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: 31 Mar 2017

Reviewer: Michael Smith

Reviewer's report:

Thanks to the authors for addressing my earlier review points - these have been adequately addressed.

However I feel that the manuscript would benefit from having a much clearer "story" and a stronger focus. It seems to me that the aim of the manuscript is to find an efficient design and prospectively define an analysis method in the presence of possible non-monotonicity of dose-response (for GSK-654321). The results of the analysis of the GSK-123456 PoC study are only relevant since non-monotonicity was found in this study. I'd suggest quite strong editing / combining of the background and motivating study sections to make it clear that non-monotonicity is being considered a problem due to the GSK-123456 and the fact that other TNF-alpha treatments have seen similar non-monotonicity. The main question is then how to design and prospectively plan analysis when this may also be seen in the follow-on compound. The trade offs in terms of Type I error and power between methods (NDLM, Emax) are then heavily influenced by the a priori belief in whether there will be non-monotonicity in the next study. It is then of interest to show readers the process of planning and evaluation of operating characteristics under different designs, analysis methods, decision criteria etc. This would make the manuscript more concise and more focussed and help the reader understand the various options being investigated and the decision process behind choosing the solution in the end.

I have made various comments via tracked changes on the Word document attached.

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

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