Reviewer’s report

Title: Fingolimod after a first unilateral episode of acute optic neuritis (MOVING) – Preliminary results from a randomized, rater-blind, active-controlled, phase 2 trial

Version: 0 Date: 22 Mar 2019

Reviewer: Philipp Albrecht

Reviewer's report:

The authors report the results of the randomized, controlled, open label MOVING trial comparing the efficacy of fingolimod vs IFNß on visual evoked potentials and optical coherence tomography outcomes in subjects suffering from a first attack of acute optic neuritis. As the trial was halted due to slow recruitment the study could only yield preliminary results. The study was well designed and the results merit publication as exploratory findings of an incomplete study, which was halted by the sponsor prior to conclusion. My main point of concern is that the authors may to some extent be overinterpreting the results and I would like to advise them to report the results more descriptively, emphasizing that due to the small sample size, inconsistent follow up measures and differences in baseline measures they have to be interpreted with great caution.

I have the following points of concern that need to be addressed:

Major points:

- The major drawback of the study is the slow recruitment and incomplete follow-up leading to insufficient sample size making it almost impossible to come to a valid conclusion.

- Furthermore, as the authors correctly state, the difference in recovery was in part driven by an unexpected deterioration of the control group. Therefore, it is impossible to tell if the differential effects observed are attributable to a positive effect of fingolimod, a detrimental effect of interferon beta, or both or even an artifact due to the low sample size and incomplete follow up. Why not state this in the discussion? Given these limitations I believe the authors may be somewhat overinterpreting their data. I would suggest to significantly taper down the conclusions keeping reporting and interpreting of the results on a very descriptive level.

- The rather high difference in mfVEP latency at baseline may also have had a substantial impact on the longitudinal findings and might also explain the differences in change rate between groups. This could be elaborated more in the discussion.

- Statistics: They use using non-parametric (rank-based) ANOVA-like analyses for longitudinal data in factorial settings, which seems like good strategy given the low sample size. However, the description of the statistical analysis lacks detail: Were only the results of the affected eyes compared or did the authors also investigate the differences to the unaffected contralateral eyes? How many eyes had signal loss? How was this dealt with? If they only report data of the affected eyes, it would be of interest to find out about the dynamics in comparison to the contralateral eyes, especially regarding the peripapillary RNFL and the GCIPL.
Minor points:

- The authors mention licensing of other oral DMTs during the course of the study as the major source for the recruitment problems. Another major point, which should be mentioned, is that only two local centers in Berlin were used for recruitment. Involving more centers could have allowed better recruitment.

- It comes to a surprise that ffVEP and mfVEP did not correlate.

- The open label design should be mentioned as a limitation of the study, especially regarding the results of the subjective measures like NEI-VFQ.

- Add numbers of patients for each timepoint in supplemental fig. 1.

- Add confidence intervals in supplemental fig. 2 and 3.

**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.

No

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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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