Author's response to reviews

Title: Comparative efficacy and safety of the fixed versus unfixed combination of latanoprost and timolol in Chinese patients with open-angle glaucoma or ocular hypertension

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Dear Dr. Alam:

We are pleased that the reviewers for BMC Ophthalmology found our manuscript to be of interest and have made revisions in response to their comments. Our “point by point” responses are in italics, below.

Reviewer: Anastasios Konstas

Reviewer's report:

The manuscript presents the results of a parallel, multicenter study which compared LTFC (latanoprost/timolol fixed combination) dosed in the evening vs unfixed therapy comprising one drop of timolol in the morning and one drop of latanoprost in the evening. The study presents useful new information (comparison of two popular combination therapies in Chinese patients). The
discussion however requires significant re-writing to assist the readership of the journal to understand the clinical message. There are a number of specific recommendations for enhancement of the manuscript.

#1 Nomenclature has always been a problem with fixed combinations. LTFC may be a more appropriate term for the fixed combination.

FCLT has been changed to LTFC and uFCLT has been changed to LTuFC throughout.

#2 Although fixed combination therapy generally demonstrates greater treatment efficacy to each of its individual components, the reduction in pressure with some fixed combinations has been less than was originally anticipated. This may be due at least in part to the potency of prostaglandin analogues when used as monotherapy and the use of timolol only once daily in the prostaglandin-timolol fixed combinations. Consequently, unfixed combinations generally provide a small, but non-statistical, greater reduction in IOP compared to the fixed combination containing the same medicines. However, all the potential reasons have not been clarified. As a consequence, most fixed combinations today (including LTFC) have not yet received FDA approval. Here in this study unfixed latanoprost and timolol combination therapy includes only one drop of timolol in the morning. This is not the typical unfixed regimen where timolol is administered twice daily. This should be addressed in the discussion.

We agree that this is an important point and address the issue in the Discussion as follows: “The meta-analysis [29] found that greater IOP lowering occurred with concomitant timolol twice daily and latanoprost once daily than with LTFC, a difference that may reflect the omission of a timolol dose with the fixed combination. Herein, timolol was administered once daily in the morning in the LTuFC arm rather than twice daily as is more typical with unfixed regimens. Instillation of one dose of timolol in the morning in both treatment arms may explain, in part, the relatively small between-group difference in mean IOP reduction.”

#3 LTFC was administered in the evening in the present study but this issue is not really discussed. There is conclusive evidence (not included here) that the relative lack of efficacy with LTFC versus latanoprost may be because this fixed combination was instilled in the morning in some studies, whereas latanoprost alone is generally dosed in the evening. Previously, Alm et al (Ophthalmology 1995), as well as Konstas et al (Am J Ophth 1999; Am J Ophth 2002; Arch Ophth 2005) have demonstrated that night time dosing of latanoprost and LTFC provide lower daytime pressures than morning dosing. A study by Konstas and associates (Arch Ophth 2005) showed that LTFC compared to latanoprost alone, both dosed in the evening, provided a wider margin (2.5 mmHg more than latanoprost) over 24-hours than the morning dosing used in the regulatory trial. Further, in another crossover study (Konstas et al Arch Ophth 2006) the fluctuation of 24-hour IOP was significantly lower with LTFC dosed in the evening (3.2 mmHg) compared with timolol alone (4.4 mmHg). Finally, Takmaz et al (Eur J Ophth 2008) reported in a direct 24-hr IOP comparison between morning and
evening administration of LTFC in POAG that evening dosing controlled IOP better. These references should be included and the discussion should highlight the dosing issue.

We thank the reviewer for this comprehensive comment and have added the following to the Discussion: “However, only 24-hour studies are appropriate when addressing morning versus evening administration, and several studies have shown that the relative efficacy of LTFC and latanoprost reflects instillation time. For example, a study by Alm et al [9] as well as several by Konstas et al [30-32] demonstrated that evening dosing of latanoprost and LTFC provided lower daytime IOP levels than morning dosing. A study by Konstas and associates [32] showed that LTFC compared to latanoprost monotherapy, both dosed in the evening, provided a wider margin (2.5 mmHg more than latanoprost) over 24 hours than the morning dosing used in a regulatory trial [33]. In another crossover study [34], 24-hour IOP fluctuation was significantly lower with LTFC dosed in the evening compared with timolol alone (3.2 mmHg vs 4.4 mmHg, respectively; P = 0.003). Finally, a direct 24-hour IOP comparison between morning and evening administration of LTFC in POAG patients found that evening dosing provided more effective IOP control [35].

#4 The duration of the study has been too short to elicit known side effects of latanoprost, or LTFC (e.g. iris hyperchromia). The statement of the authors about side effects should be modified accordingly.

We agree and have added the following to the paragraph in the Discussion concerning side effects: “It is important to note, however, that the duration of the present study was too short to identify possible long-term adverse treatment effects.”

#5 In the U.K. latanoprost study, Watson et al (Ophthalmology 1996) found a significant difference in IOP reduction obtained in ocular hypertension vs POAG (9.4 mmHg vs 7.1 mmHg). Have the authors detected an efficacy difference in Chinese patients with POAG vs those with OHT? A comment may be helpful.

This is an interesting point. As such analyses were not prespecified in the current study protocol, we have added a comment about this limitation as follows: “Although Watson et al [12] found that POAG patients treated with latanoprost monotherapy experienced a significantly greater mean IOP reduction than similarly treated OH patients (9.4 mmHg vs 7.1 mmHg, respectively), such an analysis was not prespecified in the present study; future research might profitably compare differences between these diagnosis groups in Chinese patients.”

#6 The authors can delete some of the older references for timolol (in the introduction 3-5) and include more pertinent references.

We have replaced the references with more recent citations.

#7 Studies with a few daytime measurements (and a meta-analysis like Ref 29)
cannot really prove "equivalent IOP reduction between AM and PM dosing". Only 24-hour studies are appropriate when addressing efficacy between morning vs evening administration. Such studies (e.g. by Takmaz et al Eur J Ophth 2008) report better efficacy with evening administration of LTFC.

This is indeed an important point that is now brought out in the Discussion. Please see the response to item #3, above.

Reviewer: Luca Rossetti
Reviewer’s report:
This paper is well conceived and written I have only few comments about it. First, the study has been designed as a non-inferiority trial between fixed and unfixed combinations. I don’t think that a difference of 1.5 mmHg is suitable to this purpose, as even a 1 mmHg difference between the 2 study arms is going to be quite relevant. And I would be greatly surprised if fixed and unfixed combinations showed such a big difference! Second, as quoted in the reference list, there are a number of previous comparisons between fixed and unfixed timolol-latanoprost combo. Is this paper any news?

While we agree that a difference of 1 mmHg between study arms could be clinically relevant, the protocol specified 1.5 mmHg as the noninferiority margin. In fact, the difference in mean IOP reduction at week 8 was 0.3 mmHg, indicating that the fixed combination was noninferior to the unfixed combination.

The Reviewer correctly points out that there have been prior publications comparing the fixed and unfixed combinations of latanoprost and timolol. However, as noted in the Discussion, ours is the first study to compare the efficacy and tolerability of LTFC with that of LTuFC in a Chinese population, a population that represents an increasingly large proportion of individuals with POAG or OH worldwide.

We appreciate the Reviewers’ comments, believe the changes made have strengthened the manuscript, and look forward to its publication in BMC Ophthalmology.

Please do not hesitate to contact me if you have further questions.

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