Author’s response to reviews

Title: Fingolimod (FTY720) in Japanese patients with relapsing multiple sclerosis: 12-month results of a phase 2 extension study

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Author’s response to reviews: see over
Dear Dr Robert Zivadinov,

MS: 7201276049721539
Title: Fingolimod (FTY720) in Japanese patients with relapsing multiple sclerosis: 12-month results of a phase 2 extension study

On behalf of all authors, I would like to thank you for reviewing the above manuscript. We have revised this manuscript to address the reviewer comments, and your editorial requests, and we would like to resubmit the article for publication in the BMC Neurology. Please see below for a list of the reviewers’ comments together with a point-by-point list of all changes made in response.

Editorial comments:

Please revise your manuscript to clarify whether your study has received ethical approval from your institutional ethics committee. This should be stated in your manuscript and the name of the ethics committee should also be provided.

A statement regarding ethical approval from the institutional committee of each participating medical centre has been added to page 4.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

The revised manuscript conforms to the journal style and all files are correctly formatted.

Reviewer: Robert Bermel

Reviewer’s report:
The authors describe the results of an extension study conducted in Japan of patients with MS initially randomized to fingolimod or placebo, then switched to fingolimod and followed in a systematic extension study, with safety follow-up, clinical and MRI outcomes.

Strengths of this manuscript include:

1. Excellent retention into the follow-up study (>97%).
2. Clearly written
3. Appropriate tables and figures
4. Appropriate balance between efficacy and safety data
5. Very useful description of the outcome of patients identified to be NMO-IgG positive who had been on fingolimod in the course of the study.
Minor essential revisions:
1. While the conclusions are generally supported by the data, statistical analysis (hypothesis tests with p-values) should be performed and included for the tables and figures, so that the reader can judge (especially given the small sizes of some of the groups) the significance of differences between the groups and the overall results.

The change in dose to fingolimod 0.5 mg during the study for patients initially randomized to fingolimod 1.25 mg in either the core study of extension study precluded the possibility of meaningful formal statistical comparisons. Meaningful statistical interpretation was also limited by the small sample size in each treatment group, owing to the low incidence of MS in Japan. Therefore, analyses were summarized descriptively. This is now described more fully on page 6 of the revised manuscript, and revisions have been made throughout, in line with the absence of formal statistical testing. Further details can be found below in response to reviewer two’s comments.

2. Additional description needed in the body of the manuscript about the one death, specifically the duration that he was treated with fingolimod, and whether this was determined to be a death related or unrelated to the study medication (the supplemental material seems to suggest that lymphoma was the original correct diagnosis prior to study randomization, and that the patient did not actually have MS??)

The requested description has been added to the discussion on page 9. The patient was diagnosed with MS five years before the entry to the core study and had a total of six relapses since diagnosis with five relapses treated with steroids. Although the B-cell lymphoma was diagnosed 5 months after discontinuation of study drug and after a relatively brief period of treatment with fingolimod of 9 months, a relationship between the B-cell lymphoma and the study medication cannot be excluded and was suspected by the investigator.

Reviewer: Tereza Gabelic

Reviewer’s report:
Interesting and thought provoking paper, however there is one important fact that I would point as

Major Compulsory Revisions: the lack of statistical analysis.
All data are given in descriptive form without doing statistical analyses between groups. Without statistical testing, it is impossible to draw any conclusions about drug efficiency. For all the reader knows, the presented results are due to random error. In addition, given the fact that statistical analysis were initially reported for original core paper (Reference number 10), I don’t quite understand why the authors did not do the same for this manuscript. Authors should either conduct analyses, or provide a very detailed explanation for not doing statistical analysis. All in all, the general problem lies in that several claims are made based on the results, but without statistical confirmation, those cannot be made.

The change in dose to fingolimod 0.5 mg during the study for patients initially randomized to fingolimod 1.25 mg in either the core study of extension study precluded the possibility of meaningful formal statistical comparisons. Meaningful statistical interpretation was also limited by the small sample size in each treatment group, owing to the low incidence of MS in Japan. Therefore, analyses were summarized descriptively. This is now described more fully on page 6 of the revised manuscript, and revisions have been made throughout, in line with the absence of formal statistical testing.
These include “Baseline MS disease characteristics of the extension randomized population were generally similar across treatment groups (Table 1) with the exception of mean number of relapses in the previous 1 or 2 years and the proportion of patients free of Gd-enhancing lesions”

Significance tests for baseline differences are inappropriate. A chance significant baseline imbalance is unimportant if the factor is unrelated to outcome, unless it signals errors in randomization. Conversely, if a baseline factor strongly influences outcome, a non-significant treatment imbalance may be important (please see reference: Assmann SF et al. Subgroup analyses and other (mis)uses of baseline data in clinical trials. The Lancet (2000);355:1064-1069). We agree with the reviewer that the conclusion should be amended in the absence of formal significance testing, and this has been changed on page 6 of the revised manuscript.

“In patients switched from placebo to fingolimod therapy, inflammatory MRI activity was reduced in the extension study compared with the core phase, with consistent effects across the two fingolimod doses (Table 2)”

We have not provided p-values for core-extension comparison on efficacy per the study objective. In contrast to the core study, the study was neither intended nor designed to confirm any hypothesis. Then there was no significance level specified for the extension study, and the sample size was not determined from a statistical viewpoint. We agree with the reviewer that the conclusion should be amended in the absence of formal significance testing, and this has been changed on page 7 of the revised manuscript.

“Infections and infestations were the most commonly reported AEs and occurred in generally similar proportions of continuously treated and switched patients, but were slightly more common in the fingolimod 1.25 mg groups than the 0.5 mg groups (Table 3)”.

We have not provided p-values for treatment group comparison on safety as in the core study. Additionally, no significance level was specified for the extension study, and the study was not also powered to confirm any hypothesis on safety. We agree with the reviewer that the conclusion should be amended in the absence of formal significance testing, and this has been changed on page 8 of the revised manuscript.

Minor Essential Revisions

Patients with NMO:
It is not clear at what point the authors became aware of NMO serology positive results. According to disease course described in supplemental material at the end of manuscript, there were some radiological findings that could point to alternative diagnoses. Could the authors comment why these patients were not excluded before from the study?

Patients were eligible for the study if the diagnosis of MS was confirmed by the study investigators and if they fulfilled MRI criteria. There was no exclusion criterion related to the presence of anti-AQP4 antibodies. The anti-AQP4 antibody test results were collected from medical records retrospectively for patients who consented to provide the data upon occurrence of a severe adverse event. This explanation has been added to the discussion on page 11.
Yours Sincerely,

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