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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 204-822

Drug Name: Travoprost ophthalmic solution 0.003%

Indication(s): For the reduction of elevated intraocular pressure (IOP) in patients with Open Angle Glaucoma (OAG) or Ocular Hypertension (OH).

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1 EXECUTIVE SUMMARY

In this submission, the applicant seeks approval of Travoprost ophthalmic solution 0.003% containing the preservative polyquaternium-1 (also known as PQ-preserved) for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Travoprost ophthalmic solution at a concentration 0.004% PQ is currently an approved product by the European Medicines Agency (EMA).

The primary evidence for the safety and efficacy of Travoprost solution 0.003% is based on a single Phase 3 trial (C-11-034). This trial was a multicenter, double-masked, randomized, active-controlled, 2-arm, parallel group equivalence study. The study was designed to evaluate the safety and equivalence with respect to IOP-lowering efficacy of Travoprost 0.003% to Travoprost 0.004% BAK (preserved with benzalkonium chloride) in adult patients with open-angle glaucoma or ocular hypertension. The active control arm, Travoprost 0.004% BAK (Travatan), received FDA approval in March 2001 and was marketed as Travatan.

The primary efficacy endpoint of the study was mean IOP evaluated at three on-therapy study visits at Week 2, Week 6, and Month 3 and assessment time points at 8 AM, 10 AM, and 4 PM. The change in IOP from baseline, the percent change in IOP from baseline, the percentage of patients who achieved a target IOP level of < 18 mmHg, and the percentage of patients who achieved IOP-lowering of at least 30% from baseline were supportive efficacy endpoints.

The primary efficacy analysis of the study was based on the difference in mean IOP between treatment groups (Travoprost 0.003% minus Travatan) at each assessment time point. In the primary efficacy analysis, treatment difference in the mean IOP at each on-therapy visit and time point was determined based on least square means using a mixed model repeated measures (MMRM) analysis. Equivalence of Travoprost 0.003% to Travatan in IOP lowering was concluded if the two-sided 95% confidence interval (CI) for the difference in mean IOP was within ± 1.5 mmHg at each time point of each on-therapy visit and within ± 1.0 mmHg at the majority of the time points. The primary efficacy analysis was based on observed cases in the intent-to-treat (ITT) analysis set and did not impute missing data. The ITT analysis set was defined as all patients who received study medication and had completed at least 1 scheduled on-therapy study visit.

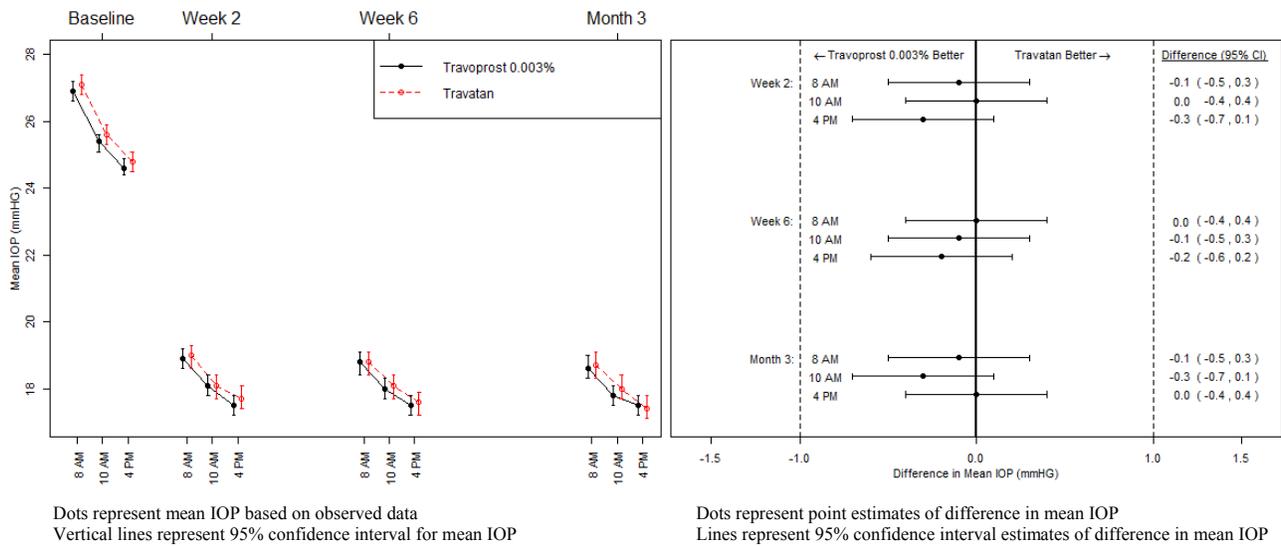
A total of 864 patients were randomized in Study C-11-034; 442 randomized to the Travoprost 0.003% group and 422 randomized to the Travatan group. Randomization was stratified by investigational center and 8 AM baseline IOP measurement for the study eye (24-27 mmHg or 28-36 mmHg). Of the 864 randomized patients, 860 (99.5%) were included in ITT analysis set. A total of 20 (2.3%) patients in the ITT analysis set discontinued from the study.

Figure 1 presents the mean IOP with 95% CI (left panel) and the point and 95% CI estimates for the difference in mean IOP from the MMRM model (right panel) at each visit and assessment time point based on the observed ITT analysis set. The two-sided 95% CIs for the difference in mean IOP between the treatment groups were within ± 1.0 mmHg at all visits and assessment time points, meeting the equivalence criteria requirement of within ± 1.5 mmHg at each time point of each visit and within ± 1.0 mmHg for the majority of time points (Figure 1 right panel). However, the point estimates for the difference in mean IOP slightly favored Travoprost 0.003% relative to Travatan (Figure 1 right panel). This might be due to the slightly lower mean baseline

IOP data observed in the Travoprost 0.003% group relative to the Travatan group (Figure 1 left panel) and the fact that the primary analysis did not adjust for the actual baseline data. When the actual baseline IOP data was accounted for through analysis of the supportive efficacy endpoint of change from baseline, the trend for the treatment difference reversed; that is, the point estimates for the treatment difference in mean IOP change from baseline slightly favored Travatan relative to Travoprost 0.003% at most of the time points (See Table 7).

As shown in Table 7, overall, both treatment groups resulted in comparable IOP reductions at all visits and assessment time points; the point estimates for the mean IOP reductions ranged from 7.6 to 8.7 mmHg in the Travoprost 0.003% group and from 7.5 to 8.8 mmHg in the Travatan group. The highest IOP reduction in both treatment groups was observed at the 8 AM assessment time point.

Figure 1: Mean IOP (95% CI) and Difference in Mean IOP (95% CI) by Visit



The safety profiles between Travoprost 0.003% and Travatan in study C-11-034 were similar; 30.3% of subjects in the Travoprost 0.003% group and 32.3% of subjects in the Travatan group experienced at least 1 treatment-emergent AE. The percentage of subjects experiencing serious AE was 1.1% in the Travoprost 0.003% group and 1.7% in the Travatan group.

Based on the primary efficacy analyses results and the safety profiles of Travoprost 0.003%, the applicant has met the primary objective of the study and demonstrated equivalence of Travoprost 0.003% PQ to Travoprost 0.004% BAK (Travatan) with respect to IOP-lowering efficacy in patients with open angle glaucoma or ocular hypertension.

2 INTRODUCTION

2.1 Overview

i) Class and Indication

This is an NDA submission for Travoprost ophthalmic solution 0.003%. Travoprost belongs to the pharmacological class of Prostaglandin F2 α Receptor agonists. It is absorbed through the cornea and is hydrolyzed to the active free acid. Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow.

The indication being sought by the applicant is reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

ii) History of Drug Development

Table below summarizes the drug development history for travoprost containing products:

Travoprost containing products	Preservative	Approval History
Travoprost 0.004% BAK (Discontinued from the market)	benzalkonium chloride (BAK)	March 2001 – US FDA November 2001 – EMA Marketed as Travatan
Travoprost 0.004% sofZia	sofZia	September 2006 – US FDA. Also marketed in Canada and Japan
Travoprost 0.004% PQ	polyquaternium-1 (PQ)	November 2010 – EMA. Also marketed in other countries.

In this submission, the applicant is seeking approval of the lower dose formulation, Travoprost 0.003% PQ, of Travoprost 0.004% PQ. The applicant indicated that the two formulations, (b) (4) the active drug concentration, (b) (4) and based on bioavailability data and dose-response relationships for various Travoprost formulations, an improved benefit-risk ratio may be achieved by reducing the active drug concentration.

iii) Specific Studies Reviewed

According to the applicant, the development plan for Travoprost 0.003% was (b) (4)

(b) (4) it was indicated that a single study together with the extensive existing database and published literature for Travoprost was sufficient to demonstrate Travoprost MDPF was equivalent in IOP-lowering efficacy and maintained a similar safety profile to Travatan. Therefore, due to the clinical development plan alignment with the MDPF product, the applicant is seeking approval of Travoprost 0.003% based only on a single Phase 3 clinical trial. This trial was a randomized, multicenter, double-masked safety and efficacy study designed to demonstrate the equivalence of Travoprost 0.003% to Travoprost 0.004% BAK, with both dosed once daily in the evening in patients with open-angle glaucoma or ocular hypertension.

Therefore, as the primary support of efficacy and safety of Travoprost 0.003%, this review will focus on the single pivotal Phase 3 efficacy trial. Table 1 provides a brief summary of the trial.

Table 1: List of Studies Included in Analysis

Protocol	Phase and Design	Dose, Route and Regimen	Treatment Period	# of Subjects per Arm	Study Population
C-11-034	Phase 3 Multicenter, double-masked, randomized, active controlled, 2-arm, parallel group, equivalence study	1 drop QD 8 PM (\pm 30 min) Topical ocular	3 Months	442 Travoprost 0.003% Solution (Travoprost 0.003%) 422 Travoprost 0.004% BAK (Travatan)	Patients diagnosed with open angle glaucoma or ocular hypertension IOP 24-36 at 8 AM 21-36 at 10 AM and 4 PM

QD: Once a day

2.2 Data Sources

The data source for this review included the final C-11-034 study report, the analysis and tabulation datasets, and integrated summary of safety dataset. These were provided in electronic submission located at <\\CDSESUB1\evsprod\NDA204822\0000>.

The data analyzed in this review is based on the single Phase 3 trial submitted as the pivotal evidence to support the efficacy of Travoprost 0.003%.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The NDA was provided in an electronic submission. It included, among other documents, the clinical study report, the finalized protocol and statistical analysis plan, both analysis and tabulation datasets, and case report forms for 36 subjects. SAS codes used to perform the analyses and to create the analysis datasets were also provided.

There were no issues identified with respect to the quality and integrity of the submitted data. Although the submitted datasets were not fully CDISC compliant, the submission included certain elements of the CDISC standards. In addition, the *Reviewer's Guide Document* and the *Define.pdf* files included with the submission document provided sufficient detail to access and to easily work with the datasets. Thus, minimal efforts were needed to process the data and hence no additional support was needed from other sources.

The applicant provided documentation of data quality control/assurance procedures in Section 9.6 and the blinding/unblinding procedures in Section 9.4.6 of the clinical study report.

Reviewer's Comment:

All tables and graphs presented in this review, unless specifically indicated otherwise, are based on analyses conducted by the reviewer using the analysis datasets submitted by the applicant and confirm results of the applicant presented in Study C-11-034 study report.

3.2 Evaluation of Efficacy

In this section, the efficacy assessment for Study C-11-034 including a description of the study design, primary and supportive efficacy endpoints, demographic and baseline characteristics, patient disposition, statistical methodology used, the applicant's results, and the reviewer's findings are provided.

3.2.1 Study Design and Endpoints

Study C-11-034 was a randomized, multicenter, double-masked, 2-arm, parallel-group, Phase 3 study designed to evaluate the safety and efficacy of Travoprost 0.003% compared to Travatan in patients 18 years or older with open-angle glaucoma or ocular hypertension.

The study had a total of 3-month duration conducted over six visits at 60 investigational centers (52 in the United States, two each in Sweden, Germany, and Austria, and one each in Spain and Finland). Patients were enrolled in the study in two sequential phases:

(a) The Screening/Eligibility Phase:

Included a screening visit followed by two Eligibility visits.

- i) *Screening Visit*: consenting subjects who qualified for the study were instructed to discontinue using ocular hypotensive and all IOP-lowering medications.
- ii) *Eligibility 1 Visit*: conducted after washout of all ocular hypotensive medications based on the appropriate schedule after screening (Ref. Table 9.4.7-1 of CSR for schedule) and
- iii) *Eligibility 2 Visit*: conducted a minimum of 3-8 days following the Eligibility 1 Visit.

At both eligibility visits, IOP was measured in both eyes at 8 AM (\pm 30 minutes), 10 AM (\pm 30 minutes), and 4 PM (\pm 30 minutes).

To qualify for the eligibility criterion, the mean IOP in at least 1 eye (the same eye) at each eligibility visit must have been \geq 24 mmHg at the 8 AM time point and \geq 21 mmHg at the 10 AM and 4 PM time points. Besides, the mean IOP must have been \leq 36 mmHg at all times points in both eyes. Mean IOP was the average of 2 successive IOP measurements in the same eye.

(b) The Treatment Phase:

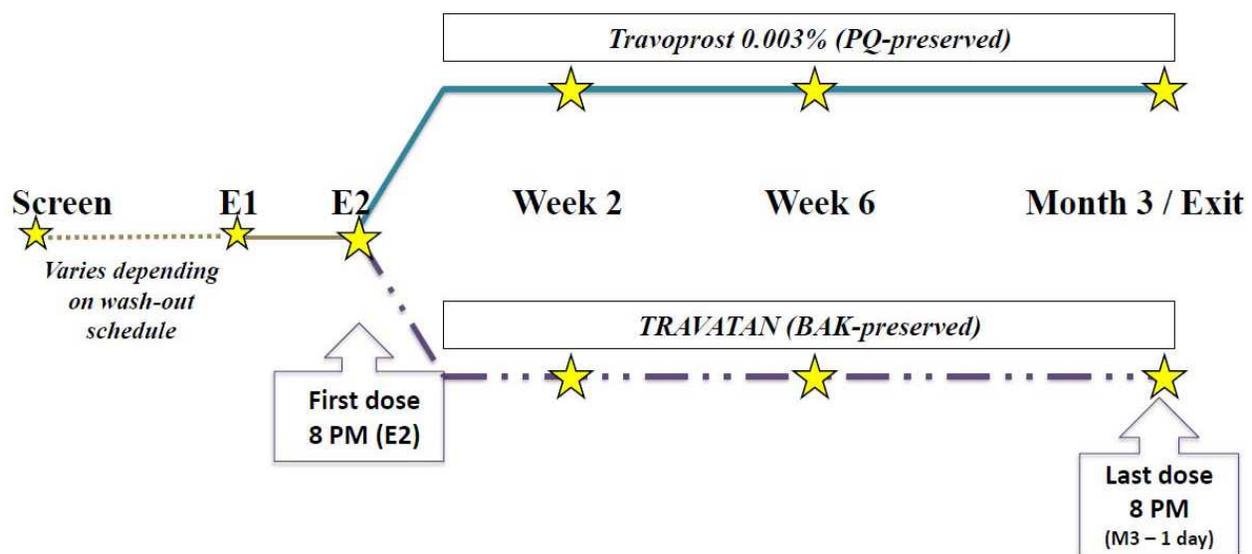
Included a 3 month evaluation of efficacy and safety with on-therapy visits scheduled at Week 2 (Day 14 \pm 1 day), Week 6 (Day 42 \pm 3 days), and Month 3 (Day 90 \pm 3 days). Visit days were relative to the timing of Eligibility 2 Visit.

Subjects that met the eligibility criterion were randomized in a 1:1 ratio to receive either Travoprost 0.003% or Travatan and entered the treatment phase. Randomization was stratified by investigational center and 8 AM baseline IOP measurement (24-27 mmHg or 28-36 mmHg) for the study eye. The study eye was defined as the dosed eye if only one eye was dosed or the worse evaluable eye if both eyes were dosed. The worse evaluable eye was defined as the eye with the higher IOP at 8 AM averaged across the 2 eligibility visits. Only the study eye was used in the efficacy analysis.

All randomized subjects were dispensed study drug during the end of Eligibility 2 Visit. During this visit, subjects were instructed to self-administer 1 drop of the assigned study drug in each study eye every night at 8 PM \pm 30 minutes for 3 months. The first dose was to be taken the night of Eligibility 2 Visit, and the last dose was to be taken the night before the Month 3/Exit Visit.

The on-therapy study visits were scheduled to occur at Week 2, Week 6, and Month 3. During each of these visits, ocular hyperemia was assessed and IOP was measured at 8 AM, 10 AM, and 4 PM; and subjects also underwent a best corrected visual acuity (BCVA) assessment and slit-lamp examinations (including flare and cells) at 8 AM on each study visit day. Figure 2 presents study C-11-034 flow chart.

Figure 2: Study C-11-034 Flow Chart



Source: Figure 10 1 -1 of Study C-11-034 Protocol
 E1: Eligibility 1 Visit; E2: Eligibility 2 Visit; M3: Month 3 Visit

Study C-11-034 was a double-masked study. That is, patients, investigators, investigational center staff, Sponsor, and the clinical monitors were not aware of the treatment assigned to the individual study patients.

Safety was evaluated through a review of adverse events (AEs), assessments of BCVA, ocular signs, visual field losses, ocular hyperemia, dilated fundus examinations, central corneal thickness (CCT) measurements, and extent of exposure tabulations.

3.2.2 Statistical Methodologies

The primary efficacy endpoint in study C-11-034 was the mean IOP at all on-therapy study visits (Week 2, Week 6, and Month 3) and assessment time points (8 AM, 10 AM, and 4 PM). The primary efficacy analysis of the study was to address a statistical evaluation of equivalence of the two treatment groups with respect to the primary efficacy endpoint and was based on the difference in mean IOP between treatment groups (Travoprost 0.003% minus Travatan) at each assessment time point.

Let $\mu_{\text{Travoprost 0.003\%}}$ and μ_{Travatan} denote the population IOP means for Travoprost 0.003% and Travatan treatment groups respectively, and let Δ denote the equivalence margin. The equivalence test is formulated as follows:

$$H_0: \left| \mu_{\text{Travoprost 0.003\%}} - \mu_{\text{Travatan}} \right| \leq \Delta ; \quad H_1: \left| \mu_{\text{Travoprost 0.003\%}} - \mu_{\text{Travatan}} \right| > \Delta$$

In the primary efficacy analysis, the treatment difference in the mean IOP at each on-therapy visit and assessment time point was determined based on least square means using a mixed model repeated measures (MMRM) analysis. The model used an unstructured covariance matrix to account for correlated IOP measurements within patient and included the fixed effects for treatment (T_i), visit (V_j), time point (H_k), investigational sites (R_m), the 8 AM baseline IOP stratum (H_k), and the interaction terms of treatment by visit (TV_{ij}), treatment by time (TH_{ik}), visit by time (VH_{jk}), and treatment by visit by time (TVH_{ijk}). The model is given by:

$$IOP_{ijklmn} = \mu + T_i + V_j + H_k + S_l + R_m + TV_{ij} + TH_{ik} + VH_{jk} + TVH_{ijk} + \rho(TSR)_{n(ilm)} + \varepsilon_{ijklmn}$$

where μ is the overall mean, the effect ρ in i^{th} treatment group at the m^{th} site in the l^{th} stratum for 8 AM baseline IOP is considered random in order to account for repeated observations on patients, and ε is the measurement error associated with the individual patient. The above model allowed treatment effect and its variability to vary over study visits and time points.

Based on the statistical model, equivalence of the two treatments in IOP-lowering was declared if the two-sided 95% CIs for the difference in mean IOP were within ± 1.5 mmHg at all on-therapy visits and time points and within ± 1.0 mmHg for the majority of time points.

The change in IOP from baseline, the percent change in IOP from baseline, the percentage of patients who achieved a target IOP level of < 18 mmHg, and the percentage of patients who achieved IOP-lowering of at least 30% from baseline were supportive endpoints. The supportive endpoints were analyzed using descriptive statistics.

The primary efficacy analysis and all supportive analyses were conducted using the ITT analysis set defined as all patients who received study drug and completed at least one scheduled on-therapy study visit. As a supportive analysis, the primary efficacy analysis was also performed using the per-protocol (PP) analysis set defined as all patients who satisfied pre-randomization inclusion/exclusion criteria, received study drug, and completed at least one scheduled on-therapy study visit.

The primary and supportive efficacy analyses using the aforementioned MMRM model were based on observed cases and did not impute missing data. These analysis methods were appropriate under the missing at random assumption.

Although the study had a small amount of missing data (< 2.5% in the ITT analysis set), as a sensitivity analyses, the primary efficacy endpoints were analyzed: (i) using the MMRM model with the last observation carried forward (LOCF) based on the ITT analysis set and (ii) using a 2-sample t-test procedure with the last observation carried forward (LOCF) based on the ITT analysis set. Further sensitivity analysis using a 2-sample t-test procedure based on the ITT analysis set was also performed for analysis of the change in IOP with LOCF measurements.

Reviewer's Comment

- i) For analyses of the primary and supportive efficacy endpoints, the applicant proposed the statistical methodology discussed in this section. The reviewer concurred with the specified statistical methodology and used the proposed methodology to confirm the primary and supportive efficacy results of the study.*
- ii) For the equivalence test, 1.0 mmHg and 1.5 mmHg were used as the equivalence margins in the study. Justification of these margins was not provided in the NDA submission. However, these margins were recommended by the FDA clinical review team for the indication sought.*
- iii) Two equivalence criteria were defined in the study; the first criterion was the two-sided 95% CIs for the difference in mean IOP to be within ± 1.5 mmHg at all visits and time points and the second criterion was to be within ± 1.0 mmHg at the majority of time points. Since the first equivalence criterion was required to be met at each time point, there was no multiplicity issue. On the other hand, for the second equivalence criterion (with 'majority of time points' defined as at least 5 out of 9 time points), there were more than 200 pathways to meet this criterion. The applicant's analysis for this criterion did not address the resultant multiplicity and thus did not control for the overall family-wise error rate. Therefore, in this review, the 1.0 mmHg equivalence margin in the study was considered a clinical criterion, not a statistical criterion.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

Table 2 presents the summary of patient disposition and reasons for study discontinuation among all randomized subjects. Overall, 864 patients were randomized in Study C-11-034; 442 subjects randomized to the Travoprost 0.003% group and 422 randomized to the Travatan group. A total of 24 (2.8%) subjects discontinued early from the study; a slightly higher percentage of patients discontinued early from the study in the Travatan group (3.3%) relative to the Travoprost 0.003% Solution group (2.3%).

The summary of study discontinuation by primary reasons is presented in Table 2. The most common reasons for discontinuation among all randomized patients were adverse events (AE) (0.8%) followed by an inadequate control of IOP (0.7%). With the exception of discontinuation due to inadequate IOP control, where a slightly higher rate was reported in the Travatan group

(1.2%) relative to the Travoprost 0.003% group (0.2%), the discontinuation rates by all other primary reasons were comparable between the treatment groups.

Table 2: Disposition of Patients and Reasons for Study Discontinuation
(All Randomized Subjects)

	Travoprost 0.003% (N = 442)	Travatan (N = 422)	Total (N = 864)
Subjects who completed the study, n (%)	432 (97.7)	408 (96.7)	840 (97.2)
Subject who discontinued the study, n (%)	10 (2.3)	14 (3.3)	24 (2.8)
Primary Reason for Early Termination, n (%)			
Adverse Events	3 (0.7)	4 (0.9)	7 (0.8)
Lost-to-Follow-up	2 (0.5)	1 (0.2)	3 (0.3)
Patient's Decision Unrelated to an Adverse Event	3 (0.7)	3 (0.7)	6 (0.7)
Noncompliance	1 (0.2)	0 (0.0)	1 (0.1)
Inadequate Control of IOP	1 (0.2)	5 (1.2)	6 (0.7)
Other	0 (0.0)	1 (0.2)	1 (0.1)

The summary of the number of subjects who completed and discontinued from the study by analyses sets are presented in Table 3. Out of a total of 864 randomized patients, 860 (99.5%) were included in the ITT analysis set, 851 (98.5%) were included in the PP analysis set, and 863 (99.9%) were included in the safety analysis set.

Table 3: Analysis Set

	Travoprost 0.003%	Travatan	Total
Randomized	442	422	864
ITT Analysis Set	442	418	860
Completed Study	432 (97.7%)	408 (97.6%)	840 (97.7%)
Discontinued	10 (2.3%)	10 (2.4%)	20 (2.3%)
PP Analysis Set	436	415	851
Completed Study	426 (97.7%)	405 (97.6%)	831 (97.6%)
Discontinued	10 (2.3%)	10 (2.4%)	20 (2.4%)
Safety Analysis Set	442	421	863
Completed Study	432 (97.7%)	408 (96.9%)	840 (97.3%)
Discontinued	10 (2.3%)	13 (3.1%)	23 (2.7%)

It should be noted that three subjects randomized to the Travatan group were excluded from the ITT and PP analysis set due to no on-therapy follow-up data, and one subject randomized to the Travatan group was excluded from the ITT, PP and safety analysis set because the subject did not receive study drug. Nine randomized subjects (6 on Travoprost 0.003% and 3 on Travatan) were excluded from the PP analysis set due to protocol violation of exclusion criteria.

Reviewer's Comment

The primary efficacy analysis presented in this review will be based on the ITT analysis set and the PP analysis set will be presented as supportive analysis.

3.2.3.2 Demographic and Baseline Characteristics

The summary of demographic and baseline characteristics for subjects in the ITT analysis set are presented in [Table 4](#). Within the ITT analysis set, the majority of subjects in the study were Caucasian (72.4%), Female (59.7%), 65 years of age and older (55.8%; overall mean age = 65.2 years), and had a brown eye color (60.3%) and a diagnosis of open-angle glaucoma (69.1%). The 8 AM baseline IOP was used as a stratification factor in the study and overall, 69.1% of the subjects had baseline IOP in the low range (24-27 mmHg). No marked difference between the treatment groups was observed in terms of the demographic characteristics.

Descriptive baseline statistics for age (years), IOP (mmHg), and corneal thickness (μm) are also presented in [Table 4](#). Overall, the mean baseline IOP level was 27.0 mmHg at 8 AM, 25.5 mmHg at 10 AM, and 24.7 mmHg at 4 PM. The largest mean IOP measurement in both treatment groups was observed at the 8 AM time point and decreased throughout the day ([Figure 3](#)); no important differences were noted in mean baseline IOP measurements between the treatment groups at any of the 3 assessment time points. The mean corneal thickness at baseline was 552.4 μm .

Figure 3: Baseline IOP Measurement by Treatment Group, Visit and Time Point (ITT Analysis Set)

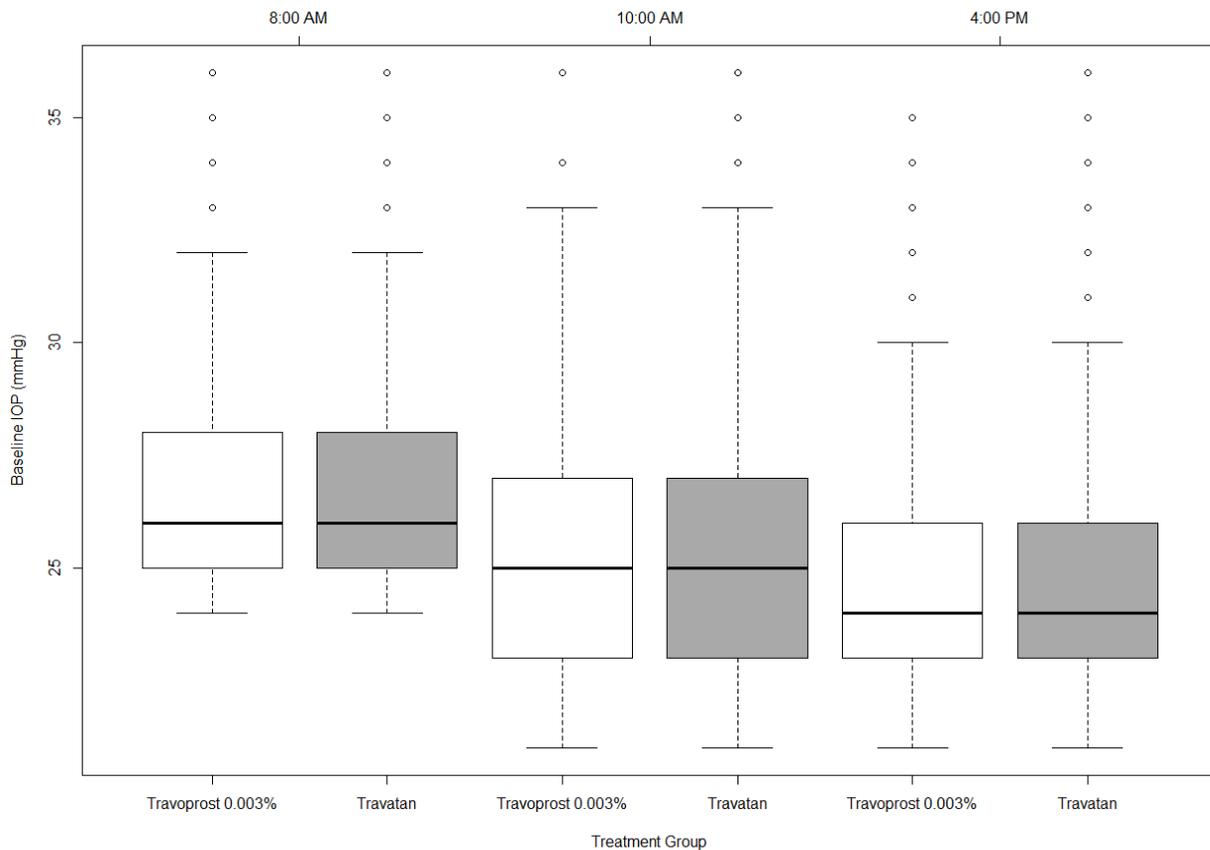


Table 4: Demographic Summary by Treatment Group
(ITT Analysis Set)

	Travoprost 0.003% (N = 442)	Travatan (N = 418)	Total (N = 860)
Age (Years), n (%)			
<65	189 (42.8)	191 (45.7)	380 (44.2)
≥65	253 (57.2)	227 (54.3)	480 (55.8)
≥65 to <75	167 (37.8)	140 (33.5)	307 (35.7)
≥75 to <85	79 (17.9)	78 (18.7)	157 (18.3)
≥85 to <95	7 (1.6)	9 (2.2)	16 (1.9)
Age (Years)			
Mean (SD)	65.4 (10.49)	65.0 (10.91)	65.2 (10.69)
Min – Med – Max	28 – 66 – 88	21 – 65 – 92	21 – 66 – 92
Sex, n (%)			
Male	173 (39.1)	174 (41.6)	347 (40.3)
Female	269 (60.9)	244 (58.4)	513 (59.7)
Ethnicity, n (%)			
Hispanic, Latino, or Spanish	47 (10.6)	58 (13.9)	105 (12.2)
Not Hispanic, Latino, or Spanish	395 (89.4)	360 (86.1)	755 (87.8)
Race, n (%)			
American Indian or Alaska	2 (0.5)	0 (0.0)	2 (0.2)
Asian	11 (2.5)	4 (1.0)	15 (1.7)
Black or African American	112 (25.3)	106 (25.4)	218 (25.3)
Native Hawaiian or Other Pacific	1 (0.2)	1 (0.2)	2 (0.2)
White	316 (71.5)	307 (73.4)	623 (72.4)
Iris Color, n (%)			
Blue	94 (21.3)	107 (25.6)	201 (23.4)
Brown	276 (62.4)	243 (58.1)	519 (60.3)
Green	22 (5.0)	26 (6.2)	48 (5.6)
Grey	4 (0.9)	3 (0.7)	7 (0.8)
Hazel	45 (10.2)	39 (9.3)	84 (9.8)
Other	1 (0.2)	0 (0.0)	1 (0.1)
Diagnosis, n (%)			
Ocular Hypertension	130 (29.4)	121 (28.9)	251 (29.2)
Open-Angle Glaucoma	304 (68.8)	290 (69.4)	594 (69.1)
Open-Angle Glaucoma with	7 (1.6)	7 (1.7)	14 (1.6)
Open-Angle Glaucoma with	1 (0.2)	0 (0.0)	1 (0.1)
Baseline IOP Stratum, n (%)			
24 - 27 mmHg	303 (68.6)	291 (69.6)	594 (69.1)
28 - 36 mmHg	139 (31.4)	127 (30.4)	266 (30.9)
Baseline IOP ^(a)			
8 AM Mean (SD)	26.9 (2.54)	27.1 (2.86)	27.0 (2.70)
Min – Med – Max	24 – 26 – 36	24 – 26 – 36	24 – 26 – 36
10 AM Mean (SD)	25.4 (2.83)	25.6 (3.15)	25.5 (2.99)
Min – Med – Max	21 – 25 – 36	21 – 25 – 36	21 – 25 – 36
4 PM Mean (SD)	24.6 (2.88)	24.8 (3.16)	24.7 (3.02)
Min – Med – Max	21 – 24 – 35	21 – 24 – 36	21 – 24 – 36
Corneal Thickness (µm)			
Mean (SD)	552.9 (35.00)	551.8 (32.10)	552.4 (33.61)
Min – Med – Max	440 – 554 – 619	443 – 553 – 619	440 – 554 – 619

(a) Baseline was the average of the two eligibility visits if both values were not missing; otherwise the non-missing value of the two visits was used
SD = Standard Deviation, Min = Minimum, Med = Median, Max = Maximum

3.2.4 Results and Conclusions

i) Primary Efficacy Endpoint

Descriptive statistics for the actual IOP measurements at all visits and time points by treatment group are presented in [Figure 1](#) (left panel) and in the appendix [Table 16](#). The mean IOP at each visit and time point were comparable between the treatment groups. [Table 5](#) presents a comparison of the mean IOP at each on-therapy visit and time point based on the least squares means derived from a linear mixed model repeated measures analysis outlined in [Section 3.2.2](#).

The two-sided 95% CIs for the difference in mean IOP between the treatment groups (Travoprost 0.003% minus Travatan) were within ± 1.0 mmHg at all visits and time points, meeting the equivalence criteria requirement of within ± 1.5 mmHg at each time point of each visit and within ± 1.0 mmHg for the majority of time points ([Table 5](#) and [Figure 1](#)). However, the point estimates for the difference in mean IOP slightly favored Travoprost 0.003% relative to Travatan group. This might be due to the slightly lower mean baseline IOP data observed in the Travoprost 0.003% group relative to the Travatan group ([Figure 1](#)) and the fact that the primary efficacy analysis did not adjust for the actual baseline data. Analysis adjusting for the actual baseline data are presented in item (ii)(a) below.

Table 5: Comparison of Mean IOP (mmHg) at Baseline, Week 2, Week 6, and Month 3 (ITT Analysis Set)

Visit	Time Point	Travoprost 0.003% (N=442)		Travatan (N=418)		Mean Difference ^{(a)(b)} (95% CI)
		N	Mean (SE)	N	Mean (SE)	
Baseline	8 AM	442	26.9 (0.12)	418	27.1 (0.14)	-0.2 (-0.5, 0.2)
	10 AM	442	25.4 (0.13)	418	25.6 (0.15)	-0.2 (-0.6, 0.2)
	4 PM	442	24.6 (0.14)	418	24.8 (0.16)	-0.2 (-0.6, 0.2)
Week 2	8 AM	442	19.4 (0.16)	416	19.5 (0.17)	-0.1 (-0.5, 0.3)
	10 AM	442	18.6 (0.16)	416	18.6 (0.16)	-0.0 (-0.4, 0.4)
	4 PM	442	18.0 (0.16)	416	18.3 (0.16)	-0.3 (-0.7, 0.1)
Week 6	8 AM	439	19.3 (0.16)	413	19.3 (0.17)	-0.0 (-0.4, 0.4)
	10 AM	440	18.5 (0.16)	413	18.6 (0.17)	-0.1 (-0.5, 0.3)
	4 PM	440	18.0 (0.16)	413	18.1 (0.17)	-0.2 (-0.6, 0.2)
Month 3	8 AM	432	19.2 (0.17)	408	19.3 (0.18)	-0.1 (-0.5, 0.3)
	10 AM	432	18.3 (0.17)	408	18.6 (0.18)	-0.3 (-0.7, 0.1)
	4 PM	431	18.0 (0.16)	408	18.0 (0.17)	0.0 (-0.4, 0.4)

SE = Standard Error; CI = Confidence Interval

- (a) Estimates for Week 2, Week 6, and Month 3 visits based on least squares mean derived from a statistical model that accounts for correlated IOP measurements within patient where site and 8 AM baseline IOP stratum are in the model
 (b) Estimates for Baseline visit at each time points were based on two sample independent t-test procedure

Results presented in [Table 5](#) were based on observed cases using the ITT analysis set. This table showed that the amount of missing data at each visit and time point was relatively small (< 2.5%) and comparable between the treatment groups. The number of subjects that discontinued at each visit and time point by treatment group is summarized in [Table 6](#).

To assess the robustness of the primary efficacy analysis result that used the observed data on the ITT analysis set, sensitivity analyses were performed using: (i) the PP analysis set based on the observed cases (See Appendix [Table 13](#)), (ii) using the MMRM model on the ITT analysis set

with LOCF (See Appendix [Table 14](#)), and (iii) using a two-sample t-test procedure on the ITT analysis set by visit with LOCF (See Appendix [Table 15](#)). All the sensitivity analyses results supported the primary efficacy analysis result presented in [Table 5](#). Therefore, the primary analysis results that used the observed data on the ITT analysis set are considered robust.

Table 6: Number of Subjects Discontinued by Visit and Time Point
(ITT Analysis Set)

	Week 2			Week 6			Month 3		
	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM
Travoprost 0.003%	0	0	0	3	2	2	10	10	11
Travatan	2	2	2	5	5	5	10	10	10
Total	2	2	2	8	7	7	20	20	21

Source: Table 11 1-1 of Study Report

Reviewer's Comment

In the clinical study report the applicant indicated that they had conducted additional imputation methods to impute missing values for dropouts and missing data; however no result of the additional imputation methods was provided in the clinical study report. This issue was communicated with the applicant during the filing review. The applicant acknowledged the issue and indicated that due to the very low missing rate in the IOP data, no additional sensitivity analyses using imputation methods other than LOCF were performed. The reviewer concurred with the applicant's response.

ii) Supportive Efficacy Endpoints

In Study C-11-043, the change in IOP from baseline, the percent change in IOP from baseline, the percentage of patients who achieved a target IOP level of < 18 mmHg, and the percentage of patients who achieved IOP-lowering of at least 30% from baseline were supportive efficacy endpoints. The supportive endpoints were analyzed using descriptive statistics, and results of these supportive efficacy endpoints are presented below.

a) Change in IOP from Baseline and Percent Change in IOP from Baseline

Descriptive statistics for the change in IOP and for the percent change in IOP from baseline at all visits and time points are presented in Appendix [Table 16](#). As shown in [Table 16](#), both treatment groups resulted in IOP reduction from baseline at all visits and time points. The descriptive mean absolute reduction and mean percent reduction in IOP from baseline, respectively, ranged from 7.1 to 8.2 mmHg and from 28.4% to 30.7% mmHg in the Travoprost 0.003% group and from 7.1 to 8.4 mmHg and from 28.5% to 31% in the Travatan group. The IOP reductions at all visits and time points were comparable between the treatment groups; however, the reductions were numerically slightly higher in the Travatan group relative to the Travoprost 0.003% group. In both treatment groups, the highest IOP reduction was observed at the 8 AM time point.

Comparison between the treatment difference in the mean IOP change from baseline at each visit and assessment time point was made using the least squares means derived from a linear mixed repeated measure model outlined in [Section 3.2.2](#). The model used IOP change from baseline as the response variable. The least square means estimates for the mean IOP change from baseline

by treatment group and visit are presented in [Table 7](#) and [Figure 4](#). At most of the visits and time points, the mean reduction in IOP was numerically slightly higher in the Travatan group relative the Travoprost 0.003% group.

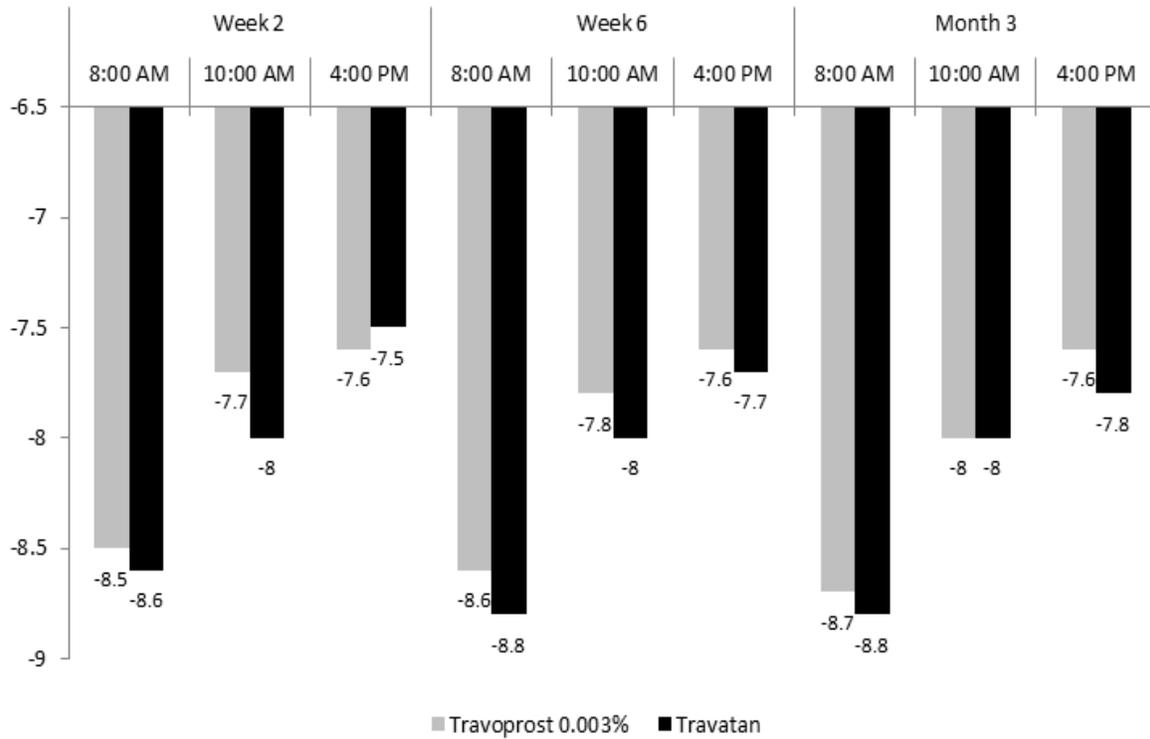
Table 7: Comparison of Mean IOP (mmHg) Change from Baseline (ITT Analysis Set)

Visit	Time Point	Travoprost 0.003% (N=442)		Travatan (N=418)		Mean Difference ^(a) (95% CI)
		N	Mean (SE)	N	Mean (SE)	
Week 2	8 AM	442	-8.5 (0.16)	416	-8.6 (0.16)	0.1 (-0.3, 0.5)
	10 AM	442	-7.7 (0.16)	416	-8.0 (0.16)	0.3 (-0.1, 0.6)
	4 PM	442	-7.6 (0.16)	416	-7.5 (0.17)	-0.1 (-0.5, 0.3)
Week 6	8 AM	439	-8.6 (0.16)	413	-8.8 (0.16)	0.2 (-0.2, 0.6)
	10 AM	440	-7.8 (0.16)	413	-8.0 (0.16)	0.2 (-0.2, 0.6)
	4 PM	440	-7.6 (0.16)	413	-7.7 (0.17)	0.1 (-0.3, 0.5)
Month 3	8 AM	432	-8.7 (0.16)	408	-8.8 (0.17)	0.1 (-0.3, 0.5)
	10 AM	432	-8.0 (0.17)	408	-8.0 (0.17)	-0.0 (-0.4, 0.4)
	4 PM	431	-7.6 (0.16)	408	-7.8 (0.17)	0.2 (-0.2, 0.7)

SE = Standard Error; CI = Confidence Interval

(a) Estimates for Week 2, Week 6, and Month 3 visits based on least squares mean derived from a statistical model that accounts for correlated IOP measurements within patient where site and 8 AM baseline IOP stratum are in the model

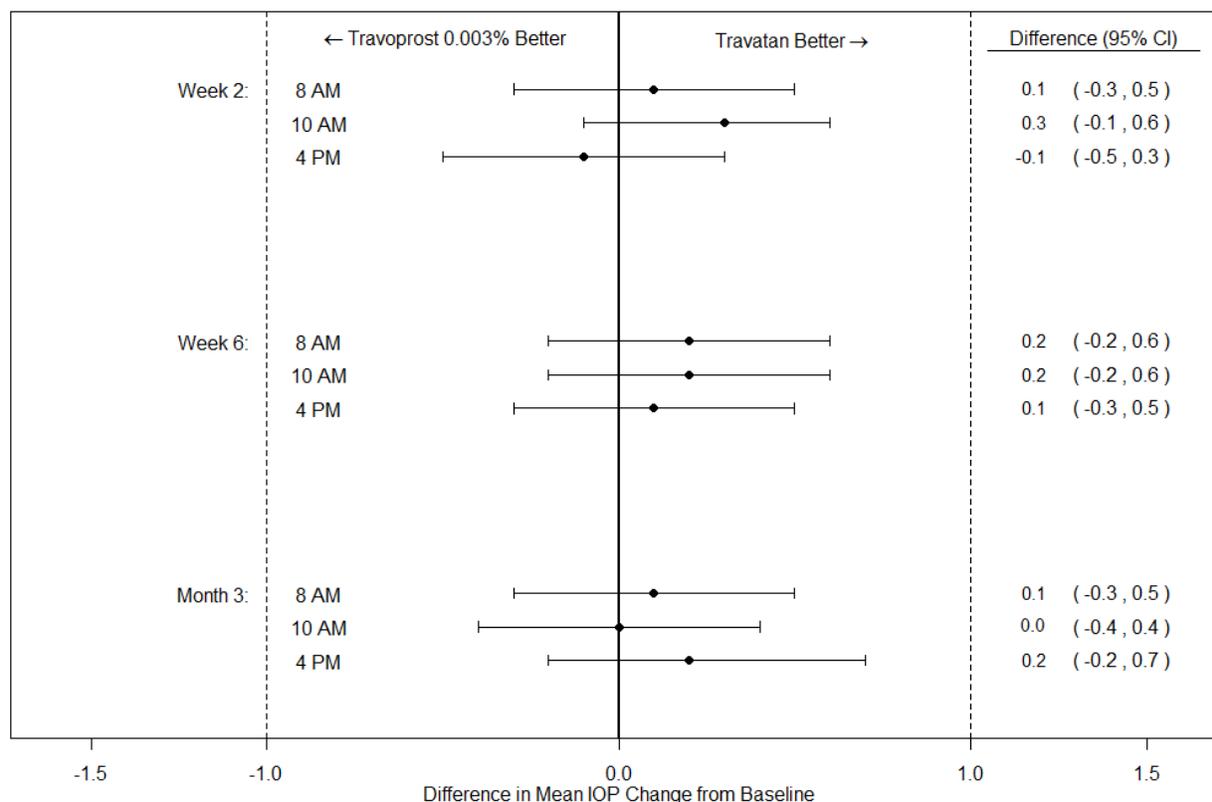
Figure 4: Mean IOP Change from Baseline by Treatment Group and Visit (ITT Analysis Set)



Source: [Table 7](#)

The point and 95% CI estimates for the difference in mean IOP change from baseline (Travoprost 0.003% minus Travatan) based on the model are presented in Table 7 and Figure 5. At most of the on-therapy visits and assessment time points, the reduction in IOP adjusting for the baseline IOP data was numerically slightly higher in the Travatan group than in the Travoprost 0.003% treatment group; however, there was no statistical significant difference between the treatment groups. The two-sided 95% CIs for the difference in mean IOP change from baseline were within ± 1.0 mmHg at all visits and time points, meeting the equivalence criteria requirement of within ± 1.5 mmHg at each time point of each visit and within ± 1.0 mmHg for the majority of time points.

Figure 5: Difference in Mean IOP Change from Baseline (mmHg)
(ITT Analysis Set)



Dots represent point estimates of treatment difference in mean IOP change from baseline; Horizontal lines represent 95% Confidence Intervals

b) Target IOP Level of < 18 mmHg and IOP-lowering of At Least 30% from Baseline

The percentage of patients who achieved a target IOP level of < 18 mmHg and IOP-lowering of at least 30% from baseline at each on-therapy visit and time point are presented in Table 8.

The percentage of subjects who achieved IOP level of < 18 mmHg and percent change in IOP of $\geq 30\%$, respectively, ranged from 33.3% to 54.5% and 43.9% to 53.7% in the Travoprost 0.003% group and from 36.8% to 52.8% and 44.2% to 54.4% in the Travatan group. In each treatment group and at each on-therapy visit, most subjects achieved a target IOP level of < 18 mmHg at the 4 PM time point and a percent change in IOP of at least 30% at the 8 AM time point.

Although the results based on both efficacy measures varied across study visit and time point, no marked difference was observed between the treatment groups with respect to both efficacy measures.

Table 8: Summary of Patients with IOP < 18 mmHG and IOP Lowering of $\geq 30\%$ (ITT Analysis Set)

Visit	Time Point	IOP < 18 mmHG		% Change in IOP $\geq 30\%$	
		Travoprost 0.003% (N=442)	Travatan (N=418)	Travoprost 0.003% (N=442)	Travatan (N=418)
Week 2	8 AM	147/ 442 (33.3%)	153/ 416 (36.8%)	219/ 442 (49.5%)	197/ 416 (47.4%)
	10 AM	208/ 442 (47.1%)	187/ 416 (45.0%)	194/ 442 (43.9%)	201/ 416 (48.3%)
	4 PM	237/ 442 (53.6%)	216/ 416 (51.9%)	208/ 442 (47.1%)	184/ 416 (44.2%)
Week 6	8 AM	172/ 439 (39.2%)	156/ 413 (37.8%)	232/ 439 (52.8%)	216/ 413 (52.3%)
	10 AM	195/ 440 (44.3%)	181/ 413 (43.8%)	200/ 440 (45.5%)	206/ 413 (49.9%)
	4 PM	240/ 440 (54.5%)	218/ 413 (52.8%)	196/ 440 (44.5%)	196/ 413 (47.5%)
Month 3	8 AM	167/ 432 (38.7%)	154/ 408 (37.7%)	232/ 432 (53.7%)	222/ 408 (54.4%)
	10 AM	211/ 432 (48.8%)	191/ 408 (46.8%)	228/ 432 (52.8%)	204/ 408 (50.0%)
	4 PM	231/ 431 (53.6%)	214/ 408 (52.5%)	192/ 431 (44.5%)	197/ 408 (48.3%)

Reviewer's Comment

Treatment comparisons based on both the mean IOP and the mean IOP change from baseline efficacy measures demonstrated equivalence of Travoprost 0.003% to Travatan in IOP lowering effect. However, the point estimates of the treatment differences based on the two efficacy measures pointed in differing directions; analysis based on the primary endpoint of mean IOP measure slightly favored Travoprost 0.003% (See [Figure 1](#) right panel) while analysis based on the mean IOP change from baseline measure slightly favored Travatan (See [Figure 5](#)).

In general, treatment differences based on both efficacy measures are expected to provide similar results when the treatment group baseline IOP measurements are comparable. However, when the baseline IOP measurements between the treatment groups are not comparable due to some unforeseen reason, treatment comparison based on mean IOP measure without adjusting for the baseline data will not accurately reflect the IOP lowering effect of the treatments. In addition, at the patient level, the IOP change from baseline is a more direct measurement of IOP lowering effect than the IOP measurement without adjusting for baseline. Therefore, the reviewer believes that in comparing the effectiveness of treatment groups in lowering IOP, the mean IOP changes from baseline at each on-therapy visit and assessment time point are a more meaningful efficacy measure than the mean IOP measurements.

3.3 Evaluation of Safety

In Study C-11-034, safety was evaluated based on all randomized subjects who received at least a single dose of double blind treatment. The safety parameters in the study included extent of exposure to study drug, adverse events (AEs), and measured safety related parameters which included visual acuity, ocular signs, visual field function tests, central corneal thickness, ocular hyperemia, and dilated fundus exam.

The safety population in the study included a total of 863 subjects; 442 subjects were included in the Travoprost 0.003% group and 421 subjects were included in the Travatan group (Table 3). Subjects included in the safety population were 21 to 92 years old who were exposed to study drug once daily for up to 3 months.

i) Exposure to Study Drug

Table 9 presents the summary of exposure to study drug. The duration of exposure to study drug was comparable between the treatment groups. In each treatment group, average exposure was about 88 days and at least 70% of subjects in the study had exposure at least 87 days and 98% of subjects had exposure at least 45 days.

Table 9: Summary of Duration of Exposure to Study Drug
(Safety Analysis Set)

	Travoprost 0.003% (N = 442)	Travatan (N = 421)
Exposure (Days)		
Mean (SD)	88.2 (8.27)	87.6 (10.76)
Median	91	90
Min - Max	19 – 100	3 - 98
Cumulative Exposure Category [N (%)]		
> 1 Day	442 (100%)	421 (100%)
> 15 Days	442 (100%)	416 (98.8%)
> 45 Days	435 (98.4%)	412 (97.9%)
> 87 Days	322 (72.9%)	301 (71.5%)

SD: Standard Deviation

ii) Adverse Events

A total of 863 subjects were exposed to the study drug in Study C-11-034. Among these subjects, 30.3% (134/442) of the subjects in the Travoprost 0.003% group and 32.3% (136/421) of the subjects in the Travatan group experienced at least 1 treatment-emergent AE; 17.9% (79/442) of the subjects in the Travoprost 0.003% group and 19.0 % (80/421) of the subjects in the Travatan group experienced at least 1 treatment related treatment-emergent AE; 1.1% (5/442) of the subjects in the Travoprost 0.003% group and 1.7 % (7/421) of the subjects in the Travatan group experienced at least one serious adverse event. All serious adverse events were nonfatal and judged by the study investigators as not related to the study drug treatment.

Three subjects in the Travoprost 0.003% group (two related to and one not related to treatment) and four subjects in the Travatan group (three related to and one not related to treatment) discontinued due to non-serious AE. Moderate eye irritation and mild conjunctival hyperaemia in the Travoprost 0.003% group and moderate ocular hyperaemia (in two subjects) and mild dizziness in the Travatan group were the reported treatment-related AE reasons for discontinuation.

Overall, the most frequently reported treatment-emergent AEs ($\geq 5\%$ of subjects by MedDRA Preferred Term) were ocular hyperaemia and conjunctival hyperaemia. The incidences of both events were numerically slightly higher in the Travatan group relative to the Travoprost 0.003% group. The summary of most frequent treatment-emergent AEs reported by at least 2% of subjects are presented in Table 10.

Table 10 Most Frequent ($\geq 2\%$ of Subjects) Treatment-Emergent AEs (Safety Analysis Set)

System Organ Class/ Preferred Term	Travoprost 0.003% (N = 442)				Travatan (N = 421)			
	Severity			Total	Severity			Total
Eye Disorders/	Mild	Moderate	Severe		Mild	Moderate	Severe	
Ocular hyperaemia	27	4	1	31 (7.0%)	29	5	0	34 (8.1%)
Conjunctival hyperaemia	25	1	0	25 (5.7%)	29	1	0	30 (7.1%)
Eye pruritus	13	2	0	15 (3.4%)	9	1	0	10 (2.4%)
Eye irritation	8	2	0	10 (2.3%)	5	1	0	6 (1.4%)

Table 11 presents a summary of the overall treatment emergent AEs by the subgroups of age, gender, and race. In terms of the overall AE summary, no marked treatment difference was observed; however, in the subgroups of age < 65, male, and black, the overall AE rates were relatively higher in the Travatan group than in the Travoprost 0.003% treatment group.

Table 11: Overall AE Summary by Subgroup (Safety Analysis Set)

		Treatment Emergent AEs Related to Treatment		Treatment Emergent AEs (Related and not related combined)	
		Travoprost 0.003%	Travatan	Travoprost 0.003%	Travatan
Subjects with at least 1 AE		79/442 (17.9%)	80/421 (19.0)	134/442 (30.3%)	136/421 (32.3%)
Age	< 65	31/189 (16.4%)	37/193 (19.2%)	49/189 (25.9%)	59/193 (30.6%)
	≥ 65	48/253 (19.0%)	43/228 (18.9%)	85/253 (33.6%)	77/228 (33.8%)
Gender	Male	31/173 (17.9%)	37/175 (21.1%)	48/173 (27.7%)	58/175 (33.1%)
	Female	48/269 (17.8%)	43/246 (17.5%)	86/269 (32.0%)	78/246 (31.7%)
Race	White	65/316 (20.6%)	64/308 (20.8%)	111/316 (35.1%)	111/308 (36.0%)
	Black	10/112 (8.9%)	14/108 (13.0%)	18/112 (16.1%)	23/108 (21.3%)
	Other	4/14 (28.6%)	2/5 (40.0%)	5/14 (35.7%)	2/5 (40.0%)

Table 12 presents a summary of the most frequent treatment-emergent AEs reported by at least 2% of subjects by the subgroups of age, gender, and race. As was seen in the overall AE summary (See Table 10), ocular hyperaemia and conjunctival hyperaemia were the most frequently reported treatment-emergent AEs in all subgroup categories. The rates for these events, with the exception of conjunctival hyperaemia in female, were slightly higher in the Travatan group than in the Travoprost 0.003% group. The rates for eye pruritus and eye irritation in most of the subgroups and conjunctival hyperaemia in female subgroup were slightly higher in the Travoprost 0.003% treatment group than in the Travatan treatment group.

Table 12: Most Frequent ($\geq 2\%$ of Subjects) Treatment-Emergent AEs by Subgroup (Safety Analysis Set)

Subgroup	Category	System Organ Class/ Preferred Term	Travoprost 0.003%	Travatan
		Eye Disorders/		
Age	< 65	Ocular hyperaemia	18 / 189 (9.5%)	21 / 193 (10.9%)
		Conjunctival hyperaemia	7 / 189 (3.7%)	8 / 193 (4.1%)
		Eye irritation	4 / 189 (2.1%)	2 / 193 (1.0%)
	≥ 65	Conjunctival hyperaemia	18 / 253 (7.1%)	22 / 228 (9.6%)
		Ocular hyperaemia	13 / 253 (5.1%)	13 / 228 (5.7%)
		Eye pruritus	12 / 253 (4.7%)	8 / 228 (3.5%)
		Eye irritation	6 / 253 (2.4%)	4 / 228 (1.8%)
Gender	Male	Ocular hyperaemia	14 / 173 (8.1%)	14 / 175 (8.0%)
		Conjunctival hyperaemia	6 / 173 (3.5%)	14 / 175 (8.0%)
		Eye pruritus	4 / 173 (2.3%)	5 / 175 (2.9%)
		Eye irritation	5 / 173 (2.9%)	2 / 175 (1.1%)
		Dry eye	2 / 173 (1.2%)	4 / 175 (2.3%)
		Vision blurred	0 / 173 (0.0%)	4 / 175 (2.3%)
	Female	Ocular hyperaemia	17 / 269 (6.3%)	20 / 246 (8.1%)
		Conjunctival hyperaemia	19 / 269 (7.1%)	16 / 246 (6.5%)
		Eye pruritus	11 / 269 (4.1%)	5 / 246 (2.0%)
Race ^(a)	White	Ocular hyperaemia	25 / 316 (7.9%)	25 / 308 (8.1%)
		Conjunctival hyperaemia	18 / 316 (5.7%)	25 / 308 (8.1%)
		Eye pruritus	11 / 316 (3.5%)	10 / 308 (3.2%)
		Eye irritation	9 / 316 (2.8%)	6 / 308 (1.9%)
		Dry eye	7 / 316 (2.2%)	5 / 308 (1.6%)
	Black	Ocular hyperaemia	6 / 112 (5.4%)	8 / 108 (7.4%)
		Conjunctival hyperaemia	4 / 112 (3.6%)	5 / 108 (4.6%)
		Eye pruritus	3 / 112 (2.7%)	0 / 108 (0.0%)

(a) Due to small sample size, the race category 'Other' was not included in the table

The safety evaluation based on measured safety related parameters that included visual acuity, ocular signs, visual field function tests, central corneal thickness, ocular hyperemia, and dilated fundus exam did not reveal any marked treatment difference.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Descriptive analyses for mean IOP and mean change in IOP from baseline were conducted by age group (<65 or ≥65 years), gender (male or female), and race (white, black, or other). Due to small sample sizes, the race categories of Asian, Native Hawaiian or Other Pacific Islander, and American Indian or Alaska Native were pooled together in the descriptive summary and presented in the ‘other’ category.

The descriptive summary results by these subgroups are presented in the appendix (See [Table 17](#), [Table 18](#), and [Table 19](#)). Overall, results of the descriptive analyses by each subgroup were similar to what was observed in the overall population.

Analysis by geographic region was not conducted since all clinical sites were in the United States.

4.2 Other Special/Subgroup Populations: Baseline 8 AM IOP, Diagnosis, and Iris Color

Descriptive summaries for mean IOP and mean change in IOP from baseline at all on-therapy visits and assessment time points were conducted by the subgroups of baseline 8 AM IOP (24-27 mmHg or 28-36 mmHg), iris color (brown, blue, hazel, or other), and diagnosis (open-angle glaucoma or ocular hypertension). Due to small sample sizes, Open-Angle Glaucoma with Pigment Dispersion and Open-Angle Glaucoma with Pseudoexfoliation diagnoses categories were summarized together with Open-Angle Glaucoma; and Green and Grey iris colors were summarized in the ‘other’ category.

The descriptive summary results by these subgroups are presented in appendix [Table 20](#), [Table 21](#), and [Table 22](#). Overall, results of the descriptive analyses for mean IOP and mean change in IOP from baseline, by the subgroups of baseline 8 AM IOP, diagnosis, and iris color were similar to what was observed in the overall population.

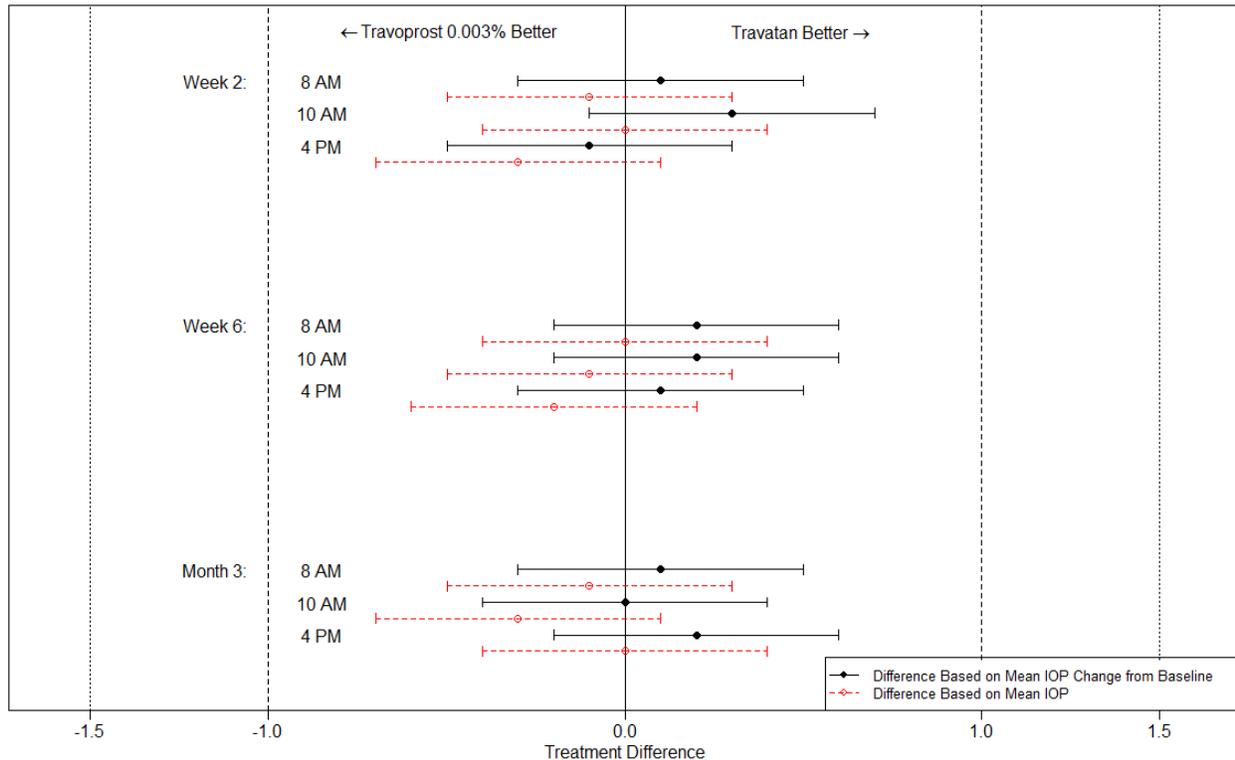
5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues for this submission. Although the primary endpoint in the study protocol was based on the comparison of mean IOP between the treatment groups evaluated at each on-therapy study visits at Week 2, Week 6, and Month 3 and assessment time points at 8 AM, 10 AM, and 4 PM, treatment comparisons at each on-therapy visit and time point were also made using the mean IOP change from baseline efficacy measure.

Based on both efficacy measures, the equivalence criterion of the two-sided 95% CIs for the treatment differences to be within ± 1.5 mmHg was successfully met. However, the point estimates for the treatment differences based on the two efficacy measures were in differing directions; analysis based on the primary endpoint of mean IOP measure slightly favored Travoprost 0.003% while analysis based on the mean IOP change from baseline efficacy measure slightly favored Travatan (See Figure 6). The disparity in the point estimates might be due to the slightly lower mean baseline IOP data observed in the Travoprost 0.003% group relative to the Travatan group (Figure 1 left panel) and the fact that the primary efficacy analysis of mean IOP comparison did not adjust for the actual baseline data.

Figure 6: Treatment Difference Based on Mean IOP and Mean IOP Change from Baseline (ITT Analysis Set)



The reviewer believes that in comparing the effectiveness of treatment groups in lowering IOP, the mean IOP changes from baseline at each on-therapy visit and assessment time point are a more meaningful efficacy measure than the mean IOP measurements.

5.2 Collective Evidence

The primary efficacy evidence to support the equivalence of Travoprost 0.003 to Travatan in IOP reduction was based on a single pivotal phase 3 trial (Study C-11-034). The trial demonstrated that at each visit (Week 2, Week 4, Month 3) and at each assessment time point (8 AM, 10 AM, and 4 PM) treatment with Travoprost 0.003% compared to Travatan provided similar IOP lowering efficacy benefit based on IOP, IOP change from baseline, and IOP percent change from baseline. Both treatment groups resulted in comparable IOP reductions at all visits and assessment time points. The highest IOP reduction in both groups was observed at the 8 AM assessment time point. The mean absolute reduction and the mean percent reduction in IOP from baseline, respectively, ranged from 7.1 to 8.2 mmHG and from 28.4% to 30.7% mmHG in the Travoprost 0.003% group and from 7.1 to 8.4 mmHG and from 28.5% to 31% in the Travatan group. The two-sided 95% CIs for the difference in mean IOP and mean IOP change from baseline between Travoprost 0.003% and Travatan were within ± 1.0 mmHG at all assessment time points, meeting the equivalence criteria requirement of within ± 1.5 mmHG at each time point and within ± 1.0 mmHG for the majority of time points.

Descriptive analyses of the primary efficacy endpoint based on IOP, IOP change from baseline, and IOP percent change from baseline was also conducted by the subgroups of age (<65 or ≥ 65), gender (male or female), race (white, black, or other), baseline 8 AM (24-27 mmHg or 28-36 mmHg), iris color (brown, blue, hazel, or other), and baseline diagnosis (ocular hypertension or open-angle glaucoma). Overall, the results for each subgroup were similar to those seen for the overall population.

In addition, the safety profiles between Travoprost 0.003% and Travatan in Study C-11-034 were similar: 30.3% of subjects in the Travoprost 0.003% group and 32.3% of subjects in the Travatan group experienced at least 1 treatment-emergent AE; 17.9% of subjects in the Travoprost 0.003% group and 19.0% of subjects in the Travatan group experienced at least 1 treatment related treatment-emergent AE; Ocular hyperaemia (7.0% in Travoprost 0.003% and 8.1% in the Travatan group) and conjunctival hyperaemia (5.7% in Travoprost 0.003% and 7.1% in the Travatan group) were the most frequently reported (in 5% of subjects) treatment-emergent AEs in the study. 1.1% of subjects in the Travoprost 0.003% group and 1.7% of subjects in the Travatan group experienced at least one serious adverse event. No patients died during the study.

5.3 Conclusions and Recommendations

Based on my review, the applicant has demonstrated the safety and efficacy of Travoprost 0.003% once daily for the proposed indication of reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

5.4 Labeling Recommendations

In Section 14 Clinical Studies, the applicant is proposing to present the point and 95% CI estimates for the difference in mean IOP between Travoprost 0.003% and Travatan at each visit and time point graphically (Figure 1 right panel). Furthermore, the applicant is proposing to include the mean IOP change from baseline (mmHg) summary data for the Travoprost 0.003% treatment group only.

The applicant's proposed graph is acceptable. However, in order to provide patients and physicians informative data regarding the IOP lowering effect of each treatment group, the table and figure below are recommended.

The table presents the least square mean IOP (mmHg), the difference in mean IOP (Travoprost 0.003% minus Travatan), and the 95% CIs for the treatment differences in mean IOP at all visits and time points.

Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP

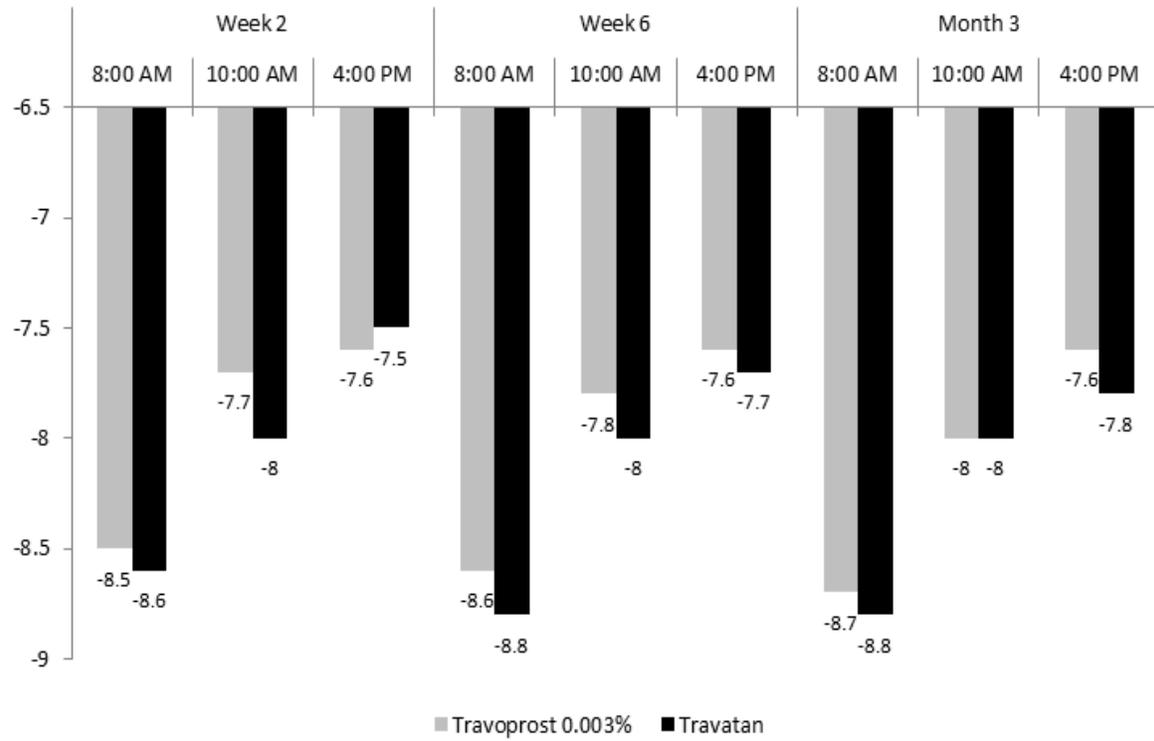
Visit/ Time Point	Travoprost 0.003% (N = 442)		Travoprost 0.004% (N = 418)		Difference (95% CI) **
	N	Mean (SE)	N	Mean (SE)	
Baseline					
8 AM	442	26.9 (0.12)	418	27.1 (0.14)	-0.2 (-0.5, 0.2)
10 AM	442	25.4 (0.13)	418	25.6 (0.15)	-0.2 (-0.6, 0.2)
4 PM	442	24.6 (0.14)	418	24.8 (0.16)	-0.2 (-0.6, 0.2)
Week 2					
8 AM	442	19.4 (0.16)	416	19.5 (0.17)	-0.1 (-0.5, 0.3)
10 AM	442	18.6 (0.16)	416	18.6 (0.16)	-0.0 (-0.4, 0.4)
4 PM	442	18.0 (0.16)	416	18.3 (0.16)	-0.3 (-0.7, 0.1)
Week 6					
8 AM	439	19.3 (0.16)	413	19.3 (0.17)	-0.0 (-0.4, 0.4)
10 AM	440	18.5 (0.16)	413	18.6 (0.17)	-0.1 (-0.5, 0.3)
4 PM	440	18.0 (0.16)	413	18.1 (0.17)	-0.2 (-0.6, 0.2)
Month 3					
8 AM	432	19.2 (0.17)	408	19.3 (0.18)	-0.1 (-0.5, 0.3)
10 AM	432	18.3 (0.17)	408	18.6 (0.18)	-0.3 (-0.7, 0.1)
4 PM	431	18.0 (0.16)	408	18.0 (0.17)	0.0 (-0.4, 0.4)

SE = Standard Error; CI = Confidence Interval

** Estimates for Week 2, Week 6, and Month 3 are based on least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where site and 8 AM baseline IOP stratum are in the model; estimates for Baseline visit at each time points are based on two sample independent t-test procedure

The figure presents the mean IOP change from baseline at Week 2, Week 6, and at Month 3.

Mean IOP Change from Baseline



APPENDICES

Table 13: Comparison of Mean IOP (mmHg) by Visit
(PP Analysis Set)

Visit	Time Point	Travoprost 0.003%		Travatan		Mean Difference ^(a) (95% CI)
		N	Mean (SE)	N	Mean (SE)	
Week 2	8 AM	435	19.4 (0.16)	409	19.5 (0.17)	-0.1 (-0.5, 0.3)
	10 AM	435	18.6 (0.16)	409	18.6 (0.17)	-0.0 (-0.4, 0.4)
	4 PM	435	18.0 (0.16)	409	18.3 (0.17)	-0.3 (-0.7, 0.1)
Week 6	8 AM	430	19.3 (0.17)	403	19.3 (0.17)	-0.0 (-0.4, 0.4)
	10 AM	430	18.5 (0.16)	403	18.6 (0.17)	-0.2 (-0.6, 0.3)
	4 PM	431	17.9 (0.16)	403	18.1 (0.17)	-0.2 (-0.6, 0.2)
Month 3	8 AM	420	19.1 (0.17)	396	19.3 (0.18)	-0.2 (-0.6, 0.3)
	10 AM	420	18.3 (0.17)	396	18.6 (0.18)	-0.3 (-0.8, 0.1)
	4 PM	419	18.0 (0.16)	396	18.0 (0.17)	-0.0 (-0.4, 0.4)

Table 14: Comparison of Mean IOP (mmHg) by Visit
(LOCF on ITT Analysis Set)

Visit	Time Point	Travoprost 0.003%		Travatan		Mean Difference ^(a) (95% CI)
		N	Mean (SE)	N	Mean (SE)	
Week 2	8 AM	442	19.4 (0.16)	416	19.5 (0.17)	-0.1 (-0.5, 0.3)
	10 AM	442	18.6 (0.16)	416	18.6 (0.16)	-0.0 (-0.4, 0.4)
	4 PM	442	18.0 (0.16)	416	18.3 (0.16)	-0.3 (-0.7, 0.1)
Week 6	8 AM	442	19.3 (0.16)	418	19.3 (0.17)	-0.0 (-0.4, 0.4)
	10 AM	442	18.5 (0.16)	418	18.6 (0.17)	-0.1 (-0.5, 0.3)
	4 PM	442	18.0 (0.16)	418	18.1 (0.17)	-0.2 (-0.6, 0.2)
Month 3	8 AM	442	19.1 (0.17)	418	19.3 (0.18)	-0.1 (-0.6, 0.3)
	10 AM	442	18.3 (0.17)	418	18.6 (0.18)	-0.3 (-0.7, 0.1)
	4 PM	442	18.0 (0.16)	418	18.0 (0.17)	0.0 (-0.4, 0.4)

Table 15: Comparison of Mean IOP (mmHg) by Visit Based on a T-Test Procedure
(LOCF on ITT Analysis Set)

Visit	Time Point	Travoprost 0.003%		Travatan		Mean Difference (95% CI) ^(b)
		N	Mean (SE)	N	Mean (SE)	
Week 2	8 AM	442	18.9 (0.16)	416	19.0 (0.18)	-0.1 (-0.5, 0.4)
	10 AM	442	18.1 (0.15)	416	18.1 (0.17)	0.1 (-0.4, 0.5)
	4 PM	442	17.5 (0.15)	416	17.7 (0.18)	-0.2 (-0.7, 0.2)
Week 6	8 AM	442	18.8 (0.17)	418	18.8 (0.18)	0.0 (-0.5, 0.5)
	10 AM	442	18.0 (0.16)	418	18.0 (0.17)	-0.0 (-0.5, 0.4)
	4 PM	442	17.5 (0.15)	418	17.6 (0.17)	-0.1 (-0.6, 0.3)
Month 3	8 AM	442	18.7 (0.17)	418	18.7 (0.19)	-0.1 (-0.6, 0.4)
	10 AM	442	17.8 (0.15)	418	18.1 (0.19)	-0.2 (-0.7, 0.2)
	4 PM	442	17.6 (0.15)	418	17.5 (0.17)	0.1 (-0.4, 0.5)

SE= Standard Error; CI = Confidence Interval; LOCF = Last on-therapy observation carried forward

(a) Estimates for Week 2, Week 6, and Month 3 visits based on least squares mean derived from a statistical model that accounts for correlated IOP measurements within patient where site and actual 8 AM baseline IOP stratum are in the model

(b) Based on a two-sample t-test procedure

Table 16: Descriptive Summary for IOP Measures by Visit and Treatment Group (ITT Analysis Set)

Summary	Visit	Time	Travoprost 0.003%			Travatan		
			N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
Actual IOP	Baseline	8 AM	442	26.9 (2.54)	(26.7, 27.2)	418	27.1 (2.86)	(26.8, 27.4)
		10 AM	442	25.4 (2.83)	(25.1, 25.6)	418	25.6 (3.15)	(25.3, 25.9)
		4 PM	442	24.6 (2.88)	(24.4, 24.9)	418	24.8 (3.16)	(24.5, 25.1)
	Week 2	8 AM	442	18.9 (3.35)	(18.6, 19.2)	416	19.0 (3.61)	(18.6, 19.3)
		10 AM	442	18.1 (3.15)	(17.8, 18.4)	416	18.1 (3.52)	(17.7, 18.4)
		4 PM	442	17.5 (3.08)	(17.2, 17.8)	416	17.7 (3.64)	(17.4, 18.1)
	Week 6	8 AM	439	18.8 (3.50)	(18.4, 19.1)	413	18.8 (3.76)	(18.4, 19.1)
		10 AM	440	18.0 (3.36)	(17.7, 18.3)	413	18.1 (3.55)	(17.7, 18.4)
		4 PM	440	17.5 (3.13)	(17.2, 17.8)	413	17.6 (3.48)	(17.2, 17.9)
	Month 3	8 AM	432	18.6 (3.59)	(18.3, 19.0)	408	18.7 (3.69)	(18.3, 19.1)
		10 AM	432	17.8 (3.19)	(17.5, 18.1)	408	18.0 (3.72)	(17.7, 18.4)
		4 PM	431	17.5 (3.10)	(17.2, 17.8)	408	17.4 (3.41)	(17.1, 17.8)
Change in IOP	Week 2	8 AM	442	-8.0 (3.02)	(-8.3, -7.7)	416	-8.1 (3.27)	(-8.4, -7.8)
		10 AM	442	-7.3 (3.08)	(-7.6, -7.0)	416	-7.5 (3.20)	(-7.8, -7.2)
		4 PM	442	-7.1 (3.21)	(-7.4, -6.8)	416	-7.1 (3.10)	(-7.4, -6.8)
	Week 6	8 AM	439	-8.1 (3.03)	(-8.4, -7.9)	413	-8.3 (3.26)	(-8.7, -8.0)
		10 AM	440	-7.4 (3.01)	(-7.6, -7.1)	413	-7.5 (3.17)	(-7.9, -7.2)
		4 PM	440	-7.2 (3.19)	(-7.5, -6.9)	413	-7.2 (3.05)	(-7.5, -6.9)
	Month 3	8 AM	432	-8.2 (3.27)	(-8.6, -7.9)	408	-8.4 (3.17)	(-8.7, -8.1)
		10 AM	432	-7.5 (3.27)	(-7.9, -7.2)	408	-7.6 (3.24)	(-7.9, -7.2)
		4 PM	431	-7.1 (3.23)	(-7.4, -6.8)	408	-7.3 (3.21)	(-7.7, -7.0)
% Change in IOP	Week 2	8 AM	442	-29.7 (10.67)	(-30.7,-28.7)	416	-29.9 (11.33)	(-31.0,-28.8)
		10 AM	442	-28.4 (10.97)	(-29.4,-27.4)	416	-29.3 (11.44)	(-30.4,-28.2)
		4 PM	442	-28.7 (11.43)	(-29.7,-27.6)	416	-28.5 (11.55)	(-29.6,-27.4)
	Week 6	8 AM	439	-30.3 (10.78)	(-31.3,-29.3)	413	-30.8 (11.36)	(-31.9,-29.7)
		10 AM	440	-28.9 (10.89)	(-30.0,-27.9)	413	-29.4 (11.36)	(-30.5,-28.3)
		4 PM	440	-28.8 (11.35)	(-29.9,-27.7)	413	-29.1 (11.11)	(-30.2,-28.0)
	Month 3	8 AM	432	-30.7 (11.29)	(-31.7,-29.6)	408	-31.0 (10.93)	(-32.1,-30.0)
		10 AM	432	-29.5 (11.44)	(-30.6,-28.5)	408	-29.5 (11.50)	(-30.6,-28.4)
		4 PM	431	-28.5 (11.48)	(-29.6,-27.4)	408	-29.4 (11.37)	(-30.5,-28.3)

SD = Standard Deviation; CI = Confidence Interval

Table 17: Descriptive IOP (mmHg) Summary by Age Group
(ITT Analysis Set)

			Travoprost 0.003%			Travatan		
Summary	Visit	Time	N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
AGE: < 65 Years								
Actual IOP	Baseline	8 AM	189	26.8 (2.39)	(26.5, 27.2)	191	27.0 (2.78)	(26.6, 27.4)
		10 AM	189	25.2 (2.60)	(24.8, 25.6)	191	25.4 (3.00)	(25.0, 25.8)
		4 PM	189	24.4 (2.71)	(24.0, 24.8)	191	24.7 (3.04)	(24.3, 25.2)
	Week 2	8 AM	189	18.6 (3.49)	(18.1, 19.1)	190	19.0 (3.53)	(18.5, 19.5)
		10 AM	189	17.6 (3.06)	(17.2, 18.0)	190	17.9 (3.33)	(17.4, 18.3)
		4 PM	189	17.2 (3.08)	(16.8, 17.6)	190	17.4 (3.52)	(16.9, 17.9)
	Week 6	8 AM	188	18.5 (3.75)	(17.9, 19.0)	188	18.5 (3.47)	(18.0, 19.0)
		10 AM	188	17.6 (3.44)	(17.1, 18.1)	188	17.8 (3.26)	(17.3, 18.2)
		4 PM	189	17.0 (3.17)	(16.5, 17.4)	188	17.3 (3.09)	(16.8, 17.7)
	Month 3	8 AM	185	18.5 (3.99)	(17.9, 19.1)	185	18.6 (3.29)	(18.1, 19.0)
		10 AM	185	17.5 (3.45)	(17.0, 18.0)	185	17.9 (3.36)	(17.4, 18.4)
		4 PM	184	17.1 (3.24)	(16.7, 17.6)	185	17.2 (3.12)	(16.8, 17.7)
Change in IOP	Week 2	8 AM	189	-8.3 (3.19)	(-8.7, -7.8)	190	-8.1 (3.41)	(-8.6, -7.6)
		10 AM	189	-7.6 (3.15)	(-8.0, -7.1)	190	-7.6 (3.40)	(-8.0, -7.1)
		4 PM	189	-7.2 (3.29)	(-7.7, -6.8)	190	-7.3 (3.21)	(-7.8, -6.8)
	Week 6	8 AM	188	-8.3 (3.21)	(-8.8, -7.9)	188	-8.5 (3.33)	(-9.0, -8.0)
		10 AM	188	-7.6 (3.09)	(-8.0, -7.1)	188	-7.6 (3.17)	(-8.1, -7.1)
		4 PM	189	-7.4 (3.35)	(-7.9, -7.0)	188	-7.4 (3.06)	(-7.9, -7.0)
	Month 3	8 AM	185	-8.3 (3.49)	(-8.8, -7.8)	185	-8.5 (3.14)	(-8.9, -8.0)
		10 AM	185	-7.7 (3.38)	(-8.2, -7.2)	185	-7.5 (3.26)	(-8.0, -7.1)
		4 PM	184	-7.3 (3.16)	(-7.7, -6.8)	185	-7.5 (3.14)	(-8.0, -7.1)

AGE: ≥ 65 Years

Actual IOP	Baseline	8 AM	253	27.0 (2.65)	(26.7, 27.3)	227	27.2 (2.93)	(26.8, 27.6)
		10 AM	253	25.5 (2.98)	(25.1, 25.9)	227	25.8 (3.26)	(25.3, 26.2)
		4 PM	253	24.8 (3.01)	(24.4, 25.2)	227	24.9 (3.27)	(24.5, 25.3)
	Week 2	8 AM	253	19.2 (3.22)	(18.8, 19.6)	226	19.0 (3.69)	(18.5, 19.5)
		10 AM	253	18.5 (3.16)	(18.1, 18.9)	226	18.2 (3.67)	(17.7, 18.7)
		4 PM	253	17.7 (3.07)	(17.3, 18.1)	226	18.0 (3.73)	(17.5, 18.5)
	Week 6	8 AM	251	19.0 (3.30)	(18.6, 19.4)	225	19.0 (3.99)	(18.4, 19.5)
		10 AM	252	18.3 (3.28)	(17.9, 18.7)	225	18.3 (3.77)	(17.8, 18.8)
		4 PM	251	17.8 (3.06)	(17.5, 18.2)	225	17.9 (3.77)	(17.4, 18.4)
	Month 3	8 AM	247	18.7 (3.27)	(18.3, 19.1)	223	18.8 (4.00)	(18.3, 19.3)
		10 AM	247	18.0 (2.96)	(17.6, 18.4)	223	18.1 (4.00)	(17.6, 18.7)
		4 PM	247	17.8 (2.98)	(17.4, 18.1)	223	17.6 (3.62)	(17.2, 18.1)
Change in IOP	Week 2	8 AM	253	-7.8 (2.88)	(-8.2, -7.5)	226	-8.2 (3.17)	(-8.6, -7.7)
		10 AM	253	-7.0 (3.01)	(-7.4, -6.7)	226	-7.5 (3.02)	(-7.9, -7.1)
		4 PM	253	-7.1 (3.15)	(-7.5, -6.7)	226	-6.9 (3.00)	(-7.3, -6.5)
	Week 6	8 AM	251	-8.0 (2.89)	(-8.4, -7.6)	225	-8.2 (3.21)	(-8.6, -7.8)
		10 AM	252	-7.2 (2.94)	(-7.6, -6.8)	225	-7.5 (3.17)	(-7.9, -7.1)
		4 PM	251	-6.9 (3.05)	(-7.3, -6.6)	225	-7.1 (3.03)	(-7.5, -6.7)
	Month 3	8 AM	247	-8.2 (3.10)	(-8.6, -7.8)	223	-8.3 (3.20)	(-8.7, -7.9)
		10 AM	247	-7.4 (3.18)	(-7.8, -7.0)	223	-7.6 (3.23)	(-8.0, -7.1)
		4 PM	247	-6.9 (3.28)	(-7.4, -6.5)	223	-7.2 (3.26)	(-7.6, -6.8)

Table 18: Descriptive IOP (mmHg) Summary by Gender
(ITT Analysis Set)

			Travoprost 0.003%			Travatan			
Summary	Visit	Time	N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)	
Male									
Actual IOP	Baseline	8 AM	173	26.9 (2.58)	(26.5, 27.3)	174	27.6 (3.07)	(27.2, 28.1)	
		10 AM	173	25.4 (2.75)	(25.0, 25.8)	174	26.2 (3.40)	(25.7, 26.7)	
		4 PM	173	24.6 (2.84)	(24.2, 25.0)	174	25.5 (3.45)	(25.0, 26.0)	
	Week 2	8 AM	173	18.8 (3.27)	(18.3, 19.3)	173	19.4 (3.66)	(18.9, 20.0)	
		10 AM	173	17.8 (3.25)	(17.4, 18.3)	173	18.6 (3.67)	(18.1, 19.2)	
		4 PM	173	17.1 (3.08)	(16.6, 17.6)	173	18.4 (3.89)	(17.8, 19.0)	
	Week 6	8 AM	173	18.5 (3.37)	(18.0, 19.0)	170	19.0 (3.76)	(18.5, 19.6)	
		10 AM	173	17.9 (3.30)	(17.4, 18.4)	170	18.4 (3.51)	(17.9, 18.9)	
		4 PM	173	17.2 (2.93)	(16.8, 17.6)	170	18.1 (3.61)	(17.5, 18.6)	
	Month 3	8 AM	171	18.1 (3.32)	(17.6, 18.6)	169	19.1 (3.62)	(18.6, 19.7)	
		10 AM	171	17.5 (2.98)	(17.0, 17.9)	169	18.6 (3.62)	(18.0, 19.1)	
		4 PM	171	17.2 (3.20)	(16.7, 17.7)	169	18.0 (3.42)	(17.5, 18.5)	
	Change in IOP	Week 2	8 AM	173	-8.1 (3.16)	(-8.6, -7.6)	173	-8.2 (3.40)	(-8.7, -7.7)
			10 AM	173	-7.6 (3.36)	(-8.1, -7.1)	173	-7.5 (3.45)	(-8.0, -7.0)
			4 PM	173	-7.5 (3.31)	(-8.0, -7.0)	173	-7.1 (3.24)	(-7.6, -6.6)
Week 6		8 AM	173	-8.3 (2.98)	(-8.8, -7.9)	170	-8.6 (3.19)	(-9.1, -8.1)	
		10 AM	173	-7.6 (3.09)	(-8.0, -7.1)	170	-7.8 (3.21)	(-8.3, -7.3)	
		4 PM	173	-7.4 (3.03)	(-7.8, -6.9)	170	-7.5 (3.02)	(-7.9, -7.0)	
Month 3		8 AM	171	-8.7 (2.96)	(-9.1, -8.2)	169	-8.5 (3.33)	(-9.0, -8.0)	
		10 AM	171	-7.9 (2.94)	(-8.4, -7.5)	169	-7.6 (3.42)	(-8.1, -7.0)	
		4 PM	171	-7.4 (3.44)	(-7.9, -6.9)	169	-7.5 (3.35)	(-8.0, -7.0)	

Female

Actual IOP	Baseline	8 AM	269	27.0 (2.52)	(26.7, 27.3)	244	26.7 (2.64)	(26.4, 27.1)	
		10 AM	269	25.3 (2.88)	(25.0, 25.7)	244	25.2 (2.89)	(24.8, 25.6)	
		4 PM	269	24.7 (2.92)	(24.3, 25.0)	244	24.3 (2.84)	(24.0, 24.7)	
	Week 2	8 AM	269	19.0 (3.40)	(18.6, 19.4)	243	18.7 (3.56)	(18.2, 19.1)	
		10 AM	269	18.3 (3.08)	(17.9, 18.7)	243	17.6 (3.35)	(17.2, 18.1)	
		4 PM	269	17.8 (3.06)	(17.4, 18.1)	243	17.3 (3.38)	(16.8, 17.7)	
	Week 6	8 AM	266	18.9 (3.59)	(18.5, 19.4)	243	18.5 (3.76)	(18.1, 19.0)	
		10 AM	267	18.1 (3.40)	(17.7, 18.5)	243	17.8 (3.57)	(17.4, 18.3)	
		4 PM	267	17.6 (3.25)	(17.2, 18.0)	243	17.2 (3.36)	(16.8, 17.7)	
	Month 3	8 AM	261	19.0 (3.73)	(18.5, 19.4)	239	18.4 (3.72)	(17.9, 18.9)	
		10 AM	261	18.0 (3.31)	(17.6, 18.4)	239	17.6 (3.74)	(17.1, 18.1)	
		4 PM	260	17.7 (3.02)	(17.3, 18.1)	239	17.0 (3.35)	(16.6, 17.5)	
	Change in IOP	Week 2	8 AM	269	-7.9 (2.93)	(-8.3, -7.6)	243	-8.1 (3.19)	(-8.5, -7.7)
			10 AM	269	-7.0 (2.87)	(-7.4, -6.7)	243	-7.6 (3.01)	(-7.9, -7.2)
			4 PM	269	-6.9 (3.13)	(-7.3, -6.5)	243	-7.1 (3.00)	(-7.5, -6.7)
Week 6		8 AM	266	-8.0 (3.07)	(-8.4, -7.6)	243	-8.2 (3.31)	(-8.6, -7.7)	
		10 AM	267	-7.2 (2.95)	(-7.6, -6.9)	243	-7.4 (3.14)	(-7.8, -7.0)	
		4 PM	267	-7.0 (3.28)	(-7.4, -6.6)	243	-7.1 (3.06)	(-7.5, -6.7)	
Month 3		8 AM	261	-8.0 (3.43)	(-8.4, -7.5)	239	-8.3 (3.05)	(-8.7, -7.9)	
		10 AM	261	-7.3 (3.44)	(-7.7, -6.9)	239	-7.6 (3.11)	(-8.0, -7.2)	
		4 PM	260	-6.9 (3.07)	(-7.3, -6.5)	239	-7.2 (3.10)	(-7.6, -6.8)	

Table 19: Descriptive IOP (mmHg) Summary by Race
(ITT Analysis Set)

			Travoprost 0.003%			Travatan		
Summary	Visit	Time	N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
White								
Actual IOP	Baseline	8 AM	316	27.0 (2.60)	(26.7, 27.3)	307	27.2 (2.82)	(26.9, 27.5)
		10 AM	316	25.4 (2.85)	(25.1, 25.8)	307	25.7 (3.10)	(25.4, 26.1)
		4 PM	316	24.6 (2.88)	(24.3, 24.9)	307	24.9 (3.10)	(24.5, 25.2)
	Week 2	8 AM	316	19.0 (3.34)	(18.6, 19.4)	306	19.1 (3.46)	(18.7, 19.4)
		10 AM	316	18.2 (3.06)	(17.9, 18.6)	306	18.2 (3.32)	(17.8, 18.5)
		4 PM	316	17.5 (3.08)	(17.2, 17.9)	306	17.7 (3.49)	(17.3, 18.1)
	Week 6	8 AM	314	18.8 (3.36)	(18.4, 19.2)	304	19.0 (3.82)	(18.5, 19.4)
		10 AM	314	18.1 (3.21)	(17.7, 18.4)	304	18.2 (3.46)	(17.8, 18.6)
		4 PM	315	17.5 (3.05)	(17.2, 17.8)	304	17.7 (3.45)	(17.3, 18.1)
	Month 3	8 AM	310	18.6 (3.72)	(18.2, 19.1)	301	18.9 (3.56)	(18.5, 19.3)
		10 AM	310	17.7 (3.11)	(17.4, 18.1)	301	18.1 (3.48)	(17.7, 18.5)
		4 PM	309	17.6 (2.99)	(17.2, 17.9)	301	17.6 (3.28)	(17.2, 18.0)
Change in IOP	Week 2	8 AM	316	-8.0 (2.98)	(-8.3, -7.6)	306	-8.1 (3.10)	(-8.5, -7.8)
		10 AM	316	-7.2 (2.90)	(-7.5, -6.9)	306	-7.6 (3.05)	(-7.9, -7.2)
		4 PM	316	-7.1 (3.09)	(-7.4, -6.7)	306	-7.1 (3.09)	(-7.5, -6.8)
	Week 6	8 AM	314	-8.2 (2.94)	(-8.5, -7.8)	304	-8.2 (3.27)	(-8.6, -7.9)
		10 AM	314	-7.4 (2.91)	(-7.7, -7.0)	304	-7.5 (3.02)	(-7.9, -7.2)
		4 PM	315	-7.1 (3.14)	(-7.4, -6.7)	304	-7.2 (3.02)	(-7.5, -6.9)
	Month 3	8 AM	310	-8.3 (3.29)	(-8.7, -7.9)	301	-8.3 (3.09)	(-8.7, -8.0)
		10 AM	310	-7.7 (3.18)	(-8.0, -7.3)	301	-7.6 (3.10)	(-8.0, -7.3)
		4 PM	309	-7.0 (3.10)	(-7.3, -6.6)	301	-7.3 (3.16)	(-7.6, -6.9)

Black

Actual IOP	Baseline	8 AM	112	26.7 (2.25)	(26.3, 27.1)	106	26.8 (2.98)	(26.2, 27.4)
		10 AM	112	25.1 (2.49)	(24.6, 25.5)	106	25.2 (3.30)	(24.6, 25.8)
		4 PM	112	24.7 (2.70)	(24.1, 25.2)	106	24.7 (3.39)	(24.0, 25.3)
	Week 2	8 AM	112	18.8 (3.28)	(18.2, 19.4)	105	18.7 (4.03)	(17.9, 19.5)
		10 AM	112	17.8 (3.31)	(17.2, 18.4)	105	17.7 (4.06)	(16.9, 18.5)
		4 PM	112	17.4 (3.04)	(16.8, 18.0)	105	17.7 (4.01)	(16.9, 18.5)
	Week 6	8 AM	112	18.5 (3.58)	(17.8, 19.2)	104	18.0 (3.53)	(17.4, 18.7)
		10 AM	112	17.7 (3.42)	(17.0, 18.3)	104	17.4 (3.73)	(16.7, 18.2)
		4 PM	112	17.3 (3.17)	(16.7, 17.9)	104	17.2 (3.61)	(16.5, 17.9)
	Month 3	8 AM	109	18.7 (3.32)	(18.1, 19.4)	103	18.2 (4.10)	(17.4, 19.0)
		10 AM	109	18.0 (3.45)	(17.3, 18.7)	103	17.7 (4.38)	(16.9, 18.6)
		4 PM	109	17.4 (3.41)	(16.7, 18.0)	103	17.1 (3.76)	(16.3, 17.8)
Change in IOP	Week 2	8 AM	112	-7.9 (3.06)	(-8.5, -7.4)	105	-8.1 (3.73)	(-8.9, -7.4)
		10 AM	112	-7.3 (3.25)	(-7.9, -6.6)	105	-7.5 (3.61)	(-8.2, -6.8)
		4 PM	112	-7.3 (3.43)	(-7.9, -6.6)	105	-7.0 (3.11)	(-7.6, -6.4)
	Week 6	8 AM	112	-8.2 (3.31)	(-8.8, -7.6)	104	-8.8 (3.26)	(-9.4, -8.1)
		10 AM	112	-7.4 (3.28)	(-8.0, -6.8)	104	-7.7 (3.52)	(-8.4, -7.0)
		4 PM	112	-7.4 (3.37)	(-8.0, -6.8)	104	-7.4 (3.17)	(-8.0, -6.8)
	Month 3	8 AM	109	-7.9 (3.16)	(-8.5, -7.3)	103	-8.6 (3.42)	(-9.3, -8.0)
		10 AM	109	-7.0 (3.16)	(-7.6, -6.4)	103	-7.4 (3.67)	(-8.2, -6.7)
		4 PM	109	-7.3 (3.38)	(-7.9, -6.6)	103	-7.6 (3.39)	(-8.2, -6.9)

			Travoprost 0.003%			Travatan		
Summary	Visit	Time	N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
Other ^(a)								
Actual IOP	Baseline	8 AM	14	27.5 (3.30)	(25.6, 29.4)	5	27.0 (2.35)	(24.1, 29.9)
		10 AM	14	26.2 (4.51)	(23.6, 28.8)	5	24.4 (2.07)	(21.8, 27.0)
		4 PM	14	25.2 (4.19)	(22.8, 27.6)	5	24.2 (1.79)	(22.0, 26.4)
	Week 2	8 AM	14	18.2 (4.08)	(15.9, 20.6)	5	20.8 (3.11)	(16.9, 24.7)
		10 AM	14	17.7 (3.87)	(15.5, 19.9)	5	18.8 (3.63)	(14.3, 23.3)
		4 PM	14	17.6 (3.56)	(15.6, 19.7)	5	18.6 (5.22)	(12.1, 25.1)
	Week 6	8 AM	13	20.5 (5.61)	(17.1, 23.8)	5	20.4 (3.51)	(16.0, 24.8)
		10 AM	14	19.3 (5.57)	(16.1, 22.5)	5	19.6 (4.39)	(14.1, 25.1)
		4 PM	13	18.2 (4.65)	(15.3, 21.0)	5	18.0 (3.16)	(14.1, 21.9)
	Month 3	8 AM	13	17.8 (2.77)	(16.1, 19.4)	4	18.5 (1.29)	(16.4, 20.6)
		10 AM	13	17.0 (2.74)	(15.3, 18.7)	4	19.0 (2.45)	(15.1, 22.9)
		4 PM	13	17.1 (3.15)	(15.2, 19.0)	4	17.0 (2.94)	(12.3, 21.7)
Change in IOP	Week 2	8 AM	14	-9.3 (3.65)	(-11.4, -7.2)	5	-6.2 (3.63)	(-10.7, -1.7)
		10 AM	14	-8.5 (5.11)	(-11.5, -5.5)	5	-5.6 (2.97)	(-9.3, -1.9)
		4 PM	14	-7.6 (4.13)	(-10.0, -5.2)	5	-5.6 (3.65)	(-10.1, -1.1)
	Week 6	8 AM	13	-7.2 (2.92)	(-9.0, -5.5)	5	-6.6 (2.07)	(-9.2, -4.0)
		10 AM	14	-6.9 (3.05)	(-8.7, -5.2)	5	-4.8 (4.09)	(-9.9, 0.3)
		4 PM	13	-7.2 (2.77)	(-8.9, -5.6)	5	-6.2 (1.92)	(-8.6, -3.8)
	Month 3	8 AM	13	-9.9 (3.40)	(-12.0, -7.9)	4	-8.0 (2.94)	(-12.7, -3.3)
		10 AM	13	-9.4 (5.06)	(-12.4, -6.3)	4	-5.3 (1.26)	(-7.3, -3.2)
		4 PM	13	-8.3 (4.68)	(-11.1, -5.5)	4	-6.8 (1.71)	(-9.5, -4.0)

(a) The race category "Other" includes Asian, Native Hawaiian or Other Pacific Islander, and American Indian or Alaska Native. Due to small sample sizes, these groups were pooled together in the descriptive summary.

Table 20: Descriptive IOP (mmHg) Summary by 8AM Baseline IOP Stratification Factor (ITT Analysis Set)

			Travoprost 0.003%			Travatan		
Summary	Visit	Time	N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
24-27 mmHg								
Actual IOP	Baseline	8 AM	303	25.5 (0.92)	(25.4, 25.6)	291	25.5 (0.93)	(25.4, 25.6)
		10 AM	303	24.1 (1.69)	(23.9, 24.3)	291	24.1 (1.67)	(23.9, 24.3)
		4 PM	303	23.4 (1.80)	(23.2, 23.6)	291	23.5 (1.75)	(23.3, 23.7)
	Week 2	8 AM	303	17.9 (2.79)	(17.6, 18.2)	290	17.9 (3.01)	(17.6, 18.3)
		10 AM	303	17.3 (2.70)	(17.0, 17.6)	290	17.1 (2.95)	(16.8, 17.5)
		4 PM	303	16.8 (2.60)	(16.5, 17.1)	290	16.7 (2.81)	(16.4, 17.0)
	Week 6	8 AM	302	17.7 (2.68)	(17.4, 18.0)	288	17.5 (2.90)	(17.2, 17.9)
		10 AM	303	17.1 (2.59)	(16.8, 17.4)	288	17.0 (2.82)	(16.7, 17.4)
		4 PM	302	16.8 (2.67)	(16.5, 17.1)	288	16.6 (2.65)	(16.3, 16.9)
	Month 3	8 AM	299	17.6 (2.69)	(17.3, 17.9)	286	17.5 (2.71)	(17.2, 17.8)
		10 AM	299	17.1 (2.70)	(16.8, 17.4)	286	17.0 (2.85)	(16.6, 17.3)
		4 PM	299	16.9 (2.70)	(16.6, 17.2)	286	16.6 (2.76)	(16.3, 16.9)
Change in IOP	Week 2	8 AM	303	-7.6 (2.71)	(-7.9, -7.3)	290	-7.6 (2.88)	(-7.9, -7.2)
		10 AM	303	-6.8 (2.69)	(-7.1, -6.5)	290	-7.0 (2.79)	(-7.3, -6.6)
		4 PM	303	-6.7 (2.73)	(-7.0, -6.3)	290	-6.8 (2.64)	(-7.1, -6.5)
	Week 6	8 AM	302	-7.8 (2.61)	(-8.1, -7.5)	288	-8.0 (2.81)	(-8.3, -7.7)
		10 AM	303	-7.0 (2.55)	(-7.3, -6.8)	288	-7.0 (2.68)	(-7.3, -6.7)
		4 PM	302	-6.6 (2.74)	(-7.0, -6.3)	288	-6.9 (2.54)	(-7.2, -6.6)
	Month 3	8 AM	299	-7.9 (2.66)	(-8.2, -7.6)	286	-8.0 (2.65)	(-8.3, -7.7)
		10 AM	299	-7.0 (2.75)	(-7.3, -6.7)	286	-7.1 (2.68)	(-7.4, -6.8)
		4 PM	299	-6.5 (2.76)	(-6.9, -6.2)	286	-6.9 (2.70)	(-7.2, -6.6)

28-36 mmHg

Actual IOP	Baseline	8 AM	139	30.1 (2.07)	(29.7, 30.4)	127	30.8 (2.37)	(30.3, 31.2)
		10 AM	139	28.1 (2.90)	(27.6, 28.6)	127	29.1 (2.94)	(28.6, 29.6)
		4 PM	139	27.2 (3.10)	(26.7, 27.7)	127	27.9 (3.57)	(27.2, 28.5)
	Week 2	8 AM	139	21.1 (3.41)	(20.6, 21.7)	126	21.4 (3.75)	(20.7, 22.1)
		10 AM	139	19.8 (3.37)	(19.3, 20.4)	126	20.2 (3.77)	(19.6, 20.9)
		4 PM	139	19.0 (3.46)	(18.5, 19.6)	126	20.1 (4.20)	(19.4, 20.9)
	Week 6	8 AM	137	21.1 (3.92)	(20.5, 21.8)	125	21.6 (4.01)	(20.9, 22.3)
		10 AM	137	20.0 (3.94)	(19.4, 20.7)	125	20.4 (3.95)	(19.7, 21.1)
		4 PM	138	18.9 (3.55)	(18.3, 19.5)	125	19.9 (4.02)	(19.2, 20.6)
	Month 3	8 AM	133	20.9 (4.26)	(20.2, 21.7)	122	21.5 (4.12)	(20.8, 22.3)
		10 AM	133	19.4 (3.61)	(18.8, 20.0)	122	20.5 (4.33)	(19.7, 21.2)
		4 PM	132	18.9 (3.48)	(18.3, 19.5)	122	19.4 (3.96)	(18.7, 20.1)
Change in IOP	Week 2	8 AM	139	-8.9 (3.45)	(-9.5, -8.4)	126	-9.4 (3.75)	(-10.0, -8.7)
		10 AM	139	-8.3 (3.60)	(-8.9, -7.7)	126	-8.9 (3.64)	(-9.5, -8.2)
		4 PM	139	-8.2 (3.88)	(-8.8, -7.5)	126	-7.7 (3.89)	(-8.4, -7.1)
	Week 6	8 AM	137	-8.9 (3.69)	(-9.6, -8.3)	125	-9.2 (4.02)	(-9.9, -8.5)
		10 AM	137	-8.1 (3.76)	(-8.7, -7.4)	125	-8.7 (3.84)	(-9.4, -8.0)
		4 PM	138	-8.3 (3.77)	(-8.9, -7.6)	125	-7.9 (3.91)	(-8.6, -7.2)
	Month 3	8 AM	133	-9.1 (4.23)	(-9.8, -8.4)	122	-9.2 (4.02)	(-10.0, -8.5)
		10 AM	133	-8.7 (3.97)	(-9.4, -8.0)	122	-8.6 (4.09)	(-9.4, -7.9)
		4 PM	132	-8.3 (3.83)	(-9.0, -7.7)	122	-8.4 (3.97)	(-9.1, -7.7)

Table 21: Descriptive IOP (mmHg) Summary by IRIS Color
(ITT Analysis Set)

			Travoprost 0.003%			Travatan		
Summary	Visit	Time	N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
Brown								
Actual IOP	Baseline	8 AM	276	27.0 (2.54)	(26.7, 27.3)	243	26.8 (2.74)	(26.5, 27.2)
		10 AM	276	25.3 (2.71)	(25.0, 25.6)	243	25.3 (3.01)	(24.9, 25.6)
		4 PM	276	24.6 (2.86)	(24.3, 25.0)	243	24.7 (3.06)	(24.3, 25.0)
	Week 2	8 AM	276	19.0 (3.58)	(18.6, 19.5)	242	18.8 (3.61)	(18.4, 19.3)
		10 AM	276	18.1 (3.40)	(17.7, 18.5)	242	17.8 (3.53)	(17.3, 18.2)
		4 PM	276	17.5 (3.20)	(17.1, 17.9)	242	17.7 (3.69)	(17.2, 18.2)
	Week 6	8 AM	274	18.8 (3.60)	(18.4, 19.2)	240	18.3 (3.34)	(17.9, 18.8)
		10 AM	275	18.1 (3.37)	(17.7, 18.5)	240	17.8 (3.46)	(17.3, 18.2)
		4 PM	275	17.4 (3.12)	(17.0, 17.8)	240	17.3 (3.35)	(16.9, 17.8)
	Month 3	8 AM	270	18.8 (3.87)	(18.3, 19.3)	238	18.5 (3.68)	(18.0, 18.9)
		10 AM	270	17.8 (3.31)	(17.4, 18.2)	238	17.8 (3.86)	(17.3, 18.3)
		4 PM	269	17.5 (3.24)	(17.1, 17.9)	238	17.3 (3.39)	(16.9, 17.7)
Change in IOP	Week 2	8 AM	276	-8.0 (3.18)	(-8.4, -7.6)	242	-8.0 (3.34)	(-8.4, -7.6)
		10 AM	276	-7.2 (3.27)	(-7.6, -6.8)	242	-7.5 (3.14)	(-7.9, -7.1)
		4 PM	276	-7.1 (3.30)	(-7.5, -6.7)	242	-7.0 (3.04)	(-7.3, -6.6)
	Week 6	8 AM	274	-8.2 (3.18)	(-8.6, -7.9)	240	-8.5 (3.05)	(-8.9, -8.1)
		10 AM	275	-7.3 (3.14)	(-7.6, -6.9)	240	-7.5 (3.30)	(-7.9, -7.1)
		4 PM	275	-7.2 (3.26)	(-7.6, -6.9)	240	-7.3 (3.00)	(-7.7, -6.9)
	Month 3	8 AM	270	-8.2 (3.42)	(-8.6, -7.8)	238	-8.4 (3.22)	(-8.8, -8.0)
		10 AM	270	-7.5 (3.33)	(-7.9, -7.1)	238	-7.4 (3.35)	(-7.8, -7.0)
		4 PM	269	-7.1 (3.25)	(-7.5, -6.7)	238	-7.4 (3.26)	(-7.8, -6.9)

Blue

Actual IOP	Baseline	8 AM	94	26.9 (2.60)	(26.4, 27.5)	107	27.8 (3.12)	(27.2, 28.4)
		10 AM	94	25.6 (3.03)	(25.0, 26.2)	107	26.2 (3.41)	(25.6, 26.9)
		4 PM	94	24.9 (3.04)	(24.3, 25.5)	107	25.0 (3.33)	(24.4, 25.7)
	Week 2	8 AM	94	18.5 (2.76)	(17.9, 19.1)	106	19.2 (3.42)	(18.5, 19.9)
		10 AM	94	18.0 (2.82)	(17.4, 18.6)	106	18.3 (3.38)	(17.6, 18.9)
		4 PM	94	17.4 (2.93)	(16.8, 18.0)	106	17.6 (3.74)	(16.9, 18.4)
	Week 6	8 AM	93	18.6 (3.33)	(17.9, 19.3)	105	19.3 (4.29)	(18.4, 20.1)
		10 AM	93	17.8 (3.25)	(17.1, 18.5)	105	18.4 (3.62)	(17.7, 19.1)
		4 PM	93	17.5 (3.04)	(16.8, 18.1)	105	17.7 (3.63)	(17.0, 18.4)
	Month 3	8 AM	91	18.2 (3.18)	(17.5, 18.8)	105	19.1 (3.89)	(18.3, 19.8)
		10 AM	91	17.8 (3.27)	(17.1, 18.4)	105	18.2 (3.37)	(17.5, 18.9)
		4 PM	91	17.5 (2.93)	(16.9, 18.1)	105	17.5 (3.44)	(16.9, 18.2)
Change in IOP	Week 2	8 AM	94	-8.4 (2.75)	(-9.0, -7.9)	106	-8.5 (2.92)	(-9.1, -8.0)
		10 AM	94	-7.6 (2.87)	(-8.2, -7.0)	106	-7.9 (3.25)	(-8.5, -7.3)
		4 PM	94	-7.5 (3.24)	(-8.1, -6.8)	106	-7.4 (3.36)	(-8.0, -6.7)
	Week 6	8 AM	93	-8.3 (3.08)	(-8.9, -7.6)	105	-8.5 (3.61)	(-9.2, -7.8)
		10 AM	93	-7.8 (2.96)	(-8.4, -7.1)	105	-7.8 (2.96)	(-8.4, -7.2)
		4 PM	93	-7.4 (3.31)	(-8.0, -6.7)	105	-7.4 (3.05)	(-8.0, -6.8)
	Month 3	8 AM	91	-8.7 (3.11)	(-9.3, -8.0)	105	-8.7 (3.23)	(-9.3, -8.0)
		10 AM	91	-7.8 (3.43)	(-8.5, -7.0)	105	-7.9 (2.90)	(-8.5, -7.4)
		4 PM	91	-7.3 (3.31)	(-8.0, -6.6)	105	-7.4 (3.18)	(-8.0, -6.8)

			Travoprost 0.003%			Travatan		
Summary	Visit	Time	N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
Hazel								
Actual IOP	Baseline	8 AM	45	26.7 (2.47)	(25.9, 27.4)	39	26.9 (2.64)	(26.0, 27.7)
		10 AM	45	25.2 (2.88)	(24.4, 26.1)	39	25.9 (3.27)	(24.9, 27.0)
		4 PM	45	24.2 (2.86)	(23.3, 25.1)	39	24.9 (3.37)	(23.8, 26.0)
	Week 2	8 AM	45	19.2 (2.86)	(18.3, 20.0)	39	18.4 (3.90)	(17.1, 19.6)
		10 AM	45	18.1 (2.41)	(17.4, 18.8)	39	18.3 (3.67)	(17.1, 19.5)
		4 PM	45	17.4 (2.85)	(16.5, 18.3)	39	17.6 (3.51)	(16.5, 18.8)
	Week 6	8 AM	45	18.9 (3.05)	(18.0, 19.8)	39	18.7 (3.73)	(17.5, 19.9)
		10 AM	45	17.6 (2.78)	(16.7, 18.4)	39	18.2 (3.75)	(16.9, 19.4)
		4 PM	45	17.3 (2.93)	(16.4, 18.2)	39	18.2 (4.04)	(16.9, 19.5)
	Month 3	8 AM	45	18.7 (3.30)	(17.7, 19.7)	39	18.7 (3.42)	(17.6, 19.8)
		10 AM	45	17.6 (2.99)	(16.7, 18.5)	39	18.2 (4.04)	(16.9, 19.5)
		4 PM	45	17.6 (3.07)	(16.7, 18.5)	39	17.6 (3.57)	(16.4, 18.7)
Change in IOP	Week 2	8 AM	45	-7.5 (2.45)	(-8.3, -6.8)	39	-8.5 (3.67)	(-9.7, -7.3)
		10 AM	45	-7.1 (2.58)	(-7.9, -6.3)	39	-7.6 (3.24)	(-8.7, -6.6)
		4 PM	45	-6.8 (3.09)	(-7.7, -5.9)	39	-7.3 (2.96)	(-8.2, -6.3)
	Week 6	8 AM	45	-7.8 (2.18)	(-8.5, -7.1)	39	-8.2 (3.59)	(-9.3, -7.0)
		10 AM	45	-7.6 (2.53)	(-8.4, -6.9)	39	-7.8 (3.09)	(-8.8, -6.8)
		4 PM	45	-6.9 (2.77)	(-7.7, -6.1)	39	-6.7 (3.58)	(-7.9, -5.5)
	Month 3	8 AM	45	-8.0 (2.77)	(-8.8, -7.2)	39	-8.2 (3.11)	(-9.2, -7.2)
		10 AM	45	-7.6 (2.89)	(-8.4, -6.7)	39	-7.7 (3.50)	(-8.8, -6.6)
		4 PM	45	-6.6 (2.77)	(-7.5, -5.8)	39	-7.3 (3.36)	(-8.4, -6.2)

Other ^(a)

Actual IOP	Baseline	8 AM	27	26.4 (2.54)	(25.4, 27.4)	29	27.3 (2.84)	(26.2, 28.4)
		10 AM	27	25.4 (3.22)	(24.1, 26.6)	29	25.8 (2.76)	(24.7, 26.8)
		4 PM	27	24.7 (2.66)	(23.6, 25.7)	29	25.4 (3.12)	(24.3, 26.6)
	Week 2	8 AM	27	18.8 (3.54)	(17.4, 20.2)	29	20.2 (3.79)	(18.8, 21.7)
		10 AM	27	18.6 (2.72)	(17.5, 19.7)	29	19.1 (3.60)	(17.8, 20.5)
		4 PM	27	17.8 (2.90)	(16.6, 18.9)	29	18.6 (3.10)	(17.4, 19.8)
	Week 6	8 AM	27	19.0 (3.89)	(17.5, 20.6)	29	20.3 (4.60)	(18.6, 22.1)
		10 AM	27	18.7 (4.44)	(16.9, 20.5)	29	18.9 (3.67)	(17.5, 20.3)
		4 PM	27	18.6 (3.80)	(17.1, 20.1)	29	18.5 (3.05)	(17.4, 19.7)
	Month 3	8 AM	26	18.4 (2.16)	(17.5, 19.3)	26	19.4 (3.35)	(18.0, 20.7)
		10 AM	26	17.9 (1.81)	(17.2, 18.7)	26	18.7 (3.25)	(17.4, 20.0)
		4 PM	26	17.7 (2.28)	(16.7, 18.6)	26	18.3 (3.21)	(17.0, 19.6)
Change in IOP	Week 2	8 AM	27	-7.6 (3.13)	(-8.8, -6.3)	29	-7.0 (3.21)	(-8.3, -5.8)
		10 AM	27	-6.8 (2.52)	(-7.8, -5.8)	29	-6.7 (3.34)	(-7.9, -5.4)
		4 PM	27	-6.9 (2.26)	(-7.8, -6.0)	29	-6.8 (2.87)	(-7.9, -5.7)
	Week 6	8 AM	27	-7.3 (2.48)	(-8.3, -6.4)	29	-7.0 (3.04)	(-8.1, -5.8)
		10 AM	27	-6.7 (2.39)	(-7.6, -5.7)	29	-6.9 (2.90)	(-8.0, -5.8)
		4 PM	27	-6.1 (2.43)	(-7.0, -5.1)	29	-6.9 (2.70)	(-8.0, -5.9)
	Month 3	8 AM	26	-7.8 (3.05)	(-9.0, -6.5)	26	-7.8 (2.47)	(-8.8, -6.8)
		10 AM	26	-7.2 (2.73)	(-8.3, -6.1)	26	-7.0 (3.19)	(-8.3, -5.7)
		4 PM	26	-6.8 (3.49)	(-8.2, -5.4)	26	-7.0 (2.63)	(-8.0, -5.9)

(a) Due to sample sizes iris colors green and grey were summarized together in the other category

Table 22: Descriptive IOP (mmHg) Summary by Diagnosis (ITT Analysis Set)

Summary	Visit	Time	Travoprost 0.003%			Travatan		
			N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
Ocular Hypertension								
Actual IOP	Baseline	8 AM	130	27.0 (2.37)	(26.6, 27.4)	121	27.3 (2.98)	(26.7, 27.8)
		10 AM	130	25.5 (2.78)	(25.0, 25.9)	121	25.6 (2.81)	(25.1, 26.1)
		4 PM	130	24.7 (2.95)	(24.2, 25.2)	121	24.9 (2.79)	(24.4, 25.4)
	Week 2	8 AM	130	19.2 (2.97)	(18.7, 19.7)	120	19.5 (3.53)	(18.9, 20.2)
		10 AM	130	18.3 (2.80)	(17.8, 18.7)	120	18.4 (3.27)	(17.8, 19.0)
		4 PM	130	17.6 (2.86)	(17.1, 18.1)	120	17.8 (3.40)	(17.2, 18.4)
	Week 6	8 AM	130	19.1 (3.16)	(18.5, 19.6)	121	19.0 (3.30)	(18.4, 19.6)
		10 AM	130	18.4 (2.98)	(17.8, 18.9)	121	18.3 (3.07)	(17.8, 18.9)
		4 PM	130	17.8 (3.13)	(17.2, 18.3)	121	17.5 (2.97)	(17.0, 18.1)
	Month 3	8 AM	127	18.8 (3.60)	(18.2, 19.4)	121	18.8 (3.00)	(18.2, 19.3)
		10 AM	127	17.9 (2.88)	(17.4, 18.4)	121	18.0 (3.15)	(17.4, 18.6)
		4 PM	127	17.6 (3.01)	(17.0, 18.1)	121	17.3 (2.91)	(16.8, 17.9)
Change in IOP	Week 2	8 AM	130	-7.8 (3.11)	(-8.3, -7.2)	120	-7.7 (3.32)	(-8.3, -7.1)
		10 AM	130	-7.2 (3.09)	(-7.7, -6.7)	120	-7.2 (2.88)	(-7.7, -6.7)
		4 PM	130	-7.2 (3.33)	(-7.7, -6.6)	120	-7.0 (2.80)	(-7.5, -6.5)
	Week 6	8 AM	130	-7.9 (3.12)	(-8.4, -7.3)	121	-8.3 (2.95)	(-8.8, -7.8)
		10 AM	130	-7.1 (3.19)	(-7.7, -6.5)	121	-7.3 (2.93)	(-7.8, -6.7)
		4 PM	130	-7.0 (3.51)	(-7.6, -6.4)	121	-7.3 (2.91)	(-7.9, -6.8)
	Month 3	8 AM	127	-8.1 (3.49)	(-8.7, -7.5)	121	-8.5 (3.06)	(-9.0, -7.9)
		10 AM	127	-7.6 (3.23)	(-8.1, -7.0)	121	-7.6 (3.04)	(-8.2, -7.1)
		4 PM	127	-7.1 (3.35)	(-7.7, -6.5)	121	-7.5 (3.14)	(-8.1, -7.0)

Open-Angle Glaucoma

Actual IOP	Baseline	8 AM	312	26.9 (2.61)	(26.6, 27.2)	297	27.0 (2.81)	(26.7, 27.4)
		10 AM	312	25.3 (2.85)	(25.0, 25.7)	297	25.6 (3.28)	(25.2, 26.0)
		4 PM	312	24.6 (2.86)	(24.3, 24.9)	297	24.8 (3.31)	(24.4, 25.2)
	Week 2	8 AM	312	18.8 (3.49)	(18.4, 19.2)	296	18.8 (3.63)	(18.4, 19.2)
		10 AM	312	18.1 (3.29)	(17.7, 18.4)	296	17.9 (3.61)	(17.5, 18.3)
		4 PM	312	17.5 (3.17)	(17.1, 17.8)	296	17.7 (3.74)	(17.3, 18.1)
	Week 6	8 AM	309	18.6 (3.63)	(18.2, 19.1)	292	18.7 (3.94)	(18.2, 19.1)
		10 AM	310	17.9 (3.50)	(17.5, 18.2)	292	17.9 (3.73)	(17.5, 18.4)
		4 PM	310	17.3 (3.13)	(17.0, 17.7)	292	17.6 (3.68)	(17.2, 18.0)
	Month 3	8 AM	305	18.6 (3.59)	(18.2, 19.0)	287	18.7 (3.95)	(18.2, 19.1)
		10 AM	305	17.8 (3.31)	(17.4, 18.1)	287	18.0 (3.94)	(17.6, 18.5)
		4 PM	304	17.5 (3.14)	(17.1, 17.8)	287	17.5 (3.60)	(17.1, 17.9)
Change in IOP	Week 2	8 AM	312	-8.1 (2.99)	(-8.4, -7.8)	296	-8.3 (3.25)	(-8.6, -7.9)
		10 AM	312	-7.3 (3.08)	(-7.6, -6.9)	296	-7.7 (3.31)	(-8.1, -7.3)
		4 PM	312	-7.1 (3.16)	(-7.5, -6.8)	296	-7.1 (3.22)	(-7.5, -6.7)
	Week 6	8 AM	309	-8.3 (2.99)	(-8.6, -7.9)	292	-8.4 (3.39)	(-8.8, -8.0)
		10 AM	310	-7.5 (2.93)	(-7.8, -7.1)	292	-7.7 (3.26)	(-8.0, -7.3)
		4 PM	310	-7.2 (3.04)	(-7.6, -6.9)	292	-7.2 (3.11)	(-7.6, -6.8)
	Month 3	8 AM	305	-8.3 (3.17)	(-8.7, -8.0)	287	-8.3 (3.22)	(-8.7, -8.0)
		10 AM	305	-7.5 (3.29)	(-7.9, -7.2)	287	-7.5 (3.33)	(-7.9, -7.1)
		4 PM	304	-7.1 (3.18)	(-7.4, -6.7)	287	-7.3 (3.23)	(-7.6, -6.9)

Open-Angle Glaucoma with Pigment Dispersion and Open-Angle Glaucoma with Pseudoexfoliation diagnoses were summarized together with Open-Angle Glaucoma

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SOLOMON CHEFO
03/26/2014

YAN WANG
03/26/2014
I concur.

DIONNE L PRICE
03/27/2014
Concur with overall conclusions

Statistics Filing Checklist for NDA - 204822

NDA Number:	204822
NDA Type:	Standard Review
Drug Name:	Travoprost ophthalmic solution 0.003%
Indication:	For the reduction of elevated intraocular pressure (IOP) in patients with Open Angle Glaucoma (OAG) or Ocular Hypertension (OH).
Applicant:	Alcon Laboratories, Inc.
Stamp Date:	July 15, 2013
Reviewer:	Solomon Chefo

1. Brief Summary of Controlled Clinical Trial(s)

Table below contains brief summary of the single clinical trial contained in the submission.

Table 1: Summary of Trial Assessed in the Statistical Review

Study Number:	C-11-034
Study Design:	<p>This was a multicenter, double-masked, randomized, active-controlled, 2-arm, parallel group, equivalence study designed to evaluate the safety and IOP-lowering efficacy of Travoprost 0.003% relative to Travoprost 0.004% BAK (Travatan) in adult patients with open-angle glaucoma or ocular hypertension.</p> <p>The study consisted of 6 visits conducted during 2 sequential phases: the Screening/Eligibility phase, which included a Screening Visit and 2 Eligibility Visits, and the treatment phase, which included 3 on therapy visits (conducted at Week 2, Week 6, and Month 3). Enrolled patients were randomized (1:1) at the second Eligibility Visit to 1 of the 2 study drugs and instructed to instill 1 drop of the assigned study drug in both eyes, once daily in the evening for 3 months. Randomization was stratified by investigational center and 8 AM baseline IOP measurement for the study eye (low: 24-27 mmHg; or high: 28-36 mmHg).</p> <p>One eye from each patient was chosen as the study eye and only the study eye was used in the efficacy analysis. If only 1 of a patient's eyes was dosed, the dosed eye was selected as the study eye. If both eyes were dosed, the worse evaluable eye was selected as the study eye. The worse eye was specifically defined as the eye with the higher IOP at 8 AM averaged across the 2 eligibility visits.</p> <p>Evaluations of safety and efficacy were performed at selected time points (8 AM, 10 AM, and 4 PM) during study visits conducted at Week 2, Week 6, and Month 3.</p>

<p>Treatment/ Sample Size:</p>	<p>Travoprost 0.003% Solution /442 Subjects and Travoprost 0.004% BAK /422 Subjects</p>
<p>Endpoint/ Analysis:</p>	<p>Primary Efficacy Endpoint: The mean IOP at each of the assessment time points (8 AM, 10 AM, and 4 PM) at each on-therapy study visit (i.e., Week 2, Week 6, and Month 3).</p> <p>The primary analysis was a statistical evaluation of equivalence of the two treatment groups with respect to the primary efficacy variable. Treatment differences in mean IOP were examined with a pair-wise test at each scheduled on- therapy visit and time point. Pair-wise tests and confidence intervals (CI) were based on the least squares means derived from a statistical model that accounts for correlated IOP measurements within patient and includes baseline IOP stratum and investigational center as covariates in the model.</p> <p>Equivalence was concluded if the two-sided 95% CI for the difference in IOP was within ± 1.5 mmHg at each of the three time points (8 AM, 10 AM and 4 PM) for each on-therapy visit (Week 2, Week 6, and Month 3). The equivalence requirement for the purpose of US Health Authority (FDA) consideration only was for the majority of the CIs to lie entirely within ± 1.0 mmHg.</p> <p>Analyses were performed for both the intent-to-treat (ITT) and per protocol (PP) data sets with the intent-to-treat data set providing the primary inference.</p> <p>The primary analysis was based on observed cases; missing data were not imputed. According to the applicant, the statistical model employed and its associated analysis was robust to data that were missing at random (MAR).</p> <p>No multiplicity adjustment was required since results at all 3 time points across all on-therapy visits were required to satisfy the equivalence.</p>
<p>Preliminary Findings</p>	<p>The IOP-lowering efficacy of Travoprost 0.003% Solution was equivalent to Travoprost 0.004% BAK at all on-therapy study visits (Weeks 2, Week 6, and Month 3) and assessment time points (8 AM, 10 AM, and 4 PM on each visit day).</p> <ul style="list-style-type: none"> • All 9 of the 95% CIs for the mean differences in IOP between treatment groups were between ± 1.5 mmHg (the pre-specified equivalence margin). • Travoprost 0.003% Solution was also equivalent to Travoprost 0.004% BAK when evaluated against an equivalence margin of ± 1.0 mmHg (i.e., all 9 of the 95% CIs were between ± 1.0 mmHg).

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information from Review of the Protocol and the Study Report

Content Parameter	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	<input checked="" type="checkbox"/>			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	<input checked="" type="checkbox"/>			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			<input checked="" type="checkbox"/>	
Appropriate references for novel statistical methodology (if present) are included.			<input checked="" type="checkbox"/>	
Safety data organized to permit analyses across clinical trials in the NDA.			<input checked="" type="checkbox"/>	
Investigation of effect of missing data and discontinued follow-up on statistical analyses as described by applicant appears adequate.	<input checked="" type="checkbox"/>			(i)

NA: Not Applicable

- (i) In the Efficacy section (Section 9.7.13) of the clinical study report under subsection Sensitivity Analyses, the applicant stated that:

In order to support the robustness of the LOCF imputation method for missing data, additional imputation methods were used to impute missing values for dropouts and missing data for both IOP and IOP change from baseline at all on-therapy study visits for the primary efficacy analysis using the ITT analysis set.

However, we couldn't find any detail description of the additional imputation methods and the associated results in the study report.

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA204822\000\m5\datasets\c11034
Dataset structure (e.g., SDTM or ADaM)	Though datasets were not presented in either SDTM or ADaM standards, the Reviewer's Guide document and Define files supplied by the applicant included sufficient detail to access and to work with datasets easily.
Based on the analysis datasets, can results of the primary endpoint(s) be reproduced? (Yes or No)	Yes
List the dataset(s) that contains the primary endpoint(s)	i) iopitt01.xpt – for intent-to treat analysis. The primary efficacy variable is iop_no01 .
Are there any concerns about site(s) that could lead to inspection? If so, list of site(s) that needs inspection and rationale	NO
Are the define files sufficiently detailed?	Yes
Safety data are organized to permit analyses across clinical trials in the NDA.	NA/ NDA was filed based on a single study.

NA: Not Applicable

4. Filing Issues

Table 4: Initial overview of the NDA/BLA application for refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	<input checked="" type="checkbox"/>			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			<input checked="" type="checkbox"/>	NDA was filed based on a single clinical study
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	<input checked="" type="checkbox"/>			(i), (ii)
Data sets in EDR are accessible and conform to applicable guidance (e.g., existence of define.pdf file for data sets).	<input checked="" type="checkbox"/>			

NA: Not Applicable

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

From the statistical preliminary review perspective, the NDA is fileable. However, the following issues were noted during the preliminary review.

- i) Descriptive summaries for the primary efficacy measure were provided for subgroup analyses by baseline IOP category, age, gender, and race. However, 95% confidence interval estimates for the mean difference between the treatment groups were not provided for these subgroups.
- ii) The applicant provided summary of overall frequency and incidence of adverse events for subgroup analysis by Age only (CSR Table 14.3.1.3.2-1). However, subgroup analysis by gender and race were not provided.
- iii) For the primary efficacy analysis, the applicant conducted a sensitivity analysis on the ITT dataset in which last-observation-carried-forward (LOCF) was used to impute values for dropouts and for missing data at all on-therapy visits and time points (CSR Table 14.2-9). However, imputation of missing data was done only for Week 6 and Month 3 visits and time points but not for Week 2 visit and time points.
- iv) As discussed in the study report and presented graphically in the draft label, the applicant's primary efficacy analysis of mean difference in IOP numerically favors the test group over the control group (Figure 1 on Page 9). However, analysis of the mean difference in IOP change from baseline numerically favors the control group over the test group in the majority of the three time points (8 AM, 10 AM and 4 PM) for each on-therapy visit (Figure 3 on Page 11).

This reviewer further conducted subgroup analysis by baseline IOP category (low: 24-27 mmHg; or high: 28-36 mmHg) for both efficacy measures of mean difference in IOP (Figure 2 on Page 10) and mean difference in IOP change from baseline (Figure 4 on Page 12). In subjects with low baseline IOP (24-27 mmHg), both efficacy measures numerically favor the control group over the test group. However, in subjects with high baseline IOP (28-36 mmHg); analysis of mean difference in IOP, as in the overall case, numerically favors the test group over the control group, but no clear pattern was observed for the mean difference in IOP change from baseline efficacy measure in this group.

Based on our preliminary review, we have the following request for the applicant:

- i) In the Efficacy section (Section 9.7.13) of the clinical study report under subsection Sensitivity Analyses, you stated that:

In order to support the robustness of the LOCF imputation method for missing data, additional imputation methods were used to impute missing values for dropouts and missing data for both IOP and IOP change from baseline at all on-therapy study visits for the primary efficacy analysis using the ITT analysis set.

However, we couldn't find any detail description of the additional imputation methods and the associated results in the clinical study report. Please clarify.

Drug Name: Travoprost ophthalmic solution 0.003%
 Indication: Reduction of elevated intraocular pressure (IOP)

Table 1: Patient Disposition (Intent-to-Treat Data)

	Total (N = 860) n (%)	Trav 0.003% (N = 442) n (%)	Travatan (N = 418) n (%)
Subjects who completed the study	840 (97.7)	432 (97.7)	408 (97.6)
Subject who discontinued the study	20 (2.3)	10 (2.3)	10 (2.4)
Primary Reason for Early Termination			
Adverse Events	5 (0.6)	3 (0.7)	2 (0.5)
Lost-to-Follow-up	3 (0.3)	2 (0.5)	1 (0.2)
Patient's Decision Unrelated to an Adverse Event	4 (0.5)	3 (0.7)	1 (0.2)
Noncompliance	1 (0.1)	1 (0.2)	0 (0.0)
Inadequate Control of IOP	6 (0.7)	1 (0.2)	5 (1.2)
Other	1 (0.1)	0 (0.0)	1 (0.2)

Source: Tables 10.1-2 and Table 10.1-6 of Applicant's submitted Study Report.

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad

Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK

Table 2.1 Descriptive Statistics at Baseline – (Intent-to-Treat Data)

	Total (N = 860)	Trav 0.003% (N = 442)	Travatan (N = 418)
Age (Years)			
Mean (SD)	65.2 (10.69)	65.4 (10.49)	65.0 (10.91)
(Min, Max)	(21, 92)	(28, 88)	(21, 92)
Intraocular Pressure (mmHg) ^(a)			
8 AM			
Mean (SD)	27.0 (2.70)	26.9 (2.54)	27.1 (2.86)
(Min, Max)	(24, 36)	(24, 36)	(24, 36)
10 AM			
Mean (SD)	25.5 (2.99)	25.4 (2.83)	25.6 (3.15)
(Min, Max)	(21, 36)	(21, 36)	(21, 36)
4 PM			
Mean (SD)	24.7 (3.02)	24.6 (2.88)	24.8 (3.16)
(Min, Max)	(21, 36)	(21, 35)	(21, 36)
Corneal Thickness (µm)			
Mean (SD)	552.4 (33.61)	552.9 (35.00)	551.8 (32.10)
(Min, Max)	(440, 619)	(440, 619)	(443, 619)

Source: Tables 11.2.1-2, 11.2.2-1, and 11.2.2-2 of Applicant's submitted Study Reports.

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad;

Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK

SD = Standard Deviation

(a) Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.

Drug Name: Travoprost ophthalmic solution 0.003%
 Indication: Reduction of elevated intraocular pressure (IOP)

Table 2.2: Demographic Statistics by Treatment Group – (Intent-to-Treat Data)			
	Total (N = 860)	Trav 0.003% (N = 442)	Travatan (N = 418)
	n (%)	n (%)	n (%)
Age (Years)			
<65	380 (44.2)	189 (42.8)	191 (45.7)
≥65	480 (55.8)	253 (57.2)	227 (54.3)
Age (≥65 Years)			
≥65 to <75	307 (35.7)	167 (37.8)	140 (33.5)
≥75 to <85	157 (18.3)	79 (17.9)	78 (18.7)
≥85 to <95	16 (1.9)	7 (1.6)	9 (2.2)
Sex			
Male	347 (40.3)	173 (39.1)	174 (41.6)
Female	513 (59.7)	269 (60.9)	244 (58.4)
Ethnicity			
Hispanic, Latino, or Spanish	105 (12.2)	47 (10.6)	58 (13.9)
Not Hispanic, Latino, or Spanish	755 (87.8)	395 (89.4)	360 (86.1)
Race			
American Indian or Alaska Native	2 (0.2)	2 (0.5)	0 (0.0)
Asian	15 (1.7)	11 (2.5)	4 (1.0)
Black or African American	218 (25.3)	112 (25.3)	106 (25.4)
Native Hawaiian or Other Pacific	2 (0.2)	1 (0.2)	1 (0.2)
White	623 (72.4)	316 (71.5)	307 (73.4)
Iris Color			
Blue	201 (23.4)	94 (21.3)	107 (25.6)
Brown	519 (60.3)	276 (62.4)	243 (58.1)
Green	48 (5.6)	22 (5.0)	26 (6.2)
Grey	7 (0.8)	4 (0.9)	3 (0.7)
Hazel	84 (9.8)	45 (10.2)	39 (9.3)
Other	1 (0.1)	1 (0.2)	0 (0.0)
Diagnosis			
Ocular Hypertension	251 (29.2)	130 (29.4)	121 (28.9)
Open-Angle Glaucoma	594 (69.1)	304 (68.8)	290 (69.4)
Open-Angle Glaucoma with Pigment Dispersion	14 (1.6)	7 (1.6)	7 (1.7)
Open-Angle Glaucoma with Pseudoexfoliation	1 (0.1)	1 (0.2)	0 (0.0)
Actual Baseline IOP Stratum			
24 - 27 mmHg	594 (69.1)	303 (68.6)	291 (69.6)
28 - 36 mmHg	266 (30.9)	139 (31.4)	127 (30.4)
Randomized Baseline IOP Stratum			
24 - 27 mmHg	594 (69.1)	303 (68.6)	291 (69.6)
28 - 36 mmHg	266 (30.9)	139 (31.4)	127 (30.4)

Source: Tables 11.2.1-1 of Applicant's submitted Study Reports.

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad

Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK

Actual Baseline IOP Stratum are constructed from the IOP data entered into EDC by the site.

Randomized Baseline IOP Stratum is constructed from the data entered in IWRS by the site at the time of randomization.

Drug Name: Travoprost ophthalmic solution 0.003%
 Indication: Reduction of elevated intraocular pressure (IOP)

**Table 3 Comparison of Mean IOP (mmHg) at Week 2, Week 6, and Month 3
 (Intent-to-Treat Data)**

Visit	Time point	Trav 0.003%		Travatan		Mean Difference ^(a)	(95% CI)
		N	Mean (SE)	N	Mean (SE)		
Week 2	8 AM	442	19.4 (0.16)	416	19.5 (0.17)	-0.1	(-0.5, 0.3)
	10 AM	442	18.6 (0.16)	416	18.6 (0.16)	0.0	(-0.4, 0.4)
	4 PM	442	18.0 (0.16)	416	18.3 (0.16)	-0.3	(-0.7, 0.1)
Week 6	8 AM	439	19.3 (0.16)	413	19.3 (0.17)	0.0	(-0.4, 0.4)
	10 AM	440	18.5 (0.16)	413	18.6 (0.17)	-0.1	(-0.5, 0.3)
	4 PM	440	18.0 (0.16)	413	18.1 (0.17)	-0.2	(-0.6, 0.2)
Month 3	8 AM	432	19.2 (0.17)	408	19.3 (0.18)	-0.1	(-0.5, 0.3)
	10 AM	432	18.3 (0.17)	408	18.6 (0.18)	-0.3	(-0.7, 0.1)
	4 PM	431	18.0 (0.16)	408	18.0 (0.17)	0.0	(-0.4, 0.4)

Source: Tables 11.4.1.1-1 of Applicant's submitted Study Reports.

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad

Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK

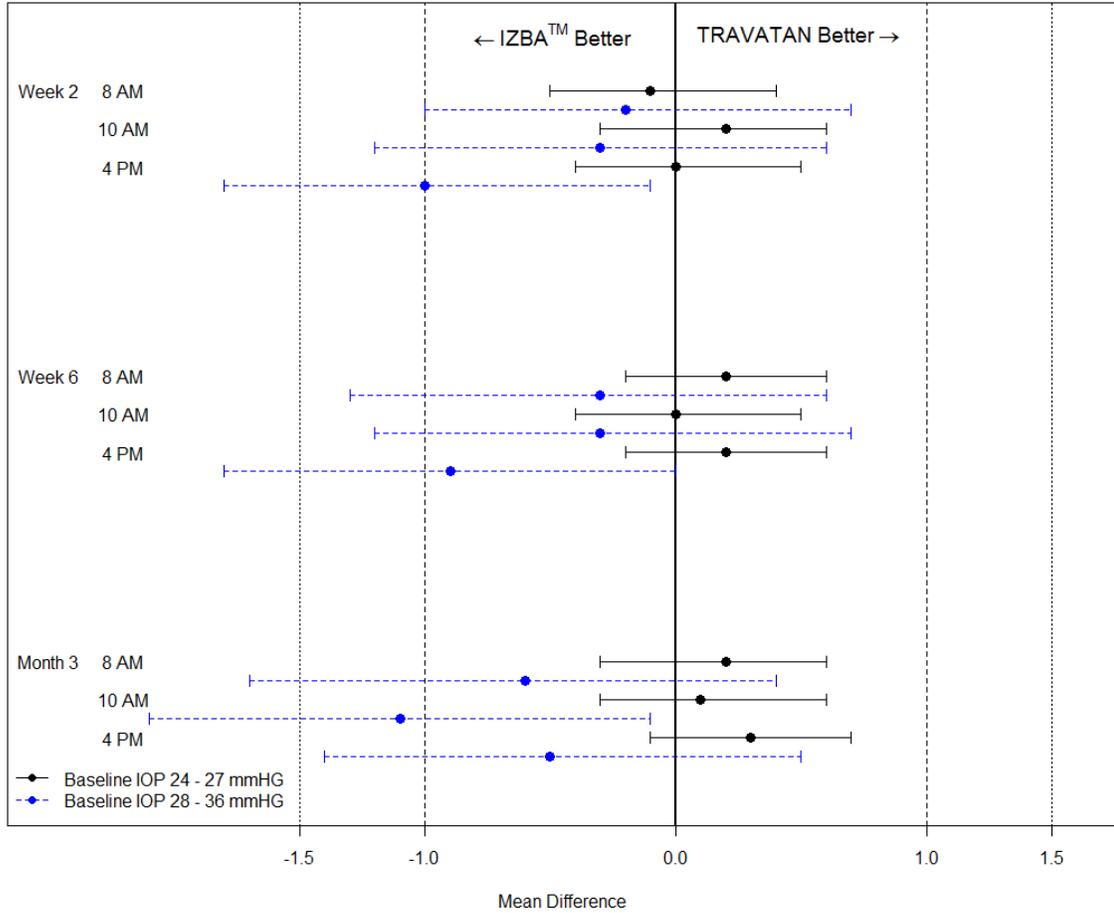
SE = Standard Error; CI = Confidence Interval

(a) Estimates based on least squares mean derived from a statistical model that accounts for correlated IOP measurements within patient where site and actual 8 AM baseline IOP stratum are in the model.



Source: From Applicant's submitted draft label.

Figure 2 Mean Difference in IOP (mmHG) by Baseline IOP Category



Reviewer created graph

Table 4 Comparison of Mean IOP Change from Baseline (mmHg) at Week 2, Week 6, and Month 3 (Intent-to-Treat Data)

Visit	Time point	Trav 0.003%		Travatan		Mean Difference ^(a)	(95% CI)
		N	Mean (SE)	N	Mean (SE)		
Week 2	8 AM	442	-8.5 (0.16)	416	-8.6 (0.17)	0.1	(-0.3, 0.5)
	10 AM	442	-7.7 (0.16)	416	-8.0 (0.17)	0.3	(-0.1, 0.7)
	4 PM	442	-7.6 (0.16)	416	-7.5 (0.17)	-0.1	(-0.5, 0.3)
Week 6	8 AM	439	-8.6 (0.16)	413	-8.8 (0.17)	0.2	(-0.2, 0.6)
	10 AM	440	-7.8 (0.16)	413	-8.0 (0.17)	0.2	(-0.2, 0.6)
	4 PM	440	-7.6 (0.16)	413	-7.7 (0.17)	0.1	(-0.3, 0.5)
Month 3	8 AM	432	-8.7 (0.16)	408	-8.9 (0.17)	0.1	(-0.3, 0.5)
	10 AM	432	-8.0 (0.16)	408	-8.0 (0.17)	-0.0	(-0.4, 0.4)
	4 PM	431	-7.6 (0.16)	408	-7.8 (0.17)	0.2	(-0.2, 0.6)

Source: Tables 11.4.1.2-3 of Applicant's submitted Study Reports.

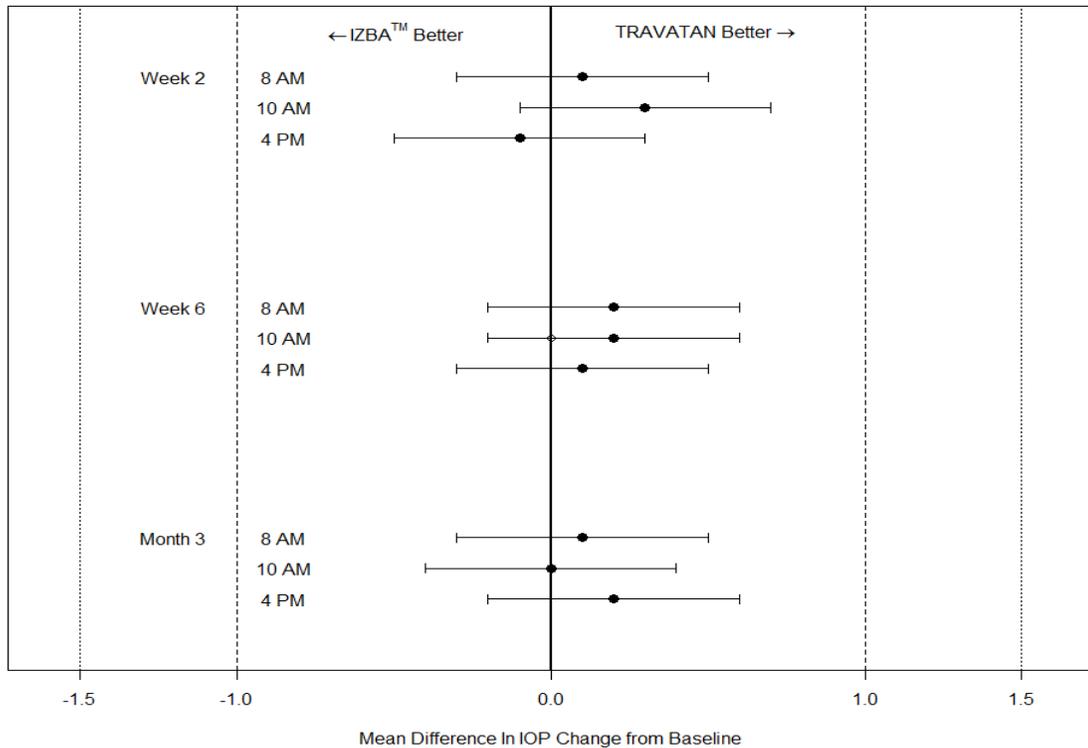
Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad

Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK

SE = Standard Error; CI = Confidence Interval

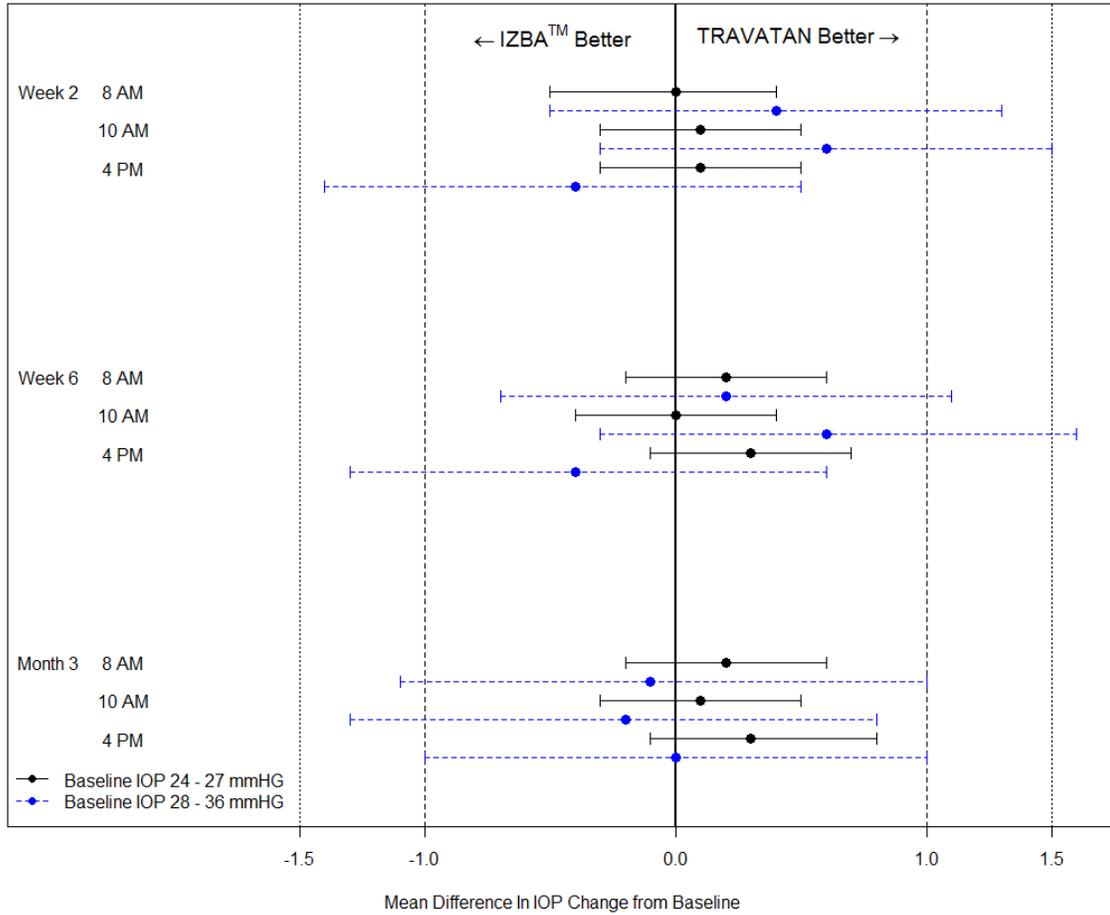
(b) Estimates based on least squares mean derived from a statistical model that accounts for correlated IOP measurements within patient where site and actual 8 AM baseline IOP stratum are in the model.

Figure 3: Mean Difference in IOP Change from Baseline (mmHG)



Reviewer created graph

Figure 4: Mean Difference in IOP Change from Baseline (mmHG) By Baseline IOP Category



Reviewer created graph

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/s/

SOLOMON CHEFO
08/27/2013

YAN WANG
08/27/2013