Author's response to reviews

Title: Bimatoprost 0.01% in treatment-naive patients with open-angle glaucoma or ocular hypertension: an observational study in the Korean clinical setting

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Author's response to reviews: see over
Dear Dr. Murray,

Thank you for your interest in our manuscript, “Bimatoprost 0.01% in treatment-naïve patients with open-angle glaucoma or ocular hypertension: an observational study in the Korean clinical setting” (MS: 1680208733140118).

We are grateful for the constructive comments and are pleased to submit the revised version of our manuscript for publication in BMC Ophthalmology. All comments are addressed below, point-by-point. Page/line numbers indicate where changes can be found in the manuscript (highlighted in yellow).

In addition to the changes to the manuscript, we have added an acknowledgement (on p. 18) for the contributions of Theorem Clinical Research to the study.

Reviewer: Dr. Giovanni Milano

1. **Comment:** The study is observational and the criteria used to design the study and to select patients are not strict and rigorous. Nevertheless, a better definition of the glaucoma diagnosis would be advisable in term of a better definition of optic nerve head change (c/d ratio, localized or diffuse rim thinning evidenced by ophthalmoscopy, stereo-photos, imaging?) and visual field defects (automated perimetry, type of defect?) (METHODS – Study design and patients par. 2).

   **Answer:** We understand Dr. Milano’s concern. The study, however, was designed to enroll patients who were diagnosed before screening by their practitioner according to the accepted standard of care. Due to the observational nature of the study, the protocol did not require any specific diagnostics. This has been clarified in the Methods section (p. 6, lines 121-123).

2. **Comment:** The authors excluded patients with hypersensitivity to any component of the study medication and with “any other abnormal condition or symptom preventing study participation”. But since the primary endpoint is Bimatoprost tolerability in term of adverse events and especially conjunctival hyperaemia, more information about systemic and ocular allergies, dry eye or other conditions affecting ocular surface, use of contact lenses or concomitant medications should be advisable (METHODS – Study design and patients par. 2). The possible presence of concomitant conditions affecting the appearance of ocular hyperaemia may allow to overcome the critical lack of a control group.

   **Answer:** Few patients in the treatment-naïve cohort had comorbidities, such as asthma, or were receiving concomitant medications that may have affected the occurrence of
hyperemia. These details are now described in the Results section of the manuscript (p. 10, lines 218-223) for transparency. Information as to whether patients had dry eye or used contact lenses was not recorded in the baseline ocular history, but corneal staining/erosion was evaluated on biomicroscopy at baseline and at each study visit, and is now also summarized in the Results section (p. 10, line 224, and p. 12, lines 264-267). Less than 1% of patients had staining in the moderate to severe category at baseline.

3. **Comment**: It should also be advisable to know how approximate the time at which the IOP has been measured throughout the study is (METHODS – Outcomes par. 2).

   **Answer**: To clarify this point, we have modified the text as follows (p. 8, lines 162-164):
   “The examiners were instructed to perform IOP measurements in the morning at approximately the same time of the day (ie, 10 AM ± 2 hours) for a given patient throughout the study.”

4. **Comment**: RESULTS - Intraocular pressure par. 1. The correct verb is “were” instead of “was”.

   **Answer**: We thank the reviewer for bringing the error to our attention. We have modified the sentence accordingly (p. 11, line 244).

5. **Comment**: TABLE 3, in the upper part of the table the first two lines are identical: cross one out.

   **Answer**: The second line in Table 4 (originally Table 3) has been deleted and a footnote has been added to indicate that all treatment-related adverse events were ocular in nature (p. 25).

6. **Comment**: FIGURE 1. Not necessary, can be deleted.

   **Answer**: At Dr. Milano’s request, we have deleted Figure 1; the reasons for discontinuation and proportion of patients discontinuing from the treatment-naive cohort have been inserted in the Results section on page 9 (lines 203-204).

**Reviewer: Dr. Enrico Martini**

1. **Comment**: Authors used a five point grading scale but results of this grading are only reported in table 1 and not exposed nor discussed, while they prefer to focus only on the collapsed grouping in two categories. So we lose some important information: if we look at table 1 there is a widespread shift towards higher degrees of hyperemia that is not evident if we look only at fig. 2 where only 12,3 and 12,7% of patients worsened. If we had a similar graph with the 5 point scale the shift towards hyperemia would be much more evident. Moreover we don't know whether the general trend is due to few cases
with significant worsening or in a generalized shift with some patients crossing the line between grade +1 and +2.

**Answer:** In the interest of space, we have addressed the reviewer’s comment by adding a table (Table 3 – as opposed to a multi-panel figure) that highlights the shift in hyperemia grading from baseline to weeks 6 and 12 using the 5-point scale (p. 24). The Results section has been modified accordingly (p. 11, lines 229-235): “Notably, the majority of patients who had none to mild hyperemia at baseline experienced no change or improved at both weeks 6 and 12 (Table 3). Moreover, most patients who had moderate to severe hyperemia at baseline improved at weeks 6 and 12 (Table 3). After collapsing the data to 2 severity categories (as reported by other groups)[14, 17], most patients showed no shift in hyperemia grading at week 6 (86.9%) and week 12 (86.8%) (Figure 1).”

2. **Comment:** the second important issue is the high attrition rate: 25% in only 12 weeks is more than expected even if Authors correctly comment on it and state that it may be due to poor tolerance and/or side effects and therefore associated with a higher rate of side effects and drug discontinuation. The issue is not obscured but remains a limit of the study and perhaps a telephonic inquiry about causes of missing follow-up visit would have been useful.

**Answer:** Per the study protocol, every effort was made to contact the patient if they did not return for a scheduled visit, and to document the patient outcome (see p. 8, lines 168-169, and p. 15, lines 331-332). The study, however, still resulted in a high attrition rate.

3. **Comment:** …abstract only refers to the collapsed data and perhaps some hint to more diffuse increase in hyperemia although not severe would be more correct.

**Answer:** To address Dr. Martini’s comment, the Results section of the abstract now includes details of hyperemia grading at baseline, weeks 6 and 12 (p. 2, lines 39-44): “…96.3% had hyperemia graded none (36.3%) to mild (17.3%). At week 12, hyperemia was graded none to mild in 83.7% (n=220). Worsening occurred in 12.3% of patients by week 6 and 12.7% by week 12. Small improvements occurred in 0.8% and 0.5% of patients at weeks 6 and 12, respectively. Hyperemia scores were generally low and the majority of patients had no change in severity during the study.”

We thank you for your kind attention and look forward to receiving your feedback.

Sincerely,
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