Author’s response to reviews

Title: Effectiveness, safety and health-related quality of life of multiple sclerosis patients treated with fingolimod: results from a 12-month, real-world, observational PERFORMS study in the Middle East

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Author’s response to reviews:

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To

Editor-in-Chief

BMC Neurology

Subject: Manuscript addressing reviewers’ comments (manuscript ID: NURL-D-16-00638)
Dear Editor,

We thank the reviewers for a thorough assessment of the manuscript and providing valuable comments and suggestions. We thank the journal for the consideration given to the manuscript and for giving us an opportunity to respond to the reviewers comments and to revise our manuscript entitled “Effectiveness, safety and health-related quality of life of multiple sclerosis patients treated with fingolimod: results from a 12-month, real-world observational PERFORMS study in the Middle East”. The changes we have made are highlighted in track mode in the revised version. We have also provided a point-by-point response to each comment raised by the reviewers.

We hope that the revisions/explanations provided make our manuscript more satisfactory for publication in BMC Neurology journal.

Looking forward to hearing from you.

Thank you again for your consideration.

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Title: Effectiveness, safety and health-related quality of life with fingolimod treatment in multiple sclerosis: a real-world observational PERFORMS study in the Middle East

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Comments to the Author

Reviewer 1

This manuscript reports original findings on a multicenter observational study on real-world clinical effectiveness as well as impact on quality of life of fingolimod in the Middle East. The manuscript is well written and discussed.

Response: Thank you for the overall positive feedback.

However, there are suggestions to ameliorate the article.

Comment 1. The major issue is the lack of neuroimaging findings. This could add to the effect of treatment. However, the authors should give any comment on this issue especially when considering the disease activity status in relapse-free patients.

Response: Thank you for the suggestion. This was an observational, non-interventional study where patients were followed based on routine clinical care by practitioners. Assessing of neuroimaging findings would require a central medical resonance imaging (MRI) laboratory in order to maintain consistency in data reading and interpretation. Given the nature of the study, central MRI reading was not practically feasible, and thus neuroimaging findings were not included as an outcome to be assessed.
Comment 2. In the design of the study, the authors should better claim that data on other DMTs constitute parallel findings and there is no comparison of cohorts. However, I don't understand why they present Kaplan-Meier analysis for time to first relapse in both cohorts.

Response: Thank you for the comment. As mentioned, the study was not designed to perform statistical comparison between both cohorts. Kaplan-Meier analysis was presented just to show the time-to-relapse and not the relapse rate/survival in fingolimod cohort. This was an exploratory analysis without any statistical comparison.

Comment 3. However, the baseline characteristics of both cohorts could be compared and a P value could be therefore added in Table1.

Response: Thank you for the feedback. Although, this was an observational, non-randomized study, patient enrolment was designed in 2:1 ratio to minimize the selection bias in the study. Participating physicians were encouraged to enrol patients in a consecutive manner during a regular visit to minimize the risk of self-selection bias. The present study was not designed to perform statistical analysis between cohorts and therefore p values were not calculated.

Comment 4. In Table 2, the results of the statistical analysis of the frequencies in the respective cohorts should be shown.

Response: Thanks for the suggestion. Table 2 is reporting shift in patients walking ability from baseline to Month 6 and Month 12/EOS. The study was not designed to perform any statistical comparison for between cohorts as well as within cohorts and therefore statistical analysis of frequencies were not calculated.

Comment 5. In figures 2, 3, 5 and 6, the significant values should be indicated.

Response: Thank you for your suggestion.

•Figure 2 reporting clinical global impression on MS improvement, there was no statistical analysis planned to compare between cohorts, therefore statistical significance was not calculated.

•Figure 3 is reporting proportion of patients with relapses in the 12–24 and 0–12 months before baseline and during the study for all the category: 0, 1, 2, 3 and >3 relapses. We did provide the p values for patients with at least one relapse vs. none in the 0–12 months before study and during the study, separately for both cohorts. These p values are mentioned in the manuscript text (results, page 12; First line). However, the study was not powered to compare the number of
relapses for all the category (0, 1, 2, 3 and >3) and therefore we do not have p values to present for each category.

• Figure 5 is reporting Box and whiskers plot for mean EDSS score during the study by time point and Figure 6 is proportion of patients free from disability progression according to EDSS score. In general, assessment of change in EDSS over 12 months is a relatively short period to observe any clinically meaningful difference in disability progression in patients. In order to avoid misinterpretation of data, we only reported number of patients free from disability progression according to EDSS from baseline to Months 6 and 12/EOS without p values. Moreover, the study was not designed to perform statistical comparison between cohorts.

Comment 6. In methods, the authors should state how they analyzed Kaplan-Meier curves and therefore, in figure 4, the P value should be indicated.

Response: Thank you for the comment. As mentioned, the study was not designed to perform statistical comparison between the cohorts. Kaplan-Meier was presented just to show the time to relapse. This was an exploratory analysis without any statistical comparison. We have mentioned in methods section (page 7) that Kaplan-Meier plot was provided to report time to the first relapse.

Reviewer 2

The manuscript is well written. The study addresses the safety and tolerability as well as QoL in a cohort of MS patients treated with fingolimod compared with patients treated with other DMT's.

Response: Thank you for the overall positive feedback.

A few details should be added to the manuscript:

Comment 1. If the information is available, how many of the patients switched to fingolimod experienced adverse events under the previous DMT? This may influence the patient-reported quality of life. If the results turn out to be significant, this should be also addressed in the Discussion section.
Response: Thank you for the comment. During the study, there were only three patients who switched from other DMTs cohort to fingolimod cohort and therefore would not be statistically meaningful to include details. As this was an observational non-interventional study wherein the enrolment of patients were based on routine medical care, we did not have the details on adverse events experienced by patients who switched from other DMTs to fingolimod prior to study entry.

Comment 2. The manuscript shows data at 1-year follow-up, so short-term. This should be added to the title and conclusion, as well as added to the limitations paragraph in the Discussion section.

Response: We thank the reviewer for the comment. As suggested, we have added 12 months (1-year) in the title. We have already specified time point (as 12 months) in conclusion part of abstract and manuscript. We do agree that a study on patient-reported outcome measures with more than 12 months could be useful. However, several published observational studies on patient-reported outcomes or quality of life in patients with multiple sclerosis have used follow-up period of between 12–24 months. Some references are cited below for your perusal (1–4). Moreover, the present observational study was designed to enrol and follow-up patients by physicians as per their routine medical care. Considering the nature of present study and supporting evidence for the use of 12-month observation period in such type of studies, we do not perceive 12 months (1-year) as a limitation of study. We hope that our response is adequate.

References


Note: The authors' response letter has also been included as a supplementary file on the 'Attach Files' page.