CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 206185
Drug Name:	Xelpros (latanoprost) ophthalmic (b) (4), 0.005%
Indication(s):	For the reduction of elevated intraocular pressure in patients with Open Angle Glaucoma or Ocular Hypertension.
Applicant:	Sun Pharma Advanced Research Company Limited
Date(s):	Stamp Date: January 31, 2013 PDUFA Date: November 30, 2014 Review Date: October 08, 2014
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Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Solomon Chefo, Ph.D.
Concurring Reviewers:	Yan Wang, Ph.D., Team Leader
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	Rhea Lloyd, MD, Medical Officer William Boyd, MD, Team Leader
Project Manager:	Diana Willard

Keywords: clinical studies, ANCOVA, mixed linear model, reduction of intraocular pressure

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1 EXECUTIVE SUMMARY

The applicant seeks approval of Xelpros (latanoprost) ophthalmic (b) (4), 0.005% administered once daily in the evening for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OH). Latanoprost 0.005% ophthalmic solution was first approved and marketed as Xalatan® (the reference listed drug) in 1996 as a second-line treatment for the reduction of elevated IOP in patients with OAG or OH, and in 2002 it was approved in the United States (U.S.) for first-line treatment of elevated IOP. Xelpros is proposed for the same indication, dosage, and administration as that of Xalatan® except that the formulation of Xalatan® contains Benzalkonium chloride (BAK) as preservative while the formulation of Xelpros contains a BAK-free preservative.

Support for the efficacy and safety of Xelpros for the reduction of IOP in patients with OAG and OH was based on four studies: a phase 3 efficacy and safety study (Study CLR_09_12) and a phase 3 safety study (Study CLR_09_13) both conducted in the U.S., and a phase 3 efficacy and safety study (Study CLR_08_01) and a pilot safety study (Study CLR_10_01) both conducted in India. All the studies with the exception of Study CLR_09_12 were open-label studies. Thus, in this review, the primary evidence to evaluate the safety and IOP lowering efficacy of Xelpros relative to Xalatan® was based on Study CLR_09_12 with the efficacy data from Study CLR_08_01 was used as supporting evidence.

Study CLR_09_12 was a multicenter, assessor-masked, Phase 3, active-controlled, parallel group, randomized study designed to evaluate the safety and IOP lowering efficacy of Xelpros relative to Xalatan® in adult patients with OAG or OH. In the study, a total of 578 subjects were randomized in a 1:1 ratio to receive either Xelpros or Xalatan® once daily at 8 PM. The study duration was 12 weeks and included four on-therapy study visits at week 1, week 4, week 8, and week 12. The primary objective of the study was to demonstrate non-inferiority of Xelpros to Xalatan® in mean IOP reduction from baseline in the study eye throughout the study.

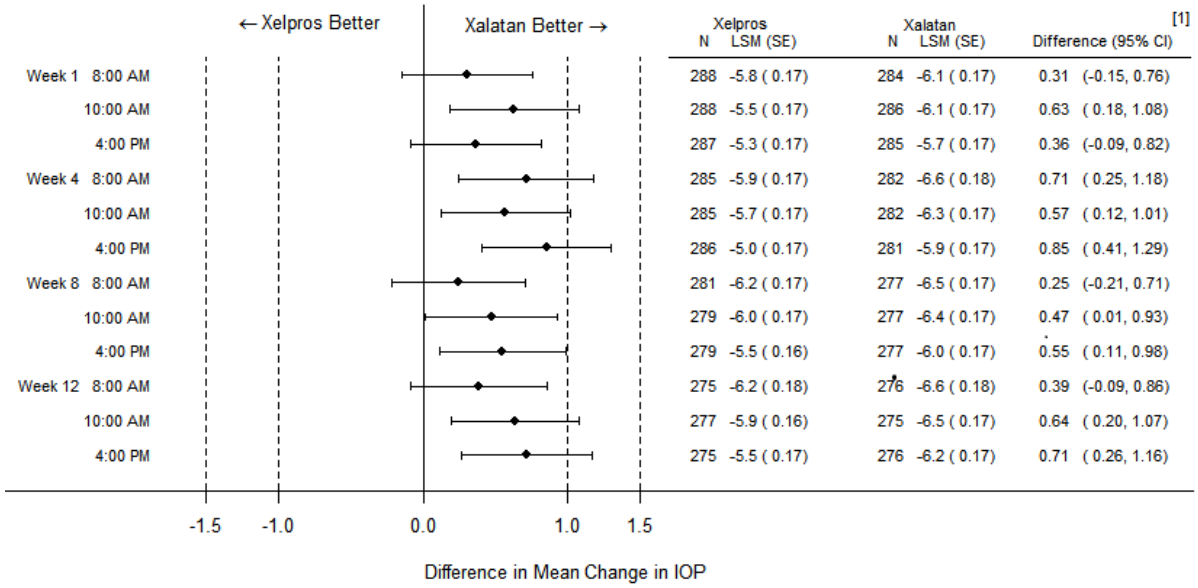
The primary efficacy endpoint of the study was the change in IOP from baseline evaluated at 8 AM, 10 AM, and 4 PM of week 1, week 4, week 8, and week 12 visits. The primary efficacy analysis of the study was based on the intent-to-treat (ITT) analysis population, and used the change from baseline in IOP as the primary efficacy variable. Analysis of covariance (ANCOVA) methodology with the change from baseline in IOP as the response variable and treatment, site, and baseline IOP as covariates was used in the reviewer's primary efficacy analysis. The difference in the mean change in IOP between the treatment groups (*Xelpros minus Xalatan*®) was determined based the least square means using the ANCOVA model. Based on the model, non-inferiority of Xelpros to Xalatan® was established if the upper limit of the 95% CI for the difference in the mean change in IOP was <1.5 mmHg throughout the study (*Statistical Criterion*) and was < 1 mmHg at the majority of time points (*Clinical Criterion*).

The mean IOP and the mean change in IOP from baseline at each time point of each visit are presented in Figure 3. The mean baseline IOP at each time point was comparable between the treatment groups, and both treatment groups demonstrated significant IOP reductions throughout the study. The IOP lowering effect of the test product, Xelpros, throughout the study was about 5.0 to 6.2 mmHg units, and about 25% to 40% of patients in the Xelpros group had at least 30% IOP reductions. However, Xelpros was less effective compared to the active-control, Xalatan®, by about 0.3 to 0.9 mmHg units throughout the study.

Even though Xelpros was numerically less effective compared to Xalatan®, the pre-defined statistical criterion for non-inferiority was met throughout the study, but the pre-defined clinical criterion for non-inferiority was not met in six of the 12 time points. In addition, in eight of the 12 time points, Xalatan® appeared to be superior to Xelpros in the mean IOP reduction.

The least square means and the two-sided 95% CIs for the difference in the mean change in IOP between the treatment groups are shown in Figure 1 below

Figure 1: Difference in Mean Change in IOP (mmHg) – ANCOVA Using Baseline IOP (CLR_09_12) (ITT Analysis Population, Observed Cases)



SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Estimates at each time point of each visit were based on ANCOVA model that included treatment, site, and actual baseline IOP as covariates Dots and horizontal bars represent the point and 95% CI estimates for the difference in mean change in IOP

As a sensitivity analysis to the ANCOVA methodology where analysis at each time point of each visit was performed separately (i.e., without accounting for correlated IOP measurements), a mixed model repeated measure (MMRM) analysis that accounted for the correlated IOP measurements was performed and the same conclusion was reached using the MMRM model.

The safety profiles between Xelpros and Xalatan® in Study CLR_09_12 were similar; approximately 80% of subjects experienced at least one AE, and at least 1.4% of subjects in the study experienced at least one serious AE. The most frequently reported AEs in each treatment group were: eye pain (56%), ocular hyperaemia (48%), conjunctival hyperaemia (20%), eye discharge (14%), growth of eyelashes (11%), eyelash thickening (6%), and eye pruritus (5%). The incidences of these events with the exception of eye pain were comparable between the treatment groups; the incidence of eye pain reported in the Xelpros group was higher by more than 15% compared to the incidence reported in the Xalatan® group.

In summary, treatment with Xelpros administered one drop once daily in the evening demonstrated significant IOP lowering effect even though it was less effective in IOP reductions than the active-control, Xalatan®. Therefore, this review concludes that there is evidence to support the efficacy of Xelpros for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

2 INTRODUCTION

2.1 OVERVIEW

In this NDA submission, the applicant seeks approval of Xelpros (latanoprost) ophthalmic [redacted], 0.005% for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

2.1.1 Class and Indication

Pressure in human eye is referred to as intraocular pressure (IOP). Elevated IOP is associated with glaucoma and damage to the optic nerve, and can lead to blindness. The pharmacological class of drug - prostaglandin analogs and prostanoid F2α receptor agonist - is the most widely used glaucoma medications in the U.S. Latanoprost ophthalmic solution belongs to this class of drug and is believed to reduce pressure in the eye by increasing aqueous humor outflow from the eyes through the uvealsclearal tract, thereby reducing the pressure within the eye and reducing the risk of nerve damage and potential blindness associated with glaucoma.

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

2.1.2 History of Drug Development

Latanoprost ophthalmic solution was approved in the U.S. in 1996 for a second-line treatment and was marketed as Xalatan® for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. In 2002, Xalatan® was approved in the U.S. for first-line treatment of elevated IOP. According to the applicant, six generic latanoprost 0.005% ophthalmic solution drug products have also been approved and a seventh generic latanoprost product has received tentative approval.

Xelpros is proposed for the same indication, dosage, and administration as that of Xalatan®. The formulation of Xelpros is also the same as that of Xalatan® except that Xalatan® contains Benzalkonium chloride (BAK) as a preservative while Xelpros contains a BAK-free preservative – it contains potassium sorbate as preservative and [redacted] The applicant indicated that BAK is a commonly used p [redacted] has been shown to exhibit inflammatory and toxic ocular effects. As a result, BAK-free Xelpros may provide a safer alternative to existing marketed BAK-containing latanoprost products and thereby addresses the medical need for a BAK-free glaucoma treatment.

The development of Xelpros for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension was submitted under IND 102842 on August 19, 2009. The study protocols and analysis plans for the test product were submitted under this IND.

2.1.3 Specific Studies Reviewed

Support for the safety and efficacy of Xelpros for the treatment of patients with OAG or OH was based on clinical data from four clinical studies: a phase 3 efficacy and safety study conducted in the U.S. (Study CLR_09_12); a phase 3 safety study conducted in the U.S. (Study CLR_09_13); a phase 3 efficacy and safety study conducted in India (Study CLR_08_01); and a pilot safety study conducted in India (Study CLR_10_01).

All of the studies with the exception of Study CLR_09_12 were open-label studies. Study CLR_09_13 was a single arm (Xelpros only) extension study of Study CLR_09_12; it was designed for safety follow-up. Study CLR_10_01 was a pilot safety study. Therefore, since a comprehensive safety evaluation is primarily covered in the FDA clinical review, the two safety studies were not covered in this review.

In this review, the primary evidence to evaluate the safety and the IOP lowering efficacy of Xelpros relative to Xalatan® was based on Study CLR_09_12. The efficacy data from Study CLR_08_01 was used as supporting evidence.

A brief summary of the two efficacy trials covered in this review are presented in Table 1 below.

Table 1: Summary of Studies Reviewed

Study Number / Study Phase	**Study Objective**	**Study Design**	**Treatment groups (Number of Subjects)**	**Duration of Treatment/ Primary Efficacy endpoint**	**Study Population**
CLR_09_12 (U.S.) / Phase 3	Test the non-inferiority of Xelpros relative to Xalatan® for the reduction of IOP	Multicenter, assessor-masked, randomized, active-controlled, parallel group, non-inferiority study. Visits on Days -35, -7, 0, 7, 28, 56, and 84.	Xelpros (N = 289) Xalatan® (N = 289)	Once daily for 12 weeks / Change from baseline in intraocular pressure (IOP)	Patients diagnosed with open angle glaucoma or ocular hypertension and had un-medicated IOP ≥ 22 mmHg at the eligibility visit
CLR_08_01 (India) / Phase 3	Compare the efficacy and safety of Xelpros with Xalatan® in subjects with OAG or OH	Multicenter, open label, randomized, active-controlled, parallel group. Visits on Days -7, 0, 8, 15, and 29.	Xelpros (N = 53) Xalatan® (N = 51)	Once daily for 4 weeks / Reduction of IOP compared to baseline	Patients diagnosed with open angle glaucoma or ocular hypertension and screening IOP≥22.

Source: Table 2.7.3-1 of Applicant's Summary of Clinical Efficacy
Note: Studies CLR_09_13 and CLR_10_01 were not covered in this review; Study CLR_09_13 was an extension of Study CLR_09_12 designed for safety follow-up and Study CLR_10_01 was a Pilot study.

2.2 DATA SOURCES

The data source for this review included the clinical study reports, the analysis and tabulation datasets, and the integrated summary of efficacy and safety datasets.

- The original submission is located at: \\CDSESUB1\evsprod\NDA206185\0000.
- The SAS programs are located at: \\CDSESUB1\evsprod\NDA206185\0005.
- The updated datasets are located at: \\CDSESUB1\evsprod\NDA206185\0012.
- The updated study reports are located at: \\CDSESUB1\evsprod\NDA206185\0013.

To support the safety and the IOP lowering efficacy of Xelpros to Xalatan®, the data analyzed in this review were based on the two Phase 3 studies: Study CLR_09_12 conducted in the U.S. and Study CLR_08_01 conducted in India.

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 few subjects. SAS codes used to perform the analyses and to create the analysis datasets were also provided.

The submitted datasets were not fully CDISC compliant, but it included certain elements of the CDISC standards. The *Reviewer's Guide Document* and the *Define.pdf* files included with the submission document provided detail to access and to work with the datasets.

Few issues were identified during the review process of Study CLR_09_12. These issues were related to: (i) the applicant's primary efficacy results and (ii) the analysis dataset that contained the primary efficacy variable.

Regarding the primary efficacy results, the reviewer was initially unable to reproduce the applicant's primary efficacy results presented in the clinical study report (CSR). The issue was brought to the attention of the applicant through an information request dated on June 5, 2014. In an email response dated on June 11, 2014, the applicant acknowledged the issue and indicated that the primary efficacy results reported in the CSR were incorrect and were produced based on using an intermediate dataset instead of using the final ADaM dataset that was submitted to the Agency. With that the applicant confirmed that even though the results reported in the CSR were incorrect, the ADaM dataset that was submitted to the Agency as part of the NDA submission was correct and agreed to submit an updated CSR. Based on the applicant's confirmation regarding the dataset, the reviewer continued using the ADaM dataset in the review.

The issue concerning the analysis dataset was related to the way data collected in the case report form (CRF) were linked to the analysis visits in the clinical database. In the CRF, data were recorded under visit names visit 1, visit 2, visit 3, and visit 4 (end-of-study visit); and irrespective of the dates these visits had occurred, the CRF data collected at visit 1, visit 2, visit 3, and visit 4 were respectively linked to analysis visits week 1, 4, 8, and 12 in the clinical database. Due to this link, the end-of-study visit data for the majority of early terminated subjects were incorrectly linked to the week 12 visit. Note that the majority of early terminated subjects withdrew the study before the week 12 visit. In the reviewer's opinion, the analysis visits should have been defined programmatically by taking the visit dates into account. This issue was also brought to the attention of the applicant through an information request dated on July 15, 2014. The applicant acknowledged the issue and submitted an updated dataset on July 23, 2014. The reviewer confirmed the corrections made to the analysis visits.

On September 03, 2014 the applicant submitted an amended CSR based on the updated dataset. Assuming updates were made only in the analysis visits, the reviewer had performed all the efficacy analyses using the original ADaM dataset with the updated analysis visits; however, the results were still not matching. After a thorough investigation of the updated dataset, the reviewer noted changes in the precision used in the primary efficacy data (IOP data) between the updated and the original ADaM dataset. In the ADaM dataset, the IOP data were rounded up (0.5 or greater) or down (0.49 or lower) to the nearest integers while no rounding was made in the updated dataset.

Although the reviewer was initially unable to reproduce the primary efficacy results due to the difference in precision in the IOP data between the two datasets, the results were finally reproduced when the unrounded IOP data were used.

In summary, the reviewer has no issue with the applicant using either the rounded or unrounded IOP data to produce the primary efficacy results; however, they should have communicated all the changes made when the updated dataset was submitted to the Agency.

3.2 EVALUATION OF EFFICACY

In this section, the efficacy assessment for Study CLR_09_12 and Study CLR_08_01 including a description of the study design; the primary, secondary, 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 CLR_09_12

3.2.1.1 Study Design and Endpoints

Study CLR_09_12 was a multicenter, assessor-masked, phase 3, active-controlled, parallel group, randomized study designed to evaluate the safety and IOP lowering efficacy of Xelpros relative to Xalatan® in adult patients with OAG or OH who had IOP ≥ 22 mmHg in one or both eyes with no more than 5 mmHg inter-eye IOP difference at the eligibility visit.

The study had a total of 12 weeks duration conducted over seven visits at 21 investigational centers: screening visit (day -35), eligibility visit (day -7), baseline visit (day 0), visit 1 (week 1), visit 2 (week 4), visit 3 (week 8) and end-of-study visit (week 12). During the screening visit consenting subjects who qualified for the study were instructed to discontinue using topical corticosteroids, glaucoma medications, and IOP-altering medications. The washout periods were one week for topical corticosteroids and for glaucoma medications, four weeks for beta-antagonists, and 72 hours for all other IOP-altering medications.

During the eligibility visit, IOP was measured at 10 AM or 4 PM and subject that met all the inclusion and none of the exclusion criteria during this visit were randomized in a 1:1 ratio to receive either Xelpros or Xalatan® once daily at approximately 8 PM starting at the end of the baseline visit to the end of the study. At each investigational center, subjects were stratified by the eligibility visit IOP group (Low: 22-28 mmHg versus High: 29-35 mmHg group) in the study eye. According to the study protocol, the study eye was defined as the eye with higher IOP at the eligibility visit or if equal, subjects with an even randomization number were assigned the left eye and with an odd number the right eye.

All subjects that qualified the eligibility visit were instructed to return to the clinic at baseline, visit 1, visit 2, visit 3, and visit 4 (end-of-study visit). During these visits, IOP was measured at 8 AM, 10 AM, and 4 PM and ophthalmic exams were conducted for visual acuity, slit lamp biomicroscopy, and conjunctival hyperemia. At the eligibility, baseline, and each of the on-therapy study visits, IOP was measured in triplicate and the mean of three measurements was recorded for the subjects study eye at each time point and visit.

At the baseline visit, study medication was dispensed to subject to start instillation from the same day at 8 PM. During visits 2 and 3, study medication was retrieved and a fresh supply was

dispensed with instructions to start instillation from same day at 8 PM. Study CLR_09_12 was assessor-masked study.

The primary objective of the study was to demonstrate non-inferiority of Xelpros to Xalatan® in mean IOP reduction in patients with OAG or OH. The primary endpoint of the study was the change in IOP from baseline at 8 AM, 10 AM, and 4 PM time points of each study visits at week 1, week 4, week 8, and week 12.

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, slit-lamp biomicroscopy, conjunctival hyperemia, dilated ophthalmoscopy, visual field, iris and eyelash, corneal endothelial cell count, and vital signs (blood pressure/pulse rate) assessments.

3.2.1.2 Statistical Methodologies

i) Analysis Population

Three analysis populations were defined in the study protocols and statistical analysis plan (SAP): (i) *Intent-To-Treat (ITT) population*: the ITT population included all randomized subjects, (ii) *Per-Protocol (PP) population*: the PP population included all ITT subjects who had completed the end-of study visit (week 12/day 84) and did not have any major protocol violations, and (iii) *Safety population*: the safety population included all ITT subjects who enrolled and received at least one dose of study medication.

ii) Primary Efficacy Analysis

The primary efficacy endpoint in study CLR_09_12 was the change in IOP from baseline in the study eye evaluated at 8 AM, 10 AM, and 4 PM of each study visits at week 1, week 4, week 8, and week 12. The applicant's primary efficacy analysis method was based on the intent-to-treat (ITT) analysis population, and used Analysis of Covariance (ANCOVA) methodology with the change in IOP from baseline values as the response variable, and treatment, site, and IOP group (Low IOP: 22-28 mmHg, and High IOP: 29-35 mmHg) as covariates. The IOP groups were derived from the eligibility visit IOP values measured at 10:00 AM for the majority of subjects (83%), at 4:00 PM for 13% of subjects, and at time point 0:00 for 4% of subjects. Based on the applicant's SAS code for the ANCOVA model, the differences in the mean change in IOP between the treatment groups were determined using the least square means (LS Means).

Two potential issues were noted with the applicant's analysis approach:

a) The applicant's modeling strategy gave equal weight across the classification variables when the overall IOP reduction in each treatment group was derived based on the LS Means. In the presence of a substantial sample size imbalance and differences in IOP reduction level across the classification variables (See Section 4.2), the applicant's analysis approach gave much more weight for patients in the higher IOP group and consequently overestimated the overall IOP reductions for both treatment groups.

   In the reviewer's opinion, the overall IOP reductions based the LS Means should have been derived proportional to the sample sizes in the classification variables. Two possible approaches to achieve that was by: (i) re-coding the IOP stratum as a binary value (say 0: low IOP and 1: high IOP) and including the binary data as a continuous variable in the model instead of including it as a classification variable, or (ii) using the default observed margin (OM) option in the LSMEANS statement of the PROC MIXED procedure.

b) The ANCOVA model did not adjust for the actual time-matched baseline IOP values as a covariate in the model. In the reviewer's opinion the time-matched baseline IOP values should have been included in the model as a covariate for the following reasons:

- When evaluating the IOP lowering effect of investigational products at each time point of each visit, time-matched adjustment is clinically meaningful since IOP measurements taken during the morning times are usually higher than during the day times.
- The estimated treatment effects are more precise. In particular, when the baseline and the change from baseline IOP data are strongly correlated, adjusting for the baseline IOP values as a covariate in the model decreases the mean square error (MSE), thereby increases the power of the treatment comparisons.

Therefore, to address these issues and to provide a more precise estimate of the treatment effects, the reviewer's primary efficacy analysis based on the ANCOVA methodology adjusted for the actual time-matched baseline IOP values instead of adjusting for the eligibility visit IOP values as a covariate. Based on the model, the difference in the mean change in IOP between the treatment groups (*Xelpros minus Xalatan*®) was determined using the LS Means, and non-inferiority of Xelpros to Xalatan® was established if the upper limit of the 95% CI for the difference in the mean change in IOP was <1.5 at all visits and time points (*Statistical Criterion*) and was < 1 at the majority of time points (*Clinical Criterion*). Note that since the statistical criterion was required to be met at each time point of each visit, there was no multiplicity issue.

The ANCOVA analysis was performed at each time point of each visit separately, i.e., without accounting for correlated IOP measurements. As a sensitivity analysis, a mixed model repeated measure (MMRM) analysis that accounted for correlated IOP measurements was performed. The model used an unstructured covariance matrix to account for correlated IOP measurements within patient and included the fixed effects for treatment, visit, time, sites, actual baseline IOP values, and the interaction terms of treatment by visit, treatment by time, visit by time, and treatment by visit by time. Treatment difference in the mean change in IOP from baseline at each time point of each visit was determined based on LS Means using the MMRM analysis.

The primary efficacy analysis based on the ANCOVA model and the sensitivity analysis using the MMRM model were based on observed cases (i.e., did not involve imputation for missing data). Note that less than 5% of subjects discontinued early in Study CLR_09_12, and hence the impact of missing data due to early dropout was expected to be minimal on the primary efficacy results. Even though the study had small number of missing data, sensitivity analyses was performed using ANCOVA model based on the last-observation-carried-forward (LOCF) imputation method on the ITT analysis population. The MMRM model relied on missing at random (MAR) assumption for the nature of missing data, and even though the MAR assumption is not testable, this assumption seems reasonable based on examination of the missing data pattern for the IOP data.

Additional sensitivity analysis based on the ANCOVA model was performed using: (i) the PP analysis population on the observed data, (ii) no covariate adjustment, (iii) treatment, site, and the eligibility visit IOP group values as covariates (to replicate the applicant's analysis), and (iv) treatment, site, and the binary IOP group as a continuous variable (instead of as a class variable) as covariates.

The difference in mean IOP, 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 analyzed as supportive efficacy variables. All the supportive efficacy variables were analyzed using descriptive statistics based on the observed data in the ITT analysis population.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.1.3.1 Patient Disposition

Table 2 presents the summary of patient disposition and reasons for study discontinuation among all randomized subjects.

Overall, 578 patients were randomized in Study CLR_09_12; 289 patients were enrolled in each of the treatment groups. A total of 28 (5%) subjects discontinued early from the study; the discontinuation rate was comparable between the treatment groups.

The most common reason for discontinuation among randomized patients in the Xalatan group was withdrawal of consent (2.4%) and in the Xelpros group was protocol violation (1.7%). The summary of study discontinuation by primary reasons is presented in Table 2.

Table 2: Disposition of Patients and Reasons for Study Discontinuation (CLR_09_12)
(All Randomized Subjects)

	Xelpros (N = 289)	Xalatan ® (N = 289)	Total (N = 578)
ITT Analysis Population, n (%)	289 (100)	289 (100)	578 (100)
Safety Analysis Population, n (%)	289 (100)	289 (100)	578 (100)
Per-Protocol Analysis Population, n (%)	270 (93.4)	275 (95.2)	545 (94.3)
Subjects who completed the study, n (%)	274 (94.8)	276 (95.5)	550 (95.2)
Subject who discontinued the study, n (%)	15 (5.2)	13 (4.5)	28 (4.8)
Primary Reason for Early Termination, n (%)			
Withdrawal of consent	3 (1.0)	7 (2.4)	10 (1.7)
Withdrawal of subject by investigator	4 (1.4)	1 (0.3)	5 (0.9)
Protocol violation	5 (1.7)	0 (0.0)	5 (0.9)
Study terminated at one site by sponsor	2 (0.7)	2 (0.7)	4 (0.7)
Adverse Events	1 (0.3)	2 (0.7)	3 (0.5)
Study medication failure	0 (0.0)	1 (0.3)	1 (0.2)

Source: Table 4 of Applicant's Clinical Study Report

3.2.1.3.1 Demographic and Baseline Characteristics

The summary of demographic and baseline characteristics for subjects in the ITT population are presented in Table 3. Within the ITT analysis population, the majority of subjects in the study were white (68%) and female (63%). The average age of patients in the study was 65 years (range 27 to 88 years), about 53% of patients in the Xelpros group and 44% of patients in the Xalatan® group were ≥ 65 years of age.

Table 3: Demographic Summary by Treatment Group (CLR_09_12)
(ITT Analysis Population)

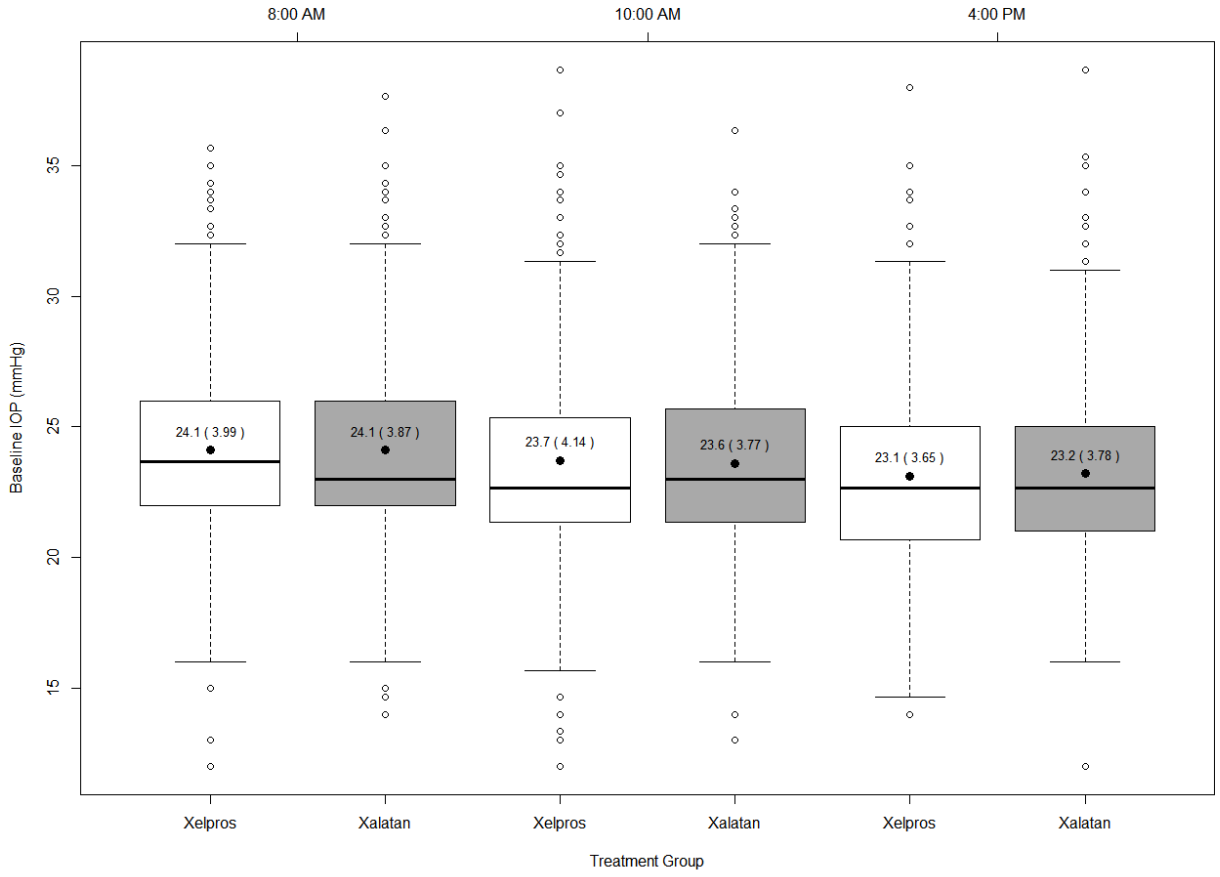
		Xelpros (N = 289)	Xalatan® (N = 289)	Total (N = 578)
Age (Years), n (%) [1]				
<65		136 (47.1)	162 (56.1)	298 (51.6)
≥65		153 (52.9)	127 (43.9)	280 (48.4)
Age (Years)				
Mean (SD)		63.8 (11.08)	63.1 (9.60)	63.4 (10.36)
Min – Med – Max		27 – 65 – 88	34 – 63 – 87	27 – 64 – 88
Sex, n (%)				
Female		188 (65.1)	186 (64.4)	374 (64.7)
Male		101 (34.9)	103 (35.6)	204 (35.3)
Ethnicity, n (%)				
Hispanic or Latino		53 (18.3)	54 (18.7)	107 (18.5)
Not Hispanic or Latino		236 (81.7)	235 (81.3)	471 (51.5)
Race, n (%)				
American Indian or Alaska Native		1 (0.4)	1 (0.4)	2 (0.4))
Asian		7 (2.4)	6 (2.1)	13 (2.3)
Black or African American		82 (28.4)	79 (27.3)	161 (27.9)
White		198 (68.5)	202 (69.9)	400 (69.2)
Other		1 (0.4)	1 (0.4)	2 (0.4))
Iris Color, n (%)				
Brown		181 (62.8)	190 (65.7)	371 (64.2)
Blue/Grey		69 (23.9)	57 (19.7)	126 (21.8)
Hazel		28 (9.7)	28 (9.7)	56 (9.7)
Green		11 (3.8)	14 (4.8)	25 (4.3)
Diagnosis, n (%)				
Primary open angle glaucoma		193 (66.8%)	200 (69.2%)	393 (66.6%)
Ocular hypertension		104 (36.0%)	97 (33.6%)	201 (34.1%)
Pseudoexfoliation		1 (0.3%)	2 (0.7%)	3 (0.5%)
Pigment dispersion		3 (1.0%)	5 (1.7%)	8 (1.4%)
IOP Stratum, n (%) [2]				
22 - 28 mmHg [Low IOP]		236 (81.7)	236 (81.7))	472 (81.7)
29 - 35 mmHg [High IOP]		53 (18.3)	53 (18.3)	106 (18.3)
IOP Group Based on Baseline IOP [1]				
8 AM	22 - 28 mmHg	253 (87.5)	254 (87.8)	507 (87.7)
	29 - 35 mmHg	36 (12.5)	35 (12.1)	71 (12.3)
10 AM	22 - 28 mmHg	250 (86.5)	259 (89.6)	509 (88.1)
	29 - 35 mmHg	39 (13.5)	30 (10.4)	69 (11.9)
4 PM	22 - 28 mmHg	269 (93.1)	264 (91.4)	533 (92.2)
	29 - 35 mmHg	20 (6.9)	25 (8.7)	45 (7.8)
Baseline IOP				
8 AM	Mean (SD)	24.1 (3.99)	24.2 (3.87)	24.1 (3.93)
	Min – Med – Max	12.0 – 23.7 – 35.7	14.0 – 23.0 – 37.7	12.0 – 23.3 – 7.7
10 AM	Mean (SD)	23.7 (4.14)	23.6 (3.76)	23.6 (3.96)
	Min – Med – Max	12.0 – 22.7 – 38.7	13.0 – 23.0 – 36.3	12.0 – 23.0 – 38.7
4 PM	Mean (SD)	23.1 (3.65)	23.2 (3.78)	23.1 (3.71)
	Min – Med – Max	14.0 – 22.7 – 38.0	12.0 – 22.7 – 38.7	12.0 – 22.7 – 38.7

Source: Table 7 of Applicant's Clinical Study Report; SD = Standard Deviation, Min = Minimum, Med = Median, Max = Maximum
[1]: Based on reviewer's analysis
[2]: IOP Stratum was derived from the eligibility visit IOP values measured either at 10:00 AM for the majority of subjects (83%), at 4:00 PM for 13% of subjects, and at time-point 0:00 for the remaining 4% of subjects

Approximately 65% of the study eyes in each treatment group had brown iris color, at least 65% had primary open angle glaucoma and 34% had ocular hypertension. The eligibility visit IOP measurement was used as a stratification factor in the study and overall, at least 80% of the subjects belonged in the low IOP group (22-28 mmHg) at this visit. No marked difference between the treatment groups was observed in terms of the demographic characteristics.

The mean baseline IOP level in each treatment group was about 24 mmHg at 8 AM, 24 mmHg at 10 AM, and 23 mmHg at 4 PM. The mean baseline IOP measurements were slightly higher at the 8 AM time point and decreased slightly throughout the day (See Figure 2); no important differences were noted in the mean baseline IOP measurements between the treatment groups at any of the three assessment time points.

Figure 2: Baseline IOP Measurement by Treatment Group and Time Point (CLR_09_12)
(ITT Analysis Population; Observed Cases)



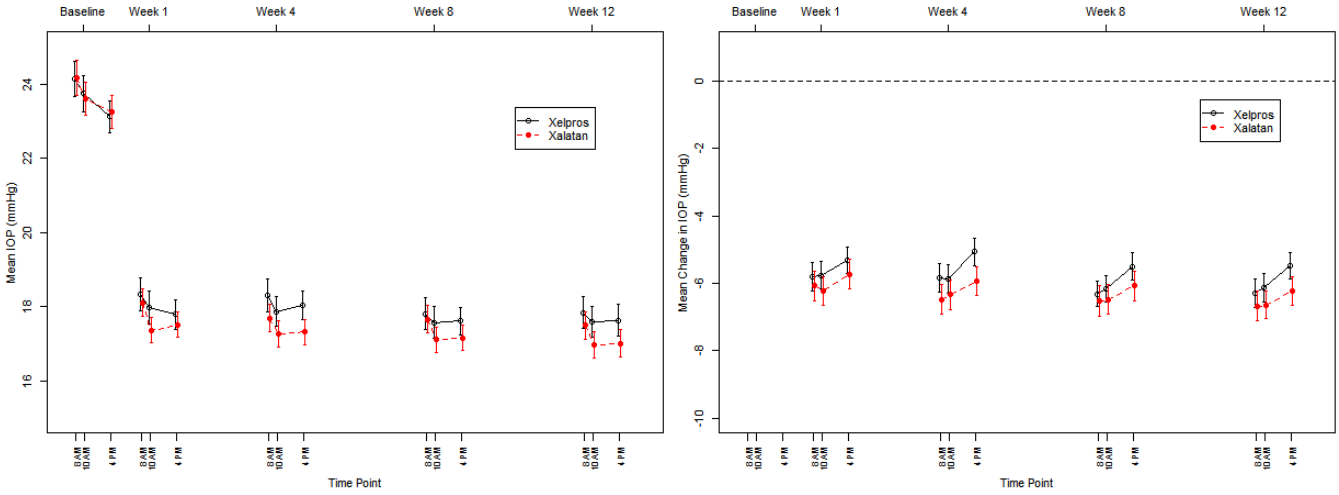
Source: Table 12
Note: Dots and horizontal lines inside boxs are mean and median IOP measures (mmHg), respectively, and numbers in brackets are standard deviations.

3.2.1.4 Results and Conclusions

3.2.1.4.1 Primary Efficacy Endpoint

The mean IOP and the mean change in IOP at each time point of each visit based on the observed data are presented in Figure 3 below, and the descriptive IOP summaries and scatter plots of the baseline IOP data versus the change in IOP from baseline data at each time of each visit are presented in appendix Table 12 and Figure 21, respectively. The mean baseline IOP at all visits and time points were comparable between the treatment groups, and there is strong association between the baseline and the change from baseline IOP data.

Figure 3: Summary of Mean IOP and Mean Change in IOP by Visit and Time Point (CLR_09_12)
(ITT Analysis Population; Observed Cases)



Sources: Table 12

The mean absolute and the percent reduction in IOP from baseline, respectively, ranged from 5.0 to 6.3 mmHg and from 21% to 25% in the Xelpros group and from 5.7 to 6.6 mmHg and from 23.4% to 26.6% in the Xalatan® group. Both treatment groups clearly demonstrated significant IOP reductions at each time point of each study visit; however, the reductions throughout the study were slightly better for patients in the Xalatan® group than in the Xelpros group.

In the primary efficacy analysis, the mean change in IOP from baseline between Xelpros and Xalatan® were compared using the least squares means derived from the ANCOVA analysis. The point and 95% CI estimates for the difference in mean change in IOP between the treatment groups (*Xelpros minus Xalatan*®) are shown in Figure 1 and Table 4.

The treatment and covariate adjusted mean IOP reductions from baseline throughout the study ranged from 5.0 to 6.2 mmHg in the Xelpros group and from 5.7 to 6.6 mmHg in the Xalatan® group. The test drug, Xelpros, clearly demonstrated significant IOP reductions from baseline throughout the study; however, it was less effective compared to the active-control, Xalatan®, by about 0.3 to 0.9 mmHg units.

Although Xelpros was less effective compared to Xalatan®, the statistical criterion for non-inferiority was met at all visits and time points; however, the pre-defined clinical criterion for non-inferiority was not met at the majority of time points since the upper limit of the 95% CI was

> 1.0 mmHg in six of the 12 time points. In addition, in eight of the 12 time points, Xalatan® appeared to be superior to Xelpros in the mean IOP reduction.

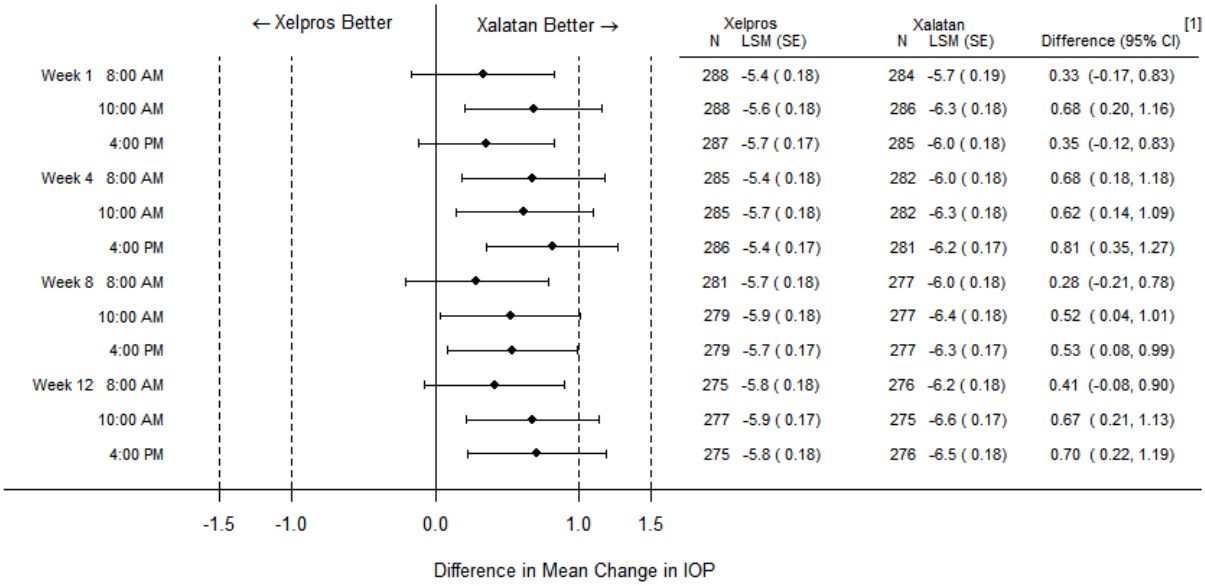
Table 4: Difference in Mean Change in IOP from Baseline - ANCOVA (CLR_09_12)
(ITT Analysis Population; Observed Cases)

Visit	Time Point	Xelpros		Xalatan ®		Difference in [1] LS Means (95 % CI)	95% CI Upper confidence limit	
		N	LS Mean (SE)	N	LS Mean (SE)		< 1.0 mmHg	< 1.5 mmHg
Week 1	8 AM	288	-5.8 (0.17)	284	-6.1 (0.17)	0.31 (-0.15, 0.76)	Y	Y
	10 AM	288	-5.5 (0.17)	286	-6.1 (0.17)	0.63 (0.18, 1.08)	N	Y
	4 PM	287	-5.3 (0.17)	285	-5.7 (0.17)	0.36 (-0.09, 0.82)	Y	Y
Week 4	8 AM	285	-5.9 (0.17)	282	-6.6 (0.18)	0.71 (0.25, 1.18)	N	Y
	10 AM	285	-5.7 (0.17)	282	-6.3 (0.17)	0.57 (0.12, 1.01)	N	Y
	4 PM	286	-5.0 (0.17)	281	-5.9 (0.17)	0.85 (0.41, 1.29)	N	Y
Week 8	8 AM	281	-6.2 (0.17)	277	-6.5 (0.17)	0.25 (-0.21, 0.71)	Y	Y
	10 AM	279	-6.0 (0.17)	277	-6.4 (0.17)	0.47 (0.01, 0.93)	Y	Y
	4 PM	279	-5.5 (0.16)	277	-6.0 (0.17)	0.55 (0.11, 0.98)	Y	Y
Week 12	8 AM	275	-6.2 (0.18)	276	-6.6 (0.18)	0.39 (-0.09, 0.86)	Y	Y
	10 AM	277	-5.9 (0.16)	275	-6.5 (0.17)	0.64 (0.20, 1.07)	N	Y
	4 PM	275	-5.5 (0.17)	276	-6.2 (0.17)	0.71 (0.26, 1.16)	N	Y

SE = Standard Error; CI = Confidence Interval; LS Mean = Least Square Mean
[1] Estimates at each time point of each visit were based on ANCOVA model that included treatment, site, and baseline IOP as covariates

The results from the ANCOVA analysis presented above were performed at each time point of each visit separately, i.e., without accounting for correlated IOP measurements. Analysis that accounted for the correlated IOP measurements was performed using MMRM as sensitivity analysis. Figure 4 shows the results from the MMRM analysis, and overall the analysis results are consistent with the results from the ANCOVA analysis.

Figure 4: Difference in Mean Change in IOP from Baseline - MMRM (CLR_09_12)
(ITT Analysis Population; Observed Cases)



SE = Standard Error; CI = Confidence Interval; LSM = Least Square Means
[1] Estimates were based on LSM derived from a statistical model that accounted for correlated IOP measurements within patient where site and baseline IOP were included in the model as covariates Dots and horizontal bars represent the point and 95% CI estimates for the difference in mean change in IOP

The primary efficacy analysis results presented above were based on the observed data (without missing data imputation) on the ITT population. To assess the impact of missing data and the use of different analysis population on the primary analysis results, sensitivity analysis was performed. With respect to the missing data, about 5% of subjects dropped out early from the study, and the number of subjects with missing data was relatively small in each treatment group.

Table 5: Number of Subjects with Missing IOP by Visit and Time Point (CLR_09_12)
(ITT Analysis Population)

	Xelpros [1] (N = 289)			Xalatan® (N = 289)		
Visit	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM
Week 1 [1]	1	1	2	5	3	4
Week 4	4	4	3	7	7	8
Week 8	8	10	10	12	12	12
Week 12	14	12	14	13	14	13

[1] In the clinical database, the week 1 data for subject 23-157 was measured on Day 21, and the baseline and week 1 data for subject 23-158 were measured on the same visit date The impact of this data issue on the overall conclusion was found to be very minimal

Even though the amount of missing data were small, the following sensitivity analyses were performed using the ANCOVA model: (i) using LOCF imputation on the ITT population (see Figure 12), (ii) using observed data on the PP population (see Figure 13), (iii) with no covariate adjustment on the ITT population (see Figure 14), (iv) using IOP group (instead of actual baseline IOP data) as a covariate (see Figure 15), and (v) using the binary IOP group as a continuous variable (instead of a class variable) as a covariate (see Figure 20). Note that with the exception of the difference in precision (i.e., difference in SE of estimates and CI for the treatment difference), the treatment effects seen in Figure 20 were very similar to the reviewer's primary efficacy analysis seen in Figure 1.

Overall, the sensitivity analyses results were consistent with the primary efficacy results yielding the same conclusion - Xelpros was less effective compared to Xalatan® throughout the study even though the statistical criterion for non-inferiority was met at all visits and time points.

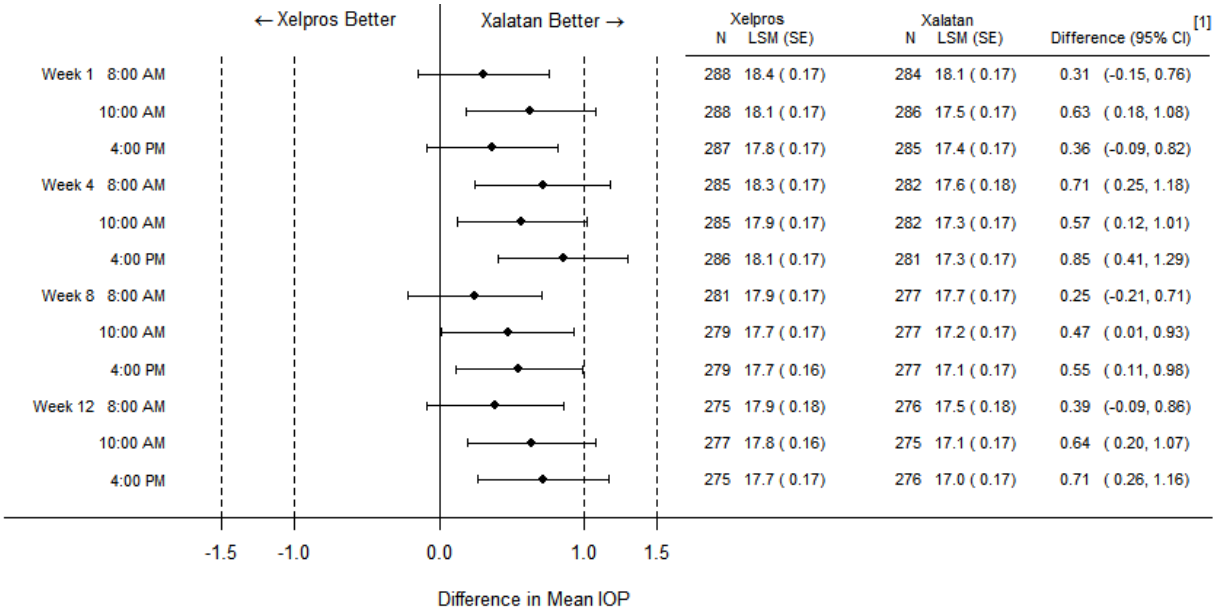
3.2.1.4.2 Supportive Efficacy Endpoints

As a supportive analysis, the efficacy benefits of Xelpros and Xalatan® were compared with respect to the mean IOP, 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.

i) Comparison of Mean IOP

The mean IOP data at each time point of each visit were compared between Xelpros and Xalatan® using the ANCOVA model based on the ITT analysis population. The point and 95% CI estimates for the difference in mean IOP between the treatment groups (*Xelpros minus Xalatan*®) are shown in Figure 5. The treatment and covariate adjusted mean IOP throughout the study ranged from 17.7 to 18.4 mmHg in the Xelpros group and from 17.0 to 18.1 mmHg in the Xalatan® group. The adjusted mean IOP at each time point of each visit was slightly lower in the Xalatan® group, and Xelpros appeared to be less effective in lowering IOP compared to Xalatan® by about 0.3 to 0.9 mmHg units throughout the study. Based on comparison of the mean IOP, the statistical criterion for non-inferiority was met throughout the study; however, the clinical criterion for non-inferiority was not met in six of the 12 time points since the upper limit of the 95% CI was > 1.0 mmHg at these time points. In addition, Xalatan® appeared to be superior to Xelpros in lowering IOP in seven of the 12 time points.

Figure 5: Difference in Mean IOP (mmHg) - ANCOVA (CLR_09_12)
(ITT Analysis Population; Observed Cases)



SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Estimates at each time point of each visit were based on ANCOVA model that included treatment, site, and baseline IOP as covariates Dots and horizontal bars represent the point and 95% CI estimates for the difference in mean change in IOP

ii) 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 study visit and time point are presented in Table 6.

Table 6: Summary of Patients with IOP < 18 mmHg and IOP Lowering of ≥ 30% (CLR_09_12)
(ITT Analysis Population; Observed Cases)

Visit	Time Point	IOP < 18 mmHG		% Change in IOP reduction ≥ 30%	
		Xelpros (N = 289)	Xalatan (N = 289)	Xelpros (N = 289)	Xalatan (N = 289)
Week 1	8 AM	136/ 288 (47.2%)	135/ 284 (47.5%)	81/ 288 (28.1%)	99/ 284 (34.9%)
	10 AM	151/ 288 (52.4%)	161/ 286 (56.3%)	92/ 288 (31.9%)	101/ 286 (35.3%)
	4 PM	150/ 287 (52.3%)	156/ 285 (54.7%)	87/ 287 (30.3%)	86/ 285 (30.2%)
Week 4	8 AM	135/ 285 (47.4%)	148/ 282 (52.5%)	90/ 285 (31.6%)	111/ 282 (39.4%)
	10 AM	149/ 285 (52.3%)	163/ 282 (57.8%)	87/ 285 (30.5%)	109/ 282 (38.7%)
	4 PM	141/ 286 (49.3%)	171/ 281 (60.9%)	74/ 286 (25.9%)	95/ 281 (33.8%)
Week 8	8 AM	147/ 281 (52.3%)	148/ 277 (53.4%)	103/ 281 (36.7%)	112/ 277 (40.4%)
	10 AM	157/ 279 (56.3%)	165/ 277 (59.6%)	100/ 279 (35.8%)	112/ 277 (40.4%)
	4 PM	149/ 279 (53.4%)	167/ 277 (60.3%)	79/ 279 (28.3%)	98/ 277 (35.4%)
Week 12	8 AM	139/ 275 (50.5%)	151/ 276 (54.7%)	104/ 275 (37.8%)	121/ 276 (43.8%)
	10 AM	150/ 277 (54.2%)	164/ 275 (59.6%)	92/ 277 (33.2%)	120/ 275 (43.6%)
	4 PM	150/ 275 (54.5%)	164/ 276 (59.4%)	76/ 275 (27.6%)	111/ 276 (40.2%)

The percentage of subjects who achieved IOP level of < 18 mmHg and the percent reduction in IOP of ≥ 30%, respectively, ranged from 47% to 56% and 26% to 38% in the Xelpros group and from 48% to 61% and 30% to 44% in the Xalatan® group. In both efficacy measures, subjects in the Xalatan® group performed slightly better at all visits and time points compared to subjects in the Xelpros group.

3.2.2 Study CLR_08_01

In this section, the efficacy assessment for Study CLR_08_01 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.

3.2.2.1 Study Design and Endpoints

Study CLR_08_01 was a multicenter, open label, Phase 3, active-controlled, parallel group, randomized study designed to evaluate the safety and IOP lowering efficacy of Xelpros relative to Xalatan® in adult patients with OAG or OH. A total of 100 subjects (50 per group) 18 years or older with OAG or OH and with IOP ≥ 22 mmHg in one or both eyes, with no more than 5 mmHg inter-eye difference at the screen visit were enrolled in the study.

The study duration was four weeks and included five visits: screen (day -7 to -1), randomization (Day 0), and three follow-up visits: Days 8 to 10 (Visit 3), Days 15 to 17 (Visit 4), and Days 29 to 31 (Visit 5). During the randomization visit, eligible subjects that fulfilled all the inclusion and none of the exclusion criteria at the screening visit were randomized in a 1:1 ratio to receive either Xelpros or Xalatan® once daily in the evening for four weeks in one or both eyes as affected. The study eye was the eye with higher IOP at enrollment or if equal, subjects with an even randomization number were assigned the left eye and an odd number the right eye.

IOP was measured twice at each study visit, − before administration of drug in the evening (trough effect) and 12-18 hours after administration of drug product in the following morning (peak effect). The primary objective of study CL_08_01 was to demonstrate equivalence in IOP lowering efficacy of Xelpros to Xalatan® at the through and peak effect of the treatment. The primary endpoint of the study was the change in IOP from baseline during the morning and evening time points of each study visits at Day 8, Day 15, and Day 29.

3.2.2.2 Statistical Methodologies

i) Analysis Population

Three analysis populations were defined in the study protocol and SAP: (i) the intent-to-treat (ITT) population includes all subjects who were randomized, received at least one dose of the study drug, and had at least one post-treatment assessment, (ii) the per-protocol (PP) population includes all subjects in the ITT population that did not have any major protocol violation, and (iii) the safety population includes all subjects who were randomized and received at least one dose of a study drug.

ii) Primary Efficacy Analysis

The primary efficacy endpoint in study CLR_08_01 was the change in IOP from baseline evaluated in the evening before drug administration (through effect) and in the morning 12 hours after drug administration (peak effect) of each study visits. The primary efficacy analysis of the study was based on the ITT analysis population, and used the change from baseline in IOP as the primary efficacy variable. The applicant used the two samples independent T-test for the primary efficacy analysis, and the difference in the mean change in IOP between the treatment groups was determined based on the t-test. In the applicant's primary analysis, missing observations were imputed by LOCF method.

The reviewer believes that when evaluating the IOP lowering effect of treatments, adjusting for the baseline IOP value as a covariate provides a more reliable treatment effect when the baseline values between the treatment groups are not comparable due to some unforeseen reason. Therefore, in this review, ANCOVA model was used as the primary efficacy analysis. The model included treatment and baseline IOP data as covariates, and the difference in the mean change in IOP between the treatment groups (*Xelpros minus Xalatan*®) was determined based the least square (LS) means using the ANCOVA model. Based on the model, equivalence was established if the 95% CI for the difference in the mean change in IOP was within ± 1 mmHg at most time points or was within ± 1.5 mmHg at both time points of each visit.

To assess the impact of missing data on the primary efficacy results, sensitivity analysis using the ANCOVA model was performed by imputing data based on the LOCF method. In the LOCF approach, the baseline IOP data was carried forward if a subject had no post-baseline IOP data.

As a sensitivity analysis to the ANCOVA model, the MMRM analysis based on the observed data was also performed to account for correlated IOP measurements.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.3.1 Patient Disposition

The summary of patient disposition and reasons for study discontinuation among all randomized subjects are shown in Table 7. Overall, 104 patients were randomized in Study CLR_08_01; 53 patients randomized to Xelpros and 51 patients randomized to Xalatan®. A total of 11 (11%) patients discontinued early from the study; the discontinuation rate was approximately three times higher in the Xelpros group than in the Xalatan® group. The most common reason for discontinuation among all randomized patients was lost to follow-up (6%) followed by withdrawal of consent (4%) for subjects in the Xelpros group.

Table 7: Disposition of Patients and Reasons for Study Discontinuation (CLR_08_01)
(All Randomized Subjects)

	Xelpros (N = 53)	Xalatan ® (N = 51)	Total (N = 104)
ITT Population, n (%)	53 (100)	51 (100)	104 (100)
Safety Population, n (%)	53 (100)	51 (100)	104 (100)
Subjects who completed the study, n (%)	45 (84.9)	48 (94.1)	93 (89.4)
Subject who discontinued the study, n (%)	8 (15.1)	3 (5.9)	11 (10.6)
Primary Reason for Early Termination, n (%)			
Major Protocol violation	1 (1.9)	1 (2.0)	2 (1.9)
Withdrawal of consent	2 (3.8)	0 (0.0)	2 (1.9)
Lost to Follow-Up	4 (7.6)	2 (3.9)	6 (5.8)
Study medication failure	1 (1.9)	0 (0.0)	1 (1.0)

Source: Table 10-2 of Applicant's Clinical Study Report

3.2.2.3.2 Demographic and Baseline Characteristics

The summary of demographic and baseline characteristics for subjects in the ITT population are presented in Table 8. All subjects in the study were Asian and the majority were male (67%). The average age of patients in the study was 59 years (range 26 to 81 years), about 38% of all randomized patients were ≥ 65 years of age. About 95% of study eyes had brown iris color, at

least 60% had primary open angle glaucoma and 28% had ocular hypertension. The morning and evening average baseline IOP among all randomized patients were 26 and 25 mmHg, respectively. Overall, the baseline and demographic characteristics were balanced and no marked difference was observed between the treatment groups.

Table 8: Demographic Summary by Treatment Group (CLR_08_01)
(ITT Analysis Population)

		Xelpros (N = 53)	Xalatan (N = 51)	Total (N = 104)
Age (Years), n (%) [1]				
<65		33 (62.3)	32 (62.8)	65 (62.5)
≥65		20 (37.7)	19 (37.3)	39 (37.5)
Age (Years)				
Mean (SD)		58.9 (10.61)	59.1 (11.21)	59.0 (10.85)
Min – Med – Max		34 – 61 – 81	26 – 61 – 74	26 – 61 – 81
Sex, n (%)				
Female		15 (28.3)	19 (37.3)	34 (32.7)
Male		38 (71.7)	32 (62.8)	70 (67.3)
Iris Color, n (%)				
Brown		51 (96.2)	48 (94.1)	99 (95.2)
Hazel		2 (3.8)	3 (5.9)	5 (4.8)
Diagnosis, n (%)				
Primary open angle glaucoma (POAG)		35 (66.0)	29 (56.9)	64 (61.5)
Ocular hypertension (OH)		11 (20.8)	18 (35.3)	29 (27.9)
POAG/Pseudoexfoliation		6 (11.3)	3 (5.6)	9 (8.7)
OH/ Pseudoexfoliation		1 (1.9)	1 (2.0)	2 (1.9)
Baseline IOP [a]				
Morning	Mean (SD)	26.1 (6.00)	25.0 (5.48)	25.6 (5.75)
	Min – Med – Max	14.7 – 25.0 – 55.3	16.0 – 24.3 – 44.0	14.7 – 24.7 – 55.3
Evening	Mean (SD)	24.6 (4.67)	24.6 (4.66)	24.6 (4.65)
	Min – Med – Max	15.0 – 24.3 – 36.3	17.0 – 24.0 – 41.0	15.0 – 24.3 – 41.0

Source: Table 11-2 of Applicant's Clinical Study Report.
[1] Based on reviewer's analysis

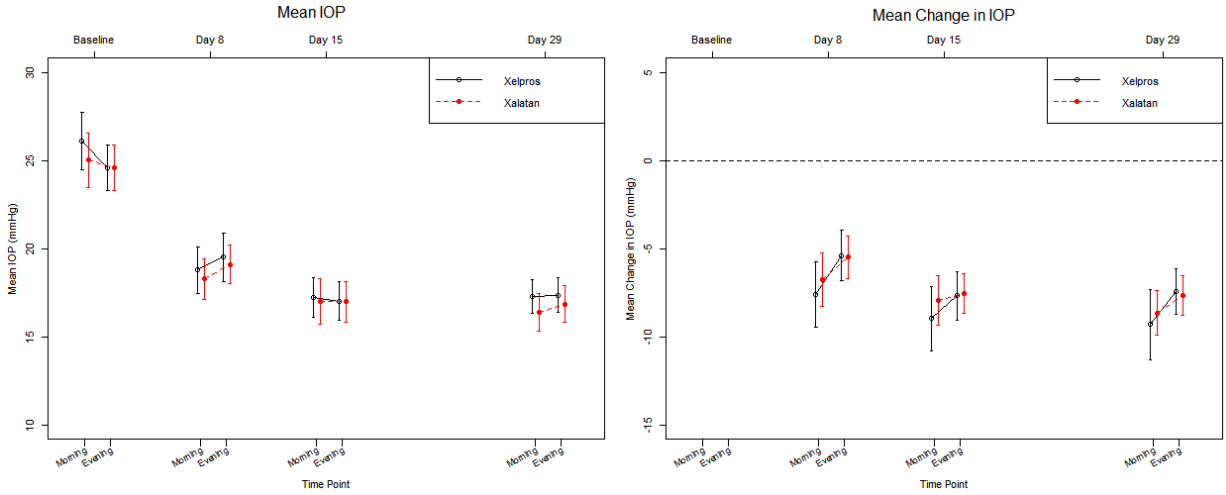
3.2.2.4 Results and Conclusions

3.2.2.4.1 Primary Efficacy Endpoint

The mean IOP and the mean change in IOP at the two time points of each study visit based on the observed data are presented in Figure 6 and the descriptive IOP summaries are presented in appendix Table 13. The baseline mean IOP between the treatment groups were comparable during the evening time point; however, the mean IOP during the morning time point was numerically higher in the Xelpros group by 1.0 mmHg unit compared to in the Xalatan® group. Consequently, the mean IOP reductions during the evening time point were comparable between the treatment groups (reduction range: 5.4 to 7.4 mmHg in the Xelpros group; 5.5 to 7.6 mmHg in the Xalatan® group) while the reductions during the morning time point were slightly better for subjects in the Xelpros group (reductions range: 7.6 to 9.3 mmHg in the Xelpros group; 6.7 to 8.6 mmHg in the Xalatan® group).

Overall, both treatment groups clearly demonstrated significant IOP reductions from baseline at both time points of each study visit (right panel of Figure 6).

Figure 6: Summary of Mean IOP and Mean Change in IOP by Visit and Time Point (CLR_08_01)
(ITT Analysis Population; Observed Cases)

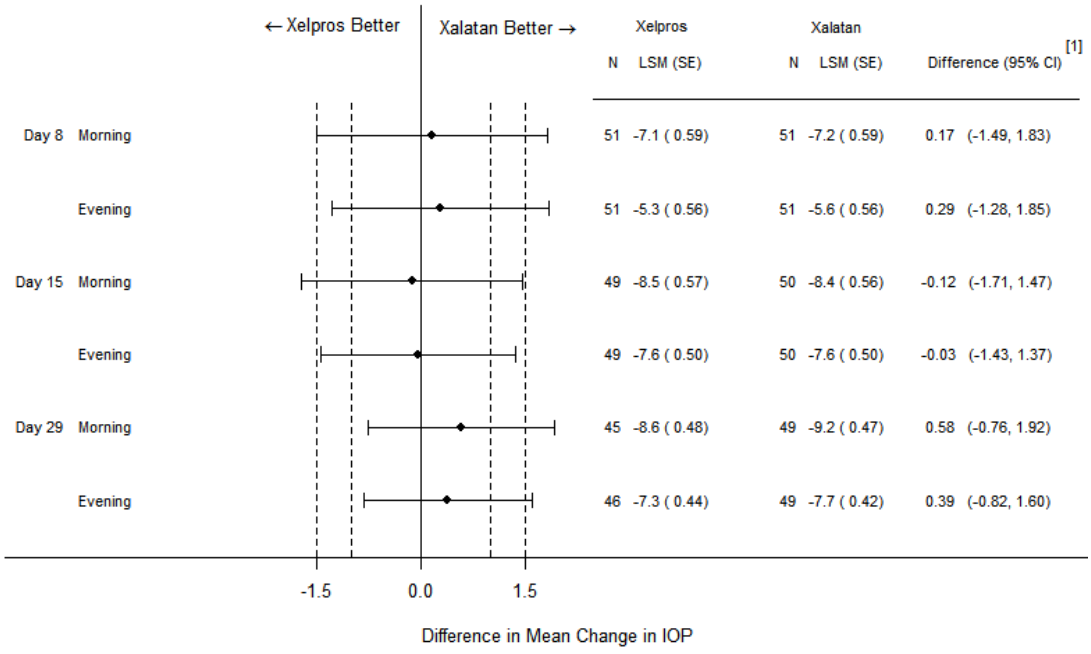


Source: Table 13

At both time points of each study visits, the mean change in IOP from baseline between Xelpros and Xalatan® were compared using the least squares means derived from the ANCOVA analysis. The results of the primary analysis are shown in Figure 7 below.

Both treatment groups clearly demonstrated significant IOP reductions throughout the study; the reductions in both treatment groups were higher at the peak effect of the drug (during the morning). Although Xelpros demonstrated significant IOP reductions throughout the study, it was less effective compared to Xalatan® at the majority of time points during the study.

Figure 7: Difference in Mean Change in IOP from Baseline – ANCOVA (CLR_08_01)
(ITT Analysis Population; Observed Cases)



SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Estimates at each time point of each visit were based on ANCOVA model that included treatment and baseline IOP as covariates Dots and horizontal bars represent the point and 95% CI estimates for the difference in mean change in IOP

Overall, there was no statistical difference in the mean change in IOP between the treatment groups at both time points of each study visit. However, the study did not meet both the statistical and clinical criteria for equivalence since at the majority of time points the two-sided 95% CIs were not within ± 1.5 mmHg. The reason for this is likely due to the small sample size.

To assess the impact of missing data on the primary efficacy results, sensitivity analysis was performed using LOCF imputation method. Additional sensitivity analysis was performed using MMRM analysis based on the observed data; the model used an unstructured covariance matrix to account for correlated IOP measurements within patient and included the fixed effects for treatment, baseline IOP, visit, time point, and the interaction terms of treatment by visit, treatment by time, visit by time, and treatment by visit by time.

The sensitivity analysis results using ANCOVA model based on LOCF (see Figure 16) and using the MMRM model based on the observed data (see Figure 17) were consistent with the primary efficacy analysis results yielding the same conclusion - Xelpros was less effective compared to Xalatan® during the study, and the study did not meet both the statistical and clinical equivalence criteria at the majority of time points.

Based on the applicant's primary analysis approach, the ANCOVA model without the baseline IOP data as a covariate was also performed by imputing data based on the LOCF method. The results are shown in appendix Figure 18 and Figure 19.

3.2.3 Efficacy Conclusion

In both Study CLR_09_12 and CLR_08_01, the test drug, Xelpros, demonstrated significant IOP reductions from baseline at all assessment time points of each on-therapy study visits.

The IOP lowering effect of Xelpros administered once daily in the evening was about 5.0 to 6.2 mmHg in study CLR_09_12, and about 25% to 40% of patients in the Xelpros group had at least 30% IOP reductions throughout the study. Although the test product, Xelpros, demonstrated significant IOP reductions throughout the study, it was less effective compared to the active-control, Xalatan®, by about 0.3 to 0.9 mmHg units. The study met the pre-defined statistical criterion for non-inferiority throughout the study; however, it did not meet the pre-defined clinical criterion at the majority of time points.

The IOP lowering effect of Xelpros administered once daily in the evening was about 5.3 to 8.6 mmHg in Study CLR_08_01; the IOP reductions were higher at the peak effect of the drug (during the morning). Although Xelpros demonstrated significant IOP reductions throughout the study, it was less effective compared to Xalatan® by about 0.2 to 0.6 mmHg units at the majority of time points. Overall, there was no statistical difference in the mean IOP reductions between the treatment groups at both time points of each study visit. However, the study did not meet both the statistical and clinical criteria since the upper limits of the 95% CIs were >1.0 mmHg at both time points of each visit and were > 1.5 mmHg at the majority of time points.

Treatment difference using the mean IOP as the efficacy endpoint was also assessed at each time point of each visit since this endpoint was utilized in several approvals for the same class of drugs and for the same indication. Based on this efficacy measure, Study CLR_09_12 successfully demonstrated the statistical criterion at all the time points of each study visits even though the clinical criterion was not met at the majority of time points.

3.3 EVALUATION OF SAFETY

In this section a high level safety summary from Study CLR_09_12 is provided; a comprehensive safety evaluation of the product is primarily covered in the FDA clinical review.

In Study C-09-12, 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, slit-lamp biomicroscopy, conjunctival hyperemia, dilated ophthalmoscopy, visual field, iris and eyelash, corneal endothelial cell count, and vital signs (blood pressure/pulse rate) assessments.

The safety population in the study included a total of 578 subjects; 289 subjects each were included in Xelpros and Xalatan® groups. Subjects included in the safety population had mean age of about 64 years at enrollment with ages ranging 27 to 88 years old, most subjects were white (69%) followed by African American (28%), and there were more women (65%) than men. Subjects were exposed to study drug once daily for up to 12 weeks.

3.3.1 Exposure to Study Drug

The summary of exposure to study drug are shown in Table 9 below. The duration of exposure to study drug was comparable between the treatment groups. In each group, average exposure was about 82 days, and about 95% of subjects in the study had exposure at least 70 days.

Table 9: Summary of Duration of Exposure to Study Drug (CLR_09_12)
(Safety Analysis Population)

	Xelpros (N = 289)	Xalatan® (N = 289)
Exposure (Days)		
Mean (SD)	81.6 (8.27)	82.0 (12.08)
Median	84	84
Min - Max	6 – 95	5 - 140
Cumulative Exposure Category [N (%)]		
>= 1 Day	289 (100%)	289 (100%)
>= 7 Days	287 (99.3%)	288 (99.7%)
>= 15 Days	286 (99.0%)	286 (99.0%)
>= 45 Days	282 (97.6%)	281 (97.2%)
>= 70 Days	274 (94.8%)	274 (94.8%)

SD: Standard Deviation

3.3.2 Adverse Events

In Study CLR_09_12, a total of 578 subjects were exposed to the study drug. Among these subjects, 85% (246/289) of the subjects in Xelpros group and 82% (238/289) of the subjects in the Xalatan® group experienced at least one treatment-emergent AE (TEAE); 80% (231/289) of the subjects in the Xelpros group and 77% (222/289) of the subjects in the Xalatan® group experienced at least one treatment related TEAE; 1.7% (5/289) of the subjects in the Xelpros group and 1.0 % (3/289) of the subjects in the Xalatan® group experienced at least one serious adverse event – all the serious adverse events were nonfatal and judged by the study investigators as not related to the study drug treatment.

One subject in the Xelpros group discontinued from the study due to mild serious macular oedema (unrelated to the treatment) and two subjects in the Xalatan® group discontinued from study (both related to the treatment) - one due to moderate non-serious Iritis and the other due to mild non-serious Meibomianitis.

In Table 10 TEAEs reported by at least 1% of subjects in any treatment group are presented.

Table 10: Treatment-Emergent AEs occurring in ≥1% of subjects in any treatment group (CLR_09_12) (Safety Analysis Population)

System Organ Class/ Preferred Term	Xelpros (N = 298)	Xalatan (N = 289)	Total (N = 578)
Eye disorders	**238 (82.4%)**	**231 (79.9%)**	**469 (81.1%)**
Eye pain	185 (64.0%)	136 (47.1%)	321 (55.5%)
Ocular hyperaemia	135 (46.7%)	143 (49.5%)	278 (48.1%)
Conjunctival hyperaemia	58 (20.1%)	55 (19.0%)	113 (19.6%)
Eye discharge	39 (13.5%)	41 (14.2%)	80 (13.8%)
Growth of eyelashes	27 (9.3%)	36 (12.5%)	63 (10.9%)
Eyelash thickening	15 (5.2%)	17 (5.9%)	32 (5.5%)
Eye pruritus	16 (5.5%)	14 (4.8%)	30 (5.2%)
Visual acuity reduced	11 (3.8%)	12 (4.2%)	23 (4.0%)
Erythema of eyelid	9 (3.1%)	13 (4.5%)	22 (3.8%)
Dry eye	12 (4.2%)	5 (1.7%)	17 (2.9%)
Foreign body sensation in eyes	6 (2.1%)	5 (1.7%)	11 (1.9%)
Punctate keratitis	1 (0.3%)	9 (3.1%)	10 (1.7%)
Vision blurred	3 (1.0%)	7 (2.4%)	10 (1.7%)
Chalazion	2 (0.7%)	7 (2.4%)	9 (1.6%)
Blepharitis	3 (1.0%)	4 (1.4%)	7 (1.2%)
Eyelash discolouration	5 (1.7%)	2 (0.7%)	7 (1.2%)
Lacrimation increased	2 (0.7%)	4 (1.4%)	6 (1.0%)
Meibomianitis	3 (1.0%)	3 (1.0%)	6 (1.0%)
Eyelid margin crusting	4 (1.4%)	1 (0.3%)	5 (0.9%)
Eyelid oedema	5 (1.7%)	0 (0.0%)	5 (0.9%)
Conjunctival oedema	3 (1.0%)	1 (0.3%)	4 (0.7%)
Conjunctival haemorrhage	0 (0.0%)	3 (1.0%)	3 (0.5%)
Infections and infestations	**20 (6.9%)**	**12 (4.2%)**	**32 (5.5%)**
Upper respiratory tract infection	8 (2.8%)	0 (0.0%)	8 (1.4%)
Sinusitis	4 (1.4%)	0 (0.0%)	4 (0.7%)
Nasopharyngitis	0 (0.0%)	3 (1.0%)	3 (0.5%)
Investigations	**4 (1.4%)**	**5 (1.7%)**	**9 (1.6%)**
Corneal staining	1 (0.3%)	3 (1.0%)	4 (0.7%)
Musculoskeletal and connective tissue	**7 (2.4%)**	**2 (0.7%)**	**9 (1.6%)**
Rotator cuff syndrome	3 (1.0%)	0 (0.0%)	3 (0.5%)
Nervous system disorders	**4 (1.4%)**	**7 (2.4%)**	**11 (1.9%)**
Headache	3 (1.0%)	5 (1.7%)	8 (1.4%)
Psychiatric disorders	**2 (0.7%)**	**4 (1.4%)**	**6 (1.0%)**
Anxiety	2 (0.7%)	3 (1.0%)	5 (0.9%)
Skin and subcutaneous tissue disorders	**10 (3.5%)**	**5 (1.7%)**	**15 (2.6%)**
Rash	3 (1.0%)	0 (0.0%)	3 (0.5%)
Vascular disorders	**1 (0.3%)**	**6 (2.1%)**	**7 (1.2%)**
Hypertension	1 (0.3%)	6 (2.1%)	7 (1.2%)

Overall, the most frequently reported treatment-emergent AEs (≥5% of subjects by MedDRA Preferred Term) were eye pain (56%), ocular hyperaemia (48%), conjunctival hyperaemia (20%), eye discharge (14%), growth of eyelashes (11%), eyelash thickening (6%), and eye

pruritus (5%). The incidences of these events with the exception of eye pain were comparable between the treatment groups; the incidence of eye pain reported in the Xelpros group was higher by more than 15% compared to the incidence reported in the Xalatan® group.

The summary of the overall treatment emergent AEs by the subgroups of age, gender, and race are presented in Table 11 below. In terms of the overall AE summary, no marked treatment difference was observed between the treatment groups by the subgroup variables.

Table 11: Overall AE Summary by Subgroup (CLR_09_12)
(Safety Analysis Population)

Subgroup	Levels	Treatment Emergent AEs Related to Treatment		Treatment Emergent AEs (Related and not related combined)	
		Xelpros	Xalatan	Xelpros	Xalatan
Age	< 65	112/136 (82.4%)	127/162 (78.4%)	119/136 (87.5%)	140/162 (86.4%)
	≥ 65	119/153 (77.8%)	95/127 (74.8%)	127/153 (83.0%)	98/127 (77.2%)
Gender	Male	80/101 (79.2%)	81/103 (78.6%)	86/101 (85.1%)	86/103 (83.5%)
	Female	151/188 (80.3%)	141/186 (75.8%)	160/188 (85.1%)	152/186 (81.7%)
Race	White	159/198 (80.3%)	162/202 (80.2%)	169/198 (85.4)	171/202 (84.7%)
	Black	64/ 82 (78.0%)	53/ 79 (67.1%)	69/82 (84.1%)	59/79 (74.7%)
	Other	64/ 82 (78.0%)	7/ 8 (87.5%)	8/9 (88.9%)	8/8 (100%)

The most frequent TEAEs reported by at least 5% of subjects by the subgroups of age, gender, and race are presented in appendix Table 14, Table 15, and Table 16, respectively. As was seen in the overall AE summary (See Table 10), eye pain, ocular hyperaemia, conjunctival hyperaemia, eye discharge, and growth of eye lashes were the most frequent treatment-emergent AEs reported by at least 10% of subjects in each of the subgroup categories. No marked difference in the incidence of TEAEs (with the exception of eye pain) was observed between the treatment groups within each subgroup levels. The incidence of eye pain reported in the Xelpros group within the levels of each subgroup was higher by more than 10%-20% compared to the incidence reported in the Xalatan® group.

3.3.3 Safety Conclusion

In both treatment groups at least 80% of subjects experienced at least one treatment-emergent adverse event, and the majority of the events as judged by the study investigators were related to the study drug treatment. At least 1.4% of subjects in the study experienced at least one serious adverse event.

In each of the treatment groups, the most frequently reported TEAEs as reported by at least 5% of subjects were eye pain (56%), ocular hyperaemia (48%), conjunctival hyperaemia (20%), eye discharge (14%), growth of eyelashes (11%), eyelash thickening (6%), and eye pruritus (5%). With the exception of eye pain, the incidences of all other events were comparable between the treatment groups. The incidence of eye pain reported in the Xelpros group was higher by more than 15% compared to the incidence reported in the Xalatan group.

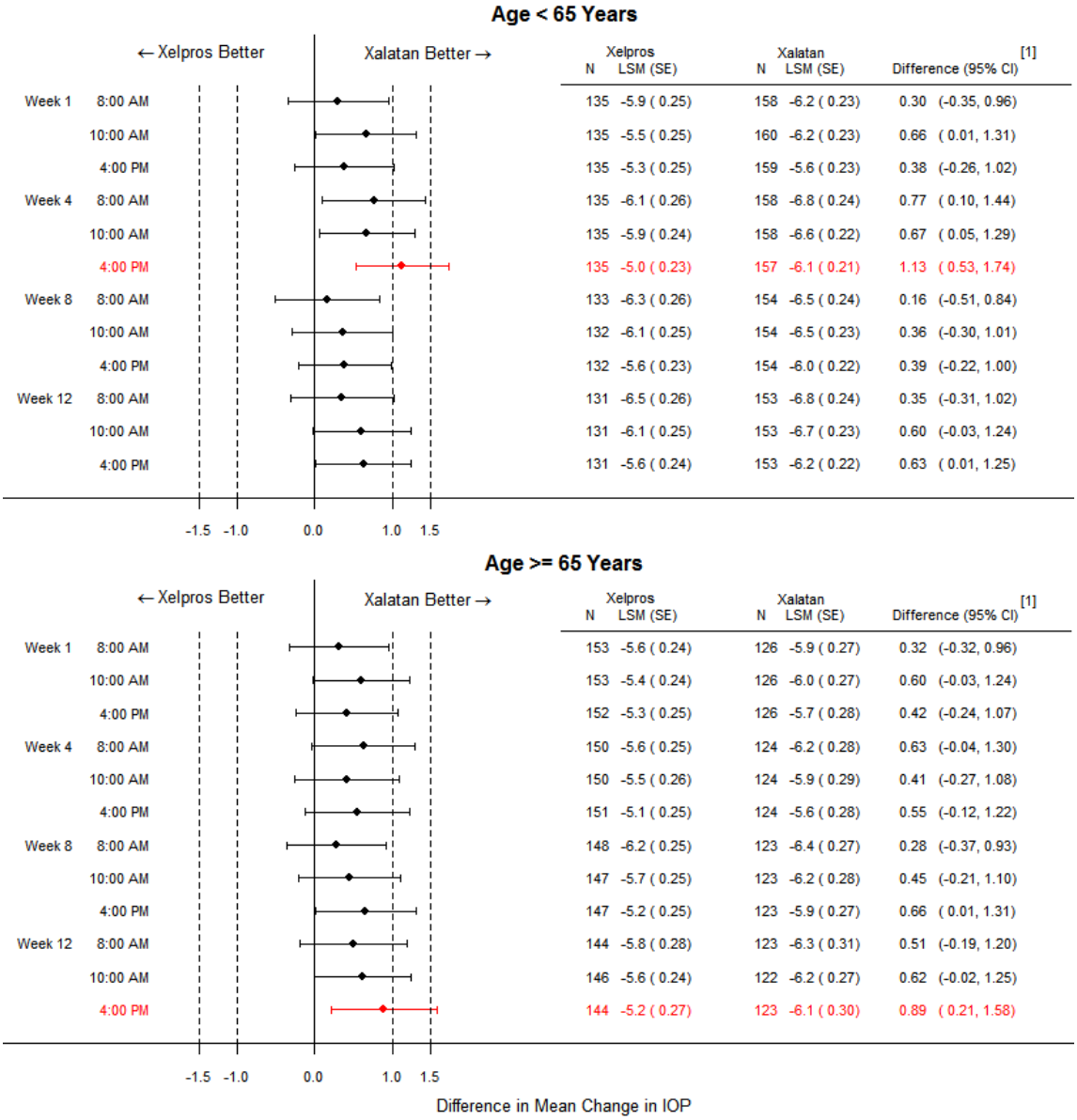
During the 12 week treatment period, three subjects (one in Xelpros and two in Xalatan) discontinued from the study due to AE. There was no death reported in the study. The overall safety profiles between the treatment groups, with the exception of the incidence of eye pain, were comparable.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 AGE, GENDER, AND RACE

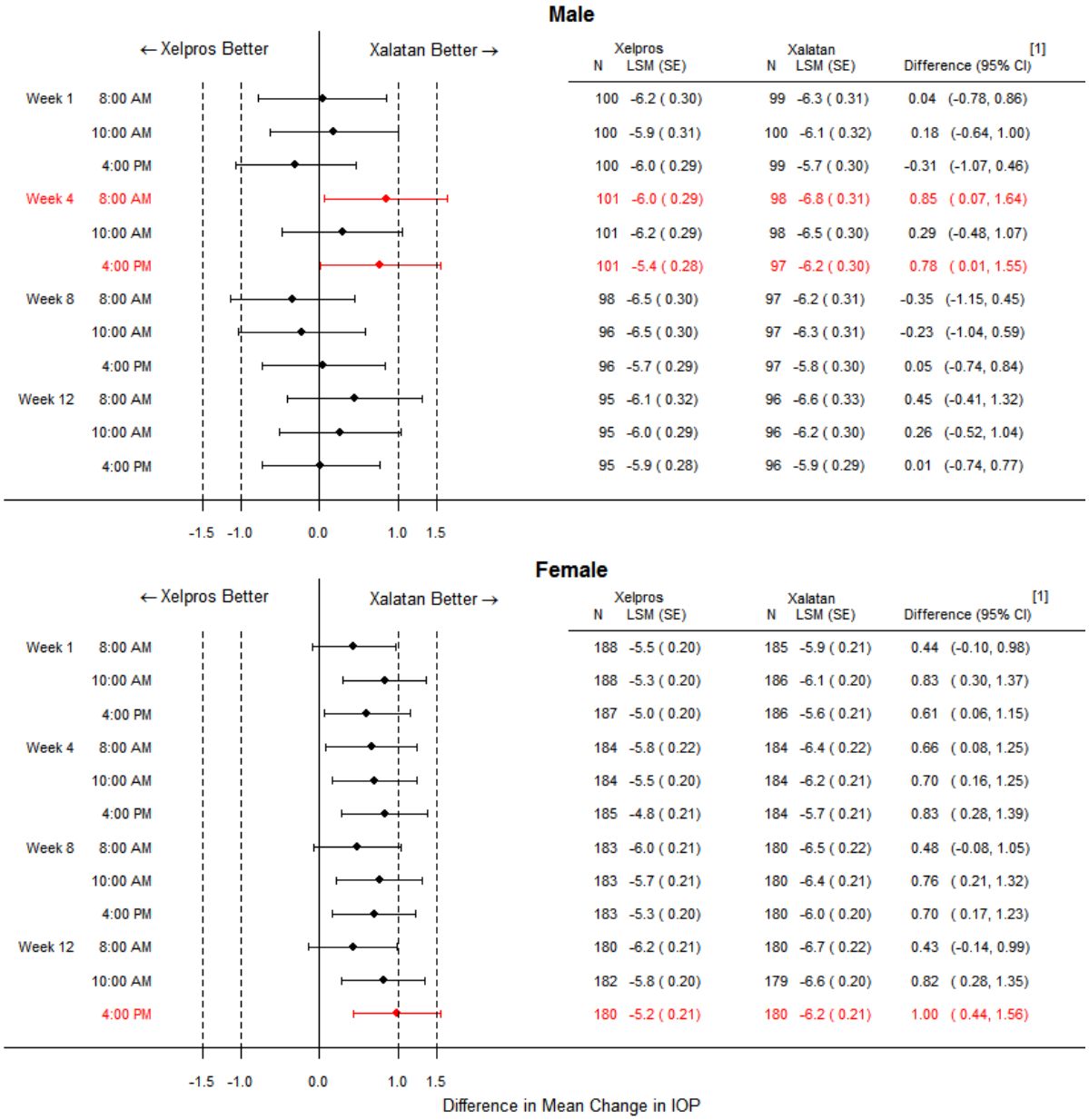
In Study CLR_09_12, the primary efficacy variable of the change in IOP from baseline to all visits and time points were analyzed by the subgroup of age, sex, and race. The LS means (dots) and 97.5% confidence intervals (horizontal bars) for the difference in mean change in IOP between the treatment groups by the subgroups of age, gender, and race based on the ANCOVA model are shown in Figure 8, Figure 9, and Figure 10, respectively.

Figure 8: Difference in Mean Change in IOP by the Subgroup of Age (CLR_09_12)
(ITT Analysis Population; Observed Cases)



Note 1: Time points with the upper limit of the 95% CI for the difference in the mean change in IOP > 1 5 mmHg are shown in red.
SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Estimates at each time point of each visit were based on ANCOVA model that included treatment, site, and baseline IOP as covariates Dots and horizontal bars represent the point and 95% CI estimates for the difference in mean change in IOP

Figure 9: Difference in Mean Change in IOP by the Subgroup of Sex (CLR_09_12)
(ITT Analysis Population; Observed Cases)

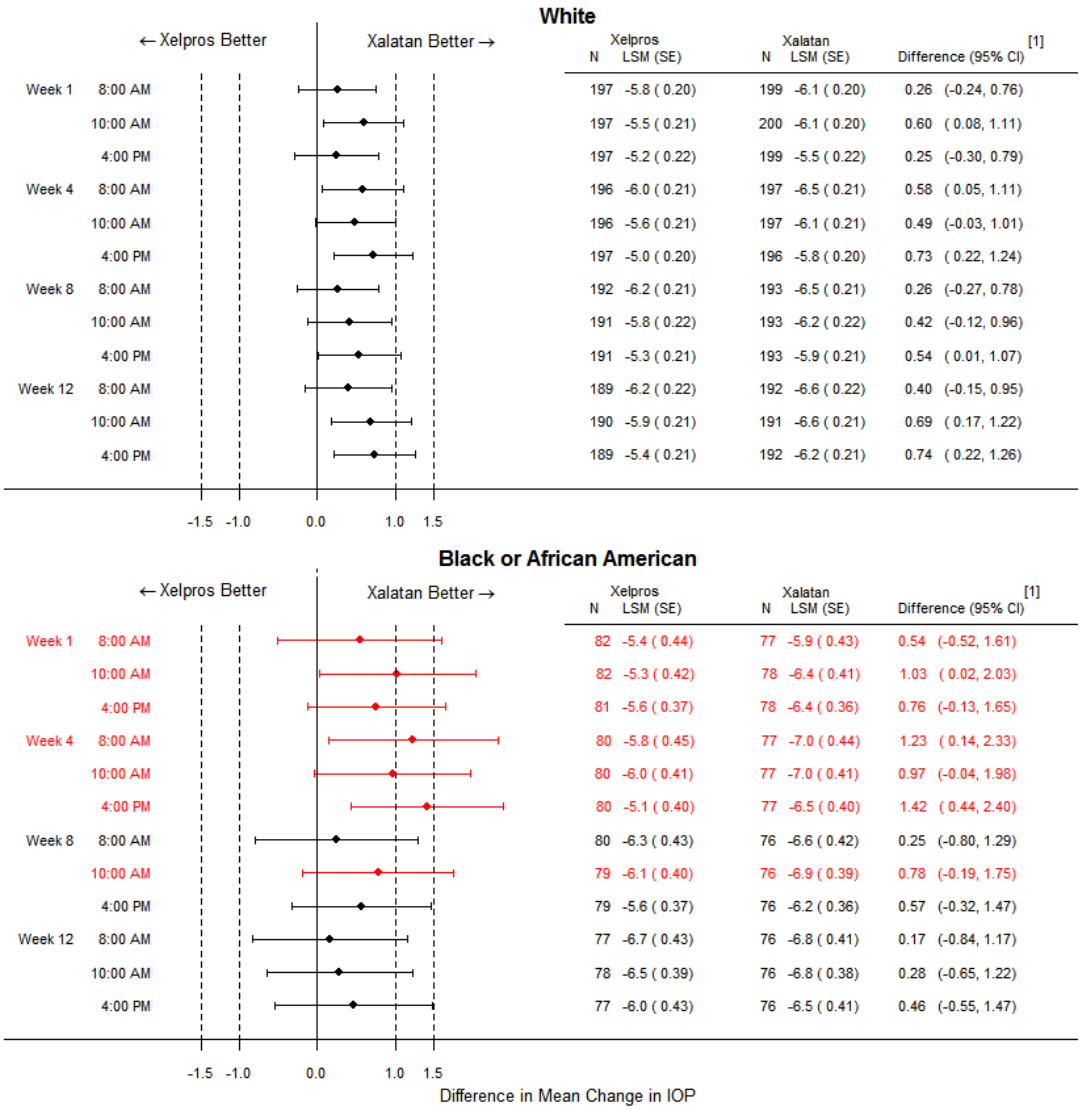


Note 1: Time points with the upper limit of the 95% CI for the difference in the mean change in IOP > 1 5 mmHg are shown in red
SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Estimates at each time point of each visit were based on ANCOVA model that included treatment, site, and baseline IOP as covariates Dots and horizontal bars represent the point and 95% CI estimates for the difference in mean change in IOP

The primary efficacy results within the levels of each of the subgroup variables were consistent with those seen in the overall population, i.e., within the levels of each subgroup variables, Xelpros appeared to be less effective compared to the active-control, Xalatan®, at the majority of time points.

At all visits and time points, the upper limit of the 95% CI for the difference in mean change in IOP was < 1.5 mmHg in the white subpopulation.

Figure 10: Difference in Mean Change in IOP (mmHg) by the Subgroup of Race (CLR_09_12)
(ITT Analysis Population; Observed Cases)



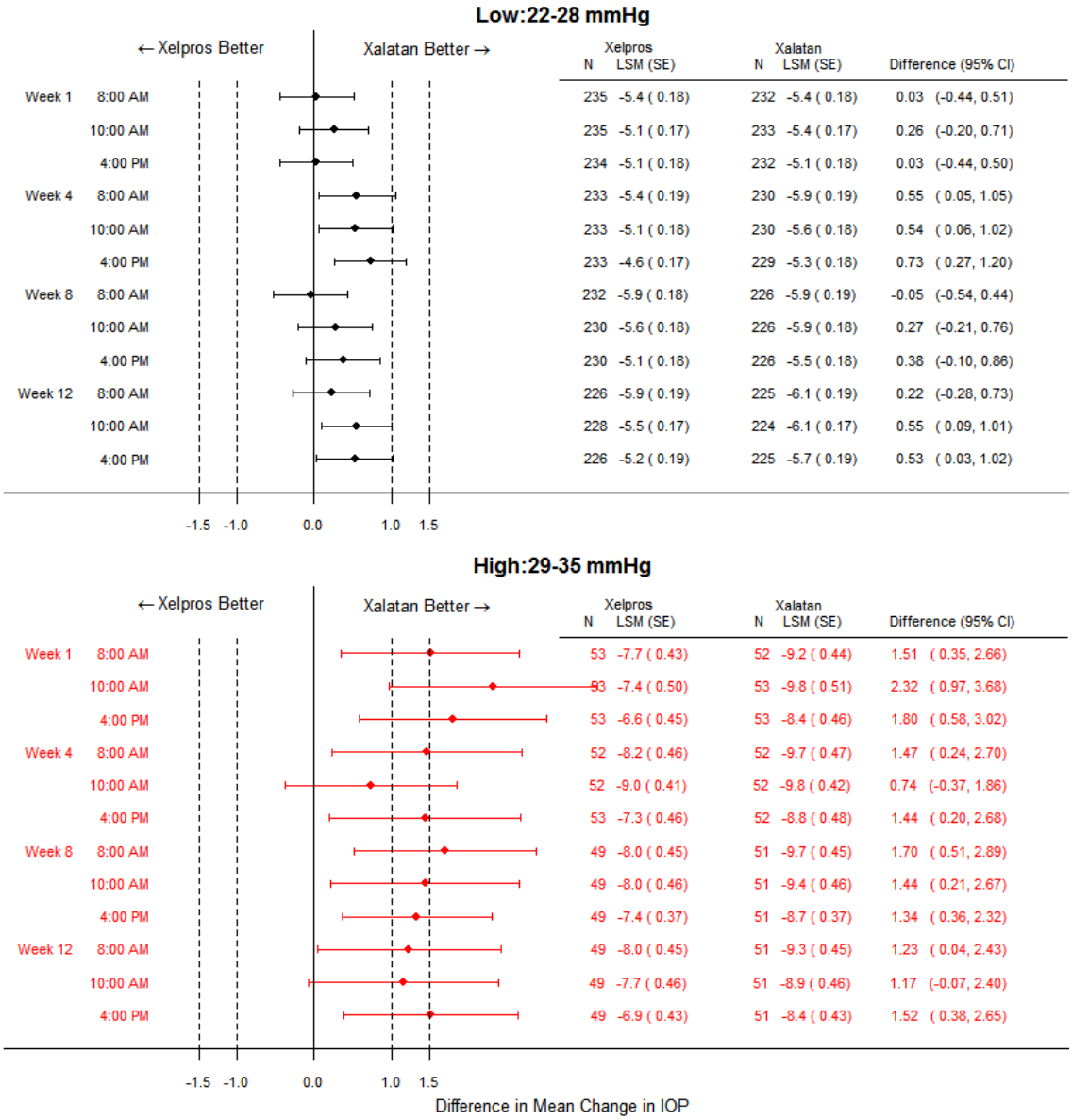
Note 1: Time points with the upper limit of the 95% CI for the difference in the mean change in IOP > 1 5 mmHg are shown in red
Note 2: Due to small sample size, the primary efficacy variable by the other race categories was not performed
SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Estimates at each time point of each visit were based on ANCOVA model that included treatment, site, and baseline IOP as covariates Dots and horizontal bars represent the point and 95% CI estimates for the difference in mean change in IOP

4.2 Other Special/Subgroup Populations: IOP Group

The primary efficacy variable of the change in IOP from baseline at all visits and time points was also analyzed by the eligibility visit IOP group (Low: 22-28 mmHg; High: 29-35 mmHg); this IOP group was used as the stratification factor in Study CLR_09_12. The mean IOP and the mean change in IOP at each time point of each visit by the IOP group based on the observed data are presented in appendix Table 17. Note that a much larger IOP reduction in the higher IOP group was observed in both treatment groups (at least 30% more IOP reductions compared to the lower IOP stratum, see appendix Table 18).

As was seen in the overall population, Xalatan® demonstrated numerically higher IOP reductions than Xelpros within the IOP groups. In the low IOP group (22-28 mmHg), the upper limit of the 95% CI for the difference in the mean change in IOP was < 1.5 mmHg throughout the study and was < 1.0 mmHg in seven of the 12 time points.

Figure 11: Difference in Mean Change in IOP (mmHg) by IOP Group (CLR_09_12)
(ITT Analysis Population; Observed Cases)



Note 1: Time points with the upper limit of the 95% CI for the difference in the mean change in IOP > 1 5 mmHg are shown in red.
SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Estimates at each time point of each visit were based on ANCOVA model that included treatment, site, and baseline IOP as covariates Dots and horizontal bars represent the point and 95% CI estimates for the difference in mean change in IOP

The sample sizes in the high IOP group and White or African American subpopulation were relatively small and the results for these subgroups may not be indicative of the overall treatment effect.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES

Few issues were identified during the review process of Study CLR_09_12. These issues were related to: (i) the analysis dataset that contained the primary efficacy variable, (ii) the applicant's primary efficacy results, and (iii) the primary efficacy analysis approach. These issues are discussed below.

1) Analysis Dataset Issue

The study had four on-therapy visits conducted at *week 1, week 4, week 8, and week 12*, and at each visit data were collected at 8 AM, 10:00 AM and 4:00 PM time points. In the clinical study CRF, data at each study visit were recorded under visit names: *visit 1, visit 2, visit 3,* and *end-of-study* visit. However, irrespective of the dates these visits had occurred, the CRF data collected during these visits were respectively linked to analysis visits *week 1*, *week 4*, *week 8*, and *week 12* in the clinical database. Due to this link, the following two data issues were discovered:

i) The *end-of-study* visit data for subjects who discontinued from the study early (before the week 12 visit) were incorrectly assigned to the *week 12* visit (irrespective of the end-of-study visit date); sixteen early discontinued subjects were affected because of this issue. As shown in Table 2, a total of 28 subjects discontinued from the study early; 19 of these subjects had an end-of-study visit assessment in the clinical database. For three of the 19 subjects, the *end-of-study* visit had occurred close to day 84 (*week 12* visit) and hence there was no issue. However, for 16 of the 19 subjects, the *end-of-study* visit occurred early on and their data during the discontinuation visit was incorrectly assigned to the *week 12* analysis visit. In the reviewer's opinion, the *end-of-visit* data for the 16 subjects should correspond to the appropriate visit (in relation to the date of the visit), but not to the *week 12* visit.

   This issue was communicated to the applicant through an information request dated on July 15, 2014. The applicant acknowledged the issue and submitted an updated dataset on July 23, 2014. The reviewer confirmed the corrections made to the analysis visits and all analyses in this report were based on the updated dataset.

ii) For some subjects, the analysis visits in the clinical database (*week 1, 4, 8*, and *12*) did not properly correspond to the assessment visit dates. Three subjects were affected due to this issue; the *week 1* visit data for subject 23-157 was measured on day 21, the *baseline* and *week 1* data for subject 23-158 were recorded on the same visit date, and the *week 12* data for subject 14-254 was measured on day 36.

   The reviewer confirmed that this data issue had very minimal impact on the primary efficacy result and on the overall efficacy conclusion.

2) Issue with Applicant's Primary Efficacy Results

The reviewer was initially unable to reproduce the applicant's primary efficacy results presented in the clinical study report. In an attempt to reproduce the applicant results, the reviewer used the applicant's proposed analysis method, SAS program, and the ADaM analysis dataset submitted as part of the NDA submission.

This issue was brought to the attention of the applicant through an information request dated on June 5, 2014. In an email dated on June 11, 2014, the applicant acknowledged the issue and indicated that the primary efficacy results reported in the CSR were incorrectly produced using an intermediate dataset instead of using the final ADaM dataset that was submitted to the Agency. With that the applicant confirmed that even though the results reported in the CSR were incorrect, the ADaM dataset that was submitted to the Agency as part of the NDA submission was correct and agreed to submit an updated CSR. Based on the applicant's confirmation regarding the dataset, the reviewer continued with the review process using the ADaM dataset.

On September 03, 2014 the applicant submitted an amended CSR based on the updated dataset. Based on the updated dataset, the reviewer was able to reproduce the applicant's primary efficacy results. Therefore, unless stated otherwise, all the efficacy analysis results reported in this review were based on the reviewer's analysis using the updated dataset submitted to the Agency on July 23, 2014.

3) Difference in The Primary Efficacy Analysis Approach

The reviewer's primary efficacy analysis results presented throughout this report were slightly different from the applicant's analysis results reported in the CSR even though the overall conclusion remained the same.

The applicant primary efficacy analysis used ANCOVA model with the change from baseline as the response variable and treatment, site, and IOP group (**low IOP**: 22-28 mmHg and **high IOP**: 29-35 mmHg) as covariates; the IOP groups were derived from the eligibility visit IOP data measured either at 10:00 AM or 4:00 PM. Based on the applicant's SAS code for the ANCOVA model, the differences in the mean change in IOP between the treatment groups were determined using the least square means (LS Means).

Two potential issues were noted with the applicant's analysis approach:

i) The applicant's modeling strategy gave equal weight across the classification variables when the overall IOP reductions in each treatment group was derived based on the LS Means. In the presence of a substantial sample size imbalance (approximately 82% patients in the lower IOP stratum versus 18% in the higher IOP stratum, see Table 3) and a much larger IOP reduction in the higher IOP stratum (at least 30% more IOP reduction compared to the lower IOP stratum, see appendix Table 18), the applicant's analysis approach gave much more weight for patients in the higher IOP stratum group and consequently overestimated the overall IOP reductions for both treatment groups.

   In the reviewer's opinion, the overall IOP reductions based the LS Means should have been derived proportional to the sample sizes in the classification variables. Two possible approaches to achieve that was by: (i) re-coding the IOP stratum as a binary data (0: low IOP and 1: high IOP) and including the binary data as a continuous variable in the model instead of including it as a classification variable, or (ii) using the default observed margin (OM) option in the LSMEANS statement of the PROC MIXED procedure.

ii) The ANCOVA model did not adjust for the actual time-matched baseline IOP data as a covariate in the model, and use of the change from baseline as a response variable at each time point without adjusting for the time-matched baseline IOP value as a covariate does not generally constitute as covariate adjustment.

In the reviewer's opinion the time-matched baseline values should have been included in the model as a covariate for the following reasons:

a) When evaluating the IOP lowering effect of investigational products at each time point of each visit, time-matched adjustment is clinically meaningful since IOP measurements taken during the morning times are usually higher than during the day times.

b) The estimated treatment effects are more precise. In particular, when the baseline and the change from baseline IOP data are strongly correlated (see Figure 21), adjusting for the baseline IOP data as a covariate in the model decreases the mean square error (MSE), thereby increases the power of the treatment comparisons.

Therefore, to address these issues and to provide a more precise estimate of the treatment effects, the reviewer's primary efficacy analysis based on the ANCOVA methodology used the change in IOP from baseline values (at each time point of each visit) as the response variable, and treatment, site, and the actual time-matched baseline IOP values (instead of the eligibility visit IOP group) as covariates. Note that the ANCOVA analysis with or without the IOP group as a covariate in a model that already contained the time-matched baseline IOP values did not change the efficacy results and the overall conclusion.

5.2 COLLECTIVE EVIDENCE

The primary efficacy evidence to support the non-inferiority of Xelpros to Xalatan® in IOP reduction was based on a pivotal phase 3 trial conducted in the US (Study CLR_09_12) and based on a supporting efficacy trial conducted in India (Study CLR_08_01).

In both Study CLR_09_12 and CLR_08_01, the test drug, Xelpros, demonstrated significant IOP reductions from baseline at all assessment time points and at all on-therapy study visits.

The IOP lowering effect of Xelpros administered once daily in the evening was about 5.0 to 6.2 mmHg in study CLR_09_12, and about 25% to 40% of patients in this group had at least 30% IOP reductions throughout the study; however, Xelpros was less effective compared to the active-control, Xalatan®, by about 0.3 to 0.9 mmHg units. Even though Xelpros was numerically less effective compared to Xalatan®, the pre-defined statistical criterion for non-inferiority was met throughout the study. However, the pre-defined clinical criterion for non-inferiority was not met in six of the 12 time points. In addition, in eight of the 12 time points, Xalatan® appeared to be superior to Xelpros in the mean IOP reduction.

The IOP lowering effect of Xelpros administered once daily in the evening was about 5.3 to 8.6 mmHg in Study CLR_08_01; the IOP reductions were higher at the peak effect of the drug (during the morning). Although Xelpros demonstrated significant IOP reductions throughout the study, it was less effective compared to Xalatan® by 0.2 to 0.6 mmHg units at the majority of time points during the study. Overall, there was no statistical difference in the mean IOP reductions between the treatment groups. However, the study did not meet both the statistical and clinical criteria of equivalence at the majority of time points.

Treatment comparison using the mean IOP as the efficacy endpoint was also evaluated at each time point of each visit since this endpoint was utilized in several approvals for the same class of drug and for the same indication. Based on this efficacy measure, Study CLR_09_12 established

the statistical criterion of non-inferiority of Xelpros to Xalatan® in IOP lowering throughout the study even though the clinical criterion was not met at the majority of time points.

In addition, the safety profiles between Xelpros and Xalatan® in Study CLR_09_12 were similar. In both treatment groups at least 80% of subjects experienced at least one treatment-emergent adverse event, and the majority of these events (as judged by the study investigators) were related to the study drug treatment. At least 1.4% of subjects in the study experienced at least one serious adverse event.

In each of the treatment groups, the most frequently reported TEAEs as reported by at least 5% of subjects were eye pain (56%), ocular hyperaemia (48%), conjunctival hyperaemia (20%), eye discharge (14%), growth of eyelashes (11%), eyelash thickening (6%), and eye pruritus (5%). With the exception of eye pain, the incidences of all other events were comparable between the treatment groups. The incidence of eye pain reported in the Xelpros group was higher by more than 15% compared to the incidence reported in the Xalatan® group.

During the 12 week treatment period, three subjects (one in Xelpros and two in Xalatan®) discontinued from the study due to AE. There was no death reported in the study.

The overall safety profiles between the treatment groups, with the exception of the incidence of eye pain, were comparable.

5.3 CONCLUSIONS AND RECOMMENDATIONS

Based on my review, treatment with Xelpros administered one drop once daily in the evening demonstrated significant IOP reductions from baseline even though it was less effective in IOP reductions than the active-control, Xalatan®.

Therefore, this review concludes that there is evidence to support the efficacy of Xelpros for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

5.4 LABELING RECOMMENDATIONS

The IOP lowering efficacy of the test product, Xelpros, relative to the active-control, Xalatan®, was evaluated in two phase 3 studies: Study CLR_09_12 (Study 1) conducted in the U.S. and Study CLR_08_01 (Study 2) conducted in India. The primary efficacy evidence was based on Study 1 with the results in Study 2 used as supporting efficacy evidence. Therefore, the reviewer recommends the efficacy results from Study 1 be included in Section 14 Clinical Studies of the U.S. Package Insert (USPI).

Labeling Recommendation Based on Study CLR_09_12:

Xelpros was evaluated in a 12 Weeks randomized, assessor-masked, Xalatan®-controlled study in adult patients with open angle glaucoma or ocular hypertension. Patient age ranged from 27 to 88 years, with a mean age of 65 years. A total of 578 patients were enrolled in the study and treated with either Xelpros or Xalatan® once daily in the evening for 12 Weeks; a total of 550 (95%) subjects completed the study.

The mean baseline IOP data are presented in Table 1.

Table 1: Mean (SD) IOP values at Baseline

Time Point	Xelpros (N = 289)	Xalatan® (N = 289)
8 AM	24.1 (3.99)	24.1 (3.87)
10 AM	23.7 (4.14)	23.6 (3.77)
4 PM	23.1 (3.65)	23.2 (3.78)

The efficacy results are presented in Table 2. The IOP lowering effect of Xelpros was about 5.0 to 6.2 mmHg; it was less effective than Xalatan® by 0.3 to 0.9 mmHg throughout the study.

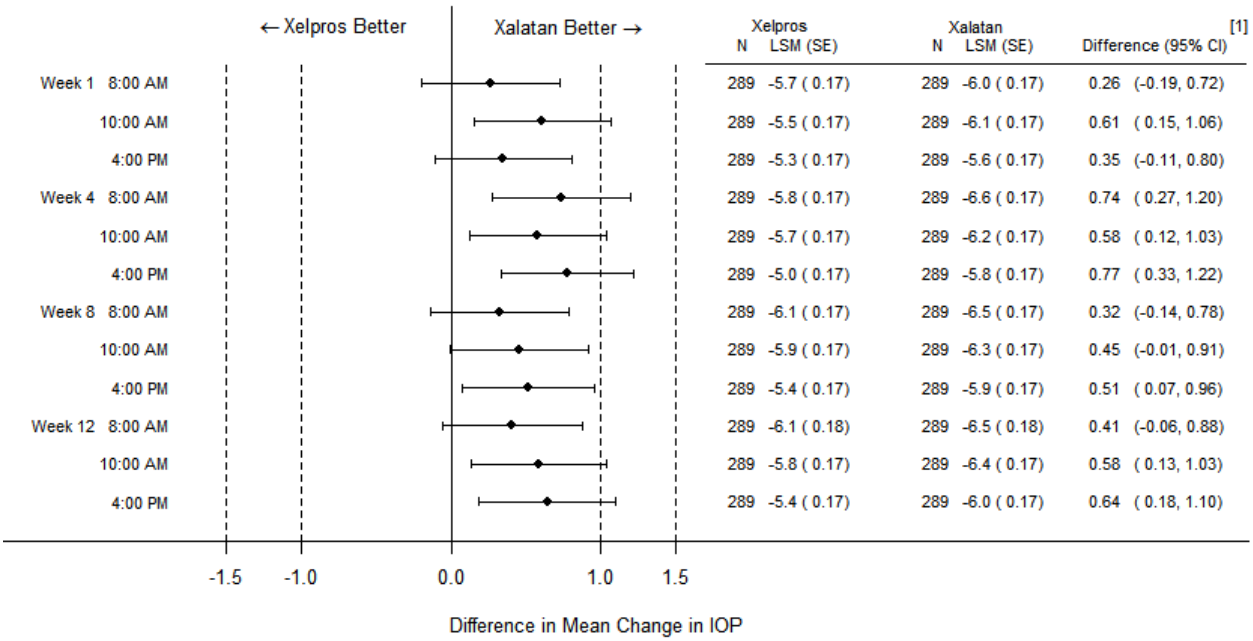
Table 2: Mean Change in IOP (mmHg) and Treatment Difference in Mean Change in IOP (ITT Analysis Population)

Visit	Time Point	Xelpros		Xalatan ®		Difference in Means [1] (95 % CI)
		N	Mean (SE)	N	Mean (SE)	
Week 1	8 AM	288	-5.8 (0.17)	284	-6.1 (0.17)	0.31 (-0.15, 0.76)
	10 AM	288	-5.5 (0.17)	286	-6.1 (0.17)	0.63 (0.18, 1.08)
	4 PM	287	-5.3 (0.17)	285	-5.7 (0.17)	0.36 (-0.09, 0.82)
Week 4	8 AM	285	-5.9 (0.17)	282	-6.6 (0.18)	0.71 (0.25, 1.18)
	10 AM	285	-5.7 (0.17)	282	-6.3 (0.17)	0.57 (0.12, 1.01)
	4 PM	286	-5.0 (0.17)	281	-5.9 (0.17)	0.85 (0.41, 1.29)
Week 8	8 AM	281	-6.2 (0.17)	277	-6.5 (0.17)	0.25 (-0.21, 0.71)
	10 AM	279	-6.0 (0.17)	277	-6.4 (0.17)	0.47 (0.01, 0.93)
	4 PM	279	-5.5 (0.16)	277	-6.0 (0.17)	0.55 (0.11, 0.98)
Week 12	8 AM	275	-6.2 (0.18)	276	-6.6 (0.18)	0.39 (-0.09, 0.86)
	10 AM	277	-5.9 (0.16)	275	-6.5 (0.17)	0.64 (0.20, 1.07)
	4 PM	275	-5.5 (0.17)	276	-6.2 (0.17)	0.71 (0.26, 1.16)

Note: ITT population included all randomized subjects
SE= Standard Error; CI = Confidence Interval; Mean = Least Square Mean
[1] Estimates at each time point of each visit were based on observed data using ANCOVA model that included treatment, site, and baseline IOP as covariates

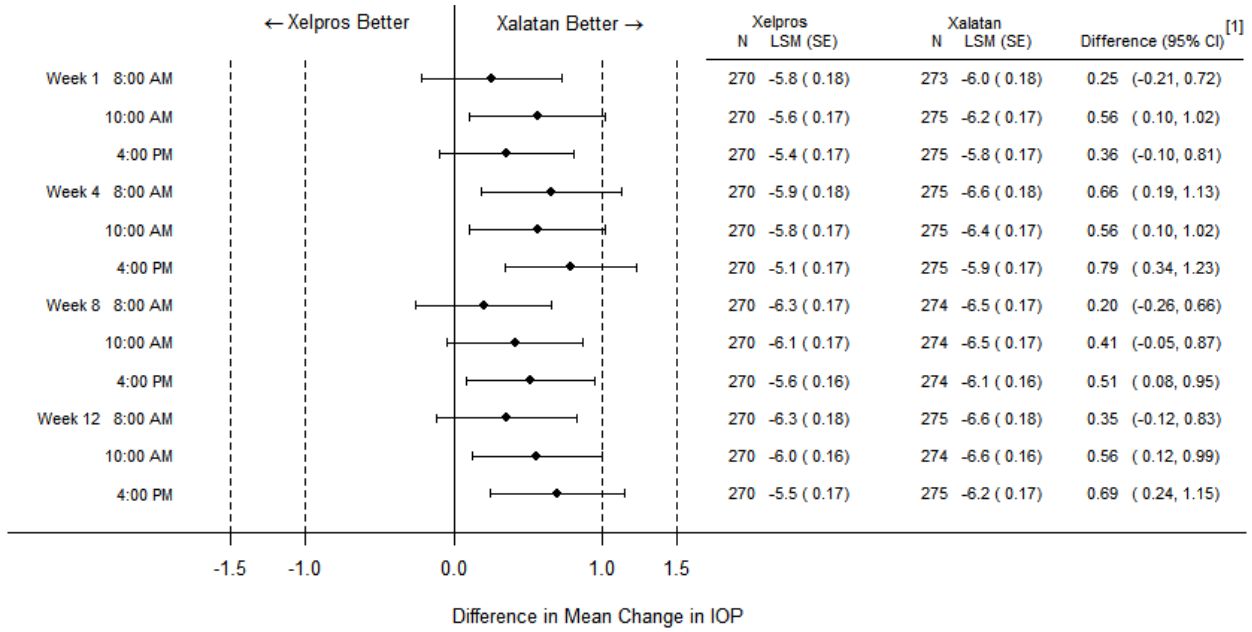
APPENDICES

Figure 12: Difference in Mean Change in IOP – ANCOVA using LOCF (CLR_09_12)
(ITT Analysis Population)



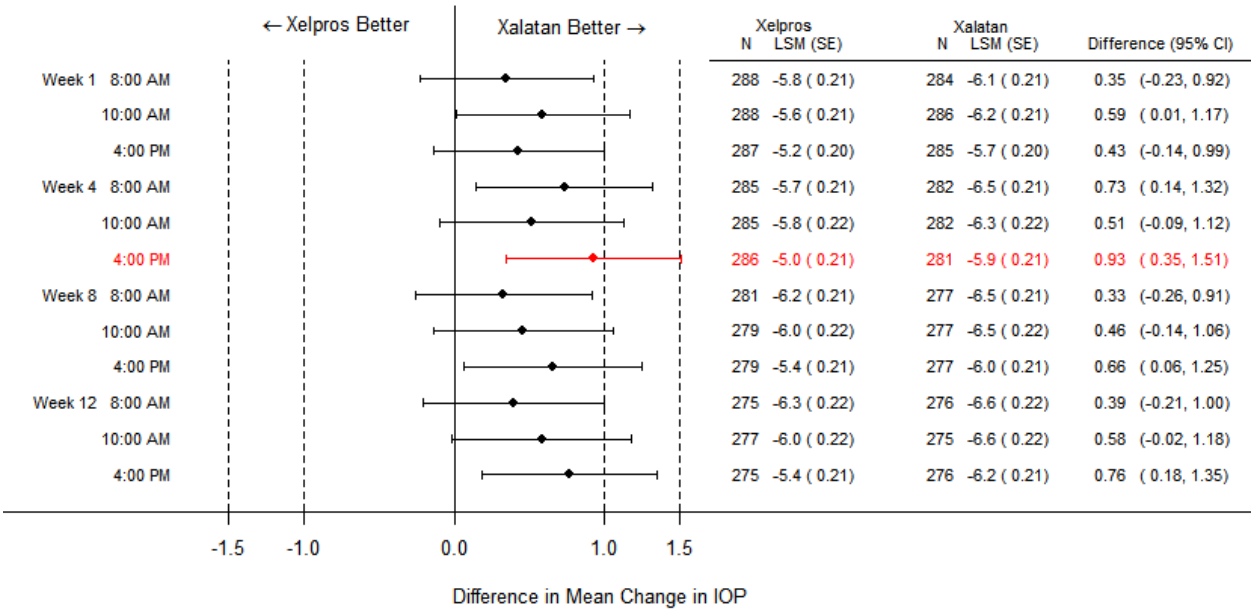
SE= Standard Error; CI = Confidence Interval; LOCF = Last observation carried forward; LSM = Least Square Mean
[1] Based on ANCOVA analysis where model at each time point of each visit was fitted separately; model included treatment, site, and baseline IOP as covariates in the model

Figure 13: Difference in Mean Change in IOP – ANCOVA using PP Analysis Population (CLR_09_12)
(PP Analysis Population)



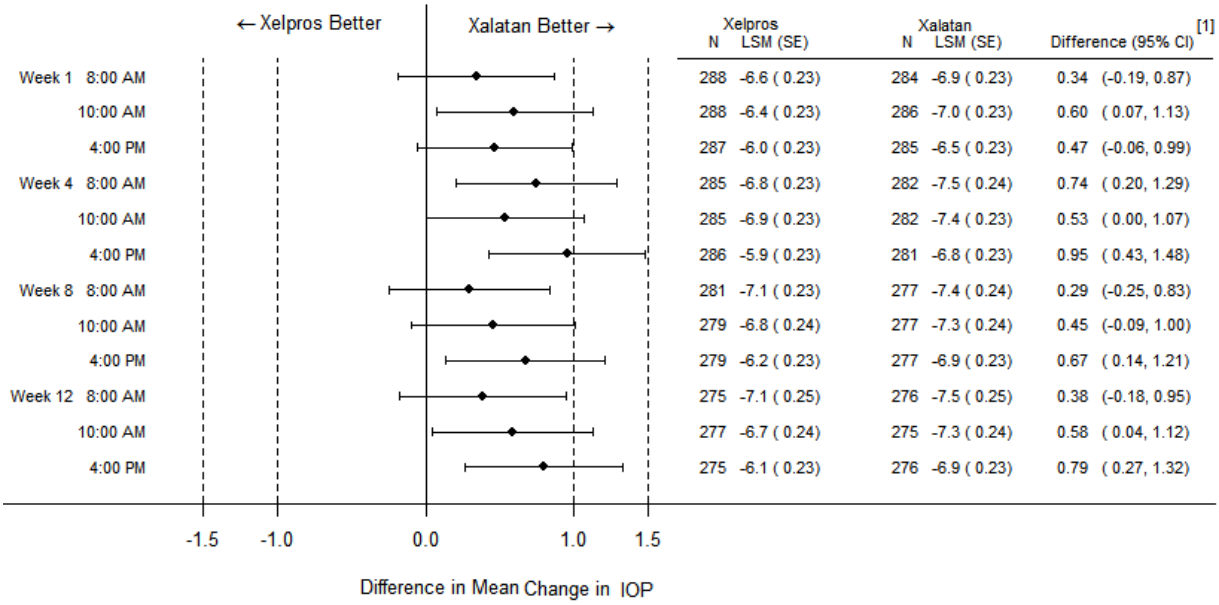
SE = Standard Error; CI = Confidence Interval; LSM = Least Square Means
[1] Based on ANCOVA analysis where model at each time point of each visit was fitted separately; model included treatment, site, and baseline IOP as covariates in the model

Figure 14: Difference in Mean Change in IOP – T-test (CLR_09_12)
(ITT Analysis Population, Observed Case)



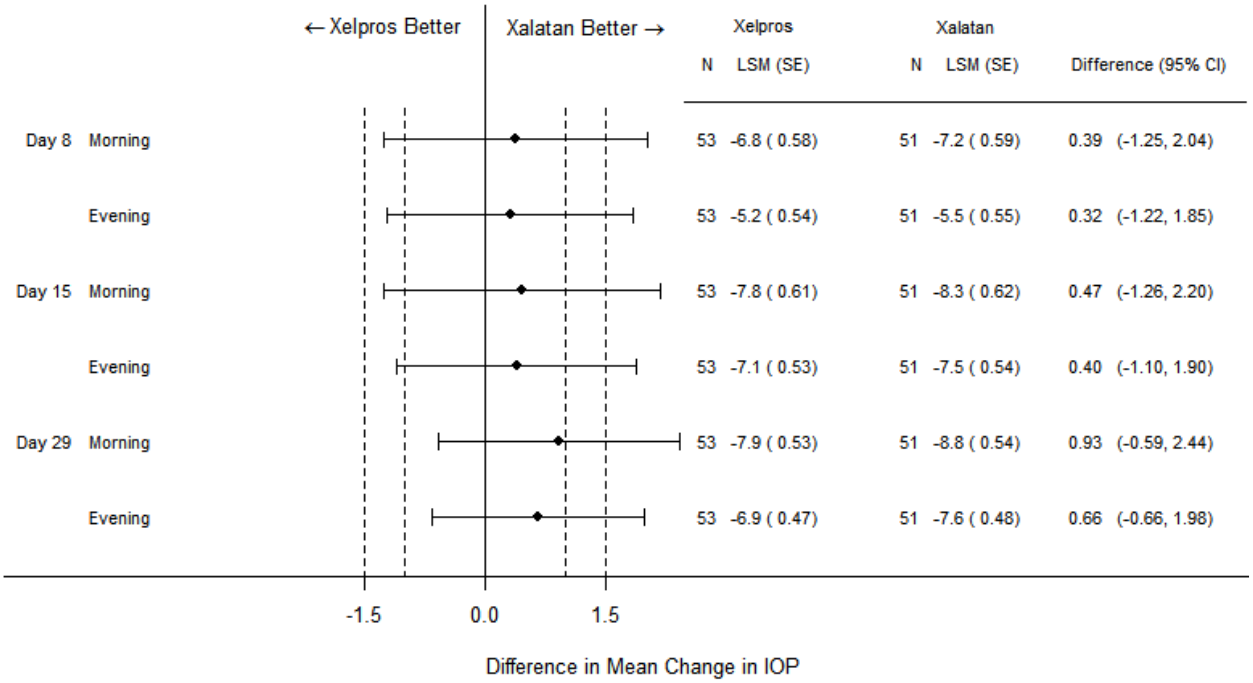
SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Based on T-test where test at each time point of each visit was performed separately

Figure 15: Difference in Mean Change in IOP – ANCOVA Using IOP Group (CLR_09_12)
(ITT Analysis Population, Observed Case)



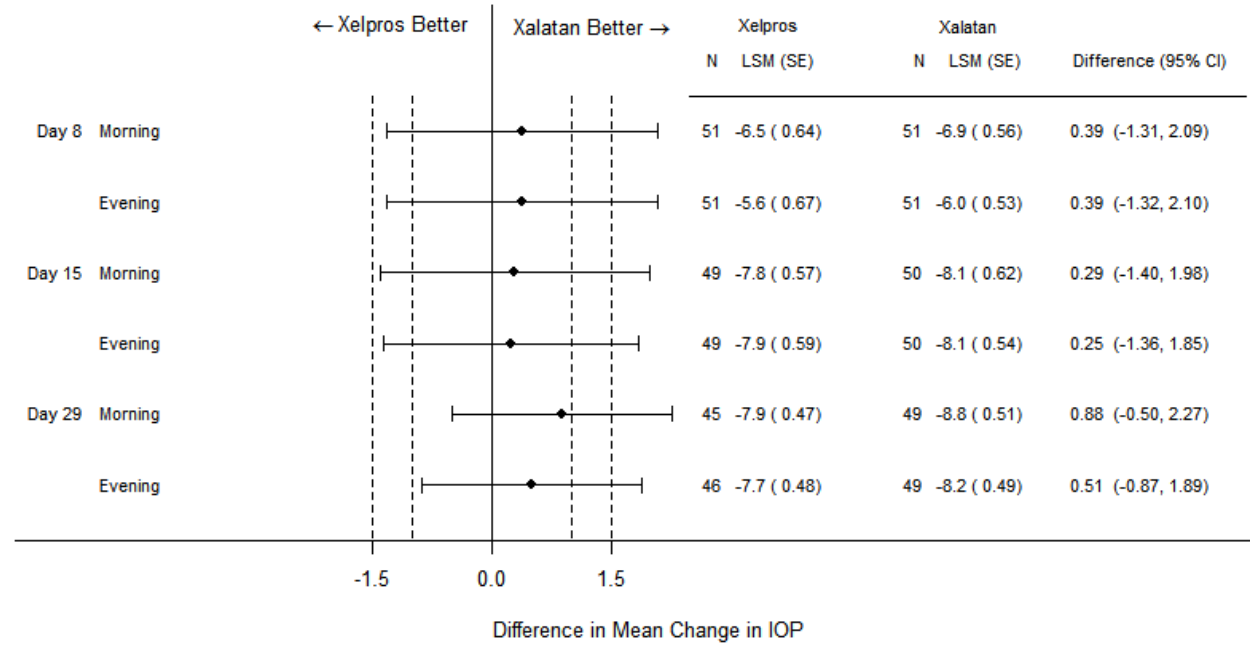
SE = Standard Error; CI = Confidence Interval; LSM = Least Square Means
[1] Based on ANCOVA analysis where model at each time point fitted separately; model included treatment, site, and IOP group as covariates in the model

Figure 16: Difference in Mean Change in IOP – ANCOVA using LOCF (CLR_01_08)
(ITT Analysis Population)



SE = Standard Error; CI = Confidence Interval; LSM = Least Square Means
[1] Based on ANCOVA analysis where model at each time point of each visit fitted separately; model included treatment and actual baseline IOP as covariates

Figure 17: Difference in Mean Change in IOP – MMRM using Baseline IOP (CLR_01_08)
(ITT Analysis Population, Observed Case)



SE= Standard Error; CI = Confidence Interval; LSM = Least Square Mean
[1] Estimates derived from MMRM model that accounted for correlated IOP measurements within patient where treatment and baseline IOP data in the model

Figure 18: Difference in Mean Change in IOP – T-test using LOCF (CLR_01_08)
(ITT Analysis Population)

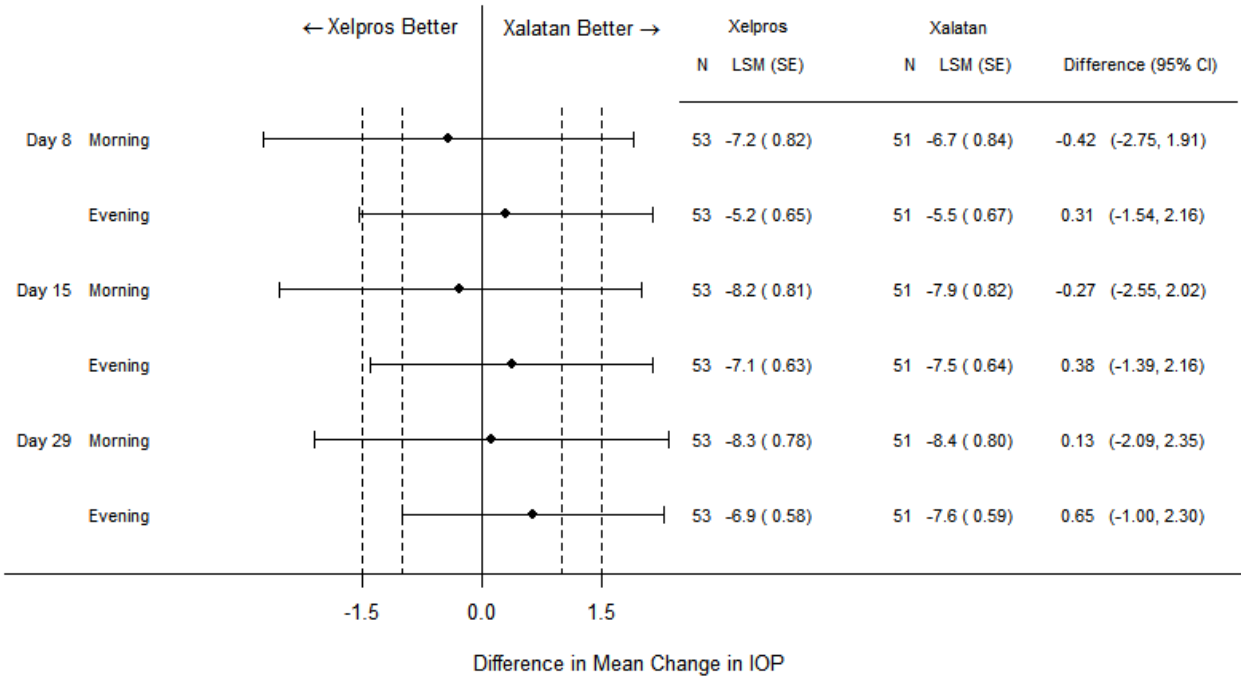


Figure 19: Difference in Mean IOP – T-test using LOCF (CLR_01_08)
(ITT Analysis Population)

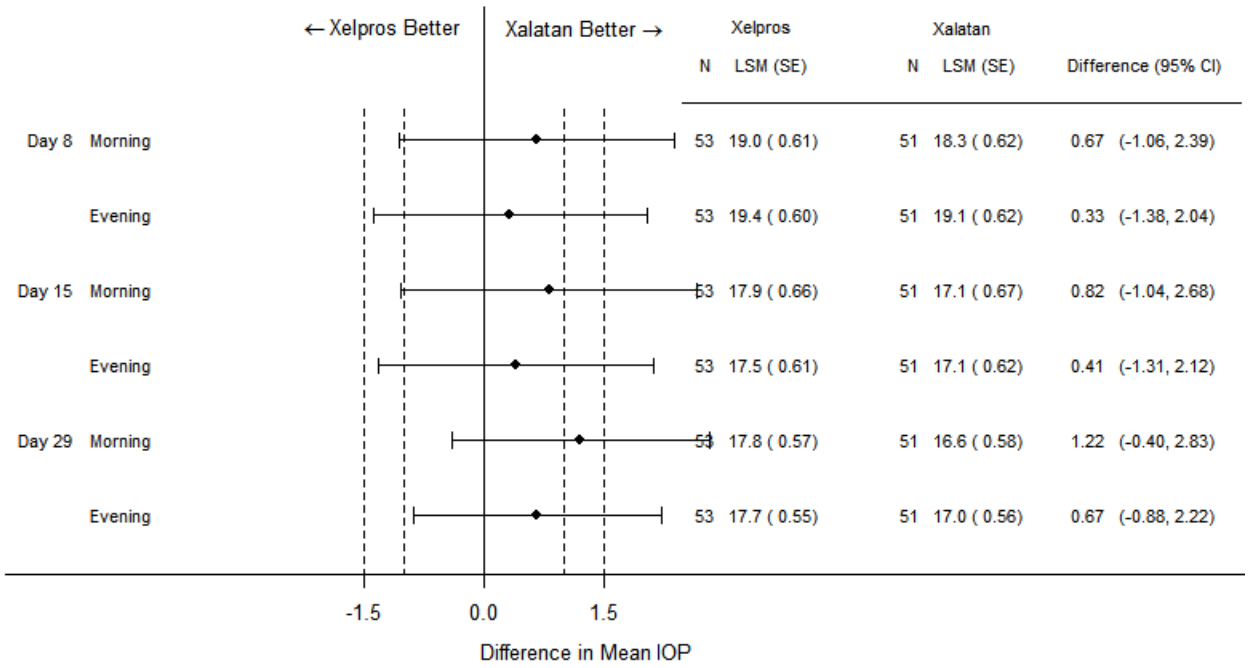


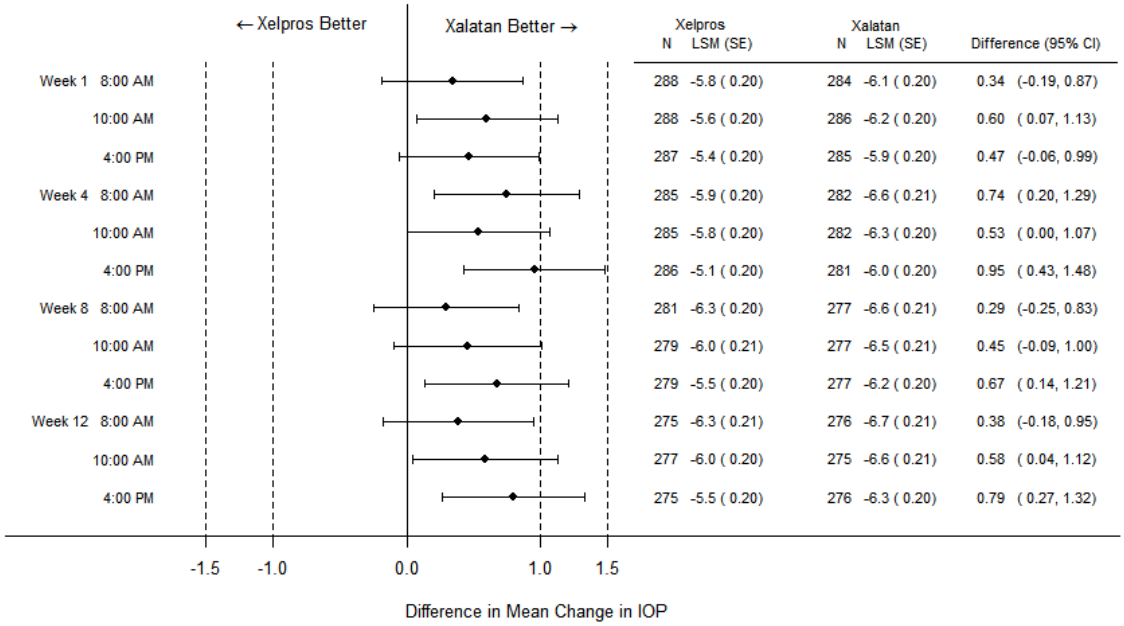
Table 12: Descriptive Summary for IOP Measures by Visit and Treatment Group (CLR_09_12)
(ITT Analysis Population)

Summary	Visit	Time Point	Xelpros			Xalatan		
			N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
Actual IOP	Baseline	8 AM	289	24.1 (3.99)	(23.7, 24.6)	288	24.1 (3.87)	(23.7, 24.6)
		10 AM	289	23.7 (4.14)	(23.2, 24.1)	289	23.6 (3.77)	(23.1, 24.0)
		4 PM	289	23.1 (3.65)	(22.7, 23.5)	289	23.2 (3.78)	(22.7, 23.6)
	Week 1	8 AM	288	18.4 (3.71)	(17.9, 18.8)	284	18.1 (3.03)	(17.7, 18.4)
		10 AM	288	18.0 (3.74)	(17.6, 18.5)	286	17.4 (2.88)	(17.0, 17.7)
		4 PM	287	17.8 (3.59)	(17.4, 18.2)	285	17.5 (2.97)	(17.2, 17.9)
	Week 4	8 AM	285	18.3 (3.71)	(17.9, 18.8)	282	17.7 (3.08)	(17.3, 18.0)
		10 AM	285	17.9 (3.42)	(17.5, 18.3)	282	17.3 (2.95)	(16.9, 17.6)
		4 PM	286	18.1 (3.34)	(17.7, 18.5)	281	17.3 (2.95)	(17.0, 17.7)
	Week 8	8 AM	281	17.9 (3.51)	(17.5, 18.3)	277	17.7 (3.20)	(17.3, 18.1)
		10 AM	279	17.6 (3.65)	(17.2, 18.1)	277	17.1 (2.92)	(16.8, 17.5)
		4 PM	279	17.7 (3.20)	(17.3, 18.0)	277	17.2 (2.97)	(16.9, 17.6)
	Week 12	8 AM	275	17.9 (3.60)	(17.5, 18.3)	276	17.5 (3.12)	(17.1, 17.9)
		10 AM	277	17.7 (3.44)	(17.3, 18.1)	275	17.0 (3.04)	(16.6, 17.4)
		4 PM	275	17.7 (3.54)	(17.2, 18.1)	276	17.0 (3.07)	(16.7, 17.4)
Change in IOP from Baseline	Week 1	8 AM	288	-5.8 (3.38)	(-6.1, -5.4)	283	-6.1 (3.59)	(-6.5, -5.7)
		10 AM	288	-5.6 (3.54)	(-6.0, -5.2)	286	-6.2 (3.51)	(-6.6, -5.8)
		4 PM	287	-5.2 (3.30)	(-5.6, -4.9)	285	-5.7 (3.59)	(-6.1, -5.3)
	Week 4	8 AM	285	-5.7 (3.52)	(-6.2, -5.3)	281	-6.5 (3.60)	(-6.9, -6.1)
		10 AM	285	-5.8 (3.61)	(-6.2, -5.4)	282	-6.3 (3.76)	(-6.7, -5.9)
		4 PM	286	-5.0 (3.44)	(-5.4, -4.6)	281	-5.9 (3.58)	(-6.3, -5.5)
	Week 8	8 AM	281	-6.2 (3.27)	(-6.6, -5.8)	276	-6.5 (3.75)	(-7.0, -6.1)
		10 AM	279	-6.0 (3.49)	(-6.4, -5.6)	277	-6.5 (3.70)	(-6.9, -6.0)
		4 PM	279	-5.4 (3.41)	(-5.8, -5.0)	277	-6.0 (3.72)	(-6.5, -5.6)
	Week 12	8 AM	275	-6.3 (3.50)	(-6.7, -5.8)	275	-6.6 (3.72)	(-7.1, -6.2)
		10 AM	277	-6.0 (3.63)	(-6.5, -5.6)	275	-6.6 (3.54)	(-7.0, -6.2)
		4 PM	275	-5.4 (3.36)	(-5.8, -5.0)	276	-6.2 (3.61)	(-6.6, -5.8)
% Change in IOP from Baseline	Week 1	8 AM	288	-23.3 (12.80)	(-24.8,-21.8)	283	-24.3 (12.70)	(-25.8,-22.8)
		10 AM	288	-23.0 (13.08)	(-24.5,-21.5)	286	-25.4 (12.17)	(-26.8,-24.0)
		4 PM	287	-22.2 (13.26)	(-23.8,-20.7)	285	-23.4 (13.00)	(-25.0,-21.9)
	Week 4	8 AM	285	-23.2 (13.24)	(-24.7,-21.6)	281	-26.0 (12.51)	(-27.4,-24.5)
		10 AM	285	-23.6 (12.94)	(-25.1,-22.0)	282	-25.6 (13.67)	(-27.2,-24.0)
		4 PM	286	-20.8 (13.03)	(-22.3,-19.3)	281	-24.4 (12.74)	(-25.9,-22.9)
	Week 8	8 AM	281	-25.1 (12.62)	(-26.6,-23.6)	276	-26.0 (13.36)	(-27.6,-24.4)
		10 AM	279	-24.7 (13.28)	(-26.3,-23.1)	277	-26.3 (13.10)	(-27.9,-24.8)
		4 PM	279	-22.5 (13.53)	(-24.1,-20.9)	277	-24.9 (13.20)	(-26.5,-23.4)
	Week 12	8 AM	275	-25.3 (12.75)	(-26.8,-23.8)	275	-26.6 (13.12)	(-28.2,-25.1)
		10 AM	277	-24.5 (13.51)	(-26.1,-22.9)	275	-27.1 (12.87)	(-28.7,-25.6)
		4 PM	275	-23.1 (13.05)	(-24.6,-21.5)	276	-25.8 (13.10)	(-27.4,-24.3)

Table 13: Descriptive Summary for IOP Measures by Visit and Treatment Group (CLR_08_01)
(ITT Analysis Population)

Summary	Visit	Time Point	Xelpros			Xalatan		
			N	Mean (SD)	(95% CI)	N	Mean (SD)	(95% CI)
Actual IOP	Baseline	Morning	53	26.1 (6.00)	(24.5, 27.8)	51	25.0 (5.48)	(23.5, 26.6)
		Evening	53	24.6 (4.67)	(23.3, 25.9)	51	24.6 (4.66)	(23.3, 25.9)
	Day 8	Morning	50	18.8 (4.66)	(17.5, 20.1)	51	18.3 (4.13)	(17.1, 19.4)
		Evening	51	19.5 (4.89)	(18.2, 20.9)	51	19.1 (3.90)	(18.0, 20.2)
	Day 15	Morning	49	17.3 (3.86)	(16.1, 18.4)	50	17.0 (4.61)	(15.7, 18.3)
		Evening	49	17.0 (3.86)	(15.9, 18.2)	50	17.0 (4.02)	(15.9, 18.2)
	Day 29	Morning	45	17.3 (3.18)	(16.4, 18.3)	48	16.4 (3.67)	(15.3, 17.4)
		Evening	46	17.4 (3.27)	(16.4, 18.3)	49	16.9 (3.60)	(15.8, 17.9)
Change in IOP from Baseline	Day 8	Morning	50	-7.6 (6.50)	(-9.4, -5.7)	51	-6.7 (5.36)	(-8.2, -5.2)
		Evening	51	-5.4 (5.18)	(-6.8, -3.9)	51	-5.5 (4.26)	(-6.7, -4.3)
	Day 15	Morning	49	-9.0 (6.39)	(-10.8, -7.1)	50	-7.9 (4.90)	(-9.3, -6.5)
		Evening	49	-7.7 (4.84)	(-9.1, -6.3)	50	-7.5 (3.94)	(-8.6, -6.4)
	Day 29	Morning	45	-9.3 (6.62)	(-11.3, -7.3)	48	-8.6 (4.32)	(-9.9, -7.4)
		Evening	46	-7.4 (4.34)	(-8.7, -6.1)	49	-7.6 (3.86)	(-8.7, -6.5)
% Change in IOP from Baseline	Day 8	Morning	50	-27.3 (15.46)	(-31.7,-22.9)	51	-25.2 (16.73)	(-29.9,-20.5)
		Evening	51	-20.3 (19.33)	(-25.7,-14.9)	51	-21.3 (13.61)	(-25.1,-17.5)
	Day 15	Morning	49	-32.3 (16.41)	(-37.0,-27.6)	50	-30.8 (16.97)	(-35.6,-26.0)
		Evening	49	-29.7 (16.07)	(-34.3,-25.1)	50	-30.2 (12.30)	(-33.7,-26.7)
	Day 29	Morning	45	-32.8 (14.81)	(-37.3,-28.4)	48	-33.5 (11.69)	(-36.9,-30.1)
		Evening	46	-28.6 (14.16)	(-32.8,-24.4)	49	-30.6 (12.36)	(-34.1,-27.0)

Figure 20: Difference in Mean Change in IOP – ANCOVA using Binary IOP Group (CLR_09_12)
(ITT Analysis Population, Observed Case)



SE = Standard Error; CI = Confidence Interval; LSM = Least Square Means
[1] Based on ANCOVA analysis where model at each time point was fitted separately; model included treatment, site, and binary IOP group as continuous variable in the model

Table 14: Treatment-Emergent AEs occurring in ≥5% of subjects by the subgroup of age (CLR_09_12)
(Safety Analysis Population)

AGEGRPN	System Organ Class/ Preferred Term	Xelpros	Xalatan	Total
Age < 65 Years	**Eye disorders**			
	Eye pain	90/136 (66.2%)	82/162 (50.6%)	172/298 (57.7%)
	Ocular hyperaemia	70/136 (51.5%)	86/162 (53.1%)	156/298 (52.3%)
	Conjunctival hyperaemia	31/136 (22.8%)	28/162 (17.3%)	59/298 (19.8%)
	Eye discharge	18/136 (13.2%)	22/162 (13.6%)	40/298 (13.4%)
	Growth of eyelashes	13/136 (9.6%)	16/162 (9.9%)	29/298 (9.7%)
	Eye pruritus	8/136 (5.9%)	8/162 (4.9%)	16/298 (5.4%)
	Eyelash thickening	8/136 (5.9%)	7/162 (4.3%)	15/298 (5.0%)
	Punctate keratitis	1/136 (0.7%)	9/162 (5.6%)	10/298 (3.4%)
Age > 65 Years	**Eye disorders**			
	Eye pain	95/153 (62.1%)	54/127 (42.5%)	149/280 (53.2%)
	Ocular hyperaemia	65/153 (42.5%)	57/127 (44.9%)	122/280 (43.6%)
	Conjunctival hyperaemia	27/153 (17.6%)	27/127 (21.3%)	54/280 (19.3%)
	Eye discharge	21/153 (13.7%)	19/127 (15.0%)	40/280 (14.3%)
	Growth of eyelashes	14/153 (9.2%)	20/127 (15.7%)	34/280 (12.1%)
	Eyelash thickening	7/153 (4.6%)	10/127 (7.9%)	17/280 (6.1%)
	Eye pruritus	8/153 (5.2%)	6/127 (4.7%)	14/280 (5.0%)
	Visual acuity reduced	8/153 (5.2%)	5/127 (3.9%)	13/280 (4.6%)

Table 15: Treatment-Emergent AEs occurring in ≥5% of subjects by the subgroup of gender (CLR_09_12)
(Safety Analysis Population)

Subgroup: Gender	System Organ Class/ Preferred Term	Xelpros	Xalatan	Total
Male	**Eye disorders**			
	Eye pain	62/101 (61.4%)	46/103 (44.7%)	108/204 (52.9%)
	Ocular hyperaemia	46/101 (45.5%)	53/103 (51.5%)	99/204 (48.5%)
	Conjunctival hyperaemia	22/101 (21.8%)	24/103 (23.3%)	46/204 (22.5%)
	Eye discharge	14/101 (13.9%)	18/103 (17.5%)	32/204 (15.7%)
	Growth of eyelashes	10/101 (9.9%)	11/103 (10.7%)	21/204 (10.3%)
	Eyelash thickening	7/101 (6.9%)	6/103 (5.8%)	13/204 (6.4%)
Female	**Eye disorders**			
	Eye pain	123/188 (65.4%)	90/186 (48.4%)	213/374 (57.0%)
	Ocular hyperaemia	89/188 (47.3%)	90/186 (48.4%)	179/374 (47.9%)
	Conjunctival hyperaemia	36/188 (19.1%)	31/186 (16.7%)	67/374 (17.9%)
	Eye discharge	25/188 (13.3%)	23/186 (12.4%)	48/374 (12.8%)
	Growth of eyelashes	17/188 (9.0%)	25/186 (13.4%)	42/374 (11.2%)
	Eye pruritus	12/188 (6.4%)	9/186 (4.8%)	21/374 (5.6%)
	Eyelash thickening	8/188 (4.3%)	11/186 (5.9%)	19/374 (5.1%)
	Erythema of eyelid	7/188 (3.7%)	10/186 (5.4%)	17/374 (4.5%)

Table 16: Treatment-Emergent AEs occurring in ≥5% of subjects by the subgroup of race (CLR_09_12)
(Safety Analysis Population)

Subgroup: Race	System Organ Class/ Preferred Term	Xelpros	Xalatan	Total
White	**Eye disorders**			
	Eye pain	126/198 (63.6%)	100/202 (49.5%)	226/400 (56.5%)
	Ocular hyperaemia	85/198 (42.9%)	105/202 (52.0%)	190/400 (47.5%)
	Conjunctival hyperaemia	48/198 (24.2%)	46/202 (22.8%)	94/400 (23.5%)
	Eye discharge	26/198 (13.1%)	30/202 (14.9%)	56/400 (14.0%)
	Growth of eyelashes	22/198 (11.1%)	30/202 (14.9%)	52/400 (13.0%)
	Eye pruritus	14/198 (7.1%)	13/202 (6.4%)	27/400 (6.8%)
	Eyelash thickening	13/198 (6.6%)	14/202 (6.9%)	27/400 (6.8%)
	Erythema of eyelid	8/198 (4.0%)	13/202 (6.4%)	21/400 (5.3%)
	Dry eye	11/198 (5.6%)	4/202 (2.0%)	15/400 (3.8%)
Black	**Eye disorders**			
	Eye pain	53/ 82 (64.6%)	32/ 79 (40.5%)	85/161 (52.8%)
	Ocular hyperaemia	43/ 82 (52.4%)	33/ 79 (41.8%)	76/161 (47.2%)
	Eye discharge	11/ 82 (13.4%)	8/ 79 (10.1%)	19/161 (11.8%)
	Conjunctival hyperaemia	7/ 82 (8.5%)	7/ 79 (8.9%)	14/161 (8.7%)
	Growth of eyelashes	4/ 82 (4.9%)	5/ 79 (6.3%)	9/161 (5.6%)
	Visual acuity reduced	5/ 82 (6.1%)	4/ 79 (5.1%)	9/161 (5.6%)
	Punctate keratitis	1/ 82 (1.2%)	5/ 79 (6.3%)	6/161 (3.7%)
Others	**Eye disorders**			
	Ocular hyperaemia	7/ 9 (77.8%)	5/ 8 (62.5%)	12/ 17 (70.6%)
	Eye pain	6/ 9 (66.7%)	4/ 8 (50.0%)	10/ 17 (58.8%)
	Conjunctival hyperaemia	3/ 9 (33.3%)	2/ 8 (25.0%)	5/ 17 (29.4%)
	Eye discharge	2/ 9 (22.2%)	3/ 8 (37.5%)	5/ 17 (29.4%)
	Eye pruritus	1/ 9 (11.1%)	1/ 8 (12.5%)	2/ 17 (11.8%)
	Eyelash thickening	1/ 9 (11.1%)	1/ 8 (12.5%)	2/ 17 (11.8%)
	Growth of eyelashes	1/ 9 (11.1%)	1/ 8 (12.5%)	2/ 17 (11.8%)
	Foreign body sensation in eyes	0	1/ 8 (12.5%)	1/ 17 (5.9%)
	Punctate keratitis	0	1/ 8 (12.5%)	1/ 17 (5.9%)
	General disorders and administration site conditions			
	Chest pain	0	1/ 8 (12.5%)	1/ 17 (5.9%)
	Vascular disorders			
	Hypertension	0	1/ 8 (12.5%)	1/ 17 (5.9%)

Table 17: Descriptive Summary for IOP Measures by Eligibility Visit IOP Group (CLR_09_12)
(ITT Analysis Population)

Summary	Visit	Time Point	IOP Group: 22 – 28 mmHg				IOP Group: 29 – 36 mmHg			
			Xelpros		Xalatan®		Xelpros		Xalatan®	
			N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Actual IOP	Baseline	8 AM	236	23.1 (3.18)	235	23.1 (3.10)	53	28.8 (3.85)	53	28.7 (3.65)
		10 AM	236	22.5 (3.13)	236	22.6 (2.97)	53	28.9 (3.99)	53	27.8 (4.02)
		4 PM	236	22.1 (2.90)	236	22.3 (3.03)	53	27.2 (3.75)	53	27.2 (4.20)
	Week 1	8 AM	235	17.6 (3.28)	232	17.7 (2.85)	53	21.5 (3.87)	52	20.0 (3.12)
		10 AM	235	17.3 (3.12)	233	17.1 (2.73)	53	21.5 (4.34)	53	18.6 (3.17)
		4 PM	234	17.1 (3.22)	232	17.2 (2.73)	53	20.8 (3.69)	53	19.0 (3.50)
	Week 4	8 AM	233	17.7 (3.33)	230	17.2 (2.90)	52	21.0 (4.12)	52	19.6 (3.13)
		10 AM	233	17.4 (3.25)	230	17.0 (2.80)	52	19.9 (3.48)	52	18.7 (3.19)
		4 PM	233	17.6 (3.04)	229	17.0 (2.76)	53	20.2 (3.84)	52	18.8 (3.33)
	Week 8	8 AM	232	17.2 (3.02)	226	17.3 (3.10)	49	21.1 (3.85)	51	19.4 (3.09)
		10 AM	230	16.9 (3.18)	226	16.7 (2.76)	49	20.9 (3.95)	51	19.0 (2.94)
		4 PM	230	17.1 (3.03)	226	16.9 (2.91)	49	20.1 (2.81)	51	18.8 (2.74)
	Week 12	8 AM	226	17.2 (3.18)	225	17.0 (2.98)	49	20.9 (3.90)	51	19.6 (2.82)
		10 AM	228	17.0 (3.00)	224	16.5 (2.80)	49	20.9 (3.56)	51	19.3 (3.07)
		4 PM	226	17.0 (3.21)	225	16.6 (2.96)	49	20.5 (3.68)	51	18.9 (2.86)
Change from Baseline in IOP	Week 1	8 AM	235	-5.4 (3.16)	231	-5.5 (3.13)	53	-7.3 (3.90)	52	-8.8 (4.21)
		10 AM	235	-5.2 (3.13)	233	-5.5 (2.93)	53	-7.5 (4.57)	53	-9.2 (4.28)
		4 PM	234	-5.0 (3.11)	232	-5.1 (3.13)	53	-6.5 (3.86)	53	-8.2 (4.33)
	Week 4	8 AM	233	-5.3 (3.29)	229	-5.9 (3.22)	52	-7.8 (3.82)	52	-9.1 (3.99)
		10 AM	233	-5.0 (3.15)	230	-5.7 (3.37)	52	-9.1 (3.70)	52	-9.1 (4.11)
		4 PM	233	-4.5 (3.11)	229	-5.3 (3.20)	53	-7.0 (4.02)	52	-8.5 (4.03)
	Week 8	8 AM	232	-5.8 (3.02)	225	-5.9 (3.35)	49	-7.9 (3.89)	51	-9.4 (4.08)
		10 AM	230	-5.5 (3.14)	226	-5.9 (3.29)	49	-8.2 (4.19)	51	-8.9 (4.40)
		4 PM	230	-5.0 (3.26)	226	-5.5 (3.32)	49	-7.2 (3.52)	51	-8.6 (4.32)
	Week 12	8 AM	226	-5.9 (3.17)	224	-6.1 (3.47)	49	-8.1 (4.31)	51	-9.0 (3.87)
		10 AM	228	-5.6 (3.25)	224	-6.2 (3.29)	49	-8.2 (4.44)	51	-8.5 (3.96)
		4 PM	226	-5.1 (3.25)	225	-5.7 (3.36)	49	-6.8 (3.50)	51	-8.4 (3.88)

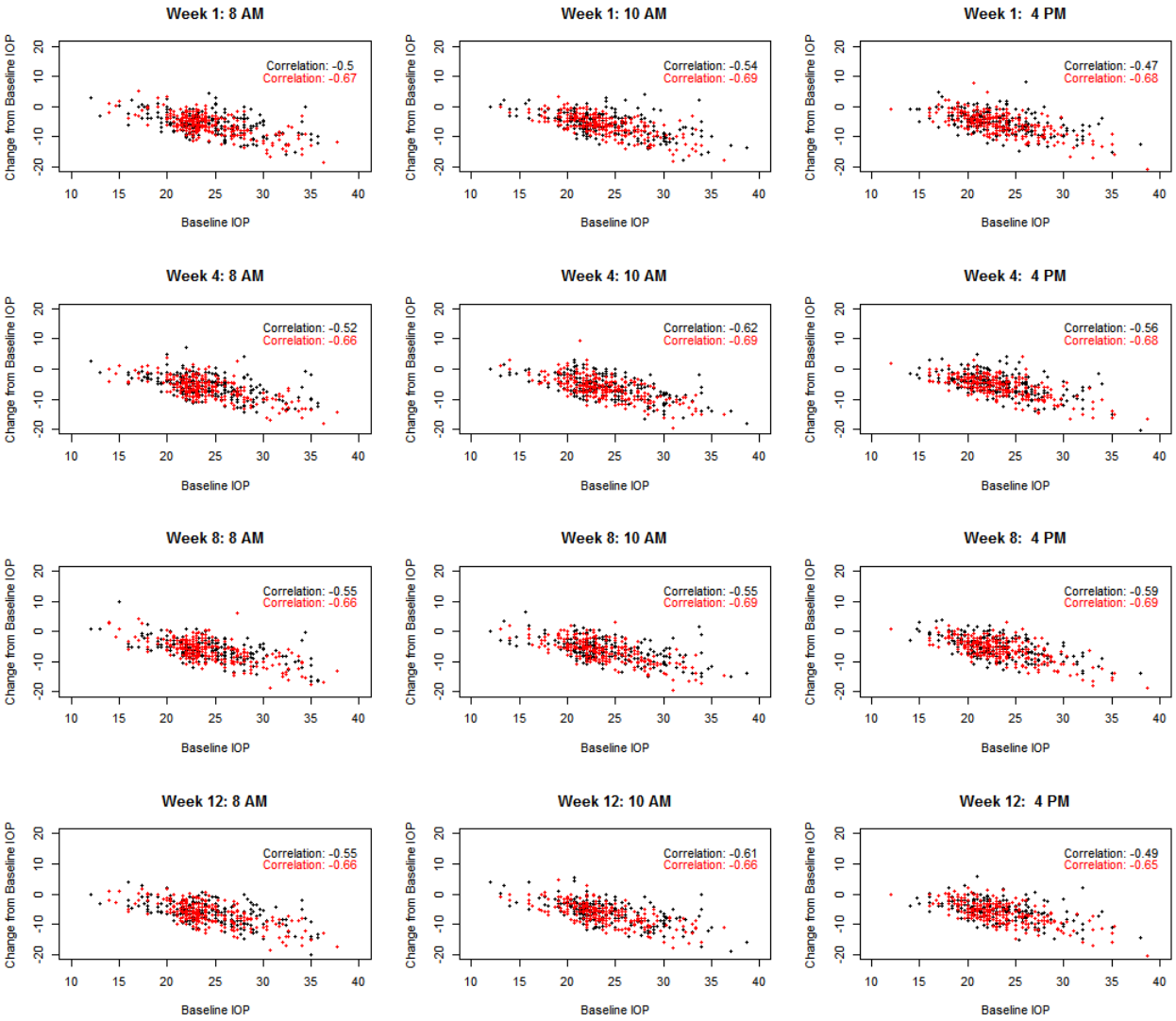
SD: Standard Deviation
Note: IOP groups were derived from the eligibility visit IOP data measured either at 10:00 AM or 4:00 PM.

Table 18: Percent IOP Reductions in the High versus Low IOP Groups (CLR_09_12)
(ITT Analysis Population)

Xelpros	**Week 1**			**Week 4**			**Week 8**			**Week 12**		
	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM
Mean Change in IOP: Low IOP Group (A)	-5.4	-5.2	-5.0	-5.3	-5.0	-4.5	-5.8	-5.5	-5.0	-5.9	-5.6	-5.1
Mean Change in IOP: High IOP Group (B)	-7.3	-7.5	-6.5	-7.8	-9.1	-7.0	-7.9	-8.2	-7.2	-8.1	-8.2	-6.8
% Reduction [1]	**35.0**	**44.3**	**30.2**	**47.3**	**80.6**	**56.5**	**34.6**	**47.9**	**44.6**	**38.5**	**48.0**	**32.7**
Xalatan ®												
Mean Change in IOP: Low IOP Group (A)	-5.5	-5.5	-5.1	-5.9	-5.7	-5.3	-5.9	-5.9	-5.5	-6.1	-6.2	-5.7
Mean Change in IOP: High IOP Group (B)	-8.8	-9.2	-8.2	-9.1	-9.1	-8.5	-9.4	-8.9	-8.6	-9.0	-8.5	-8.4
% Reduction [1]	**60.5**	**65.5**	**60.9**	**55.6**	**61.7**	**60.0**	**60.4**	**50.2**	**56.7**	**47.9**	**38.5**	**46.1**

[1] Percent IOP reductions in the high versus low IOP groups was computed as: **100*(B – A)/A**
Low IOP Group: 22-28 mmHg; High IOP Group: 29-36 mmHg

Figure 21: Scatter Plots of Baseline IOP versus Change in IOP from Baseline
(ITT Analysis Population, Observed Data)



Black and red dots respectively represent Xelpros and Xalatan® treatment groups.

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
10/14/2014

YAN WANG
10/14/2014
I concur.