Author's response to reviews

Title: A Swiss real world best practice experience in three different clinical settings of the 6 hour fingolimod first dose observation procedure

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Author's response to reviews: see over
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To

The Editor-in-chief, BMC Pharmacology and Toxicology

Subject: Manuscript revision as per editorial and peer reviewers’ comments

Dear Sir/Madam,

The manuscript (MS: 6371000113692752, Research article), titled “A Swiss real world best practice experience in three different clinical settings of the 6 hour fingolimod first dose observation procedure” has been revised as per the editorial and peer reviewer comments.

We are grateful to the editors and external advisers of BMC Pharmacology and Toxicology for reviewing our manuscript and providing us an opportunity to respond to the editorial and peer reviewers’ comments. We now submit for your consideration a revised manuscript and point by point response to each of the referee comments.

Editorial Requests:

1. Please include an ethics statement in the 'Methods' section of the manuscript stating that the local or institutional ethics committee waived the review of the study and include the full name of the ethics committee.

Response: As suggested we have added the below statement to line 56 after modifying previous statement in the methods section of the manuscript.

The Cantonal Ethics Committee Zurich waived the review of this study (Additional file 1) Ethics committee review was not necessary for this research, as the data were obtained from retrospective chart reviews, and the information was…

2. Please remove the Trial registration from the abstract.

Response: As suggested we have removed the Trial registration from the abstract.

Reviewer #1 (Brenda Banwell):

1. Abstract - is concise and to the point; however, the abstract doesn't sell the article and doesn't explain why this article is important or needs to be read.

RESPONSE: We thank the reviewer for highlighting this. Now we have modified the abstract’s background section to explain the importance of this article as below:

Background: The Swiss label of oral fingolimod (0.5 mg once daily) requires a 6-hour first dose observation (FDO) including an ECG prior to and 6 hours after the first intake but in comparison
to other countries such as Austria, Australia and Canada there are no restrictions regarding the clinical settings of the FDO procedure in Switzerland. We present here our real-world experience of the 6 hour FDO procedure in three different clinical settings, following fingolimod treatment initiation. This is the first report on the FDO of fingolimod in these real-world clinical settings in Swiss patients with MS.

Also, the following changes have been made in the background section (lines 37-39) in the manuscript text:

Here, we report for the first time the real-world experience of fingolimod treatment initiation and 6 hours FDO procedure in three different clinical settings outside of University Hospitals (MS centre, day clinic, private practice) since there are no restrictions on location of the FDO procedure in Switzerland.

2. In the Methods section - The authors should contrast the international monitoring recommendations with those in place in Switzerland. It is unclear how these differ

**RESPONSE:** The authors thank the reviewer for bringing this lack of clarity to our attention.

As mentioned in the background section (lines 34-37), the Swiss regulatory agency recommendations are similar to the recommendations of other international health authorities.

The US Food & Drug Administration (FDA) label and European public assessment report (EPAR) of Gilenya were first approved in September 2010 and February 2011, respectively. Subsequently, there were revisions in these recommendations and the new US FDA label and the European summary of product characteristics (EuSmPC) were released in April 2012.

From line 45 of the methods section we wanted to convey that the new recommendations published by the Swiss regulatory agency in October 2012 were not encompassed in this study. These new recommendations were based on the subsequent revisions of the US FDA label and EuSmPC in 2012 and were just an addition (annex) to the old recommendations. These amendments were related to the observation of patients with pre-existing cardiac conditions (PCCs), with the addition of hourly Holter ECG monitoring post the first dose. The details of warnings and precautions needed while monitoring this special population of patients with cardiac problems was also added.

As this was a retrospective study cohort from 2011, these recommendations were not encompassed in this study.

3. In the Results and discussion section - The authors focus almost entirely on the cardiac monitoring and only report cardiac side effects. They should discuss the full spectrum of potential toxicities and report on how many patients had retinal changes, infection, and specifically herpes re-activation.

**RESPONSE:** We thank the reviewer for this feedback. However, this is not in the scope of our study. As highlighted in the title of this research article, this study focussed on the 6 hour
fingolimod first dose observation (FDO) which was administered in 3 different settings with appropriate resources for management of symptomatic bradycardia. As per the EuSmPC the initiation of Gilenya (fingolimod) therapy is associated with symptomatic bradycardia within the first 6 hours of first dose administration, although the observation period may extend from 2 hours up till the time the symptoms are resolved. Further detailed recommendations regarding the FDO procedure and precautions needed in special patient population (with PCCs) are present in the label which pertains to cardiac monitoring post the first dose.

Thus, this paper is entirely concentrated on cardiac monitoring and reports only cardiac side effects observed as a part of the FDO.

**Reviewer #2 (Yara D Fragoso):**

1. This is a relevant, interesting and well-conducted study that shows the real life experience with the first dose of fingolimod. I strongly recommend the authors to cite two previous studies on the same subject, as below. The authors can compare their results with those from other authors, which would enrich their conclusions.

**RESPONSE:** The authors thank the reviewer for providing these references. Similar to our study where only 4.4% of patients experienced cardiac side effects and the majority i.e. 96% of patients continued with fingolimod therapy, these two other FDO real-world observation studies, based in Brazil (Fragoso YD et al) and Italy (Laroni A, et al.) also revealed that approximately 99% patients continued with fingolimod therapy and reported some cardiovascular adverse events, mainly bradycardia and atrio-ventricular block.

We have added both of these references and cited them in the conclusions section (line 96) as follows:

All 3 participating sites capably facilitated the FDO procedure. Our data, which are in line with the phase 3 trial data [3, 4], and other FDO related real-world observational studies [6,7] show that despite strict FDO…

On behalf of all the authors, I thank you in advance for your consideration of this manuscript for publication in the BMC Pharmacology and Toxicology. We look forward to hearing from you soon.

Sincerely,

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