Author's response to reviews

Title: Rationale and design of the randomised clinical trial comparing early medication change (EMC) strategy with treatment as usual (TAU) in patients with Major Depressive Disorder - the EMC trial

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Version: 2 Date: 18 February 2010

Author's response to reviews: see over
Dear Editors-in-Chief,

Please find attached our revised Ms. 1845477624325058 by Tadić et al. We are grateful to your decision and to the reviewer for his recommendations. According to your decision we have improved and revised our manuscript according to the reviewer’s comments. In detail, we have dealt as follows with the reviewer’s comments (changes in the revised MS are given in italics and underlined):

Comment 1: The submitted protocol is generally clear and well written. However, it would benefit from clarification in a number of areas:

A) The trial participants are described as hospitalised at recruitment. Does this mean inpatient? In the UK that would mean only the most severely ill. Or outpatient? Care systems for depression vary greatly across Europe and expansion in the description of pathways to care and case mix in the trial will aid interpretation.

Reply: Indeed, the term “hospitalised at recruitment” means inpatient.

Action taken: According to the reviewer’s suggestion we expanded the description of pathways to care and case mix in the trial in the revised manuscript (p.8, lines 7ff.).

B) The randomisation is not stratified by severity of symptoms (or duration). Given the influence of severity on AD response this decision should be explained.

Reply: The very close relation between early non-improvement and final treatment failure during antidepressant treatment has been identified in several clinical studies covering a broad range of severities and durations of depression. We identified the same relation in patients with mild major, minor or subsyndromal depression (Tadić et al. J Affect Disord. 2010; 120: 86-93). Taken together, the currently available data support the idea that early non-improvement is a general marker of inefficacy of antidepressant treatment and that this very close relation between early non-improvement and final failure of treatment response exists independently of severity or duration of depression. Therefore, randomisation is not stratified by severity of symptoms or duration.
Action taken: According to the reviewer’s suggestion, we explain this decision in the revised manuscript (p.10, lines 2ff.).

C) It appears from my reading (is this correct) that adverse events and severe adverse events will not be sought by routine standardised inquiry - only that those identified by study psychiatrists will be recorded on a standardised format. There is no mention of recording of episodes of self harm, attempted or completed suicide.

Reply: AEs will be assessed by the investigator in weekly intervals (please, see also figure 2 of the manuscript). Additionally, inpatients will receive daily clinical visits by the ward physician; in case of a new symptom the investigator will be contacted in order to decide whether the new symptom fulfils the criteria of an AE, SAE, SAR or SUSAR. All AEs (whether serious or non-serious) reported by the subject or detected by the investigator will be documented on the “Adverse Event” pages of the CRF and in the subject’s medical record. If the adverse event is serious (see below), the investigator must complete, in addition to the “Adverse Event” page, a “Serious Adverse Event” form in the ISF at the time the SAE is detected. This form must be immediately sent to responsible SAE Management of the independent Interdisciplinary Centre for Clinical Trials (IZKS) at the University Medical Center Mainz. The occurrence of episodes of self harm, attempted or completed suicides are comprised by the definition of SAE; therefore, they will be recorded in each case; additionally, they will be reported to the coordinating investigator and the Data and Safety Monitoring Committee (DSMC).

Action taken: In the revised manuscript, we restructured and expanded the passage on the procedures of assessment and documentation of adverse events (p. 12f.) in order to clarify the procedures during the EMC trial.

D) The section on analysis of primary endpoint (top P.14) is unclear. Will missing data in the ITT be replaced with LRCF? And how will classifying patients with all missing data as non-responders be dealt with if the researchers are wrong and data are not missing at random? Why are other more rigorous approaches to missing data, such as multiple imputation, not being considered?

Reply: The reviewer is right, in the primary analysis HAMD17 sum scores will be carried forward from day 28 on (please, see p.14, line 4f. of the original MS or p15, line 24f in the revised MS). Patients with no HAMD score available between day 28 and 56 will be classified as non-remitters; this approach is rather conservative but, in our opinion, justified because all of these patients are non-improvers at week 2 and it is more likely that these patients would have become final non-remitters after being non-improver at week 2.

There are quite a few methods for multiple imputation available. The choice of the appropriate method depends on several factors including the missing value pattern. Here, we prefer a method for replacing missing data that can be unambiguously specified in advance, which is essential in confirmatory trials. Nevertheless, we will incorporate an analysis imputing missing values multiply as a further sensitivity analysis.

Action taken: We added these explanations to the revised version of the manuscript (p. 15, lines 26ff.).

Comment 2: The discussion is largely taken up with a repetition of the points made in the background. I would have liked to see some consideration of a number of design issues.
A) The advantages and disadvantages of other designs, such as randomising all participants to TAU programme vs. programme where EMC is a protocol option rather than only randomising early non-responders.
B) The disadvantage of primary outcome being at only 56 days given what we know about the later course of depression.
C) The absence of an integrated economic analysis, especially given claims made in the protocol for the economic importance of the findings from the trial.

Reply: We are grateful to the reviewer for these comments. Action taken: According to his recommendation we now discuss the advantages of the design of the EMC trial compared to other designs (p. 18, lines 23ff.), the disadvantages and advantages of the primary outcome at 56 days (p. 18, lines 36ff.), as well as the absence of a comprehensive integrated economic analysis (p19., lines 38 ff.).

We again wish to thank the reviewer for his helpful comments and we hope that you will find our revised manuscript now fully suitable for publication.

With best regards,

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