Author’s response to reviews

Title: Effect of Peginterferon Beta-1a on MRI Measures and Achieving No Evidence of Disease Activity: Results from a Randomized Controlled Trial in Relapsing-Remitting Multiple Sclerosis

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Author’s response to reviews: see over
Dear Dr. Bagnato,

RE: MS: 4781146371346737

Manuscript Title: Effect of Peginterferon Beta-1a on MRI Measures and Achieving No Evidence of Disease Activity: Results from a Randomized Controlled Trial in Relapsing-Remitting Multiple Sclerosis

Thank you for providing feedback on our manuscript. Please find below our responses to the reviewers’ comments. Please let us know if you require any further details or additional information.

Please also note that in our review, we made two editorial changes:

1. Freedom from Measured Disease Activity (FMDA) has been changed to No Evidence of Disease Activity (NEDA) throughout the text
2. Q2W and Q4W have been changed to “every two weeks” and “every 4 weeks” respectively throughout the text
3. The Authors’ Contributions section was streamlined to state in the first sentence that all authors were involved in revising the manuscript.

Responses to Reviewers’ comments

Reviewer 1 – R Naismith

1. In the introduction, authors mention FMDA may permit comparison across trials. I would remove this, FMDA is largely driven by MRI, which varies by baseline characteristics and analysis center. I’m not sure why creating ORs is more valid for cross-trial comparisons that are absolute numbers, as was listed in the discussion.

Response: Thank you for your feedback. The reason that Odds Ratios (ORs) are presented in the manuscript is to provide an alternative comparison across trials, rather than only focusing the absolute percentage of NEDA. This is because ORs also take into account the placebo effect (it is the ratio between the active treatment and the placebo arm from the same study).

Due to the potential patient population difference between studies, we believe that it is prudent to present results as absolute results of NEDA alongside ORs to account for this placebo effect.

2. There are many graphs that are demonstrating the essential same effects. The authors should select the key graphs for the manuscript and make the remainder as online-only graphs. Figure 2 can be online, Figure 1d is adding little additional information to figure
1a. Figure 4 and 5 can be online only.

Response: We understand your perspective regarding the information displayed in Figure 1d and Figure 2. Accordingly, we have moved Fig.1d to ‘additional file 1’ and we have converted Figure 2 to a table (Table 2). Furthermore, in line with your suggestion, we agree that Figures 4 and 5 convey similar information to Figure 3, hence we have changed Figures 4 and 5 to ‘additional files 2 and 3’ (respectively). We hope these changes are suitable.

3. It is a little confusing to see MRI endpoints and FMDA at 48 weeks for placebo, since placebo was only used for the first year only. I would include a graph of the study design and highlight what the 48 week placebo endpoints represent in the graphs.

Response: The current study examines the effects of peginterferon vs placebo for year 1 only (baseline to 48 weeks) of the ADVANCE study. Previous publications have figuratively illustrated the study design. However, in order to improve the clarity, we have modified the text. We hope that this meets with your expectations.

All figure numbers have been changed accordingly

Reviewer 2 – HP Hartung

1. The authors should mention in the figure legends that the depicted 48 week data on T2 lesions, T1 hypointensity lesions, new active lesions have already been published in the Lanc Neurol paper (table 2 and appendix).

Response: Thank you for your feedback. We have amended the figure legends to include the correct reference.

Reference: