical outcomes”, a new paragraph related to Table S1 was also inserted (new lines 579-586), and a sentence at the end of the discussion section (new lines 721-723).

In context of Table S1 and more clarity, the Consort flow chart of patients and periods (Fig. 2) has been considerably improved (new lines 1065-1072). The description related to the Consort flow chart was extended under Methods (new lines 151-152 and 154-157). The number of patients completing the post-study 12 months period were n=28 instead of 29. This has been corrected throughout the study, including Fig. 1 (new lines 1057-1064).
Authors’ remarks to the Editor:

Dear Dr. Sridhar,

We appreciated the thorough review of statistical reviewer 3 who addressed some details worthy of more in-depth consideration, indeed. The most helpful comment was requesting an additional Table providing more information on whether and to which extent amantadine treatment in Period I would impact the clinical response on the placebo treatment in Period II. This issue touched the cross-over design of the study which has already been raised by reviewer 2. In revision 2 of the manuscript, the ethical reason requesting cross-over have explained but also drawbacks due to possible carry-over effects which had excluded in-depth statistical analysis of Period II.

However, the request of reviewer 3 of an additional Table showing the clinical response of each period at the level of individual patients could really provide valuable information beyond in-depth statistics. We included the new Table as Additional file 3: Table S1. Data analysis revealed that amantadine in Period I had an unexpectedly strong impact on the placebo Period II in that the response was doubling the placebo response in Period I. This led to further strengthening the sustainability issue of amantadine in our study.

In our point-by-point response to Reviewer 3, please find our explanations and corresponding changes in the manuscript (revision 3) (lines indicated).

We believe the third revision of our manuscript could benefit from the very helpful comments of reviewer 3.

We acknowledge the fair and effective review process up to now, provided by all reviewers and the former editor in charge of our manuscript. This allowed us to clearly improve the manuscript up to the present third revision.

We like to thank you very much for your assistance and hope to receive a favourable answer soon.

Yours sincerely,

Prof. Detlef E. Dietrich, corresponding author,
Dr. Liv Bode, co-corresponding author