Reviewer’s report

Title: Evaluation of neurological changes in secondary progressive multiple sclerosis patients treated with immune modulator MIS416: Results from a Feasibility Study

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Reviewer: Anna-Marie Jones

Reviewer's report:

My initial understanding of the problem outlined in this paper was that the Expanded Disability Status Scale (EDSS) was not very sensitive to change for people with severe secondary progressive multiple sclerosis and so the authors were investigating using a new measure that they hope to be introduced in the literature as an alternative. They take pre post patient reported outcome scores and performance rated outcomes scores as well as a number of biomarkers. The authors state that they have used the CONSORT to report findings but I found myself having to go backwards and forwards between the methods, results and the tables to work out things like which exact measurements were being used, what they meant by clinical responder status and immunological response. It would help the reader to have all the outcomes and definitions of responder described in the measurements section. The Fatigue Severity Scale is mentioned early on but then is not mentioned again. Then there are different numbers of subgroups from the SF 36 quoted as being of interested: 4 early on but all 8 in the results table. It was good to see MICs reported and that section was clear. This section could also have stated what the 4 (or 8) PROs were too.

With regard to the patient's immunological response profile to MIS416 therapy, they describe that for the analysis they used the maximum-recorded response across all time points abut later on in the results it looks like they used the maximum post scores from time point 1-4 which would make more sense. They talk about normalizing the data but then don't explain how they normalised it.

They describe immune factors/parameters and resemblances between individuals to identify clusters of patients. MDS needs writing in full. I am not clear how the authors define 'immunological response'. For the PROs and the PerFOs it was a 0/1 response but I am not sure if it's a 0/1 for immunological response. Then are they comparing these for the 4 PROs only? a cluster of size n=2 is also very small to draw any conclusions from.
Biomarker levels for patients were then compared across groups according to their clinical responder status where n=5 high, n=3 medium and n=3 low and then an ANOVA was applied. It is not clear where the cut offs for high, medium and low have come from. However, I feel that the group sizes are too small for these analyses.

Some of the detail from line 250 I think describe methodology rather than results.

I find the discussion section unclear also, what are they aiming for? How are they planning to determine what a good response is and what is better than the EDSS score that they started out. Are they claiming that 5 people responding to change on one outcome (EDSS) is worse than 7 people responding to change across 4 Perfos? Have ceiling effects been thought about. How are they deciding that they can proceed to a larger study? They describe including more PROs in the next study, but then how would they choose between them?

It would be helpful to set up criteria of what a new and better outcome should be - they mention sensitivity to change and MIC on some outcomes, but what about on the biomarkers? I think it would be helpful to concentrate on looking at the potential new PROs and describing the level of change and sensitivity in relation to the biomarkers or perfos that are deemed most important and then have clear criteria relating to the process of carrying out this piece of research as well as determining if what they have found means the feasibility is a success or not.

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