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**PROPRIETARY DRUG NAME®/GENERIC DRUG NAME:** Xalacom™ / Latanoprost and Timolol

**PROTOCOL NO.:** A6641038

**PROTOCOL TITLE:** A 12-Week Randomized, Evaluator-Masked, Parallel-Group, Multinational, Multi-Center Study Comparing the Efficacy and Safety of the Fixed Combination of Latanoprost and Timolol (Xalacom™) With the Fixed Combination of Dorzolamide and Timolol (Cosopt®) in Subjects With Open-Angle Glaucoma or Ocular Hypertension

**Study Centers:** A total of 25 centers took part in the study and randomized subjects; 6 each in Germany and Italy, 5 in France, and 4 each in Greece and Sweden.

**Study Initiation Date and Final Completion Date:** 08 July 2005 to 25 July 2006

**Phase of Development:** Phase 3b

**Study Objectives:**

Primary Objective: To demonstrate the mean diurnal intraocular pressure (IOP) reducing effect of latanoprost and timolol administered once daily (QD) in the evening is non-inferior to that of dorzolamide and timolol administered twice daily (BD) from baseline to Week 12.

Secondary Objective: To compare the following for the two treatment groups: the mean diurnal IOP measurements at Week 4, the mean IOP measurements at each time point (8 AM, 12 PM and 4 PM) after 4 and 12 weeks of treatment, and safety over the 12-week period.

**METHODS:** This was a 12-week, multi-center, randomized, evaluator-masked, parallel group study.

Subjects had their IOP measured at 8 AM at the screening visit and those with a mean IOP measurement of >21 mm Hg and <37 mm Hg started a 4-week washout of their current therapies. During the washout period, subjects returned to the study center for safety assessments at the discretion of the Investigator. Subjects who completed the 4-week washout period, and who had a mean IOP of the 8 AM, 12 noon and 4 PM measurements between ≥24 mm Hg and <37 mm Hg were eligible for randomization. Subjects were randomized to one of two groups, latanoprost and timolol or dorzolamide and timolol, for the 12-week evaluator-masked treatment period.

Subsequent study visits were then conducted at Week 4 and Week 12, at which ocular examinations and IOP measurements were performed. All ocular examinations were performed for both eyes, with the right eye preceding the left. Subjects returned to the study center for their final visit at Week 12. The total maximum duration of subject participation was 16 weeks, comprising 4-week washout and a 12-week treatment period.

A schedule of study events is presented in Table 1.

## Table 1. Schedule of Study Events/Assessments

| Protocol Activities and Forms to be Completed | Treatment (Day) | | | | |
|---|---|---|---|---|---|
| | Visit 1 Screening[a] -4 Weeks (-7 Days) | Visit 2 Safety Check -2 Weeks (±3 Days) | Visit 3 Baseline 0 Weeks | Visit 4 Week 4 ±1 Week | Visit 5 Week 12/ Early Discontinuation ±1 Week |
| **Examination Hours** | **8 AM (±30 Minutes)** | **Any Time** | **8 AM 12 Noon 4 PM** | **8 AM[b] (Predose) 12 Noon 4 PM** | **8 AM[b] (Predose) 12 Noon 4 PM** |
| Signed informed consent | X | | | | |
| Inclusion/exclusion | X | | X | | |
| Pregnancy test | X | | X | | X |
| Demographics | X | | | | |
| Medical/ocular history | X | | | | |
| Randomization | | | X | | |
| Visual fields | X[c] | | | | |
| Gonioscopy | X[d] | | | | |
| Visual acuity | X | | X | X | X |
| Refraction | X | | | | X |
| Biomicroscopy (slit lamp examination) | X | | X | X | X |
| IOP | X | X | X[e] | X | X |
| Ophthalmoscopy | X | | | | X |
| Concomitant medications | X | X | X | X | X |
| Previous IOP reducing meds. | X | | | | |
| Adverse events | X | X | X | X | X |
| Study drug dispensed (D) and returned (R) | | | D | R/D | R |

IOP = intraocular pressure.

a. All current ocular hypotensive therapy were required to be discontinued. The Investigator could have substituted a therapy with a shorter washout period for subjects on a therapy requiring a 4 week washout, but the subject had to fulfill the required washout for all therapies prior to baseline. The required washout periods for common treatments were: 4 weeks for β-adrenergic antagonists and prostaglandin analogues (including latanoprost, bimatoprost, travoprost and unoprostone), 2 weeks for adrenergic agonists and 5 days for cholinergic agonists and carbonic anhydrase inhibitors. The screening period was a minimum of 28 days.

b. It was essential that the drops were instilled at the correct times on the day prior to the day of the visit. In addition, the 8 AM IOP was to be performed pre-dose for the weeks 4 and 12.

c. No visual field examination was required if it had been performed and documented within the past year.

d. No gonioscopy was required if it was documented during the previous 5 years.

e. The mean of the 8 am, 12 noon and 4 pm IOP measurements in the eye with the higher of this mean IOP was to be between ≥24 mm Hg to <37 mm Hg for further participation in the study. Subjects were assigned treatment only after required washout periods of up to 4 weeks. Subjects with IOP measurements ≥37 mm Hg were not randomized.

**Number of Subjects (Planned and Analyzed):** A total of 238 subjects were planned for enrollment into the study. A total of 300 subjects were enrolled into the washout period. Of these, 270 subjects (135 in each group) were randomized: 108 in Germany, 62 in Italy, 42 in Greece, 38 in Sweden, and 20 in France.

**Diagnosis and Main Criteria for Inclusion:** Both male and female subjects aged 18 years and older who were diagnosed with uni- or bilateral primary open angle glaucoma or ocular hypertension and who were receiving beta-blocker monotherapy or dual therapy, in which at least 1 medication was a beta-blocker, for 4 weeks prior to screening were included in this

study. Subjects with closed/barely open anterior chamber angle or history of acute angle closure glaucoma, and subjects with history of Argon Laser Trabeculoplasty (ALT) or selective laser (SLT) within 3 months prior to screening were excluded.

**Study Treatment:** Study drugs were supplied as ophthalmic solutions in commercially labeled bottles packed in small black cylinders. Each subject was provided with 6 black cylinders packed in a box for 12-week treatment period.

Each mL of latanoprost-timolol maleate ophthalmic solution contained latanoprost 50 µg (0.005%) and timolol maleate 6.83 mg equivalent to 5 mg (0.5%) timolol. Each mL of dorzolamide hydrochloride-timolol maleate ophthalmic solution contained 20 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg timolol (6.83 mg timolol maleate).

Study treatments were administered as follows:

Latanoprost 50 µg/mL and timolol solution 5 mg/mL: one drop instilled topically to each study eye(s) QD at 8 PM for 12 weeks; or

Dorzolamide 20 mg/mL and timolol solution 5 mg/mL: one drop instilled topically to each study eye(s) BID at 8 AM and 8 PM for 12 weeks.

The first drop was to be instilled in the morning after the baseline visit. The last drop was to be administered in the evening before the final visit date at Week 12. A ±30-minute window was allowed for instillation of study drug into each eye. Treatment with study medication was not continued after the completion of the study. Subjects could then receive IOP-reducing therapy at the discretion of the Investigator.

**Efficacy and Safety Endpoints:**

Primary Endpoint: Mean diurnal IOP change from baseline to Week 12. The diurnal IOP is calculated as the mean of the IOP measurements taken at 8 AM (before dosing), 12 noon, and 4 PM.

Secondary Efficacy Endpoints:

- The mean diurnal IOP change from baseline to Week 4;
- The mean IOP change from baseline to Week 4 at 8 AM;
- The mean IOP change from baseline to Week 4 at 12 PM;
- The mean IOP change from baseline to Week 4 at 4 PM;
- The mean IOP change from baseline to Week 12 at 8 AM;
- The mean IOP change from baseline to Week 12 at 12 PM;

- The mean IOP change from baseline to Week 12 at 4 PM;
- The proportions of subjects with percent reductions at Week 4 from baseline of ≥5%, ≥10%, ≥15%, ≥20%, ≥25%, ≥30%, ≥35%, and ≥40% in diurnal IOP;
- The proportions of subjects with percent reductions at Week 12 from baseline of ≥5%, ≥10%, ≥15%, ≥20%, ≥25%, ≥30%, ≥35%, and ≥40% in diurnal IOP;
- The proportions of subjects achieving diurnal IOP ≤15 mm Hg, ≤16 mm Hg, ≤17 mm Hg, ≤18 mm Hg, ≤19 mm Hg, ≤20 mm Hg, ≤21 mm Hg, and ≤22 mm Hg at Week 4;
- The proportions of subjects achieving diurnal IOP ≤15 mm Hg, ≤16 mm Hg, ≤17 mm Hg, ≤18 mm Hg, ≤19 mm Hg, ≤20 mm Hg, ≤21 mm Hg, and ≤22 mm Hg at Week 12.

Secondary Safety Endpoints: Any ocular and systemic treatment-emergent adverse events (TEAEs) during the 12-week treatment period. Ocular safety assessments (i.e., visual acuity, distance refractive error, cup/disc ratios, biomicroscopy-lid and slit lamp examination of conjunctiva, cornea, iris, anterior chamber and lens, and ophthalmoscopy) at specified visits.

**Safety Evaluations:** Safety evaluations included assessment of TEAEs for their seriousness, severity (mild, moderate, severe), causal association with the study drug; ocular safety assessments including determination of refractive error, any clinically relevant decrease in visual acuity, biomicroscopy performed on the conjunctiva, cornea, anterior chamber, iris, and lens, examination of upper and lower lids, and ophthalmoscopy.

**Statistical Methods:**

The following populations were identified for analysis purposes: the modified intent-to-treat (MITT) population, which comprised of all randomized subjects; the per protocol (PP) population, which comprised of all subjects who qualified for the MITT population and who met the following evaluability criteria: subjects who had no major pre-existing protocol violations, completed IOP measurements according to the scheduled time with the allowed windows, completed at least 75 days of treatment (last dose taken 1 day before or day of Week 12 visit) and did not take any prohibited concurrent medication; and the safety population, which included all subjects who were randomized and received at least 1 dose of study medication.

The analysis of covariance (ANCOVA) model was used to analyze the mean change in diurnal IOP, with baseline diurnal IOP as the covariate, and treatment and center as factors. For mean change in IOP at each time point, the ANCOVA was used, with baseline IOP as the covariate, and treatment and center as factors. Two-sided 95% confidence intervals were constructed for the adjusted means. For the analysis of the proportions, the Cochran-Mantel-Haenszel test controlling for center was used.

The non-inferiority margin was determined to be of 1.5 mm Hg (assuming an equal standard deviation [SD] of 4.0 mm Hg). The PP cohort was used to perform the test of non-inferiority; the MITT cohort was used to support the test of non-inferiority.

Only the IOP measurements of the study eye(s) were used in the efficacy analysis.

**RESULTS:**

**Subject Disposition and Demography:** Table 2 presents a summary of subject disposition and subjects analyzed. A total of 300 subjects were enrolled and entered the washout.

**Table 2. Subject Disposition and Subjects Analyzed**

| Number of Subjects (%) | Latanoprost-Timolol | Dorzolamide-Timolol |
|---|---|---|
| Assigned to study treatment | 135 (100%) | 135 (100%) |
| Treated | 135 (100%) | 135 (100%) |
| Completed study | 128 (94.8%) | 129 (95.6%) |
| Discontinued | 7 (5.2%) | 6 (4.4%) |
| Related to study drug | 5 (3.7%) | 5 (3.7%) |
| Adverse event | 5 (3.7%) | 5 (3.7%) |
| Not related to study drug | 2 (1.5%) | 1 (0.7%) |
| Adverse event | 1 (0.7%) | 0 |
| Other | 1[a] (0.7%) | 0 |
| Subject defaulted | 0 | 1[b] (0.7%) |
| Analyzed for efficacy | | |
| MITT population | 133 (98.5%) | 133 (98.5%) |
| Per protocol population | 121 (89.6%) | 117 (86.7%) |
| Analyzed for safety | | |
| Safety population | 135 (100%) | 135 (100%) |

MITT = modified intent-to-treat.
a. Discontinued due to protocol violation.
b. Subject withdrew consent.

The baseline demographic characteristics are summarized in Table 3. The treatment groups were generally well matched with respect to age, race, weight, and height.

**Table 3. Summary of Demography (All Randomized Subjects)**

| | Latanoprost-Timolol (N=135) | Dorzolamide-Timolol (N=135) |
|---|---|---|
| Sex, n | | |
| Male | 67 | 54 |
| Female | 68 | 81 |
| Age (years) | | |
| Mean (SD) | 65.8 (11.3) | 66.6 (10.0) |
| Range | 25-90 | 27-85 |
| 18-44 years | 5 (3.7%) | 4 (3.0%) |
| 45-64 years | 51 (37.8%) | 45 (33.3%) |
| ≥65 years | 79 (58.5%) | 86 (63.7%) |
| Ethnic origin, n (%) | | |
| White | 126 (93.3%) | 128 (94.8%) |
| Asian | 1 (0.7%) | 0 |
| Other | 7 (5.2%) | 7 (5.2%) |
| Unspecified | 1 (0.7%) | 0 |

N = number of subjects in each treatment group; n = number of subjects with specified criteria; SD = standard deviation.

A total of 92 (68.15%) subjects versus 100 (74.07%) subjects in the latanoprost-timolol group versus dorzolamide-timolol group were diagnosed with primary open angle glaucoma, 11 (8.15%) versus 12 (8.89%) and 32 (23.70%) versus 23 (17.04%) in the latanoprost-timolol group versus dorzolamide-timolol group were diagnosed with pseudoexfoliation glaucoma and ocular hypertension of the study eye(s), respectively.

**Efficacy Results:** The mean diurnal IOP at baseline was 26.64 mm Hg (SD 2.82) in the latanoprost-timolol group and 27.30 mm Hg (SD 3.21) in the dorzolamide-timolol group. There was no statistical difference in baseline IOP between the 2 treatment groups. Treatment groups were well balanced in terms of demography and baseline characteristics including baseline IOP.

Table 4 presents IOP change from baseline to Week 12 for both treatment groups for the PP and MITT populations.

**Table 4. Diurnal Intraocular Pressure (mm Hg): Change From Baseline to Week 12**

| | | Latanoprost-Timolol | Dorzolamide-Timolol | Treatment Difference (SE) | 95% CI | Between Treatment p-value |
|---|---|---|---|---|---|---|
| Per protocol population | N | 121 | 117 | -0.19 (0.29) | (-0.772, 0.382) | 0.506 |
| | Min | -19.89 | -19.11 | | | |
| | Max | -2.33 | -2.78 | | | |
| | LS Mean | -9.71 | -9.52 | | | |
| | SE | 0.22 | 0.23 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |
| Modified intent-to-treat population | N | 133 | 133 | -0.52 (0.29) | (-1.095, 0.060) | 0.079 |
| | Min | -19.89 | -19.11 | | | |
| | Max | -1.06 | -1.00 | | | |
| | LS Mean | -9.65 | -9.13 | | | |
| | SE | 0.22 | 0.22 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |

CI = confidence interval; LS Mean = least square mean; Max = maximum; Min = minimum; N = number of subjects in each treatment group; SE = standard error.

The secondary efficacy endpoints of change from baseline to Weeks 4 and 12 in diurnal IOP and the 3 time points also support that latanoprost-timolol was non-inferior to dorzolamide-timolol.

Table 5 presents IOP change from baseline to Week 4 for both treatment groups for the MITT population.

**Table 5. Intraocular Pressure (mm Hg): Change From Baseline to Week 4 (MITT Population)**

| | | Latanoprost-Timolol (N=133) | Dorzolamide-Timolol (N=133) | Treatment Difference (SE) | 95% CI | Between Treatment p-value |
|---|---|---|---|---|---|---|
| Diurnal | N | 133 | 133 | -0.57 (0.26) | (-1.089, -0.061) | 0.028 |
| | Min | -21.11 | -19.89 | | | |
| | Max | -0.78 | -0.67 | | | |
| | LS Mean | -9.54 | -8.96 | | | |
| | SE | 0.2 | 0.2 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |
| 8:00 AM | N | 133 | 132 | -0.94 (0.30) | (-1.539, -0.344) | 0.002 |
| | Min | -24 | -21.33 | | | |
| | Max | 0.33 | 1.67 | | | |
| | LS Mean | -9.75 | -8.81 | | | |
| | SE | 0.23 | 0.23 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |
| 12 noon | N | 133 | 133 | -0.32 (0.29) | (-0.883, 0.247) | 0.269 |
| | Min | -18.67 | -23 | | | |
| | Max | -0.67 | 1 | | | |
| | LS Mean | -9.55 | -9.23 | | | |
| | SE | 0.22 | 0.22 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |
| 4:00 PM | N | 133 | 131 | -0.44 (0.28) | (-0.997, 0.116) | 0.120 |
| | Min | -22.33 | -18.67 | | | |
| | Max | -0.5 | 0.17 | | | |
| | LS Mean | -9.33 | -8.89 | | | |
| | SE | 0.21 | 0.22 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |

CI = confidence interval; LS Mean = least square mean; Max = maximum; Min = minimum;
MITT = modified intent-to-treat; N = number of subjects in each treatment group; SE = standard error.

Table 6 presents mean IOP change from baseline to Week 12 at 8 AM, 12 PM, and 4 PM.

## Table 6. Intraocular Pressure (mm Hg): Change From Baseline to Week 12 At Specified Time Points

| | | Latanoprost-Timolol | Dorzolamide-Timolol | Treatment Difference (SE) | 95% CI | Between Treatment p-value |
|---|---|---|---|---|---|---|
| **Per Protocol Population** | | | | | | |
| 8:00 AM | N | 121 | 117 | -0.32 (0.32) | (-0.962, 0.315) | 0.319 |
| | Min | -21.67 | -21.00 | | | |
| | Max | 0.50 | -3.00 | | | |
| | LS Mean | -9.81 | -9.48 | | | |
| | SE | 0.24 | 0.25 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |
| 12 noon | N | 121 | 117 | -0.12 (0.32) | (-0.750, 0.519) | 0.720 |
| | Min | -19.00 | -21.00 | | | |
| | Max | -4.00 | -0.67 | | | |
| | LS Mean | -9.76 | -9.65 | | | |
| | SE | 0.24 | 0.25 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |
| 4:00 PM | N | 121 | 117 | -0.26 (0.33) | (-0.913, 0.392) | 0.433 |
| | Min | -19.33 | -21.67 | | | |
| | Max | 1.67 | 6.33 | | | |
| | LS Mean | -9.64 | -9.38 | | | |
| | SE | 0.24 | 0.26 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |
| **Modified Intent-to-Treat Population** | | | | | | |
| 8:00 AM | N | 133 | 132 | -0.59 (0.32) | (-1.214, 0.042) | 0.067 |
| | Min | -21.67 | -21 | | | |
| | Max | 0.5 | 2 | | | |
| | LS Mean | -9.74 | -9.16 | | | |
| | SE | 0.24 | 0.24 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |
| 12 noon | N | 133 | 133 | -0.47 (0.32) | (-1.102, 0.158) | 0.141 |
| | Min | -19 | -21 | | | |
| | Max | -1 | 1 | | | |
| | LS Mean | -9.68 | -9.21 | | | |
| | SE | 0.24 | 0.24 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |

**Table 6. Intraocular Pressure (mm Hg): Change From Baseline to Week 12 At Specified Time Points**

| | | Latanoprost-Timolol | Dorzolamide-Timolol | Treatment Difference (SE) | 95% CI | Between Treatment p-value |
|---|---|---|---|---|---|---|
| 4:00 PM | N | 133 | 132 | -0.52 (0.32) | (-1.164, 0.116) | 0.108 |
| | Min | -19.33 | -21.67 | | | |
| | Max | 1.67 | 6.33 | | | |
| | LS Mean | -9.58 | -9.06 | | | |
| | SE | 0.24 | 0.25 | | | |
| | Within treatment p-value | <0.0001 | <0.0001 | | | |

CI = confidence interval; LS Mean = least square mean; Max = maximum; Min = minimum; N = number of subjects in each treatment group; SE = standard error.

Table 7 presents proportions of subjects who achieved specified percent reductions of diurnal IOP of study eye at Week 4 and Week 12.

**Table 7. Proportions of Subjects Who Achieved Specified Percent Reductions of Diurnal IOP of Study Eye-MITT Population (With Observed Cases)**

| Percent Reduction From Baseline in Diurnal IOP | Latanoprost-Timolol (N=133) n (%) | Dorzolamide-Timolol (N=133) n (%) | p-Value |
|---|---|---|---|
| **Week 4** | | | |
| ≥40% | 42 (31.58%) | 28 (21.05%) | 0.032 |
| ≥35% | 65 (48.87%) | 56 (42.11%) | 0.138 |
| ≥30% | 90 (67.67%) | 85 (63.91%) | 0.4 |
| ≥25% | 110 (82.71%) | 105 (78.95%) | 0.301 |
| ≥20% | 126 (94.74%) | 124 (93.23%) | 0.516 |
| ≥15% | 130 (97.74%) | 128 (96.24%) | 0.35 |
| ≥10% | 130 (97.74%) | 131 (98.50%) | 0.797 |
| ≥5% | 132 (99.25%) | 132 (99.25%) | 0.823 |
| **Week 12** | | | |
| ≥40% | 39 (29.32%) | 33 (24.81%) | 0.299 |
| ≥35% | 66 (49.62%) | 55 (41.35%) | 0.095 |
| ≥30% | 94 (70.68%) | 86 (64.66%) | 0.2 |
| ≥25% | 106 (79.70%) | 106 (79.70%) | 0.984 |
| ≥20% | 124 (93.23%) | 121 (90.98%) | 0.478 |
| ≥15% | 126 (94.74%) | 125 (93.99%) | 0.794 |
| ≥10% | 127 (95.49%) | 127 (95.49%) | 0.957 |
| ≥5% | 128 (96.24%) | 128 (96.24%) | 0.941 |

IOP = intraocular pressure; MITT = modified intent-to-treat; N = number of subjects in each group; n = number of subjects with specified criteria.

Table 8 presents proportions of subjects achieving specified diurnal IOP of study eye at Week 4 and Week 12.

**Table 8. Proportions of Subjects Reaching Specific Levels of Diurnal IOP of Study Eye at-MITT Population (With Observed Cases)**

| Intraocular Pressure | Latanoprost-Timolol (N=133) n (%) | Dorzolamide-Timolol (N=133) n (%) | p-Value |
|---|---|---|---|
| **Week 4** | | | |
| ≤15 mm Hg | 31 (23.31%) | 14 (10.53%) | 0.003 |
| ≤16 mm Hg | 48 (36.09%) | 26 (19.55%) | 0 |
| ≤17 mm Hg | 61 (45.87%) | 51 (38.35%) | 0.098 |
| ≤18 mm Hg | 78 (58.65%) | 70 (52.63%) | 0.189 |
| ≤19 mm Hg | 105 (78.95%) | 97 (72.93%) | 0.195 |
| ≤20 mm Hg | 114 (85.71%) | 108 (81.20%) | 0.259 |
| ≤21 mm Hg | 120 (90.23%) | 118 (88.72%) | 0.66 |
| ≤22 mm Hg | 125 (93.99%) | 123 (92.48%) | 0.638 |
| **Week 12** | | | |
| ≤15 mm Hg | 32 (24.06%) | 18 (13.53%) | 0.010 |
| ≤16 mm Hg | 48 (36.09%) | 28 (21.05%) | 0.001 |
| ≤17 mm Hg | 65 (48.87%) | 57 (42.86%) | 0.212 |
| ≤18 mm Hg | 85 (63.91%) | 76 (57.14%) | 0.214 |
| ≤19 mm Hg | 101 (75.94%) | 94 (70.68%) | 0.325 |
| ≤20 mm Hg | 108 (81.20%) | 107 (80.45%) | 0.889 |
| ≤21 mm Hg | 116 (87.22%) | 117 (87.97%) | 0.769 |
| ≤22 mm Hg | 122 (91.73%) | 120 (90.23%) | 0.726 |

IOP = intraocular pressure; MITT = modified intent-to-treat; N = number of subjects in each group; n = number of subjects with specified criteria.

**Safety Results:** A summary of all causality and treatment-related TEAEs is presented in Table 9. The number of subjects reporting AEs was 41 subjects (30.4%) in the dorzolamide-timolol group and 35 subjects (25.9%) in the latanoprost-timolol group.

**Table 9. Summary of Treatment Emergent Adverse Events (All Causality and Treatment-Related)-Safety Population**

| | Latanoprost-Timolol (N=135) n (%) | | Dorzolamide-Timolol (N=135) n (%) | |
|---|---|---|---|---|
| | All Causality | Treatment-Related | All Causality | Treatment-Related |
| Number (%) of subjects | | | | |
| Number of adverse events | 57 | 33 | 60 | 36 |
| Subjects with adverse events | 35 (25.9%) | 25 (18.5%) | 41 (30.4%) | 27 (20.0%) |
| Subjects with serious adverse events | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| Subjects with severe adverse events | 2 (1.5%) | 0 | 1 (0.7%) | 0 |
| Subjects discontinued due to adverse events | 6 (4.4%) | 5 (3.7%) | 5 (3.7%) | 5 (3.7%) |
| Subjects with dose reduced or temporary discontinuation due to adverse events | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |

Adverse events and serious adverse events are not separated out.
Except for the number of adverse events subjects were counted only once per treatment in each row.
Serious adverse events-according to the Investigator's assessment.
N = number of subjects in each treatment group; n = number of subjects with specified criteria.

Table 10 presents TEAEs reported during the study by system organ class and preferred term.

The most commonly reported AEs affected the eye. The overall incidence of ocular-related AEs was similar in the dorzolamide-timolol group (14.8%) and the latanoprost-timolol group (12.6%). The most frequently occurring ocular AEs in the dorzolamide-timolol group were related to eye pain (3.0%), blurred vision (3.0%), and visual acuity reduction (3.0%). In the latanoprost-timolol group, the most frequently occurring ocular AEs were eye pruritus (2.2%) and ocular hyperaemia (2.2%).

The other commonly reported AEs occurred in the following body systems: general disorders and administration site conditions (6.7% in the latanoprost-timolol group and 7.4% in the dorzolamide-timolol group), nervous system disorders (1.5% in the latanoprost-timolol group and 4.4% in the dorzolamide-timolol group) and infections and infestations (3.7% in the latanoprost-timolol group and 3.0% in the dorzolamide-timolol group).

## Table 10. Treatment-Emergent Adverse Events (All Causalities)-Safety Population

| System Organ Class<br>Preferred Term | Latanoprost-Timolol (N=135)<br>n (%) | Dorzolamide-Timolol (N=135)<br>n (%) |
|---|---|---|
| Total preferred term events | 57 | 60 |
| Cardiac disorders | 2 (1.5) | 1 (0.7) |
| Bradycardia | 1 (0.7) | 0 |
| Coronary artery stenosis | 1 (0.7) | 0 |
| Extrasystoles | 0 | 1 (0.7) |
| Ear and labyrinth disorders | 1 (0.7) | 0 |
| Vertigo | 1 (0.7) | 0 |
| Endocrine disorders | 0 | 1 (0.7) |
| Hypothyroidism | 0 | 1 (0.7) |
| Eye disorders | 17 (12.6) | 20 (14.8) |
| Abnormal sensation in eye | 1 (0.7) | 0 |
| Blepharitis | 1 (0.7) | 0 |
| Cataract | 0 | 2 (1.5) |
| Chalazion | 2 (1.5) | 0 |
| Conjunctival haemorrhage | 1 (0.7) | 0 |
| Conjunctival hyperaemia | 2 (1.5) | 0 |
| Conjunctival irritation | 0 | 1 (0.7) |
| Conjunctivitis | 0 | 1 (0.7) |
| Dry eye | 1 (0.7) | 0 |
| Eye discharge | 0 | 1 (0.7) |
| Eye irritation | 2 (1.5) | 3 (2.2) |
| Eye pain | 0 | 4 (3.0) |
| Eye pruritus | 3 (2.2) | 0 |
| Lacrimation increased | 1 (0.7) | 0 |
| Lenticular opacities | 0 | 1 (0.7) |
| Ocular hyperaemia | 3 (2.2) | 0 |
| Optic nerve cupping | 0 | 1 (0.7) |
| Pseudoexfoliation of lens capsule | 1 (0.7) | 1 (0.7) |
| Sicca syndrome | 0 | 1 (0.7) |
| Vision blurred | 1 (0.7) | 4 (3.0) |
| Visual acuity reduced | 2 (1.5) | 4 (3.0) |
| Visual disturbance | 1 (0.7) | 1 (0.7) |
| Gastrointestinal disorders | 1 (0.7) | 3 (2.2) |
| Diarrhoea | 1 (0.7) | 0 |
| Gastric ulcer | 1 (0.7) | 0 |
| Gastritis | 0 | 1 (0.7) |
| Nausea | 0 | 2 (1.5) |
| General disorders and administration site conditions | 9 (6.7) | 10 (7.4) |
| Application site irritation | 4 (3.0) | 4 (3.0) |
| Application site reaction | 1 (0.7) | 1 (0.7) |
| Instillation site erythema | 1 (0.7) | 0 |
| Instillation site irritation | 3 (2.2) | 4 (3.0) |
| Instillation site reaction | 0 | 1 (0.7) |
| Oedema peripheral | 1 (0.7) | 0 |
| Immune system disorders | 2 (1.5) | 0 |
| Hypersensitivity | 2 (1.5) | 0 |
| Infections and infestations | 5 (3.7) | 4 (3.0) |
| Bronchitis | 1 (0.7) | 0 |
| Influenza | 1 (0.7) | 1 (0.7) |
| Keratitis herpetic | 1 (0.7) | 0 |
| Nasopharyngitis | 1 (0.7) | 2 (1.5) |
| Tracheitis | 0 | 1 (0.7) |
| Urinary tract infection | 1 (0.7) | 0 |
| Injury, poisoning and procedural complications | 1 (0.7) | 2 (1.5) |
| Corneal abrasion | 0 | 1 (0.7) |
| Fall | 0 | 1 (0.7) |
| Limb injury | 1 (0.7) | 0 |

## Table 10. Treatment-Emergent Adverse Events (All Causalities)-Safety Population

| System Organ Class<br>Preferred Term | Latanoprost-Timolol (N=135)<br>n (%) | Dorzolamide-Timolol (N=135)<br>n (%) |
|---|---|---|
| Investigations | 1 (0.7) | 1 (0.7) |
| Alanine aminotransferase increased | 0 | 1 (0.7) |
| Aspartate aminotransferase increased | 0 | 1 (0.7) |
| Urine output increased | 1 (0.7) | 0 |
| Musculoskeletal and connective tissue disorders | 1 (0.7) | 1 (0.7) |
| Bone pain | 0 | 1 (0.7) |
| Pain in extremity | 1 (0.7) | 0 |
| Nervous system disorders | 2 (1.5) | 6 (4.4) |
| Burning sensation | 2 (1.5) | 0 |
| Dysgeusia | 0 | 4 (3.0) |
| IIIrd nerve paralysis | 0 | 1 (0.7) |
| Visual field defect | 0 | 1 (0.7) |
| Psychiatric disorders | 1 (0.7) | 0 |
| Anxiety | 1 (0.7) | 0 |
| Renal and urinary disorders | 1 (0.7) | 0 |
| Nephrolithiasis | 1 (0.7) | 0 |
| Reproductive system and breast disorders | 1 (0.7) | 0 |
| Benign prostatic hyperplasia | 1 (0.7) | 0 |
| Respiratory, thoracic and mediastinal disorders | 2 (1.5) | 1 (0.7) |
| Cough | 1 (0.7) | 1 (0.7) |
| Suffocation feeling | 1 (0.7) | 0 |
| Skin and subcutaneous tissue disorders | 2 (1.5) | 1 (0.7) |
| Dermatitis allergic | 1 (0.7) | 0 |
| Eczema | 1 (0.7) | 0 |
| Rash | 0 | 1 (0.7) |
| Surgical and medical procedures | 0 | 1 (0.7) |
| Tooth extraction | 0 | 1 (0.7) |
| Vascular disorders | 1 (0.7) | 1 (0.7) |
| Circulatory collapse | 0 | 1 (0.7) |
| Hypertension | 1 (0.7) | 1 (0.7) |

Adverse events and serious adverse events are not separated out.
MedDRA (version 9.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment group; n = number of subjects with specified criteria.

Table 11 presents treatment-related TEAEs reported during the study by system organ class and preferred term. Ocular events considered treatment-related occurred at an equal frequency in both groups (8.9% in each group).

## Table 11. Treatment-Emergent Treatment-Related Adverse Events – Safety Population

| System Organ Class<br>Preferred Term | Latanoprost-Timolol (N=135)<br>n (%) | Dorzolamide-Timolol (N=135)<br>n (%) |
|---|---|---|
| Total preferred term events | 33 | 36 |
| Cardiac disorders | 1 (0.7) | 1 (0.7) |
| Bradycardia | 1 (0.7) | 0 |
| Extrasystoles | 0 | 1 (0.7) |
| Ear and labyrinth disorders | 1 (0.7) | 0 |
| Vertigo | 1 (0.7) | 0 |
| Eye disorders | 12 (8.9) | 12 (8.9) |
| Abnormal sensation in eye | 1 (0.7) | 0 |
| Conjunctival hyperaemia | 2 (1.5) | 0 |
| Conjunctival irritation | 0 | 1 (0.7) |
| Conjunctivitis | 0 | 1 (0.7) |
| Dry eye | 1 (0.7) | 0 |
| Eye discharge | 0 | 1 (0.7) |
| Eye irritation | 2 (1.5) | 3 (2.2) |
| Eye pain | 0 | 4 (3.0) |
| Eye pruritus | 3 (2.2) | 0 |
| Lacrimation increased | 1 (0.7) | 0 |
| Lenticular opacities | 0 | 1 (0.7) |
| Ocular hyperaemia | 3 (2.2) | 0 |
| Vision blurred | 0 | 4 (3.0) |
| Visual acuity reduced | 1 (0.7) | 0 |
| Visual disturbance | 1 (0.7) | 0 |
| Gastrointestinal disorders | 0 | 2 (1.5) |
| Nausea | 0 | 2 (1.5) |
| General disorders and administration site conditions | 8 (5.9) | 10 (7.4) |
| Application site irritation | 4 (3.0) | 4 (3.0) |
| Application site reaction | 1 (0.7) | 1 (0.7) |
| Instillation site erythema | 1 (0.7) | 0 |
| Instillation site irritation | 3 (2.2) | 4 (3.0) |
| Instillation site reaction | 0 | 1 (0.7) |
| Immune system disorders | 2 (1.5) | 0 |
| Hypersensitivity | 2 (1.5) | 0 |
| Investigations | 0 | 1 (0.7) |
| Alanine aminotransferase increased | 0 | 1 (0.7) |
| Aspartate aminotransferase increased | 0 | 1 (0.7) |
| Nervous system disorders | 2 (1.5) | 4 (3.0) |
| Burning sensation | 2 (1.5) | 0 |
| Dysgeusia | 0 | 4 (3.0) |
| Psychiatric disorders | 1 (0.7) | 0 |
| Anxiety | 1 (0.7) | 0 |
| Respiratory, thoracic and mediastinal disorders | 1 (0.7) | 1 (0.7) |
| Cough | 1 (0.7) | 1 (0.7) |
| Skin and subcutaneous tissue disorders | 1 (0.7) | 1 (0.7) |
| Dermatitis allergic | 1 (0.7) | 0 |
| Rash | 0 | 1 (0.7) |

Adverse events and serious adverse events are not separated out.
Includes data up to 30 days after last dose of study drug.
MedDRA (version 9.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each treatment group; n = number of subjects with specified criteria.

Two subjects in the latanoprost-timolol group experienced 1 severe event (coronary artery stenosis, limb injury). One subject in the dorzolamide-timolol group experienced a severe event (cataract).

Table 12 presents serious AEs (SAEs) reported during the study. Two subjects experienced non-fatal SAEs, 1 in each treatment group. These events were not considered related to study medication and both resolved. There were no deaths reported.

**Table 12. Serious Adverse Events – Safety Population**

| Serial Number | MedDRA Preferred Term | Intensity | Start/ Stop (Days) | Study Drug Action/Causality | Outcome |
|---|---|---|---|---|---|
| Latanoprost-timolol | | | | | |
| 1 | Coronary artery stenosis | Severe | 65/69 | None; not study drug related | Recovered |
| Dorzolamide-timolol | | | | | |
| 2 | Circulatory collapse | Moderate | 84/89 | Temporarily stopped; related to other illness | Recovered |

MedDRA = Medical Dictionary for Regulatory Activities.

Table 13 summarizes the AEs that led to permanent discontinuation by system organ class and preferred term. In both treatment groups, the incidence of discontinuations due to AEs was low.

**Table 13. Permanent Discontinuation Due to Adverse Events**

| System Organ Class<br>Preferred Term | Latanoprost-Timolol (N=135) | Dorzolamide-Timolol (N=135) |
|---|---|---|
| Number of subjects (%) who discontinued due to adverse events | 6 (4.4%) | 5 (3.7%) |
| Skin and subcutaneous tissue disorders | | |
| Allergic eczema | 1 | 0 |
| Periocular skin rash | 0 | 1 |
| Immune system disorders | | |
| Allergic-type reaction | 2 | 0 |
| Infections and infestations | | |
| Herpes keratitis | 1 | 0 |
| Eye disorders | | |
| Burning eyes | 1 | 1 |
| Conjunctivitis | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | |
| Suffocative sensation | 1 | 0 |
| Cardiac disorders | | |
| Bradycardiac | 1 | 0 |
| Extra-systoles exacerbation | 0 | 1 |
| Psychiatric disorders | | |
| Anxiety sensation | 1 | 0 |
| Investigations | | |
| Elevated liver enzymes (ALAT) | 0 | 1 |
| Elevated liver enzymes (ASAT) | 0 | 1 |

Subjects reporting more than 1 adverse event may be counted more than once.
MedDRA (version 9.1) coding dictionary applied.
ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activitie; N = number of subjects in each treatment group.

There was no statistical significance between the findings of best corrected visual acuity for the 2 groups at baseline, Week 4 and Week 12. There were minimal new findings or worsening of conditions (from baseline) for the lid and slit lamp examinations at both Week 4 and Week 12. There were no changes recorded in ophthalmoscopy from the screening visit to Week 12/early discontinuation. There were no statistically significant

differences in cup/disc ratio for change from screening visit to Week 12/early discontinuation between the 2 treatment groups.

**CONCLUSIONS:** The study achieved the primary objective to demonstrate the mean diurnal IOP-reducing effect of latanoprost-timolol administered QD in the evening was non-inferior to that of dorzolamide-timolol administered BD. Both treatments demonstrated decreases in IOP post-baseline and were generally well tolerated.