Author’s response to reviews

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

Authors:

Gill Webster (gill@innateimmuno.com)

Dalice Sim (dalice.sim@otago.ac.nz)

Anne LaFlamme (Anne.LaFlamme@vuw.ac.nz)

Nancy Mayo (nancy.mayo@mcgill.ca)

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Author’s response to reviews:

A: Page 9. please make the main heading Statistical Analysis and then have subheadings Patient Centered Outcomes and Immunological parameters (or factors).

B: This has been done

A:Page 10. The section on Quantification of plasma MIS416 immune biomarkers analysis should be moved under the measures section before the Statistical Analysis section. In this section please explain the 21 immune factors briefly listing them and explain what units they are measured in (pg/ML). How much increase in plasma levels should be seen for it to be classified as a response? Please specify.

B:This has been done. Additional text has been inserted to clarify why these immune factors were chosen to evaluate the patient immune response. In the following section, Immunological factors, language has been altered to clarify that all the plasma levels measured in the patients were included in the initial analysis to determine the patient immune response clustering patterns. The term immune response does not require that there should be a minimum amount of increase, rather this is an analysis of absolute values including those that may be zero. This accommodates the possibility that some patients may infact not show much, or any increase for a particular factor, which may be important to understanding the extent to which MIS416 treatment impacted on their disease status. Analysis to determine which of the 21 immune factors
drove the immune response pattern clustering highlighted a subset of factors that mainly accounted for this (figure 2). It is clear in figure 2 that all patients showed an increase in plasma levels of these factors, but the extent of the increase varied according to clinical response group.

A: On page 9 in the last paragraph please explain how responder status is defined as high, medium and low (ie. >=3, 2, <=1) with respect to total number of observed responses for each patient. It is defined later in the text but should come here also. Please also explain here how 0/1 responder status is defined (ready for understanding Tables 2 & 3).

Medium responses are referred to as ‘medium’ or ‘mid’ or ‘intermediate’ (page 17, line 338) throughout the text please use the same one term throughout (would suggest medium).

B: This has been done

A: Pages 10-11. Please use the same term to describe immune factors throughout (factors or parameters). Factors seems more appropriate. Please amend text accordingly.

B: This has been done

A: At bottom of page 10 (I,j) should be (i,j). In the equation at the top of page 11, please delete parameters and add 21 (or i=1 to 21) to show summing over 21 immune factors. The ‘W’ should be a small ‘w’ in ‘where’ on line 250. On line 254 ‘immune responses’ rather than ‘parameters’.

B: This has been done


B: The definition of this has been added

A: There are many abbreviations used in the paper and this makes reading not easy. In Table 1 please write in full the 8 abbreviations listed under SF-36. In Tables 2 & 3 please add (RS) in the title so we know what RS means in the table. In Table 3 please write the abbreviations out in full
in the headings (ie PF, GH, VIT, MH). Please right align the numbers presented in the Change and RS columns in Tables 2 & 3.

B: All these changes have been made

A: Page 15 table 4, there is a discrepancy in the table with entry DC12 – it does not conform with the definition of medium as there are 3 responses (should this not be high?). Also why are DC07 and DC12 tied ranks when they have different totals

B: The entry for DC12 was incorrect in this table and has been amended to 2 responses. This did not alter the rank however, since of the four patients showing 2 responses, DC12 still tied with patient DC7 since they both had 2 responses on PerfRO compared to DC9 and DC6 which also had 2 responses, but only 1 or neither of them were on PerfRO for DC9 and DC6 respectively. As stated in the text, priority was given to responses on PerfRO over PRO where there was a tie. Thus DC12 and DC7 cannot be ranked separately.

The list of abbreviations on page 21 is incomplete.

Further abbreviations have been added including those used in the nomenclature of individual immune factors

A: In Figure 2 please ensure all the x-axis abbreviations are explained in the legend also. Eg. 24 Hr PD2.

B: This has been done

A: In the discussion one limitation is the small numbers for the statistical analysis using ANOVA. Please add a caveat that the results using p-values should be treated with caution due to small sample size

B: This has been done