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A double-masked, randomized, parallel comparison of a fixed combination of bimatoprost 0.03%/timolol 0.5% with non-fixed combination use in patients with glaucoma or ocular hypertension

To the Editor,

I read the recent report of Hommer et al (1) regarding a three-armed randomized glaucoma clinical trial with interest. The study compared the efficacy and safety of a fixed combination of bimatoprost 0.03%/ timolol 0.5% (Ganfort®) to concomitant qd bimatoprost 0.03% and bid timolol 0.5%, as well as to a qd bimatoprost 0.03% monotherapy validation arm. According to the authors, the fixed combination of bimatoprost administered once daily was comparable in ocular hypotensive efficacy to the separately dosed combination therapy. I also noted that the incidence of conjunctival hyperemia with the fixed combination was less than that with bimatoprost 0.03% given alone. However, I have several reservations concerning these conclusions.

First, the authors claim that Ganfort® is comparable to the combination of the individual medications given separately and has a superior benefit/risk assessment. Might I refer them to a recent editorial (2) coauthored by both the US Food and Drug Administration (FDA) and editors from three major journals which gives guidelines for the use of the terms safe and effective. These guidelines strongly suggest that this article can neither claim safety nor superiority.

The authors also compare the results in this short-term manuscript with those of others in which combination products of prostaglandin analogues and nonselective beta-blockers are analyzed. First, the duration of this study (3 weeks) is far less than the duration of almost all studies evaluating the longer-term efficacy of prostaglandin analogues and beta blockers. This duration is inadequate to accurately evaluate the long-term effects of these medications in patients with glaucoma. The current article also deals with patients naïve to any ocular hypotensive therapy, a situation which is clearly inappropriate for the evaluation of a combination medication. This should be taken into account when generalizing the results to daily practice. Combination medications should most certainly only be used when an individual patient has had inadequate intraocular pressure (IOP) lowering from one of the two component medications (3). This patient population is therefore quite dissimilar to those of other studies and no comparisons should be made. Additionally, comparisons can also only legitimately be made if the comparison is directly made.

The Ganfort® European Public Assessment Report (EPAR) (3) describes the design of this study in detail. Analysis rules applying to claims of noninferiority, presumably laid out by the trial sponsors and/or the EMEA, were established a priori and clearly defined: «In this study, the requirements for noninferiority of the Ganfort combination compared to the concurrent use of the single agents was that the difference between the mean IOP in the combination group and in the concurrent group should not only be less than 1.5 mmHg at the 3 timepoints, but also less than 1.0 mmHg for at least 2 of the 3 timepoints». The last condition was not fulfilled by Hommer et al, as only one of the three timepoints reached the 1.0 mmHg noninferiority threshold. A change of inference rules a posteriori is considered a fault, as clearly stated by the Committee for Proprietary Medicinal Products (4): «… since the choice of Delta (maximum difference) is generally a difficult one, there is ample room for bias here, however well intentioned the researcher may be». This supports the EPAR conclusions: «Strictly, the non-inferiority criteria were not fulfilled, as the non-inferiority margin of 1.0 mm Hg was met at only one and not at two timepoints, as requested». Moreover, two analyses are required for a noninferiority trial, one involving the per protocol population and the other the intention to treat population (4). Both analyses should lead to similar conclusions and be reported to readers; however, the per protocol analysis in this case was represented by a simple claim of similar results. Furthermore, the claim of comparable efficacy is semantically wrong and should be restated in the context of a noninferiority trial, e.g., «The lesser efficacy of Ganfort® over the non-fixed combination is clinically acceptable due to the lower number of instillations».

The conclusion of a lower Ganfort® conjunctival hyperemia incidence rate is supported by weak evidence. The authors never define the conjunctival grading scale and how differences were recorded. In Table VI, there is no statistical difference among the three treatment groups (p=0.218), which contradicts the results reported in the abstract. This discrepancy might be explained by different definitions of conjunctival hyperemia, but only self-reported adverse events (Tab. VI) are clinically relevant. More-

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over, the comparison of all three hyperemia rates (abstract: 8.5%, 18.9%, and 12.5%), together, was not statistically significant ($p>0.05$, Fisher exact test). In order to demonstrate a difference between the fixed combination and bimatoprost monotherapy ($p=0.014$), the authors are compelled to perform pairwise comparisons without a global significance test. Additionally, it appears that more patients are documented for efficacy (Tab. V) than for safety (Tab. VI), which is curious.

In summary, the results of a 3-week study using over 30 investigators to evaluate a medication intended for those with glaucoma who had failed on one medication, but used in a group of naïve subjects, has proven neither noninferiority nor a superior benefit/risk relationship. Perhaps what is most unique are conclusions derived from methods that diverge from the official view of the European Agency for the Evaluation of Medicinal Products.

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Author reply

I thank Dr. Robin for providing some interesting and insightful feedback on our recent article (1). I would like to clarify the rationale in designing this study and provide more support on how we reached our conclusions.

First, Dr. Robin cites an editorial by Schachat et al (2) as a caveat to the phrase «safe and effective», which has special meaning under US law. We did not use this phrase in our article. Also, this trial was conducted under Good Clinical Practices consistent with FDA guidelines, and the full report of investigation was submitted to both the US and European Health Authorities.

Dr. Robin next questions some aspects of the study design. The 3-week design of this Phase 2 study was selected for the particular question of noninferiority of the fixed combination relative to the individual components. Two Phase 3, 12-month studies were conducted in 1061 patients (3). The maximal effects of Ganfort® in those studies were reached within 2 weeks of starting treatment. With respect to naiveté to β-adrenoceptor antagonists, we specifically selected this population in order to avoid the potential bias of the development of tolerance to the β-adrenoceptor antagonist in this study. The study populations in the Phase 3 studies did not have this restriction, and thus the results are more generalizable and consistent with the European licensing of this product, which is for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues (3).

I reiterate the demonstration of the noninferiority of Ganfort® to the nonfixed bimatoprost/timolol combination. In our study, a noninferiority margin of 1.5 mmHg was met at all three time points for mean IOP. Although our original noninferiority criterion of 1.0 mmHg was not met, the European Medicines Agency noted that «this demand is ambitious as usually the 1.5 mmHg is applied as a limit for non-inferiority» (3). Indeed, the 1.5 mmHg criterion for noninferiority was adopted by Diestelhorst et al and Hughes et al in noninferiority studies for latanoprost/timolol and travoprost/timolol fixed combinations, respectively (5, 6). The 1.0 mmHg criterion was used in an earlier study by Diestelhorst et al, but the latanoprost/timolol fixed combination failed to meet this criterion (7). Given the accepted difficulty in meeting the 1.0 mmHg criterion, it is encouraging to note that Ganfort® met this criterion

at the 4 PM timepoint and was below 1.3 mmHg at both the 8 AM and 10 AM timepoints (1).

In our article, we reported conjunctival hyperemia both as observed by the investigators upon biomicroscopic investigation and as reported by the patients. Pairwise probability comparisons were performed when the among-group p value was ≤0.05. The former were presented in the text as 8.5% (15/176), 12.5% (22/176), and 18.9% (17.90) in the fixed combination, non-fixed combination, and bimatoprost groups, respectively (among-group p value, 0.050; fixed combination vs bimatoprost, p value = 0.014; fixed combination vs nonfixed, p-value = 0.224). The latter are presented in Table VI as noted by Dr. Robin (19.3%, 34/176, 25.6%, 45/176, and 27.8%, 25/90) in the fixed combination, non-fixed combination, and bimatoprost groups, respectively (among-group p value, 0.218). While the absolute magnitude and p values differ, the fixed combination clearly has lower values than the other two groups. While we believe that the observations of the ophthalmologist are more important, we present both in the Results section so that the reader may make his or her own judgment.

With regard to the sample size, we clearly state that the enrollment was 445 patients, and we present demographics and efficacy data on this intent-to-treat population, consistent with our a priori plan. We also clearly state that the safety analysis was based upon the 442 patients confirmed to have received at least one dose of study medication.

In summary, we reiterate our conclusions: 1) the fixed combination of bimatoprost 0.03%/timolol 0.5% administered once daily was comparable in ocular hypotensive efficacy to the nonfixed combination, and 2) the lower propensity of the fixed combination to elicit conjunctival hyperemia suggests a superior comparative benefit/risk assessment of the fixed combination in the treatment of elevated IOP.

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