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 #:	NDA215092
Drug Name:	(b) (4) (DE-117 ophthalmic solution)
Indication(s):	Reduction of Intraocular Pressure in Patients with Ocular Hypertension or Open-Angle Glaucoma
Applicant:	Santen INC.
Date(s):	Stamp date: November 21, 2020
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Keywords: Intraocular Pressure, Open-angle Glaucoma, Ocular Hypertension

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1 EXECUTIVE SUMMARY

This is a statistical review of the New Drug Application (NDA) submitted by Santen, Inc (Applicant) for DE-117 ophthalmic solution (DE-117). The proposed indication is for the reduction of intraocular pressure (IOP) in subjects with open-angle glaucoma (OAG) and ocular hypertension (OHT). The primary objective of this review is to evaluate whether the safety and efficacy results in three Phase 3 studies [01171505 (Asia), 011709IN (US) and 011710IN (US)] submitted in this NDA, support the proposed indication.

The three studies were all randomized, double-masked, active-controlled studies. The active control in Study 01171505 was latanoprost 0.005% QD. The two US based studies (011709IN and 011710IN) used timolol 0.5% BID as the active control. All three studies had a 3-month comparative treatment period. In addition, Study 011709IN included a 9-month open-label safety extension period, during which, all subjects received DE-117. Three hundred-seventy subjects in Study 01171505, 426 subjects in Study 011709IN, and 409 subjects in Study 011710IN were randomized in a 1:1 ratio to receive DE-117 or the corresponding active control. In Study 01171505, randomization was stratified by mean diurnal IOP in the study eye at baseline (<25 mmHg/≥25 mmHg) and diagnosis (OAG/OHT). Studies 011710IN and 011709IN planned to enroll pediatric subjects (<18 years of age) and accordingly, the randomizations of these 2 studies were to be stratified by age (pediatric/adult). However, although Study 011709IN enrolled few pediatric subjects (n=13), no pediatric subjects were enrolled in Study 011710IN. Consequently, randomization was stratified by age in Study 011709IN only.

For studies 011710IN and 011709IN, the primary efficacy endpoint was IOP in the study eye measured at three scheduled times of the day (08:00, 10:00, and 16:00hrs) on each of the three follow-up visits, Week 1, Week 6, and Month 3 (i.e., IOP at 9 measurement timepoints). For Study 01171505, the primary efficacy endpoint was the mean diurnal IOP (average of IOP at 3 time points: 09:00,13:00, and 17:00hrs) at Month 3. However, to meet the FDA's requirement, this study also evaluated IOP at three scheduled timepoints (09:00,13:00, and 17:00hrs) at Week 1, Week 6, and Month 3 (i.e., IOP at 9 measurement timepoints). This endpoint is consistent with primary endpoints considered for this indication where latanoprost is used as an active comparator.

Reviewer's remark: Note, timolol is given twice daily (at 08:00hrs and 20:00hrs) while DE-117 (20:00hrs) and latanoprost (21:00hrs) are given once daily. To preserve masking in studies 011709IN and 011710IN, a vehicle is given at 08:00hrs for subjects in the DE-117 arm. In addition, to match the timing of the active comparator, DE-117 is given at 21:00hrs in Study 01171505. Also note that, the IOP comparisons are made at multiple times to account for the natural fluctuation of IOP during the day and to match times of the day when the peak and trough effects of the active controls are expected. For example, based on previous data, the peak IOP lowering effect of timolol is observed 1-2 hours after treatment which corresponds to

around 10:00hrs. Similarly, the peak effect of latanoprost is observed 12 hours after treatment which corresponds to around 09:00hrs.

The primary efficacy analyses provided the least squares mean difference (DE-117 – timolol/ latanoprost) and the associated two-sided 95% confidence interval (CI) using a mixed effects model for repeated measures (MMRM). The non-inferiority of DE-117 against timolol/latanoprost was established if the upper limit of the 95% CI of the treatment difference is less than the pre-specified non-inferiority margin of 1.5 mmHg at each of the 9 timepoints (Statistical requirement) and is less than 1.0 mmHg for at least 5 of the 9 timepoints (Clinical requirement). The Applicant's findings in studies 011710IN and 01171505 established the non-inferiority of DE-117 against timolol and latanoprost, respectively. However, because the upper limit of the 95% CI is greater than 1.5 mmHg at 3 of the 9 timepoints, Study 011709IN has not established the non-inferiority of DE-117 against timolol (Figure 4-Figure 6). The Applicant also presented the analyses of the primary efficacy endpoint across various patient subgroups and analysis populations. Results from these analyses are generally consistent with the primary analysis findings.

Regarding safety, a higher incidence of ocular adverse events was reported in the DE-117 arm (23.0%) compared to the timolol arm (13.8%) and the latanoprost arm (11.9%). In addition, adverse events leading to study discontinuation accounted for 5.0% of the subjects treated with DE-117, compared to 1.9% of the subjects treated with timolol, and 1.1% treated with latanoprost. The most frequently reported adverse events in the DE-117 arm were conjunctival hyperemia (8.5%) and photophobia (5.3%). The corresponding figures in the timolol arm were 3.8% [conjunctival hyperemia], 0.5% [photophobia]. The incidence rate of these events in the latanoprost arm were 5.4% [conjunctival hyperemia] and 0.5% [photophobia]. Two deaths, one in the DE-117 arm and one in the timolol arm, were reported. In the three studies combined, serious adverse events (SAEs) were reported in a total of 13 (2.2%) subjects treated with DE-117. Of these, only three were ocular events (cystoid macular edema).

Reviewer's remark: IOP reductions were observed in all treatment arms across the three studies. In the DE-117 arm, the reduction from baseline in IOP ranged from 5.3-7.3 mm Hg. The corresponding figures for the timolol and latanoprost arms were 5.4-7.0 mm Hg and 6.1-7.9mm Hg, respectively. The DE-117 arm had higher numerical reduction from baseline in IOP at Week 1 at all the timepoints (08:00, 16:00, 20:00hrs) compared to timolol; and at one timepoint (09:00hrs) compared to latanoprost. However, the mean IOP for the DE-117 arm was numerically higher than both timolol and latanoprost at each of the six time points evaluated at Week 6 and Month 3.

Reviewer's remark: The mean IOP for the DE-117 arm appears consistent across the two timolol-controlled studies. On the other hand, the mean IOP for timolol was slightly lower in Study 0117109IN (where non-inferiority was not established) compared to the time-matched values in Study 011710IN. Specifically, the timolol arm has performed better in Study 011709IN than in Study 011710IN for the timepoints at which the non-inferiority margin is crossed, while

the DE-117 arm had comparative results in both studies for these same timepoints. For example, at 08:00hrs on Month 3, the mean IOP in the DE-117 arm is 19.7 mm Hg in Study 011709IN and 20 mm Hg in Study 011710IN, for a difference of 0.3mm Hg. Conversely, the mean IOP at the same time point for the timolol arm is 18.5 and 19.6 mmHg in Study 011709IN and Study 011710IN, respectively for a difference of 1.1 mm Hg (Table A1). Besides, the mean IOP for the DE-117 treated subjects in Study 01171505 is numerically lower (better) than the corresponding values for DE-117 treated subjects in the two-timolol controlled studies. Based on this, the reason for the failure of Study 0117109IN to meet the non-inferiority criteria could be partly attributed to the higher effect of timolol observed in this study.

Table A1: Summary of mean IOP

Time	DE-117			timolol		
	011709IN	011710IN	diff	011709IN	011710IN	diff
Week 1: 8:00	19.0	19.4	-0.4	19.1	19.7	-0.6
Week 1: 10:00	18.0	18.5	-0.5	18.2	18.9	-0.7
Week 1: 16:00	17.5	17.9	-0.4	17.9	18.6	-0.7
Week 6: 8:00*	19.8	20.4	-0.6	18.4	19.5	-1.1
Week 6: 10:00	18.9	19.5	-0.6	18.0	18.8	-0.8
Week 6: 16:00	18.5	19.2	-0.7	17.7	18.8	-1.1
Month 3: 8:00*	19.7	20.0	-0.3	18.5	19.6	-1.1
Month 3: 10:00*	18.8	19.4	-0.6	17.7	18.9	-1.2
Month 3: 16:00	18.6	19.1	-0.5	17.8	19.0	-1.2

**time points at which the non-inferiority margin is crossed.*

Reviewer's remark: Note also that, although not significant, there were some differences in the composition of subjects in the two timolol-controlled studies. For example, Study 011710IN enrolled 10% more subjects with open angel glaucoma in the DE-117 arm compared to the timolol arm. Besides, Study 011709IN enrolled 13 pediatric subjects while no pediatric subjects were enrolled in Study 011710IN.

Reviewer's remark: Alternative IOP-lowering medications (rescue medications) were provided at the discretion of the investigators in studies 011709IN and 011710IN. The studies did not outline specific rescue criteria. Rescue use was more prevalent in the DE-117 arm compared to timolol in both studies. A total of 37 subjects in the DE-117 arm received rescue medication compared to only 2 timolol treated subjects. Of the 37 subjects who received rescue medication, 26 were from Study 011709IN. Note, IOP data collected after rescue medication use was not included in the primary efficacy analysis. Also note that, the reviewer's analysis with all observed data, including data collected after rescue medication use, provided results that are consistent with the Applicant's findings.

Conclusion and Recommendations

Based on the totality of evidence, this reviewer concludes that DE-117 is effective for the reduction of IOP in subjects with OAG or OHT. However, compared to both active controls, a higher incidence of adverse events, including adverse events that led to treatment

discontinuation, were observed for subjects who received DE-117 in all the three studies. Therefore, the final regulatory decision of approval should be made based on the risk-benefit evaluation and is deferred to the Clinical review team.

2 INTRODUCTION

This is a statistical review of the NDA submitted by Santen, Inc. for DE-117. The proposed indication is for the reduction of IOP in subjects with OAG and OHT. The primary evidence for the safety and efficacy of DE-117 comes from three Phase 3 studies [01171505 (Asia), 011709IN (US) and 011710IN (US)]. The three studies were all randomized, double-masked, active-controlled studies. The active control in Study 01171505 was latanoprost 0.005% QD. The two US based studies (011709IN and 011710IN) used timolol 0.5% BID as the active control. All three studies had a 3-month comparative treatment period. In addition, Study 011709IN included a 9-month open-label safety extension period, during which, all subjects received DE-117. Three hundred-seventy subjects in Study 01171505, 426 subjects in Study 011709IN, and 409 subjects in Study 011710IN were randomized in a 1:1 ratio to receive DE-117 or the corresponding active control.

The Applicant proposes to include findings from 01171505, 011709IN and 011710IN into the "Clinical Studies" (Section 14) of the US Prescribing Information (USPI) to describe the efficacy of DE-117 in the treatment of OAG and OHT. This review investigates whether the findings from these studies support the proposed indication and provides recommendations for the USPI to be considered by the Division of Ophthalmology (DO), if the product is approved.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the Applicant's summary of the specific studies reviewed.

2.1.1 Drug Class and Indication

DE-117 is an ophthalmic solution indicated for the reduction of elevated IOP in patients with OAG and OHT.

2.1.2 History of Drug Development

The study protocols and statistical analysis plans for the development of DE-117 were reviewed under IND111518, with the first pre-IND meeting held on May 11, 2011. The Applicant had a planned End-of-Phase 2 meeting with the Agency on June 15, 2015. The primary purpose of this meeting was to obtain agreement with the Agency on the proposed clinical, nonclinical, and CMC plans to support the progression to a Phase III and the subsequent NDA. As part of the meeting questions, (b) (4) In

addition, the Applicant inquired if timolol is an appropriate comparator for the proposed indication. (b) (4) The Agency agreed with the Applicant's proposed active comparator. After receiving the preliminary comments, the Applicant cancelled the meeting.

On October 16, 2017, the Applicant had a second End-of-Phase 2 meeting with the Agency. During this meeting, the Applicant asked the Agency if one US study with timolol as an active comparator and one Asian study with latanoprost as an active comparator would be sufficient to support the filing of NDA for the proposed indication; the Agency agreed. The Agency and the Applicant also agreed on the statistical and clinical criteria to establish non-inferiority. The Agency accepted the proposed design and analysis for the Asian study. However, because different endpoints are considered for the US-FDA and other regulatory agencies for the Asian Phase 3 study, the Agency recommended the Applicant to submit a separate statistical analysis plan for the FDA.

On February 26, 2019, the Applicant had a meeting with the Agency to discuss the statistical analysis plans for the pivotal studies. As part of the discussion, the Applicant requested the Agency if the mean diurnal IOP at Month 3 could be considered as another primary endpoint along with IOP at each scheduled timepoint (08:00, 10:00, and 16:00hrs) at Week 1, Week 6, and Month 3 (as opposed to a key secondary endpoint as discussed in the protocol). The Agency stated that mean diurnal IOP at Month 3 is not considered clinically relevant (b) (4) The Applicant then requested if it would be acceptable to sequentially test the mean diurnal IOP at Month 3 and the FDA's preferred primary endpoint (IOP at each scheduled timepoints). The Agency stated that, while we have no objection to the sequential testing, we recommend that the protocol explicitly state that the primary endpoint to be used in the US will differ from the primary used for other regions of the world. The Agency agreed to the proposed mixed model for repeated measures (MMRM) approach for the primary efficacy analysis and the sensitivity analyses based on a multiple imputation and a tipping point analysis.

On July 12, 2019, the Applicant had a pre-NDA meeting with the Agency. During this meeting, the Applicant requested if data from the two US studies could be pooled for the integrated summary of efficacy (ISE). The Agency stated that the efficacy summaries and data for all studies involving the study drug separately in addition to the ISE need to be submitted for review to support the non-inferiority claim. Agreement was reached on the format and content of the NDA package. The Agency also agreed to the Applicant's proposal to only include data from the three Phase 3 studies in the integrated summary of safety (ISS).

On June 10, 2020, the Applicant had a second pre-NDA meeting with the Agency. In response to the Applicant's request whether the results of the three pivotal Phase 3 studies (01171505, 011709IN and 011710IN) support the proposed indication, the Agency stated that the studies intended to support the NDA appeared to be adequate and well-controlled and that the data

package would most likely be fileable, but determination of approvability would be based on the review of the complete submission.

2.1.3 Studies Reviewed

In this NDA, data from three Phase 3 studies (01171505, 011709IN and 011710IN) were included to support the safety and efficacy of DE-117 in reduction of IOP in patients with OAG or OHT. The summaries of these studies, as presented in the Applicant's study reports, are given in Table 1.

Table 1: Summary Primary Efficacy Endpoint

Design	Treatment (Sample Size)	Endpoints/Analysis	Applicant's findings[2]
011709IN [1]MC, RD, DM, PG, AC	o DE-117 (N=212) o Timolol (N=213)	**Primary Endpoint**: IOP at 9 timepoints, i.e., at 08:00, 10:00, and 16:00 at Week 1, Week 6, and Month 3. The primary efficacy analysis provided the least squares mean difference between the DE-117 group and the Timolol group and its two-sided 95% CI at each of the 9 timepoints using a MMRM. The primary efficacy analysis was conducted based on the full analysis set (FAS) which included all randomized subjects who received at least one dose of study medication and provided baseline IOP data (at any timepoint) and at least one post-baseline IOP measurement (at any timepoint).	The study **did not meet** its primary objective of demonstrating the non-inferiority of DE-117 against Timolol. The upper limit of the 95% confidence interval for the treatment difference was greater than the non-inferiority margin of 1.5mmHg for 3 of the 9 timepoints (Statistical requirement).
011710IN [1]MC, RD, DM, PG, AC	o DE-117 (N=204) o Timolol (N=205)	**Primary Endpoint**: IOP at 9 timepoints, i.e., at 08:00, 10:00, and 16:00 at Week 1, Week 6, and Month 3. The primary efficacy analysis provided the least squares mean difference between the DE-117 group and the Timolol group and its two-sided 95% CI at each of the 9 timepoints using an MMRM. The primary efficacy analysis was conducted based on the full analysis set (FAS) which included all randomized subjects who received at least one dose of study medication and provided baseline IOP data (at any timepoint) and at least one post-baseline IOP measurement (at any timepoint).	The study **met** its primary objective of demonstrating the non-inferiority of DE-117 against Timolol. The upper limit of the 95% confidence interval for the treatment difference was less than the non-inferiority margin of 1.5mmHg for all 9 timepoints (Statistical requirement); and less than 1mmHg for the majority of time points (Clinical requirement).

011705[3] [1]MC, RD, DM, PG, AC	o DE-117 (N=184) o Latanoprost (N=185)	**Primary Endpoint**: Mean diurnal IOP at Month 3 (average of IOP at 3 time points: 09:00, 13:00, and 17:00) **Key Secondary**: IOP at 9 timepoints, i.e., at 09:00, 13:00, and 17:00 at Week 1, Week 6, and Month 3. The primary efficacy analysis provided the least squares mean difference between the DE-117 group and the latanoprost group and its two-sided 95% CI using a MMRM. The primary efficacy analysis was conducted based on the full analysis set (FAS) which included all subjects who received at least 1 dose of study medication and provided at least 1 post-baseline IOP measurement.	The study **met** its primary objective of demonstrating the non-inferiority of DE-117 against latanoprost. The upper limit of the 95% confidence interval for the treatment difference in mean diurnal IOP was less than the non-inferiority margin of 1.5mmHg. Note that, the Applicant evaluated IOP at 9 timepoints (09:00, 13:00, and 17:00 at Week1, Week6 and Month 3) as a key secondary efficacy endpoint in this study. This study demonstrated the non-inferiority of DE-117 to latanoprost with respect to this endpoint as well.

[1]MC: multicenter, RD: randomized, DM: double-masked, PG: parallel-group, AC: active-controlled. MMRM: mixed model for repeated measures. [2]See Statistical methods section for missing data and analysis methods. [3]FDA does not accept the mean diurnal IOP at month 3 as a primary efficacy endpoint.

2.2 Data Sources

This NDA was submitted electronically and includes full study reports as well as standardized datasets using SDTM and ADaM formats that are relevant for the analyses of studies 01171505, 011709IN and 011710IN presented in this review. Datasets and corresponding definition files can be found at the following location: \\cdsesub1\evsprod\NDA215092\0001\m5\datasets.

For each study, the following datasets submitted by the Applicant are used in this statistical review:

- adsl.xpt contains the demographic and disposition data
- adeff.xpt contains the IOP efficacy data
- adae.xpt contains the adverse event data

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the datasets and analyses conducted by the Applicant are acceptable. The data definition files, and reviewer's guide submitted in this NDA were sufficiently detailed to facilitate replication of the findings from the Applicant's primary analysis and other major analyses using the submitted datasets.

3.2 Evaluation of Efficacy

This section summarizes the design of studies 01171505, 011709IN and 011710IN and the corresponding efficacy results submitted by the Applicant and produced by the reviewer's analyses.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

The three studies were all multicenter, double-masked, randomized, parallel-group, active-controlled, non-inferiority studies. The primary objective of these studies was to evaluate the safety and efficacy of DE-117 compared with timolol 0.5% BID (011709IN and 011710IN) or with latanoprost 0.005% QD (01171505) in subjects with OAG and OHT. To be eligible for these studies, patients had to meet the following ocular inclusion criteria:

- Must have a diagnosis of OAG (including Pigmentary Glaucoma or Pseudoexfoliative Glaucoma) or OHT in both eyes, or one eye with OAG and the other with OHT.
- Best corrected visual acuity (BCVA) 20/80 or better in each eye.
- Central corneal thickness ≥480 µm and ≤ 600 µm in each eye.
- Anterior chamber angle grade ≥2 (Shaffer scale) in each eye.
- IOP between 22 and 34 mmHg at all measurements (08:00, 10:00 and 16:00) at baseline (Day 1).

3.2.1.2 Randomization and Treatment

All the three studies used a 1:1 randomization ratio for allocating eligible patients to DE-117 and the corresponding active control:

- DE-117: One drop of DE-117 0.002% at 20:00 for three months**
- Timolol: One drop of Timolol maleate 0.5% twice daily (at 8:00 and 20:00) for three months
- Latanoprost: One drop of Latanoprost ophthalmic solution 0.005% at 21:00 for three months

*** To preserve masking of the study treatment, in studies 011709IN and 011710IN, a vehicle is given at 08:00 for subjects in the DE-117 arm. In addition, to match the timing of the active comparator, DE-117 is given at 21:00 in Study 01171505.*

The total duration of the double-masked treatment period in all the three studies is 3 months. However, Study 011709IN includes a 9-month safety extension open-label period. During this period, all subjects were to receive DE-117 regardless of their initial randomized treatment. The studies had scheduled visits at Screening, Baseline (Day 1), Week 6, and Month 3.

Randomization in Study 01171505 was stratified by mean diurnal IOP in the study eye at baseline (<25 mmHg/≥25 mmHg) and diagnosis (OAG/OHT). Studies 011709IN and 011710IN planned to enroll pediatric subjects (<18 years of age) and accordingly, the randomizations of these 2 studies were to be stratified by age (pediatric/adult). However, although Study 011709IN enrolled few pediatric subjects (n=13), no pediatric subjects were enrolled in Study 011710IN. Consequently, the randomization was stratified by age in Study 011709IN only.

Figure 1: Study Design Schema (011709IN)

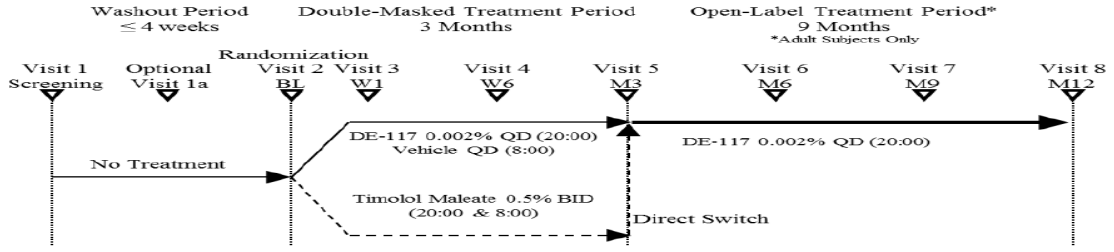


Figure 2: Study Design Schema (011710IN)

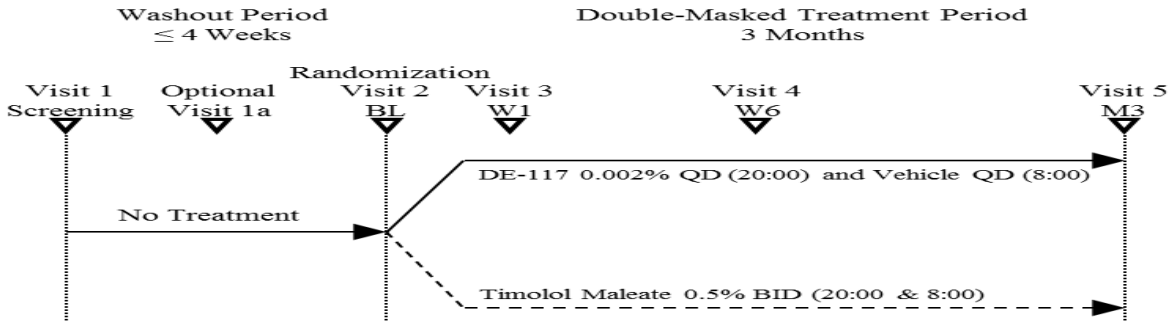
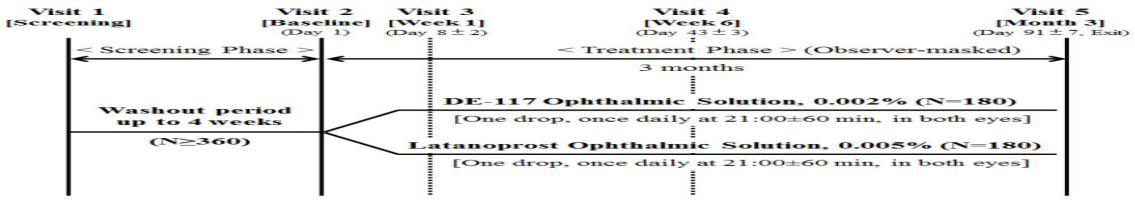


Figure 3: Study Design Schema (01171505)



3.2.1.3 Efficacy Endpoints

For studies 011709IN and 011710IN, the primary efficacy endpoint was IOP in the study eye at each scheduled timepoint (08:00, 10:00, and 16:00hrs) at each of the three follow-up visits, Week 1, Week 6, and Month 3 (i.e., IOP at 9 measurement timepoints). For study 01171505, the primary efficacy endpoint was the mean diurnal IOP (average of IOP at 3 time points: 09:00,13:00, and 17:00hrs) at Month 3. However, to meet the FDA's requirement, this study evaluated IOP at three scheduled timepoints (09:00,13:00, and 17:00hrs) at Week 1, Week 6, and Month 3 (i.e., IOP at 9 measurement timepoints) as an alpha-adjusted key-secondary efficacy endpoint. This endpoint is consistent with primary efficacy endpoints considered for this indication in previous submissions where latanoprost is used as an active comparator.

3.2.2 Statistical Methods

This section describes the statistical hypotheses, sample size calculation, analyses populations and the efficacy analyses presented in this review that are performed by the Applicant, as described in the statistical analysis plans (SAPs) for studies 011710IN, 011709IN and 01171505, as well as independent analyses performed by the statistical reviewer. All statistical analyses are performed at the 0.05 significance level (two-sided).

3.2.2.1 Statistical Hypotheses and Sample size

Hypotheses Testing

A conclusion that DE-117 is non-inferior to timolol/latanoprost is made if the upper bound for the 2-sided 95% confidence interval (CI) for the difference in means is less than the pre-specified non-inferiority margin, 1.5, for all time points (Statistical criteria) and is less than 1.0 for at least 5 of the 9 time points (Clinical criteria). Therefore, the primary null and alternative hypotheses for the statistical criteria can be mathematically stated as follows:

$$H_{o1}: \mu_D - \mu_T > 1.5: \text{for at least one time point}$$
$$H_a: \mu_D - \mu_T \leq 1.5: \text{at all nine time points}$$

where μ_D, μ_T, are the mean IOP values for the DE-117 and timolol/latanoprost arms respectively.

In studies 011710IN and 011709IN, if the non-inferiority criteria for the primary endpoint of mean IOP at each of the 9 time points is met, additional comparisons to timolol were to be made with respect to secondary efficacy endpoints. To control the overall Type I error at the 0.05 level (two-sided), a hypothesis test in the pre-specified sequence (see below) could only be performed if the testing for each of the tests prior to it in the sequence had resulted in rejection of the null hypothesis:

1. Mean diurnal IOP at Month 3 (non-inferiority).

2. IOP at each scheduled timepoint (08:00, 10:00, and 16:00) at Week 1, Week 6, and Month 3 in the study eyes with mean diurnal IOP < 25 mmHg at the Baseline visit (non-inferiority).

3. Mean diurnal IOP at Week 1 (Superiority).

4. Mean diurnal IOP at Month 3 (Superiority).

5. IOP at each scheduled timepoint (08:00, 10:00, and 16:00) at Week 1, Week 6, and Month 3 in the study eyes with mean diurnal IOP < 25 mmHg at the Baseline visit (Superiority).

6. IOP at each scheduled timepoint (08:00, 10:00, and 16:00) at Week 1, Week 6, and Month 3 (Superiority).

As stated earlier, for study 01171505, the primary efficacy endpoint was the mean diurnal IOP (average of IOP at 3 time points: 09:00,13:00, and 17:00hrs) at Month 3. Therefore, the FDA required endpoint, IOP at three scheduled timepoints (09:00,13:00, and 17:00hrs) at Week 1, Week 6 and Month 3 (i.e., IOP at 9 measurement timepoints) will only be evaluated if the non-inferiority of DE-117 against latanoprost with respect to mean diurnal IOP at Month 3 is established. Following, the test of non-inferiority based on the FDA required endpoint, the study planned to evaluate the superiority of DE-117 against latanoprost with respect to mean diurnal IOP at Month 3.

Sample Size Calculation

Studies 011710IN and 011709IN planned to enroll approximately 200 subjects in each treatment arm. This sample size calculation assumed a 90% power, a non-inferiority margin of 1.5mmHg; a treatment difference of 0 mmHg, a standard deviation of 4.0 mm Hg and a correlation coefficient of 0.6 among the repeated IOP measures. For Study 01171505, a sample size of 360 subjects (180 per arm) was planned assuming a treatment difference of 0 mmHg, a standard deviation of 4.0 mmHg, a 90% power and a dropout rate of 16%. Because the sample size calculation for this study was made based on the mean diurnal at Month 3, the correlation among the repeated IOP measures was not taken into consideration.

Reviewer's remark: Studies 011709IN, 011710IN and 01171505 ended up enrolling 426, 417 and 370 subjects, respectively.

3.2.2.2 Analysis Populations

The following analysis populations are defined in the SAP:

- The safety population: Includes all treated subjects (subjects who received at least one dose of the study medications).

- The intent-to-treat (ITT): Includes all randomized subjects.

- The full analysis population (FAS): All randomized subjects who received at least one dose of study medication and provided at least one baseline and one post-baseline IOP measurement.

- The per-protocol (PP): Includes a subset of FAS who do not have protocol deviations that could impact the primary efficacy variable.

The primary efficacy analysis in all the three studies was conducted based on the FAS population.

3.2.2.3 Analysis Methods

A. Primary Efficacy analysis

The FDA required primary efficacy analyses in all the three studies provided the treatment difference in the mean IOP at each of the 9 time points and the corresponding 2-sided 95% confidence interval using a mixed effects model for repeated measure (MMRM). The model was fitted for each time of the day separately, and included time-matched baseline IOP, treatment, visit (Week 1, 6 and Month 3) and treatment by visits interaction. The within-subject correlation was captured via an unstructured covariance matrix. Missing IOP data was assumed to follow the missing at random (MAR) mechanism and was not explicitly imputed.

B. Sensitivity Analysis of the Primary Efficacy Endpoint

To assess the sensitivity to departure from the MAR assumption, based on which the MMRM approach is valid, the Applicant used a pattern-mixture model (PMM) with delta-adjustment. In this approach, first, all missing data is imputed using a multiple imputation approach under the MAR assumption. Second, for subjects who had missing data because they discontinued the study due to adverse events or lack of efficacy and those who received rescue medication prior to the evaluation of the efficacy outcome, the imputed IOP values were shifted by a magnitude of 1 to 5. Missing data due to other reasons is still assumed MAR and hence no shift is added. The

analysis of the imputed data for each shift parameter was conducted using the MMRM approach used for the primary efficacy analysis.

C. Analysis of Key Secondary Efficacy Endpoints

The analyses of the key secondary efficacy endpoints were conducted using the MMRM approach that was used for the analysis of the primary efficacy endpoint.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Demographic and Baseline Characteristics

Within each study, no significant baseline imbalances between the two arms in the demographics of age, gender, race or ethnicity or iris color is observed. Most subjects in all the three studies, with nearly all subjects in Study 01171505, have brown iris color.

There were however differences in the composition of study participants across the three studies. For example, studies 011709IN and 011710IN enrolled more female subjects than male, whereas the proportion of female subjects was lower than male in Study 01171505. Studies 011709IN and 011710IN enrolled very few Asian subjects while Study 01171505 was conducted exclusively in Asia. Over half of the study participants in Studies 011709IN and 011710IN were 65 years or older while only 22-25% of study participants in Study 01171505 were 65 years or older. Consequently, the average age of the patient population was lower in Study 01171505 compared the two US based studies. Note, Studies 011709IN and 011710IN planned to enroll pediatric subjects. However, only Study 011709IN enrolled 13 pediatric subjects.

Table 2: Demographic Characteristics (Full Analysis Set)

	Study 011709IN		**Study 011710IN**		**Study 01171505**	
	DE-117 (N=212)	**Timolol (N=213)**	**DE-117 (N=204)**	**Timolol (N=205)**	**DE-117 (N=184)**	**LAT (N=185)**
Age						
Mean (SD)	64.7 (14.91)	63.5 (14.48)	64.0 (11.43)	64.8 (11.56)	54.6 (12.9)	52.6 (13.1)
Median	68.0	65.0	65.5	66.0	55.0	53.0
Min, Max	12, 93	13, 90	21, 82	23, 91	19, 82	19, 82
Age Group (year)						
< 18	6 (2.8%)	7 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 18 and < 65	83 (39.2%)	91 (42.7%)	89 (43.6%)	87 (42.4%)	137 (74.5%)	143 (77.3%)
≥ 65	123 (58.0%)	115 (54.0%)	115 (56.4%)	118 (57.6%)	47 (25.5%)	42 (22.7%)
Sex						
Male	89 (42.0%)	78 (36.6%)	83 (40.7%)	96 (46.8%)	106 (57.6%)	88 (47.6%)
Female	123 (58.0%)	135 (63.4%)	121 (59.3%)	109 (53.2%)	78 (42.4%)	97 (52.4%)
Race						
American Indian or Alaska Native	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	2 (0.9%)	8 (3.9%)	8 (3.9%)	184 (100%)	185 (100%)
Black or African American	48 (22.6%)	52 (24.4%)	72 (35.3%)	54 (26.3%)	0 (0.0%)	0 (0.0%)

Native Hawaiian or Other Pacific Islander	2 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
White	160 (75.5%)	155 (72.8%)	122 (59.8%)	140 (68.3%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple	2 (0.9%)	3 (1.4%)	2 (1.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Ethnicity						
Hispanic or Latino	45 (21.2%)	42 (19.7%)	13 (6.4%)	22 (10.7%)		
Not Hispanic or Latino	167 (78.8%)	171 (80.3%)	190 (93.1%)	183 (89.3%)		
Unknown	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)		
Iris color						
Brown	123 (58.0%)	133 (62.4%)	125 (61.3%)	124 (60.5%)	181 (98.4%)	183 (98.9%)
Yellow brown	2 (0.9%)	3 (1.4%)	9 (4.4%)	3 (1.5%)	0 (0.0%)	1 (0.5%)
Green brown	10 (4.7%)	7 (3.3%)	8 (3.9%)	8 (3.9%)	0 (0.0%)	0 (0.0%)
Green with slightly brown	11 (5.2%)	14 6.6%)	6 (2.9%)	10 (4.9%)	0 (0.0%)	0 (0.0%)
Green	3 (1.4%)	4 (1.9%)	1 (0.5%)	6 (2.9%)	0 (0.0%)	1 (0.5%)
Blue/gray brown	5 (2.4%)	3 (1.4%)	5 (2.5%)	5 (2.4%)	0 (0.0%)	0 (0.0%)
Blue/gray with slightly brown	16 (7.5%)	19 (8.9%)	15 (7.4%)	17 (8.3%)	0 (0.0%)	0 (0.0%)
Blue/gray	42 (19.8%)	30 (14.1%)	35 (17.2%)	32 (15.6%)	3 (1.6%)	0 (0.0%)

Source: Table 13 (Study 011709IN) and Table 12 (Study 011710IN) and Table 6 (01171505) of the study reports

The summary of selected baseline and disease characteristics is presented in Table 3 (Studies 011709IN and 011710IN) and Table 4 (Study 01171505). In all the three studies, the majority of subjects had OAG. Study 011710IN enrolled 10% more subjects with OAG in the DE-117 arm compared to the timolol arm. In Studies 011709IN and 011710IN, the proportion of subjects who used prior IOP lowering medications ranged between 63-66% in both arms. The corresponding figure for Study 01171505 was between 47-59%.

Table 3: Baseline and Disease Characteristics (Full analysis Set: Study 011709IN and Study 011710IN)

	Study 011709IN		**Study 011710IN**	
	DE-117 (N=212)	**Timolol (N=213)**	**DE-117 (N=204)**	**Timolol (N=205)**
Primary Diagnosis				
Primary Open-angle Glaucoma	148 (71.8%)	142 (68.9%)	139 (68.1%)	120 (58.5%)
Pseudoexfoliative Glaucoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Pigmentary Glaucoma	2 (1.0%)	1 (0.5%)	3 (1.5%)	3 (1.5%)
Ocular Hypertension	56 (27.2%)	63 (30.6%)	62 (30.4%)	80 (39.0%)
Juvenile Open Angle Glaucoma*	6 (100%)	7 (100%)	N/A	N/A
Prior Use of IOP-Lowering Medication(s)				
Oral/topical Carbonic Anhydrase Inhibitors (CAIs)	22 (10.4%)	14 (6.6%)	29 (14.2%)	31 (15.1%)
Alpha agonists	6 (2.8%)	14 (6.6%)	11 (5.4%)	13 (6.3%)
Beta-Blockers	30 (14.2%)	23 (10.8%)	30 (14.7%)	25 (12.2%)

PG/PG Analogues	112 (52.8%)	122 (57.3%)	102 (50.0%)	97 (47.3%)
Rho kinase inhibitor	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
None	73 (34.4%)	72 (33.8%)	73 (35.8%)	76 (37.1%)
Prostaglandin Naive				
Yes	56 (26.4%)	53 (24.9%)	58 (28.4%)	58 (28.3%)
No	156 (73.6%)	160 (75.1%)	146 (71.6%)	147 (71.7%)
Lens Status				
Phakic	159 (75.0%)	179 (84.0%)	178 (87.3%)	172 (83.9%)
Pseudophakic	53 (25.0%)	34 (16.0%)	26 (12.7%)	33 (16.1%)
Mean Diurnal IOP (mmHg)				
Mean (SD)	24.7 (2.12)	24.8 (2.12)	25.2 (2.31)	24.8 (2.17)
Median	24.2	24.2	24.7	24.3
Min, Max	21, 33	22, 34	22, 33	22, 34
IOP at 8:00 (mmHg)				
Mean (SD)	25.3 (2.75)	25.5 (2.75)	25.9 (2.93)	25.5 (2.69)
Median	24.5	25.0	25.0	25.0
Min, Max	22, 34	22, 34	22, 34	22, 34
IOP at 10:00 (mmHg)				
Mean (SD)	24.7 (2.42)	24.6 (2.36)	25.0 (2.66)	24.8 (2.45)
Median	24.0	24.0	24.0	24.0
Min, Max	21, 34	22, 34	22, 33	22, 34
IOP at 16:00 (mmHg)				
Mean (SD)	24.2 (2.08)	24.4 (2.31)	24.7 (2.52)	24.2 (2.23)
Median	24.0	24.0	24.0	23.5
Min, Max	21, 32	22, 34	22, 34	22, 34
BCVA (Log MAR)				
Mean (SD)	0.060 (0.118)	0.047 (0.1125)	0.052 (0.116)	0.06 (0.118)
Median	0.020	0.020	0.040	0.040
Min, Max	-0.26, 0.56	-0.24, 0.42	-0.30, 0.50	-0.24, 0.50
Central Corneal Thickness (µm)				
Mean (SD)	552.24 (29.29)	555.53 (31.423)	552.12 (29.672)	552.94 (28.14)
Median	554.00	558.00	555.00	558.00
Min, Max	486.0, 600.0	482.0, 600.0	480.0, 600.0	482.0, 599.0
Glaucomatous Optic Nerve Findings				
None	125 (59.0%)	129 (60.6%)	132 (64.7%)	131 (63.9%)
Mild	73 (34.4%)	68 (31.9%)	46 (22.5%)	51 (24.9%)
Moderate	12 (5.7%)	16 (7.5%)	26 (12.7%)	23 (11.2%)
Severe	2 (0.9%)	0 (0.0%)	132 (64.7%)	131 (63.9%)

Anterior Chamber Angle Classification (Shaffer Scale)				
20 degrees	9 (4.3%)	18 (8.5%)	8 (3.9%)	6 (2.9%)
30 degrees	71 (34.0%)	77 (36.3%)	80 (39.2%)	66 (32.2%)
40 degrees or more	129 (61.7%)	117 (55.2%)	116 (56.9%)	133 (64.9%)

Source: Table 13 of the study reports

Table 4: Baseline and Disease Characteristics (Full analysis Set: Study 01171505)

	DE-117 (N=184)	**Latanoprost (N=185)**	**Overall (N=369)**
Primary Diagnosis			
Open Angle Glaucoma	125 (67.9%)	122 (65.9%)	247 (66.9%)
Primary Open Angle Glaucoma	120 (65.2%)	118 (63.8%)	238 (64.5%)
Exfoliation Glaucoma	2 (1.1%)	4 (2.2%)	6 (1.6%)
Pigmentary Glaucoma	3 (1.6%)	0	3 (0.8%)
Ocular Hypertension	59 (32.1%)	63 (34.1%)	122 (33.1%)
Prior Use of IOP-Lowering Medication(s)			
None	76 (41.3%)	97 (52.4%)	173 (46.9%)
Beta-adrenergic antagonist	38 (20.7%)	32 (17.3%)	70 (19.0%)
Prostamides or prostaglandin analogues	41 (22.3%)	29 (15.7%)	70 (19.0%)
Alpha-adrenergic agonist	14 (7.6%)	6 (3.2%)	20 (5.4%)
Carbonic anhydrase inhibitors	64 (34.8%)	55 (29.7%)	119 (32.2%)
Miotic agent	1 (0.5%)	1 (0.5%)	2 (0.5%)
Other	3 (1.6%)	0	3 (0.8%)
Lens Status			
Phakic	159 (86.4%)	173 (93.5%)	332 (90.0%)
Pseudophakic	25 (13.6%)	12 (6.5%)	37 (10.0%)
Mean Diurnal IOP (mmHg)			
Mean (SD)	24.6 (2.29)	24.5 (2.06)	24.5 (2.18)
Median	24.0	24.0	24.0
Min, Max	22, 34	22, 31	22, 34
IOP at 09:00 (mmHg)			
Mean (SD)	24.9 (2.56)	24.7 (2.37)	24.8 (2.46)
Median	24.0	24.0	24.0
Min, Max	22, 34	22, 33	22, 34
IOP at 13:00 (mmHg)			
Mean (SD)	24.5 (2.40)	24.5 (2.27)	24.5 (2.33)
Median	24.0	24.0	24.0
Min, Max	22, 34	22, 33	22, 34
IOP at 17:00 (mmHg)			
Mean (SD)	24.3 (2.46)	24.3 (2.21)	24.3 (2.34)
Median	24.0	24.0	24.0
Min, Max	21, 34	22, 32	21, 34
Central Corneal Thickness (um)			

Mean (SD)	546.8 (29.4)	540.2 (31.4)	543.5 (30.6)
Median	547.5	540.0	545.0
Min, Max	482, 600	480, 600	480, 600
Degree of Angle Closure (Shaffer Scale)			
Grade 2	12 (6.5%)	14 (7.6%)	26 (7.0%)
Grade 3	76 (41.3%)	76 (41.1%)	152 (41.2%)
Grade 4	96 (52.2%)	95 (51.4%)	191 (51.8%)
Glaucomatous Visual Field Loss			
No	79 (42.9%)	83 (44.9%)	162 (43.9%)
Yes	104 (56.5%)	101 (54.6%)	205 (55.6%)
Missing	1 (0.5%)	1 (0.5%)	2 (0.5%)
Glaucomatous Findings in Fundus			
None	59 (32.1%)	59 (31.9%)	118 (32.0%)
Mild	68 (37.0%)	72 (38.9%)	140 (37.9%)
Moderate	54 (29.3%)	52 (28.1%)	106 (28.7%)
Severe	3 (1.6%)	2 (1.1%)	5 (1.4%)

Source: Table 7 of the study reports

3.2.3.2 Patient Disposition

The disposition of all randomized subjects and reasons for premature treatment discontinuation during the 3-month treatment period are presented in Table 5. The proportion of subjects who discontinued treatment prior to Month 3 ranged from 4.4% to 10.4% across all treatment groups of the three studies. The most common reasons for premature discontinuation across treatment groups were AE(s) and "Other." A greater proportion of subjects in the DE-117 groups of each study discontinued the studies due to AE(s) compared with both timolol and latanoprost. The "Other" category mostly consists of subjects who discontinued the study drug due to reasons specified as either lost to follow up, site closed or decision by the investigator.

Table 5: Patient Disposition

	011709IN		**011710IN**		**01171505**	
	DE-117	**Timolol**	**DE-117**	**Timolol**	**DE-117**	**Latanoprost**
Intent-to-Treat Population	212 (100.0%)	214 (100.0%)	208 (100.0%)	209(100.0%)	185 (100.0%)	185 (100.0%)
Safety Population[1]	211 (99.5%)	215 (100.5%)	204 (98.1%)	205 (98.1%)	185 (100.0%)	185 (100.0%)
Full Analysis Set	212 (100.0%)	213 (99.5%)	204 (98.1%)	205 (98.1%)	184 (99.5%)	185 (100.0%)
Safety Population	211	215	204	205	185	185
Completed Study Drug	189 (89.6%)	204 (94.9%)	187 (91.7%)	196 (95.6%)	170 (91.9%)	177 (95.7%)
Discontinued Study Drug	22 (10.4%)	11 (5.1%)	17 (8.3%)	9 (4.4%)	15 (8.1%)	8 (4.3%)
Adverse Event	10 (4.7%)	3 (1.4%)	13 (6.4%)	3 (1.5%)	4 (2.2%)	2 (1.1%)
Withdrawal by Subject	N/A	N/A	N/A	N/A	8 (4.3%)	5 (2.7%)
Lack of Efficacy	5 (2.4%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol Deviation	N/A	N/A	N/A	N/A	2 (1.1%)	0 (0.0%)
Death	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	7 (3.3%)	5 (2.3%)	3 (1.5%)	6 (2.9%)	1 (0.5%)	1 (0.5%)

Source: Table 9 (Study 011709IN and Study 011710IN) and Table 5 (01171505) of the study reports

[1]One subject (b) (6) was randomized to the DE-117 arm but incorrectly dispensed a timolol kit at baseline. N/A = Not applicable– Distinct recording and summary of study drug discontinuations for Withdrawal by Subject and Protocol Deviation was only done for study 01171505. For subjects in studies 011709IN and 011710IN, discontinuing study drug early for reasons other than *Adverse Event* or *Lack of Efficacy*, was reported as "Other".

Reviewer's remark: Alternative IOP-lowering medications (rescue medications) were provided at the discretion of the investigators in studies 011709IN and 011710IN. The studies did not outline specific rescue criteria. Rescue use was more prevalent in the DE-117 arm compared to timolol in both studies. A total of 37 subjects in the DE-117 arm (26 from Study 011709IN and 11 Study 011710IN) received rescue medication compared to only 2 timolol treated subjects (both in Study 011709IN).

Reviewer's remark: There is only minor difference between the number of subjects included in the ITT and FAS populations. Studies 011709IN and 011710IN encouraged subjects who discontinued the study drug prior to Month 3 to remain in the study and complete the protocol mandated evaluations (including IOP) at each of the scheduled visits. In Study 011709IN, 9 of the 22 subjects who discontinued DE-117, and 1 of the 11 subjects who discontinued timolol, remained in the study and were evaluated for the duration of the study. Similarly, for Study 011710IN, 8 of the 17 subjects and 1 of 9 subjects who discontinued DE-117 and timolol, respectively, remained in the study and completed the study evaluations. However, most of the subjects who discontinued the study drug but remained in the study eventually received rescue medication.

Reviewer's remark: IOP values measured after study drug discontinuation, <u>but prior to administration rescue medication,</u> were included in the primary efficacy analysis. However, all IOP values collected after rescue medication use were treated as missing.

Reviewer's remark: The summary of subjects with observed IOP data (with or without additional rescue medication) and subjects with missing data is presented in Table A.2. As can be seen, more subjects in the DE-117 arm received rescue medications and had missing data. The rate of missing data increased over time with between 4.6%-5.8% subjects in the DE-117 arm having missing data at the Month 3 visit.

Reviewer's remark: Note that, because IOP data after rescue medication is not included in the analysis, the total amount of "missing data" for the primary analysis is the sum of observed data with rescue and the actual missing data. For example, in Study 011709IN, 16/212 (7.5%) DE-117 treated subjects had "missing" data for the primary efficacy analysis at 16:00hrs at the Month 3 visit compared to 11/214 (5.1%) of timolol treated subjects (Table A.2).

Table A.2: Summary of Missing and Observed Data

Visit	*Time*	*Category*	*011709IN*		*011710IN*	
			DE-117 N=212	*Timolol N=214*	*DE-117 N=208*	*Timolol N=209*
Week 1	*08:00*	*Observed*	*210 (99%)*	*211 (98.6%)*	*202 (97.1%)*	*203 (97.1%)*
		Observed Rescue	*0 (0%)*	*0 (0%)*	*2 (1%)*	*0 (0%)*
		Missing	*2 (1%)*	*3 (1.4%)*	*4 (1.9%)*	*6 (2.9%)*
	10:00	*Observed*	*209*	*211 (98.6%)*	*201 (96.1%)*	*203 (97.1%)*
		Observed Rescue	*1(0.5%)*	*0 (0%)*	*2 (1%)*	*0 (0%)*
		Missing	*2 (1%)*	*3 (1.4%)*	*5 (2.4%)*	*6 (2.9%)*

	16:00	*Observed*	*211(99.5%)*	*210 (98.1%)*	*198 (95.2%)*	*200 (95.7%)*
		Observed Rescue	*1(0.5%)*	*0 (0%)*	*2 (1%)*	*0 (0%)*
		Missing	*0 (0%)*	*4 (1.9%)*	*8 (3.8%)*	*9 (4.3%)*
Week 6	*08:00*	*Observed*	*202 (95%)*	*208 (97.2%)*	*194 (93.3%)*	*199 (95.2%)*
		Observed Rescue	*4 (1.9%)*	*3 (1.4%)*	*4 (1.9%)*	*0 (0%)*
		Missing	*6 (2.8%)*	*3 (1.4%)*	*10 (4.8%)*	*10 (4.8%)*
	10:00	*Observed*	*203 (95.7%)*	*208 (97.2%)*	*194 (93.3%)*	*198 (94.7%)*
		Observed Rescue	*4 (1.9%)*	*3 (1.4%)*	*4 (1.9%)*	*0 (0%)*
		Missing	*5 (2.3%)*	*3 (1.4%)*	*10 (4.8%)*	*11 (5.3%)*
	16:00	*Observed*	*201 (94.8%)*	*208 (97.2%)*	*193 (92.8%)*	*197 (94.2%)*
		Observed Rescue	*5 (2.3%)*	*3 (1.4%)*	*4 (1.9%)*	*0 (0%)*
		Missing	*6 (2.8%)*	*3 (1.4%)*	*11 (5.2%)*	*12 (5.7%)*
Month 3	*08:00*	*Observed*	*196 (92.4%)*	*203 (94.8%)*	*189 (90.9%)*	*197 (94.2%)*
		Observed Rescue	*6 (2.8%)*	*1(0.5%)*	*8 (3.8%)*	*0 (0%)*
		Missing	*10 (4.6%)*	*10 (4.7%)*	*11 (5.3%)*	*12 (5.7%)*
	10:00	*Observed*	*197 (92.5%)*	*203 (94.8%)*	*188 (90.4%)*	*197 (94.2%)*
		Observed Rescue	*6 (2.8%)*	*1(0.5%)*	*8 (3.8%)*	*0 (0%)*
		Missing	*9 (4.2%)*	*10 (4.7%)*	*12 (5.8%)*	*12 (5.7%)*
	16:00	*Observed*	*196 (92.4%)*	*203 (94.8%)*	*188 (90.4%)*	*197 (94.2%)*
		Observed Rescue	*6 (2.8%)*	*1(0.5%)*	*8 (3.8%)*	*0 (0%)*
		Missing	*10 (4.7%)*	*10 (4.7%)*	*12 (5.8%)*	*12 (5.7%)*

Observed=IOP data collected; Observed Rescue=IOP data collected after receipt of rescue medication use. Missing=No IOP data collected.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

This section presents the efficacy summaries including the results of sensitivity analyses conducted by the reviewer and the Applicant. Unless otherwise indicated, tables and figures presented in this section are based on analyses conducted by this reviewer using the analysis datasets submitted by the Applicant. Unless stated otherwise, the mean IOP values presented are the least square means from a MMRM. The standard error estimates for the least square means are presented in corresponding parenthesis.

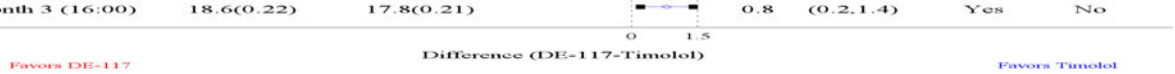
3.2.4.1.1 Primary Efficacy Analysis

The protocol-defined primary efficacy analyses results are presented in Figure 4-Figure 6. In Studies 011710IN and 01171505, the upper limits of the 95% confidence intervals (UCL) for the mean differences in IOP were less than the pre-specified non-inferiority margin of 1.5 mmHg for all measurement times (Statistical Criteria). Additionally, the UCLs did not exceed 1.0 mmHg at the majority of the nine post-baseline time points (Clinical Criteria). Therefore, the two studies met both the statistical and clinical criteria for non-inferiority.

However, because the UCLs are higher than 1.5 mm Hg for 3 of the 9 timepoints [Week 6 (08:00), Month 3 (08:00 & 10:00)], Study 011709IN did not demonstrate the non-inferiority of DE-117 over timolol.

Figure 4: Primary Efficacy Endpoint Summary: LS means and 95% CI (011709IN)

Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Baseline (8:00)	25.3(0.19)	25.5(0.19)	-0.18 (-0.7,0.35)		
Baseline (10:00)	24.7(0.16)	24.6(0.16)	0.05 (-0.41,0.51)		
Baseline (16:00)	24.2(0.15)	24.4(0.15)	-0.19 (-0.61,0.23)		
Week 1 (8:00)	19(0.22)	19.1(0.21)	-0.1 (-0.7,0.5)	Yes	Yes
Week 1 (10:00)	18(0.21)	18.2(0.21)	-0.2 (-0.8,0.4)	Yes	Yes
Week 1 (16:00)	17.5(0.21)	17.9(0.21)	-0.4 (-1,0.1)	Yes	Yes
Week 6 (8:00)	19.8(0.2)	18.4(0.2)	1.3 (0.8,1.9)	No	No
Week 6 (10:00)	18.9(0.2)	18(0.2)	0.8 (0.3,1.4)	Yes	No
Week 6 (16:00)	18.5(0.21)	17.7(0.21)	0.8 (0.2,1.4)	Yes	No
Month 3 (8:00)	19.7(0.24)	18.5(0.24)	1.2 (0.5,1.9)	No	No
Month 3 (10:00)	18.8(0.21)	17.7(0.21)	1.1 (0.5,1.7)	No	No
Month 3 (16:00)	18.6(0.22)	17.8(0.21)	0.8 (0.2,1.4)	Yes	No



Source: Adapted from Table 20 of the study report.

Figure 5: Primary Efficacy Endpoint Summary: LS means and 95% CI (011710IN)

Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Baseline (8:00)	25.9(0.2)	25.5(0.2)	0.44 (-0.11,0.99)		
Baseline (10:00)	25.1(0.18)	24.8(0.18)	0.24 (-0.26,0.74)		
Baseline (16:00)	24.7(0.17)	24.2(0.17)	0.46 (-0.01,0.92)		
Week 1 (8:00)	19.4(0.23)	19.7(0.23)	-0.3 (-0.9,0.3)	Yes	Yes
Week 1 (10:00)	18.5(0.22)	18.9(0.22)	-0.4 (-1,0.3)	Yes	Yes
Week 1 (16:00)	17.9(0.23)	18.6(0.22)	-0.6 (-1.3,0)	Yes	Yes
Week 6 (8:00)	20.4(0.22)	19.5(0.21)	0.9 (0.3,1.5)	Yes	No
Week 6 (10:00)	19.5(0.2)	18.8(0.2)	0.7 (0.1,1.2)	Yes	No
Week 6 (16:00)	19.2(0.21)	18.8(0.21)	0.3 (-0.2,0.9)	Yes	Yes
Month 3 (8:00)	20(0.22)	19.6(0.22)	0.4 (-0.2,1)	Yes	Yes
Month 3 (10:00)	19.4(0.23)	18.9(0.22)	0.5 (-0.1,1.1)	Yes	No
Month 3 (16:00)	19.1(0.23)	19(0.22)	0.1 (-0.5,0.7)	Yes	Yes

Source: Adapted from Table 18 of the study report.

Figure 6: Primary Efficacy Endpoint Summary: LS means and 95% CI (01171505)

Visit (Time)	DE-117 Mean (SE)	Latanoprost Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Baseline (9:00)	24.9(0.18)	24.7(0.18)	0.15 (-0.36,0.65)		
Baseline (13:00)	24.5(0.17)	24.5(0.17)	0.05 (-0.43,0.52)		
Baseline (17:00)	24.3(0.17)	24.3(0.17)	0.03 (-0.45,0.51)		
Week 1 (9:00)	19(0.28)	18.8(0.29)	0.2 (-0.5,0.9)	Yes	Yes
Week 1 (13:00)	18.4(0.28)	18.4(0.29)	0 (-0.7,0.7)	Yes	Yes
Week 1 (17:00)	18(0.28)	18.3(0.28)	-0.2 (-0.9,0.5)	Yes	Yes
Week 6 (9:00)	17.8(0.26)	17.4(0.26)	0.4 (-0.3,1)	Yes	Yes
Week 6 (13:00)	17.6(0.27)	17.2(0.27)	0.4 (-0.3,1)	Yes	Yes
Week 6 (17:00)	17.5(0.26)	17.1(0.27)	0.4 (-0.3,1)	Yes	Yes
Month 3 (9:00)	17.9(0.27)	17(0.27)	0.9 (0.2,1.5)	Yes	No
Month 3 (13:00)	17.2(0.25)	16.7(0.26)	0.6 (0,1.2)	Yes	No
Month 3 (17:00)	17.2(0.26)	16.7(0.27)	0.5 (-0.2,1.1)	Yes	No

Source: Adapted from Table 16 of the study report.

Reviewer's remark: The mean IOP for the DE-117 arm appears consistent across the two timolol-controlled studies. On the other hand, the mean IOP for timolol was slightly lower (better) in Study 0117109IN (where non-inferiority is not established) compared to the time-matched values in Study 011710IN. Specifically, the timolol arm has performed better in Study 011709IN than in Study 011710IN for the timepoints at which the UCL>1.5; while the DE-117 arm had comparative results in both studies for these same time points. For example, at 08:00 on Month 3, the mean IOP in the DE-117 arm is 19.7 mm Hg in Study 011709IN and 20 mm Hg in Study 011710IN, for a difference of 0.3mm Hg. Conversely, the mean IOP at the same time point for the timolol arm is 18.5 and 19.6 mmHg in Study 011709IN and Study 011710IN, respectively for a difference of 1.1 mm Hg (Table A3). Based on this, the reason for the failure of Study 0117109IN to meet the non-inferiority criteria could be partly attributed to the higher effect of timolol observed in this study.

Table A3: Summary of mean IOP

Time	DE-117			timolol		
	011709IN	011710IN	diff	011709IN	011710IN	diff
Week 1: 8:00	19.0	19.4	-0.4	19.1	19.7	-0.6
Week 1: 10:00	18.0	18.5	-0.5	18.2	18.9	-0.7
Week 1: 16:00	17.5	17.9	-0.4	17.9	18.6	-0.7
Week 6: 8:00*	19.8	20.4	-0.6	18.4	19.5	-1.1
Week 6: 10:00	18.9	19.5	-0.6	18.0	18.8	-0.8
Week 6: 16:00	18.5	19.2	-0.7	17.7	18.8	-1.1
Month 3: 8:00*	19.7	20.0	-0.3	18.5	19.6	-1.1
Month 3: 10:00*	18.8	19.4	-0.6	17.7	18.9	-1.2
Month 3: 16:00	18.6	19.1	-0.5	17.8	19.0	-1.2

**time points at which the non-inferiority margin is crossed.*

3.2.4.1.2 Sensitivity Analyses

To assess the robustness of the results of the primary efficacy analyses, both the reviewer and the Applicant conducted sensitivity analyses. This section summarizes the results of these analyses. The results from these analyses are overall consistent with the primary efficacy analysis findings.

A. Applicant's Sensitivity Analysis

Recall, in the primary efficacy analyses, data after treatment discontinuation and data collected after the receipt of IOP lowering medication (rescue therapy) was treated as missing and assumed to follow the missing at random (MAR) mechanism. To assess the impact of deviation from this assumption, which is the basis for the MMRM approach, the Applicant performed a pattern mixture modeling approach in which a positive shift parameter between 1 mm Hg and 5 mm Hg were added to the imputed values for subjects in both arms who received a rescue medication or discontinued the study due to either adverse events or lack of efficacy.

The Applicant conducted this analysis for studies 011709IN and 011710IN. The reviewer included the results for 01171505. As shown in Table 6, the tipping point, the shift parameter

that led to the conclusion of non-inferiority to change, was 1 in 011710IN and 2 in 01171505. The detailed results are presented in Table 13- Table 15.

Table 6: Summary of the pattern mixture approach

Study	Shift	Upper limit of 95% CI		FDA criteria Met
		≤1.5 mm Hg	≤1.0 mm Hg	
011709IN	0	6 out of 9	3 out of 9	No
	1	6 out of 9	3 out of 9	No
	2	6 out of 9	3 out of 9	No
	3	5 out of 9	3 out of 9	No
	4	5 out of 9	3 out of 9	No
	5	5 out of 9	3 out of 9	No
011710IN	0	9 out of 9	7 out of 9	Yes
	1	9 out of 9	5 out of 9	Yes
	2	8 out of 9	5 out of 9	No
	3	8 out of 9	5 out of 9	No
	4	8 out of 9	4 out of 9	No
	5	7 out of 9	3 out of 9	No
01171505*	0	9 out of 9	6 out of 9	Yes
	1	9 out of 9	6 out of 9	Yes
	2	9 out of 9	6 out of 9	Yes
	3	8 out of 9	6 out of 9	No
	4	8 out of 9	4 out of 9	No
	5	8 out of 9	4 out of 9	No

Source: Reviewer's analysis. Shift=0 is the primary efficacy analysis. * For this study, subjects were not given IOP lowering rescue medications. The shift thus is applied to subjects who discontinued the study for lack of efficacy and adverse event.

Reviewer's remark: As shown in Table 6, the tipping points for studies 011710IN and 01171505 are 1 and 2, respectively. However, in these studies, the upper limit of the 95% CI is ≤1.5 in at least 7 out of 9 timepoints for shift parameters of 3-5mm Hg. Furthermore, for Study 011709IN, the upper limit of the 95% CI is ≤1.5 in 6 of the 9 timepoints for a shift parameter of 2mm Hg and in 5 of the 9 timepoints for the shift parameters of 3-5mm Hg.

B. Reviewer's Supplemental Analysis

The reviewer conducted the following supplemental analyses. The results of these analyses are overall consistent with the Applicant's findings.

i. Accounting for correlations in repeated measures

The primary efficacy analysis was conducted based on an MMRM model for each time of the day separately. This analysis ignores the possible correlation among IOP measurements taken

from the same subject on a given visit. This could potentially result in biased estimates, as well as incorrect standard errors of the estimated treatment differences. To this end, this reviewer performed the analysis of the primary endpoint accounting for the within visit and across visit correlations. The results of this analysis are generally consistent with the primary efficacy analyses results. However, there was one time point each in Study 011710IN and Study 01171505 at which the upper limit of the 95% confidence interval crossed the pre-specified non-inferiority margin of 1.5 mm Hg (Figure 7-Figure 9).

ii. Addressing Intercurrent Events

Neither the protocols nor the statistical analysis plans for the three Phase 3 studies specified the primary estimand of interest. The primary analysis with the MMRM is likely an evaluation of the "hypothetical estimand", that is, the difference in mean IOP in a hypothetical scenario where the intercurrent events of treatment discontinuation and rescue medication use had not occurred. For non-inferiority studies in IOP indications, the Agency has accepted this estimand in the past.

Note, studies 011709IN and 011710IN allowed subjects who discontinued the study treatment to remain in the study and provide data. In the Applicant's primary efficacy analysis, data collected post-treatment discontinuation (prior to recue medication use) is used in the analysis. To evaluate the effect of including data from these subjects on the hypothetical estimand (which is evaluated under the scenario that treatment discontinuation had not occurred), the reviewer conducted the analysis of the primary efficacy endpoints by treating post-treatment discontinuation data as missing. The analysis is done using the same MMRM model used for the primary efficacy analysis (Figure 10-Figure 11).

Reviewer's remark: Note, because most subjects who discontinued the study drug but elected to remain in the study eventually received rescue medications, only few had IOP data post-treatment discontinuation without the receipt of rescue medications. Consequently, the results from these analyses are very similar to the primary efficacy analyses results.

Also note, in the absence of an explicitly pre specified, justified, and accepted primary estimand of interest, one must evaluate alternative clinically meaningful estimands that are estimable with minimal assumptions. One such estimand, which has regulatory relevance, is the treatment policy estimand. As noted, studies 011709IN and 011710IN provided alternative IOP-lowering medications (rescue therapy).

For some subjects, data post-rescue medication was collected. However, the data was not used in the primary efficacy analyses. This reviewer conducted the analysis of the primary efficacy endpoint by using all observed data including data collected following a rescue medication use (Figure 13 and Figure 14) as an estimate of this estimand. Apart from a slightly improved effect for the DE-117 arm, the overall conclusion of non-inferiority has not changed in this analysis.

3.2.4.1.3 Secondary Efficacy Analysis

A. Mean Diurnal IOP

The mean diurnal IOP at Week 1 and Month 3 were the secondary efficacy endpoints of interest. The summary of these endpoints is presented in Table 7-
Table 9. Except for the mean diurnal IOP at Month 3 in Study 011709IN, the upper limits of the 95% confidence intervals for the treatment differences are ≤ 1.5 mm Hg. However, in all three studies, the mean IOP for the DE-117 arm was numerically higher than both timolol and latanoprost at Week 6 and Month 3.

Table 7: Summary of Mean Diurnal IOP (Study 011709IN)

	Treatments		
Visit	DE-117	timolol	Diff (95% CI)
Week 1	18.2 (0.19)	18.4 (0.19)	-0.3 (0.8, 0.3)
Week 6	19.0 (0.18)	18.1 (0.18)	1.0 (0.5, 1.5)
Month 3	19.0 (0.2)	18.0 (0.19)	1.0 (0.5, 1.6)

Source: Table 26 of the Study reports

Table 8: Summary of Mean Diurnal IOP (Study 011710IN)

	Treatments		
Visit	DE-117	timolol	Diff (95% CI)
Week 1	18.6 (0.2)	19.1 (0.20)	-0.5 (-1.0, 0.1)
Week 6	19.7 (0.18)	19.1 (0.18)	0.6 (0.1, 1.1)
Month 3	19.5 (0.19)	19.2 (0.19)	0.3 (-0.2, 0.8)

Source: Table 29 of the Study reports

Table 9: Summary of Mean Diurnal IOP (Study 01171505)

	Treatments		Diff (95% CI)
Visit	DE-117	latanoprost	
Week 1	18.5 (0.26)	18.5 (0.27)	0.0 (-0.7, 0.7)
Week 6	17.6 (0.25)	17.2 (0.25)	0.4 (-0.2, 1.0)
Month 3	17.5 (0.25)	16.8 (0.25)	0.6 (0.0, 1.2)

Source: Table 24 of the Study reports

B. Change from Baseline IOP

The analysis of the change from baseline IOP at each time point was conducted using the same MMRM approach used for the primary efficacy analysis. The summary results are presented in Figure 15-Figure 17. The mean baseline IOP at each time point was comparable between the treatment groups. All treatment groups demonstrated IOP reductions at each of the nine points. In the DE-117 arm, the reduction in IOP ranged from 5.3-7.3 mm Hg across all three studies. The corresponding figures for the timolol and latanoprost arms were 5.4-7.0 mm Hg and 6.1-7.9 mm Hg, respectively.

Note, the DE-117 arm had slightly higher numerical reduction from baseline in IOP at Week 1 at all the timepoints (08:00, 16:00, 20:00hrs) compared to timolol; and at one timepoint (09:00hrs) compared to latanoprost. However, the reduction in IOP for the DE-117 arm was numerically lower than both timolol and latanoprost at each of the six time points evaluated at Week 6 and Month 3. The differences ranged between 0.1 to 1.3 mm Hg against timolol and between 0.4-0.9 mm Hg against latanoprost.

C. IOP for Subjects with Mean Baseline Diurnal IOP<25 mm Hg

The analysis of the primary efficacy endpoint for subjects with mean baseline diurnal IOP <25 provided results that are consistent with the results for the overall population; non-inferiority is established in studies 011710IN and 01171505 but not in Study 011709IN (Figure 18-Figure 20).

3.3 Evaluation of Safety

In this section, safety summary reported in the three pivotal studies during the double-masked (3-month period) will be presented.

3.3.1 Treatment Exposure

Per the Applicant, dose levels ranging between 0.0003% and 0.03% were evaluated. However, the optimal concentration and dose/regimen for DE-117 was identified as DE-117 0.002% QD one drop in each eye in the evening, for which the Applicant is seeking approval. In the three studies combined, 600 subjects (including 6 pediatric subjects) received at least one dose of DE-117 0.002% during the three months masked period of the studies. The median number of days of treatment exposure to DE-117 was around 91 days (Table 10).

Table 10: Summary of Duration of Exposure

Duration (Days)	011709IN		011710IN		01171505		Integrated Summary		
	DE-117	Timolol	DE-117	Timolol	DE-117	LAT	DE-117*	DE-117**	Timolol
Mean (SD)	85.5 (19.8)	89.3 (14.7)	85.6 (17.0)	88.0 (15.8)	85.2 (17.9)	87.3 (13.6)	85.6 (18.5)	85.4 (18.3)	88.7 (15.2)
Median	92.0	92.0	91.0	92.0	90.0	91.0	91.0	91.0	92.0
Min, Max	3, 121	8, 134	3, 101	2, 124	7, 112	3, 103	3, 121	3, 121	2, 134
1 – 30 days	10 (4.7%)	5 (2.3%)	6 (2.9%)	6 (2.9%)	10 (5.4%)	5 (2.7%)	16 (3.9%)	26 (4.3%)	11 (2.6%)
31 – 60 days	7 (3.3%)	4 (1.9%)	7 (3.4%)	3 (1.5%)	3 (1.6%)	3 (1.6%)	14 (3.4%)	17 (2.8%)	7 (1.7%)
61 – 90 days	58 (27.5%)	49 (22.8%)	73 (35.8%)	59 (28.8%)	84 (45.4%)	81 (43.8%)	131 (31.6%)	215 (35.8%)	108 (25.7%)
> 90 days	136 (64.5%)	157 (73.0%)	118 (57.8%)	137 (66.8%)	87 (47.0%)	96 (51.9%)	254 (61.2%)	341 (56.8%)	294 (70.0%)
Unknown***	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)

Source: Table 14.1.7.2 of ISS. SD = standard deviation. * Pooled studies are 011709IN and 011710IN. ** Pooled studies are 011709IN, 011710IN and 01171505. LAT: latanoprost. *** Treatment end date is missing.

3.3.1 Adverse Events

As shown in Table 11, in the three studies combined, 41.0% of DE-117 treated subjects reported at least one AE compared to 34.3% treated with timolol and 29.7% treated with latanoprost. Ocular AEs comprised of most reported AEs in all treatment groups.

The most frequently reported adverse events in the DE-117 group were conjunctival hyperemia (8.5%) and photophobia (5.3%). The corresponding figures in the timolol group were 3.8% [conjunctival hyperemia], 0.5% [photophobia]. The incidence rate of these events in the latanoprost group were 5.4% [conjunctival hyperemia] and 0.5% [photophobia]. Two deaths (one in the DE-117 group and one in the timolol group) have been reported. In the three studies combined, serious adverse events (SAEs) were reported in a total of 13 (2.2%) subjects treated with DE-117. Of these, only three were ocular events (cystoid macular edema).

Table 11: Adverse Events: Overall (3-Month Double-Masked Period)

	011709IN		**011710IN**		**01171505**		**Integrated Summary**		
	DE-117 (N=211)	**Timolol (N=215)**	**DE-117 (N=204)**	**Timolol (N=205)**	**DE-117 (N=185)**	**LAT (N=185)**	***DE-117 (N=415)**	**** DE-117 (N=600)**	**Timolol (N=420)**
AE(s)	88(41.7%)	77(35.8%)	84(41.2%)	67(32.7%)	74(40.0%)	55(29.7%)	172(41.4%)	246 41.0%)	144(34.3%)
SAE(s)	4 (1.9%)	4 (1.9%)	7 (3.4%)	1 (0.5%)	2 (1.1%)	2 (1.1%)	11 (2.7%)	13 (2.2%)	5 (1.2%)
SAR(s)	51 24.2%)	32 14.9%)	47 23.0%)	27 13.2%)	43 23.2%)	22 11.9%)	98 23.6%)	141(23.5%)	59 14.0%)
Serious SAR(s)	1 (0.5%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.5%)	0 (0.0%)
AE(s) Leading to Study Drug Discontinuation	13 (6.2%)	5 (2.3%)	13 (6.4%)	3 (1.5%)	4 (2.2%)	2 (1.1%)	26 (6.3%)	30 (5.0%)	8 (1.9%)
Death	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Ocular AE(s)	69(32.7%)	50(23.3%)	65(31.9%)	45(22.0%)	68(36.8%)	39(21.1%)	134(32.3%)	202(33.7%)	95 (22.6%)
SAE(s)	1 (0.5%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.5%)	0 (0.0%)
SAR(s)	49(23.2%)	32(14.9%)	46(22.5%)	26(12.7%)	43(23.2%)	22(11.9%)	95 (22.9%)	138(23.0%)	58 (13.8%)
Serious SAR(s)	1 (0.5%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.5%)	0 (0.0%)
AE(s) Leading to Study Drug Discontinuation	12 (5.7%)	3 (1.4%)	12 (5.9%)	2 (1.0%)	4 (2.2%)	1 (0.5%)	24 (5.8%)	28 (4.7%)	5 (1.2%)
Non-Ocular AE(s)	28(13.3%)	36(16.7%)	32(15.7%)	33(16.1%)	14 (7.6%)	25(13.5%)	60 (14.5%)	74 (12.3%)	69 (16.4%)
SAE(s)	3 (1.4%)	4 (1.9%)	5 (2.5%)	1 (0.5%)	2 (1.1%)	2 (1.1%)	8 (1.9%)	10 (1.7%)	5 (1.2%)
SAR(s)	4 (1.9%)	0 (0.0%)	2 (1.0%)	2 (1.0%)	2 (1.1%)	0 (0.0%)	6 (1.4%)	8 (1.3%)	2 (0.5%)
Serious SAR(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE(s) Leading to Study Drug Discontinuation	3 (1.4%)	2 (0.9%)	1 (0.5%)	2 (1.0%)	0 (0.0%)	1 (0.5%)	4 (1.0%)	4 (0.7%)	4 (1.0%)

Source: Table 14.3.1.1. of the ISS. * Pooled studies are 011709IN and 011710IN. ** Pooled studies are 011709IN, 011710IN and 01171505.
LAT: latanoprost. AE: Adverse events. SAR: Suspected adverse events. SAE: Serious adverse events.

Table 12: Adverse Events: Summary of Adverse Events by System Organ Class and Preferred Term (3-Month Double-Masked Period)

	011709IN		**011710IN**		**01171505**		**Integrated Summary**		
	DE-117 (N=211)	**Timolol (N=215)**	**DE-117 (N=204)**	**Timolol (N=205)**	**DE-117 (N=185)**	**LAT (N=185)**	***DE-117 (N=415)**	**** DE-117 (N=600)**	**Timolol (N=420)**
Any AE(s)	88 (41.7%)	77 (35.8%)	84 (41.2%)	67(32.7%)	74(40.0%)	55(29.7%)	172 (41.4%)	246 (41.0%)	144 (34.3%)
Eye disorders	60 (28.4%)	40 (18.6%)	56 (27.5%)	30(14.6%)	64(34.6%)	35(18.9%)	116 (28.0%)	180 (30.0%)	70 (16.7%)

Conjunctival hyperaemia	13 (6.2%)	9 (4.2%)	16 (7.8%)	7 (3.4%)	22(11.9%)	10 (5.4%)	29 (7.0%)	51 (8.5%)	16 (3.8%)
Photophobia	10 (4.7%)	1 (0.5%)	12 (5.9%)	1 (0.5%)	10 (5.4%)	1 (0.5%)	22 (5.3%)	32 (5.3%)	2 (0.5%)
Vision blurred	11 (5.2%)	3 (1.4%)	6 (2.9%)	2 (1.0%)	4 (2.2%)	2 (1.1%)	17 (4.1%)	21 (3.5%)	5 (1.2%)
Dry eye	4 (1.9%)	2 (0.9%)	2 (1.0%)	2 (1.0%)	9 (4.9%)	4 (2.2%)	6 (1.4%)	15 (2.5%)	4 (1.0%)
Ocular hyperaemia	6 (2.8%)	3 (1.4%)	4 (2.0%)	2 (1.0%)	4 (2.2%)	4 (2.2%)	10 (2.4%)	14 (2.3%)	5 (1.2%)
Eye pain	4 (1.9%)	5 (2.3%)	4 (2.0%)	2 (1.0%)	5 (2.7%)	6 (3.2%)	8 (1.9%)	13 (2.2%)	7 (1.7%)
Visual impairment	4 (1.9%)	0 (0.0%)	2 (1.0%)	3 (1.5%)	2 (1.1%)	0 (0.0%)	6 (1.4%)	8 (1.3%)	3 (0.7%)
Corneal thickening	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (3.8%)	2 (1.1%)	0 (0.0%)	7 (1.2%)	0 (0.0%)
Eye irritation	3 (1.4%)	8 (3.7%)	1 (0.5%)	1 (0.5%)	3 (1.6%)	2 (1.1%)	4 (1.0%)	7 (1.2%)	9 (2.1%)
Vitreous detachment	3 (1.4%)	1 (0.5%)	3 (1.5%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	6 (1.4%)	6 (1.0%)	2 (0.5%)
Punctate keratitis	2 (0.9%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	2 (1.1%)	4 (1.0%)	5 (0.8%)	2 (0.5%)
Anterior chamber cell	1 (0.5%)	1 (0.5%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.0%)	4 (0.7%)	1 (0.2%)
Conjunctival haemorrhage	2 (0.9%)	0 (0.0%)	2 (1.0%)	3 (1.5%)	0 (0.0%)	1 (0.5%)	4 (1.0%)	4 (0.7%)	3 (0.7%)
Growth of eyelashes	2 (0.9%)	3 (1.4%)	2 (1.0%)	5 (2.4%)	0 (0.0%)	1 (0.5%)	4 (1.0%)	4 (0.7%)	8 (1.9%)
Infections and infestations	9 (4.3%)	15 (7.0%)	14 (6.9%)	14 (6.8%)	7 (3.8%)	12 (6.5%)	23 (5.5%)	30 (5.0%)	29 (6.9%)
Upper respiratory tract infection	0 (0.0%)	3 (1.4%)	5 (2.5%)	3 (1.5%)	0 (0.0%)	1 (0.5%)	5 (1.2%)	5 (0.8%)	6 (1.4%)
Bronchitis	2 (0.9%)	0 (0.0%)	2 (1.0%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	4 (1.0%)	4 (0.7%)	3 (0.7%)
General disorders and administration site conditions	8 (3.8%)	13 (6.0%)	13 (6.4%)	13 (6.3%)	1 (0.5%)	0 (0.0%)	21 (5.1%)	22 (3.7%)	26 (6.2%)
Instillation site pain	5 (2.4%)	12 (5.6%)	11 (5.4%)	13 (6.3%)	0 (0.0%)	0 (0.0%)	16 (3.9%)	16 (2.7%)	25 (6.0%)
Investigations	7 (3.3%)	6 (2.8%)	11 (5.4%)	1 (0.5%)	2 (1.1%)	1 (0.5%)	18 (4.3%)	20 (3.3%)	7 (1.7%)
Vital dye staining cornea present	7 (3.3%)	5 (2.3%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	9 (2.2%)	10 (1.7%)	6 (1.4%)
Intraocular pressure increased	0 (0.0%)	0 (0.0%)	5 (2.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	5 (1.2%)	6 (1.0%)	0 (0.0%)
Nervous system disorders	5 (2.4%)	4 (1.9%)	7 (3.4%)	1 (0.5%)	3 (1.6%)	2 (1.1%)	12 (2.9%)	15 (2.5%)	5 (1.2%)
Headache	4 (1.9%)	2 (0.9%)	3 (1.5%)	0 (0.0%)	2 (1.1%)	2 (1.1%)	7 (1.7%)	9 (1.5%)	2 (0.5%)

Source: Table 14.3.1.2 of ISS. * Pooled studies are 011709IN and 011710IN; ** Pooled studies are 011709IN, 011710IN and 01171505. LAT: latanoprost.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The summary results for the comparison of the DE-117 to timolol and latanoprost arms with respect to the FDA required primary efficacy endpoint based on selected baseline and demographic characteristics is summarized in Figure 21- Figure 48. Unless stated otherwise, all analyses are performed based on the FAS. The subgroup analysis results presented in this section are considered descriptive and should only be used to characterize the observed treatment differences between subgroups. Therefore, conclusive statements regarding statistical significance could not be made on the magnitude of the treatment effect for any subgroup.

4.1 Age, Sex and Race

Overall, the subgroup analyses results based on age, sex and race were consistent with the primary efficacy analysis results.

4.2 Other Subgroups

Additional analyses based on subgroups formed based on prior IOP lowering medication use (Yes or No) and diagnosis (OAG or OHT) was performed. The IOP lowering effect of DE-117 is more pronounced for subjects with OAG compared to subjects with OHT. Overall, subjects with prior IOP lowering medication seemed to have benefited more from the treatment with DE-117.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major statistical issues were identified in this review.

5.2 Collective Evidence

The safety and efficacy of DE-117 was evaluated in three Phase 3 studies [01171505 (Asia), 011709IN (US) and 011710IN (US)]. In the three studies, IOP reductions at each of the nine points were observed for all treatment arms. In the DE-117 arm, the reduction in IOP ranged from 5.3-7.3 mm Hg across all three studies. The corresponding figures for the timolol and latanoprost arms were 5.4-7.0 mm Hg and 6.1-7.9mm Hg, respectively. However, while studies 011710IN and 01171505 established the non-inferiority of DE-117 against timolol and latanoprost, respectively, the results in Study 011709IN did not meet the FDA's criteria for the non-inferiority of DE-117 against timolol.

The DE-117 arm had a higher numerical reduction from baseline in IOP at Week 1 at all the timepoints (08:00, 16:00, 20:00hrs) compared to timolol and at one timepoint (09:00hrs) compared to latanoprost. However, the reduction in IOP for the DE-117 arm was numerically lower than both timolol and latanoprost at each of the six time points evaluated at Week 6 and Month 3.

The most frequently reported adverse events in the DE-117 group were conjunctival hyperemia (8.5%) and photophobia (5.3%). The corresponding figures in the timolol group were 3.8% [conjunctival hyperemia], 0.5% [photophobia]. The incidence rate of these events in the latanoprost group were 5.4% [conjunctival hyperemia] and 0.5% [photophobia].

5.3 Conclusions and Recommendations

Overall, the results of the Applicant's and the reviewer's analyses presented in this review provide evidence to support the efficacy of DE-117 for the reduction of IOP in subjects with OAG or OHT. As noted, compared to both timolol and latanoprost, the efficacy of DE-117 appears to be numerically lower after the first week of treatment. Moreover, compared to both timolol and latanoprost, a higher incidence of AEs including AEs that led to treatment discontinuation were observed for subjects who received DE-117. Besides, more DE-117 treated

subjects received alternative IOP lowering medications. Therefore, the final regulatory decision of approval should be made based on the risk-benefit evaluation and is deferred to the Clinical review team.

5.4 Labeling Recommendations

In the current version of the drug labeling Section 14 (Clinical Studies), the Applicant presented the following text:

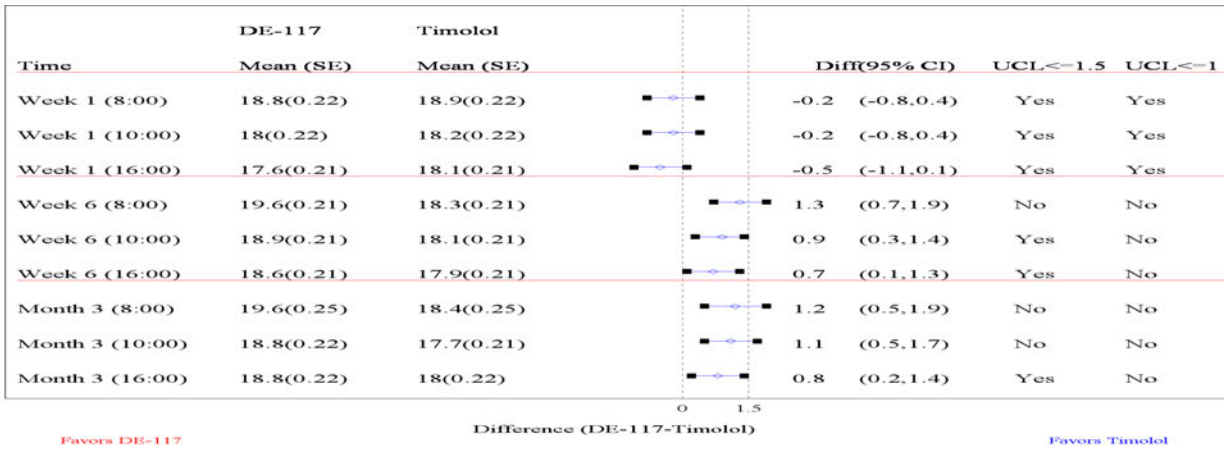
(b) (4) *was evaluated in three randomized and controlled clinical trials in subjects with open-angle glaucoma or ocular hypertension with average baseline IOP of 24-26 mmHg. The treatment duration was 3 months in all 3 studies. The third study* (b) (4)

(b) (4)

6 Appendix

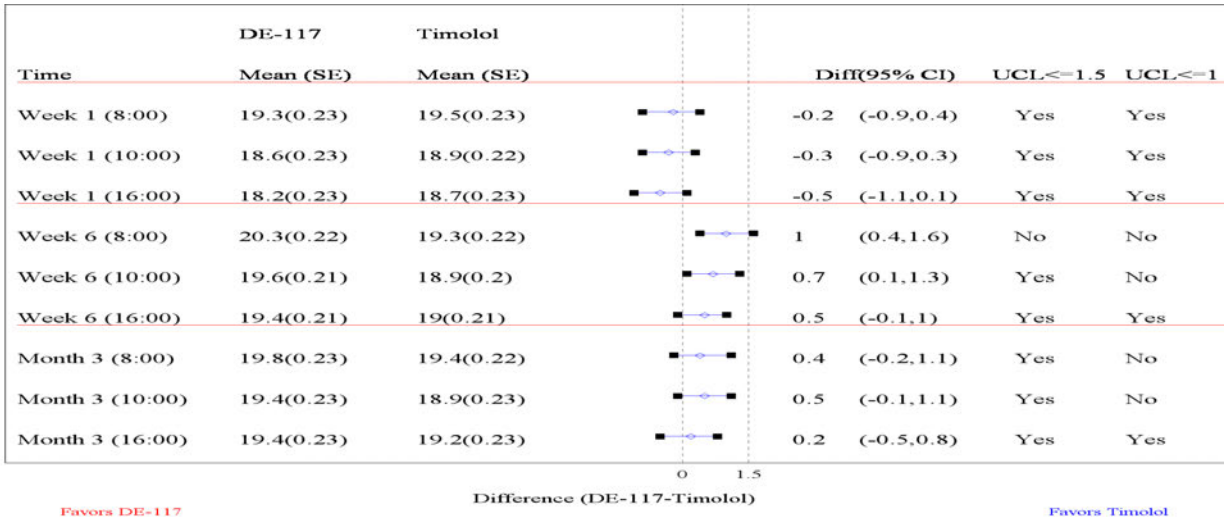
6.1 Supplemental Figures

Figure 7: Primary Efficacy Endpoint with Fully Unstructured Correlation (Study 011709IN)



Source: Reviewer's analysis: An MMRM model accounting for correlations among IOP measurements within a day and across measurement visits is accounted for.

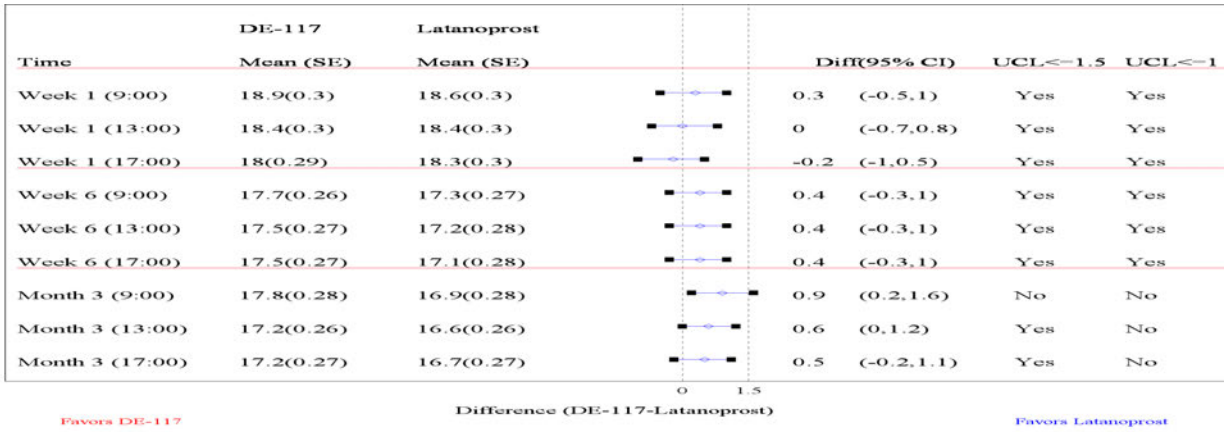
Figure 8: Primary Efficacy Endpoint with Fully Unstructured Correlation (Study 011710IN)



Source: Reviewer's analysis: An MMRM model accounting for correlations among IOP measurements within a day and across measurement visits is accounted for.

Figure 9: Primary Efficacy Endpoint with Fully Unstructured Correlation (Study 01171505)

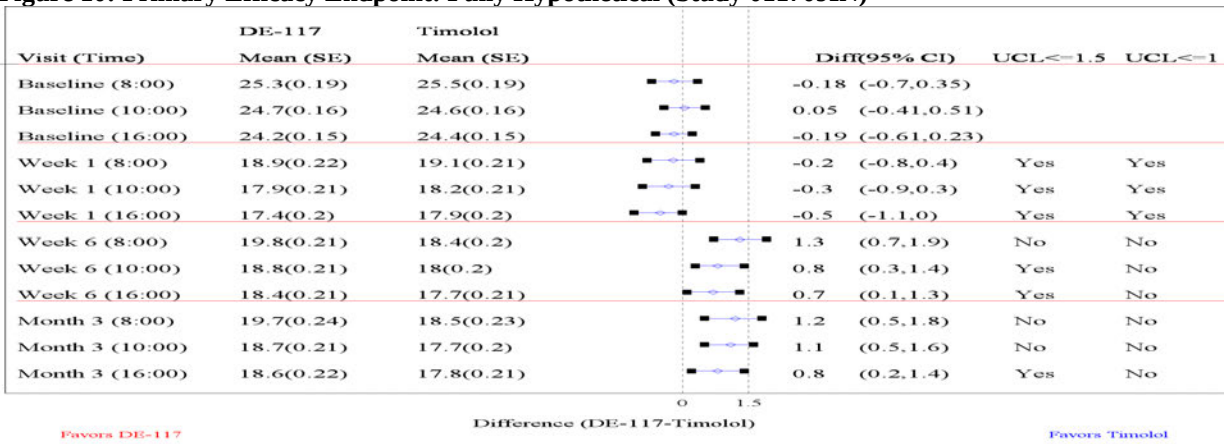
Time	DE-117 Mean (SE)	Latanoprost Mean (SE)	Diff	95% CI	UCL<=1.5	UCL<=1
Week 1 (9:00)	18.9(0.3)	18.6(0.3)	0.3	(-0.5,1)	Yes	Yes
Week 1 (13:00)	18.4(0.3)	18.4(0.3)	0	(-0.7,0.8)	Yes	Yes
Week 1 (17:00)	18(0.29)	18.3(0.3)	-0.2	(-1,0.5)	Yes	Yes
Week 6 (9:00)	17.7(0.26)	17.3(0.27)	0.4	(-0.3,1)	Yes	Yes
Week 6 (13:00)	17.5(0.27)	17.2(0.28)	0.4	(-0.3,1)	Yes	Yes
Week 6 (17:00)	17.5(0.27)	17.1(0.28)	0.4	(-0.3,1)	Yes	Yes
Month 3 (9:00)	17.8(0.28)	16.9(0.28)	0.9	(0.2,1.6)	No	No
Month 3 (13:00)	17.2(0.26)	16.6(0.26)	0.6	(0,1.2)	Yes	No
Month 3 (17:00)	17.2(0.27)	16.7(0.27)	0.5	(-0.2,1.1)	Yes	No



Source: Reviewer's analysis: An MMRM model accounting for correlations among IOP measurements within a day and across measurement visits is accounted for.

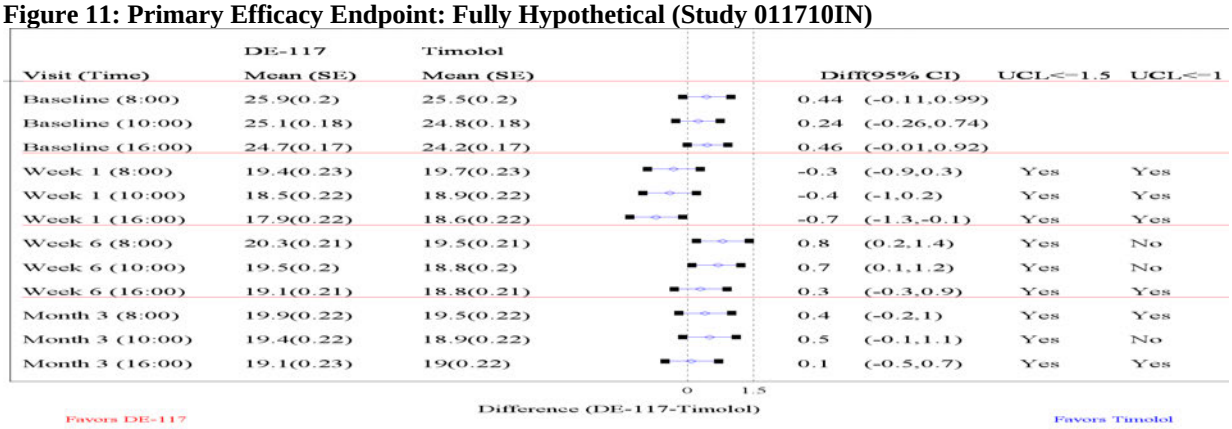
Figure 10: Primary Efficacy Endpoint: Fully Hypothetical (Study 011709IN)

Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff	95% CI	UCL<=1.5	UCL<=1
Baseline (8:00)	25.3(0.19)	25.5(0.19)	-0.18	(-0.7,0.35)		
Baseline (10:00)	24.7(0.16)	24.6(0.16)	0.05	(-0.41,0.51)		
Baseline (16:00)	24.2(0.15)	24.4(0.15)	-0.19	(-0.61,0.23)		
Week 1 (8:00)	18.9(0.22)	19.1(0.21)	-0.2	(-0.8,0.4)	Yes	Yes
Week 1 (10:00)	17.9(0.21)	18.2(0.21)	-0.3	(-0.9,0.3)	Yes	Yes
Week 1 (16:00)	17.4(0.2)	17.9(0.2)	-0.5	(-1.1,0)	Yes	Yes
Week 6 (8:00)	19.8(0.21)	18.4(0.2)	1.3	(0.7,1.9)	No	No
Week 6 (10:00)	18.8(0.21)	18(0.2)	0.8	(0.3,1.4)	Yes	No
Week 6 (16:00)	18.4(0.21)	17.7(0.21)	0.7	(0.1,1.3)	Yes	No
Month 3 (8:00)	19.7(0.24)	18.5(0.23)	1.2	(0.5,1.8)	No	No
Month 3 (10:00)	18.7(0.21)	17.7(0.2)	1.1	(0.5,1.6)	No	No
Month 3 (16:00)	18.6(0.22)	17.8(0.21)	0.8	(0.2,1.4)	Yes	No



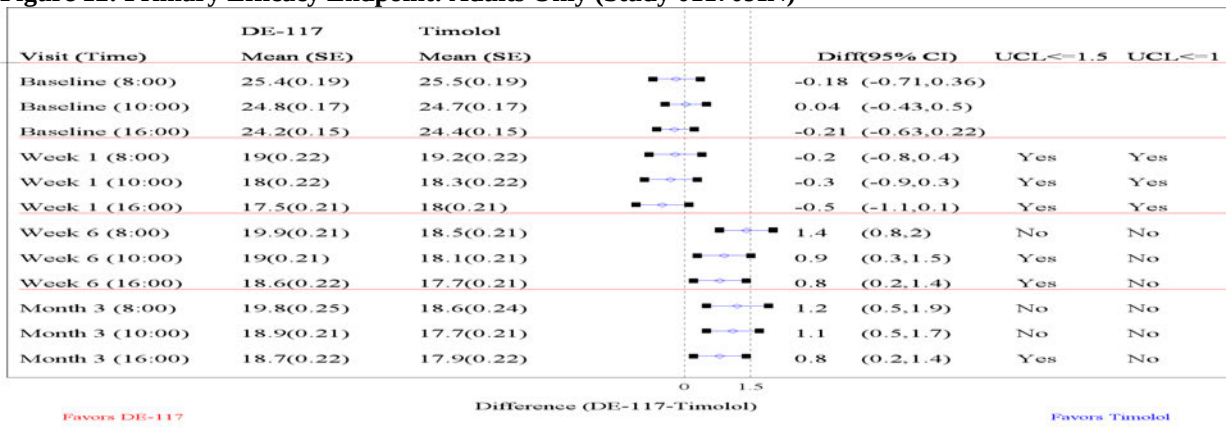
Source: Reviewer's analysis: All data after treatment discontinuation is handled under the MAR assumption.

Figure 11: Primary Efficacy Endpoint: Fully Hypothetical (Study 011710IN)



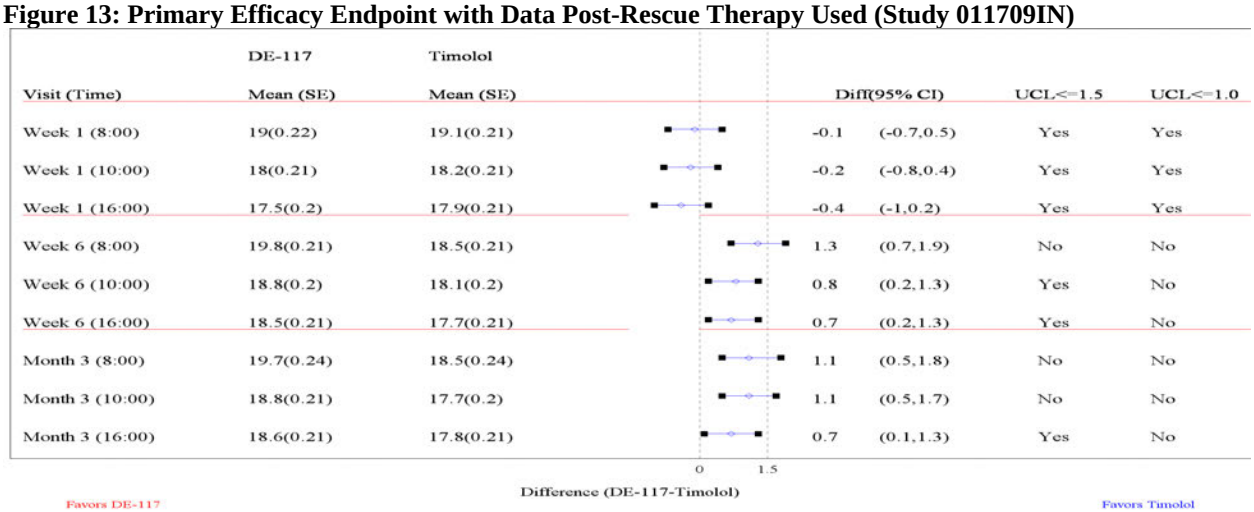
Source: Reviewer's analysis: All data after treatment discontinuation is handled under the MAR assumption.

Figure 12: Primary Efficacy Endpoint: Adults Only (Study 011709IN)



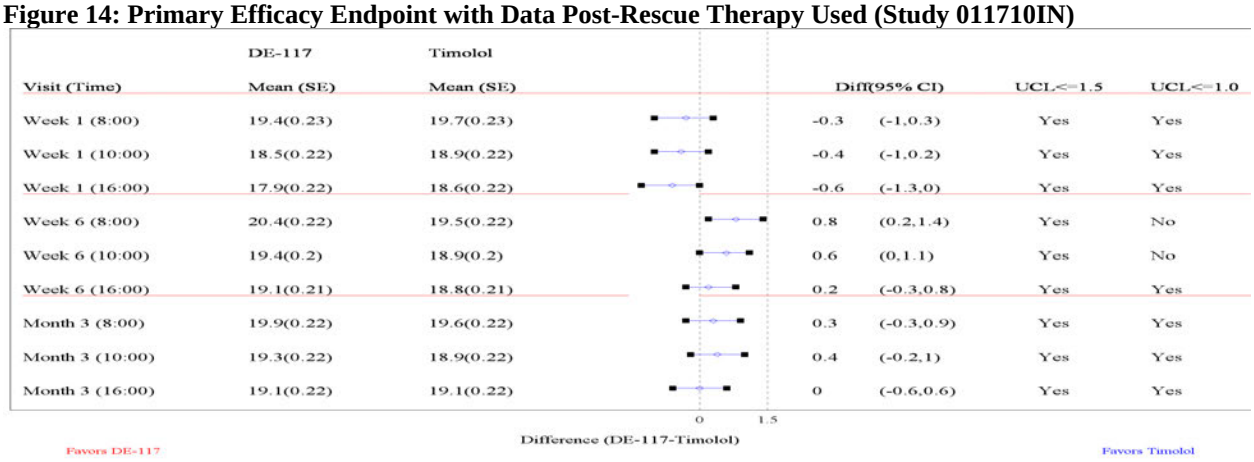
Source: Reviewer's analysis:

Figure 13: Primary Efficacy Endpoint with Data Post-Rescue Therapy Used (Study 011709IN)



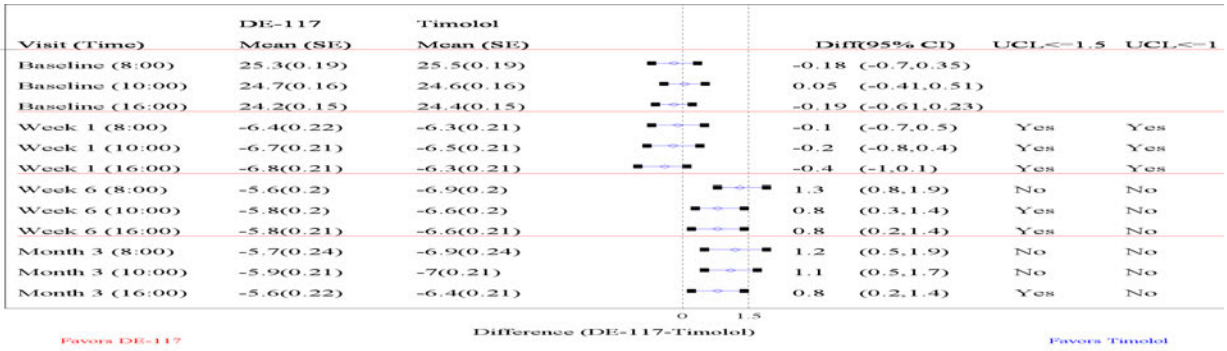
Source: Reviewer's analysis: All observed data including data collected after rescue therapy is included.

Figure 14: Primary Efficacy Endpoint with Data Post-Rescue Therapy Used (Study 011710IN)



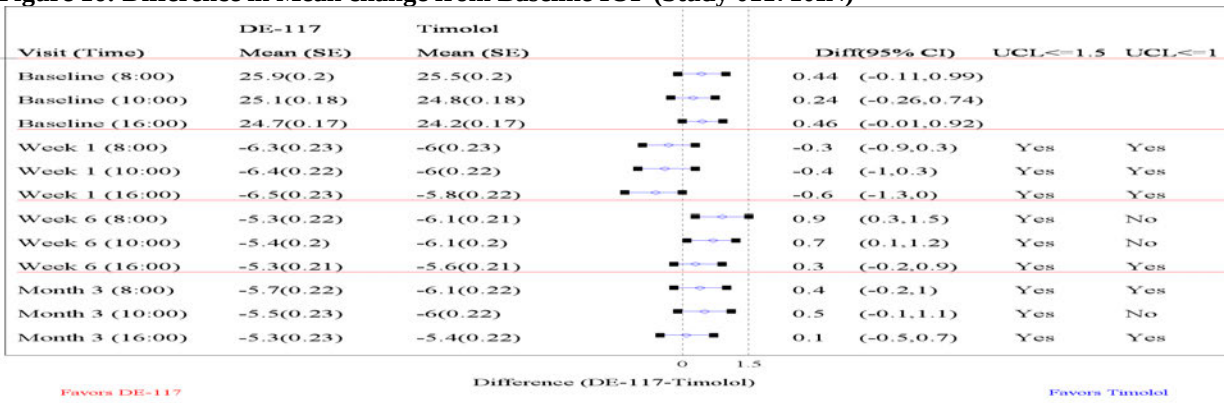
Source: Reviewer's analysis: All observed data including data collected after rescue therapy is included.

Figure 15: Difference in Mean Change from Baseline IOP (Study 011709IN)



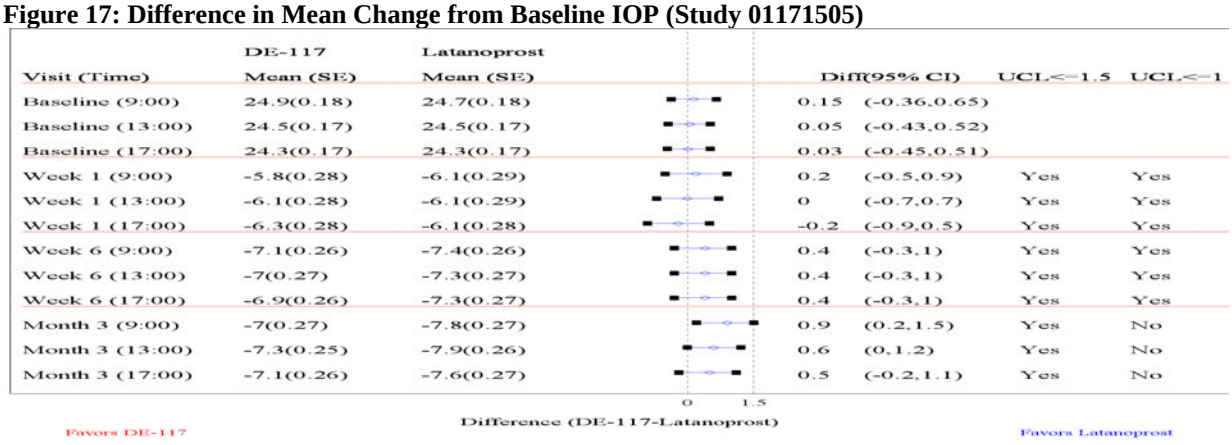
Source: Reviewer's Analysis Change from baseline IOP is used as dependent variable in the MMRM model

Figure 16: Difference in Mean change from Baseline IOP (Study 011710IN)



Source: Reviewer's Analysis Change from baseline IOP is used as dependent variable in the MMRM model

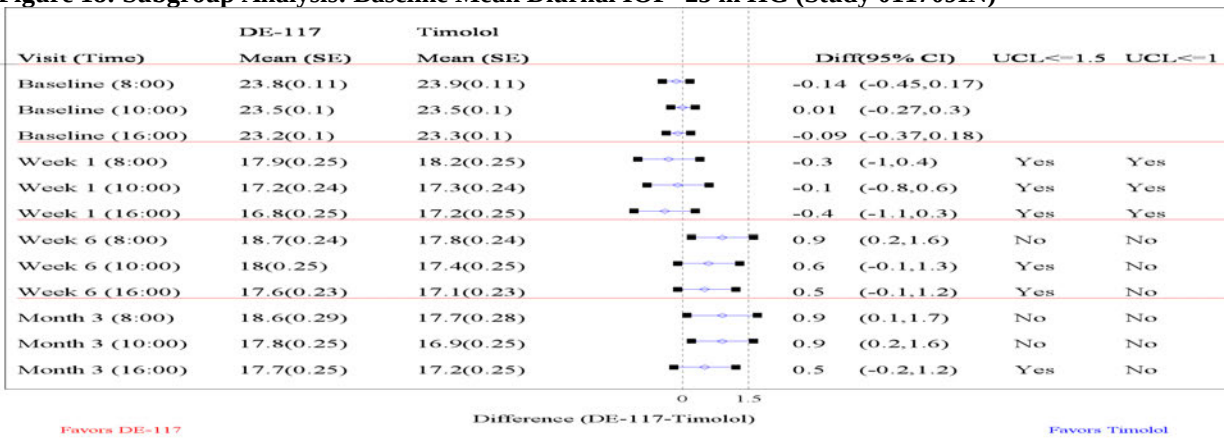
Figure 17: Difference in Mean Change from Baseline IOP (Study 01171505)



Visit (Time)	DE-117 Mean (SE)	Latanoprost Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Baseline (9:00)	24.9(0.18)	24.7(0.18)	0.15 (-0.36,0.65)		
Baseline (13:00)	24.5(0.17)	24.5(0.17)	0.05 (-0.43,0.52)		
Baseline (17:00)	24.3(0.17)	24.3(0.17)	0.03 (-0.45,0.51)		
Week 1 (9:00)	-5.8(0.28)	-6.1(0.29)	0.2 (-0.5,0.9)	Yes	Yes
Week 1 (13:00)	-6.1(0.28)	-6.1(0.29)	0 (-0.7,0.7)	Yes	Yes
Week 1 (17:00)	-6.3(0.28)	-6.1(0.28)	-0.2 (-0.9,0.5)	Yes	Yes
Week 6 (9:00)	-7.1(0.26)	-7.4(0.26)	0.4 (-0.3,1)	Yes	Yes
Week 6 (13:00)	-7(0.27)	-7.3(0.27)	0.4 (-0.3,1)	Yes	Yes
Week 6 (17:00)	-6.9(0.26)	-7.3(0.27)	0.4 (-0.3,1)	Yes	Yes
Month 3 (9:00)	-7(0.27)	-7.8(0.27)	0.9 (0.2,1.5)	Yes	No
Month 3 (13:00)	-7.3(0.25)	-7.9(0.26)	0.6 (0,1.2)	Yes	No
Month 3 (17:00)	-7.1(0.26)	-7.6(0.27)	0.5 (-0.2,1.1)	Yes	No

Source: Reviewer's Analysis Change from baseline IOP is used as dependent variable in the MMRM model

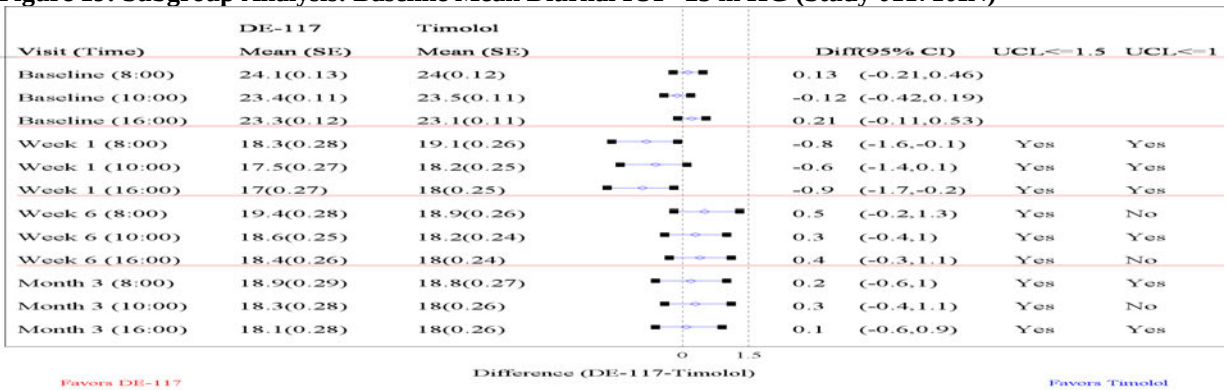
Figure 18: Subgroup Analysis: Baseline Mean Diurnal IOP<25 m HG (Study 011709IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Baseline (8:00)	23.8(0.11)	23.9(0.11)	-0.14 (-0.45,0.17)		
Baseline (10:00)	23.5(0.1)	23.5(0.1)	0.01 (-0.27,0.3)		
Baseline (16:00)	23.2(0.1)	23.3(0.1)	-0.09 (-0.37,0.18)		
Week 1 (8:00)	17.9(0.25)	18.2(0.25)	-0.3 (-1,0.4)	Yes	Yes
Week 1 (10:00)	17.2(0.24)	17.3(0.24)	-0.1 (-0.8,0.6)	Yes	Yes
Week 1 (16:00)	16.8(0.25)	17.2(0.25)	-0.4 (-1.1,0.3)	Yes	Yes
Week 6 (8:00)	18.7(0.24)	17.8(0.24)	0.9 (0.2,1.6)	No	No
Week 6 (10:00)	18(0.25)	17.4(0.25)	0.6 (-0.1,1.3)	Yes	No
Week 6 (16:00)	17.6(0.23)	17.1(0.23)	0.5 (-0.1,1.2)	Yes	No
Month 3 (8:00)	18.6(0.29)	17.7(0.28)	0.9 (0.1,1.7)	No	No
Month 3 (10:00)	17.8(0.25)	16.9(0.25)	0.9 (0.2,1.6)	No	No
Month 3 (16:00)	17.7(0.25)	17.2(0.25)	0.5 (-0.2,1.2)	Yes	No

Source: Reviewer's Analysis

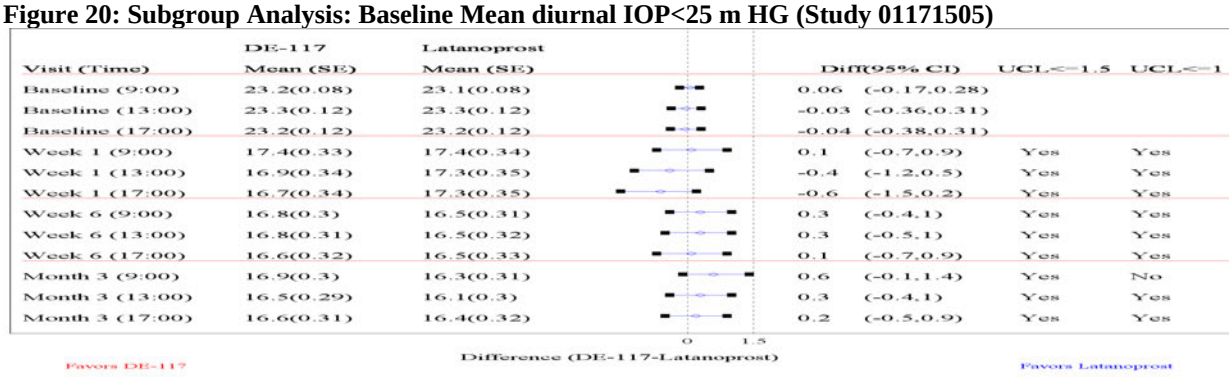
Figure 19: Subgroup Analysis: Baseline Mean Diurnal IOP<25 m HG (Study 011710IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Baseline (8:00)	24.1(0.13)	24(0.12)	0.13 (-0.21,0.46)		
Baseline (10:00)	23.4(0.11)	23.5(0.11)	-0.12 (-0.42,0.19)		
Baseline (16:00)	23.3(0.12)	23.1(0.11)	0.21 (-0.11,0.53)		
Week 1 (8:00)	18.3(0.28)	19.1(0.26)	-0.8 (-1.6,-0.1)	Yes	Yes
Week 1 (10:00)	17.5(0.27)	18.2(0.25)	-0.6 (-1.4,0.1)	Yes	Yes
Week 1 (16:00)	17(0.27)	18(0.25)	-0.9 (-1.7,-0.2)	Yes	Yes
Week 6 (8:00)	19.4(0.28)	18.9(0.26)	0.5 (-0.2,1.3)	Yes	No
Week 6 (10:00)	18.6(0.25)	18.2(0.24)	0.3 (-0.4,1)	Yes	Yes
Week 6 (16:00)	18.4(0.26)	18(0.24)	0.4 (-0.3,1.1)	Yes	No
Month 3 (8:00)	18.9(0.29)	18.8(0.27)	0.2 (-0.6,1)	Yes	Yes
Month 3 (10:00)	18.3(0.28)	18(0.26)	0.3 (-0.4,1.1)	Yes	No
Month 3 (16:00)	18.1(0.28)	18(0.26)	0.1 (-0.6,0.9)	Yes	Yes

Source: Reviewer's Analysis

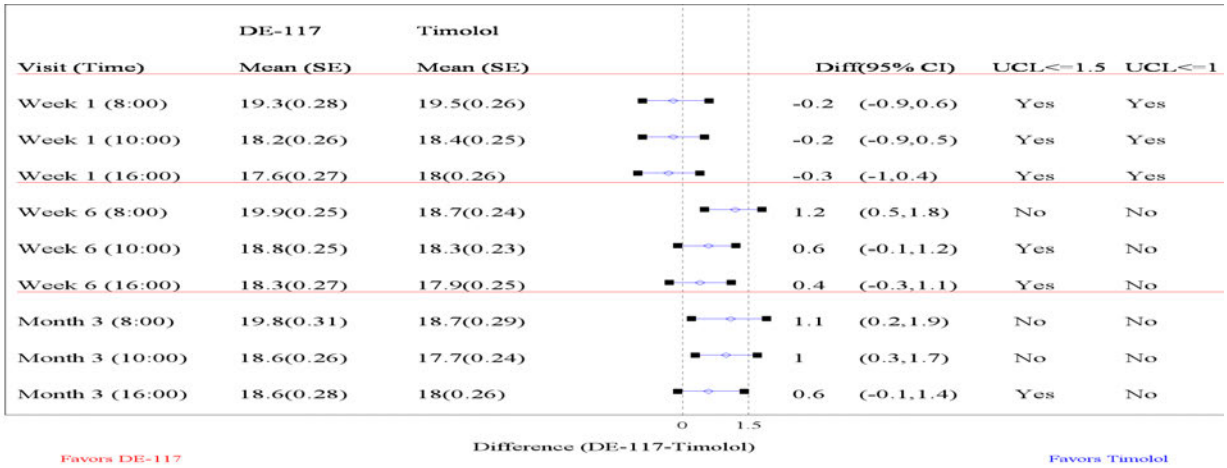
Figure 20: Subgroup Analysis: Baseline Mean diurnal IOP<25 m HG (Study 01171505)



Visit (Time)	DE-117 Mean (SE)	Latanoprost Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Baseline (9:00)	23.2(0.08)	23.1(0.08)	0.06 (-0.17,0.28)		
Baseline (13:00)	23.3(0.12)	23.3(0.12)	-0.03 (-0.36,0.31)		
Baseline (17:00)	23.2(0.12)	23.2(0.12)	-0.04 (-0.38,0.31)		
Week 1 (9:00)	17.4(0.33)	17.4(0.34)	0.1 (-0.7,0.9)	Yes	Yes
Week 1 (13:00)	16.9(0.34)	17.3(0.35)	-0.4 (-1.2,0.5)	Yes	Yes
Week 1 (17:00)	16.7(0.34)	17.3(0.35)	-0.6 (-1.5,0.2)	Yes	Yes
Week 6 (9:00)	16.8(0.3)	16.5(0.31)	0.3 (-0.4,1)	Yes	Yes
Week 6 (13:00)	16.8(0.31)	16.5(0.32)	0.3 (-0.5,1)	Yes	Yes
Week 6 (17:00)	16.6(0.32)	16.5(0.33)	0.1 (-0.7,0.9)	Yes	Yes
Month 3 (9:00)	16.9(0.3)	16.3(0.31)	0.6 (-0.1,1.4)	Yes	No
Month 3 (13:00)	16.5(0.29)	16.1(0.3)	0.3 (-0.4,1)	Yes	Yes
Month 3 (17:00)	16.6(0.31)	16.4(0.32)	0.2 (-0.5,0.9)	Yes	Yes

Source: Reviewer's Analysis

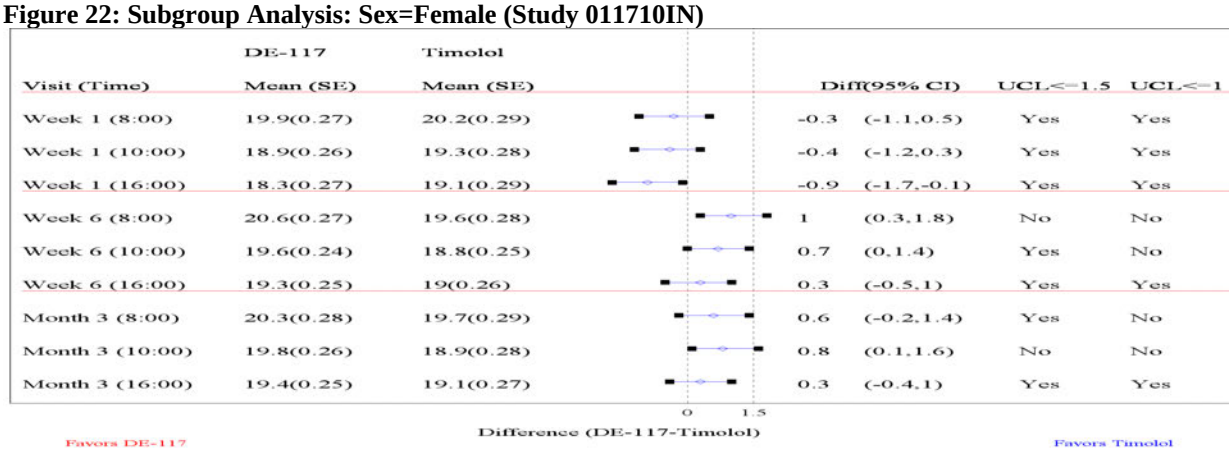
Figure 21: Subgroup Analysis: Sex=Female (Study 011709IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Week 1 (8:00)	19.3(0.28)	19.5(0.26)	-0.2 (-0.9,0.6)	Yes	Yes
Week 1 (10:00)	18.2(0.26)	18.4(0.25)	-0.2 (-0.9,0.5)	Yes	Yes
Week 1 (16:00)	17.6(0.27)	18(0.26)	-0.3 (-1,0.4)	Yes	Yes
Week 6 (8:00)	19.9(0.25)	18.7(0.24)	1.2 (0.5,1.8)	No	No
Week 6 (10:00)	18.8(0.25)	18.3(0.23)	0.6 (-0.1,1.2)	Yes	No
Week 6 (16:00)	18.3(0.27)	17.9(0.25)	0.4 (-0.3,1.1)	Yes	No
Month 3 (8:00)	19.8(0.31)	18.7(0.29)	1.1 (0.2,1.9)	No	No
Month 3 (10:00)	18.6(0.26)	17.7(0.24)	1 (0.3,1.7)	No	No
Month 3 (16:00)	18.6(0.28)	18(0.26)	0.6 (-0.1,1.4)	Yes	No

Source: Reviewer's Analysis

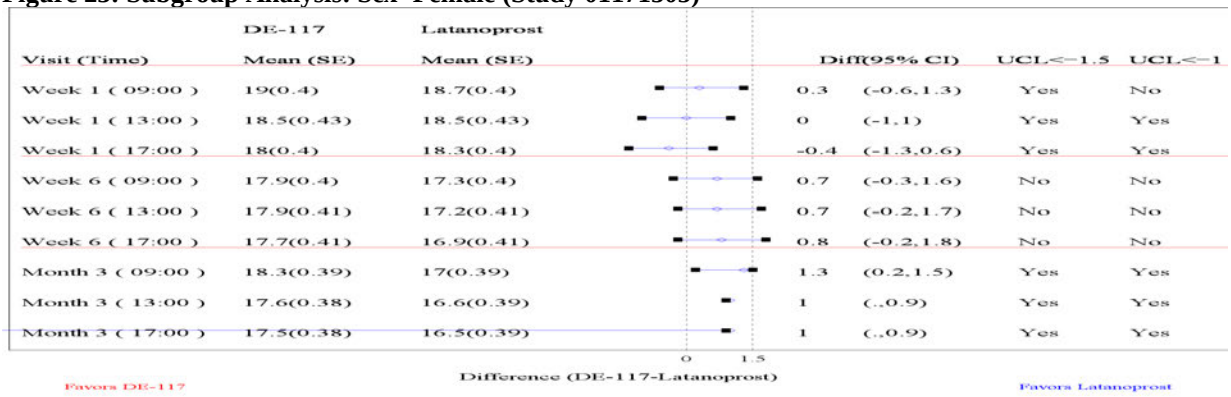
Figure 22: Subgroup Analysis: Sex=Female (Study 011710IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Week 1 (8:00)	19.9(0.27)	20.2(0.29)	-0.3 (-1.1,0.5)	Yes	Yes
Week 1 (10:00)	18.9(0.26)	19.3(0.28)	-0.4 (-1.2,0.3)	Yes	Yes
Week 1 (16:00)	18.3(0.27)	19.1(0.29)	-0.9 (-1.7,-0.1)	Yes	Yes
Week 6 (8:00)	20.6(0.27)	19.6(0.28)	1 (0.3,1.8)	No	No
Week 6 (10:00)	19.6(0.24)	18.8(0.25)	0.7 (0,1.4)	Yes	No
Week 6 (16:00)	19.3(0.25)	19(0.26)	0.3 (-0.5,1)	Yes	Yes
Month 3 (8:00)	20.3(0.28)	19.7(0.29)	0.6 (-0.2,1.4)	Yes	No
Month 3 (10:00)	19.8(0.26)	18.9(0.28)	0.8 (0.1,1.6)	No	No
Month 3 (16:00)	19.4(0.25)	19.1(0.27)	0.3 (-0.4,1)	Yes	Yes

Source: Reviewer's Analysis

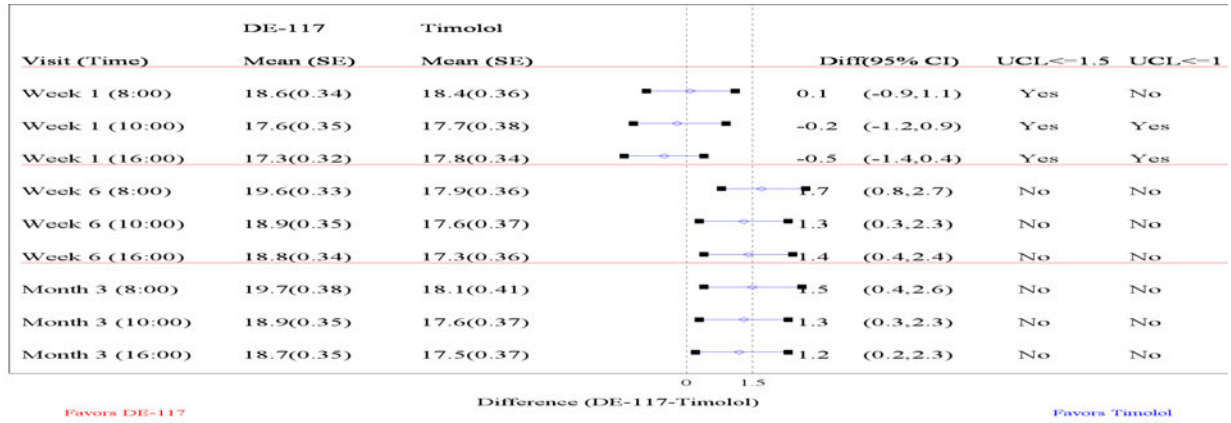
Figure 23: Subgroup Analysis: Sex=Female (Study 01171505)



Visit (Time)	DE-117 Mean (SE)	Latanoprost Mean (SE)	Diff	95% CI	UCL<=1.5	UCL<=1
Week 1 (09:00)	19(0.4)	18.7(0.4)	0.3	(-0.6,1.3)	Yes	No
Week 1 (13:00)	18.5(0.43)	18.5(0.43)	0	(-1,1)	Yes	Yes
Week 1 (17:00)	18(0.4)	18.3(0.4)	-0.4	(-1.3,0.6)	Yes	Yes
Week 6 (09:00)	17.9(0.4)	17.3(0.4)	0.7	(-0.3,1.6)	No	No
Week 6 (13:00)	17.9(0.41)	17.2(0.41)	0.7	(-0.2,1.7)	No	No
Week 6 (17:00)	17.7(0.41)	16.9(0.41)	0.8	(-0.2,1.8)	No	No
Month 3 (09:00)	18.3(0.39)	17(0.39)	1.3	(0.2,1.5)	Yes	Yes
Month 3 (13:00)	17.6(0.38)	16.6(0.39)	1	(.,0.9)	Yes	Yes
Month 3 (17:00)	17.5(0.38)	16.5(0.39)	1	(.,0.9)	Yes	Yes

Source: Reviewer's Analysis

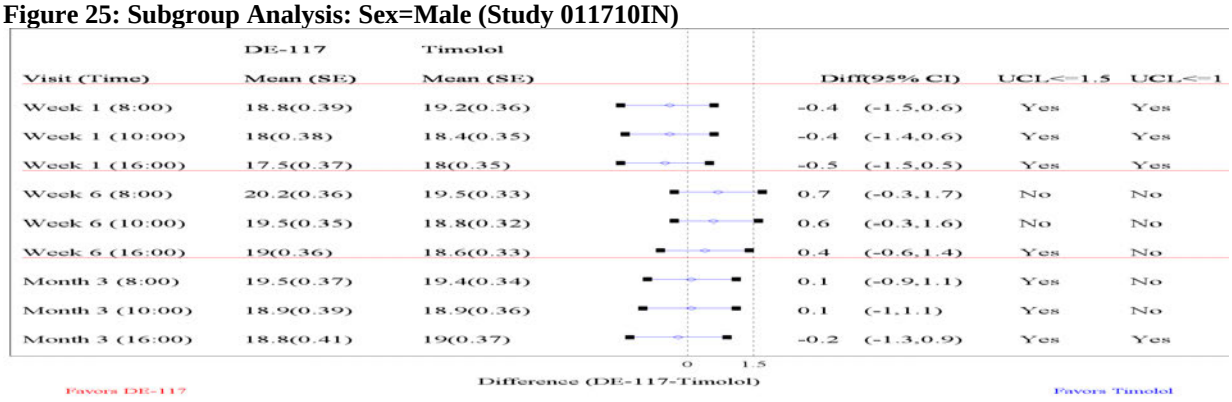
Figure 24: Subgroup Analysis: Sex=Male (Study 011709IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff	95% CI	UCL<=1.5	UCL<=1
Week 1 (8:00)	18.6(0.34)	18.4(0.36)	0.1	(-0.9,1.1)	Yes	No
Week 1 (10:00)	17.6(0.35)	17.7(0.38)	-0.2	(-1.2,0.9)	Yes	Yes
Week 1 (16:00)	17.3(0.32)	17.8(0.34)	-0.5	(-1.4,0.4)	Yes	Yes
Week 6 (8:00)	19.6(0.33)	17.9(0.36)	1.7	(0.8,2.7)	No	No
Week 6 (10:00)	18.9(0.35)	17.6(0.37)	1.3	(0.3,2.3)	No	No
Week 6 (16:00)	18.8(0.34)	17.3(0.36)	1.4	(0.4,2.4)	No	No
Month 3 (8:00)	19.7(0.38)	18.1(0.41)	1.5	(0.4,2.6)	No	No
Month 3 (10:00)	18.9(0.35)	17.6(0.37)	1.3	(0.3,2.3)	No	No
Month 3 (16:00)	18.7(0.35)	17.5(0.37)	1.2	(0.2,2.3)	No	No

Source: Reviewer's Analysis

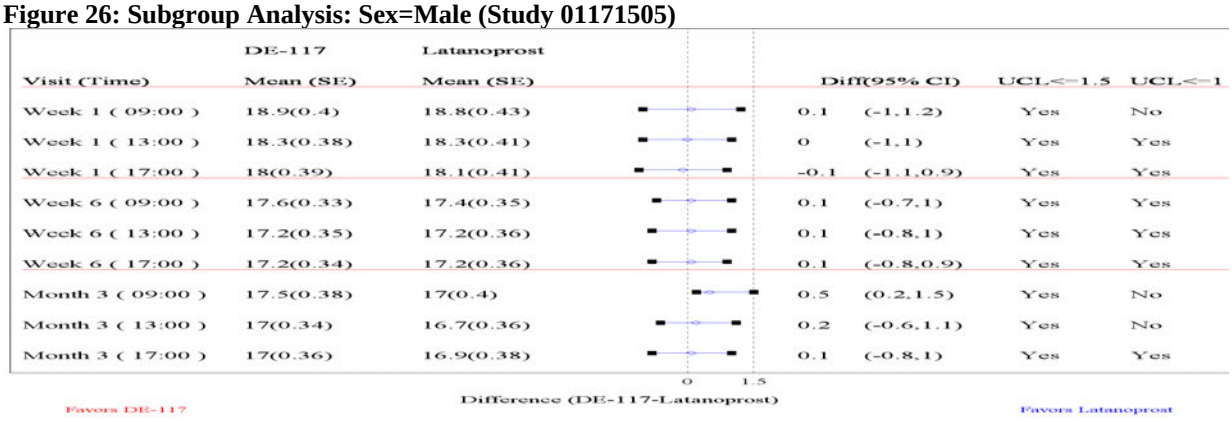
Figure 25: Subgroup Analysis: Sex=Male (Study 011710IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff	95% CI	UCL<=1.5	UCL<=1
Week 1 (8:00)	18.8(0.39)	19.2(0.36)	-0.4	(-1.5,0.6)	Yes	Yes
Week 1 (10:00)	18(0.38)	18.4(0.35)	-0.4	(-1.4,0.6)	Yes	Yes
Week 1 (16:00)	17.5(0.37)	18(0.35)	-0.5	(-1.5,0.5)	Yes	Yes
Week 6 (8:00)	20.2(0.36)	19.5(0.33)	0.7	(-0.3,1.7)	No	No
Week 6 (10:00)	19.5(0.35)	18.8(0.32)	0.6	(-0.3,1.6)	No	No
Week 6 (16:00)	19(0.36)	18.6(0.33)	0.4	(-0.6,1.4)	Yes	No
Month 3 (8:00)	19.5(0.37)	19.4(0.34)	0.1	(-0.9,1.1)	Yes	No
Month 3 (10:00)	18.9(0.39)	18.9(0.36)	0.1	(-1,1.1)	Yes	No
Month 3 (16:00)	18.8(0.41)	19(0.37)	-0.2	(-1.3,0.9)	Yes	Yes

Source: Reviewer's Analysis

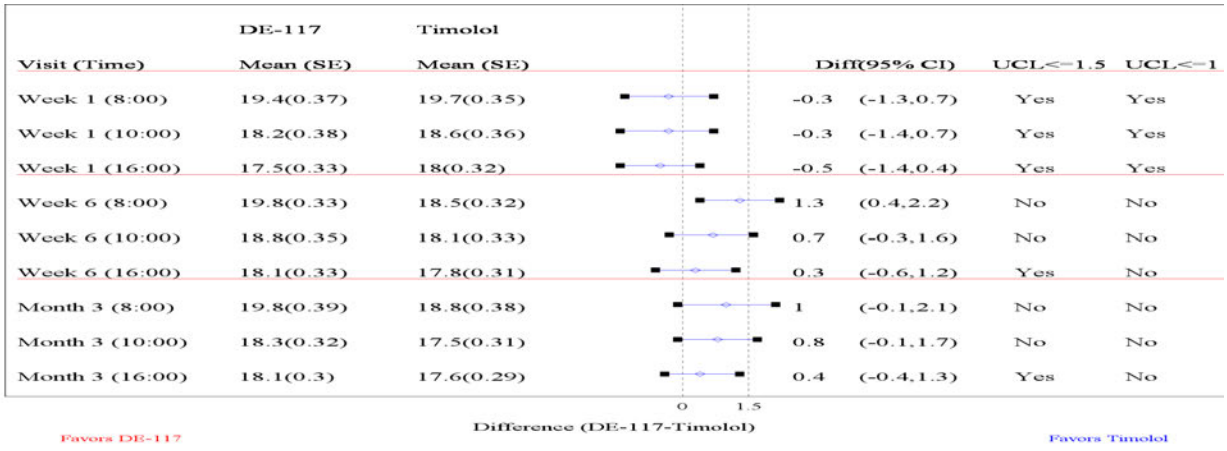
Figure 26: Subgroup Analysis: Sex=Male (Study 01171505)



Visit (Time)	DE-117 Mean (SE)	Latanoprost Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Week 1 (09:00)	18.9(0.4)	18.8(0.43)	0.1 (-1,1.2)	Yes	No
Week 1 (13:00)	18.3(0.38)	18.3(0.41)	0 (-1,1)	Yes	Yes
Week 1 (17:00)	18(0.39)	18.1(0.41)	-0.1 (-1.1,0.9)	Yes	Yes
Week 6 (09:00)	17.6(0.33)	17.4(0.35)	0.1 (-0.7,1)	Yes	Yes
Week 6 (13:00)	17.2(0.35)	17.2(0.36)	0.1 (-0.8,1)	Yes	Yes
Week 6 (17:00)	17.2(0.34)	17.2(0.36)	0.1 (-0.8,0.9)	Yes	Yes
Month 3 (09:00)	17.5(0.38)	17(0.4)	0.5 (0.2,1.5)	Yes	No
Month 3 (13:00)	17(0.34)	16.7(0.36)	0.2 (-0.6,1.1)	Yes	No
Month 3 (17:00)	17(0.36)	16.9(0.38)	0.1 (-0.8,1)	Yes	Yes

Source: Reviewer's Analysis

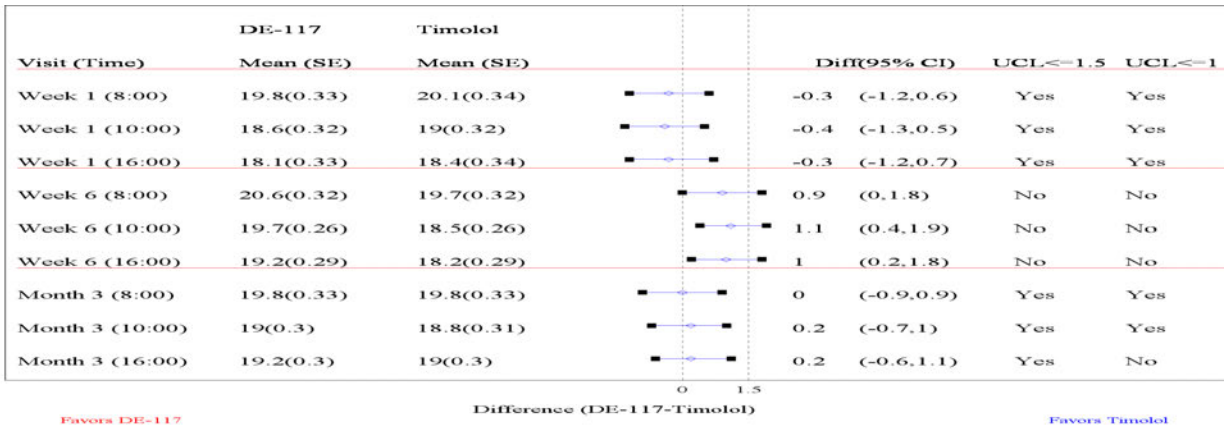
Figure 27: Subgroup Analysis: Age<65 (Study 011709IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Week 1 (8:00)	19.4(0.37)	19.7(0.35)	-0.3 (-1.3,0.7)	Yes	Yes
Week 1 (10:00)	18.2(0.38)	18.6(0.36)	-0.3 (-1.4,0.7)	Yes	Yes
Week 1 (16:00)	17.5(0.33)	18(0.32)	-0.5 (-1.4,0.4)	Yes	Yes
Week 6 (8:00)	19.8(0.33)	18.5(0.32)	1.3 (0.4,2.2)	No	No
Week 6 (10:00)	18.8(0.35)	18.1(0.33)	0.7 (-0.3,1.6)	No	No
Week 6 (16:00)	18.1(0.33)	17.8(0.31)	0.3 (-0.6,1.2)	Yes	No
Month 3 (8:00)	19.8(0.39)	18.8(0.38)	1 (-0.1,2.1)	No	No
Month 3 (10:00)	18.3(0.32)	17.5(0.31)	0.8 (-0.1,1.7)	No	No
Month 3 (16:00)	18.1(0.3)	17.6(0.29)	0.4 (-0.4,1.3)	Yes	No

Source: Reviewer's Analysis

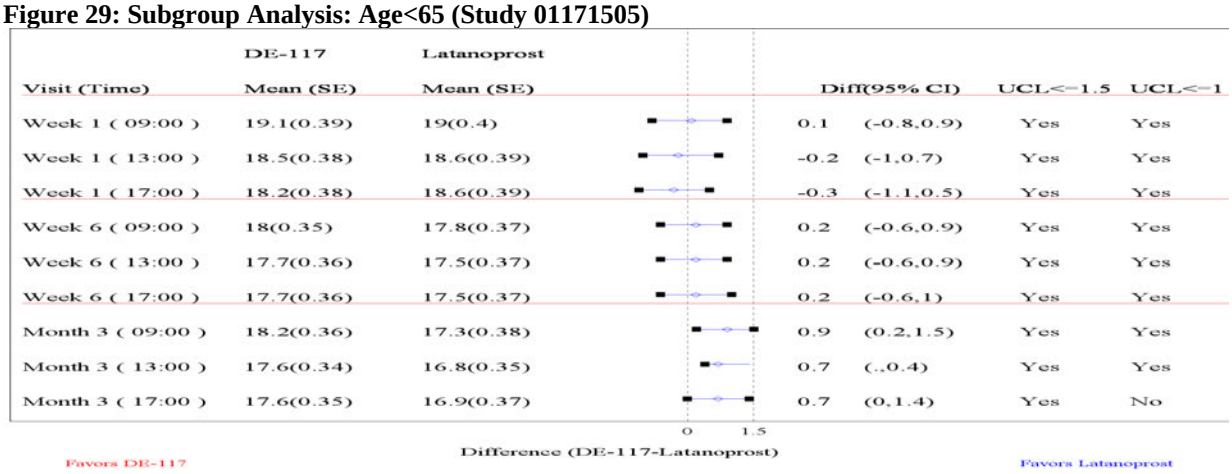
Figure 28: Subgroup Analysis: Age<65 (Study 011710IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Week 1 (8:00)	19.8(0.33)	20.1(0.34)	-0.3 (-1.2,0.6)	Yes	Yes
Week 1 (10:00)	18.6(0.32)	19(0.32)	-0.4 (-1.3,0.5)	Yes	Yes
Week 1 (16:00)	18.1(0.33)	18.4(0.34)	-0.3 (-1.2,0.7)	Yes	Yes
Week 6 (8:00)	20.6(0.32)	19.7(0.32)	0.9 (0,1.8)	No	No
Week 6 (10:00)	19.7(0.26)	18.5(0.26)	1.1 (0.4,1.9)	No	No
Week 6 (16:00)	19.2(0.29)	18.2(0.29)	1 (0.2,1.8)	No	No
Month 3 (8:00)	19.8(0.33)	19.8(0.33)	0 (-0.9,0.9)	Yes	Yes
Month 3 (10:00)	19(0.3)	18.8(0.31)	0.2 (-0.7,1)	Yes	Yes
Month 3 (16:00)	19.2(0.3)	19(0.3)	0.2 (-0.6,1.1)	Yes	No

Source: Reviewer's Analysis

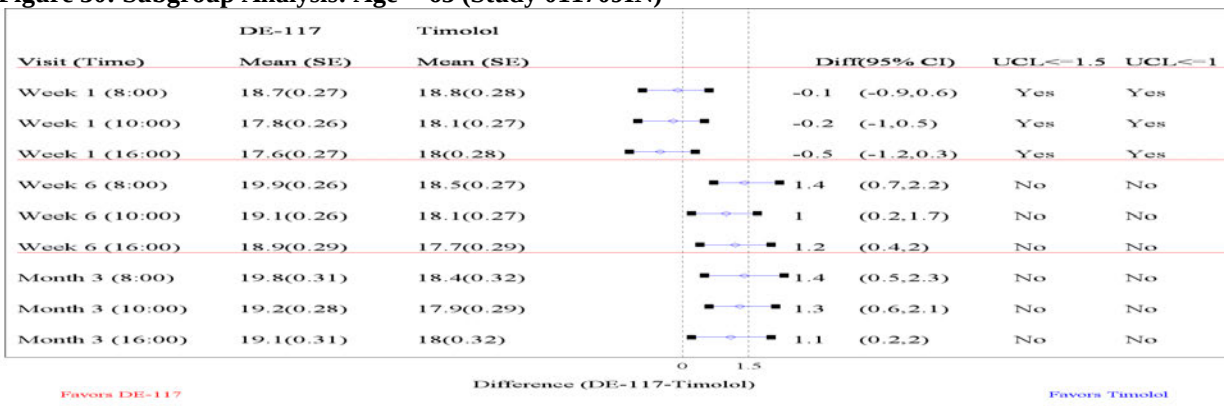
Figure 29: Subgroup Analysis: Age<65 (Study 01171505)



Visit (Time)	DE-117 Mean (SE)	Latanoprost Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Week 1 (09:00)	19.1(0.39)	19(0.4)	0.1 (-0.8,0.9)	Yes	Yes
Week 1 (13:00)	18.5(0.38)	18.6(0.39)	-0.2 (-1,0.7)	Yes	Yes
Week 1 (17:00)	18.2(0.38)	18.6(0.39)	-0.3 (-1.1,0.5)	Yes	Yes
Week 6 (09:00)	18(0.35)	17.8(0.37)	0.2 (-0.6,0.9)	Yes	Yes
Week 6 (13:00)	17.7(0.36)	17.5(0.37)	0.2 (-0.6,0.9)	Yes	Yes
Week 6 (17:00)	17.7(0.36)	17.5(0.37)	0.2 (-0.6,1)	Yes	Yes
Month 3 (09:00)	18.2(0.36)	17.3(0.38)	0.9 (0.2,1.5)	Yes	Yes
Month 3 (13:00)	17.6(0.34)	16.8(0.35)	0.7 (.,0.4)	Yes	Yes
Month 3 (17:00)	17.6(0.35)	16.9(0.37)	0.7 (0,1.4)	Yes	No

Source: Reviewer's Analysis

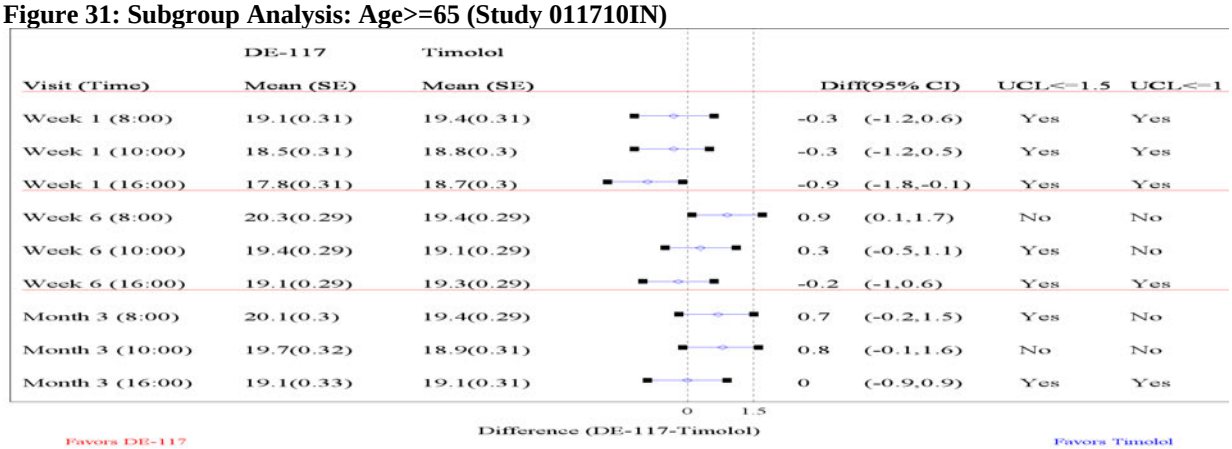
Figure 30: Subgroup Analysis: Age>=65 (Study 011709IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Week 1 (8:00)	18.7(0.27)	18.8(0.28)	-0.1 (-0.9,0.6)	Yes	Yes
Week 1 (10:00)	17.8(0.26)	18.1(0.27)	-0.2 (-1,0.5)	Yes	Yes
Week 1 (16:00)	17.6(0.27)	18(0.28)	-0.5 (-1.2,0.3)	Yes	Yes
Week 6 (8:00)	19.9(0.26)	18.5(0.27)	1.4 (0.7,2.2)	No	No
Week 6 (10:00)	19.1(0.26)	18.1(0.27)	1 (0.2,1.7)	No	No
Week 6 (16:00)	18.9(0.29)	17.7(0.29)	1.2 (0.4,2)	No	No
Month 3 (8:00)	19.8(0.31)	18.4(0.32)	1.4 (0.5,2.3)	No	No
Month 3 (10:00)	19.2(0.28)	17.9(0.29)	1.3 (0.6,2.1)	No	No
Month 3 (16:00)	19.1(0.31)	18(0.32)	1.1 (0.2,2)	No	No

Source: Reviewer's Analysis

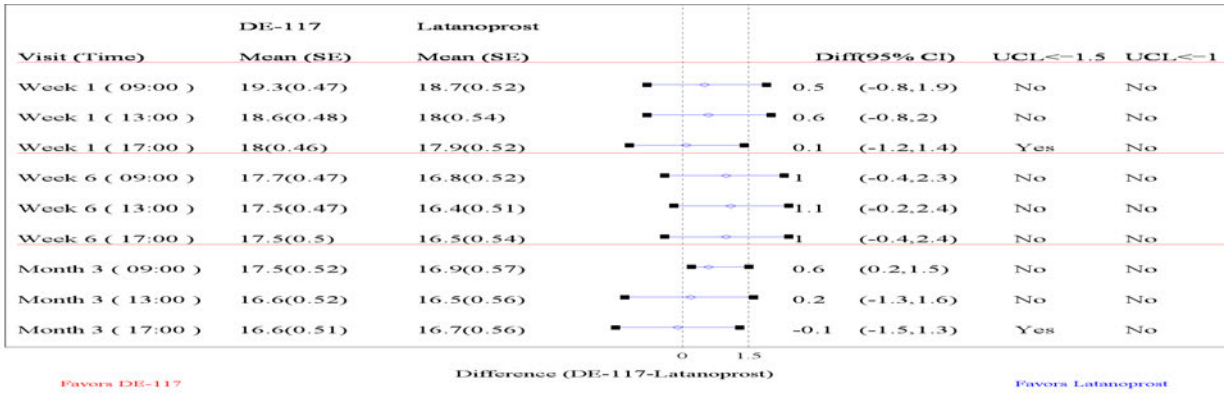
Figure 31: Subgroup Analysis: Age>=65 (Study 011710IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1
Week 1 (8:00)	19.1(0.31)	19.4(0.31)	-0.3 (-1.2,0.6)	Yes	Yes
Week 1 (10:00)	18.5(0.31)	18.8(0.3)	-0.3 (-1.2,0.5)	Yes	Yes
Week 1 (16:00)	17.8(0.31)	18.7(0.3)	-0.9 (-1.8,-0.1)	Yes	Yes
Week 6 (8:00)	20.3(0.29)	19.4(0.29)	0.9 (0.1,1.7)	No	No
Week 6 (10:00)	19.4(0.29)	19.1(0.29)	0.3 (-0.5,1.1)	Yes	No
Week 6 (16:00)	19.1(0.29)	19.3(0.29)	-0.2 (-1,0.6)	Yes	Yes
Month 3 (8:00)	20.1(0.3)	19.4(0.29)	0.7 (-0.2,1.5)	Yes	No
Month 3 (10:00)	19.7(0.32)	18.9(0.31)	0.8 (-0.1,1.6)	No	No
Month 3 (16:00)	19.1(0.33)	19.1(0.31)	0 (-0.9,0.9)	Yes	Yes

Source: Reviewer's Analysis

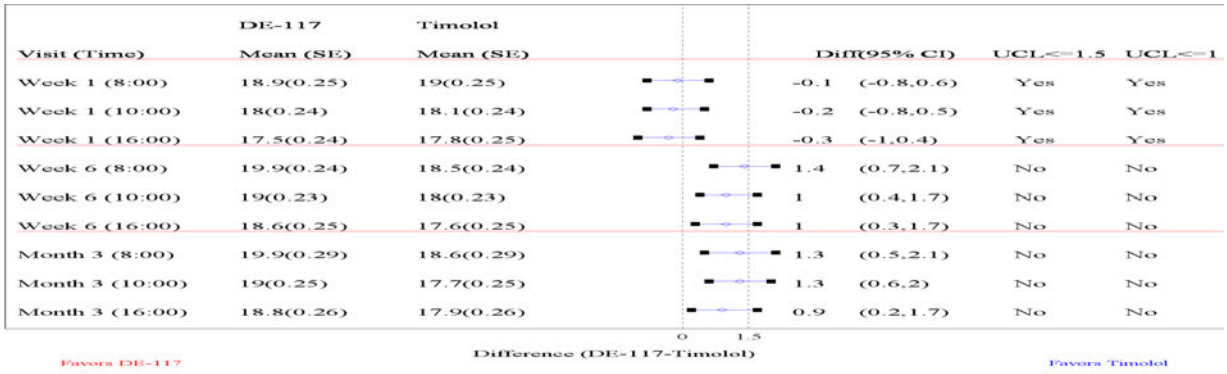
Figure 32: Subgroup Analysis: Age>=65 (Study 01171505)



Visit (Time)	DE-117 Mean (SE)	Latanoprost Mean (SE)	Diff	95% CI	UCL<=1.5	UCL<=1
Week 1 (09:00)	19.3(0.47)	18.7(0.52)	0.5	(-0.8,1.9)	No	No
Week 1 (13:00)	18.6(0.48)	18(0.54)	0.6	(-0.8,2)	No	No
Week 1 (17:00)	18(0.46)	17.9(0.52)	0.1	(-1.2,1.4)	Yes	No
Week 6 (09:00)	17.7(0.47)	16.8(0.52)	1	(-0.4,2.3)	No	No
Week 6 (13:00)	17.5(0.47)	16.4(0.51)	1.1	(-0.2,2.4)	No	No
Week 6 (17:00)	17.5(0.5)	16.5(0.54)	1	(-0.4,2.4)	No	No
Month 3 (09:00)	17.5(0.52)	16.9(0.57)	0.6	(-0.2,1.5)	No	No
Month 3 (13:00)	16.6(0.52)	16.5(0.56)	0.2	(-1.3,1.6)	No	No
Month 3 (17:00)	16.6(0.51)	16.7(0.56)	-0.1	(-1.5,1.3)	Yes	No

Source: Reviewer's Analysis

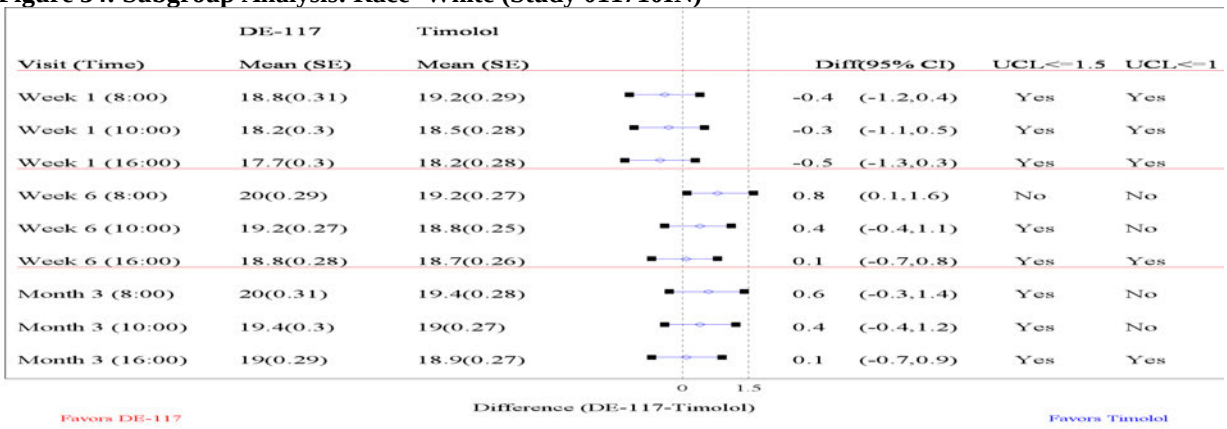
Figure 33: Subgroup Analysis: Race=White (Study 011709IN)



Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff	95% CI	UCL<=1.5	UCL<=1
Week 1 (8:00)	18.9(0.25)	19(0.25)	-0.1	(-0.8,0.6)	Yes	Yes
Week 1 (10:00)	18(0.24)	18.1(0.24)	-0.2	(-0.8,0.5)	Yes	Yes
Week 1 (16:00)	17.5(0.24)	17.8(0.25)	-0.3	(-1,0.4)	Yes	Yes
Week 6 (8:00)	19.9(0.24)	18.5(0.24)	1.4	(0.7,2.1)	No	No
Week 6 (10:00)	19(0.23)	18(0.23)	1	(0.4,1.7)	No	No
Week 6 (16:00)	18.6(0.25)	17.6(0.25)	1	(0.3,1.7)	No	No
Month 3 (8:00)	19.9(0.29)	18.6(0.29)	1.3	(0.5,2.1)	No	No
Month 3 (10:00)	19(0.25)	17.7(0.25)	1.3	(0.6,2)	No	No
Month 3 (16:00)	18.8(0.26)	17.9(0.26)	0.9	(0.2,1.7)	No	No

Source: Reviewer's Analysis

Figure 34: Subgroup Analysis: Race=White (Study 011710IN)

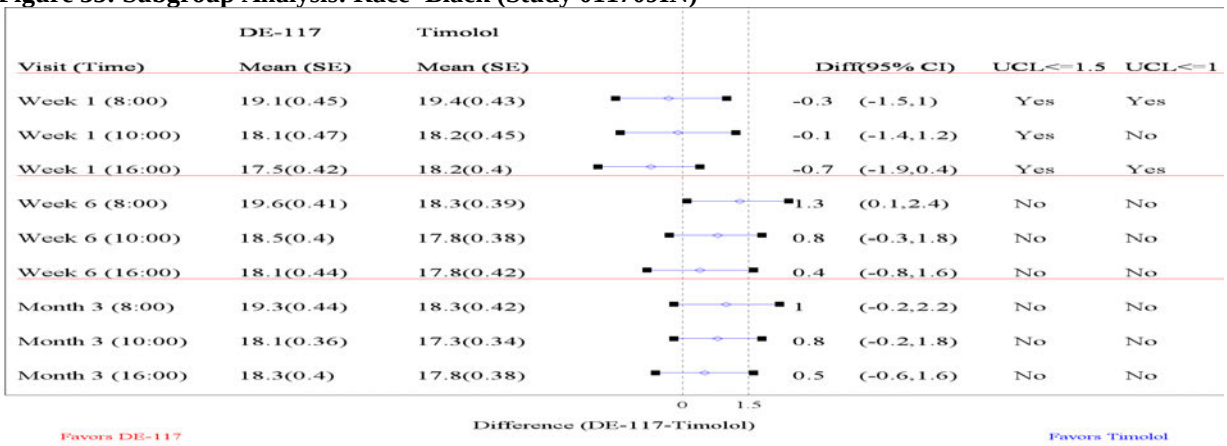


Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff	95% CI	UCL<=1.5	UCL<=1
Week 1 (8:00)	18.8(0.31)	19.2(0.29)	-0.4	(-1.2,0.4)	Yes	Yes
Week 1 (10:00)	18.2(0.3)	18.5(0.28)	-0.3	(-1.1,0.5)	Yes	Yes
Week 1 (16:00)	17.7(0.3)	18.2(0.28)	-0.5	(-1.3,0.3)	Yes	Yes
Week 6 (8:00)	20(0.29)	19.2(0.27)	0.8	(0.1,1.6)	No	No
Week 6 (10:00)	19.2(0.27)	18.8(0.25)	0.4	(-0.4,1.1)	Yes	No
Week 6 (16:00)	18.8(0.28)	18.7(0.26)	0.1	(-0.7,0.8)	Yes	Yes
Month 3 (8:00)	20(0.31)	19.4(0.28)	0.6	(-0.3,1.4)	Yes	No
Month 3 (10:00)	19.4(0.3)	19(0.27)	0.4	(-0.4,1.2)	Yes	No
Month 3 (16:00)	19(0.29)	18.9(0.27)	0.1	(-0.7,0.9)	Yes	Yes

Source: Reviewer's Analysis

Figure 35: Subgroup Analysis: Race=Black (Study 011709IN)

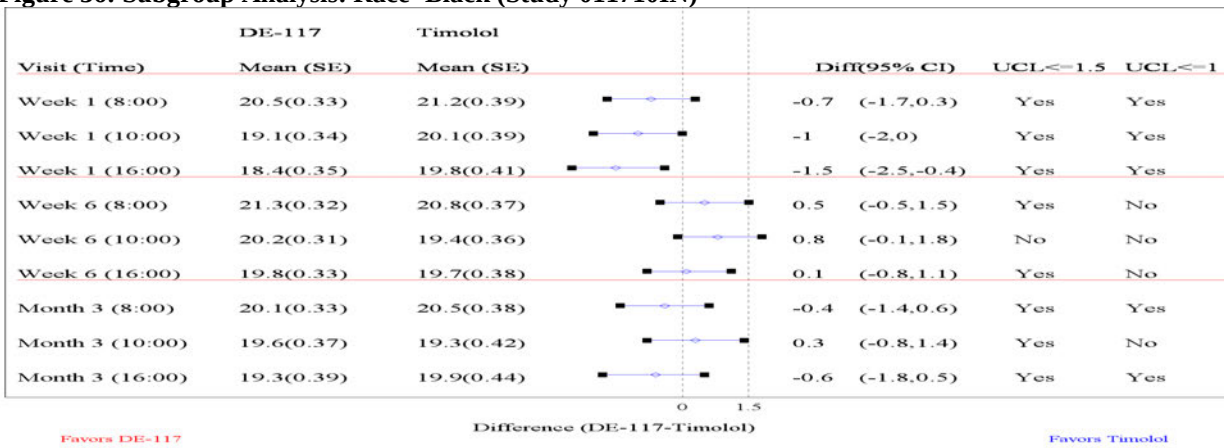
Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)		UCL<=1.5	UCL<=1
Week 1 (8:00)	19.1(0.45)	19.4(0.43)	-0.3	(-1.5,1)	Yes	Yes
Week 1 (10:00)	18.1(0.47)	18.2(0.45)	-0.1	(-1.4,1.2)	Yes	No
Week 1 (16:00)	17.5(0.42)	18.2(0.4)	-0.7	(-1.9,0.4)	Yes	Yes
Week 6 (8:00)	19.6(0.41)	18.3(0.39)	1.3	(0.1,2.4)	No	No
Week 6 (10:00)	18.5(0.4)	17.8(0.38)	0.8	(-0.3,1.8)	No	No
Week 6 (16:00)	18.1(0.44)	17.8(0.42)	0.4	(-0.8,1.6)	No	No
Month 3 (8:00)	19.3(0.44)	18.3(0.42)	1	(-0.2,2.2)	No	No
Month 3 (10:00)	18.1(0.36)	17.3(0.34)	0.8	(-0.2,1.8)	No	No
Month 3 (16:00)	18.3(0.4)	17.8(0.38)	0.5	(-0.6,1.6)	No	No



Source: Reviewer's Analysis

Figure 36: Subgroup Analysis: Race=Black (Study 011710IN)

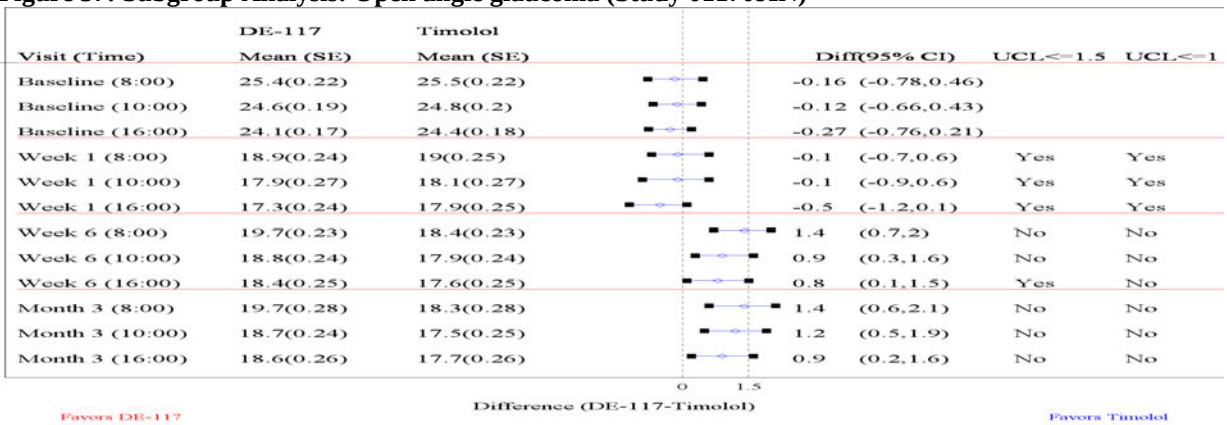
Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)		UCL<=1.5	UCL<=1
Week 1 (8:00)	20.5(0.33)	21.2(0.39)	-0.7	(-1.7,0.3)	Yes	Yes
Week 1 (10:00)	19.1(0.34)	20.1(0.39)	-1	(-2,0)	Yes	Yes
Week 1 (16:00)	18.4(0.35)	19.8(0.41)	-1.5	(-2.5,-0.4)	Yes	Yes
Week 6 (8:00)	21.3(0.32)	20.8(0.37)	0.5	(-0.5,1.5)	Yes	No
Week 6 (10:00)	20.2(0.31)	19.4(0.36)	0.8	(-0.1,1.8)	No	No
Week 6 (16:00)	19.8(0.33)	19.7(0.38)	0.1	(-0.8,1.1)	Yes	No
Month 3 (8:00)	20.1(0.33)	20.5(0.38)	-0.4	(-1.4,0.6)	Yes	Yes
Month 3 (10:00)	19.6(0.37)	19.3(0.42)	0.3	(-0.8,1.4)	Yes	No
Month 3 (16:00)	19.3(0.39)	19.9(0.44)	-0.6	(-1.8,0.5)	Yes	Yes



Source: Reviewer's Analysis

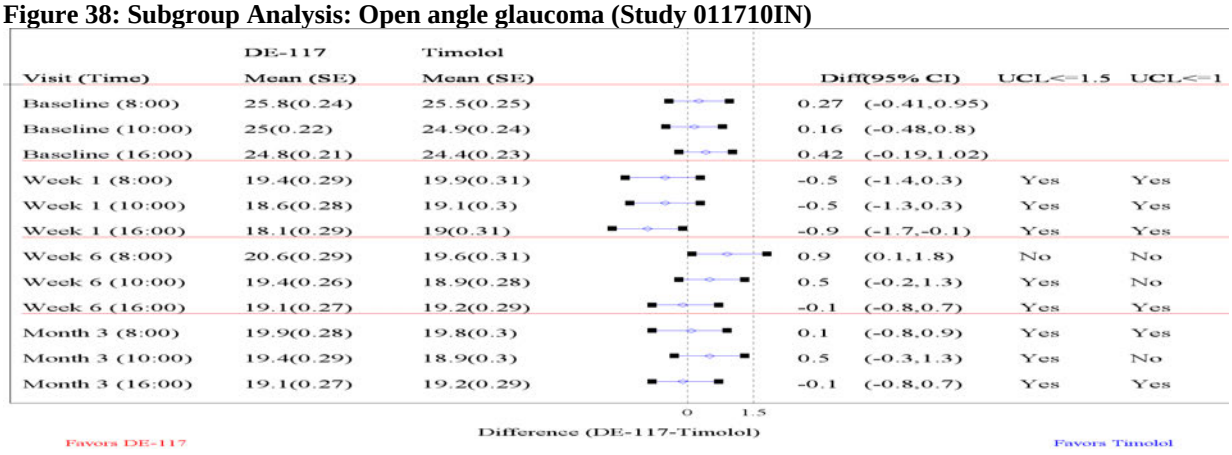
Figure 37: Subgroup Analysis: Open angle glaucoma (Study 011709IN)

Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)		UCL<=1.5	UCL<=1
Baseline (8:00)	25.4(0.22)	25.5(0.22)	-0.16	(-0.78,0.46)		
Baseline (10:00)	24.6(0.19)	24.8(0.2)	-0.12	(-0.66,0.43)		
Baseline (16:00)	24.1(0.17)	24.4(0.18)	-0.27	(-0.76,0.21)		
Week 1 (8:00)	18.9(0.24)	19(0.25)	-0.1	(-0.7,0.6)	Yes	Yes
Week 1 (10:00)	17.9(0.27)	18.1(0.27)	-0.1	(-0.9,0.6)	Yes	Yes
Week 1 (16:00)	17.3(0.24)	17.9(0.25)	-0.5	(-1.2,0.1)	Yes	Yes
Week 6 (8:00)	19.7(0.23)	18.4(0.23)	1.4	(0.7,2)	No	No
Week 6 (10:00)	18.8(0.24)	17.9(0.24)	0.9	(0.3,1.6)	No	No
Week 6 (16:00)	18.4(0.25)	17.6(0.25)	0.8	(0.1,1.5)	Yes	No
Month 3 (8:00)	19.7(0.28)	18.3(0.28)	1.4	(0.6,2.1)	No	No
Month 3 (10:00)	18.7(0.24)	17.5(0.25)	1.2	(0.5,1.9)	No	No
Month 3 (16:00)	18.6(0.26)	17.7(0.26)	0.9	(0.2,1.6)	No	No



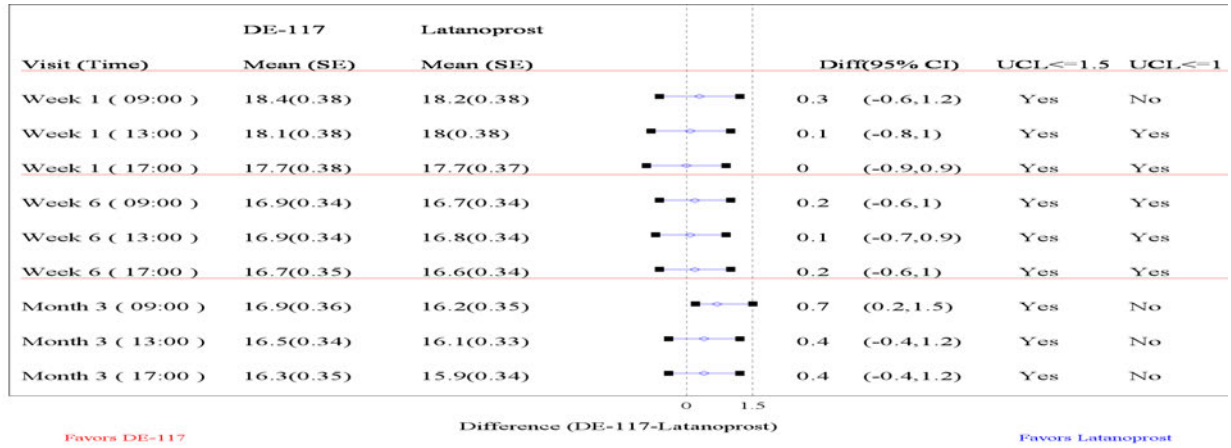
Source: Reviewer's Analysis

Figure 38: Subgroup Analysis: Open angle glaucoma (Study 011710IN)



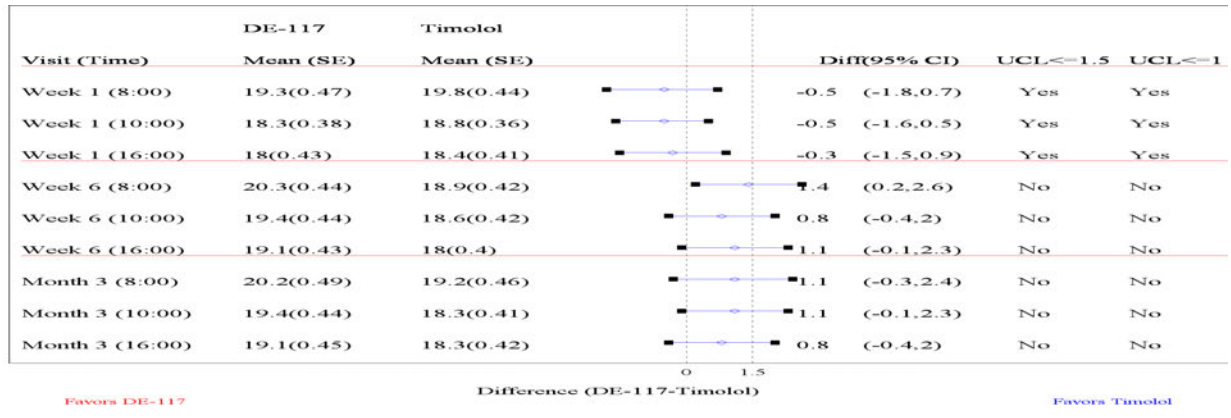
Source: Reviewer's Analysis

Figure 39: Subgroup Analysis: Open angle glaucoma (Study 01171505)



Source: Reviewer's Analysis

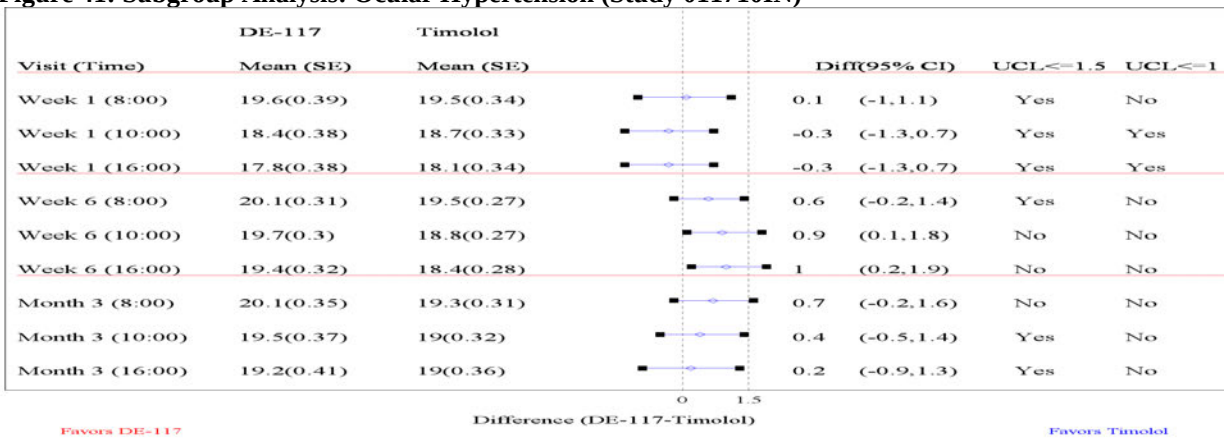
Figure 40: Subgroup Analysis: Ocular Hypertension (Study 011709IN)



Source: Reviewer's Analysis

Figure 41: Subgroup Analysis: Ocular Hypertension (Study 011710IN)

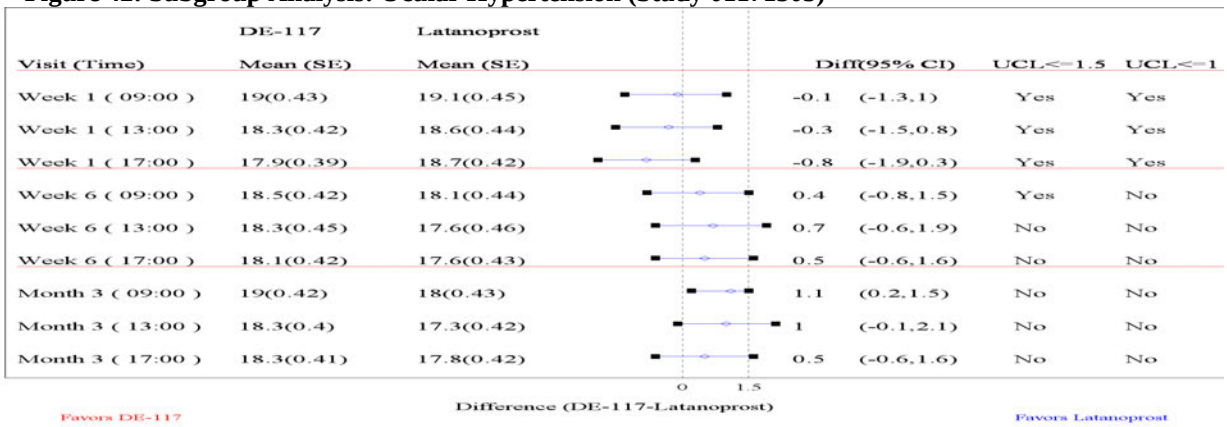
	DE-117	Timolol				
Visit (Time)	Mean (SE)	Mean (SE)	Diff	(95% CI)	UCL<=1.5	UCL<=1
Week 1 (8:00)	19.6(0.39)	19.5(0.34)	0.1	(-1,1.1)	Yes	No
Week 1 (10:00)	18.4(0.38)	18.7(0.33)	-0.3	(-1.3,0.7)	Yes	Yes
Week 1 (16:00)	17.8(0.38)	18.1(0.34)	-0.3	(-1.3,0.7)	Yes	Yes
Week 6 (8:00)	20.1(0.31)	19.5(0.27)	0.6	(-0.2,1.4)	Yes	No
Week 6 (10:00)	19.7(0.3)	18.8(0.27)	0.9	(0.1,1.8)	No	No
Week 6 (16:00)	19.4(0.32)	18.4(0.28)	1	(0.2,1.9)	No	No
Month 3 (8:00)	20.1(0.35)	19.3(0.31)	0.7	(-0.2,1.6)	No	No
Month 3 (10:00)	19.5(0.37)	19(0.32)	0.4	(-0.5,1.4)	Yes	No
Month 3 (16:00)	19.2(0.41)	19(0.36)	0.2	(-0.9,1.3)	Yes	No



Source: Reviewer's Analysis

Figure 42: Subgroup Analysis: Ocular Hypertension (Study 01171505)

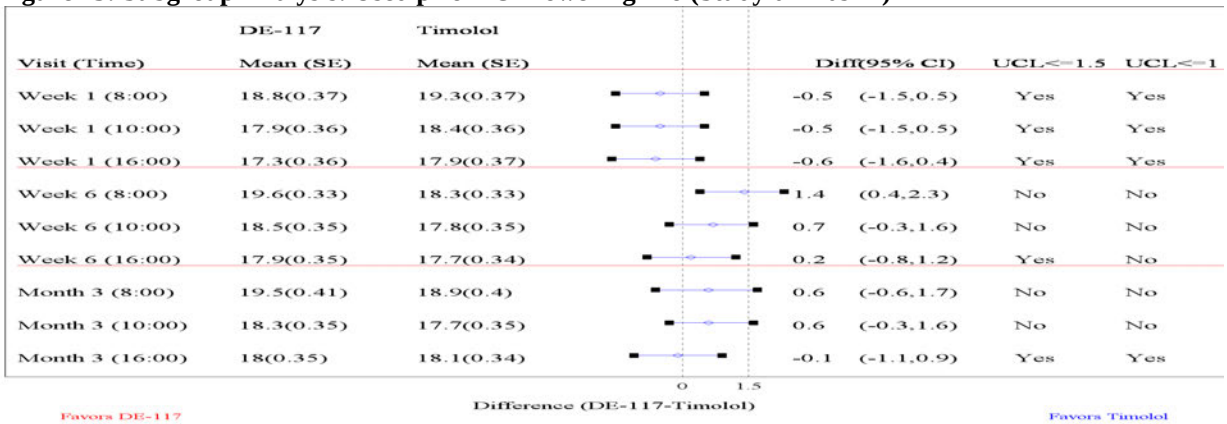
	DE-117	Latanoprost				
Visit (Time)	Mean (SE)	Mean (SE)	Diff	(95% CI)	UCL<=1.5	UCL<=1
Week 1 (09:00)	19(0.43)	19.1(0.45)	-0.1	(-1.3,1)	Yes	Yes
Week 1 (13:00)	18.3(0.42)	18.6(0.44)	-0.3	(-1.5,0.8)	Yes	Yes
Week 1 (17:00)	17.9(0.39)	18.7(0.42)	-0.8	(-1.9,0.3)	Yes	Yes
Week 6 (09:00)	18.5(0.42)	18.1(0.44)	0.4	(-0.8,1.5)	Yes	No
Week 6 (13:00)	18.3(0.45)	17.6(0.46)	0.7	(-0.6,1.9)	No	No
Week 6 (17:00)	18.1(0.42)	17.6(0.43)	0.5	(-0.6,1.6)	No	No
Month 3 (09:00)	19(0.42)	18(0.43)	1.1	(0.2,1.5)	No	No
Month 3 (13:00)	18.3(0.4)	17.3(0.42)	1	(-0.1,2.1)	No	No
Month 3 (17:00)	18.3(0.41)	17.8(0.42)	0.5	(-0.6,1.6)	No	No



Source: Reviewer's Analysis

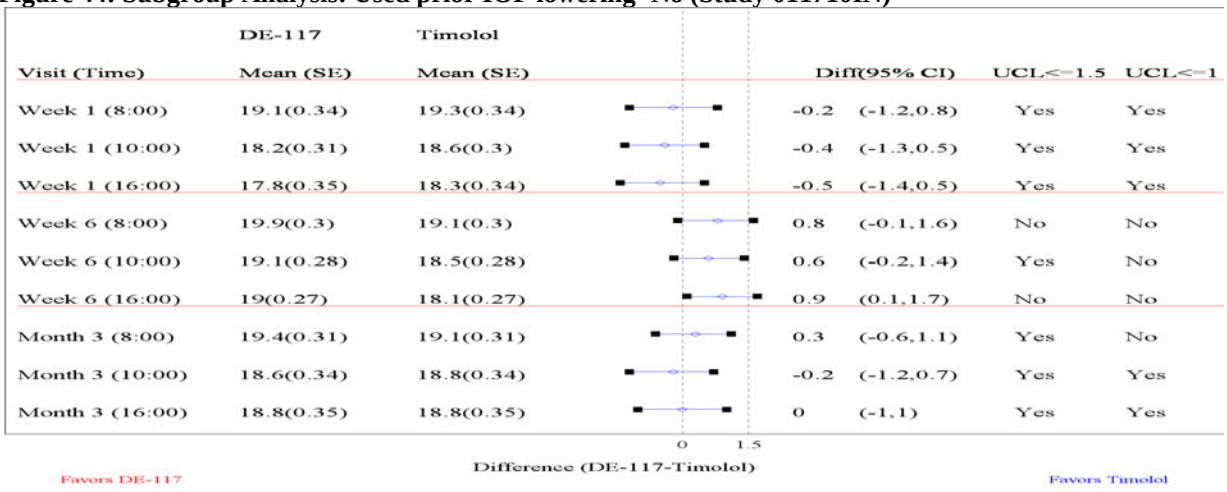
Figure 43: Subgroup Analysis: Used prior IOP lowering=No (Study 011709IN)

	DE-117	Timolol				
Visit (Time)	Mean (SE)	Mean (SE)	Diff	(95% CI)	UCL<=1.5	UCL<=1
Week 1 (8:00)	18.8(0.37)	19.3(0.37)	-0.5	(-1.5,0.5)	Yes	Yes
Week 1 (10:00)	17.9(0.36)	18.4(0.36)	-0.5	(-1.5,0.5)	Yes	Yes
Week 1 (16:00)	17.3(0.36)	17.9(0.37)	-0.6	(-1.6,0.4)	Yes	Yes
Week 6 (8:00)	19.6(0.33)	18.3(0.33)	1.4	(0.4,2.3)	No	No
Week 6 (10:00)	18.5(0.35)	17.8(0.35)	0.7	(-0.3,1.6)	No	No
Week 6 (16:00)	17.9(0.35)	17.7(0.34)	0.2	(-0.8,1.2)	Yes	No
Month 3 (8:00)	19.5(0.41)	18.9(0.4)	0.6	(-0.6,1.7)	No	No
Month 3 (10:00)	18.3(0.35)	17.7(0.35)	0.6	(-0.3,1.6)	No	No
Month 3 (16:00)	18(0.35)	18.1(0.34)	-0.1	(-1.1,0.9)	Yes	Yes



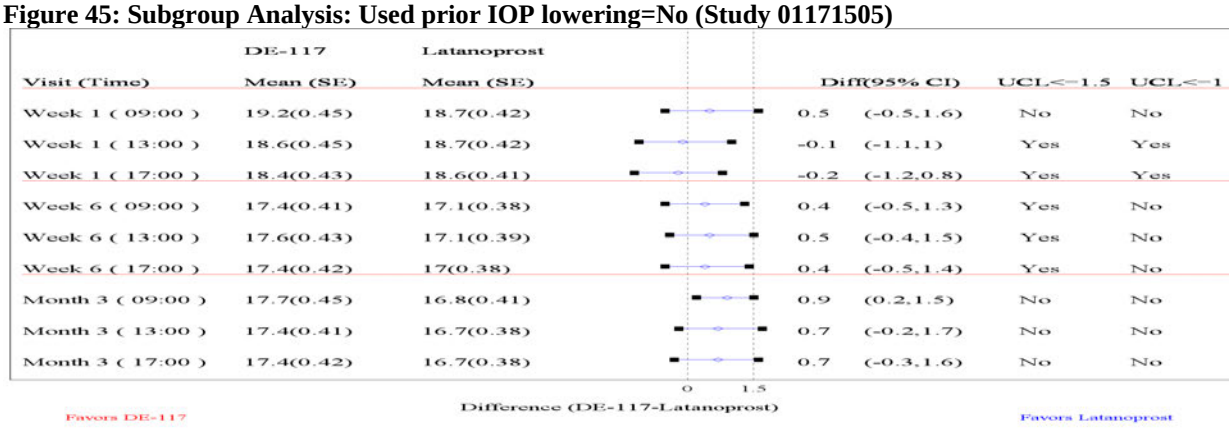
Source: Reviewer's Analysis

Figure 44: Subgroup Analysis: Used prior IOP lowering=No (Study 011710IN)



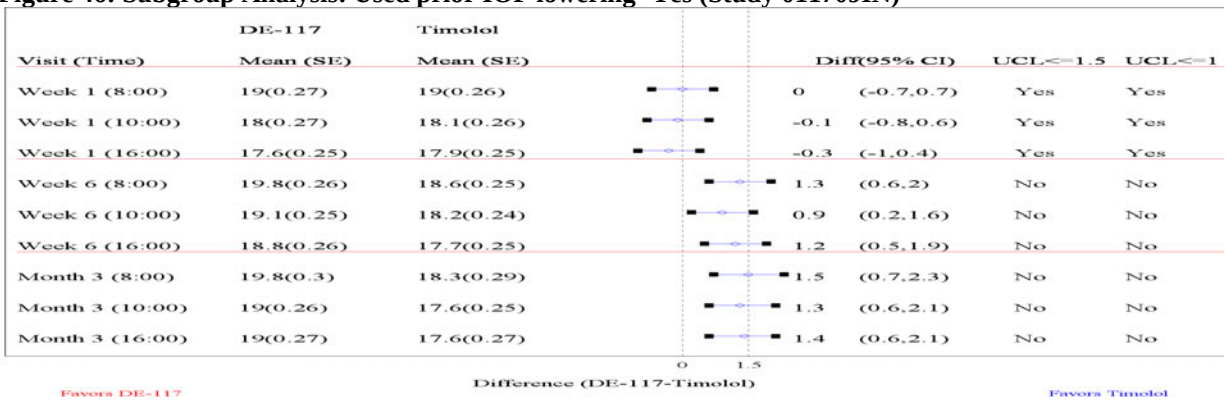
Source: Reviewer's Analysis

Figure 45: Subgroup Analysis: Used prior IOP lowering=No (Study 01171505)



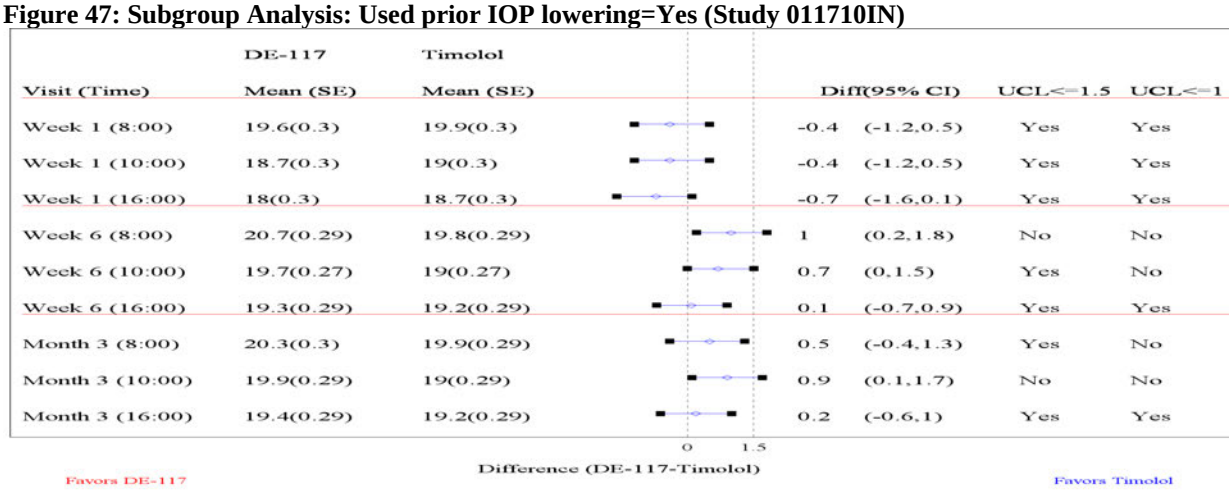
Source: Reviewer's Analysis

Figure 46: Subgroup Analysis: Used prior IOP lowering=Yes (Study 011709IN)



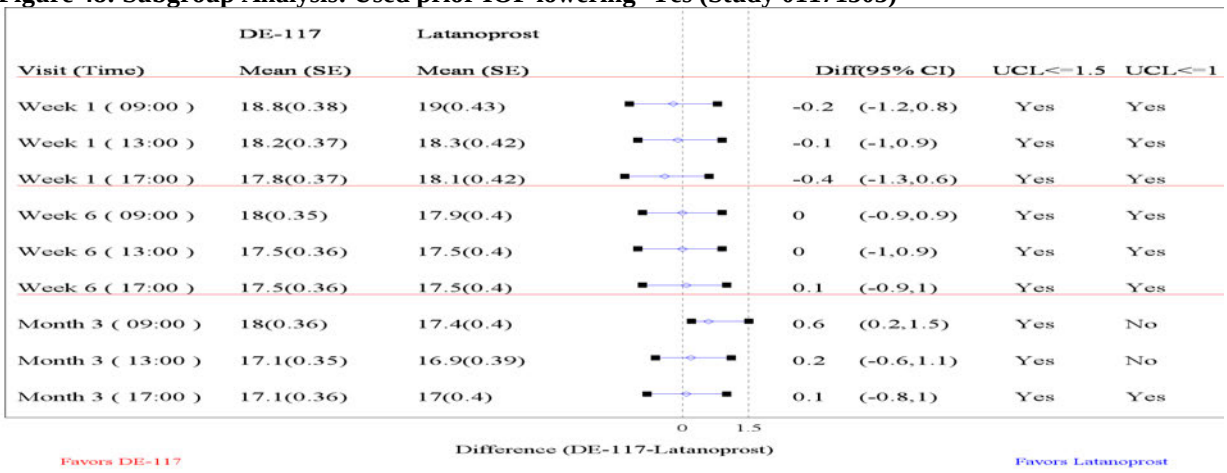
Source: Reviewer's Analysis

Figure 47: Subgroup Analysis: Used prior IOP lowering=Yes (Study 011710IN)



Source: Reviewer's Analysis

Figure 48: Subgroup Analysis: Used prior IOP lowering=Yes (Study 01171505)



Source: Reviewer's Analysis

Table 13: Summary of Pattern Mixture Model (Study 011709IN)

Visit	Time	Shift	DE117	timolol	diff	UCL<=1.5	UCL<=1.0
Week 1	8	0	18.9 (18.5, 19.4)	19.1 (18.7, 19.5)	-0.1 (-0.7, 0.4)	Yes	Yes
Week 1	10	0	18.0 (17.5, 18.4)	18.2 (17.8, 18.6)	-0.2 (-0.8, 0.4)	Yes	Yes
Week 1	16	0	17.5 (17.1, 17.9)	17.9 (17.5, 18.3)	-0.4 (-1.0, 0.1)	Yes	Yes
Week 6	8	0	19.8 (19.4, 20.2)	18.5 (18.1, 18.8)	1.3 (0.8, 1.9)	No	No
Week 6	10	0	18.9 (18.5, 19.3)	18.0 (17.6, 18.4)	0.8 (0.3, 1.4)	Yes	No
Week 6	16	0	18.5 (18.1, 18.9)	17.7 (17.3, 18.1)	0.8 (0.2, 1.4)	Yes	No
Month 3	8	0	19.7 (19.2, 20.2)	18.5 (18.1, 19.0)	1.2 (0.5, 1.8)	No	No
Month 3	10	0	18.8 (18.4, 19.2)	17.7 (17.3, 18.1)	1.1 (0.5, 1.7)	No	No

Visit	Time	Shift	DE117	timolol	diff	UCL<=1.5	UCL<=1.0
Month 3	16	0	18.6 (18.2, 19.1)	17.8 (17.4, 18.2)	0.8 (0.2, 1.4)	Yes	No
Week 1	8	1	19.0 (18.5, 19.4)	19.1 (18.7, 19.5)	-0.1 (-0.7, 0.5)	Yes	Yes
Week 1	10	1	18.0 (17.5, 18.4)	18.2 (17.8, 18.6)	-0.2 (-0.8, 0.4)	Yes	Yes
Week 1	16	1	17.5 (17.1, 17.9)	17.9 (17.5, 18.3)	-0.4 (-1.0, 0.1)	Yes	Yes
Week 6	8	1	19.8 (19.4, 20.2)	18.5 (18.1, 18.9)	1.3 (0.8, 1.9)	No	No
Week 6	10	1	18.9 (18.5, 19.3)	18.1 (17.7, 18.5)	0.8 (0.3, 1.4)	Yes	No
Week 6	16	1	18.5 (18.1, 18.9)	17.7 (17.3, 18.1)	0.8 (0.2, 1.4)	Yes	No
Month 3	8	1	19.8 (19.3, 20.2)	18.6 (18.1, 19.0)	1.2 (0.5, 1.9)	No	No
Month 3	10	1	18.8 (18.4, 19.2)	17.7 (17.3, 18.1)	1.1 (0.5, 1.7)	No	No
Month 3	16	1	18.7 (18.3, 19.2)	17.9 (17.4, 18.3)	0.9 (0.3, 1.5)	Yes	No
Week 1	8	2	19.0 (18.5, 19.4)	19.1 (18.7, 19.5)	-0.1 (-0.7, 0.5)	Yes	Yes
Week 1	10	2	18.0 (17.6, 18.4)	18.2 (17.8, 18.6)	-0.2 (-0.8, 0.4)	Yes	Yes
Week 1	16	2	17.5 (17.1, 17.9)	17.9 (17.5, 18.3)	-0.4 (-1.0, 0.1)	Yes	Yes
Week 6	8	2	19.8 (19.4, 20.2)	18.5 (18.1, 18.9)	1.3 (0.8, 1.9)	No	No
Week 6	10	2	18.9 (18.5, 19.3)	18.1 (17.7, 18.5)	0.9 (0.3, 1.4)	Yes	No
Week 6	16	2	18.6 (18.1, 19.0)	17.7 (17.3, 18.1)	0.8 (0.3, 1.4)	Yes	No
Month 3	8	2	19.8 (19.3, 20.3)	18.6 (18.1, 19.1)	1.2 (0.6, 1.9)	No	No
Month 3	10	2	18.9 (18.5, 19.3)	17.7 (17.3, 18.2)	1.1 (0.5, 1.7)	No	No
Month 3	16	2	18.8 (18.4, 19.2)	17.9 (17.5, 18.3)	0.9 (0.3, 1.5)	Yes	No
Week 1	8	3	19.0 (18.5, 19.4)	19.1 (18.7, 19.5)	-0.1 (-0.7, 0.5)	Yes	Yes
Week 1	10	3	18.0 (17.6, 18.4)	18.2 (17.8, 18.6)	-0.2 (-0.8, 0.4)	Yes	Yes
Week 1	16	3	17.5 (17.1, 17.9)	17.9 (17.5, 18.3)	-0.4 (-1.0, 0.1)	Yes	Yes
Week 6	8	3	19.9 (19.4, 20.3)	18.5 (18.1, 18.9)	1.4 (0.8, 1.9)	No	No
Week 6	10	3	18.9 (18.5, 19.3)	18.1 (17.7, 18.5)	0.9 (0.3, 1.4)	Yes	No
Week 6	16	3	18.6 (18.2, 19.0)	17.7 (17.3, 18.2)	0.9 (0.3, 1.5)	Yes	No
Month 3	8	3	19.9 (19.4, 20.4)	18.6 (18.2, 19.1)	1.2 (0.6, 1.9)	No	No
Month 3	10	3	18.9 (18.5, 19.4)	17.8 (17.4, 18.2)	1.1 (0.5, 1.7)	No	No
Month 3	16	3	18.9 (18.4, 19.3)	17.9 (17.5, 18.4)	0.9 (0.3, 1.6)	No	No
Week 1	8	4	19.0 (18.5, 19.4)	19.1 (18.7, 19.5)	-0.1 (-0.7, 0.5)	Yes	Yes
Week 1	10	4	18.0 (17.6, 18.4)	18.2 (17.8, 18.6)	-0.2 (-0.8, 0.4)	Yes	Yes
Week 1	16	4	17.5 (17.1, 17.9)	17.9 (17.5, 18.3)	-0.4 (-1.0, 0.1)	Yes	Yes
Week 6	8	4	19.9 (19.5, 20.3)	18.5 (18.1, 18.9)	1.4 (0.8, 1.9)	No	No

Visit	Time	Shift	DE117	timolol	diff	UCL<=1.5	UCL<=1.0
Week 6	10	4	19.0 (18.6, 19.4)	18.1 (17.7, 18.5)	0.9 (0.3, 1.4)	Yes	No
Week 6	16	4	18.6 (18.2, 19.1)	17.7 (17.3, 18.2)	0.9 (0.3, 1.5)	Yes	No
Month 3	8	4	19.9 (19.5, 20.4)	18.7 (18.2, 19.2)	1.3 (0.6, 2.0)	No	No
Month 3	10	4	19.0 (18.5, 19.4)	17.8 (17.4, 18.3)	1.2 (0.5, 1.8)	No	No
Month 3	16	4	19.0 (18.5, 19.4)	18.0 (17.5, 18.4)	1.0 (0.3, 1.6)	No	No
Week 1	8	5	19.0 (18.5, 19.4)	19.1 (18.7, 19.5)	-0.1 (-0.7, 0.5)	Yes	Yes
Week 1	10	5	18.0 (17.6, 18.4)	18.2 (17.8, 18.6)	-0.2 (-0.8, 0.4)	Yes	Yes
Week 1	16	5	17.5 (17.1, 17.9)	17.9 (17.5, 18.3)	-0.4 (-1.0, 0.2)	Yes	Yes
Week 6	8	5	19.9 (19.5, 20.3)	18.5 (18.1, 18.9)	1.4 (0.8, 2.0)	No	No
Week 6	10	5	19.0 (18.6, 19.4)	18.1 (17.7, 18.5)	0.9 (0.3, 1.5)	Yes	No
Week 6	16	5	18.7 (18.2, 19.1)	17.8 (17.3, 18.2)	0.9 (0.3, 1.5)	Yes	No
Month 3	8	5	20.0 (19.5, 20.5)	18.7 (18.2, 19.2)	1.3 (0.6, 2.0)	No	No
Month 3	10	5	19.0 (18.6, 19.5)	17.9 (17.4, 18.3)	1.2 (0.5, 1.8)	No	No
Month 3	16	5	19.0 (18.6, 19.5)	18.0 (17.6, 18.5)	1.0 (0.3, 1.7)	No	No

Source: Reviewer's Analysis

Table 14: Summary of Pattern Mixture Model (Study 011710IN)

Visit	Time	Shift	DE117	Timolol	diff	UCL<=1.5	UCL<=1.0
Week 1	8	0	19.4 (19.0, 19.9)	19.7 (19.3, 20.2)	-0.3 (-0.9, 0.3)	Yes	Yes
Week 1	10	0	18.5 (18.1, 19.0)	18.9 (18.5, 19.3)	-0.4 (-1.0, 0.3)	Yes	Yes
Week 1	16	0	18.0 (17.5, 18.4)	18.6 (18.2, 19.0)	-0.6 (-1.3, 0.0)	Yes	Yes
Week 6	8	0	20.4 (20.0, 20.9)	19.5 (19.1, 20.0)	0.9 (0.3, 1.5)	Yes	No
Week 6	10	0	19.5 (19.1, 19.9)	18.9 (18.5, 19.3)	0.7 (0.1, 1.2)	Yes	No
Week 6	16	0	19.2 (18.8, 19.6)	18.8 (18.4, 19.3)	0.3 (-0.2, 0.9)	Yes	Yes
Month 3	8	0	20.0 (19.5, 20.4)	19.6 (19.2, 20.0)	0.4 (-0.2, 1.0)	Yes	Yes
Month 3	10	0	19.4 (19.0, 19.9)	18.9 (18.5, 19.4)	0.5 (-0.1, 1.1)	Yes	No
Month 3	16	0	19.2 (18.7, 19.6)	19.1 (18.6, 19.5)	0.1 (-0.5, 0.7)	Yes	Yes
Week 1	8	1	19.4 (19.0, 19.9)	19.7 (19.3, 20.2)	-0.3 (-0.9, 0.4)	Yes	Yes
Week 1	10	1	18.5 (18.1, 19.0)	18.9 (18.5, 19.3)	-0.4 (-1.0, 0.3)	Yes	Yes
Week 1	16	1	18.0 (17.5, 18.4)	18.6 (18.2, 19.0)	-0.6 (-1.2, 0.0)	Yes	Yes
Week 6	8	1	20.5 (20.1, 20.9)	19.5 (19.1, 20.0)	0.9 (0.3, 1.5)	Yes	No
Week 6	10	1	19.6 (19.2, 20.0)	18.9 (18.5, 19.3)	0.7 (0.1, 1.2)	Yes	No
Week 6	16	1	19.2 (18.8, 19.6)	18.9 (18.4, 19.3)	0.4 (-0.2, 0.9)	Yes	Yes

Visit	Time	Shift	DE117	Timolol	diff	UCL<=1.5	UCL<=1.0
Month 3	8	1	20.1 (19.6, 20.5)	19.6 (19.2, 20.0)	0.5 (-0.2, 1.1)	Yes	No
Month 3	10	1	19.5 (19.1, 20.0)	18.9 (18.5, 19.4)	0.6 (-0.1, 1.2)	Yes	No
Month 3	16	1	19.3 (18.8, 19.7)	19.1 (18.6, 19.5)	0.2 (-0.4, 0.8)	Yes	Yes
Week 1	8	2	19.4 (19.0, 19.9)	19.7 (19.3, 20.2)	-0.3 (-0.9, 0.4)	Yes	Yes
Week 1	10	2	18.6 (18.1, 19.0)	18.9 (18.5, 19.3)	-0.3 (-1.0, 0.3)	Yes	Yes
Week 1	16	2	18.0 (17.5, 18.4)	18.6 (18.2, 19.0)	-0.6 (-1.2, 0.0)	Yes	Yes
Week 6	8	2	20.5 (20.1, 20.9)	19.6 (19.1, 20.0)	1.0 (0.4, 1.6)	No	No
Week 6	10	2	19.6 (19.2, 20.0)	18.9 (18.5, 19.3)	0.7 (0.2, 1.3)	Yes	No
Week 6	16	2	19.3 (18.8, 19.7)	18.9 (18.5, 19.3)	0.4 (-0.2, 1.0)	Yes	Yes
Month 3	8	2	20.1 (19.7, 20.6)	19.6 (19.2, 20.1)	0.5 (-0.1, 1.2)	Yes	No
Month 3	10	2	19.6 (19.1, 20.0)	18.9 (18.5, 19.4)	0.6 (0.0, 1.3)	Yes	No
Month 3	16	2	19.3 (18.9, 19.8)	19.1 (18.6, 19.5)	0.2 (-0.4, 0.9)	Yes	Yes
Week 1	8	3	19.5 (19.0, 19.9)	19.7 (19.3, 20.2)	-0.3 (-0.9, 0.4)	Yes	Yes
Week 1	10	3	18.6 (18.1, 19.0)	18.9 (18.5, 19.3)	-0.3 (-0.9, 0.3)	Yes	Yes
Week 1	16	3	18.0 (17.5, 18.4)	18.6 (18.2, 19.0)	-0.6 (-1.2, 0.0)	Yes	Yes
Week 6	8	3	20.6 (20.1, 21.0)	19.6 (19.1, 20.0)	1.0 (0.4, 1.6)	No	No
Week 6	10	3	19.6 (19.2, 20.0)	18.9 (18.5, 19.3)	0.7 (0.2, 1.3)	Yes	No
Week 6	16	3	19.3 (18.9, 19.7)	18.9 (18.5, 19.3)	0.4 (-0.2, 1.0)	Yes	Yes
Month 3	8	3	20.2 (19.8, 20.7)	19.6 (19.2, 20.1)	0.6 (-0.0, 1.2)	Yes	No
Month 3	10	3	19.7 (19.2, 20.1)	18.9 (18.5, 19.4)	0.7 (0.1, 1.4)	Yes	No
Month 3	16	3	19.4 (18.9, 19.9)	19.1 (18.6, 19.5)	0.3 (-0.3, 0.9)	Yes	Yes
Week 1	8	4	19.5 (19.0, 19.9)	19.7 (19.3, 20.2)	-0.3 (-0.9, 0.4)	Yes	Yes
Week 1	10	4	18.6 (18.1, 19.0)	18.9 (18.5, 19.3)	-0.3 (-0.9, 0.3)	Yes	Yes
Week 1	16	4	18.0 (17.6, 18.4)	18.6 (18.2, 19.0)	-0.6 (-1.2, 0.0)	Yes	Yes
Week 6	8	4	20.6 (20.2, 21.0)	19.6 (19.1, 20.0)	1.0 (0.4, 1.6)	No	No
Week 6	10	4	19.7 (19.3, 20.1)	18.9 (18.5, 19.3)	0.8 (0.2, 1.3)	Yes	No
Week 6	16	4	19.3 (18.9, 19.8)	18.9 (18.5, 19.3)	0.5 (-0.1, 1.1)	Yes	No
Month 3	8	4	20.3 (19.8, 20.8)	19.6 (19.2, 20.1)	0.7 (0.0, 1.3)	Yes	No
Month 3	10	4	19.7 (19.3, 20.2)	19.0 (18.5, 19.4)	0.8 (0.1, 1.4)	Yes	No
Month 3	16	4	19.5 (19.0, 19.9)	19.1 (18.6, 19.6)	0.4 (-0.3, 1.0)	Yes	Yes
Week 1	8	5	19.5 (19.0, 19.9)	19.7 (19.3, 20.2)	-0.2 (-0.9, 0.4)	Yes	Yes
Week 1	10	5	18.6 (18.1, 19.0)	18.9 (18.5, 19.3)	-0.3 (-0.9, 0.3)	Yes	Yes

Visit	Time	Shift	DE117	Timolol	diff	UCL<=1.5	UCL<=1.0
Week 1	16	5	18.0 (17.6, 18.5)	18.6 (18.2, 19.0)	-0.6 (-1.2, 0.0)	Yes	Yes
Week 6	8	5	20.6 (20.2, 21.1)	19.6 (19.1, 20.0)	1.0 (0.4, 1.7)	No	No
Week 6	10	5	19.7 (19.3, 20.1)	18.9 (18.5, 19.3)	0.8 (0.2, 1.4)	Yes	No
Week 6	16	5	19.4 (18.9, 19.8)	18.9 (18.5, 19.3)	0.5 (-0.1, 1.1)	Yes	No
Month 3	8	5	20.4 (19.9, 20.9)	19.7 (19.2, 20.1)	0.7 (0.1, 1.4)	Yes	No
Month 3	10	5	19.8 (19.3, 20.3)	19.0 (18.5, 19.4)	0.9 (0.2, 1.5)	Yes	No
Month 3	16	5	19.5 (19.1, 20.0)	19.1 (18.6, 19.6)	0.4 (-0.2, 1.1)	Yes	No

Source: Reviewer's Analysis

Table 15: Summary of Pattern Mixture Model (Study 01171505)

Visit	Time	Shift	DE117	Latanoprost	diff	UCL<=1.5	UCL<=1.0
Week 1	9	0	18.8 (18.3, 19.3)	18.6 (18.1, 19.1)	0.2 (-0.5, 0.9)	Yes	Yes
Week 1	13	0	18.3 (17.8, 18.8)	18.3 (17.8, 18.8)	-0.0 (-0.7, 0.7)	Yes	Yes
Week 1	17	0	17.9 (17.4, 18.4)	18.2 (17.7, 18.7)	-0.3 (-1.0, 0.4)	Yes	Yes
Week 6	9	0	17.6 (17.2, 18.1)	17.3 (16.8, 17.7)	0.3 (-0.3, 1.0)	Yes	Yes
Week 6	13	0	17.4 (17.0, 17.9)	17.1 (16.6, 17.6)	0.3 (-0.3, 1.0)	Yes	Yes
Week 6	17	0	17.3 (16.9, 17.8)	17.0 (16.5, 17.4)	0.4 (-0.3, 1.0)	Yes	Yes
Month 3	9	0	17.7 (17.2, 18.2)	16.9 (16.4, 17.4)	0.8 (0.1, 1.5)	Yes	No
Month 3	13	0	17.1 (16.7, 17.6)	16.6 (16.1, 17.0)	0.5 (-0.1, 1.2)	Yes	No
Month 3	17	0	17.1 (16.6, 17.6)	16.6 (16.2, 17.1)	0.5 (-0.2, 1.1)	Yes	No
Week 1	9	1	18.8 (18.3, 19.3)	18.6 (18.1, 19.1)	0.2 (-0.5, 0.9)	Yes	Yes
Week 1	13	1	18.3 (17.8, 18.8)	18.3 (17.8, 18.8)	-0.0 (-0.7, 0.7)	Yes	Yes
Week 1	17	1	17.9 (17.4, 18.4)	18.2 (17.7, 18.7)	-0.3 (-1.0, 0.4)	Yes	Yes
Week 6	9	1	17.6 (17.2, 18.1)	17.3 (16.8, 17.7)	0.3 (-0.3, 1.0)	Yes	Yes
Week 6	13	1	17.4 (17.0, 17.9)	17.1 (16.6, 17.6)	0.3 (-0.3, 1.0)	Yes	Yes
Week 6	17	1	17.4 (16.9, 17.8)	17.0 (16.5, 17.4)	0.4 (-0.3, 1.0)	Yes	Yes
Month 3	9	1	17.7 (17.3, 18.2)	16.9 (16.4, 17.4)	0.8 (0.2, 1.5)	Yes	No
Month 3	13	1	17.1 (16.7, 17.6)	16.6 (16.1, 17.0)	0.6 (-0.1, 1.2)	Yes	No
Month 3	17	1	17.1 (16.7, 17.6)	16.7 (16.2, 17.1)	0.5 (-0.2, 1.1)	Yes	No
Week 1	9	2	18.8 (18.3, 19.3)	18.6 (18.1, 19.1)	0.2 (-0.5, 0.9)	Yes	Yes
Week 1	13	2	18.3 (17.8, 18.8)	18.3 (17.8, 18.8)	-0.0 (-0.7, 0.7)	Yes	Yes
Week 1	17	2	17.9 (17.4, 18.4)	18.2 (17.7, 18.7)	-0.3 (-1.0, 0.4)	Yes	Yes
Week 6	9	2	17.6 (17.2, 18.1)	17.3 (16.8, 17.7)	0.4 (-0.3, 1.0)	Yes	Yes

Visit	Time	Shift	DE117	Latanoprost	diff	UCL<=1.5	UCL<=1.0
Week 6	13	2	17.5 (17.0, 17.9)	17.1 (16.6, 17.6)	0.4 (-0.3, 1.0)	Yes	Yes
Week 6	17	2	17.4 (16.9, 17.8)	17.0 (16.5, 17.5)	0.4 (-0.3, 1.0)	Yes	Yes
Month 3	9	2	17.8 (17.3, 18.3)	16.9 (16.4, 17.4)	0.9 (0.2, 1.5)	Yes	No
Month 3	13	2	17.2 (16.7, 17.6)	16.6 (16.2, 17.0)	0.6 (-0.0, 1.2)	Yes	No
Month 3	17	2	17.2 (16.7, 17.6)	16.7 (16.2, 17.1)	0.5 (-0.2, 1.2)	Yes	No
Week 1	9	3	18.8 (18.3, 19.3)	18.6 (18.1, 19.1)	0.2 (-0.5, 0.9)	Yes	Yes
Week 1	13	3	18.3 (17.8, 18.8)	18.3 (17.8, 18.8)	-0.0 (-0.7, 0.7)	Yes	Yes
Week 1	17	3	17.9 (17.4, 18.4)	18.2 (17.7, 18.7)	-0.3 (-1.0, 0.4)	Yes	Yes
Week 6	9	3	17.7 (17.2, 18.1)	17.3 (16.9, 17.7)	0.4 (-0.3, 1.0)	Yes	Yes
Week 6	13	3	17.5 (17.0, 17.9)	17.1 (16.6, 17.6)	0.4 (-0.3, 1.0)	Yes	Yes
Week 6	17	3	17.4 (16.9, 17.9)	17.0 (16.5, 17.5)	0.4 (-0.3, 1.0)	Yes	Yes
Month 3	9	3	17.8 (17.3, 18.3)	16.9 (16.5, 17.4)	0.9 (0.2, 1.6)	No	No
Month 3	13	3	17.2 (16.8, 17.7)	16.6 (16.2, 17.1)	0.6 (-0.0, 1.2)	Yes	No
Month 3	17	3	17.2 (16.7, 17.7)	16.7 (16.2, 17.1)	0.5 (-0.2, 1.2)	Yes	No
Week 1	9	4	18.8 (18.3, 19.3)	18.6 (18.1, 19.1)	0.2 (-0.5, 0.9)	Yes	Yes
Week 1	13	4	18.3 (17.8, 18.8)	18.3 (17.8, 18.8)	-0.0 (-0.7, 0.7)	Yes	Yes
Week 1	17	4	17.9 (17.4, 18.4)	18.2 (17.7, 18.7)	-0.3 (-1.0, 0.4)	Yes	Yes
Week 6	9	4	17.7 (17.2, 18.1)	17.3 (16.9, 17.7)	0.4 (-0.3, 1.0)	Yes	Yes
Week 6	13	4	17.5 (17.0, 18.0)	17.1 (16.7, 17.6)	0.4 (-0.3, 1.0)	Yes	Yes
Week 6	17	4	17.4 (16.9, 17.9)	17.0 (16.5, 17.5)	0.4 (-0.3, 1.1)	Yes	No
Month 3	9	4	17.8 (17.3, 18.3)	16.9 (16.5, 17.4)	0.9 (0.2, 1.6)	No	No
Month 3	13	4	17.2 (16.8, 17.7)	16.6 (16.2, 17.1)	0.6 (-0.0, 1.3)	Yes	No
Month 3	17	4	17.2 (16.7, 17.7)	16.7 (16.2, 17.2)	0.5 (-0.1, 1.2)	Yes	No
Week 1	9	5	18.8 (18.3, 19.3)	18.6 (18.1, 19.1)	0.2 (-0.5, 0.9)	Yes	Yes
Week 1	13	5	18.3 (17.8, 18.8)	18.3 (17.8, 18.8)	-0.0 (-0.7, 0.7)	Yes	Yes
Week 1	17	5	17.9 (17.4, 18.4)	18.2 (17.7, 18.7)	-0.3 (-1.0, 0.4)	Yes	Yes
Week 6	9	5	17.7 (17.2, 18.1)	17.3 (16.9, 17.8)	0.4 (-0.2, 1.0)	Yes	Yes
Week 6	13	5	17.5 (17.0, 18.0)	17.1 (16.7, 17.6)	0.4 (-0.3, 1.1)	Yes	No
Week 6	17	5	17.4 (17.0, 17.9)	17.0 (16.6, 17.5)	0.4 (-0.2, 1.1)	Yes	No
Month 3	9	5	17.9 (17.4, 18.4)	17.0 (16.5, 17.5)	0.9 (0.2, 1.6)	No	No
Month 3	13	5	17.3 (16.8, 17.7)	16.6 (16.2, 17.1)	0.6 (-0.0, 1.3)	Yes	No
Month 3	17	5	17.3 (16.8, 17.7)	16.7 (16.2, 17.2)	0.5 (-0.1, 1.2)	Yes	No

Source: Reviewer's Analysis

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