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CLINICAL STUDY

Efficacy and safety of fixed combinations of latanoprost/timolol and dorzolamide/timolol in open-angle glaucoma or ocular hypertension

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Abstract

Aims **To compare intraocular pressure (IOP) reductions with fixed-combination (FC) latanoprost/timolol once daily in the evening *vs* FC dorzolamide/timolol twice daily.**
Methods **This evaluator-masked, multicentre, controlled clinical trial randomized subjects with primary open-angle glaucoma or ocular hypertension with IOP insufficiently responsive to β-blocker therapy (screening IOP > 21 and < 37 mm Hg) to FC latanoprost–timolol ($N = 135$) or FC dorzolamide/timolol ($N = 135$). At screening, baseline, and after 4 and 12 weeks of therapy, IOP was measured three times at 0800, 1200, and 1600 hours. Adverse events were recorded at each visit. The primary efficacy end point was whether either FC could be shown to be inferior to the other with respect to change in mean daytime IOP from baseline to week 12.**
Results **Mean daytime IOP levels were similar at baseline. Mean reductions in daytime IOP from baseline to week 12 were −9.7 mm Hg for FC latanoprost–timolol and −9.5 mm Hg for FC dorzolamide/timolol. The difference between FC latanoprost/timolol–FC dorzolamide–timolol was −0.2 mm Hg (95% confidence interval (CI), −0.8 to –0.4 mm Hg). The upper bound of the 95% CI was < 1.5 mm Hg, indicating that neither FC is inferior to the other. However, a significantly greater percentage of subjects treated with FC latanoprost/timolol achieved IOP levels ⩽16 and ⩽15 mm Hg ($P \leqslant 0.01$). Both treatments were well tolerated.**
Conclusions **When β-blocker therapy is inadequate, either FC may achieve the desired IOP level, but FC latanoprost/timolol more oftenly achieves a pressure of ⩽16 mm Hg. Both FCs were well tolerated.**

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Keywords: dorzolamide; fixed combination; latanoprost; ocular hypertension; open-angle glaucoma; timolol

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Introduction

In many patients with glaucoma or ocular hypertension, targeted intraocular pressure (IOP) control is not obtained with a single topical ocular hypotensive agent;[1,2] multidrug regimens or fixed-combination (FC) therapies are often warranted. The β-adrenergic receptor antagonist timolol, which primarily acts by decreasing the rate of production of aqueous humour by the ciliary epithelium, commonly has been combined with other drugs to lower IOP in an additive or synergistic manner.[3–8] Latanoprost (Xalatan, Pfizer Inc, New York, NY, USA), a prostaglandin $F_{2\alpha}$ analog that is effective and relatively safe in the treatment of glaucoma and ocular hypertension,[9–13] acts by increasing the outflow,[14–16] a mechanism possibly complementary to that of timolol. Studies have confirmed the additive effect of this combination in lowering IOP.[17–19]

Combining the two medications in an FC formulation is preferable to the administration of two individual agents to maximize patient medication adherence and quality of life.[20–24] The FC of latanoprost 0.005% and timolol 0.5% (Xalacom, Pfizer Inc., NY, USA) was first

approved in December 2000 by the Medical Products Agency in Sweden and since then has been registered and/or approved for marketing in 60 other countries.[25] Recently, a trend towards a greater daytime reduction with nighttime dosing of FC latanoprost/timolol has been shown, whereas morning dosing tended to give lower nighttime pressures.[26]

Another available effective FC product combines timolol 0.5% and the topical anhydrase inhibitor dorzolamide 2.0%, which acts similarly to timolol in suppressing the production of aqueous humour[27] but is dosed twice daily (Cosopt, Merck & Co., Inc., Blue Bell, PA, USA).

The purpose of this study was to compare IOP reductions after treatment with FC latanoprost/timolol administered once daily in the evening with reductions associated with twice-daily administration of FC dorzolamide/timolol over a 12-week period. The primary objective was to show the noninferiority of FC timolol/latanoprost; the experimental design also served to determine the converse, that is, whether FC dorzolamide/timolol is inferior to FC latanoprost/timolol. Considering the results of previous studies,[9,26,28] a greater IOP reduction in daytime IOP levels was expected with an evening dosing of FC latanoprost/timolol.

Materials and methods

Study design

This 12-week, randomized, parallel-group, evaluator-masked study was conducted at 25 centres in Europe (Germany, 6; Italy, 6; France, 5; Greece, 4; and Sweden, 4; NCT00140049). The final protocol and informed consent documentation were reviewed and approved by the Independent Ethics Committees at each participating investigational centre. The study was conducted in compliance with the Declaration of Helsinki's principle and with all International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from all subjects before study enrollment. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Subjects

See Table 1 for study inclusion and exclusion criteria. Note that according to the European Glaucoma Society Guidelines,[20] if monotherapy is inadequately effective (or has no effect), the agent should be withdrawn and substituted before adding a second drug. However, if the first-choice agent effectively lowers the IOP but not to the target level, adjunctive therapy can be added. In cases in which two therapies are needed, an FC is preferable to individual drugs.[20] Although investigators were expected to follow these guidelines, for practical reasons, data were not collected on IOP levels before therapy, on each of the two monotherapies, and on combination therapy. Therefore, the degree of nonresponsiveness to β-blocker therapy was not documented or analysed or may have varied among investigators, but should represent the usual practice within the regions represented by the investigators.

Treatments and assessments

Potentially eligible subjects were assessed at a screening visit 7 days to 4 weeks before study entry. Medical and ocular histories were recorded; visual acuity was measured; and visual field (if not performed within the previous year), gonioscopy (if not documented during the previous 5 years), lid and slit-lamp examination, and ophthalmoscopy were performed. Intraocular pressure levels were measured with a calibrated Goldmann applanation tonometer. All ocular measurements were performed in both eyes. Required washout periods before the baseline visit were 4 weeks for β-adrenergic antagonists and prostaglandin analogues, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists and carbonic anhydrase inhibitors. Subjects requiring a 4-week washout returned after 2 weeks for an IOP safety check.

Study visits occurred at baseline and at weeks 4 and 12. At the baseline visit, visual acuity measurement and lid and slit-lamp examinations were repeated, and masked evaluators measured and recorded IOP levels three times in each eye, starting with the right eye, at 0800, 1200, and 1600 hours. To be eligible for randomization, the mean of these IOP measurements must be $\geqslant 24$ and <37 mm Hg in the eye with the higher mean IOP. If both eyes of a subject met all inclusion and no exclusion criteria and had identical IOP levels, the right eye was used for randomization. Eligible subjects were assigned consecutively to one of the two treatment groups (1 : 1 ratio) using a randomized code generated by Pfizer Inc. and retained at Global Pharmacy Operations. Randomization was performed independently within each centre with a fixed block size of 4. Subjects assigned to latanoprost/timolol FC were instructed to instill one drop of study drug once daily in the evening; those assigned to dorzolamide/timolol FC were instructed to administer one drop of study drug in the morning and in the evening.

All study drugs were supplied in commercially labeled bottles. The study was evaluator masked, but subjects could not be masked because of differences in the

Table 1 Study entry criteria

Inclusion criteria	*Exclusion criteria*
Age $\geqslant$18 years	Closed or basely open anterior chamber angle, history of acute angle closure glaucoma, or history of any ocular filtering surgical intervention (unfiltered eye could be enrolled)
Unilateral or bilateral open-angle glaucoma, including pseudoexfoliative glaucoma, or ocular hypertension	Argon laser trabeculoplasty, selective laser trabeculoplasty, ocular surgery, or inflammation in the study eye within 3 months before baseline (unlasered/unfiltered eye could be enrolled)
Received β-adrenergic receptor antagonists either as monotherapy or as part of dual therapy for at least 4 weeks before screening	Changed ocular hypotensive therapy within 1 month before screening visit
Insufficient response to current IOP-lowering monotherapy or dual therapy at screening (mean of 0800 h measurements $>$21 and $<$37 mm Hg in at least one eye)	Known hypersensitivity to benzalkonium chloride or any other component of the study drug solutions
Baseline mean IOP of 0800, 1200, and 1600 h measurements $>$24 and $<$37 mm Hg in at least one eye at baseline	Ocular infection within 3 weeks before screening visit in study eye or use of an investigational medication within 30 days preceding screening
Best-corrected visual acuity $\geqslant$20 of 200	Any abnormal ocular conditions/symptoms or any uncontrolled systemic disease that would prevent study entry (opinion of investigator)
Able to adhere to the treatment/visit plan; highly motivated to complete all study visits; capable of understanding/signing an informed consent	Use of a systemic medication known to affect IOP levels (including β-adrenergic antagonists) unless subject and dosage were stable for 3 months before screening and dosage was not expected to change during the study Conditions in which treatment with a β-adrenergic receptor antagonist was contraindicated Woman of childbearing potential who was not using adequate contraceptive methods or was pregnant or nursing

Abbreviation: IOP, intraocular pressure.

frequency of administration of study medications. Subjects were cautioned not to reveal the study assignment or the frequency of administration to the masked evaluator, and bottles were packaged in small black cylinders to protect the evaluator masking. Each subject received two black cylinders at baseline and three black cylinders at week 4; each bottle was expected to last for 4 weeks. For subjects assigned to FC latanoprost/timolol, the first drop was instilled the evening after the baseline visit. Those assigned to FC dorzolamide/timolol instilled the first drop the morning after the baseline visit; at week 4 and 12 visits, to preserve masking, the morning dose was instilled after an IOP level measurement was performed without the investigator's presence. It was requested that the same examiner measure the IOP levels using the same calibrated tonometer at each time point and at each visit for a given subject. At weeks 4 and 12, visual acuity was measured and lid and slit-lamp examinations were repeated; refraction and ophthalmoscopy were performed at week 12.

Adverse events were monitored and recorded by investigators throughout the study. The severity of events and the investigator's opinion of the relationship with the study treatment were noted. An event was classified as serious if it was life threatening, required inpatient hospitalization or prolonged hospitalization, resulted in persistent or significant disability/incapacity, or resulted in a congenital anomaly/birth defect. Adverse events were followed until they resolved or stabilized.

Variables and analyses

The primary end point was the mean change in daytime IOP from baseline to week 12 in the study eye. The daytime IOP for a given subject at any visit was calculated as the mean of IOP level measurements at 0800, 1200, and 1600 hours; if the IOP measurement at any time point was missing, daytime IOP was calculated as the mean of nonmissing IOP measurements.
The analysis of covariance (ANCOVA) model was used to analyse the mean change in daytime IOP, with baseline daytime IOP as the covariate, and treatment and centre as factors. The treatment difference (FC latanoprost/timolol–FC dorzolamide/timolol) and a two-sided

95% confidence interval (CI) for the difference were calculated. FC latanoprost/timolol was considered to be noninferior to FC dorzolamide/timolol if the upper limit of the 95% CI of the difference was <1.5 mm Hg; FC latanoprost/timolol was considered to be superior if the upper limit of the 95% CI was <0 mm Hg.

Secondary efficacy end points included mean daytime IOP change from baseline to week 4; change from baseline in the mean IOP at weeks 4 and 12 at all measurement time points; the percentage of subjects reaching prespecified percentage reductions in IOP from baseline to weeks 4 and 12 (from $\geqslant 5$ to $\geqslant 40\%$ in 5% increments); and the percentage of subjects attaining prespecified IOP levels after 4 and 12 weeks of treatment (from $\leqslant 22$ to $\leqslant 15$ mm Hg in 1 mm Hg increments). An ANCOVA model was applied to the analysis of mean change in daytime IOP from baseline to week 4, with baseline IOP as the covariate and treatment and centre as factors; two-sided 95% CIs were calculated. Between-group differences in percentages were evaluated with the Cochran–Mantel–Haenszel test or the Fisher's exact test if the expected marginal size was <5. Adverse events were classified by body system and preferred term using the Medical Dictionary for Regulatory Activities coding system.

The intent-to-treat population (ITT) included all randomized subjects who had at least one postbaseline IOP measurement; the per protocol (PP) population included all those in the ITT population who had no major protocol violations, who completed IOP measurements within the allowed time frames, who completed $\geqslant 75$ days of treatment with the last dose administered before or on the day of the week 12 visit, and who did not take prohibited concurrent medication. Analyses using the ITT populations used the last observation carried-forward method; missing observations at weeks 4 or 12 were extrapolated by carrying forward the last postbaseline nonmissing observation. No imputation was applied to the PP population. The PP population was used to perform tests of noninferiority for daytime IOP levels and IOP levels at the three measurement time points at week 12. The ITT population was used to support tests of noninferiority at week 12, to evaluate noninferiority at week 4, and for analyses of between-group differences in percentages of subjects reaching prespecified percentage reductions in IOP and attaining prespecified IOP levels. Safety analyses included all randomized subjects. Statistical analyses were performed using SAS/UNIX Version 8.2 (SAS Institute, Cary, NC, USA).

The sample size was calculated using a *t*-test with a one-sided significance level of 2.5 and 80% power. Before the study it was determined that a sample of 113 evaluable subjects per treatment group was required to test a noninferiority margin of 1.5 mm Hg assuming a common standard deviation of the between-group difference of 4.0 mm Hg. Assuming an attrition rate of 5%, 238 subjects were targeted for enrollment. Sample size calculations were performed using the MTT0 program in nQuery, Version 4.0 (Statistical Solutions, Saugus, MA, USA).

Results

A total of 300 subjects entered the washout period, and 270 subjects were randomized, 135 to each treatment group. Most subjects completed the study (95%; 257 of 270), 128 in the FC latanoprost/timolol group and 129 in the FC dorzolamide/timolol group. The number of subjects withdrawing from the study was comparable across groups. The PP population included 121 subjects in the FC latanoprost/timolol group and 117 in the FC dorzolamide/timolol group; the ITT population included 133 subjects per treatment group.

At baseline, treatment groups generally were similar with regard to demographic and clinical characteristics (Table 2). Although the female to male ratio was higher in the FC dorzolamide/timolol group, the between-group difference was not statistically significant. The average spherical equivalent was close to plano for both treatment groups, with mean (SD) reported as -0.45 (3.07) in the FC latanoprost/timolol group and as -0.35 (2.68) in the FC dorzolamide/timolol group. In all, 134 of 135 (99.3%) subjects in the FC latanoprost/timolol group and 135 of 135 (100%) subjects in the FC dorzolamide/timolol group had been treated for the primary diagnosis before the start of the study. Systemic β-blockers were administered concomitantly during the study in 22 (18%) subjects in the FC latanoprost/timolol group and in 12 (10%) subjects in the FC dorzolamide/timolol group.

Efficacy

In the PP population, mean daytime IOP levels at baseline were 26.6 mm Hg (SD, 2.8) and 27.3 mm Hg (SD, 3.2) in the FC latanoprost/timolol and dorzolamide/timolol groups, respectively (Table 3). Least square mean (standard error (SE)) changes in daytime IOP from baseline to week 12 (primary efficacy end point) were -9.7 mm Hg (0.2) in the FC latanoprost/timolol group and -9.5 mm Hg (0.2) in the FC dorzolamide/timolol group (Table 3). The treatment difference was -0.2 mm Hg (0.3) with a 95% CI of -0.8 to 0.4 mm Hg, favouring the latanoprost/timolol FC. The upper bound of 95% CI was <1.5 mm Hg, indicating that neither FC was inferior to the other ($P=0.51$). These results were only minimally impacted when the variable 'gender' was added to the ANCOVA model. The noninferiority of the

Table 2 Baseline demographic and clinical characteristics by treatment group

	Fixed-combination latanoprost/timolol (N = *135*)	*Fixed-combination dorzolamide/timolol* (N = *135*)
Age, years; mean (SD)	65.8 (11.3)	66.6 (10.0)
Gender		
Male	67 (49.6%)	54 (40.0%)
Female	68 (50.4%)	81 (60.0%)
Ethnic origin		
Caucasian	126 (93.3%)	128 (94.8%)
Other	9 (6.7%)	7 (5.2%)
Primary diagnosis, study eye		
POAG	92 (68.2%)	100 (74.1%)
PEX glaucoma	11 (8.2%)	12 (8.9%)
OHT	32 (23.7%)	23 (17.0%)
Study eye		
Right	26 (19.3%)	24 (17.8%)
Left	25 (18.5%)	27 (20.0%)
Both	84 (62.2%)	84 (62.2%)
Screening IOP at 0800 h	23.28 (1.91)	23.13 (2.02)
Baseline daytime IOP	26.54 (2.74)	26.98 (3.16)
Drug treatment for primary diagnosis before study		
Any treatment	134	135
α-Adrenergic agonist	7	2
β-Adrenergic receptor antagonist	125	125
Carbonic anhydrase inhibitor	10	12
Prostaglandin analog	23	18
Parasympathomimetic	2	0
Combination (including β-adrenergic receptor antagonists)	22	20
Other	2	1

Abbreviations: IOP, intraocular pressure; OHT, ocular hypertension; PEX, pseudoexfoliation; POAG, primary open-angle glaucoma; SD, standard deviation.

agents at week 12 with regard to changes in daytime IOP levels was supported by results of a parallel analysis in the ITT population ($P = 0.08$ for between-group difference).

Mean daytime IOP levels at weeks 4 and 12 were similar in the two treatment groups and were consistent in the PP and ITT populations (Figure 1). At week 12, treatment differences in IOP changes from baseline at 0800, 1200, and 1600 hours were small and not statistically significant in either PP (Table 3) or ITT populations (data not shown). No significant differences were noted with regard to percentages of subjects achieving prespecified percentages of mean daytime IOP reduction at the end of the treatment. Percentages of subjects reaching specific levels of daytime IOP at week 12 generally were similar with no statistically significant differences between treatment groups at levels of $\geqslant$17 mm Hg (Figure 2). However, significantly greater percentages of those treated with FC latanoprost/timolol achieved IOP levels $\leqslant$16 and $\leqslant$15 mm Hg at week 12 ($P \leqslant 0.01$; Figure 2).

Safety

Both FC agents were well tolerated. In all, 35 of 135 (25.9%) subjects in the FC latanoprost/timolol group and 41 of 135 (30.4%) in the FC dorzolamide/timolol group reported adverse events. The most frequently occurring adverse events were ocular, which affected similar numbers of subjects in the two groups (17 of 135 (12.6%) *vs* 20 of 135 (14.8%), respectively). The most commonly noted ocular adverse events in the FC latanoprost/timolol group were eye pruritus and ocular hyperaemia (each occurring in 3 of 135 subjects; 2.2%); most frequently reported ocular adverse events in the FC dorzolamide/timolol group were eye pain, blurred vision, and visual acuity reduction (each occurring in 4 of 135 subjects; 3.0%). Ocular events, which are considered to be treatment related, were reported in 8.9% (12 of 135) of subjects in both groups. With regard to systemic adverse events, nervous system disorders occurred in 2 of 135 (1.5%) subjects in the FC latanoprost/timolol group and in 6 of 135 (4.4%) subjects in the FC dorzolamide/timolol group; systemic adverse event profiles for all other nonocular body systems were similar (<2% between-group difference). Two subjects reported serious adverse events, one in each treatment group; neither event was considered to be related to study medication and both resolved. No deaths were reported.

Discussion

This 12-week, multicentre, randomized, evaluator-masked, parallel-group study, which included a 4-week washout period between screening and baseline, is the largest study to date comparing FC latanoprost/timolol administered once daily in the evening with FC dorzolamide/timolol instilled twice daily. There was no demonstrable difference in effectiveness between the two FC eye drops, neither being inferior to the other, when mean daytime IOP levels based on 0800, 1200, and 1600-hour measurements were compared after 4 and 12 weeks of treatment. Least square mean changes in daytime IOP levels from baseline to week 12 (primary efficacy end point) were −9.7 and −9.5 mm Hg in the latanoprost/timolol and dorzolamide/timolol FC groups, respectively.

Table 3 Least square mean (SE) change in IOP from baseline to week 12 by treatment group[a]

Measurement time	*Baseline IOP (mm Hg) mean (SD)*		*IOP change from baseline to week 12 (mm Hg) least square mean (SE)*		*95% CI*	*Between-group P-value*
	Fixed-combination latanoprost/timolol (N = 121)	*Fixed-combination dorzolamide/timolol (N = 117)*	*Fixed-combination latanoprost/timolol (N = 121)*	*Fixed-combination dorzolamide/timolol (N = 117)*		
Daytime	26.6 (2.8)	27.3 (3.2)	−9.7 (0.2)[b]	−9.5 (0.2)[b]	−0.8, 0.4	0.51
0800 hours	26.8 (3.4)	27.7 (3.9)	−9.8 (0.2)[b]	−9.5 (0.3)[b]	−0.96, 0.3	0.32
1200 hours	26.9 (3.0)	27.5 (3.5)	−9.8 (0.2)[b]	−9.7 (0.3)[b]	−0.8, 0.5	0.72
1600 hours	26.3 (3.1)	26.7 (3.1)	−9.6 (0.2)[b]	−9.4 (0.3)[b]	−0.9, 0.4	0.43

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; IOP, intraocular pressure; SD, standard deviation; SE, standard error.
ANCOVA model, including treatment and pooled-centre as factors and baseline IOP as covariate.
[a]Per protocol population.
[b]Within-treatment change from baseline, $P<0.0001$.

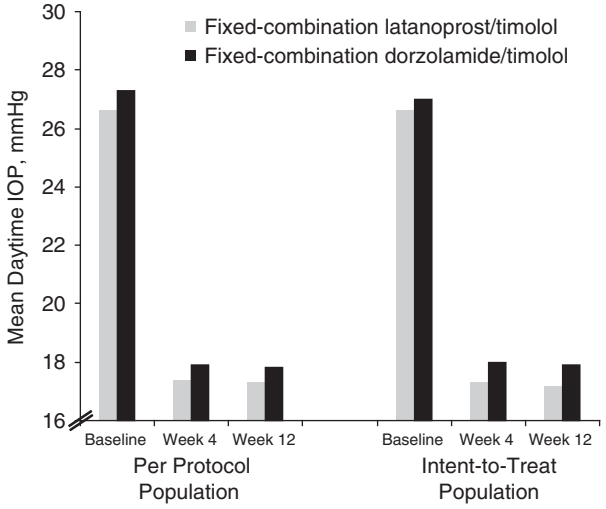

Figure 1 Mean daytime intraocular pressure (IOP) levels by visit for the per protocol and intent-to-treat populations.

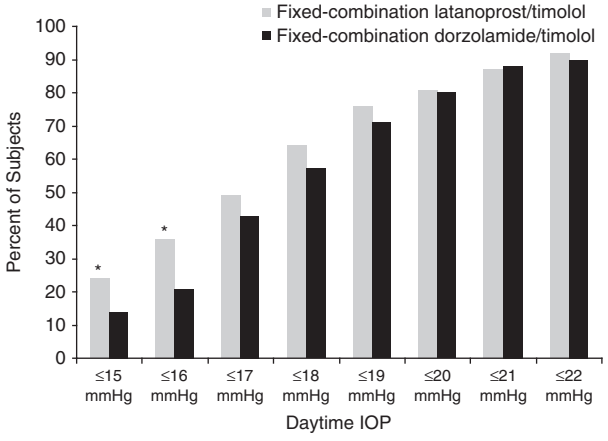

Figure 2 Subjects reaching prespecified mean daytime intraocular pressure (IOP) levels at week 12 (intent-to-treat population); *$P \leqslant 0.01$. *P*-values are based on pooled, center-stratified Cochran–Mantel–Haenszel analysis comparing FC latanoprost/timolol with FC dorzolamide/timolol.

The finding of equivalent effectiveness parallels the results of two previous studies in which FC latanoprost/timolol was administered in the evening.[29,30] A 3-month crossover study[29] of second-line therapy in 31 patients insufficiently controlled on latanoprost monotherapy with open-angle glaucoma or exfoliative glaucoma found no statistical differences between the two FCs in mean 24-h IOP levels, maximum or minimum IOP levels, or IOP levels measured at six individual time points. Another crossover study[30] of 32 newly diagnosed, open-angle glaucoma, treatment-naive patients found that both treatments significantly reduced the IOP levels (measured once in the morning) between baseline and month 1. Two additional studies[31,32] compared the outcomes in subjects treated with FC latanoprost/timolol administered in the morning *vs* FC dorzolamide/timolol instilled twice daily. A double-masked, 8-week, crossover study in 33 patients[32] found mean daytime IOP levels to be statistically similar across treatments. In contrast, a 3-month, randomized, parallel-group, evaluator-masked study[31] in 253 subjects found that FC latanoprost/timolol reduced the mean daytime IOP by 1 mm Hg more than the comparator ($P = 0.005$) and that mean IOP levels after 3 months of treatment were significantly lower in the FC latanoprost/timolol group at 0800 and 1600 hours ($P < 0.01$ for both comparisons).

In this study, the decrease in IOP was somewhat less marked than expected in view of the results of previous studies showing increased efficacy with nighttime dosing of latanoprost.[17,28] In the present research, both combination therapies showed a mean IOP-reducing effect from baseline of about 35%. As far as FC latanoprost/timolol is concerned, this level of reduction is toward the high end of the range of decreases found in previous studies[31,33–39] with morning dosing and no timolol run-in (range, 31.5–36.0%). With regard to the FC

dorzolamide/timolol; however, the percentage daytime IOP reduction found herein is considerably larger than those reported in five of six previously published studies (range, 25.2–31.2%). Although systemic β-blockers are known to potentially interfere with the reduction of IOP induced by timolol,[40] use of systemic β-blockers was not an exclusion criterion in this study if the subject and dosage were stable for 3 months before screening and if the dosage was not expected to change during the study. Use of systemic β-blockers occurred in 22 (18%) of the FC latanoprost/timolol group and in 12 (10%) subjects in the FC dorzolamide/timolol group.

At 12 weeks, similar numbers of subjects in each treatment group achieved prespecified percent IOP reductions from baseline, but a significantly greater percentage of subjects achieved IOP levels of $\leqslant$16 mm Hg with FC latanoprost/timolol (36 *vs* 21%; $P = 0.001$). This finding may reflect differences in the mechanisms of action of the individual agents.[41] Both timolol and dorzolamide lower the rate of aqueous humour formation affecting the inflow pathway, whereas latanoprost facilitates the outflow pathways.

In general, both treatments were well tolerated and safe. Overall, there was no specific trend in occurrence of either ocular or systemic adverse events, and the number of subjects withdrawn because of an adverse event was low in both treatment groups.

In patients in whom a given monotherapy does not sufficiently reduce IOP levels, the practitioner may first consider a trial with alternative monotherapy. In those patients for whom individual ocular hypotensive therapy provides a response but does not reduce the IOP to the target level (insufficient response), European Glaucoma Society Guidelines[20] advise that adjunctive therapy can be initiated and that combination therapy is preferable to individual therapies. Topical treatment with multiple agents should be avoided where possible to enhance compliance.[20]

This study had several strengths and limitations. For example, we used an evaluator-masked approach to reduce bias in clinical assessments, and investigator masking was maintained by packaging the treatments into small black cylinders to protect the identity of the bottles within. Generally, treatment groups were well balanced in terms of baseline demographic and clinical characteristics, including baseline IOP; the potential impact of the nonstatistically significant between-group imbalance in the male to female ratio was tested in the ANCOVA model for the primary analysis and was found to impact the results only minimally. This study was limited by its relatively short time frame, as 12 weeks is not sufficiently long enough to evaluate long-term efficacy or safety, changes in visual acuity, visual field, or cup-to-disc ratio.

In conclusion, the study showed that, when β-blocker therapy is inadequate, both FC treatments result in clinically and statistically significant decreases in post-baseline IOP levels and are well tolerated.

Summary

What was known before

- Small studies have compared fixed-combination latanoprost/timolol administered once daily in the evening with fixed-combination dorzolamide/timolol instilled twice daily.

What this study adds

- Fixed-combination latanoprost/timolol administered once daily in the evening was at least as effective as fixed-combination dorzolamide/timolol administered twice daily in reducing mean daytime intraocular pressure.
- Both treatments were associated with post-baseline decreases in intraocular pressure levels and were well tolerated.

Conflict of interest

Dr Grunden and Mr Kwok are employees of Pfizer Inc. Dr Miglior declares no conflict of interest.

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Appendix A

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