**THELANCETPSYCH-D-17-00232**

**Manuscript Number: THELANCETPSYCH-D-17-00232**

**Title: Treatment of Bipolar Depression with Minocycline and/or Aspirin: An adaptive, 2 X 2 double-blind, randomized, placebo-controlled clinical trial**

Clinically relevant clinical trial exploring the individual and combined effects of 7-week treatments with aspirine (A) and minocycline (M) on depressive symptoms and remission rates. The authors initially randomly assigned participants to 4 groups (AM, AP, MP, PP) and, based on an adaptive study design approach, further on dropped MP and AP from enrollment. The outcome measures were treatment response and remission rates (based on MADRS scores). They also collected inflammatory measure prior and following treatment. The primary finding was that administration of A+M has anti-depressant and pro-remission effects compared to PP. There was a main effect of A and responders with high baseline IL6 levels responded better to M than those with lower levels. The topic of this manuscript is clinically relevant and is one of the few successfully managing to tackle the long-standing and never really confirmed “inflammatory hypothesis” in bipolar disorder. The rationale is sound, data collection and study design are appropriate, and the authors used accurate statistical tools and analyses to address recruitment and missing data issues, as well as reduced sample size. I have a few comments regarding data visualization and would like the authors to provide some clarification regarding some of the statistical analyses.

-Statistical analyses. Please explain what exactly you did to address the AIC score requirements and add references. Also please thoroughly describe your analysis of deviance test, LME, and clarify why you included subject IDs and autoregressive covariance as a random effect. Is this to control for interindividual differences? Did you check the distribution of variables, multicollinearity, and independence of errors? How did you correct for potential multiple comparisons, what was your statistical threshold? Did you use other correction methods such as permutations or used sampling distribution? Please provide appropriate references for R.

-please provide some explanation for selecting the suggested score cutoffs for remission and treatment response and make sure to define in your abstract what treatment response refer to. Also please remind the reader as why you chose to look at depression/ MADRS scores only.

-what were the ingredients of the placebo treatments and how did you test compliance for M? I can only see a reference to compliance for A (in terms of urine tests).

-overall improve and/or provide adequate captions for all figures. The rule of thumb for captions is that they should be “standalone objects” and would provide sufficient information to the reader so that they don’t have to refer to the text.

-Table 2. Please consider transposing columns/rows so that, for instance, you would have a row for MP listing V2 to V7, and provide F, p values. It would much easier to read and compare changes across groups. Add asterisks to highlight significance. Please explain acronyms.

Supplementary table. Please provide F, p values and effect size. Can you please define what the nervous and respiratory disorders refer to? Were they significantly different? Please be consistent with labels (you used M and A so far, now you use Mino and Aspirin.

-Figure 1 (CONSORT). Please add reasons for excluding the initial 102 pts and pts from analyses

-Figure 2. Please provide better labels for X and Y axis (e.g. Percent Response should specify that it was for the MADRS). Consider using \* or # for significance instead of providing OR, p etc. Overall values related to OR, X2 etc. should be included in a table (I would recommend the authors to do so).

-Figure 3. Please choose adequate and easy to read patterns that print well in black and white. Also please consider changing or clarifying what the label “baseline log IL-6” refers to. Explain what a responder is. And please explain what does the diamond figure in Figure 3 refer to? Please consider using \* or # to highlight the significance in differences between Responders to MP instead of having all the parameters in the figure. These could be provided in a separate table or be described in the caption.

Figure S2 explain acronyms (e.g. TXB)

Figure S3. Highlight relevant findings in the figure (e.g. arrow etc.). As is the figure does not print well in black and white and is not easy to interpret. For instance you can state in your caption what the take-home message is.

Figure 4. I am not sure what median reduction in MADRS score refers to, are there significant differences?

Minor details

-I would add a sentence explicitly stating that minocycline has been used exert a variety of biological actions that are independent of their anti-microbial activity, such as anti-inflammatory and anti-apoptotic activities, and inhibition of proteolysis, angiogenesis and tumour metastasis etc.

-I would state somewhere that M and A cross the BBB. This would strengthen the importance of using it in BD and would make it more understandable to health professionals unfamiliar with this kind of literature