Reviewer’s report

Title: Design Considerations and Analysis Planning of a Phase 2a Proof of Concept Study in Rheumatoid Arthritis in the presence of possible non-monotonicity

Version: 0 Date: 21 Apr 2017

Reviewer: Joseph Koopmeiners

Reviewer's report:

Review of Manuscript ID: BMRM-D-17-00093

Title: Bayesian NDLM model and Emax model of Design Consideration of a Phase 2a Proof of Concept Study in Rheumatoid Arthritis

I would like to thank the authors for the opportunity to review a revised version of their manuscript. The authors were responsive to my previous comments, which resulted in a dramatic improvement over the initial submission. I do, though, have a few remaining comments that I hope will add clarity throughout the manuscript.

Specific Comments:

1. I appreciated the authors thorough response to my initial comments about the type-I error rate and appreciate their concerns about calibrating the various designs to achieve the same type-I error rate, in all cases. That said, I think there are some additional summaries to further answer my questions that would not take substantially more work. Specifically, for the fixed design, could the authors summarize the type-I error rate (i.e. probability of rejecting for the placebo case) and power by an ROC curve? That is, for each of the three alternative scenarios, you could create an ROC curve by varying the threshold (currently fixed at 95%; should be varied from 0 to 100) for concluding success and presenting the type-I error rate and power for all thresholds. This would allow for a fair comparison of power without the need for recalibrating each design.

2. Can you add the DIC values from your response to the manuscript (response to my previous comment 14)?

3. Can you add the justification for the prior means for beta_2 and beta_3 to the manuscript (response to my previous comment 8)?

4. Lines 212 to 215 - please provide the exact priors used for these parameters.
5. The first three paragraphs of the Section title "Retrospective analysis using NDLM" repeat a lot of information and could be condensed. Also, you should presumably reference Figure 1 at some point in this section as it presents the estimated NDLM model.

6. Throughout the manuscript, you make reference to the Emax model not fitting correctly. Could the authors provide further explanation for why this would be the case? You're still using proper (albeit vague) priors for all model parameters - shouldn't you get a proper posterior?

7. Please double check the title of the manuscript - it seems that there might be a typo or some words missing.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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