Reviewer's report

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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Reviewer: Anastasios Konstas

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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.

#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.

#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 mm Hg 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 mm Hg) compared with timolol alone (4.4 mm Hg). 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.

#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.

#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 mm Hg vs 7.1 mm Hg). Have the authors detected an efficacy difference in Chinese patients with POAG vs those with OHT? A comment may be helpful.

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

#7 Studies with a few daytime measurements (and a meta-analysis like Ref 29) can not 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.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests