CENTER FOR DRUG EVALUATION AND RESEARCH

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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 #:	NDA207795
Drug Name:	Vyzulta: Latanoprostene ophthalmic solution, 0.024%
Indication(s):	Reduction of Intraocular Pressure in Patients with Ocular Hypertension or Open-Angle Glaucoma
Applicant:	Bausch and Lomb INC.
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Keywords: New Molecular Entity, Intraocular Pressure, Open-angle Glaucoma, Ocular Hypertension

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1 EXECUTIVE SUMMARY

This NDA seeks approval of Vyzulta (latanoprostene ophthalmic solution, 0.024%), administered one drop once daily for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OH). The primary evidence for the safety and efficacy of Vyzulta comes from two randomized, multicenter, double-masked, parallel-group studies (Study 769 and Study 770). The primary objective of the two studies was to demonstrate the non-inferiority of Vyzulta relative to Timolol maleate 0.5% (Timolol) with respect to the reduction of IOP. The primary efficacy endpoint was the mean IOP in the study eye measured at the specified time points: 8 AM, 12 PM, and 4 PM at Week 2, Week 6, and Month 3. In each study, 420 subjects were randomized in a 2:1 ratio to receive either Vyzulta or Timolol. Both studies had a three month masked efficacy period followed by an open-label safety extension period during which all subjects were to receive Vyzulta. The safety extension period was nine months in Study 769 and three months in Study 770.

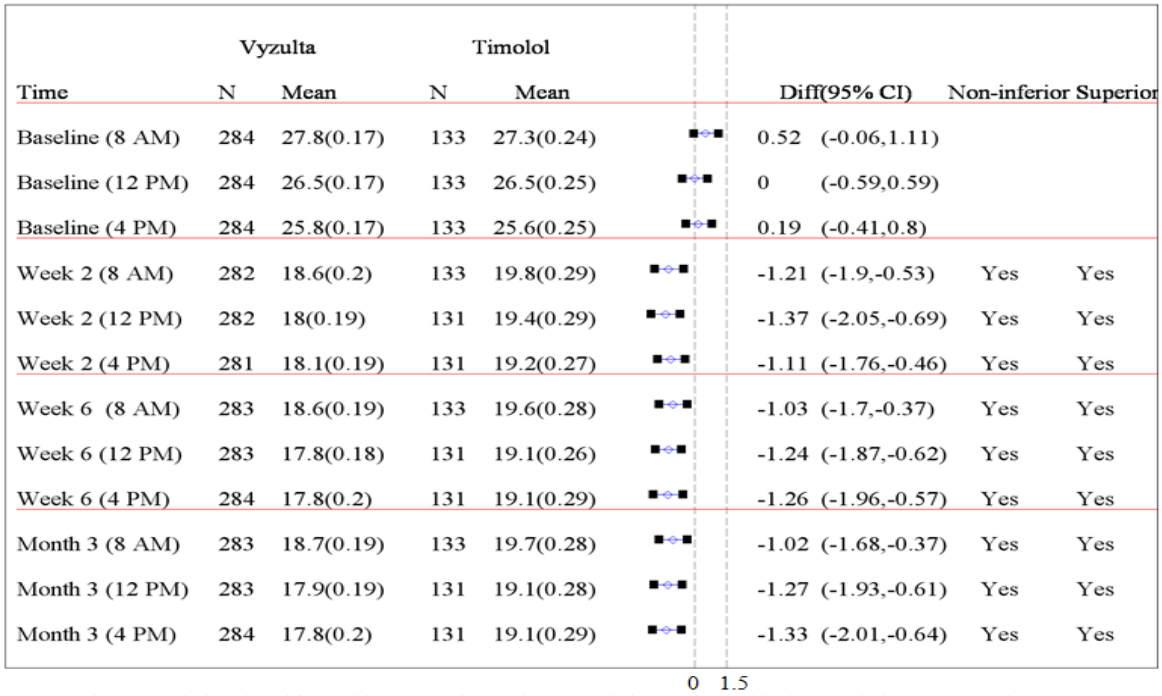
The protocol-defined primary efficacy analysis was conducted based on randomized and treated subjects with a baseline and at least one post-baseline assessment (referred to as Bausch-ITT). The analysis of covariance (ANCOVA) model with terms for treatment and time-matched baseline IOP was applied for each time point of each visit separately. The difference in the mean IOP between the treatment groups (Vyzulta minus Timolol) was determined based on the least square means from the ANCOVA model. Non-inferiority of Vyzulta to Timolol was established if the upper limit of the 95% confidence interval for the difference in the mean IOP was <1.5 mmHg at each of the nine post-baseline time points (Statistical Criterion) and was < 1 mmHg at the majority of time points (Clinical Criterion).

The mean baseline IOP values were comparable between the two treatment groups and both treatment groups demonstrated IOP reductions at each of the nine post-baseline time points. There was an IOP reduction between 7.5 to 9.0 mmHg in the Vyzulta arm compared to 6.5 to 7.9 mmHg in the Timolol arm. Because the upper limits of the 95% confidence intervals for the mean difference in IOP were less than 1.0 mmHg, both the statistical and clinical criteria for non-inferiority were met. However, there was one post-baseline time point at which Vyzulta was not statistically superior to Timolol in Study 770. Therefore, the secondary objective of superiority of Vyzulta over Timolol was not met in Study 770 (Figure 1 and Figure 2). The reviewer conducted an ANCOVA analysis using the population of all randomized and treated subjects (referred to as FDA-ITT). Additionally, a repeated measures ANCOVA accounting for possible correlation between IOP measurements was conducted. Both analyses provided results which were consistent with the applicant's findings.

At least one ocular adverse event (AE) in the study eye was reported in about 20% of the subjects in the Vyzulta arm and 12% of the subjects in the Timolol arm. None of the reported ocular AEs were serious. The most frequently reported AE in the study eye in the Vyzulta arm was conjunctival hyperemia which occurred in 47(5.8%) subjects. One person in the Vyzulta arm died during the study. In conclusion, the two studies provided adequate evidence of safety and efficacy for one drop once daily use of Vyzulta in patients with open-angle glaucoma or ocular hypertension.

Figure 1: Difference in Mean IOP (Bausch-ITT: Study 769)

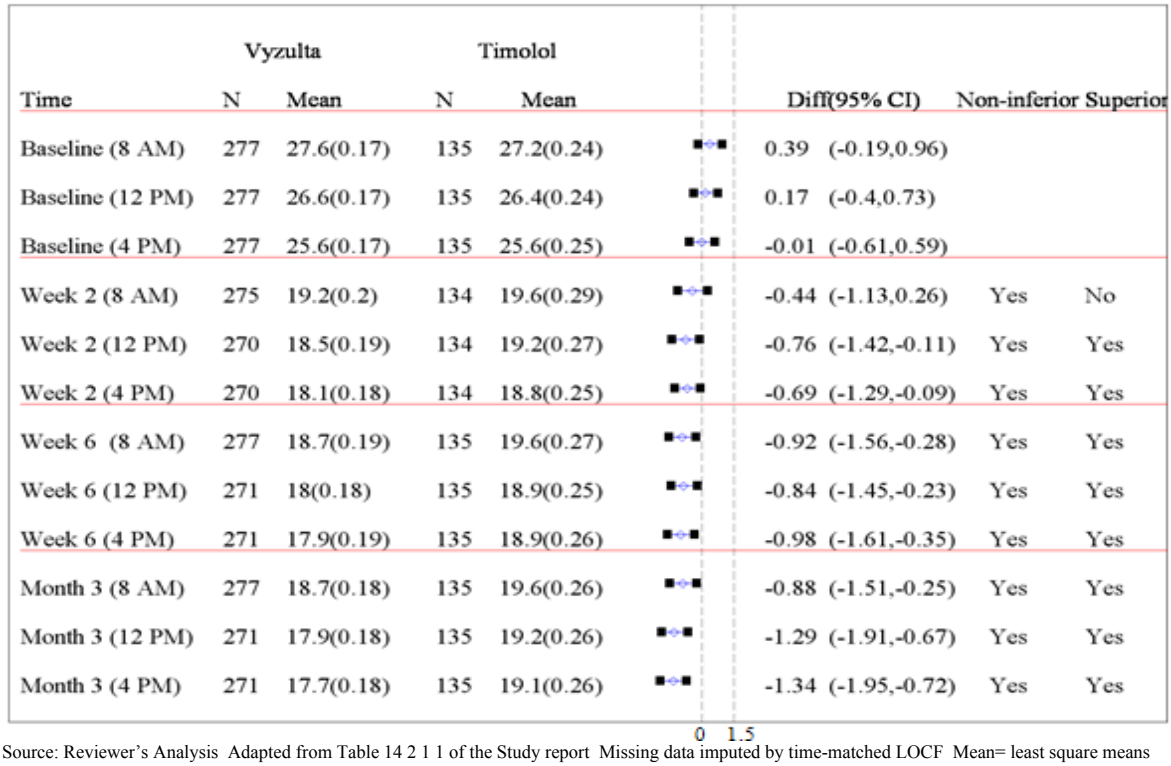
	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	284	27.8(0.17)	133	27.3(0.24)	0.52 (-0.06,1.11)		
Baseline (12 PM)	284	26.5(0.17)	133	26.5(0.25)	0 (-0.59,0.59)		
Baseline (4 PM)	284	25.8(0.17)	133	25.6(0.25)	0.19 (-0.41,0.8)		
Week 2 (8 AM)	282	18.6(0.2)	133	19.8(0.29)	-1.21 (-1.9,-0.53)	Yes	Yes
Week 2 (12 PM)	282	18(0.19)	131	19.4(0.29)	-1.37 (-2.05,-0.69)	Yes	Yes
Week 2 (4 PM)	281	18.1(0.19)	131	19.2(0.27)	-1.11 (-1.76,-0.46)	Yes	Yes
Week 6 (8 AM)	283	18.6(0.19)	133	19.6(0.28)	-1.03 (-1.7,-0.37)	Yes	Yes
Week 6 (12 PM)	283	17.8(0.18)	131	19.1(0.26)	-1.24 (-1.87,-0.62)	Yes	Yes
Week 6 (4 PM)	284	17.8(0.2)	131	19.1(0.29)	-1.26 (-1.96,-0.57)	Yes	Yes
Month 3 (8 AM)	283	18.7(0.19)	133	19.7(0.28)	-1.02 (-1.68,-0.37)	Yes	Yes
Month 3 (12 PM)	283	17.9(0.19)	131	19.1(0.28)	-1.27 (-1.93,-0.61)	Yes	Yes
Month 3 (4 PM)	284	17.8(0.2)	131	19.1(0.29)	-1.33 (-2.01,-0.64)	Yes	Yes



Source: Reviewer's Analysis Adapted from Table 14 2 1 1 of the study report Missing data imputed by time-matched LOCF Mean= least square means (standard error)

Figure 2: Difference in Mean IOP (Bausch-ITT: Study 770)

	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	277	27.6(0.17)	135	27.2(0.24)	0.39 (-0.19,0.96)		
Baseline (12 PM)	277	26.6(0.17)	135	26.4(0.24)	0.17 (-0.4,0.73)		
Baseline (4 PM)	277	25.6(0.17)	135	25.6(0.25)	-0.01 (-0.61,0.59)		
Week 2 (8 AM)	275	19.2(0.2)	134	19.6(0.29)	-0.44 (-1.13,0.26)	Yes	No
Week 2 (12 PM)	270	18.5(0.19)	134	19.2(0.27)	-0.76 (-1.42,-0.11)	Yes	Yes
Week 2 (4 PM)	270	18.1(0.18)	134	18.8(0.25)	-0.69 (-1.29,-0.09)	Yes	Yes
Week 6 (8 AM)	277	18.7(0.19)	135	19.6(0.27)	-0.92 (-1.56,-0.28)	Yes	Yes
Week 6 (12 PM)	271	18(0.18)	135	18.9(0.25)	-0.84 (-1.45,-0.23)	Yes	Yes
Week 6 (4 PM)	271	17.9(0.19)	135	18.9(0.26)	-0.98 (-1.61,-0.35)	Yes	Yes
Month 3 (8 AM)	277	18.7(0.18)	135	19.6(0.26)	-0.88 (-1.51,-0.25)	Yes	Yes
Month 3 (12 PM)	271	17.9(0.18)	135	19.2(0.26)	-1.29 (-1.91,-0.67)	Yes	Yes
Month 3 (4 PM)	271	17.7(0.18)	135	19.1(0.26)	-1.34 (-1.95,-0.72)	Yes	Yes



Source: Reviewer's Analysis Adapted from Table 14 2 1 1 of the Study report Missing data imputed by time-matched LOCF Mean= least square means (standard error)

2 INTRODUCTION

This NDA included data from two Phase 3 studies (769 and 770) to support the safety and efficacy of Vyzulta (latanoprostene ophthalmic solution, 0.024%) administered one drop once daily for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OH). Both studies had a three month masked efficacy period followed by an open-label safety extension period. The safety extension period was 9 months in Study 769 and 3 months in Study 770. These two studies were the main focus of this review. Brief efficacy and safety summaries for two Phase 2 studies (659 & 803) and a Phase 3 safety study (811) are provided in the appendix.

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 specific studies reviewed.

2.1.1 Drug Class and Indication

Vyzulta (latanoprostene ophthalmic solution, 0.024%) administered once daily is a new molecular entity developed for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma (OAG) or ocular hypertension (OH).

2.1.2 History of Drug Development

According to the applicant, Vyzulta (latanoprostene ophthalmic solution, 0.024%) is the first ocular medication containing a nitric oxide (NO) active moiety to be submitted for marketing authorization in the United States (US) for the claimed indication. They state that Vyzulta is a new chemical entity that is metabolized into latanoprost acid and a NO-donating moiety when exposed to the ocular environment.

Before the licensing was transferred to the applicant, the original owner of the product (Pfizer) conducted two Phase 2 studies (Study A9441001 and Study A9441003). The applicant conducted an additional Phase 2 dose ranging study (Study 659, See appendix), which identified latanoprostene bunod 0.024% administered 1 drop in the evening as the safest and most effective dose. A Japanese Phase 3 study (Study 811) to evaluate the long-term safety of Vyzulta was also conducted. The dose finding study and the two Phase 3 studies were submitted under IND 73435.

The applicant had two End-of-Phase 2 meetings with the agency, the first on September 26, 2012 and the second on June 11, 2013. During the first End-of-Phase 2 meeting, the applicant discussed the non-clinical, clinical and regulatory development of Vyzulta. The agency accepted the applicant's proposal to use the results of the dose-finding study (Study 659; See Section 6.3) to support the proposed design for the two pivotal studies (Study 769 and 770). The applicant also inquired whether the per-protocol population (PP) could be used as the primary analysis population with the ITT population comprised of all randomized and treated subjects with baseline and at least one post-baseline assessment as the secondary study population. The agency recommended the use of the ITT population consisting of all

randomized subjects as the main analysis population and the PP population as a secondary analysis population. The applicant's proposed analysis of covariance (ANCOVA) model with fixed terms for treatment and baseline IOP as covariate was accepted by the Agency. The second End-of-Phase 2 meeting was mainly focused on the discussion of the chemistry manufacture and controls development of Vyzulta. No clinical issues were discussed during this meeting.

The applicant also had a pre-NDA meeting with the agency on February 09 2015. During this meeting, the applicant requested to modify the statistical analysis plan for the integrated summary of efficacy (ISE) and integrated summary of safety (ISS). The applicant proposed to perform the ISE on a re-defined ITT population which excludes subjects who did not receive the study treatment and subjects who received the study treatment but have no baseline and at least one post-baseline assessment. The agency stated that excluding randomized and treated subjects from the primary efficacy analysis is not recommended as this could potentially introduce bias. The agency further stated that the primary efficacy analysis should be conducted on the ITT population which includes all randomized subjects with LOCF used to deal with missing data as per-the discussion at the EOP-2 meeting. The agency also recommended that the worst possible outcome from subject's treatment group be imputed for randomized and treated subjects with no IOP measurement at all visits.

The applicant also asked the agency whether the ISE based on the pooled analysis of the two pivotal studies (Study 769 and 770) was sufficient to support the non-inferiority and superiority to Timolol. 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 and superiority claims. To support a non-inferiority claim, at least two trials, each demonstrating the non-inferiority of Vyzulta to Timolol would be expected. Similarly, a superiority claim requires at least two trials, each demonstrating the superiority of Vyzulta to Timolol.

2.1.3 Studies Reviewed

In this NDA, data from two phase 3 studies (769 and 770) were included to support the safety and efficacy of Vyzulta in reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OH). The studies were both double-masked, active-controlled, and randomized studies. The studies included sites from the US and abroad. The brief summaries of these studies are given in Table 1.

In Study 769, 420 subjects from a total of 45 sites located in Bulgaria, Czech Republic, and the United States (US) were enrolled. Similarly, Study 770 randomized 420 subjects from 45 clinical sites 40 of which were in the US. The remaining sites were located in the United Kingdom, Germany and Italy.

Table 1: Brief Summary of Pivotal Studies (769 & 770)

Study	Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
769	A Phase 3, Multicenter, Masked, Randomized, active-Controlled Trial to Assess the Safety and Efficacy of Vyzulta relative to Timolol in the reduction of IOP in patients with open-angle glaucoma or ocular hypertension	– Vyzulta: N=286 – Timolol: N=134 Note: Vyzulta is dosed QD in the evening at approximately 8 PM whereas Timolol is dosed BID in the morning at approximately 8 AM and in the evening at approximately 8 PM. To ensure masking, subjects in the Vyzulta arm were also dosed with vehicle QD in the morning at approximately 8 AM.	Primary: Mean IOP assessed at 3 visits (Week 2, Week 6, and Month 3) at 3 time points (8 AM, 12 PM, 4 PM). The primary efficacy analyses will be performed using an analysis covariance (ANCOVA) based on the ITT population with missing data imputed using the LOCF method. The 2 treatments, Vyzulta and Timolol, will be compared for each time point by visit. The least squares mean of each treatment group, the difference in the least squares mean (Vyzulta minus timolol), and the 2-sided 95% CI for the difference will be obtained. Non-inferiority will be claimed if the upper limit of the CIs do not exceed 1.5 mmHg at all time points (8 AM, 12 PM and 4 PM) at Visits 4, 5 and 6 (Week 2, Week 6, and Month 3, respectively) and do not exceed 1.00 mmHg for the majority (at least 5 out of the 9 time points) of the time points. If non-inferiority is determined, superiority at each time point will be claimed if the upper limit of the 95% CI does not exceed 0 mmHg at each of the 3 visits during the efficacy evaluation (Visits 4, 5, and 6).	The ANCOVA results for the comparison of the LS means of mean IOP between treatment groups demonstrate the non-inferiority of LBN ophthalmic solution 0.024% QD to timolol maleate 0.5% BID in the ITT population because the upper limit of the 95% CIs did not exceed 1.0 mmHg at all 9 time points (8 AM, 12 PM, and 4 PM at Visits 4, 5, and 6 [Week 2, Week 6, and Month 3, respectively]) and did not exceed 0 mmHg at all of these same time points and visits.
770	A Phase 3, Multicenter, Masked, Randomized, active-Controlled Trial to Assess the Safety and Efficacy of Vyzulta relative to Timolol in the reduction of IOP in patients with open-angle glaucoma or ocular hypertension	– Vyzulta: N=283 – Timolol: N=137 Note: Vyzulta is dosed QD in the evening at approximately 8 PM whereas Timolol is dosed BID in the morning at approximately 8 AM and in the evening at approximately 8 PM. To ensure masking, subjects in the Vyzulta arm were also dosed with vehicle QD in the morning at approximately 8 AM.	Primary: Mean IOP assessed at 3 visits (Week 2, Week 6, and Month 3) at 3 time points (8 AM, 12 PM, 4 PM). The primary efficacy analyses will be performed using an analysis covariance (ANCOVA) based on the ITT population with missing data imputed using the LOCF method. The 2 treatments, Vyzulta and Timolol, will be compared for each time point by visit. The least squares mean of each treatment group, the difference in the least squares mean (Vyzulta minus timolol), and the 2-sided 95% CI for the difference will be obtained. Non-inferiority will be claimed if the upper limit of the CIs do not exceed 1.5 mmHg at all time points (8 AM, 12 PM and 4 PM) at Visits 4, 5 and 6 (Week 2, Week 6, and Month 3, respectively) and do not exceed 1.00 mmHg for the majority (at least 5 out of the 9 time points) of the time points. If non-inferiority is determined, superiority at each time point will be claimed if the upper limit of the 95% CI does not exceed 0 mmHg at each of the 3 visits during the efficacy evaluation (Visits 4, 5, and 6).	The ANCOVA results for the comparison of the LS means of mean IOP between treatment groups demonstrate the non-inferiority of LBN ophthalmic solution 0.024% QD to timolol maleate 0.5% BID in the ITT population because the upper limit of the 95% CIs did not exceed 1.0 mmHg at all time points (8 AM, 12 PM, and 4 PM) at Visits 4, 5, and 6 (Week 2, Week 6, and Month 3, respectively). Superiority of LBN ophthalmic solution 0.024% QD to timolol maleate 0.5% BID cannot be claimed because the upper limit of the 95% CI exceeded 0 mmHg at the 8 AM time point at Visit 4 (Week 2).

Source: Applicant's submitted study reports

2.2 Data Sources

The data sources for this review included the applicant's clinical study reports for both studies and the integrated safety and efficacy analysis reports. Additionally, the applicant submitted SAS datasets electronically. Both SDTM and ADAM data formats were used. The original data sets used in this review are located at: \\CDSESUB1\evsprod\NDA207795\0000\m5\datasets. The applicant later submitted an updated summary and data for study 769. The updated data and summary for Study 769 is located at: \\CDSESUB1\evsprod\NDA207795\0006.

The change from baseline and the actual IOP both at baseline and subsequent measurement times were included in the "adiop.xpt" dataset with variable names CHG and AVAL respectively. For the primary efficacy analysis, the variable AVAL was used. A data type variable DTYPE was also included to distinguish between imputed and observed values and the type of imputation involved (LOCF, WOCF, WOV, and BOV). The treatment variable, given both as numeric (TRT01P) and character (TRT01PN), was also included in the above dataset. The adverse events and the first and subsequent times of treatment exposures were included in the "adae.xpt" dataset.

3 STATISTICAL EVALUATION

This section provides a detailed review of the two pivotal studies.

3.1 Data and Analysis Quality

The data were generally of good quality. The final statistical analysis plans and the amended protocols were all submitted. In the original submission, the applicant did not submit the SAS codes used for efficacy analyses. As a result of an information request, the applicant updated the submission including all SAS codes used to produce the study results. Additionally, the applicant provided explanation for some datasets which appeared to have duplicate measurements for some subjects at the same time points. The applicant's response to the information request is located at: \\CDSESUB1\evsprod\NDA207795\0005.

3.2 Evaluation of Efficacy

This section summarizes the design of the two studies and the corresponding efficacy results submitted by the applicant and the reviewer's analysis.

3.2.1 Study Design and Endpoints

In both studies initial screening procedures were performed at the screening visit. Patients were to discontinue all ocular hypotensive agents according to the recommended washout schedule. Following the washout period, patients returned for the Eligibility 1 Visit and then 3 to 8 days later for the Eligibility 2 visit. At both of the Eligibility Visits, IOP was measured in both eyes at 8 AM, 12 PM, and 4 PM. Subjects were expected to meet the following IOP requirements at the eligibility visit (Day 1):

- mean/ median IOP ≥ 26 mmHg at a minimum of 1 time point, ≥ 24 mmHg at a minimum of 1 time point and ≥ 22 mmHg at 1 time point in the same eye, and

- IOP ≤ 36 mmHg at all 3 measurement time points in both eyes

Patients who had IOP measurements within the specified range were randomized in a 2:1 ratio to receive treatment with either Vyzulta or Timolol. Subjects in the Vyzulta treatment group were dosed QD in the evening at approximately 8 PM. The first dose was instilled at 8 PM the evening of Visit 3 (Eligibility, Day 1). To ensure masking, these subjects were also dosed with vehicle QD in the morning at approximately 8 AM. Subjects in the Timolol maleate 0.5% treatment group were dosed BID. The first dose was instilled at 8 PM the evening of Visit 3 (Eligibility, Day 1). These subjects were subsequently dosed BID in the morning at approximately 8 AM and in the evening at approximately 8 PM.

Treatment duration was approximately 6 months in Study 769 and 12 Months in Study 770. If both eyes of a subject had a diagnosis of OAG or OHT, both eyes were treated for the duration of study, even if only 1 eye was eligible. The study eye was the eye that qualified per inclusion criteria at Visit 3; if both eyes qualified, the study eye was the eye that had the highest IOP value at Visit 3 or the right eye if both eyes had the same IOP value at Visit 3. Efficacy evaluations were made at Visit 4 (Week 2), Visit 5 (Week 6), and Visit 6 (Month 3), with ongoing safety evaluations made at Visit 7 (Month 6). The visit windows used for analysis purposes are given in the following table.

Visit	Scheduled Day	IOP for ITT Analysis	IOP for PP Analysis
Week 0	1	< 1	
Week 2	14	2-28	Day 14 ± 2 days
Week 6	42	29-55	Day 42 ± 3 days
Month 3	90	56-124	Day 90 ± 10 days
Month 6	184	> 125	Day 184 ± 10 days

Abbreviations: IOP = intraocular pressure; ITT = Intent-to-Treat; PP = Per-Protocol

According to the study protocols, IOP were measured using a Goldmann applanation tonometer before pupillary dilation. The IOP in both eyes were measured, with the right eye preceding the left eye. For each eye, IOP measurements were taken twice consecutively. If the two measurements were within 2 mmHg or less of each other, the mean of the 2 readings was recorded as the IOP at that time point. If the 2 readings were more than 2 mmHg of each other, a third (consecutive) reading was taken and the median (middle) IOP was recorded as the IOP at that time point.

The primary efficacy endpoint was the mean IOP in subjects' study eye measured at the specified post-baseline time points: 8 AM, 12 PM, and 4 PM at Visit 4 (Week 2), Visit 5 (Week 6), and Visit 6 (Month 3). The studies had the following two key secondary efficacy endpoints:

- Proportion of subjects with IOP ≤ 18 mmHg consistently at all 9 time points in the first 3 months

- Proportion of subjects with IOP reduction ≥ 25% consistently at all 9 time points in the first 3 months

The safety endpoints of these studies included the incidence of ocular and systemic AEs and the best-corrected visual acuity (BCVA).

3.2.2 Statistical Methods

The protocol-defined primary efficacy analysis was conducted based on randomized and treated subjects with a baseline and at least one post-baseline assessment (referred to here as Bausch-ITT). The analysis of covariance (ANCOVA) model with terms for treatment and time-matched baseline IOP was applied for each time point of each visit separately. The difference in the mean IOP between the treatment groups (Vyzulta minus Timolol) was determined based on the least square means from the ANCOVA model. The last non-missing post-baseline time-matched IOP was carried forward for missing post-baseline IOP values (LOCF). For example, missing data at 8 AM at the Month 3 visit could only be imputed using 8AM data from Week 6 or Week 2 (if Week 6 was also missing). Note that, because only time-matched post-baseline values could be carried forward, the LOCF approach could not be implemented in cases where there was no time-matched prior post-baseline IOP data. For instance, in the example above, if a subject also had missing 8 AM data at both Weeks 2 and 6, the LOCF approach would leave all data at 8 AM missing. Consequently, in the applicant's primary efficacy analysis, some measurement times were left with missing IOP values after the LOCF approach had been used.

The reviewer conducted the analysis of the primary efficacy endpoint using the same ANCOVA model based on all randomized subjects (ITT) and based on all randomized and treated subjects regardless of post-baseline measurements (referred to as FDA-ITT). A hybrid of the LOCF and the worst/best imputation approach was used as a potentially conservative estimate of effectiveness. In this approach, the worst (maximum) and best (minimum) time-matched post-baseline IOP values in the Vyzulta and Timolol arms respectively were imputed for the post-baseline time points where the LOCF could not be implemented. For missing baseline IOP, the hybrid of the LOCF and the worst/best imputation approach planned to impute the best time-matched baseline value for the Vyzulta arm and the worst time-matched baseline value for the Timolol arm. Note that, the applicant also conducted the same analysis based on all randomized subjects using the same hybrid LOCF and worst/best imputation for each individual study separately as well as the integrated summary of efficacy (ISE). The summary results from these analyses however were only included in the ISE document and were not the applicant's primary efficacy analyses.

The reviewer performed sensitivity analyses using the repeated measures analysis of covariance, multiple imputations (as did the applicant) and a tipping point analysis to further evaluate the robustness of the results. In the tipping point analysis, missing data imputed through the multiple imputation approach were shifted up by different magnitudes to evaluate the deviation from the missing at random (MAR) assumption which is the basis for the multiple imputation approach. The repeated measure analysis of covariance approach that accounted for correlated IOP measurements used an unstructured covariance matrix and included the fixed effects for treatment, visit, time, baseline IOP values, and the interaction of treatment by visit

by time. Time was included in the model as a categorical variable. The applicant also conducted additional sensitivity analysis using the worst observation carried forward (WOCF) method. In this method, for each subject, the post-baseline time-matched worst IOP was carried forward. Similar to the LOCF approach, some measurement times were left with missing data after the WOCF approach has been used.

Regardless of the analysis method used, non-inferiority of Vyzulta to Timolol was established if the upper limit of the 95% CI for the difference in the mean IOP was <1.5 mmHg at each of the nine time points (Statistical Criterion) and was < 1 mmHg at the majority (5 or more) of time points (Clinical Criterion). If non-inferiority is established, the studies plan to test for superiority of Vyzulta over Timolol as a secondary objective. Superiority of Vyzulta to Timolol was established if the upper limit of the 95% CI for the difference in the mean IOP was <0 mmHg for all time points. The two treatment arms were also compared with respect to the two key secondary efficacy endpoints using chi-square tests.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Demographic and Baseline Characteristics

There were no significant baseline imbalances between the two arms in the demographics of age, gender, race or treatment naivety. There were slightly more subjects from the US in Study 770 than in Study 769. In both studies, there were more female participants than male participants; and most of the study participants were white, had previous IOP treatment experience (not treatment naïve) and had brown Iris color (Table 2).

Table 2: Baseline and Demographics (Randomized Subjects)

	Study 769		Study 770	
	Vyzulta N=286	Timolol N=134	Vyzulta N=283	Timolol N=137
Sex				
Female	168(58.7%)	78(58.2%)	165(58.3%)	79(57.7%)
Male	118(41.3%)	56(41.8%)	118(41.7%)	58(42.3%)
Age				
Mean (SD)	64.7 (10.3)	63.0	64.8 (9.8)	64.1 (9.7)
Median	65	64	65	65
Min, Max	22, 88	23, 83	23, 87	37, 88
Age Group				
<65 Years	139(48.6%)	68(50.7%)	131(46.3%)	64(46.7%)
≥ 65 Years	147(51.4%)	66(49.3%)	152(53.7%)	73(53.3%)
Race				
White	219(76.6%)	109(81.3%)	208(73.5%)	89(65%)
Black or African American	64(22.4%)	24(17.9%)	70(24.7%)	46(33.6%)
Asian	1(0.3%)	1(0.7%)	4(1.4%)	2(1.5%)
Other	2(0.7%)	0(0%)	1(0.4%)	0(0%)
Iris Color				
Blue	68(24%)	41(30.6%)	58(20.9%)	32(23.7%)
Brown	170(60.1%)	69(51.5%)	166(59.9%)	82(60.7%)
Green	12(4.2%)	6(4.5%)	11(4%)	4(3%)
Hazel	32(11.3%)	17(12.7%)	42(15.2%)	16(11.9%)
Other	1(0.4%)	1(0.7%)	0(0%)	1(0.7%)

Ethnicity				
Hispanic or Latino	30(10.5%)	13(9.7%)	37(13.1%)	19(13.9%)
Not Hispanic or Latino	256(89.5%)	121(90.3%)	246(86.9%)	118(86.1%)
Treatment Naïve?				
Yes	83(29%)	34(25.4%)	85(30%)	35(25.5%)
No	203(71%)	100(74.6%)	198(70%)	102(74.5%)
Country				
US	246(86%)	110(82.1%)	274(96.8%)	133(97.1%)
Other	40(14%)	24(17.9%)	9(3.2%)	4(2.9%)

Source: Reviewer's Analysis

3.2.3.2 Patient Disposition

The studies had two periods: the efficacy period and the safety extension period. The efficacy period spanned from day of first dose up to and including Month 3. The open-label safety extension period lasted 9 months in Study 769 and 3 months in Study 770. During the safety extension period, all subjects were to receive Vyzulta. In both studies, over 92% of subjects in each arm completed the efficacy period of the study. The major reason for study discontinuation was adverse events (Study 769) and failure to follow the study procedure Study 770 (Table 3). The number of subjects who completed the study visits during the efficacy period of the study (Baseline, Weeks 2 and 6 and Month 3) is presented in Table 4. The number of subjects with observed IOP measurements at each time point (not carried forward) is presented in Table 5.

Table 3: Patient Disposition (Randomized Subjects)

	Vyzulta	**Timolol**	**Total**
Study 769			
Subjects Randomized	286 (100%)	134 (100%)	420
Subjects Randomized and Treated (Safety population)	284 (99.3%)	134 (100%)	418
Subjects Who completed the Study			
Completed the Efficacy Phase	264 (92.3%)	123 (91.8%)	387 (91.7%)
Completed the Entire Study[1]	96 (34.05)	39(28.9%)	135 (32.4%)
Reason for Discontinuation (Efficacy Phase: Safety Population)			
Withdraw Consent	6 (2.1%)	1(0.8%)	7 (1.7%)
Lost-to-Follow-up	1 (0.4%)	0 (0.0%)	1 (0.2%)
Adverse Events	4 (1.4%)	5 (3.7%)	9 (2.2%)
Investigator Decision	1 (0.4%)	2 (1.5%)	3 (0.7%)
Failure to follow the required study procedure	2 (0.7%)	2 (1.5%)	4 (1.0%)
Other	6 (2.1%)	1 (0.8%)	7 (1.7%)
Study 770			
	Vyzulta	**Timolol**	**Total**
Subjects Randomized	283 (100%)	137 (100%)	420
Subjects Randomized and Treated (Safety population)	279 (95.6%)	136 (99.3%)	415
Subjects Who completed the Study			
Completed the Efficacy Phase	259 (91.5%)	128 (93.4%)	387 (92.1%)
Completed the Entire Study[1]	253 (89.4%)	125 (91.2%)	378 (90.0%)
Reason for Discontinuation (Efficacy Phase: Safety Population)			
Withdraw Consent	3 (1.1%)	2(1.5%)	5 (1.2%)
Lost-to-Follow-up	0 (0.0%)	1 (0.7%)	1 (0.5%)

Administrative Issue	1 (0.4%)	0 (0.0%)	1 (0.2%)
Adverse Events	4 (1.4%)	1 (0.7%)	5 (1.2%)
Investigator Decision	1 (0.4%)	0 (0.0%)	1 (0.2%)
Failure to follow the required study procedure	4 (1.4%)	2 (1.5%)	6 (1.4%)
Other	7 (3.2%)	2 (1.5%)	9 (2.2%)

Source: Tables 14 1 1 1 1 1, 4 1 1 1 2, 4 1 1 1 3 of Applicant's Study Reports 1The entire study refers to both the efficacy phase and the safety extension phase

Table 4: Summary of Randomized Subjects who completed visits during the efficacy phase

	Study 769		**Study 770**	
Visit	**Vyzulta N=286**	**Timolol N=134**	**Vyzulta N=283**	**Timolol N=137**
Baseline	286(100%)	134(100%)	283(100%)	137(100%)
Week 2	284(99.3%)	134(100%)	280(98.9%)	135(98.5%)
Week 6	280(97.9%)	130(97%)	270(95.4%)	132(96.4%)
Month 3	273(95.5%)	126(94%)	263(92.9%)	130(94.9%)

Source: Reviewer's Analysis

Table 5: Summary of subjects with observed IOP (Not imputed: Randomized subjects)

Time	Study 769		Study 770	
	Vyzulta N=286	Timolol N=134	Vyzulta N=283	Timolol N=137
Baseline				
8 AM	286(100.0%)	134(100.0%)	282(99.6%)	137(100.0%)
12 PM	286(100.0%)	134(100.0%)	282(99.6%)	137(100.0%)
4 PM	286(100.0%)	134(100.0%)	282(99.6%)	137(100.0%)
Week 2				
8 AM	282(98.6%)	133(99.3%)	278(98.2%)	135(98.5%)
12 PM	282(98.6%)	131(97.8%)	272(95.8%)	135(98.5%)
4 PM	282(98.3%)	131(97.8%)	272(95.8%)	135(98.5%)
Week 6				
8 AM	273(95.5%)	129(96.3%)	266(94%)	130(94.9%)
12 PM	271(94.8%)	128(95.5%)	265(93.6%)	129(94.2%)
4 PM	272(95.1%)	128(95.5%)	264(93.3%)	128(93.4%)
Month 3				
8 AM	270(94.4%)	124(92.5%)	260(91.9%)	129(94.2%)
12 PM	268(93.7%)	124(92.5%)	260(91.9%)	129(94.2%)
4 PM	269(94.1%)	124(92.5%)	259(91.5%)	129(94.2%)

Source: Reviewer's Analysis

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 an ANCOVA model. The standard error estimates for the least square means are presented in corresponding parenthesis. In the efficacy summaries, non-inferior (yes) means the upper limit of the 95% confidence interval for the treatment difference (Vyzulta -Timolol) at that particular time point is less than the non-inferiority margin of 1.5 mmHg, and superior (yes) means that the upper limit of the 95% confidence interval for the

treatment difference at that particular time point is less than 0 mmHg. The following analysis populations were considered:

- Bausch-ITT refers to the applicant's ITT population which included all randomized and treated subjects with baseline and at least one post-baseline assessment.

- FDA-ITT refers to the reviewer's ITT population which includes all randomized and treated subjects.

- The per-protocol population (PP) is comprised of subjects who remained in the study through Month 3 with non-missing IOP assessments at all nine post-baseline efficacy phase time points and who did not have major protocol deviations during the efficacy phase.

The summary of the number of subjects included in the different analysis populations and the number of randomized and treated subjects excluded from Bausch-ITT is presented in Table 6 and Table 7. There were a total of 4 randomized and treated subjects (2 in each arm) in the two studies combined that were excluded altogether from the applicant's primary efficacy analysis. Three of the four subjects were excluded because they have no post-baseline IOP and the fourth subject which was from the Vyzulta arm in Study 770 was excluded because the study eye could not be designated based on the protocol specification. In addition, a combined total of 14 (4 in the Timolol arm and 10 in the Vyzulta arm) randomized and treated subjects were excluded from the applicant's analysis as a consequence of the way the LOCF imputation was applied. Of the 10 subjects in the Vyzulta arm, 3 withdrew their consent, 2 failed to follow the study procedures, and 2 were excluded based on the investigators decision. One subject in the Vyzulta arm and two subjects in the Timolol arm completed the study but the reason for missed IOP is not specified. One subject in the Timolol arm withdrew consent.

Table 6: Summary of subjects included in different analysis populations

Population	**Study 769**		**Study 770**	
	Vyzulta	**Timolol**	**Vyzulta**	**Timolol**
All Randomized (ITT)	286(100%)	134(100%)	283(100%)	137(100%)
Bausch-ITT	284(99.3%)	133(99.2%)	277(97.9%)	135(98.5%)
FDA-ITT	284(99.3%)	134(100%)	279(98.6%)	136(99.3%)
Per-Protocol	192 (67.1%)	80 (59.7%)	183 (64.7%)	87 (63.5%)

Source: Reviewer's Analysis Percentages are computed relative to the randomized subjects

Table 7: Number of randomized and treated subjects excluded from Bausch-ITT

Time	Study 769		Study 770	
	Vyzulta N=284	Timolol N=134	Vyzulta N=279	Timolol N=136
Week 2				
8 AM	2 (2)	1 (0)	2 (0)	2 (1)
12 PM	2 (2)	3 (2)	9 (7)	2 (1)
4 PM	3 (3)	3 (2)	9 (7)	2 (1)
Week 6				
8 AM	1 (1)	1 (0)	2 (0)	1 (0)
12 PM	1 (1)	3 (2)	8 (6)	1 (0)
4 PM	0 (0)	3 (2)	8 (6)	1 (0)
Month 3				

8 AM	1 (1)	1 (0)	2 (0)	1 (0)
12 PM	1 (1)	3 (2)	8 (6)	1 (0)
4 PM	0 (0)	3 (2)	8 (6)	1 (0)

Source: Reviewer's Analysis Total number excluded (excluded due to LOCF)

Note that the major protocol violations that led to the exclusion of subjects from the per-protocol population were that the subject's visit fell outside the visit window followed by missed IOP measurements before the Month 3 assessment. The remaining reasons included: disallowed medications, missed doses and treatment compliance.

3.2.4.1.1 *Primary Efficacy Analysis*

The protocol-defined primary efficacy analyses based on all randomized and treated subjects with baseline and at least one post-baseline assessment (Bausch-ITT) is presented in Figure 3 and Figure 4. The mean baseline IOP at each time point was comparable between the treatment groups. Both treatment groups demonstrated IOP reductions at each of the nine points with Vyzulta having consistently lower mean IOP at all nine time points.

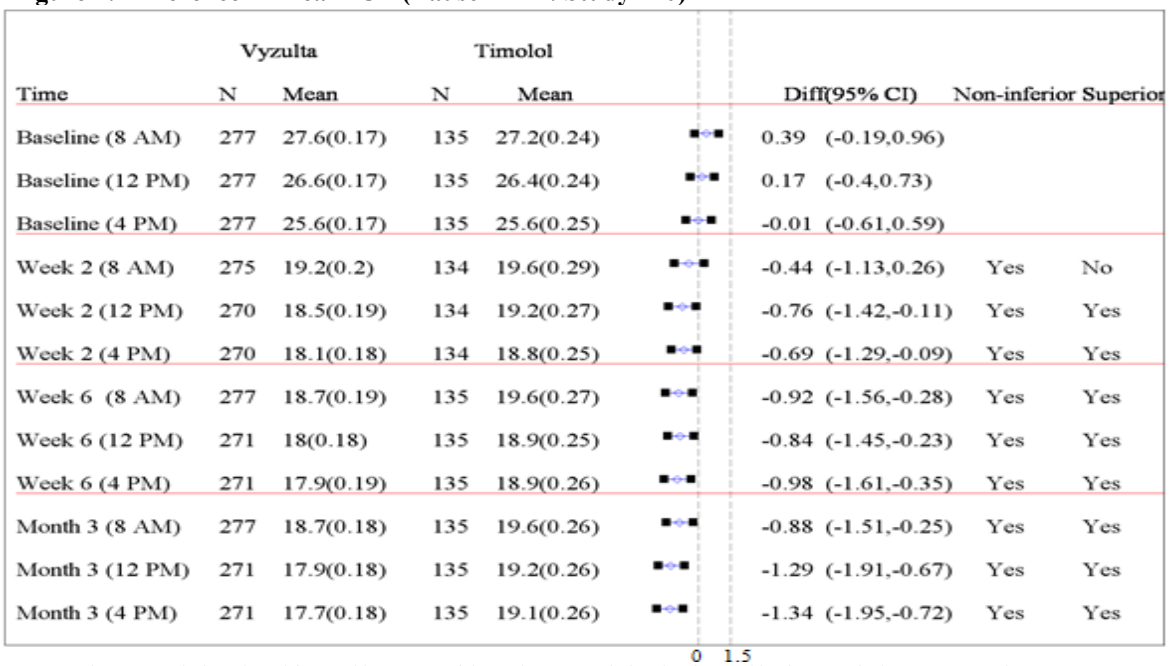
The upper limits of the 95% confidence intervals for the mean difference in IOP were less than the pre-specified non-inferiority margin of 1.5 mmHg for all measurement times (Statistical Criteria). Additionally, the upper limits did not exceed 1.0 mmHg at the each of the nine post-baseline time points (Clinical Criteria). Therefore, the two studies met both the statistical and clinical criteria for non-inferiority. However, Vyzulta did not demonstrate statistical superiority over Timolol for one time point in Study 770.

Figure 3: Difference in Mean IOP (Bausch-ITT: Study 769)

	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	284	27.8(0.17)	133	27.3(0.24)	0.52 (-0.06,1.11)		
Baseline (12 PM)	284	26.5(0.17)	133	26.5(0.25)	0 (-0.59,0.59)		
Baseline (4 PM)	284	25.8(0.17)	133	25.6(0.25)	0.19 (-0.41,0.8)		
Week 2 (8 AM)	282	18.6(0.2)	133	19.8(0.29)	-1.21 (-1.9,-0.53)	Yes	Yes
Week 2 (12 PM)	282	18(0.19)	131	19.4(0.29)	-1.37 (-2.05,-0.69)	Yes	Yes
Week 2 (4 PM)	281	18.1(0.19)	131	19.2(0.27)	-1.11 (-1.76,-0.46)	Yes	Yes
Week 6 (8 AM)	283	18.6(0.19)	133	19.6(0.28)	-1.03 (-1.7,-0.37)	Yes	Yes
Week 6 (12 PM)	283	17.8(0.18)	131	19.1(0.26)	-1.24 (-1.87,-0.62)	Yes	Yes
Week 6 (4 PM)	284	17.8(0.2)	131	19.1(0.29)	-1.26 (-1.96,-0.57)	Yes	Yes
Month 3 (8 AM)	283	18.7(0.19)	133	19.7(0.28)	-1.02 (-1.68,-0.37)	Yes	Yes
Month 3 (12 PM)	283	17.9(0.19)	131	19.1(0.28)	-1.27 (-1.93,-0.61)	Yes	Yes
Month 3 (4 PM)	284	17.8(0.2)	131	19.1(0.29)	-1.33 (-2.01,-0.64)	Yes	Yes

Source: Reviewer's Analysis Adapted from Table 14 2 1 1 of the study report Missing data imputed by time-matched LOCF Mean= least square means (standard error)

Figure 4: Difference in Mean IOP (Bausch-ITT: Study 770)



	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	277	27.6(0.17)	135	27.2(0.24)	0.39 (-0.19,0.96)		
Baseline (12 PM)	277	26.6(0.17)	135	26.4(0.24)	0.17 (-0.4,0.73)		
Baseline (4 PM)	277	25.6(0.17)	135	25.6(0.25)	-0.01 (-0.61,0.59)		
Week 2 (8 AM)	275	19.2(0.2)	134	19.6(0.29)	-0.44 (-1.13,0.26)	Yes	No
Week 2 (12 PM)	270	18.5(0.19)	134	19.2(0.27)	-0.76 (-1.42,-0.11)	Yes	Yes
Week 2 (4 PM)	270	18.1(0.18)	134	18.8(0.25)	-0.69 (-1.29,-0.09)	Yes	Yes
Week 6 (8 AM)	277	18.7(0.19)	135	19.6(0.27)	-0.92 (-1.56,-0.28)	Yes	Yes
Week 6 (12 PM)	271	18(0.18)	135	18.9(0.25)	-0.84 (-1.45,-0.23)	Yes	Yes
Week 6 (4 PM)	271	17.9(0.19)	135	18.9(0.26)	-0.98 (-1.61,-0.35)	Yes	Yes
Month 3 (8 AM)	277	18.7(0.18)	135	19.6(0.26)	-0.88 (-1.51,-0.25)	Yes	Yes
Month 3 (12 PM)	271	17.9(0.18)	135	19.2(0.26)	-1.29 (-1.91,-0.67)	Yes	Yes
Month 3 (4 PM)	271	17.7(0.18)	135	19.1(0.26)	-1.34 (-1.95,-0.72)	Yes	Yes

Source: Reviewer's Analysis Adapted from Table 14 2 1 1 of the study report Missing data imputed by time-matched LOCF Mean= least square means (standard error)

Note that, neither the protocols nor the statistical analysis plans for the two Phase 3 studies specified the estimand of interest. In the absence of an explicitly pre specified, justified, and accepted primary estimand of interest, one must evaluate whether each possible estimand is "meaningful for all study participants, and estimable with minimal assumptions," as recommended in the National Research Council (NRC) report. For example, the primary ANCOVA analysis with LOCF could be interpreted as an evaluation of the "last available observation" (LAO) estimand, that is, the difference in mean IOP until each time point at which patients adhere to the assigned treatment. Although this estimand is likely a reasonable measure of drug activity, it may not provide a meaningful measure of effectiveness for all patients. Therefore, an evaluation of the effectiveness of Vyzulta should not be based solely on the primary analysis of the LAO estimand.

One estimand that could provide a measure of effectiveness is the difference in mean IOP at each time point in all randomized patients, regardless of adherence to the assigned treatment. This reviewer suggests that the analysis on all randomized subjects with a hybrid LOCF/ worst (best) imputation approach, proposed by the applicant as an additional analysis, could provide a conservative estimate for this estimand. The results of the analyses on all randomized subjects with a hybrid of LOCF and worst/best imputation are provided in Figure 5 and Figure 6. Additionally, the reviewer conducted the analysis of the primary efficacy endpoint based on all randomized and treated subjects regardless of post-baseline assessment (FDA-ITT). The results for this analysis are summarized in Figure 7 and Figure 8. In both of these analyses, the two studies met the statistical as well as the clinical criteria for non-inferiority. However, potentially because the best/worst imputation used in these analyses favors the Timolol arm, the superiority of Vyzulta against Timolol was not established for at least one time point in both studies (more time points in the analysis based on all randomized subjects). The summary

of the best (minimum) and worst (maximum) IOP values used to impute missing data and two sample cases showing the different missing data imputations is presented in Table 18-Table 20 in the appendix.

Figure 5: Difference in Mean IOP (Randomized Subjects: Study 769)

Time	Vyzulta N=286	Timolol N=134	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.8(0.17)	27.3(0.24)	0.54 (-0.04,1.12)		
Baseline (12 PM)	26.5(0.17)	26.5(0.25)	0.01 (-0.58,0.59)		
Baseline (4 PM)	25.8(0.17)	25.6(0.25)	0.2 (-0.4,0.8)		
Week 2 (8 AM)	18.8(0.22)	19.8(0.32)	-0.92 (-1.68,-0.16)	Yes	Yes
Week 2 (12 PM)	18.2(0.22)	19.2(0.32)	-0.91 (-1.68,-0.14)	Yes	Yes
Week 2 (4 PM)	18.4(0.22)	19(0.32)	-0.6 (-1.36,0.16)	Yes	No
Week 6 (8 AM)	18.8(0.21)	19.5(0.31)	-0.78 (-1.51,-0.05)	Yes	Yes
Week 6 (12 PM)	18(0.2)	18.9(0.3)	-0.86 (-1.57,-0.15)	Yes	Yes
Week 6 (4 PM)	17.9(0.21)	18.9(0.31)	-0.94 (-1.68,-0.2)	Yes	Yes
Month 3 (8 AM)	18.9(0.21)	19.6(0.3)	-0.77 (-1.49,-0.05)	Yes	Yes
Month 3 (12 PM)	18.1(0.21)	18.9(0.31)	-0.88 (-1.61,-0.14)	Yes	Yes
Month 3 (4 PM)	17.9(0.21)	18.9(0.31)	-0.99 (-1.72,-0.25)	Yes	Yes

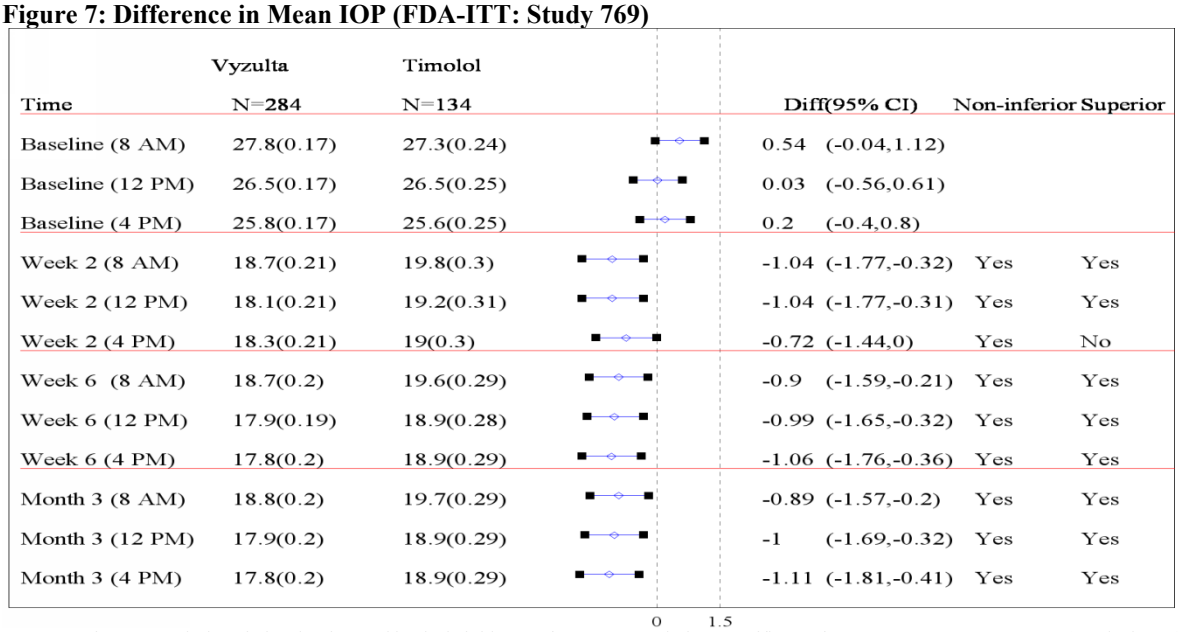
Source: Reviewer's Analysis Adapted from Table 8-13 of the ISE Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

Figure 6: Difference in Mean IOP (Randomized Subjects: Study 770)

Time	Vyzulta N=283	Timolol N=137	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.6(0.17)	27.2(0.24)	0.41 (-0.16,0.98)		
Baseline (12 PM)	26.6(0.16)	26.4(0.23)	0.21 (-0.35,0.77)		
Baseline (4 PM)	25.7(0.17)	25.6(0.25)	0.07 (-0.52,0.67)		
Week 2 (8 AM)	19.5(0.22)	19.5(0.32)	-0.05 (-0.81,0.72)	Yes	No
Week 2 (12 PM)	18.8(0.21)	19.1(0.3)	-0.25 (-0.98,0.48)	Yes	No
Week 2 (4 PM)	18.6(0.22)	18.7(0.31)	-0.03 (-0.77,0.72)	Yes	No
Week 6 (8 AM)	19(0.21)	19.5(0.3)	-0.58 (-1.31,0.15)	Yes	No
Week 6 (12 PM)	18.4(0.2)	18.8(0.29)	-0.36 (-1.06,0.34)	Yes	No
Week 6 (4 PM)	18.4(0.22)	18.8(0.32)	-0.39 (-1.16,0.38)	Yes	No
Month 3 (8 AM)	19(0.21)	19.5(0.3)	-0.55 (-1.27,0.17)	Yes	No
Month 3 (12 PM)	18.3(0.21)	19.1(0.3)	-0.8 (-1.51,-0.09)	Yes	Yes
Month 3 (4 PM)	18.3(0.22)	19(0.32)	-0.74 (-1.49,0.02)	Yes	No

Source: Reviewer's Analysis Adapted from Table 8-13 of the ISE Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

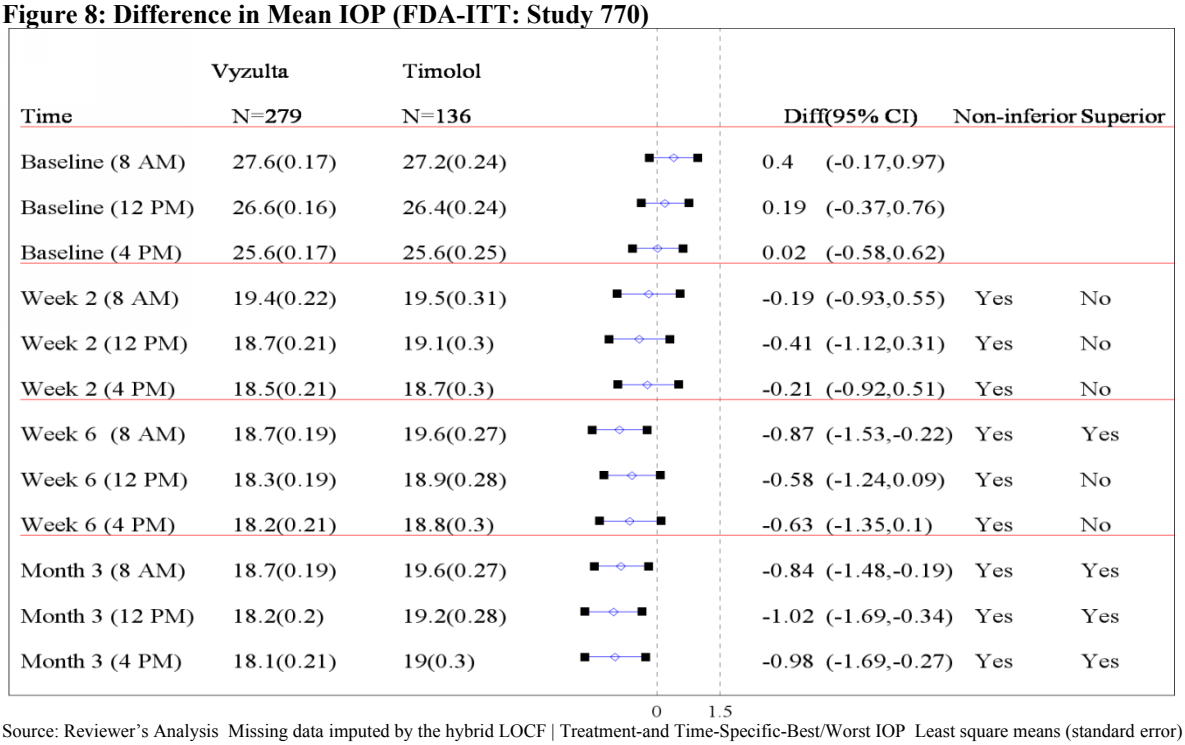
Figure 7: Difference in Mean IOP (FDA-ITT: Study 769)



Time	Vyzulta N=284	Timolol N=134	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.8(0.17)	27.3(0.24)	0.54 (-0.04,1.12)		
Baseline (12 PM)	26.5(0.17)	26.5(0.25)	0.03 (-0.56,0.61)		
Baseline (4 PM)	25.8(0.17)	25.6(0.25)	0.2 (-0.4,0.8)		
Week 2 (8 AM)	18.7(0.21)	19.8(0.3)	-1.04 (-1.77,-0.32)	Yes	Yes
Week 2 (12 PM)	18.1(0.21)	19.2(0.31)	-1.04 (-1.77,-0.31)	Yes	Yes
Week 2 (4 PM)	18.3(0.21)	19(0.3)	-0.72 (-1.44,0)	Yes	No
Week 6 (8 AM)	18.7(0.2)	19.6(0.29)	-0.9 (-1.59,-0.21)	Yes	Yes
Week 6 (12 PM)	17.9(0.19)	18.9(0.28)	-0.99 (-1.65,-0.32)	Yes	Yes
Week 6 (4 PM)	17.8(0.2)	18.9(0.29)	-1.06 (-1.76,-0.36)	Yes	Yes
Month 3 (8 AM)	18.8(0.2)	19.7(0.29)	-0.89 (-1.57,-0.2)	Yes	Yes
Month 3 (12 PM)	17.9(0.2)	18.9(0.29)	-1 (-1.69,-0.32)	Yes	Yes
Month 3 (4 PM)	17.8(0.2)	18.9(0.29)	-1.11 (-1.81,-0.41)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

Figure 8: Difference in Mean IOP (FDA-ITT: Study 770)



Time	Vyzulta N=279	Timolol N=136	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.6(0.17)	27.2(0.24)	0.4 (-0.17,0.97)		
Baseline (12 PM)	26.6(0.16)	26.4(0.24)	0.19 (-0.37,0.76)		
Baseline (4 PM)	25.6(0.17)	25.6(0.25)	0.02 (-0.58,0.62)		
Week 2 (8 AM)	19.4(0.22)	19.5(0.31)	-0.19 (-0.93,0.55)	Yes	No
Week 2 (12 PM)	18.7(0.21)	19.1(0.3)	-0.41 (-1.12,0.31)	Yes	No
Week 2 (4 PM)	18.5(0.21)	18.7(0.3)	-0.21 (-0.92,0.51)	Yes	No
Week 6 (8 AM)	18.7(0.19)	19.6(0.27)	-0.87 (-1.53,-0.22)	Yes	Yes
Week 6 (12 PM)	18.3(0.19)	18.9(0.28)	-0.58 (-1.24,0.09)	Yes	No
Week 6 (4 PM)	18.2(0.21)	18.8(0.3)	-0.63 (-1.35,0.1)	Yes	No
Month 3 (8 AM)	18.7(0.19)	19.6(0.27)	-0.84 (-1.48,-0.19)	Yes	Yes
Month 3 (12 PM)	18.2(0.2)	19.2(0.28)	-1.02 (-1.69,-0.34)	Yes	Yes
Month 3 (4 PM)	18.1(0.21)	19(0.3)	-0.98 (-1.69,-0.27)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

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. The reviewer conducted a repeated measures ANCOVA to account for possible correlation between repeated IOP measurements, a tipping

point analysis, and analysis of the primary efficacy endpoint using different missing data imputation methods.

A. Missing data

First, to evaluate the impact of the worst/best imputation, the reviewer conducted the analysis of the primary efficacy endpoint based FDA-ITT with a hybrid of LOCF and the time and treatment specific mean IOP (as opposed to worst/best IOP) imputed for subjects with missing post-baseline IOP in both arms. The results from this analysis are presented in Figure 9 and Figure 10. Although the numerical values are slightly different, the conclusion from this analysis is in agreement with the applicant's primary efficacy analysis regarding both the non-inferiority and statistical superiority of Vyzulta over Timolol.

One of the recommendations provided by the agency regarding missing data was that the time and treatment matched worst IOP values be imputed for subjects in both arms with no post-baseline IOP (in cases where LOCF cannot be used). The applicant however did not consider this approach. The reviewer conducted the analysis of the primary efficacy endpoint based on FDA-ITT with the hybrid of LOCF and the time and treatment specific worst IOP (as opposed to worst/best IOP). Additionally, the reviewer also conducted the analysis of the primary efficacy endpoint based on the FDA-ITT with missing post-baseline IOP imputed using the last non-missing IOP from the same time including baseline (LOCF/BOCF). The results from these two analyses are presented in Figure 11-Figure 14. In both analyses, the non-inferiority criteria were met. However, the superiority of Vyzulta over Timolol was not established in at least four of the nine time points compared to only one time point in the applicant's analysis in Study 770. The analysis on the per-protocol population with observed data only and the multiple imputations on FDA-ITT were also fairly consistent with the primary efficacy analysis results (Figure 15-Figure 18).

B. Tipping point analysis

To assess the impact of deviation from the missing at random (MAR) assumption, which is the basis for the multiple imputation approach, the reviewer performed two types of tipping point analyses. In the first approach, a positive shift parameter between 0 and 10 mm Hg was added to the imputed values for subjects in the Vyzulta arm only. In the second approach, which is less conservative, the same shift parameter was added on the imputed values in both arms. The summary result for the most conservative case (a shift parameter of 10 added to Vyzulta arm only) is presented in Figure 19 and Figure 20. The conclusion of non-inferiority has not changed even after the imputed values in the Vyzulta arm were increased by 10 units.

In summary, it appears that the overall study conclusion regarding the primary objectives of the two studies namely non-inferiority of Vyzulta to Timolol, was not impacted by the method used to handle missing data and the analysis population considered. The results of the superiority comparison however were slightly different from one analysis to the next although the overall conclusion seemed to be in the same direction.

C. Unadjusted Analysis

During the pre-NDA meeting, the agency recommended the analysis of the primary efficacy endpoint without adjusting for time-matched baseline IOP as part of the sensitivity analyses. The results for this analysis are summarized in Figure 21- Figure 24. The results are in agreement with the baseline adjusted primary efficacy analysis regarding the non-inferiority of Vyzulta to Timolol in reducing IOP. The superiority conclusions are also similar with the majority of adjusted analyses.

D. Repeated Measures ANCOVA

The ANCOVA analysis performed at each time point of each visit separately does not take the possible correlation between IOP measurements taken from the same subject. The reviewer thus performed a repeated measure analysis of covariance that accounted for correlated IOP measurements as part of the sensitivity analyses. The model used an unstructured covariance matrix and included the fixed effects for treatment, visit, time, baseline IOP values, and the interaction of treatment by visit by time. Time was included in the model as a categorical variable. Treatment differences in the mean IOP at each time point of each visit was determined based on least squares means using the above model.

The results of the analysis of the primary efficacy endpoint using the repeated measures ANCOVA on all randomized and treated subjects with missing data imputed using the hybrid LOCF best/worst approach, on Bausch-ITT with LOCF, and the analysis on all randomized and treated subjects with available data only provided results that are in agreement with the non-inferiority conclusion of the primary efficacy analysis. In all analyses results, Vyzulta was non-inferior to Timolol at all nine post-baseline time points for both studies. However, there was at least one time point at which Vyzulta was not superior to Timolol (Figure 25- Figure 30).

3.2.4.1.3 *Secondary Efficacy Analysis*

A. Change from baseline IOP

Descriptive IOP summaries and mean plots for the reductions in IOP from baseline are presented in the appendix (Table 16-Table 17 and Figure 48- Figure 49). For both studies, the Vyzulta arm had consistently higher reduction in IOP from baseline for each time point. For both treatment arms, the highest reductions occurred at 8AM. Note that, subjects in the Vyzulta treatment group were dosed QD in the evening at approximately 8 PM whereas those in the Timolol group were dosed BID with the first dose instilled at 8 PM the evening of Day 1. Thus, the decline in IOP reduction during the two time points (12 PM & 4 PM) could be attributed to the wearing off of the treatment effects during the day.

The analysis of the change from baseline IOP at each time point using the same ANCOVA model with terms for time-matched baseline IOP and treatment as covariates was performed. The summary results both for the analysis on FDA-ITT and Bausch-ITT are presented in Figure 31-Figure 34. Both treatment groups demonstrated IOP reductions at each of the nine time points. There was an IOP reduction of between 7.5 to 9.0 mmHg in the Vyzulta arm

compared to between 6.5 to 7.9 mmHg in the Timolol arm. Therefore, as expected, similar to the results seen for mean IOP, the change from baseline in mean IOP was better (greater decrease from baseline) for the Vyzulta arm compared to Timolol at all nine time points.

B. IOP <=18 mm Hg and >=25% reduction in IOP from baseline

The IOP lowering effect of Vyzulta was further evaluated based on two key secondary efficacy endpoints: the proportion of subjects with IOP ≤ 18 mmHg consistently at all 9 time points and the proportion of subjects with IOP reduction of ≥ 25% consistently from baseline at all 9 time points. The Vyzulta arm had a significantly higher proportion of subjects who attained an IOP ≤ 18 mmHg at all 9 time points in Study 769 but the difference was not statistically significant in Study 770. The proportion of subjects with an IOP reduction of ≥ 25% from baseline consistently at all 9 time points was significantly higher in the Vyzulta arm in both studies (Table 8-Table 11).

Table 8: Summary of Key Secondary Endpoints (Bausch-ITT: Study 769)

Response Criteria	Vyzulta N=284	Timolol N=133	Diff (95% CI)
Mean IOP ≤ 18 mmHg at all 9 Efficacy Phase Time Points	65(22.9%)	15 (11.3)	11.6% (4.3%, 18.9%)
Percent Reduction from Baseline in Mean IOP ≥ 25% at all 9 Efficacy Phase Time Points	99 (34.9%)	26 (19.5%)	15.3% (6.6%, 24.8%)

Source: Reviewer's Analysis Adapted from Table 14 2 3 1 of the study report Missing data imputed by time matched LOCF

Table 9: Summary of Key Secondary Endpoints (Bausch-ITT: Study 770)

Response Criteria	Vyzulta N=277	Timolol N=135	Diff (95% CI)
Mean IOP ≤ 18 mmHg at all 9 Efficacy Phase Time Points	49 (17.7%)	15 (11.1)	6.6% (-0.4%, 13.5%)
Percent Reduction from Baseline in Mean IOP ≥ 25% at all 9 Efficacy Phase Time Points	86 (31.0%)	25 (18.5%)	12.5% (4.0%, 21.1%)

Source: Reviewer's Analysis Adapted from Table 14 2 3 1 of the study report Missing data imputed by time matched LOCF

Table 10: Summary of Key Secondary Endpoints (FDA-ITT: Study 769)

Response Criteria	Vyzulta N=284	Timolol N=134	Diff (95% CI)
Mean IOP ≤ 18 mmHg at all 9 Efficacy Phase Time Points	65(22.9%)	16 (11.9)	10.9% (3.6%, 18.3%)
Percent Reduction from Baseline in Mean IOP ≥ 25% at all 9 Efficacy Phase Time Points	99 (34.9%)	27 (20.1%)	14.9% (5.9%, 23.5%)

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Table 11: Summary of Key Secondary Endpoints (FDA-ITT: Study 770)

Response Criteria	Vyzulta N=279	Timolol N=136	Diff (95% CI)
Mean IOP ≤ 18 mmHg at all 9 Efficacy Phase Time Points	49 (17.6%)	15 (11.3)	6.5% (-0.4%, 13.4%)
Percent Reduction from Baseline in Mean IOP ≥ 25% at all 9 Efficacy Phase Time Points	86 (30.8%)	26 (18.4%)	12.4% (4.0%, 20.9%)

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

3.3 Evaluation of Safety

Because 250 of the 271 subjects randomized to the Timolol arm received Vyzulta during the safety extension period of the studies, the safety population in the two studies combined is consisted of 1082 subjects who received at least one dose of either drug (811 and 271 subjects in the Vyzulta and Timolol arms respectively). Note the safety summary for the Timolol arm is for the efficacy phase of the study as no subject received Timolol during the safety extension phase of the study.

During the efficacy phase of the study, the mean duration of exposure for subjects in both arms was 90.2 days. During the efficacy phase, the majority of subjects (531 [94.7%]) treated with Vyzulta were exposed between 67 to ≤ 135 days and no subjects were exposed for more than 135 days. A similar proportion of subjects treated with Timolol (254 [93.7%] subjects) were exposed between 67 to ≤ 135 days and no subjects were exposed for over 135 days during the efficacy phase (Table 12).

Table 12: Summary of Duration of Exposure

Duration of Exposure (days)	Vyzulta		Timolol
	Efficacy Phase N=561	All Study Period N=811	Efficacy Phase N=271
1 to ≤28	15 (2.7%)	19 (2.3%)	10 (3.7%)
29 to ≤66	15 (2.7%)	21 (2.6%)	7 (2.6%)
67 to ≤135	531 (94.7%)	189 (23.3%)	254 (93.7%)
136 to ≤225	0 (0.0%)	377 (46.5%)	0 (0.0%)
226 to ≤318	0 (0.0%)	97 (12.0%)	0 (0.0%)
≥319	0 (0.0%)	108 (13.3%)	0 (0.0%)
Mean (SD)	90.2 (16.05)	192.5 (94.71)	90.0 (17.58)
Median	92.0	187.0	92.0
Min, Max	1, 134	1, 548	1, 117

Source: Table 9-3 of the ISS

A total of 158 (19.5%) subjects who received at least one dose of Vyzulta reported at least one ocular AE in the study eye. Similarly, a total of 32 (11.8%) subjects reported at least one ocular AE during the efficacy phase of the study while taking Timolol. The most frequently reported ocular AEs in the study eye in the Vyzulta arm were conjunctival hyperaemia (47 (5.8%)), eye irritation 35 (4.3%)), eye pain (25 (3.1%)), administrative site conditions (21 (2.6%)) and installation site pain (17 (2.1%)). A similar safety pattern was observed in the treated fellow eye with higher proportion of subjects who received Vyzulta reporting conjunctival hyperaemia

in the treated fellow eye. None of the reported ocular adverse events in the study eye were serious.

A total of 120 (14.8%) subjects who received at least one dose of Vyzulta reported at least one non-ocular AE. All of the reported non-ocular adverse events occurred in less than 2% of the safety population for both arms. Thirteen subjects (1.6%) who received at least one dose of Vyzulta during the entire duration of the study reported at least one serious non-ocular AE. During the efficacy phase of the study, 2 (0.7%) subjects who received at least one dose of Timolol reported at least one serious non-ocular AE. One subject in the Vyzulta arm died during the study (Table 13 and Table 14). The person who died during the study was a 68-year-old man with a medical history that included coronary artery stenosis, coronary artery bypass surgery, hypercholesterolemia, and hypertension. The applicant reported that the autopsy report showed that the person died of severe ischemic heart disease.

The best corrected visual acuity was also measured as a safety parameter at baseline, Weeks 2 and 6 and Months 3 and 6. The summary of the mean BCVA (LogMar) is presented in Table 15. There does not appear to be any difference in the mean BCVA (LogMar) between the two treatment arms and that there was no noticeable change over time in either arm.

Table 13: Summary of Adverse Events in the study eye

	Treatment: N (%)	
Adverse event	Vyzulta N=811	Timolol N=271
Any non-ocular AE	120 (14.8%)	37 (13.7%)
Any serious non-ocular AE	13 (1.6%)	2 (0.7%)
Any ocular AE	158 (19.5%)	32 (11.8%)
Conjunctival hyperaemia	47 (5.8%)	3 (1.1%)
Eye irritation	35 (4.3%)	7 (2.6%)
Eye Pain	25 (3.1%)	6 (2.2%)
General disorders	21 (2.6%)	5 (1.8%)
Instillation site pain	17 (2.1%)	4 (1.5%)

Source: Tables 10-6 of ISS

Table 14: Summary of Adverse Events the treated fellow eye

	Treatment: N (%)	
Adverse event	Vyzulta N=788	Timolol N=267
Any ocular AE	160 (20.3%)	33 (12.4%)
Any Serious ocular AE	1 (0.1%)	0 (0.0%)
Conjunctival hyperaemia	49 (6.2%)	4 (1.5%)
Eye irritation	31(3.9%)	7 (2.6%)
Eye Pain	28 (3.6%)	5 (1.9%)
General disorders	21 (2.7%)	5 (1.9%)
Instillation site pain	17 (2.1%)	4 (1.5%)

Source: Tables 10-7 of ISS

Table 15: Mean BCVA in the Study Eye

Visit	**Study 769**		
	Vyzulta N=283	**Timolol N=135**	**Diff (95% CI)**
Baseline	0.09(0.137)	0.07(0.124)	0.021(-0.01,0.05)

Week 2	0.08(0.136)	0.06(0.125)	0.013(-0.01,0.04)
Week 6	0.08(0.131)	0.06(0.124)	0.02(-0.01,0.05)
Month 3	0.08(0.134)	0.07(0.139)	0.017(-0.01,0.05)
Month 6	0.08(0.136)	0.05(0.117)	0.03(0,0.06)
	Study 770		
	Vyzulta N=277	**Timolol N=135**	**Diff (95% CI)**
Baseline	0.09(0.135)	0.07(0.122)	0.02(-0.01,0.05)
Week 2	0.09(0.124)	0.06(0.121)	0.021(0,0.05)
Week 6	0.08(0.123)	0.07(0.113)	0.008(-0.02,0.03)
Month 3	0.08(0.121)	0.07(0.133)	0.011(-0.02,0.04)
Month 6	0.08(0.122)	0.08(0.129)	0.004(-0.02,0.03)

Source: Reviewer's Analysis.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The summary results for the comparison of the Vyzulta and Timolol arms with respect to the primary efficacy endpoint of mean IOP based on baseline demographics are summarized below. These subgroup analyses are based on the pooled data from the two Phase 3 studies. The subgroup analysis results presented in this section are considered descriptive and should only be used to characterize the observed treatment differences between subgroups. Unless stated otherwise, all analyses are performed on all randomized and treated subjects (FDA-ITT) with a hybrid LOCF and worst/best IOP used to impute missing data.

4.1 Age Gender Race and Region and Iris Color

Overall, the subgroup analysis results based on baseline demographics were consistent with the primary efficacy analysis results. Although the non-inferiority criteria was not met for one subgroup (EU subjects), conclusive statements regarding statistical significance could not be made on the magnitude of the treatment effect for any subgroup, as the studies were not designed to test the treatment effect for any subgroup (Figure 35 -Figure 45).

4.2 Other Special/Subgroup Populations

Additional subgroup analysis for subgroups formed based any prior treatment (yes versus no) is summarized below. Here also, the subgroup analysis results were consistent with the primary efficacy analysis results. Treatment naïve patients who received Vyzulta seem to have a higher reduction in IOP compared to their non-treatment naïve counterparts in the same arm.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Two statistical issues were encountered in this review: the applicant's choice of analysis population and the subsequent handling of missing data. The applicant conducted the primary efficacy analysis on the intent-to-treat (ITT) population which included all randomized and treated subjects with a baseline and at least one post-baseline assessment (referred to in this review as Bausch-ITT). A last non-missing post-baseline observation from a prior visit at the

same time of the day was carried forward for missing post-baseline IOP (LOCF). Consequently, subjects with no post-baseline observation at the same time of the day for all prior post-baseline visits would still have missing data.

Note that, although the number of randomized and treated subjects excluded entirely from the applicant's analysis was small, the LOCF approach used by the applicant further excluded additional randomized and treated subjects at different time points. Since excluding randomized, treated patients who did not have a post-baseline assessment could introduce potential bias, the reviewer's analysis included all randomized and treated subjects (FDA-ITT). A hybrid of the LOCF and the worst/best imputation approach was used as a potentially conservative estimate of effectiveness. In this approach, the worst and best time-matched IOP values in the Vyzulta and Timolol arms respectively were imputed for the time points where the LOCF could not be implemented. The applicant also performed the analysis of the primary efficacy endpoint based on all randomized subjects using the hybrid of the LOCF and the worst/best imputation approach for each individual study separately and for the integrated summary of efficacy (ISE).

5.2 Collective evidence

The primary efficacy evidence to support the non-inferiority of Vyzulta to Timolol in IOP reduction comes from two identical Phase 3 studies (Study 769 and 770) conducted across sites in the US and abroad. The studies had a three month masked efficacy period and an open-label safety extension period of 9 and 3 months for study 769 and 770 respectively. During the safety extension period, subjects in the Timolol arm were to cross over to the Vyzulta arm. In each study, 420 subjects were randomized in a 2:1 ratio to receive Vyzulta or Timolol. In both arms, over 92% of study participants completed the efficacy period of the study in each study. In the safety extension period, 250 of the 271 subjects randomized to the Timolol received Vyzulta.

In both studies, Vyzulta demonstrated non-inferiority to Timolol in IOP reduction at all pre-specified post-baseline time points. The mean IOP in the Vyzulta arm was consistently lower than the corresponding value in the Timolol arm. There was an IOP reduction of between 7.5 to 9.0 mmHg in the Vyzulta arm compared to between 6.5 to 7.9 mmHg in the Timolol arm. However, the statistical superiority of Vyzulta over Timolol was not established in at least one time point. Therefore, the applicant could not make a superiority claim based on the results of the two pivotal studies.

The reviewer 's sensitivity analyses involving the multiple imputations method which takes the uncertainty of the imputed values into consideration and the analysis using the repeated measures analysis of covariance both of which are valid under a slightly stricter (compared to MCAR) missing at random assumption (MAR) were consistent with the primary analysis results. Additionally, a conservative tipping point analysis in which the imputed values in the Vyzulta arm shifted by a magnitude of 10 units did not alter the non-inferiority conclusion. Thus, the overall study conclusion regarding the primary efficacy objective of the non-inferiority of Vyzulta against Timolol appears to be robust and does not seem to have been significantly impacted by the method used to handle missing data and the analysis population considered. The IOP lowering effect of the Vyzulta was further confirmed by its significantly

better results in the proportion of subjects with IOP ≤ 18 mmHg consistently at all 9 time points and the proportion of subjects with IOP reduction of ≥ 25% consistently from baseline at all 9 time points.

With respect to safety, about 20% of the 811subjects who received at least one dose of Vyzulta reported at least one ocular adverse event (AE) in the study eye. The corresponding figure for the 271 subjects who received at least one dose of Timolol was 12%. The most frequently reported AEs in the study eye in the Vyzulta arm were conjunctival hyperemia (5.8%), eye irritation (4.3%) and eye pain (3.1%). None of the reported ocular AEs in the study eye were serious. At least one non-ocular AE was reported in 13% and 12% subjects in the Vyzulta and Timolol arms respectively. One person in the Vyzulta arm died during the study.

5.3 Conclusions and Recommendations

Based on the results of the two pivotal Phase 3 studies, there is adequate evidence of efficacy to support the indication of the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension for once daily use of Vyzulta.

5.4 Labeling Recommendations

In the current version of the drug labeling Section 14 Clinical Studies, the Applicant presented

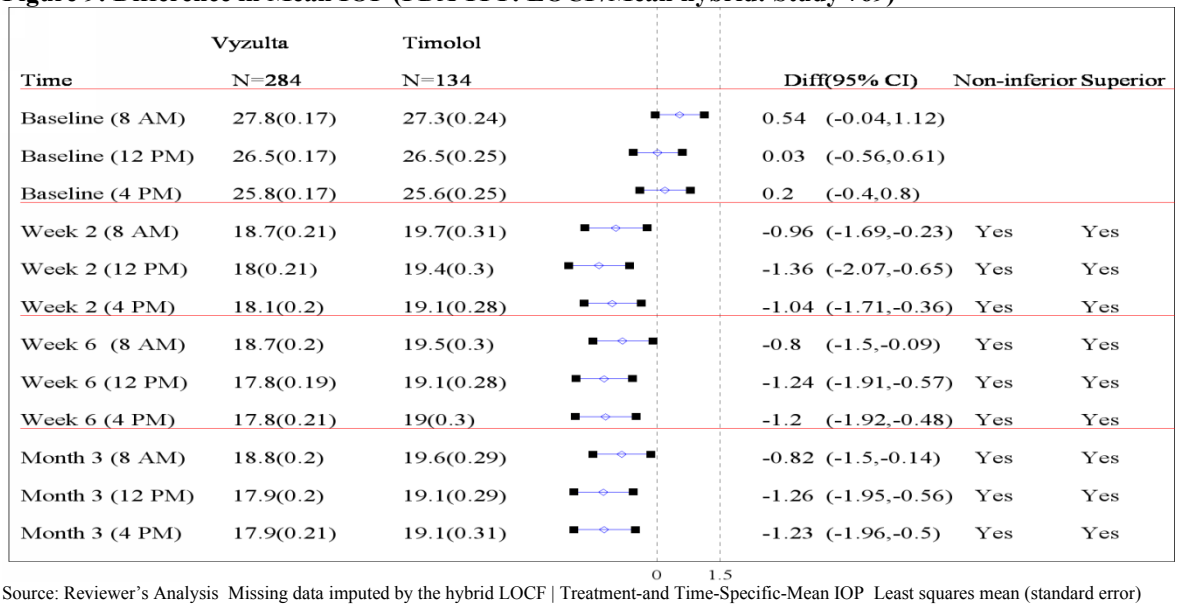
(b) (4)

The final content of the drug labeling will be decided during the labeling review in consultation with the clinical review team.

6 Appendix

6.1 Supplemental Figures

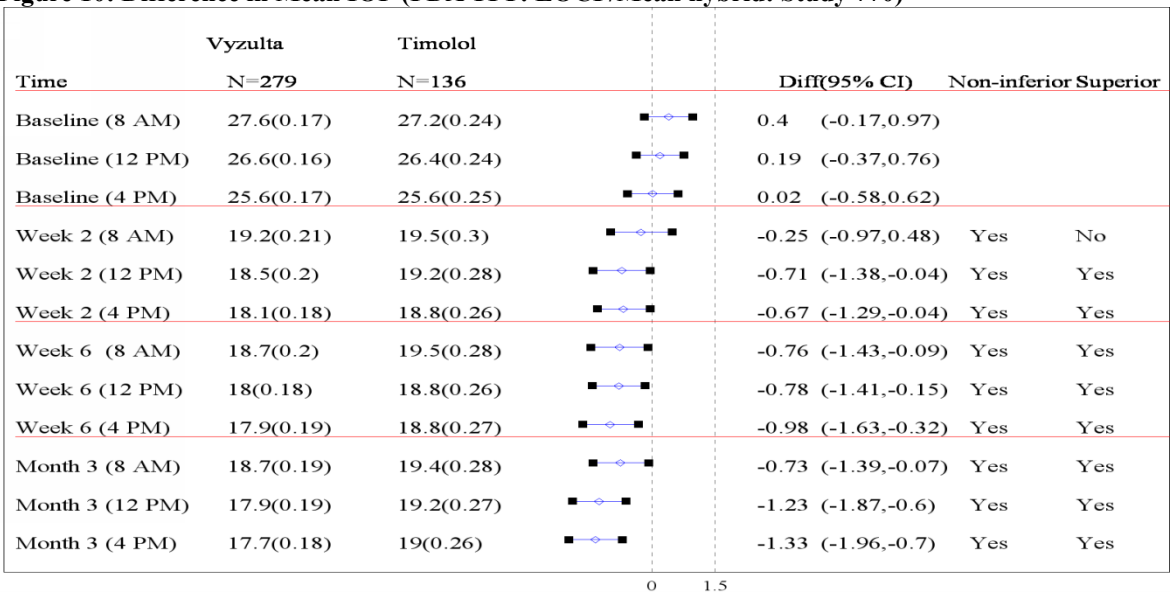
Figure 9: Difference in Mean IOP (FDA-ITT: LOCF/Mean hybrid: Study 769)



Time	Vyzulta N=284	Timolol N=134	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.8(0.17)	27.3(0.24)	0.54 (-0.04,1.12)		
Baseline (12 PM)	26.5(0.17)	26.5(0.25)	0.03 (-0.56,0.61)		
Baseline (4 PM)	25.8(0.17)	25.6(0.25)	0.2 (-0.4,0.8)		
Week 2 (8 AM)	18.7(0.21)	19.7(0.31)	-0.96 (-1.69,-0.23)	Yes	Yes
Week 2 (12 PM)	18(0.21)	19.4(0.3)	-1.36 (-2.07,-0.65)	Yes	Yes
Week 2 (4 PM)	18.1(0.2)	19.1(0.28)	-1.04 (-1.71,-0.36)	Yes	Yes
Week 6 (8 AM)	18.7(0.2)	19.5(0.3)	-0.8 (-1.5,-0.09)	Yes	Yes
Week 6 (12 PM)	17.8(0.19)	19.1(0.28)	-1.24 (-1.91,-0.57)	Yes	Yes
Week 6 (4 PM)	17.8(0.21)	19(0.3)	-1.2 (-1.92,-0.48)	Yes	Yes
Month 3 (8 AM)	18.8(0.2)	19.6(0.29)	-0.82 (-1.5,-0.14)	Yes	Yes
Month 3 (12 PM)	17.9(0.2)	19.1(0.29)	-1.26 (-1.95,-0.56)	Yes	Yes
Month 3 (4 PM)	17.9(0.21)	19.1(0.31)	-1.23 (-1.96,-0.5)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Mean IOP Least squares mean (standard error)

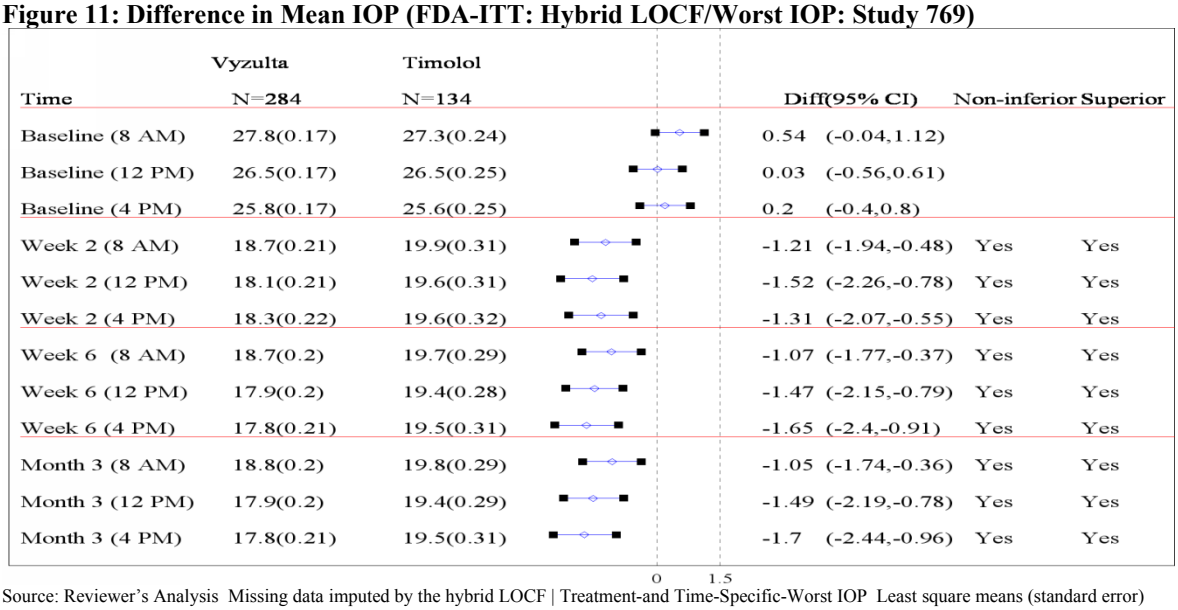
Figure 10: Difference in Mean IOP (FDA-ITT: LOCF/Mean hybrid: Study 770)



Time	Vyzulta N=279	Timolol N=136	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.6(0.17)	27.2(0.24)	0.4 (-0.17,0.97)		
Baseline (12 PM)	26.6(0.16)	26.4(0.24)	0.19 (-0.37,0.76)		
Baseline (4 PM)	25.6(0.17)	25.6(0.25)	0.02 (-0.58,0.62)		
Week 2 (8 AM)	19.2(0.21)	19.5(0.3)	-0.25 (-0.97,0.48)	Yes	No
Week 2 (12 PM)	18.5(0.2)	19.2(0.28)	-0.71 (-1.38,-0.04)	Yes	Yes
Week 2 (4 PM)	18.1(0.18)	18.8(0.26)	-0.67 (-1.29,-0.04)	Yes	Yes
Week 6 (8 AM)	18.7(0.2)	19.5(0.28)	-0.76 (-1.43,-0.09)	Yes	Yes
Week 6 (12 PM)	18(0.18)	18.8(0.26)	-0.78 (-1.41,-0.15)	Yes	Yes
Week 6 (4 PM)	17.9(0.19)	18.8(0.27)	-0.98 (-1.63,-0.32)	Yes	Yes
Month 3 (8 AM)	18.7(0.19)	19.4(0.28)	-0.73 (-1.39,-0.07)	Yes	Yes
Month 3 (12 PM)	17.9(0.19)	19.2(0.27)	-1.23 (-1.87,-0.6)	Yes	Yes
Month 3 (4 PM)	17.7(0.18)	19(0.26)	-1.33 (-1.96,-0.7)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Mean IOP Least squares mean (standard error)

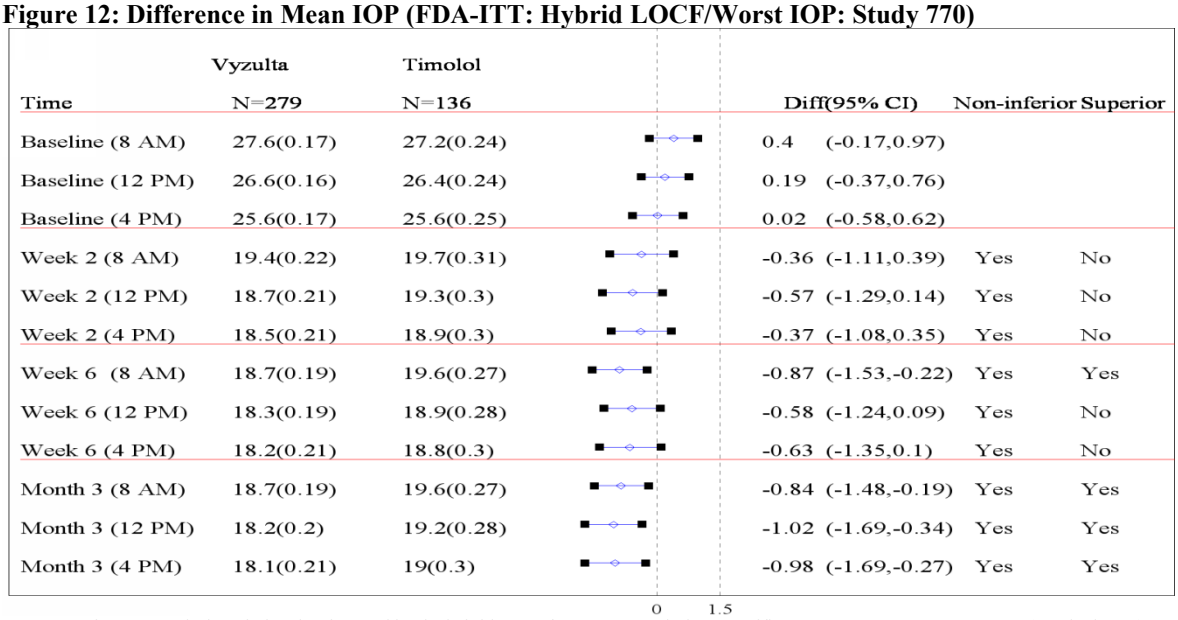
Figure 11: Difference in Mean IOP (FDA-ITT: Hybrid LOCF/Worst IOP: Study 769)



Time	Vyzulta N=284	Timolol N=134	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.8(0.17)	27.3(0.24)	0.54 (-0.04,1.12)		
Baseline (12 PM)	26.5(0.17)	26.5(0.25)	0.03 (-0.56,0.61)		
Baseline (4 PM)	25.8(0.17)	25.6(0.25)	0.2 (-0.4,0.8)		
Week 2 (8 AM)	18.7(0.21)	19.9(0.31)	-1.21 (-1.94,-0.48)	Yes	Yes
Week 2 (12 PM)	18.1(0.21)	19.6(0.31)	-1.52 (-2.26,-0.78)	Yes	Yes
Week 2 (4 PM)	18.3(0.22)	19.6(0.32)	-1.31 (-2.07,-0.55)	Yes	Yes
Week 6 (8 AM)	18.7(0.2)	19.7(0.29)	-1.07 (-1.77,-0.37)	Yes	Yes
Week 6 (12 PM)	17.9(0.2)	19.4(0.28)	-1.47 (-2.15,-0.79)	Yes	Yes
Week 6 (4 PM)	17.8(0.21)	19.5(0.31)	-1.65 (-2.4,-0.91)	Yes	Yes
Month 3 (8 AM)	18.8(0.2)	19.8(0.29)	-1.05 (-1.74,-0.36)	Yes	Yes
Month 3 (12 PM)	17.9(0.2)	19.4(0.29)	-1.49 (-2.19,-0.78)	Yes	Yes
Month 3 (4 PM)	17.8(0.21)	19.5(0.31)	-1.7 (-2.44,-0.96)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Worst IOP Least square means (standard error)

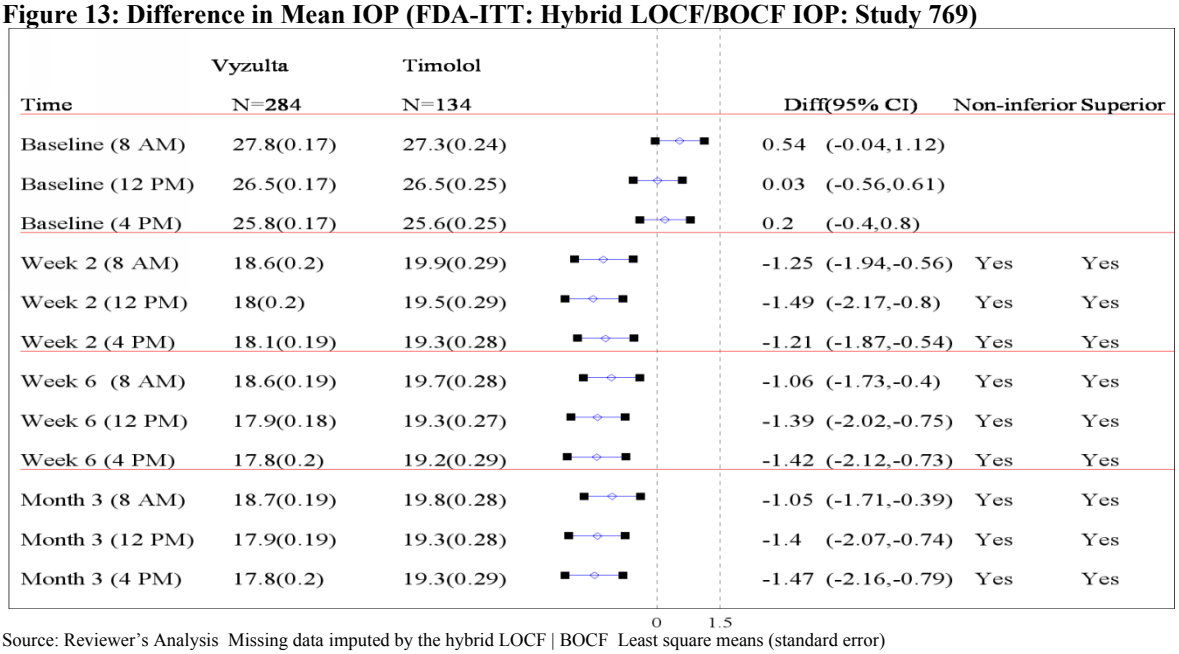
Figure 12: Difference in Mean IOP (FDA-ITT: Hybrid LOCF/Worst IOP: Study 770)



Time	Vyzulta N=279	Timolol N=136	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.6(0.17)	27.2(0.24)	0.4 (-0.17,0.97)		
Baseline (12 PM)	26.6(0.16)	26.4(0.24)	0.19 (-0.37,0.76)		
Baseline (4 PM)	25.6(0.17)	25.6(0.25)	0.02 (-0.58,0.62)		
Week 2 (8 AM)	19.4(0.22)	19.7(0.31)	-0.36 (-1.11,0.39)	Yes	No
Week 2 (12 PM)	18.7(0.21)	19.3(0.3)	-0.57 (-1.29,0.14)	Yes	No
Week 2 (4 PM)	18.5(0.21)	18.9(0.3)	-0.37 (-1.08,0.35)	Yes	No
Week 6 (8 AM)	18.7(0.19)	19.6(0.27)	-0.87 (-1.53,-0.22)	Yes	Yes
Week 6 (12 PM)	18.3(0.19)	18.9(0.28)	-0.58 (-1.24,0.09)	Yes	No
Week 6 (4 PM)	18.2(0.21)	18.8(0.3)	-0.63 (-1.35,0.1)	Yes	No
Month 3 (8 AM)	18.7(0.19)	19.6(0.27)	-0.84 (-1.48,-0.19)	Yes	Yes
Month 3 (12 PM)	18.2(0.2)	19.2(0.28)	-1.02 (-1.69,-0.34)	Yes	Yes
Month 3 (4 PM)	18.1(0.21)	19(0.3)	-0.98 (-1.69,-0.27)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Worst IOP Least square means (standard error)

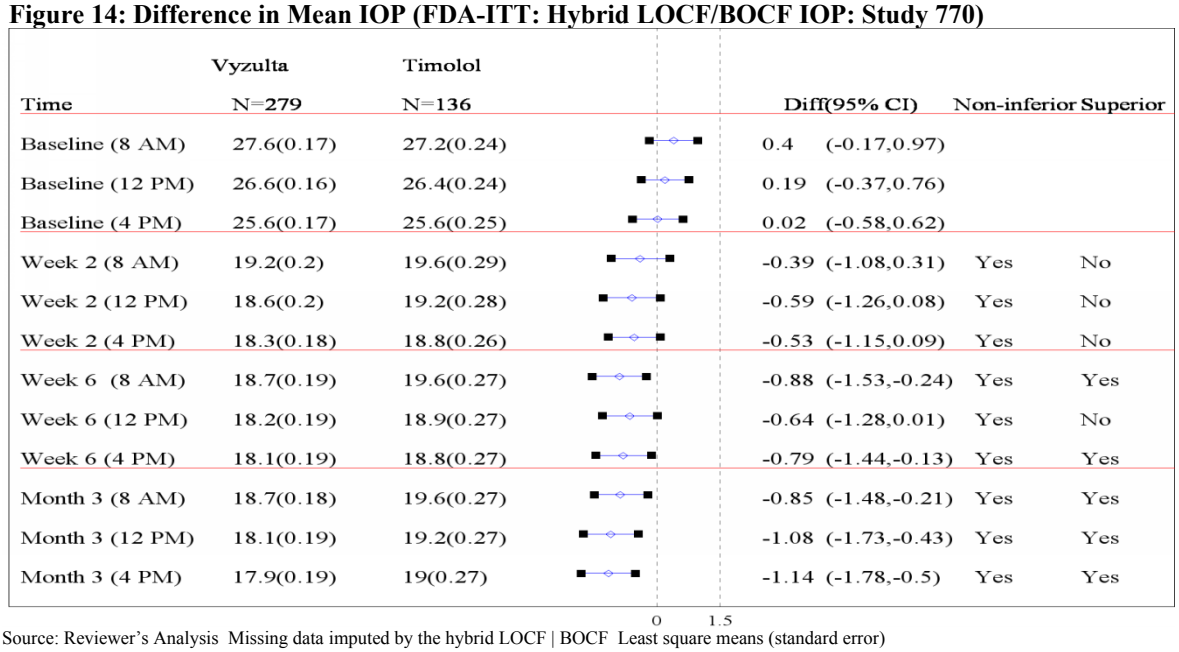
Figure 13: Difference in Mean IOP (FDA-ITT: Hybrid LOCF/BOCF IOP: Study 769)



Time	Vyzulta N=284	Timolol N=134	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.8(0.17)	27.3(0.24)	0.54 (-0.04,1.12)		
Baseline (12 PM)	26.5(0.17)	26.5(0.25)	0.03 (-0.56,0.61)		
Baseline (4 PM)	25.8(0.17)	25.6(0.25)	0.2 (-0.4,0.8)		
Week 2 (8 AM)	18.6(0.2)	19.9(0.29)	-1.25 (-1.94,-0.56)	Yes	Yes
Week 2 (12 PM)	18(0.2)	19.5(0.29)	-1.49 (-2.17,-0.8)	Yes	Yes
Week 2 (4 PM)	18.1(0.19)	19.3(0.28)	-1.21 (-1.87,-0.54)	Yes	Yes
Week 6 (8 AM)	18.6(0.19)	19.7(0.28)	-1.06 (-1.73,-0.4)	Yes	Yes
Week 6 (12 PM)	17.9(0.18)	19.3(0.27)	-1.39 (-2.02,-0.75)	Yes	Yes
Week 6 (4 PM)	17.8(0.2)	19.2(0.29)	-1.42 (-2.12,-0.73)	Yes	Yes
Month 3 (8 AM)	18.7(0.19)	19.8(0.28)	-1.05 (-1.71,-0.39)	Yes	Yes
Month 3 (12 PM)	17.9(0.19)	19.3(0.28)	-1.4 (-2.07,-0.74)	Yes	Yes
Month 3 (4 PM)	17.8(0.2)	19.3(0.29)	-1.47 (-2.16,-0.79)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | BOCF Least square means (standard error)

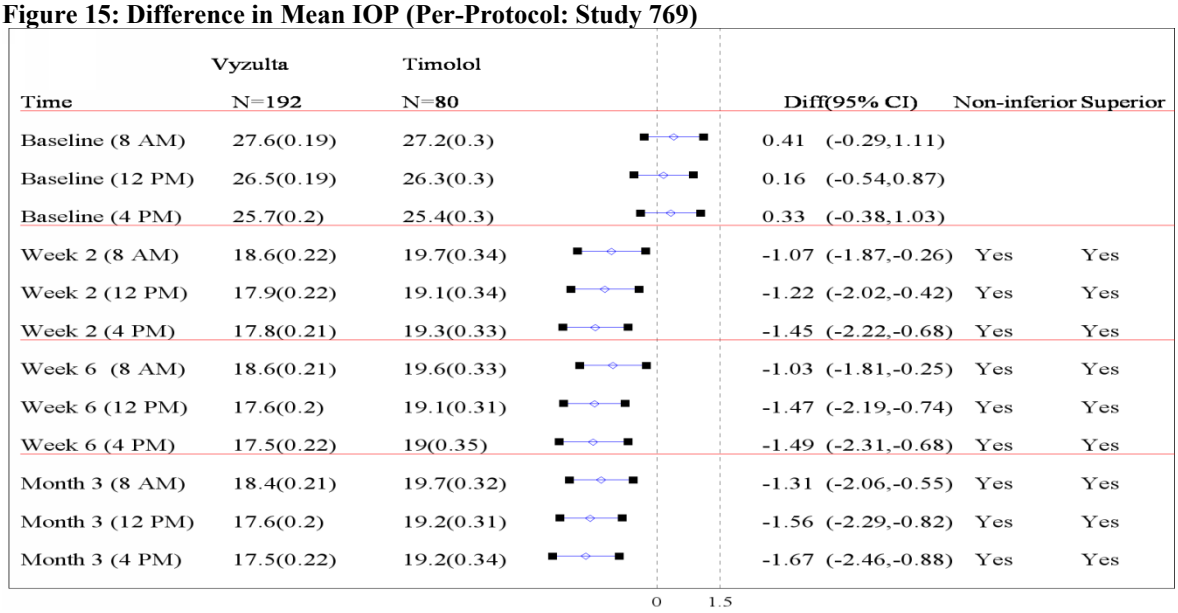
Figure 14: Difference in Mean IOP (FDA-ITT: Hybrid LOCF/BOCF IOP: Study 770)



Time	Vyzulta N=279	Timolol N=136	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.6(0.17)	27.2(0.24)	0.4 (-0.17,0.97)		
Baseline (12 PM)	26.6(0.16)	26.4(0.24)	0.19 (-0.37,0.76)		
Baseline (4 PM)	25.6(0.17)	25.6(0.25)	0.02 (-0.58,0.62)		
Week 2 (8 AM)	19.2(0.2)	19.6(0.29)	-0.39 (-1.08,0.31)	Yes	No
Week 2 (12 PM)	18.6(0.2)	19.2(0.28)	-0.59 (-1.26,0.08)	Yes	No
Week 2 (4 PM)	18.3(0.18)	18.8(0.26)	-0.53 (-1.15,0.09)	Yes	No
Week 6 (8 AM)	18.7(0.19)	19.6(0.27)	-0.88 (-1.53,-0.24)	Yes	Yes
Week 6 (12 PM)	18.2(0.19)	18.9(0.27)	-0.64 (-1.28,0.01)	Yes	No
Week 6 (4 PM)	18.1(0.19)	18.8(0.27)	-0.79 (-1.44,-0.13)	Yes	Yes
Month 3 (8 AM)	18.7(0.18)	19.6(0.27)	-0.85 (-1.48,-0.21)	Yes	Yes
Month 3 (12 PM)	18.1(0.19)	19.2(0.27)	-1.08 (-1.73,-0.43)	Yes	Yes
Month 3 (4 PM)	17.9(0.19)	19(0.27)	-1.14 (-1.78,-0.5)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | BOCF Least square means (standard error)

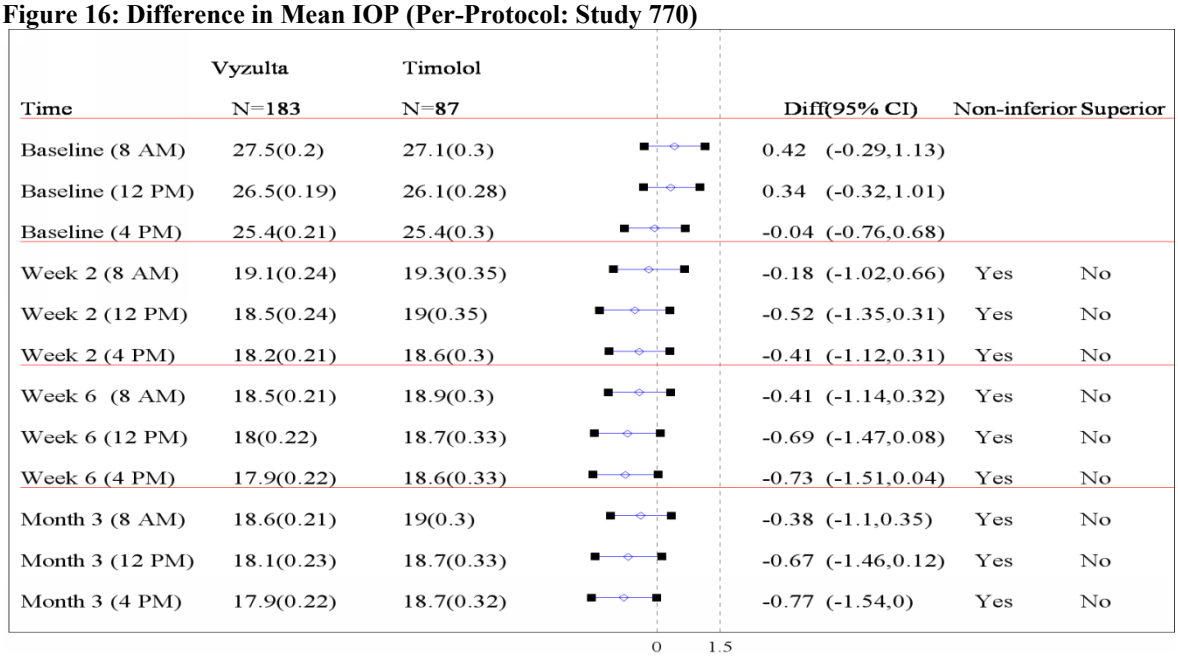
Figure 15: Difference in Mean IOP (Per-Protocol: Study 769)



Time	Vyzulta N=192	Timolol N=80	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.6(0.19)	27.2(0.3)	0.41 (-0.29,1.11)		
Baseline (12 PM)	26.5(0.19)	26.3(0.3)	0.16 (-0.54,0.87)		
Baseline (4 PM)	25.7(0.2)	25.4(0.3)	0.33 (-0.38,1.03)		
Week 2 (8 AM)	18.6(0.22)	19.7(0.34)	-1.07 (-1.87,-0.26)	Yes	Yes
Week 2 (12 PM)	17.9(0.22)	19.1(0.34)	-1.22 (-2.02,-0.42)	Yes	Yes
Week 2 (4 PM)	17.8(0.21)	19.3(0.33)	-1.45 (-2.22,-0.68)	Yes	Yes
Week 6 (8 AM)	18.6(0.21)	19.6(0.33)	-1.03 (-1.81,-0.25)	Yes	Yes
Week 6 (12 PM)	17.6(0.2)	19.1(0.31)	-1.47 (-2.19,-0.74)	Yes	Yes
Week 6 (4 PM)	17.5(0.22)	19(0.35)	-1.49 (-2.31,-0.68)	Yes	Yes
Month 3 (8 AM)	18.4(0.21)	19.7(0.32)	-1.31 (-2.06,-0.55)	Yes	Yes
Month 3 (12 PM)	17.6(0.2)	19.2(0.31)	-1.56 (-2.29,-0.82)	Yes	Yes
Month 3 (4 PM)	17.5(0.22)	19.2(0.34)	-1.67 (-2.46,-0.88)	Yes	Yes

Source: Reviewer's Analysis Observed Case: No missing data is imputed Least square means (standard error)

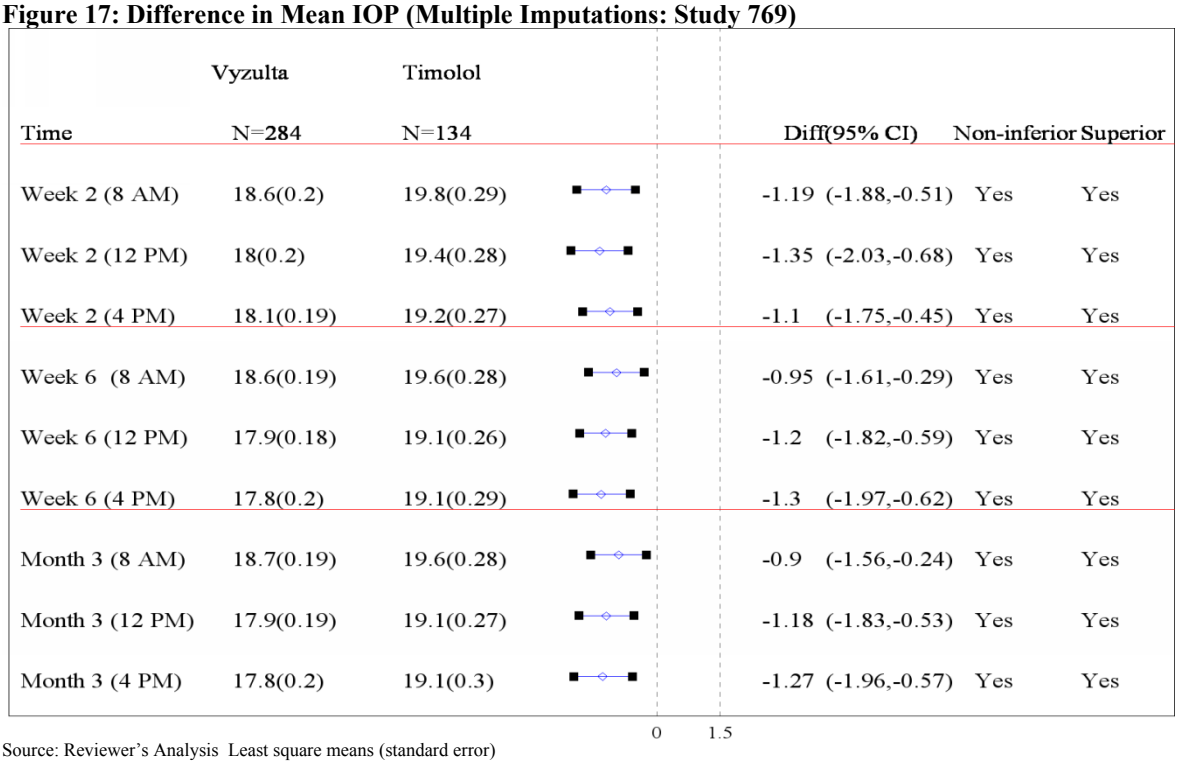
Figure 16: Difference in Mean IOP (Per-Protocol: Study 770)



Time	Vyzulta N=183	Timolol N=87	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.5(0.2)	27.1(0.3)	0.42 (-0.29,1.13)		
Baseline (12 PM)	26.5(0.19)	26.1(0.28)	0.34 (-0.32,1.01)		
Baseline (4 PM)	25.4(0.21)	25.4(0.3)	-0.04 (-0.76,0.68)		
Week 2 (8 AM)	19.1(0.24)	19.3(0.35)	-0.18 (-1.02,0.66)	Yes	No
Week 2 (12 PM)	18.5(0.24)	19(0.35)	-0.52 (-1.35,0.31)	Yes	No
Week 2 (4 PM)	18.2(0.21)	18.6(0.3)	-0.41 (-1.12,0.31)	Yes	No
Week 6 (8 AM)	18.5(0.21)	18.9(0.3)	-0.41 (-1.14,0.32)	Yes	No
Week 6 (12 PM)	18(0.22)	18.7(0.33)	-0.69 (-1.47,0.08)	Yes	No
Week 6 (4 PM)	17.9(0.22)	18.6(0.33)	-0.73 (-1.51,0.04)	Yes	No
Month 3 (8 AM)	18.6(0.21)	19(0.3)	-0.38 (-1.1,0.35)	Yes	No
Month 3 (12 PM)	18.1(0.23)	18.7(0.33)	-0.67 (-1.46,0.12)	Yes	No
Month 3 (4 PM)	17.9(0.22)	18.7(0.32)	-0.77 (-1.54,0)	Yes	No

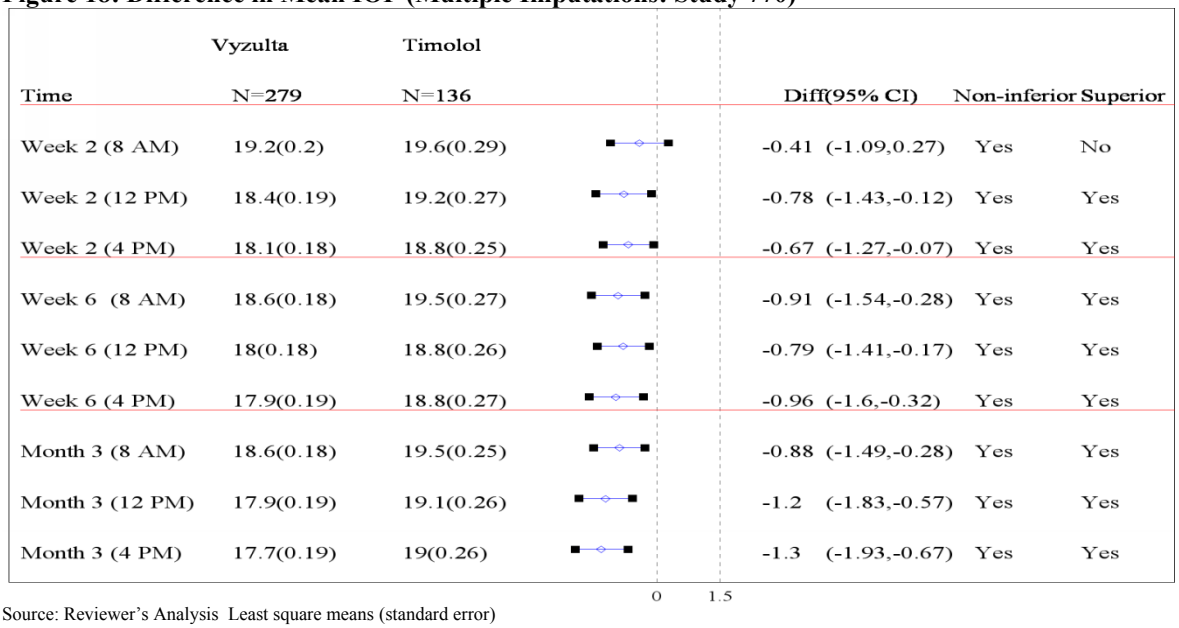
Source: Reviewer's Analysis Observed Case: No missing data is imputed Least square means (standard error)

Figure 17: Difference in Mean IOP (Multiple Imputations: Study 769)



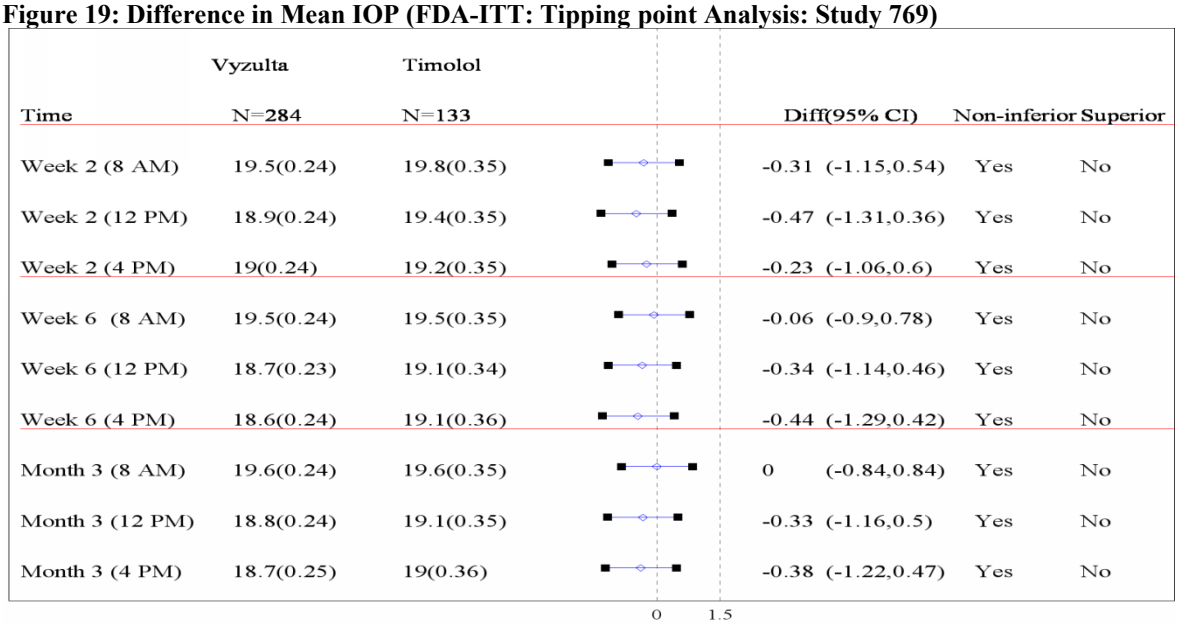
Source: Reviewer's Analysis Least square means (standard error)

Figure 18: Difference in Mean IOP (Multiple Imputations: Study 770)



Source: Reviewer's Analysis Least square means (standard error)

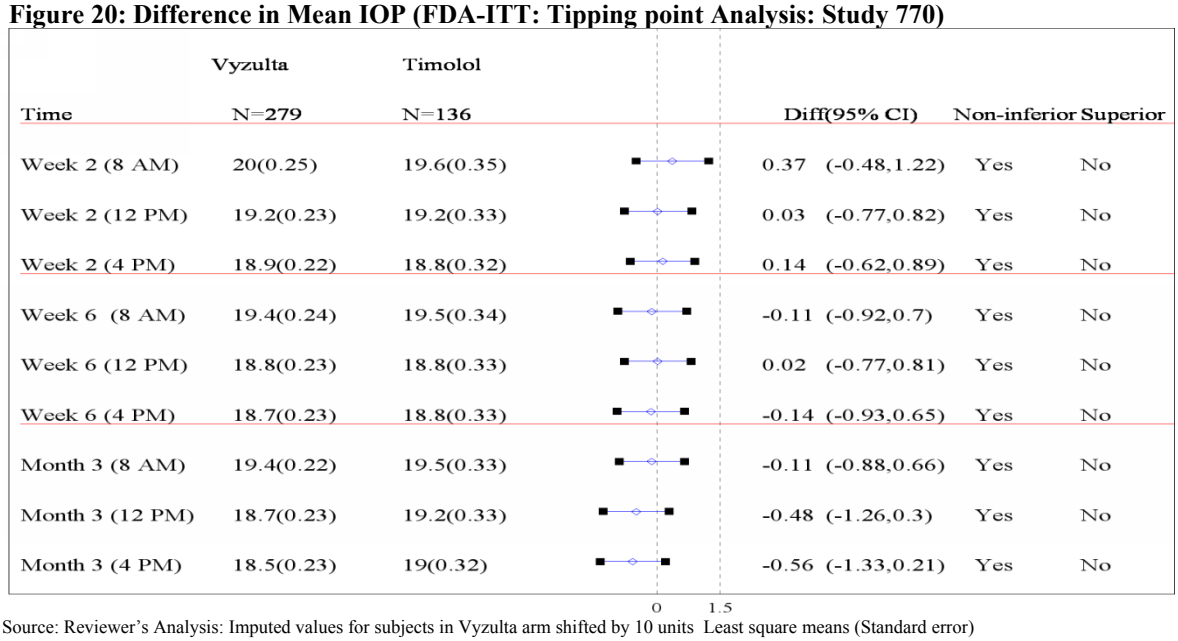
Figure 19: Difference in Mean IOP (FDA-ITT: Tipping point Analysis: Study 769)



Time	Vyzulta N=284	Timolol N=133	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	19.5(0.24)	19.8(0.35)	-0.31 (-1.15,0.54)	Yes	No
Week 2 (12 PM)	18.9(0.24)	19.4(0.35)	-0.47 (-1.31,0.36)	Yes	No
Week 2 (4 PM)	19(0.24)	19.2(0.35)	-0.23 (-1.06,0.6)	Yes	No
Week 6 (8 AM)	19.5(0.24)	19.5(0.35)	-0.06 (-0.9,0.78)	Yes	No
Week 6 (12 PM)	18.7(0.23)	19.1(0.34)	-0.34 (-1.14,0.46)	Yes	No
Week 6 (4 PM)	18.6(0.24)	19.1(0.36)	-0.44 (-1.29,0.42)	Yes	No
Month 3 (8 AM)	19.6(0.24)	19.6(0.35)	0 (-0.84,0.84)	Yes	No
Month 3 (12 PM)	18.8(0.24)	19.1(0.35)	-0.33 (-1.16,0.5)	Yes	No
Month 3 (4 PM)	18.7(0.25)	19(0.36)	-0.38 (-1.22,0.47)	Yes	No

Source: Reviewer's Analysis: Imputed values for subjects in Vyzulta arm shifted by 10 units Least square means (Standard error)

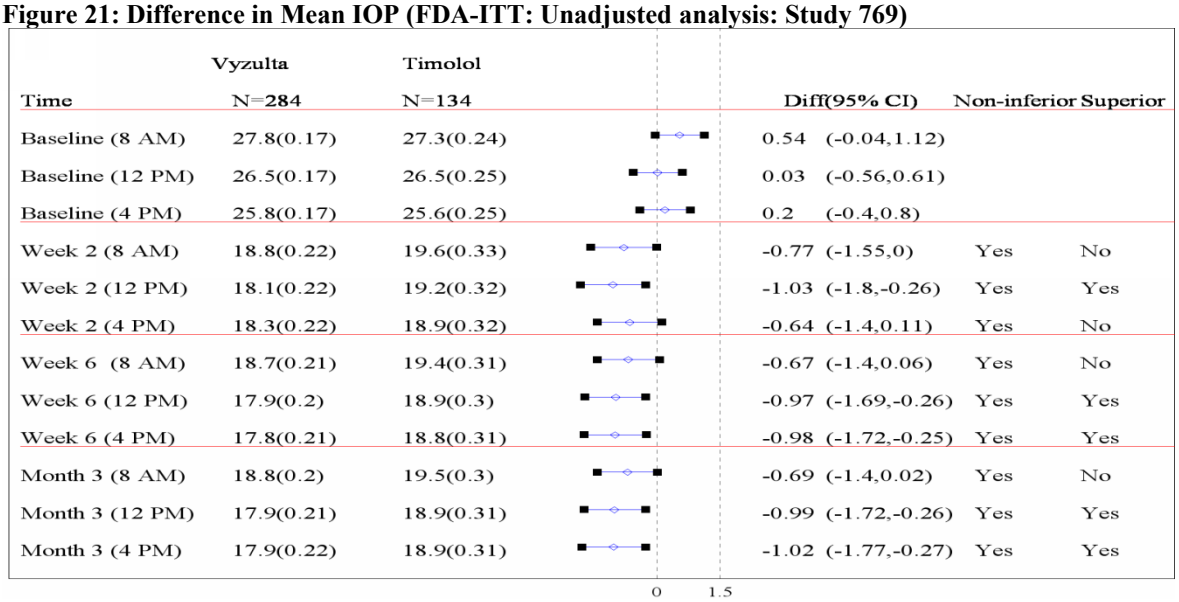
Figure 20: Difference in Mean IOP (FDA-ITT: Tipping point Analysis: Study 770)



Time	Vyzulta N=279	Timolol N=136	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	20(0.25)	19.6(0.35)	0.37 (-0.48,1.22)	Yes	No
Week 2 (12 PM)	19.2(0.23)	19.2(0.33)	0.03 (-0.77,0.82)	Yes	No
Week 2 (4 PM)	18.9(0.22)	18.8(0.32)	0.14 (-0.62,0.89)	Yes	No
Week 6 (8 AM)	19.4(0.24)	19.5(0.34)	-0.11 (-0.92,0.7)	Yes	No
Week 6 (12 PM)	18.8(0.23)	18.8(0.33)	0.02 (-0.77,0.81)	Yes	No
Week 6 (4 PM)	18.7(0.23)	18.8(0.33)	-0.14 (-0.93,0.65)	Yes	No
Month 3 (8 AM)	19.4(0.22)	19.5(0.33)	-0.11 (-0.88,0.66)	Yes	No
Month 3 (12 PM)	18.7(0.23)	19.2(0.33)	-0.48 (-1.26,0.3)	Yes	No
Month 3 (4 PM)	18.5(0.23)	19(0.32)	-0.56 (-1.33,0.21)	Yes	No

Source: Reviewer's Analysis: Imputed values for subjects in Vyzulta arm shifted by 10 units Least square means (Standard error)

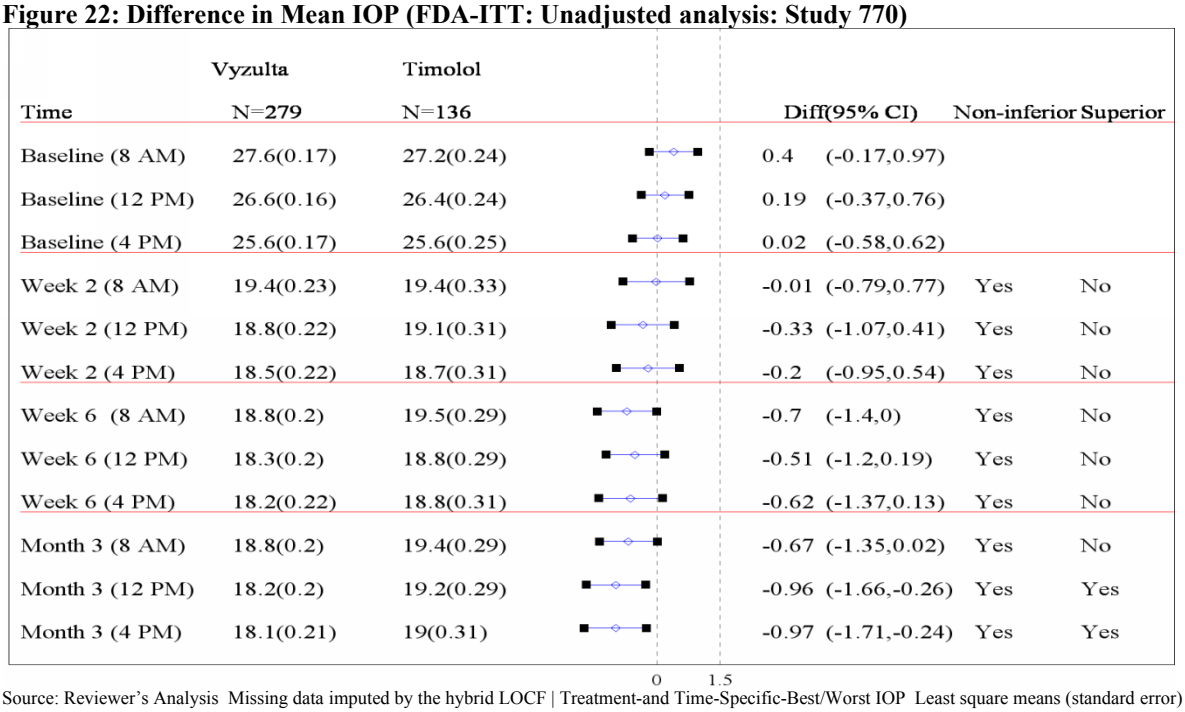
Figure 21: Difference in Mean IOP (FDA-ITT: Unadjusted analysis: Study 769)



Time	Vyzulta N=284	Timolol N=134	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.8(0.17)	27.3(0.24)	0.54 (-0.04,1.12)		
Baseline (12 PM)	26.5(0.17)	26.5(0.25)	0.03 (-0.56,0.61)		
Baseline (4 PM)	25.8(0.17)	25.6(0.25)	0.2 (-0.4,0.8)		
Week 2 (8 AM)	18.8(0.22)	19.6(0.33)	-0.77 (-1.55,0)	Yes	No
Week 2 (12 PM)	18.1(0.22)	19.2(0.32)	-1.03 (-1.8,-0.26)	Yes	Yes
Week 2 (4 PM)	18.3(0.22)	18.9(0.32)	-0.64 (-1.4,0.11)	Yes	No
Week 6 (8 AM)	18.7(0.21)	19.4(0.31)	-0.67 (-1.4,0.06)	Yes	No
Week 6 (12 PM)	17.9(0.2)	18.9(0.3)	-0.97 (-1.69,-0.26)	Yes	Yes
Week 6 (4 PM)	17.8(0.21)	18.8(0.31)	-0.98 (-1.72,-0.25)	Yes	Yes
Month 3 (8 AM)	18.8(0.2)	19.5(0.3)	-0.69 (-1.4,0.02)	Yes	No
Month 3 (12 PM)	17.9(0.21)	18.9(0.31)	-0.99 (-1.72,-0.26)	Yes	Yes
Month 3 (4 PM)	17.9(0.22)	18.9(0.31)	-1.02 (-1.77,-0.27)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

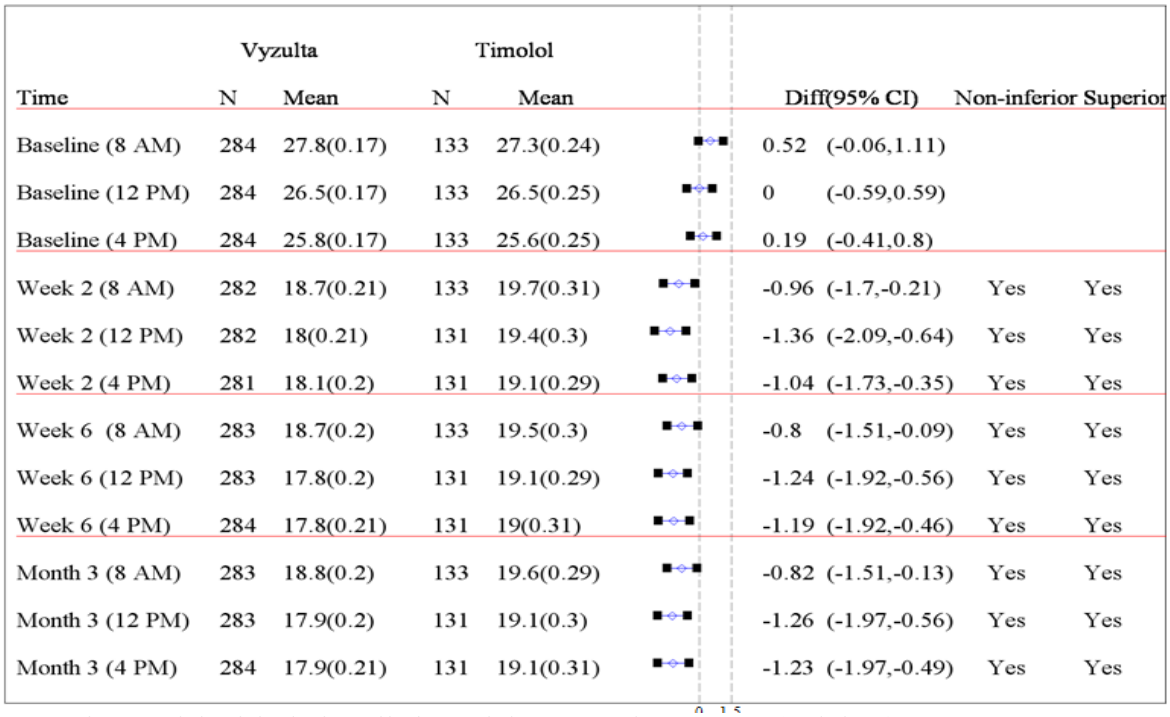
Figure 22: Difference in Mean IOP (FDA-ITT: Unadjusted analysis: Study 770)



Time	Vyzulta N=279	Timolol N=136	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.6(0.17)	27.2(0.24)	0.4 (-0.17,0.97)		
Baseline (12 PM)	26.6(0.16)	26.4(0.24)	0.19 (-0.37,0.76)		
Baseline (4 PM)	25.6(0.17)	25.6(0.25)	0.02 (-0.58,0.62)		
Week 2 (8 AM)	19.4(0.23)	19.4(0.33)	-0.01 (-0.79,0.77)	Yes	No
Week 2 (12 PM)	18.8(0.22)	19.1(0.31)	-0.33 (-1.07,0.41)	Yes	No
Week 2 (4 PM)	18.5(0.22)	18.7(0.31)	-0.2 (-0.95,0.54)	Yes	No
Week 6 (8 AM)	18.8(0.2)	19.5(0.29)	-0.7 (-1.4,0)	Yes	No
Week 6 (12 PM)	18.3(0.2)	18.8(0.29)	-0.51 (-1.2,0.19)	Yes	No
Week 6 (4 PM)	18.2(0.22)	18.8(0.31)	-0.62 (-1.37,0.13)	Yes	No
Month 3 (8 AM)	18.8(0.2)	19.4(0.29)	-0.67 (-1.35,0.02)	Yes	No
Month 3 (12 PM)	18.2(0.2)	19.2(0.29)	-0.96 (-1.66,-0.26)	Yes	Yes
Month 3 (4 PM)	18.1(0.21)	19(0.31)	-0.97 (-1.71,-0.24)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

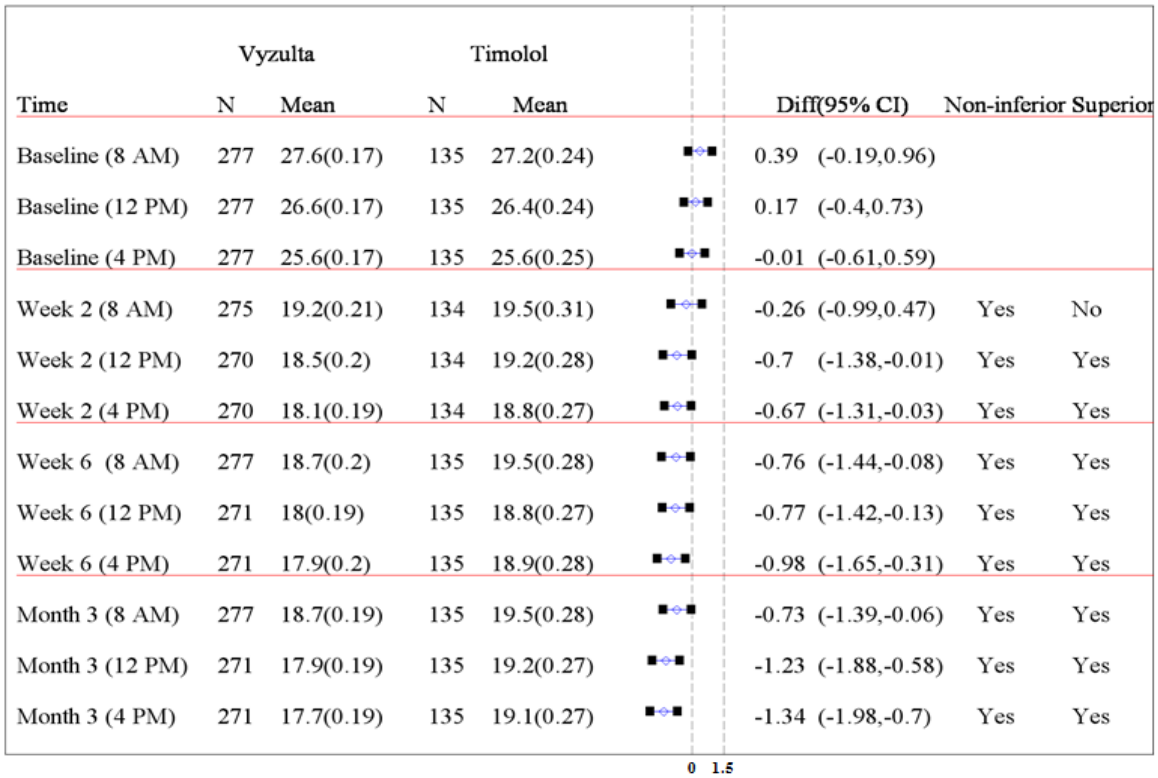
Figure 23: Difference in Mean IOP (Bausch-ITT: Unadjusted analysis: Study 769)



	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	284	27.8(0.17)	133	27.3(0.24)	0.52 (-0.06,1.11)		
Baseline (12 PM)	284	26.5(0.17)	133	26.5(0.25)	0 (-0.59,0.59)		
Baseline (4 PM)	284	25.8(0.17)	133	25.6(0.25)	0.19 (-0.41,0.8)		
Week 2 (8 AM)	282	18.7(0.21)	133	19.7(0.31)	-0.96 (-1.7,-0.21)	Yes	Yes
Week 2 (12 PM)	282	18(0.21)	131	19.4(0.3)	-1.36 (-2.09,-0.64)	Yes	Yes
Week 2 (4 PM)	281	18.1(0.2)	131	19.1(0.29)	-1.04 (-1.73,-0.35)	Yes	Yes
Week 6 (8 AM)	283	18.7(0.2)	133	19.5(0.3)	-0.8 (-1.51,-0.09)	Yes	Yes
Week 6 (12 PM)	283	17.8(0.2)	131	19.1(0.29)	-1.24 (-1.92,-0.56)	Yes	Yes
Week 6 (4 PM)	284	17.8(0.21)	131	19(0.31)	-1.19 (-1.92,-0.46)	Yes	Yes
Month 3 (8 AM)	283	18.8(0.2)	133	19.6(0.29)	-0.82 (-1.51,-0.13)	Yes	Yes
Month 3 (12 PM)	283	17.9(0.2)	131	19.1(0.3)	-1.26 (-1.97,-0.56)	Yes	Yes
Month 3 (4 PM)	284	17.9(0.21)	131	19.1(0.31)	-1.23 (-1.97,-0.49)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by time-matched LOCF Mean= least square means (standard error)

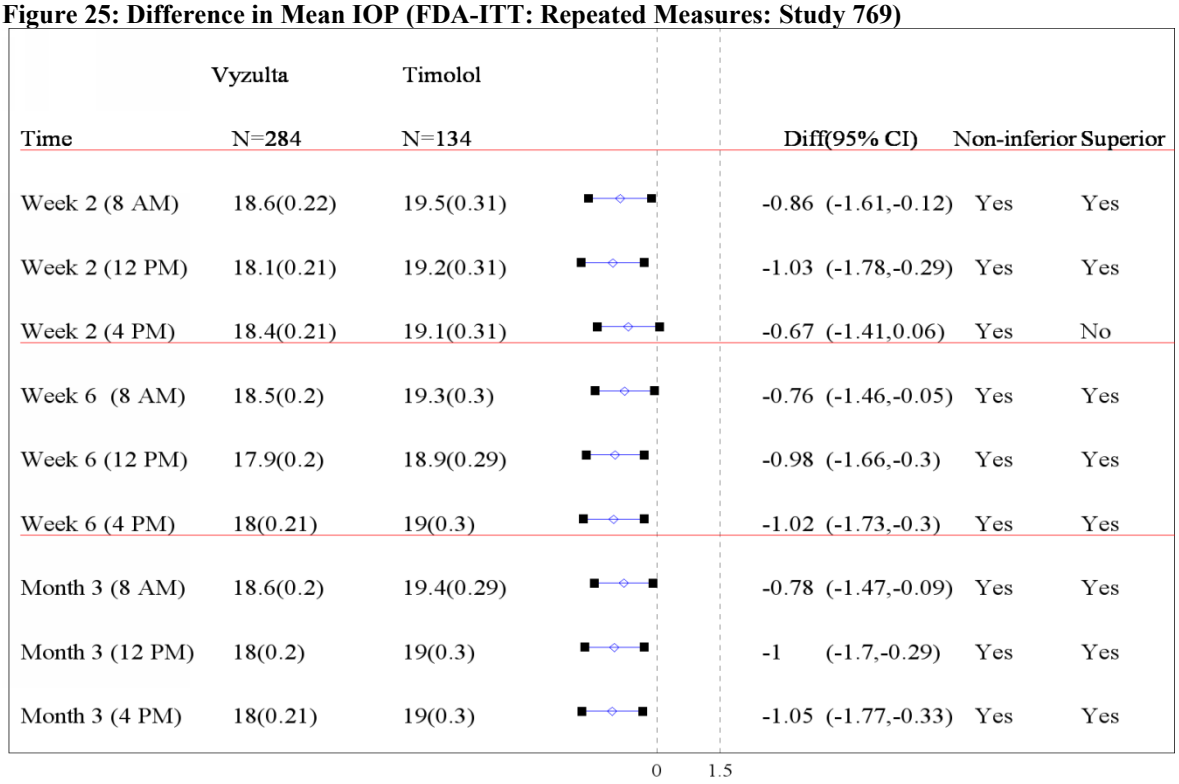
Figure 24: Difference in Mean IOP (Bausch-ITT: Unadjusted analysis: Study 770)



	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	277	27.6(0.17)	135	27.2(0.24)	0.39 (-0.19,0.96)		
Baseline (12 PM)	277	26.6(0.17)	135	26.4(0.24)	0.17 (-0.4,0.73)		
Baseline (4 PM)	277	25.6(0.17)	135	25.6(0.25)	-0.01 (-0.61,0.59)		
Week 2 (8 AM)	275	19.2(0.21)	134	19.5(0.31)	-0.26 (-0.99,0.47)	Yes	No
Week 2 (12 PM)	270	18.5(0.2)	134	19.2(0.28)	-0.7 (-1.38,-0.01)	Yes	Yes
Week 2 (4 PM)	270	18.1(0.19)	134	18.8(0.27)	-0.67 (-1.31,-0.03)	Yes	Yes
Week 6 (8 AM)	277	18.7(0.2)	135	19.5(0.28)	-0.76 (-1.44,-0.08)	Yes	Yes
Week 6 (12 PM)	271	18(0.19)	135	18.8(0.27)	-0.77 (-1.42,-0.13)	Yes	Yes
Week 6 (4 PM)	271	17.9(0.2)	135	18.9(0.28)	-0.98 (-1.65,-0.31)	Yes	Yes
Month 3 (8 AM)	277	18.7(0.19)	135	19.5(0.28)	-0.73 (-1.39,-0.06)	Yes	Yes
Month 3 (12 PM)	271	17.9(0.19)	135	19.2(0.27)	-1.23 (-1.88,-0.58)	Yes	Yes
Month 3 (4 PM)	271	17.7(0.19)	135	19.1(0.27)	-1.34 (-1.98,-0.7)	Yes	Yes

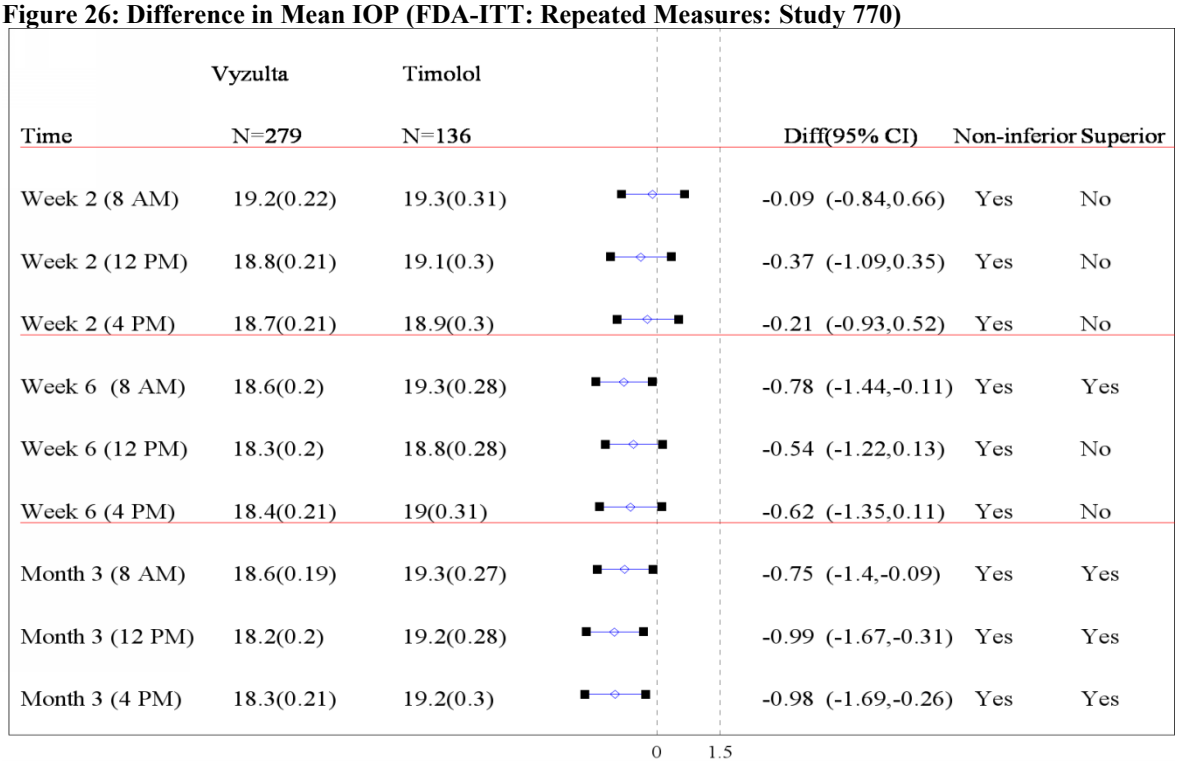
Source: Reviewer's Analysis Missing data imputed by time-matched LOCF Mean= least square means (standard error)

Figure 25: Difference in Mean IOP (FDA-ITT: Repeated Measures: Study 769)



Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

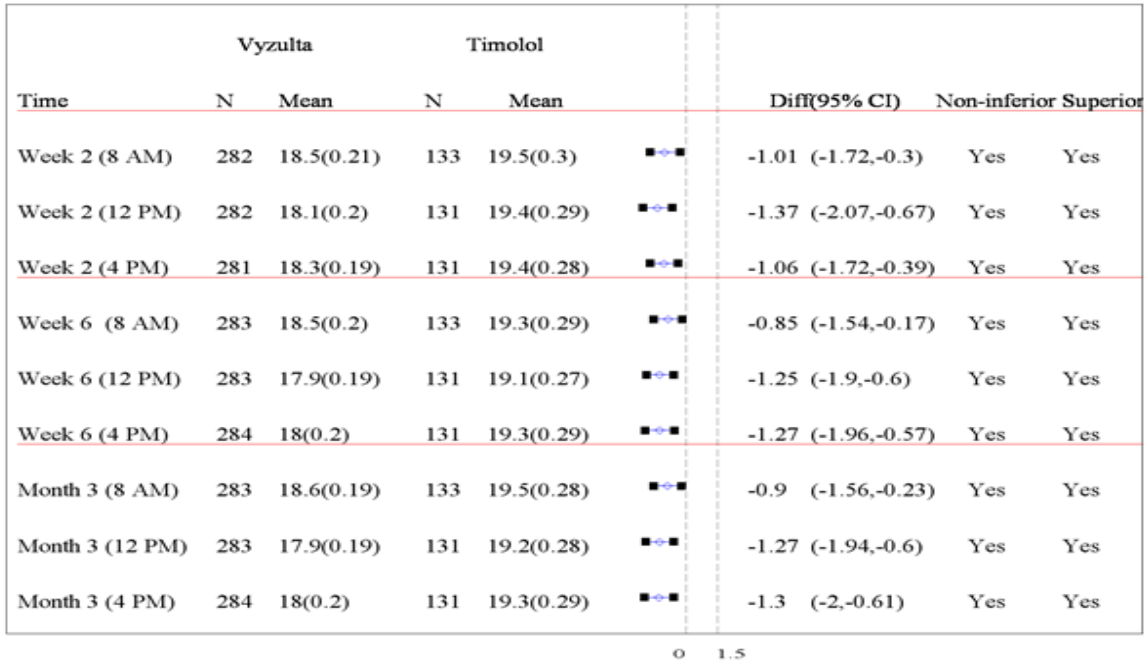
Figure 26: Difference in Mean IOP (FDA-ITT: Repeated Measures: Study 770)



Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

Figure 27: Difference in Mean IOP (Bausch-ITT: Repeated Measures: Study 769)

	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	282	18.5(0.21)	133	19.5(0.3)	-1.01 (-1.72,-0.3)	Yes	Yes
Week 2 (12 PM)	282	18.1(0.2)	131	19.4(0.29)	-1.37 (-2.07,-0.67)	Yes	Yes
Week 2 (4 PM)	281	18.3(0.19)	131	19.4(0.28)	-1.06 (-1.72,-0.39)	Yes	Yes
Week 6 (8 AM)	283	18.5(0.2)	133	19.3(0.29)	-0.85 (-1.54,-0.17)	Yes	Yes
Week 6 (12 PM)	283	17.9(0.19)	131	19.1(0.27)	-1.25 (-1.9,-0.6)	Yes	Yes
Week 6 (4 PM)	284	18(0.2)	131	19.3(0.29)	-1.27 (-1.96,-0.57)	Yes	Yes
Month 3 (8 AM)	283	18.6(0.19)	133	19.5(0.28)	-0.9 (-1.56,-0.23)	Yes	Yes
Month 3 (12 PM)	283	17.9(0.19)	131	19.2(0.28)	-1.27 (-1.94,-0.6)	Yes	Yes
Month 3 (4 PM)	284	18(0.2)	131	19.3(0.29)	-1.3 (-2,-0.61)	Yes	Yes



Source: Reviewer's Analysis Missing data imputed by time-matched LOCF Mean= least square means (standard error)

Figure 28: Difference in Mean IOP (Bausch-ITT: Repeated Measures: Study 770)

	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	275	19(0.21)	134	19.4(0.29)	-0.34 (-1.04,0.37)	Yes	No
Week 2 (12 PM)	270	18.5(0.2)	134	19.2(0.28)	-0.72 (-1.39,-0.05)	Yes	Yes
Week 2 (4 PM)	270	18.3(0.18)	134	19(0.26)	-0.67 (-1.3,-0.05)	Yes	Yes
Week 6 (8 AM)	277	18.5(0.19)	135	19.4(0.27)	-0.85 (-1.49,-0.2)	Yes	Yes
Week 6 (12 PM)	271	18(0.18)	135	18.8(0.26)	-0.8 (-1.42,-0.18)	Yes	Yes
Week 6 (4 PM)	271	18.1(0.19)	135	19(0.27)	-0.97 (-1.61,-0.32)	Yes	Yes
Month 3 (8 AM)	277	18.5(0.18)	135	19.3(0.26)	-0.81 (-1.44,-0.18)	Yes	Yes
Month 3 (12 PM)	271	17.9(0.18)	135	19.2(0.26)	-1.26 (-1.88,-0.63)	Yes	Yes
Month 3 (4 PM)	271	17.9(0.18)	135	19.2(0.26)	-1.33 (-1.95,-0.71)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by time-matched LOCF Mean= least square means (standard error)

Figure 29: Difference in Mean IOP (Available Cases: Repeated Measures: Study 769)

	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	282	18.5(0.21)	133	19.5(0.3)	-1.03 (-1.73,-0.32)	Yes	Yes
Week 2 (12 PM)	282	18.1(0.2)	131	19.4(0.29)	-1.37 (-2.06,-0.67)	Yes	Yes
Week 2 (4 PM)	281	18.3(0.19)	131	19.4(0.28)	-1.05 (-1.71,-0.39)	Yes	Yes
Week 6 (8 AM)	273	18.5(0.2)	129	19.3(0.28)	-0.84 (-1.51,-0.16)	Yes	Yes
Week 6 (12 PM)	271	17.9(0.18)	128	19.1(0.27)	-1.25 (-1.89,-0.61)	Yes	Yes
Week 6 (4 PM)	272	17.9(0.2)	128	19.2(0.29)	-1.29 (-1.98,-0.6)	Yes	Yes
Month 3 (8 AM)	270	18.5(0.19)	124	19.4(0.27)	-0.82 (-1.47,-0.17)	Yes	Yes
Month 3 (12 PM)	268	17.9(0.19)	124	19.2(0.28)	-1.23 (-1.9,-0.57)	Yes	Yes
Month 3 (4 PM)	269	18(0.2)	124	19.2(0.29)	-1.25 (-1.95,-0.56)	Yes	Yes

Source: Reviewer's Analysis Observed cases: No missing data is imputed Mean= least square means (standard error)

Figure 30: Difference in Mean IOP (Available Cases: Repeated Measures: Study 770)

	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	278	19(0.2)	135	19.4(0.29)	-0.32 (-1.01,0.38)	Yes	No
Week 2 (12 PM)	272	18.4(0.19)	135	19.2(0.27)	-0.75 (-1.4,-0.09)	Yes	Yes
Week 2 (4 PM)	272	18.3(0.18)	135	19(0.25)	-0.68 (-1.29,-0.07)	Yes	Yes
Week 6 (8 AM)	266	18.4(0.19)	130	19.3(0.26)	-0.85 (-1.48,-0.21)	Yes	Yes
Week 6 (12 PM)	265	18(0.18)	129	18.8(0.26)	-0.75 (-1.38,-0.12)	Yes	Yes
Week 6 (4 PM)	264	18(0.19)	128	19(0.27)	-0.95 (-1.6,-0.3)	Yes	Yes
Month 3 (8 AM)	260	18.4(0.18)	129	19.3(0.25)	-0.85 (-1.46,-0.24)	Yes	Yes
Month 3 (12 PM)	260	17.9(0.19)	129	19.2(0.26)	-1.26 (-1.89,-0.63)	Yes	Yes
Month 3 (4 PM)	259	17.9(0.18)	129	19.2(0.26)	-1.39 (-2.01,-0.76)	Yes	Yes

Source: Reviewer's Analysis Observed cases: No missing data is imputed Mean= least square means (standard error)

Figure 31: Difference in Mean Change from baseline IOP (FDA-ITT: Study 769)

Time	Vyzulta N=284	Timolol N=134	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	-8.9(0.21)	-7.9(0.3)	-1.04 (-1.77,-0.32)	Yes	Yes
Week 2 (12 PM)	-8.4(0.21)	-7.4(0.31)	-1.04 (-1.77,-0.31)	Yes	Yes
Week 2 (4 PM)	-7.5(0.21)	-6.8(0.3)	-0.72 (-1.44,0)	Yes	No
Week 6 (8 AM)	-9(0.2)	-8.1(0.29)	-0.9 (-1.59,-0.21)	Yes	Yes
Week 6 (12 PM)	-8.6(0.19)	-7.6(0.28)	-0.99 (-1.65,-0.32)	Yes	Yes
Week 6 (4 PM)	-7.9(0.2)	-6.9(0.29)	-1.06 (-1.76,-0.36)	Yes	Yes
Month 3 (8 AM)	-8.9(0.2)	-8(0.29)	-0.89 (-1.57,-0.2)	Yes	Yes
Month 3 (12 PM)	-8.6(0.2)	-7.6(0.29)	-1 (-1.69,-0.32)	Yes	Yes
Month 3 (4 PM)	-7.9(0.2)	-6.8(0.29)	-1.11 (-1.81,-0.41)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

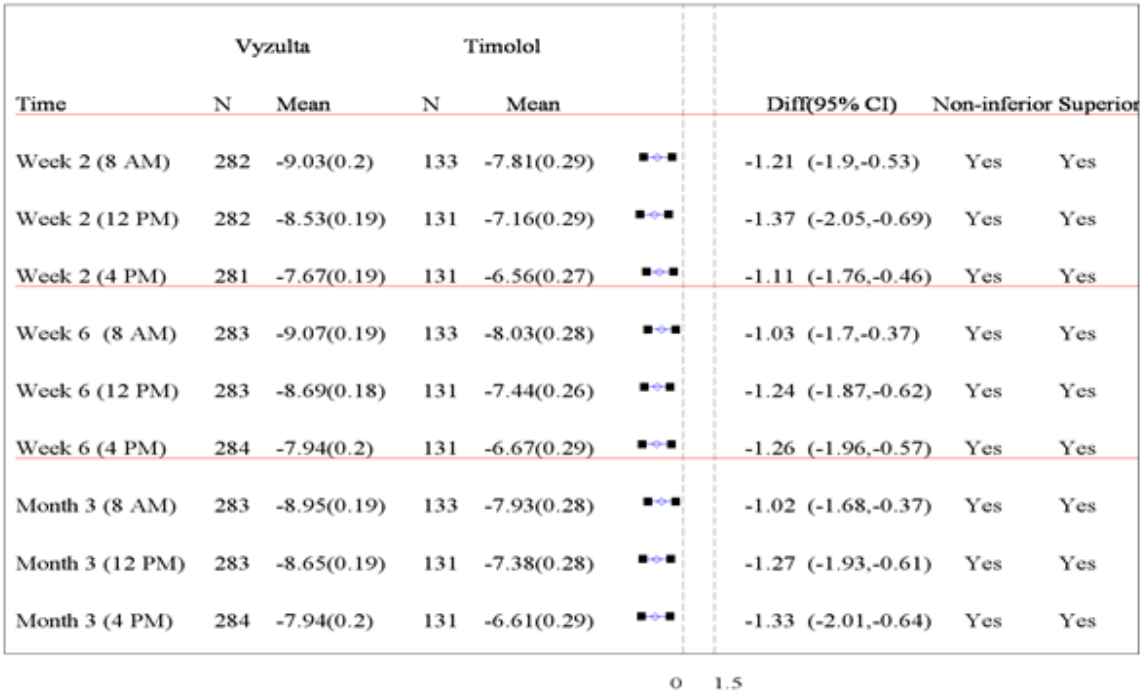
Figure 32: Difference in Mean Change from baseline IOP (FDA-ITT: Study 770)

Time	Vyzulta N=279	Timolol N=136	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	-8.1(0.22)	-7.9(0.31)	-0.19 (-0.93,0.55)	Yes	No
Week 2 (12 PM)	-7.8(0.21)	-7.4(0.3)	-0.41 (-1.12,0.31)	Yes	No
Week 2 (4 PM)	-7.1(0.21)	-6.9(0.3)	-0.21 (-0.92,0.51)	Yes	No
Week 6 (8 AM)	-8.8(0.19)	-7.9(0.27)	-0.87 (-1.53,-0.22)	Yes	Yes
Week 6 (12 PM)	-8.3(0.19)	-7.7(0.28)	-0.58 (-1.24,0.09)	Yes	No
Week 6 (4 PM)	-7.4(0.21)	-6.8(0.3)	-0.63 (-1.35,0.1)	Yes	No
Month 3 (8 AM)	-8.8(0.19)	-7.9(0.27)	-0.84 (-1.48,-0.19)	Yes	Yes
Month 3 (12 PM)	-8.4(0.2)	-7.3(0.28)	-1.02 (-1.69,-0.34)	Yes	Yes
Month 3 (4 PM)	-7.5(0.21)	-6.6(0.3)	-0.98 (-1.69,-0.27)	Yes	Yes

Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP Least square means (standard error)

Figure 33: Difference in Mean Change from baseline IOP (Bausch-ITT: Study769)

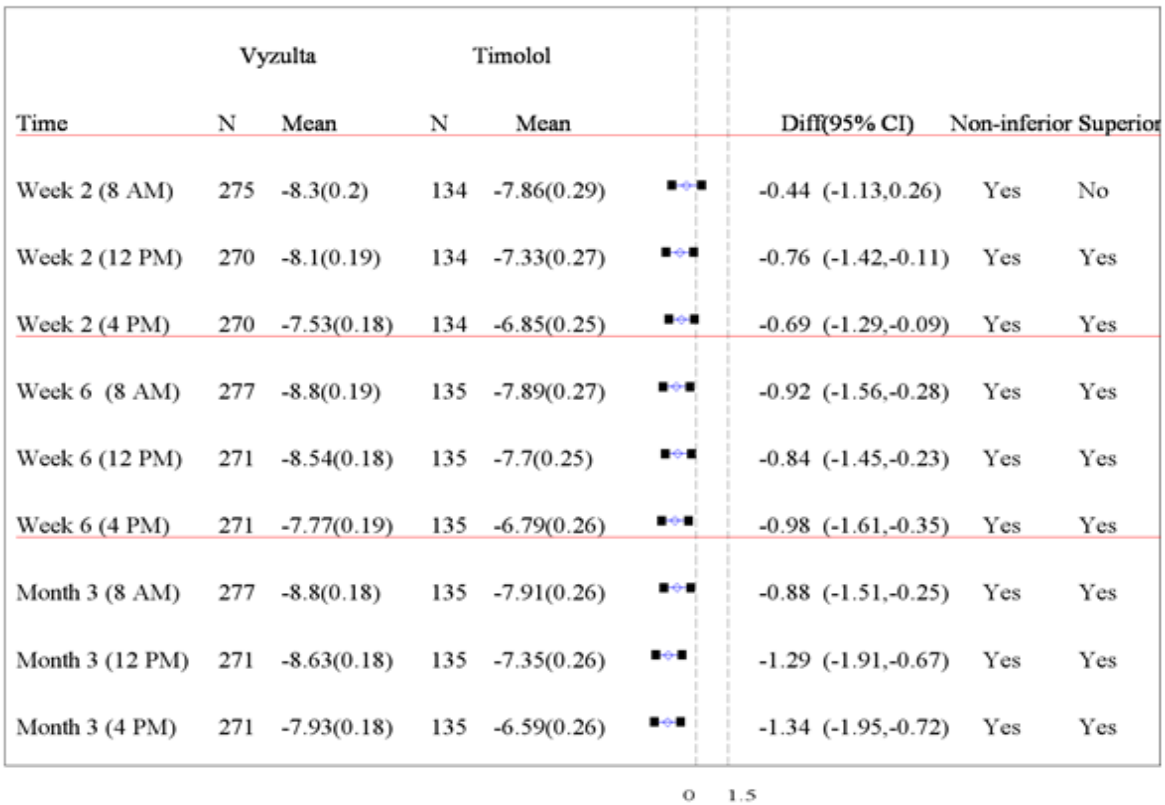
	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	282	-9.03(0.2)	133	-7.81(0.29)	-1.21 (-1.9,-0.53)	Yes	Yes
Week 2 (12 PM)	282	-8.53(0.19)	131	-7.16(0.29)	-1.37 (-2.05,-0.69)	Yes	Yes
Week 2 (4 PM)	281	-7.67(0.19)	131	-6.56(0.27)	-1.11 (-1.76,-0.46)	Yes	Yes
Week 6 (8 AM)	283	-9.07(0.19)	133	-8.03(0.28)	-1.03 (-1.7,-0.37)	Yes	Yes
Week 6 (12 PM)	283	-8.69(0.18)	131	-7.44(0.26)	-1.24 (-1.87,-0.62)	Yes	Yes
Week 6 (4 PM)	284	-7.94(0.2)	131	-6.67(0.29)	-1.26 (-1.96,-0.57)	Yes	Yes
Month 3 (8 AM)	283	-8.95(0.19)	133	-7.93(0.28)	-1.02 (-1.68,-0.37)	Yes	Yes
Month 3 (12 PM)	283	-8.65(0.19)	131	-7.38(0.28)	-1.27 (-1.93,-0.61)	Yes	Yes
Month 3 (4 PM)	284	-7.94(0.2)	131	-6.61(0.29)	-1.33 (-2.01,-0.64)	Yes	Yes



Source: Reviewer's Analysis Missing data imputed by time-matched LOCF Mean= least square means (standard error)

Figure 34: Difference in Mean Change from baseline IOP (Bausch-ITT: Study 770)

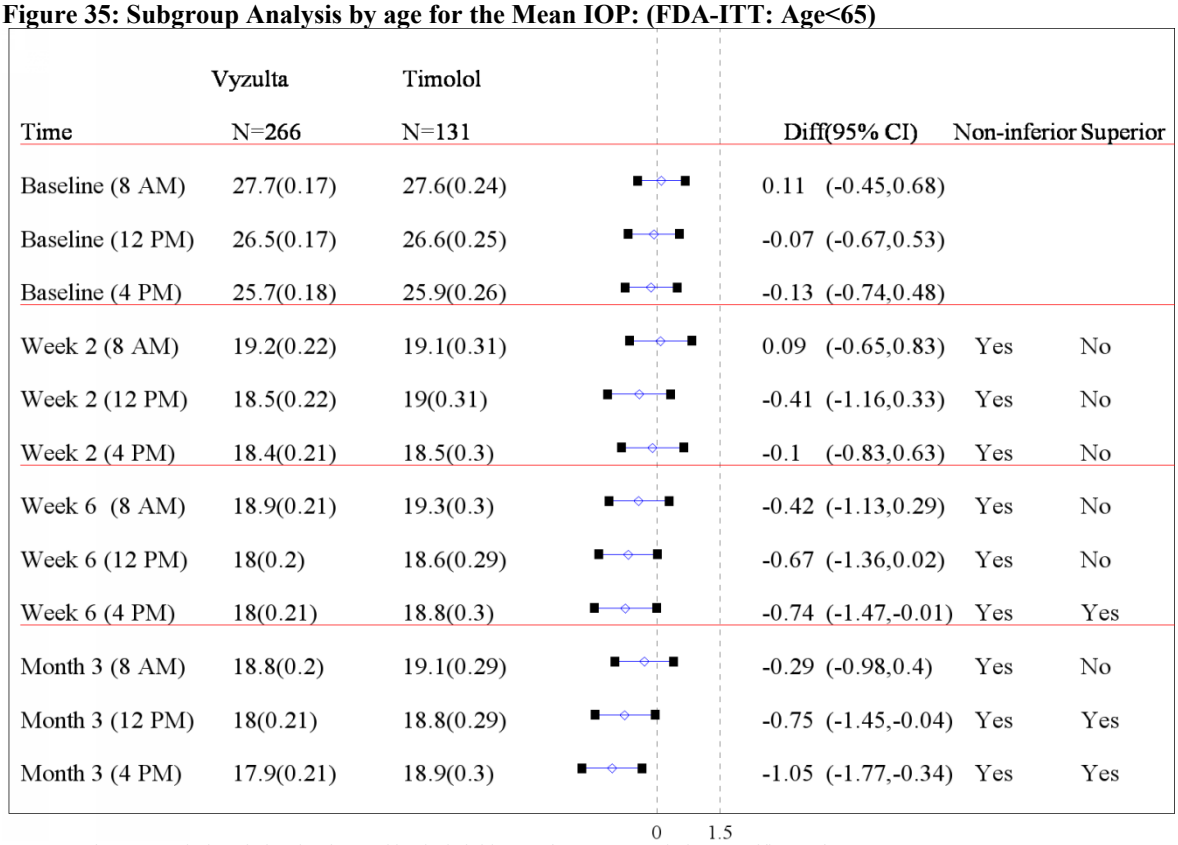
	Vyzulta		Timolol				
Time	N	Mean	N	Mean	Diff(95% CI)	Non-inferior	Superior
Week 2 (8 AM)	275	-8.3(0.2)	134	-7.86(0.29)	-0.44 (-1.13,0.26)	Yes	No
Week 2 (12 PM)	270	-8.1(0.19)	134	-7.33(0.27)	-0.76 (-1.42,-0.11)	Yes	Yes
Week 2 (4 PM)	270	-7.53(0.18)	134	-6.85(0.25)	-0.69 (-1.29,-0.09)	Yes	Yes
Week 6 (8 AM)	277	-8.8(0.19)	135	-7.89(0.27)	-0.92 (-1.56,-0.28)	Yes	Yes
Week 6 (12 PM)	271	-8.54(0.18)	135	-7.7(0.25)	-0.84 (-1.45,-0.23)	Yes	Yes
Week 6 (4 PM)	271	-7.77(0.19)	135	-6.79(0.26)	-0.98 (-1.61,-0.35)	Yes	Yes
Month 3 (8 AM)	277	-8.8(0.18)	135	-7.91(0.26)	-0.88 (-1.51,-0.25)	Yes	Yes
Month 3 (12 PM)	271	-8.63(0.18)	135	-7.35(0.26)	-1.29 (-1.91,-0.67)	Yes	Yes
Month 3 (4 PM)	271	-7.93(0.18)	135	-6.59(0.26)	-1.34 (-1.95,-0.72)	Yes	Yes



Source: Reviewer's Analysis Missing data imputed by time-matched LOCF Mean= least square means (standard error)

Figure 35: Subgroup Analysis by age for the Mean IOP: (FDA-ITT: Age<65)

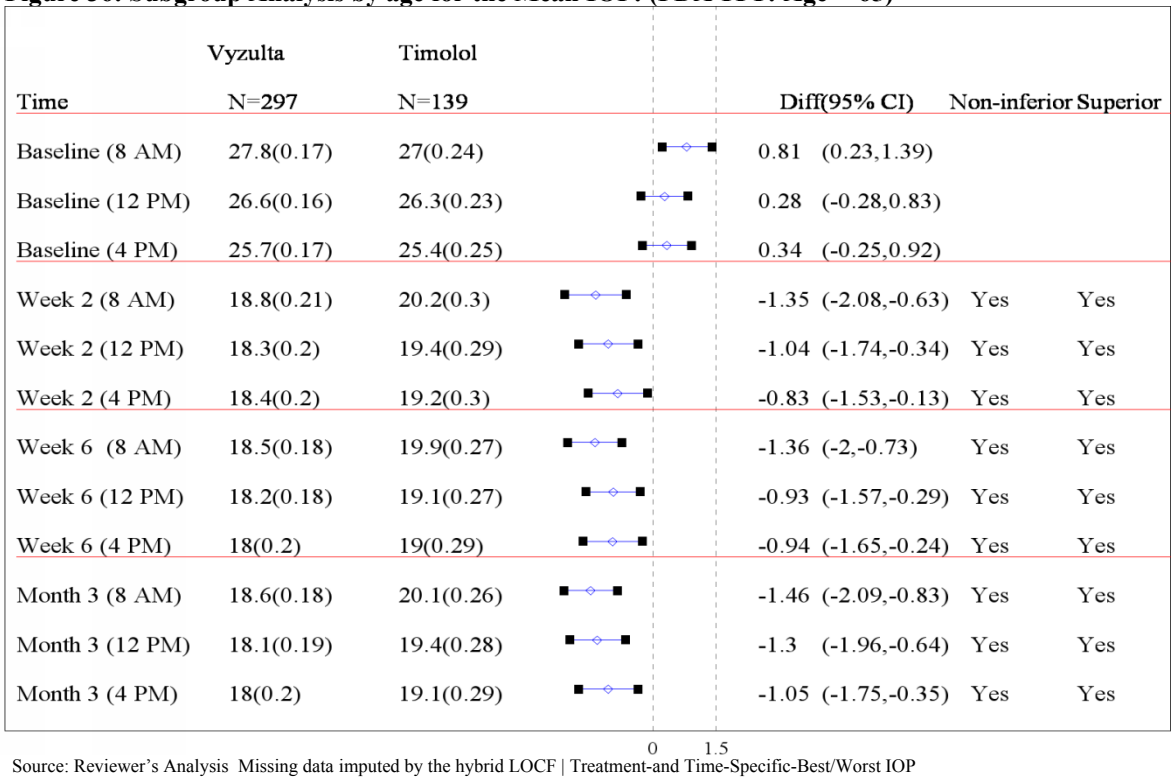
Time	Vyzulta N=266	Timolol N=131	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.7(0.17)	27.6(0.24)	0.11 (-0.45,0.68)		
Baseline (12 PM)	26.5(0.17)	26.6(0.25)	-0.07 (-0.67,0.53)		
Baseline (4 PM)	25.7(0.18)	25.9(0.26)	-0.13 (-0.74,0.48)		
Week 2 (8 AM)	19.2(0.22)	19.1(0.31)	0.09 (-0.65,0.83)	Yes	No
Week 2 (12 PM)	18.5(0.22)	19(0.31)	-0.41 (-1.16,0.33)	Yes	No
Week 2 (4 PM)	18.4(0.21)	18.5(0.3)	-0.1 (-0.83,0.63)	Yes	No
Week 6 (8 AM)	18.9(0.21)	19.3(0.3)	-0.42 (-1.13,0.29)	Yes	No
Week 6 (12 PM)	18(0.2)	18.6(0.29)	-0.67 (-1.36,0.02)	Yes	No
Week 6 (4 PM)	18(0.21)	18.8(0.3)	-0.74 (-1.47,-0.01)	Yes	Yes
Month 3 (8 AM)	18.8(0.2)	19.1(0.29)	-0.29 (-0.98,0.4)	Yes	No
Month 3 (12 PM)	18(0.21)	18.8(0.29)	-0.75 (-1.45,-0.04)	Yes	Yes
Month 3 (4 PM)	17.9(0.21)	18.9(0.3)	-1.05 (-1.77,-0.34)	Yes	Yes



Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

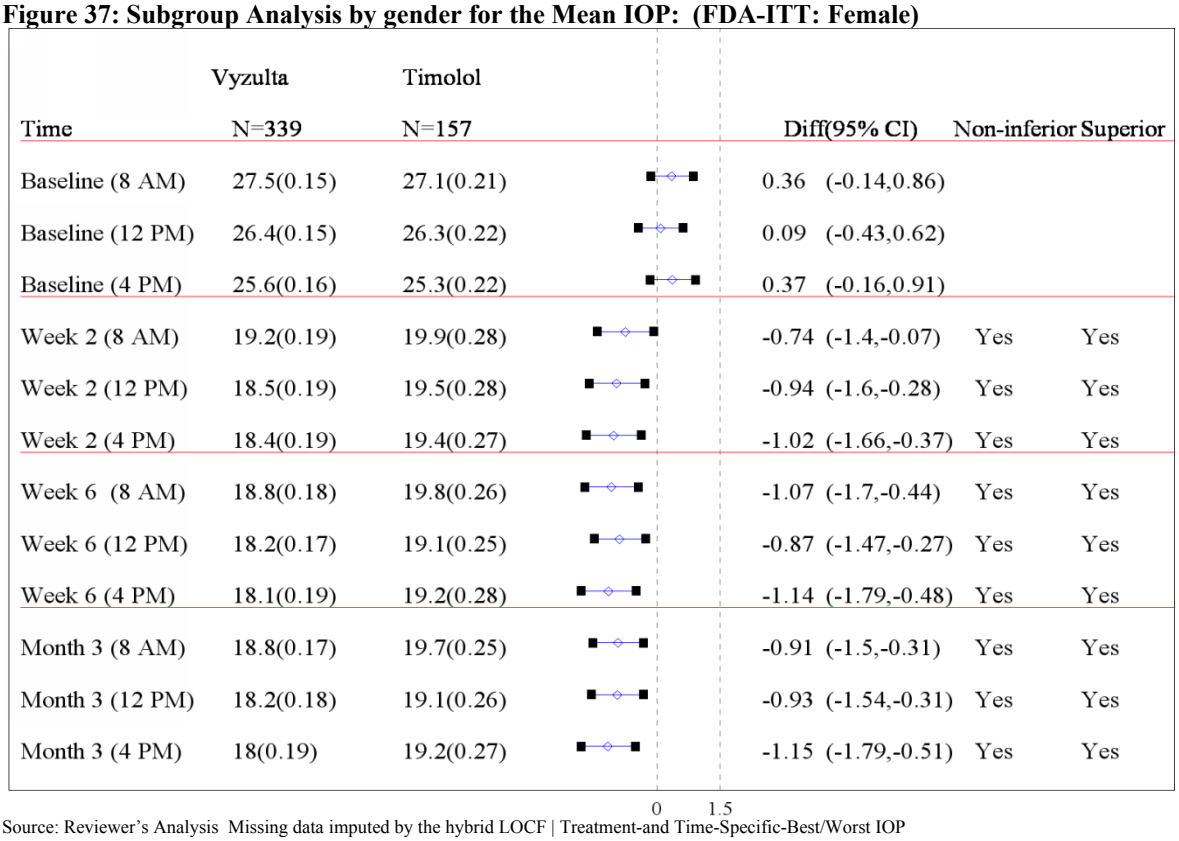
Figure 36: Subgroup Analysis by age for the Mean IOP: (FDA-ITT: Age>=65)

Time	Vyzulta N=297	Timolol N=139	Diff(95% CI)	Non-inferior	Superior
Baseline (8 AM)	27.8(0.17)	27(0.24)	0.81 (0.23,1.39)		
Baseline (12 PM)	26.6(0.16)	26.3(0.23)	0.28 (-0.28,0.83)		
Baseline (4 PM)	25.7(0.17)	25.4(0.25)	0.34 (-0.25,0.92)		
Week 2 (8 AM)	18.8(0.21)	20.2(0.3)	-1.35 (-2.08,-0.63)	Yes	Yes
Week 2 (12 PM)	18.3(0.2)	19.4(0.29)	-1.04 (-1.74,-0.34)	Yes	Yes
Week 2 (4 PM)	18.4(0.2)	19.2(0.3)	-0.83 (-1.53,-0.13)	Yes	Yes
Week 6 (8 AM)	18.5(0.18)	19.9(0.27)	-1.36 (-2,-0.73)	Yes	Yes
Week 6 (12 PM)	18.2(0.18)	19.1(0.27)	-0.93 (-1.57,-0.29)	Yes	Yes
Week 6 (4 PM)	18(0.2)	19(0.29)	-0.94 (-1.65,-0.24)	Yes	Yes
Month 3 (8 AM)	18.6(0.18)	20.1(0.26)	-1.46 (-2.09,-0.83)	Yes	Yes
Month 3 (12 PM)	18.1(0.19)	19.4(0.28)	-1.3 (-1.96,-0.64)	Yes	Yes
Month 3 (4 PM)	18(0.2)	19.1(0.29)	-1.05 (-1.75,-0.35)	Yes	Yes



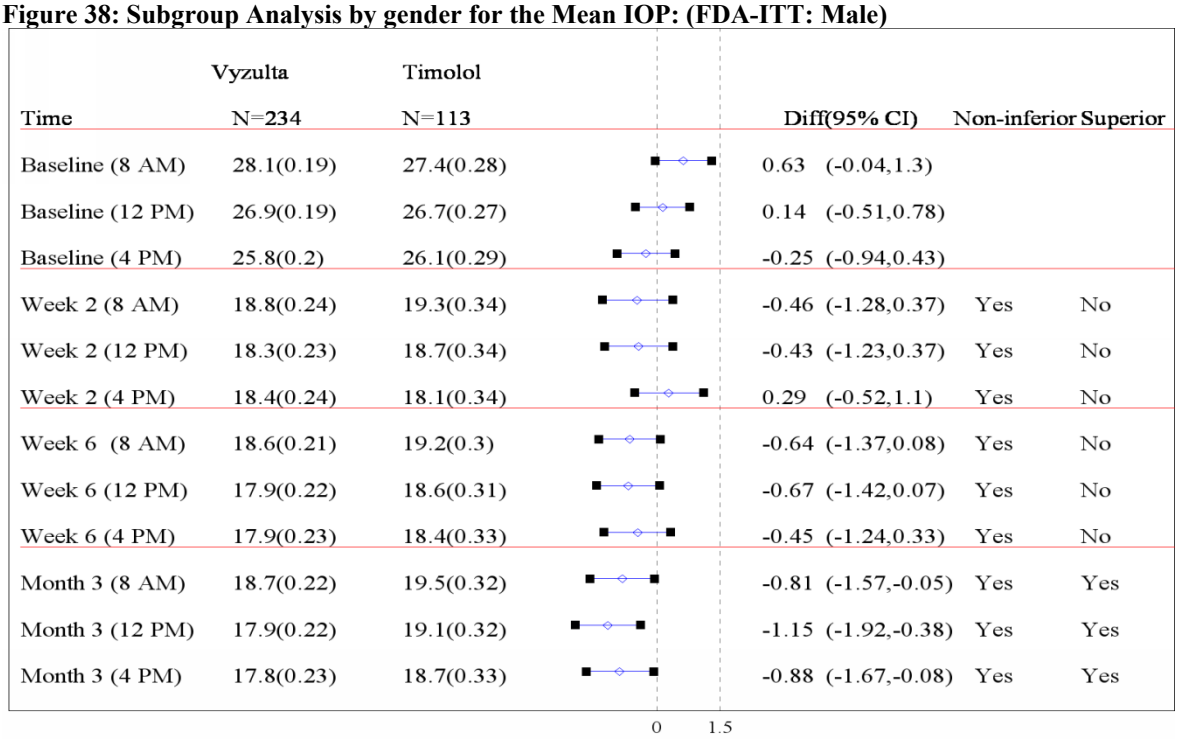
Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Figure 37: Subgroup Analysis by gender for the Mean IOP: (FDA-ITT: Female)



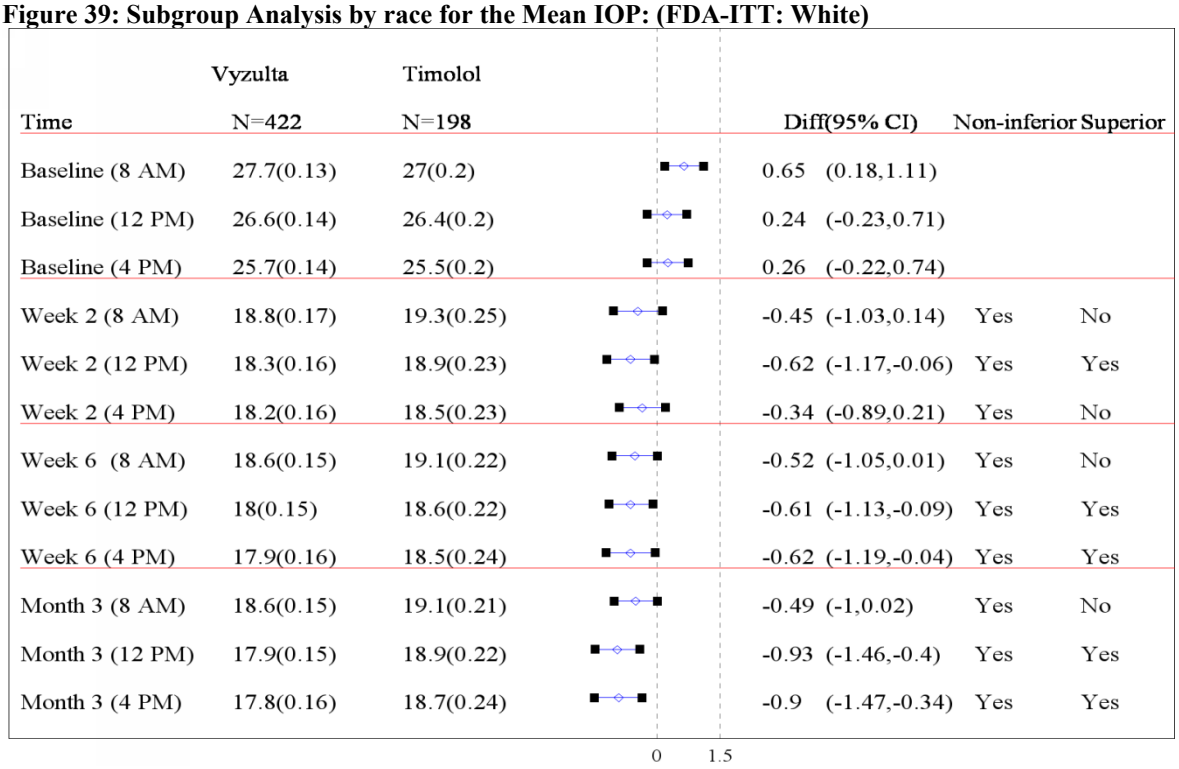
Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Figure 38: Subgroup Analysis by gender for the Mean IOP: (FDA-ITT: Male)



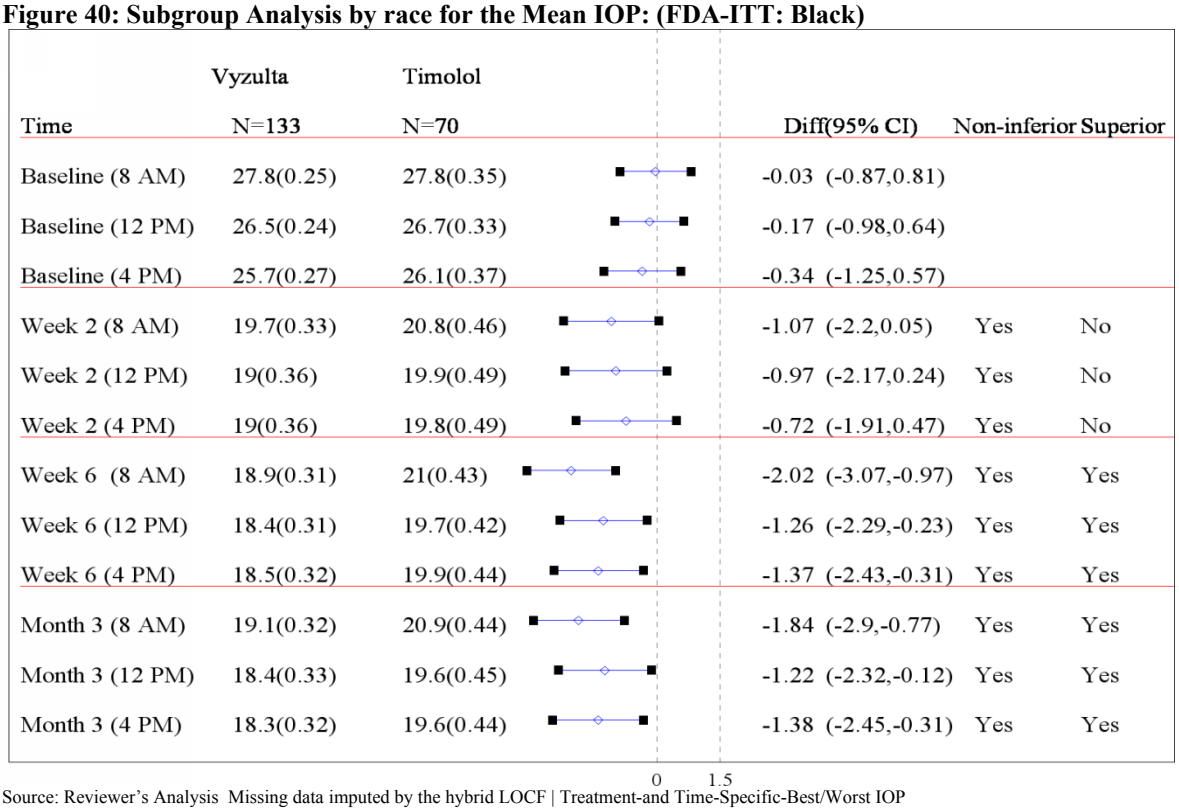
Source: Reviewer's Analysis The missing is imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst

Figure 39: Subgroup Analysis by race for the Mean IOP: (FDA-ITT: White)



Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Figure 40: Subgroup Analysis by race for the Mean IOP: (FDA-ITT: Black)



Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

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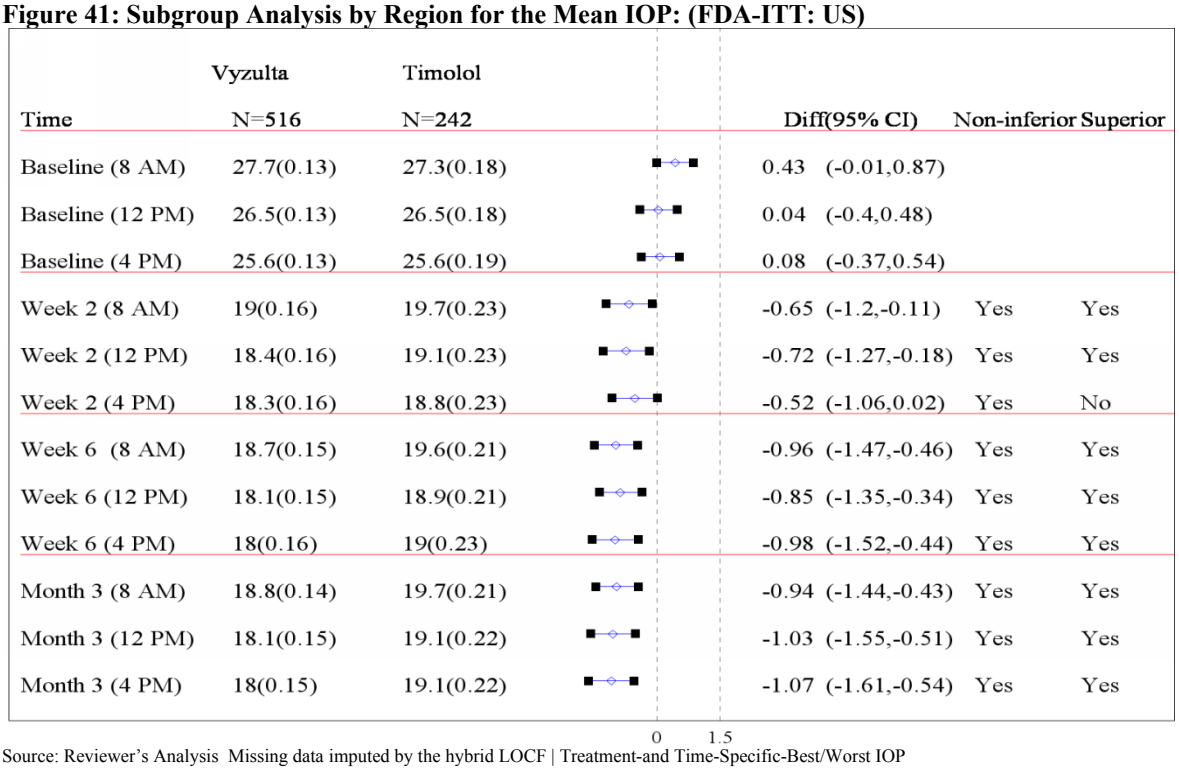
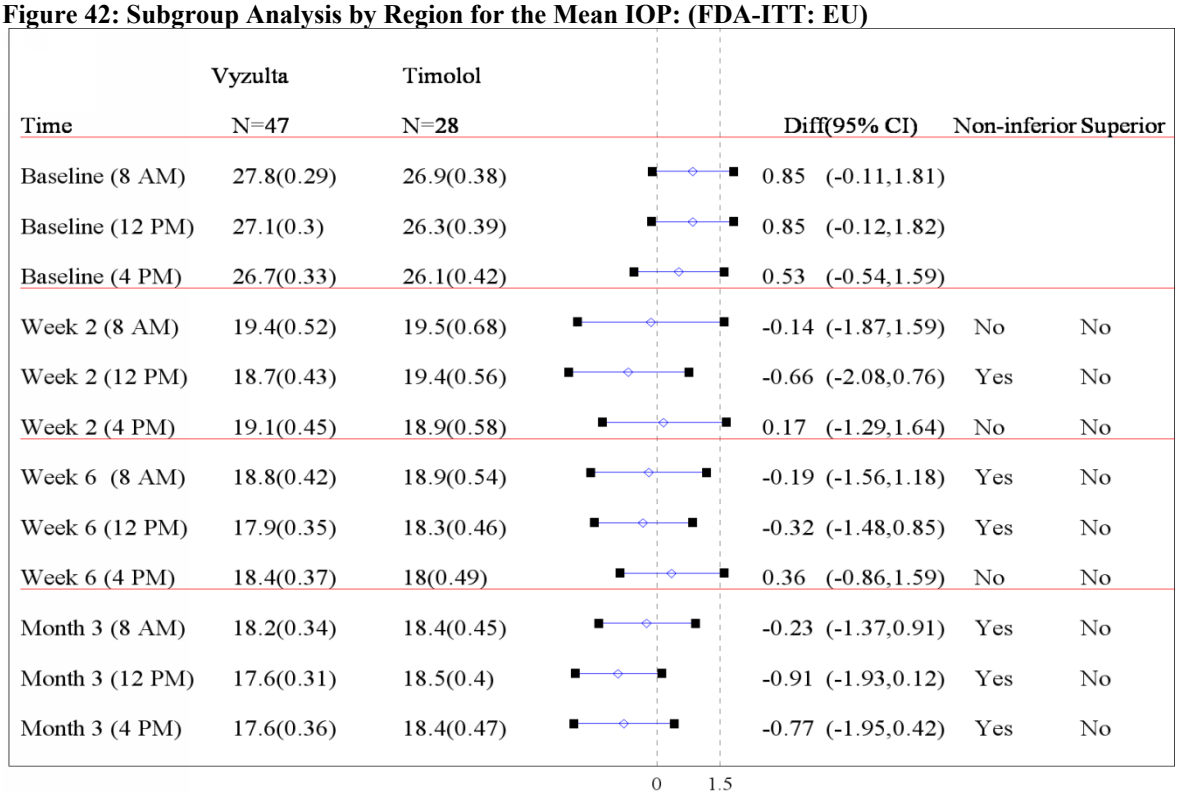
Figure 41: Subgroup Analysis by Region for the Mean IOP: (FDA-ITT: US)



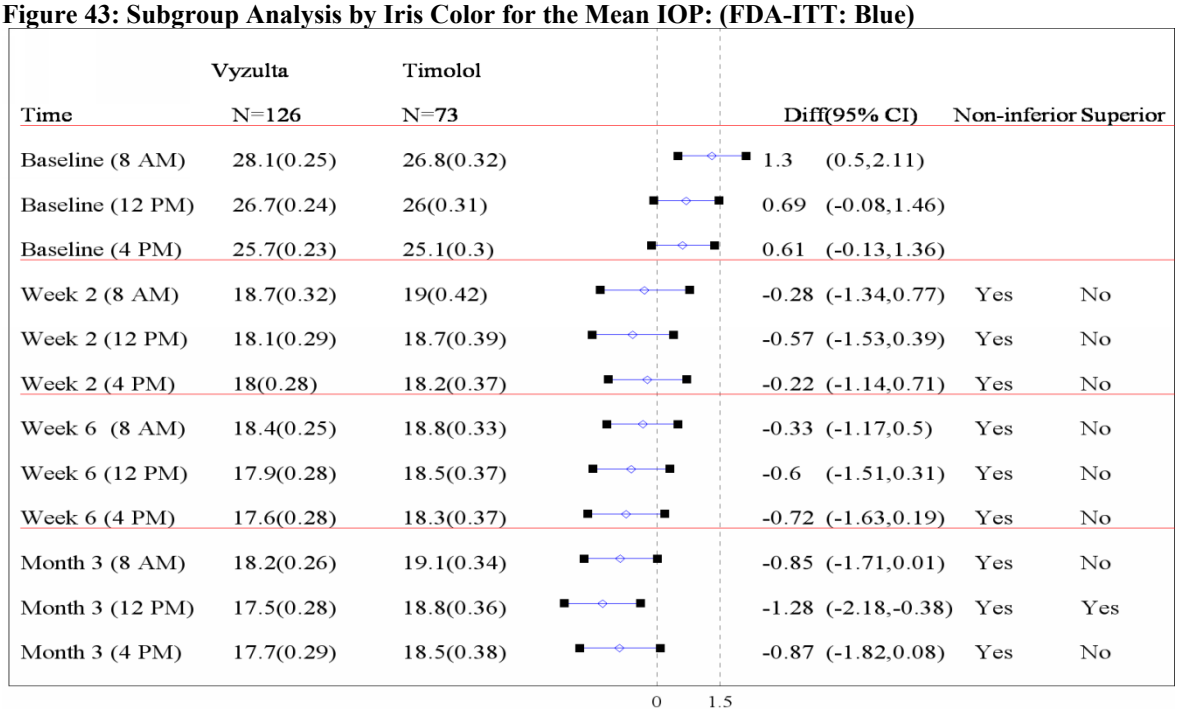
Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Figure 42: Subgroup Analysis by Region for the Mean IOP: (FDA-ITT: EU)



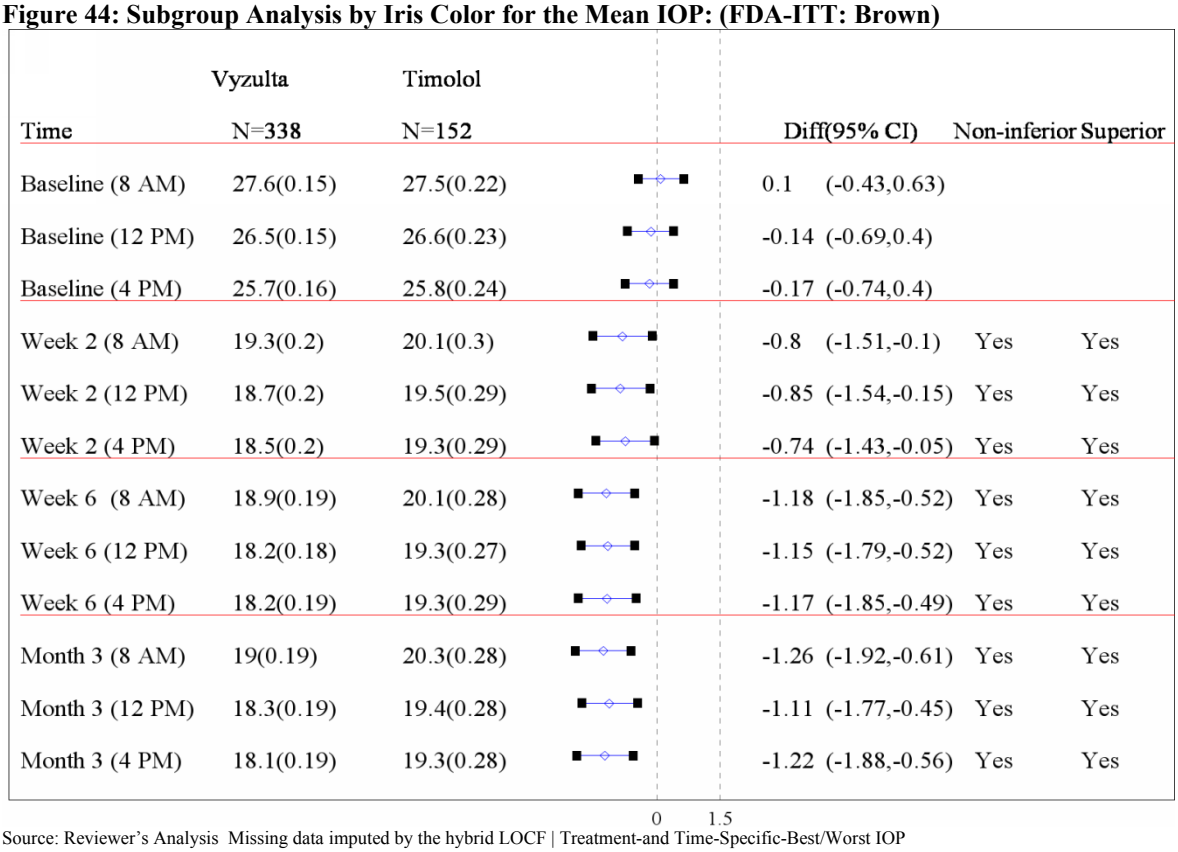
Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Figure 43: Subgroup Analysis by Iris Color for the Mean IOP: (FDA-ITT: Blue)



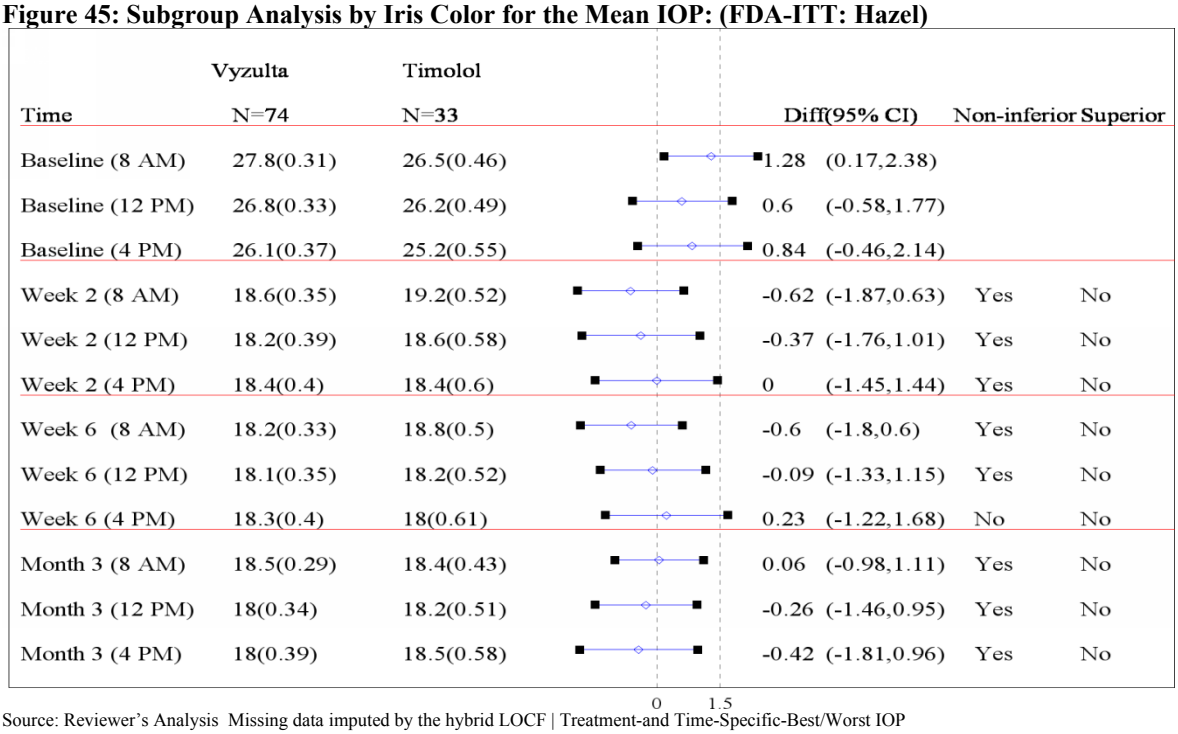
Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Figure 44: Subgroup Analysis by Iris Color for the Mean IOP: (FDA-ITT: Brown)



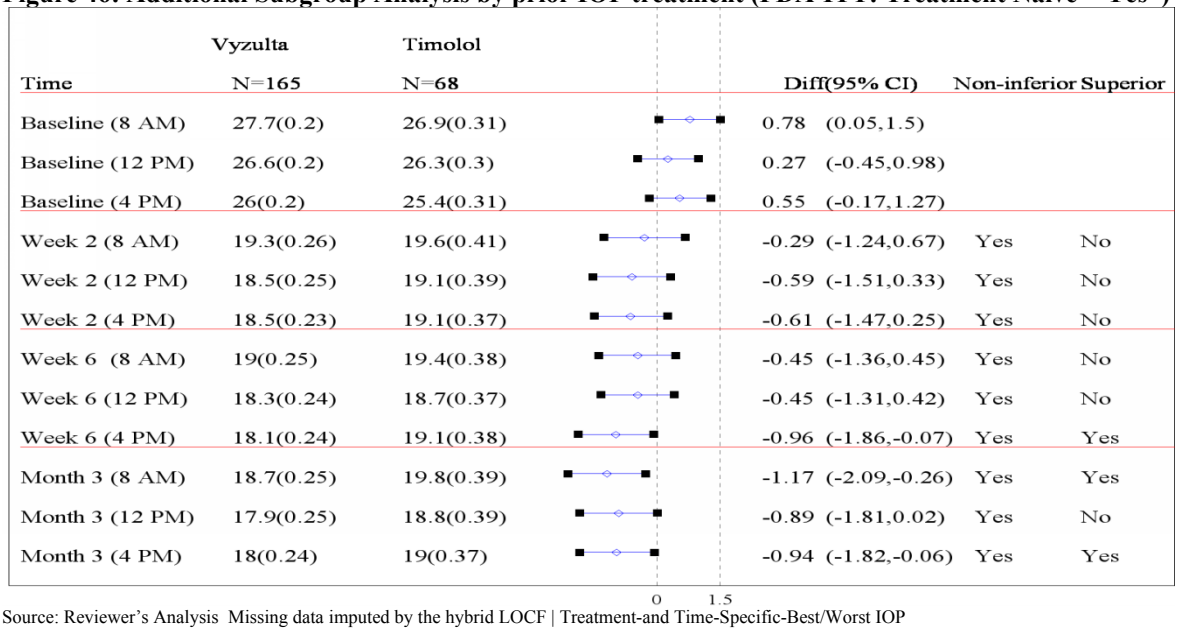
Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Figure 45: Subgroup Analysis by Iris Color for the Mean IOP: (FDA-ITT: Hazel)



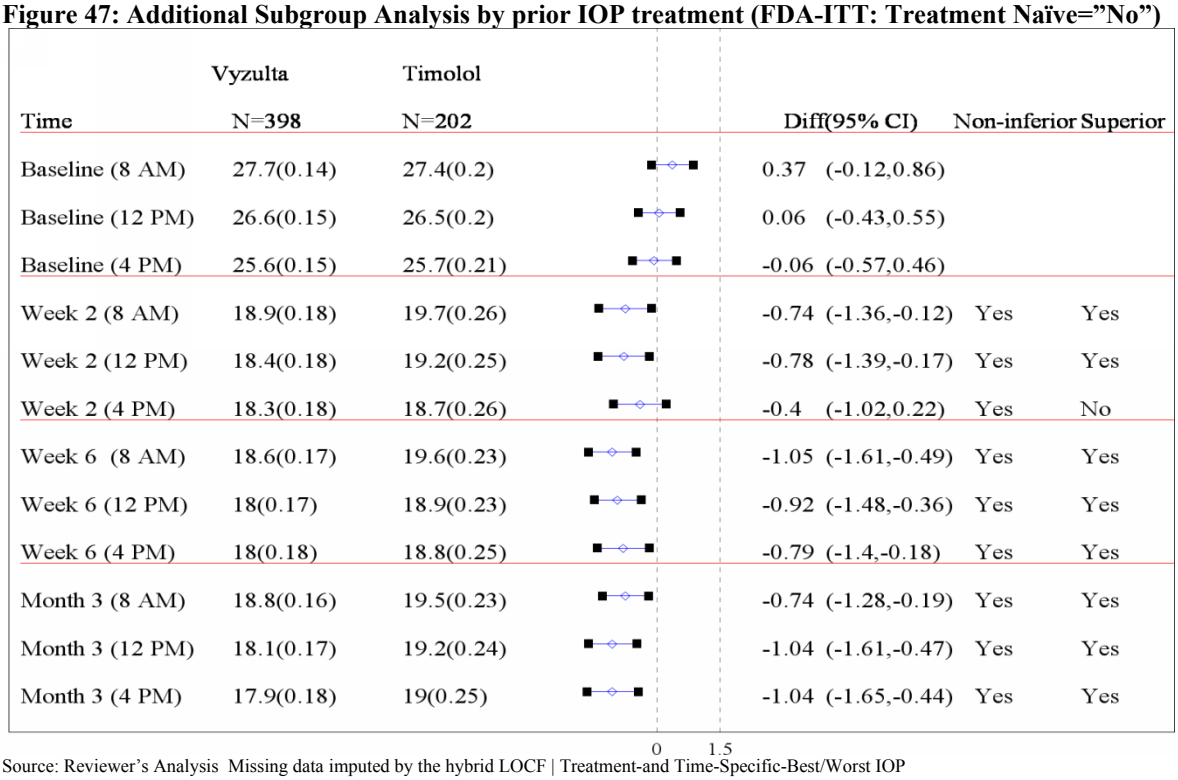
Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Figure 46: Additional Subgroup Analysis by prior IOP treatment (FDA-ITT: Treatment Naïve="Yes")



Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

Figure 47: Additional Subgroup Analysis by prior IOP treatment (FDA-ITT: Treatment Naïve="No")



Source: Reviewer's Analysis Missing data imputed by the hybrid LOCF | Treatment-and Time-Specific-Best/Worst IOP

6.2 Descriptive IOP summaries and Mean plots of change from base line IOP

Table 16: Descriptive IOP summary (Study 769)

Visit	Time	Vyzulta				Timolol			
		Mean (Std)	Min	Max	Median	Mean (Std)	Min	Max	Median
Baseline	8 AM	27.8(2.9)	22.0	36	27.0	27.3(2.7)	22.0	36.0	27.0
Baseline	12 PM	26.5(2.9)	22.0	36	26.0	26.5(2.7)	22.0	36.0	26.0
Baseline	4 PM	25.8(2.9)	22.0	36	25.0	25.6(2.9)	22.0	36.0	25.0
Week 2	8 AM	18.7(3.5)	10.5	35	18.5	19.7(3.7)	10.5	31.0	19.5
Week 2	12 PM	18(3.4)	10.0	35	18.0	19.4(3.7)	10.0	31.5	19.0
Week 2	4 PM	18.1(3.3)	10.0	35	18.0	19.2(3.4)	11.0	30.0	19.0
Week 6	8 AM	18.6(3.3)	11.0	30	18.5	19.3(3.2)	11.5	31.0	19.0
Week 6	12 PM	17.8(3.1)	11.0	29	17.5	19.1(3.2)	11.0	26.5	19.0
Week 6	4 PM	17.8(3.3)	8.0	29	17.5	19(3.5)	11.0	32.0	18.5
Month 3	8 AM	18.7(3.2)	12.0	32	18.5	19.4(3.1)	14.0	33.0	19.0
Month 3	12 PM	17.8(3.2)	8.5	31	17.5	19(3.3)	12.0	29.0	18.5
Month 3	4 PM	17.7(3.3)	8.5	30	17.5	18.9(3.6)	10.0	36.0	18.0

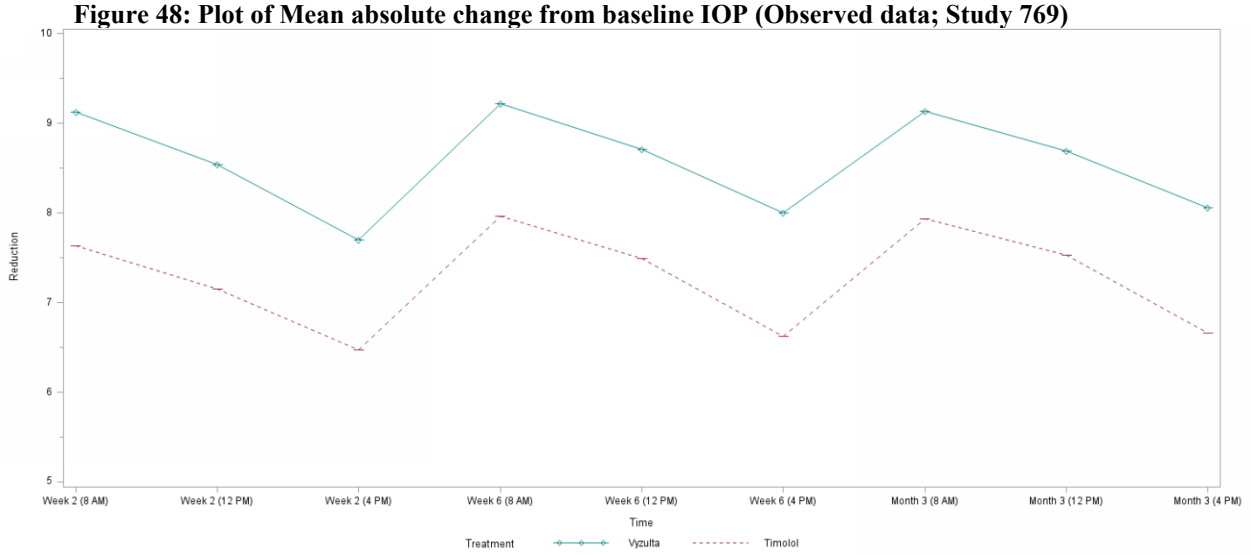
Source: Reviewer's Analysis Observed data

Table 17: Descriptive IOP summary (Study 770)

Visit	Time	Vyzulta				Timolol			
		Mean (Std)	Min	Max	Median	Mean (Std)	Min	Max	Median
Baseline	8 AM	27.6(2.7)	22.0	36.0	27.0	27.2(2.8)	22.0	36.0	26.50
Baseline	12 PM	26.6(2.9)	22.0	36.0	26.0	26.4(2.4)	22.0	34.0	26.00
Baseline	4 PM	25.6(2.9)	22.0	35.5	25.0	25.6(3)	22.0	35.0	25.00
Week 2/Day 14	8 AM	19.2(3.7)	9.5	35.0	19.0	19.5(3.1)	12.5	26.0	19.25
Week 2/Day 14	12 PM	18.5(3.3)	9.0	28.0	18.5	19.2(3.2)	9.5	32.0	19.00
Week 2/Day 14	4 PM	18.1(3.1)	11.0	29.0	18.0	18.8(3)	11.0	28.0	18.50
Week 6	8 AM	18.6(3.1)	11.0	35.5	18.5	19.4(3.3)	12.0	34.0	19.00
Week 6	12 PM	18(3.1)	10.5	29.0	18.0	18.7(3.2)	11.0	31.0	19.00
Week 6	4 PM	17.8(3.1)	10.0	28.5	17.5	18.8(3.4)	11.0	31.5	18.75
Month 3	8 AM	18.6(2.8)	12.0	27.0	18.0	19.4(3.3)	11.5	30.0	19.00
Month 3	12 PM	17.9(3.1)	8.0	28.0	18.0	19.1(3.1)	11.0	26.0	19.00
Month 3	4 PM	17.6(3.1)	10.0	32.0	17.0	19.1(2.9)	12.0	27.5	19.00

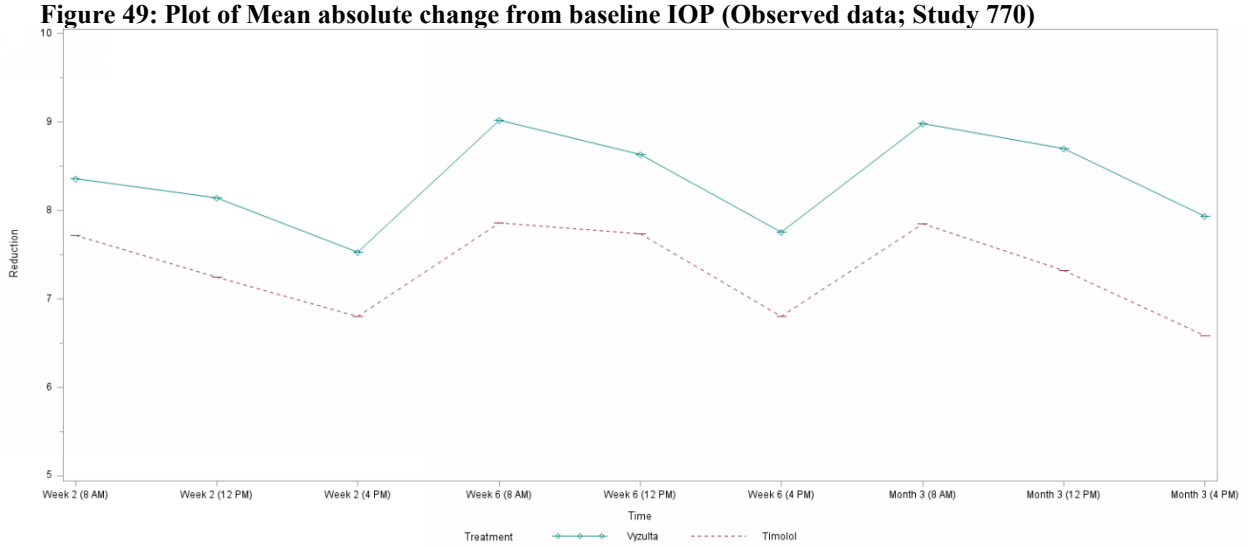
Source: Reviewer's Analysis Observed data

Figure 48: Plot of Mean absolute change from baseline IOP (Observed data; Study 769)



Source: Reviewer's Analysis.

Figure 49: Plot of Mean absolute change from baseline IOP (Observed data; Study 770)



Source: Reviewer's Analysis

Table 18: Summary of Best (Worst) IOP values by time of the Day

	Study 769		Study 770	
	Vyzulta	Timolol	Vyzulta	Timolol
Time	Best (Worst)	Best (Worst)	Best (Worst)	Best (Worst)
8 AM	10.5 (35)	10 (33)	9.5 (35.5)	10 (34)
12 PM	8.5 (35)	10 (31.5)	8 (29)	10 (32)
4 PM	8 (35)	9.5 (36)	10 (32)	9.5 (31.5)

Source: Reviewer's Analysis. Observed data

Table 19: Summary of different imputed values (Sample in the Vyzulta arm)

Visit	Time	Observed	Post-baseline LOCF	Hybrid LOCF/worst	Pure LOCF: Including baseline
Baseline	8 AM	29.0	29.0	29.0	29.0
Baseline	12 PM	24.5	24.5	24.5	24.5
Baseline	4 PM	25.0	25.0	25.0	25.0
Week 2/Day 14	8 AM	15.5.	15.5	15.5	15.5
Week 2/Day 14	12 PM	.	.	**29.0[1]**	**24.5[1]**
Week 2/Day 14	4 PM	.	.	**32.0[1]**	**25.0[1]**
Week 6	8 AM	.	**15.5[1]**	15.5[1]	15.5[1]
Week 6	12 PM	.	.	**29.0[1]**	**24.5[1]**
Week 6	4 PM	.	.	**32.0[1]**	**25.0[1]**
Month 3	8 AM	.	**15.5[1]**	15.5[1]	15.5[1]
Month 3	12 PM	.	.	**29.0[1]**	**24.5[1]**
Month 3	4 PM	.	.	**32.0[1]**	**25.0[1]**

Source: Reviewer's Analysis. [1] Imputed value

Table 20: Summary of different imputed values (Sample in the Timolol arm)

Visit	Time	Observed	Post-baseline LOCF	Hybrid LOCF/best	Pure LOCF: Including baseline
Baseline	8 AM	29	29	29.0	29.0
Baseline	12 PM	31	31	31.0	31.0
Baseline	4 PM	30	30	30.0	30.0
Week 2/Day 14	8 AM	23.5	23.5	23.5	23.5
Week 2/Day 14	12 PM	.	.	**10.0[1]**	**31[1]**
Week 2/Day 14	4 PM	.	.	**9.5[1]**	**30[1]**
Week 6	8 AM	.	**23.5[1]**	23.5[1]	23.5[1]
Week 6	12 PM	.	.	**10.0[1]**	**31[1]**
Week 6	4 PM	.	.	**9.5[1]**	**30[1]**
Month 3	8 AM	.	**23.5[1]**	23.5[1]	23.5[1]
Month 3	12 PM	.	.	**10.0[1]**	**31[1]**
Month 3	4 PM	.	.	**9.5[1]**	**30[1]**

Source: Reviewer's Analysis. [1] Imputed value

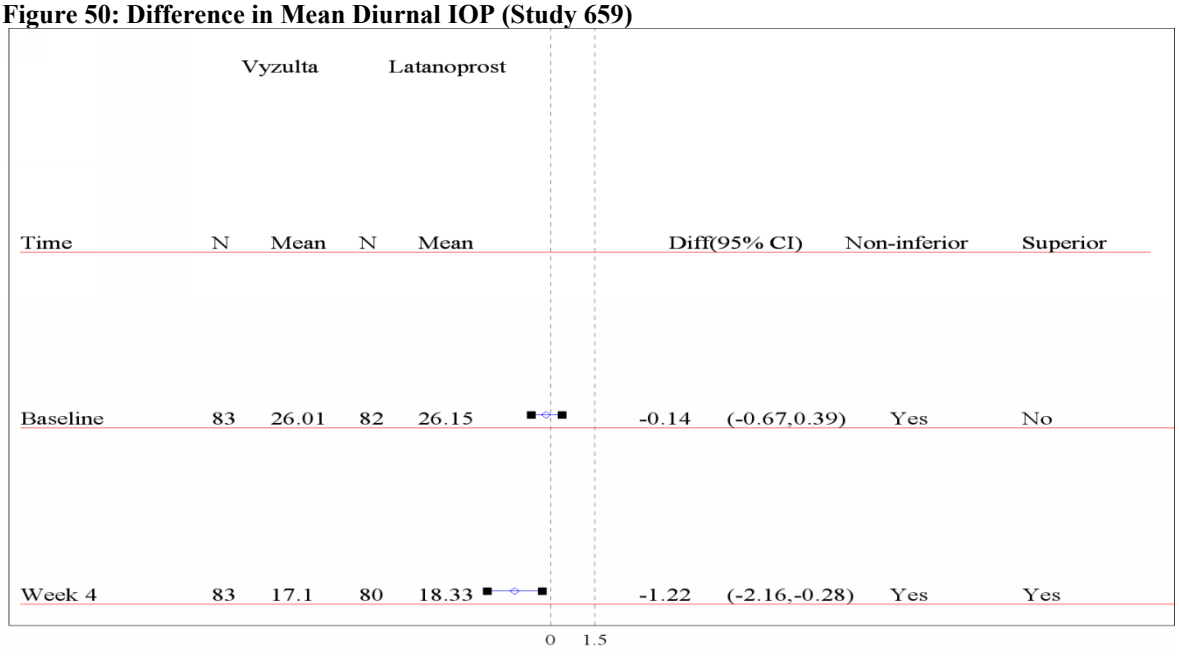
6.3 Summary Results: Study 659

This was a randomized, multicenter, single-masked, parallel-group, dose-ranging 28-day trial. The primary objective of this study was to determine the most effective drug concentration(s) of BOL-303259-X in the reduction of intraocular pressure (IOP) in order to support further clinical development of an appropriate dose with regard to efficacy, and ocular and systemic safety. The primary analysis endpoint was the mean diurnal IOP change from baseline (Day 1) at Day 28. The primary efficacy analysis was conducted using an analysis of covariance (ANCOVA) model with terms for baseline IOP and treatment. The least squares means from this model was computed together with the 95% confidence interval.

In this study, 413 subjects with open-angle glaucoma or ocular hypertension were randomized in a 1:1:1:1 ratio to one of the four doses of latanoprostene bunod ophthalmic solution (0.006%, 0.012%, 0.024% [Vyzulta] and 0.040%) or latanoprost ophthalmic solution 0.005%.

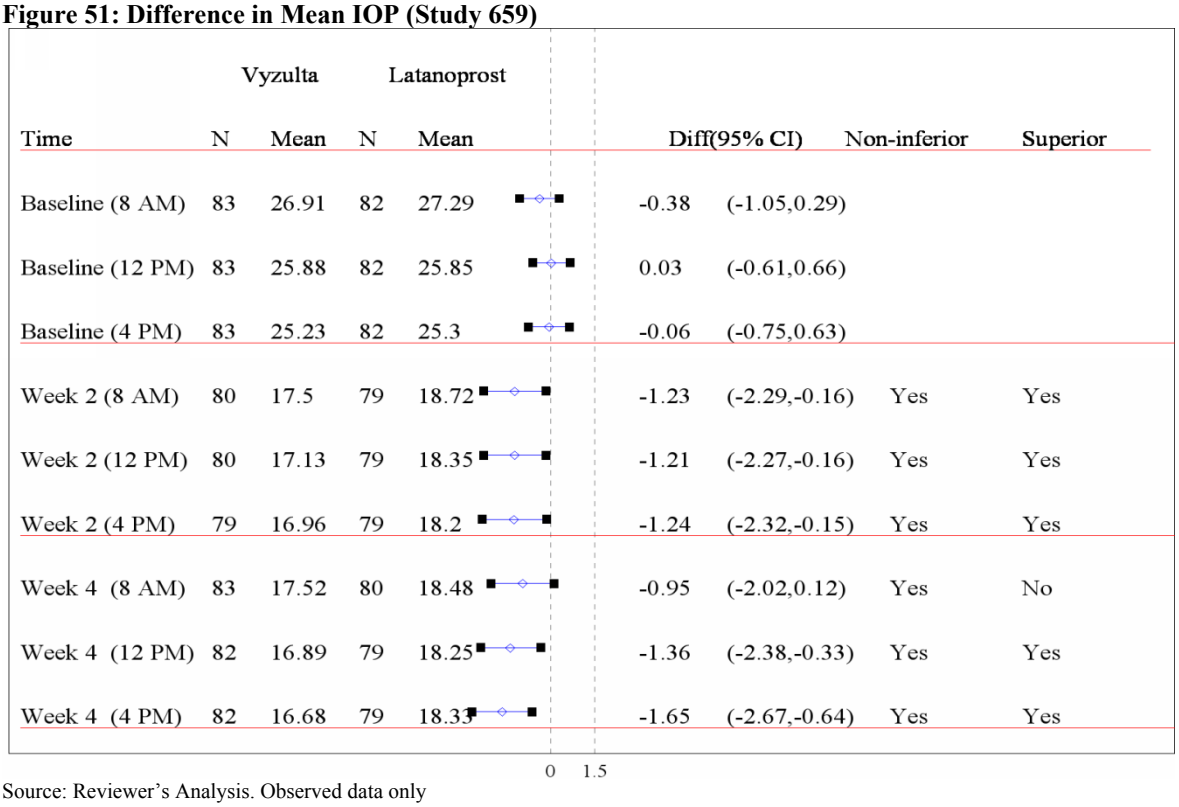
Selected summary results for this study are presented in Figure 50-Figure 52. There was a difference of 1.22 mmHg in mean change in diurnal intraocular pressure between Vyzulta and latanoprost ophthalmic solution 0.005% at Day 28. A higher percentage of subjects in the Vyzulta group compared with the latanoprost 0.005% group had a study eye mean diurnal intraocular pressure of ≤18 mmHg at Day 28, 68.7% versus 47.5%. With respect to safety, a higher percentage of subjects in the Vyzulta arm (21.4%) reported at least one ocular adverse event compared to the latanoprost 0.005% group (12.2%). Note that the sample size calculation for the two pivotal studies (779 &770) used information from this dose finding study.

Figure 50: Difference in Mean Diurnal IOP (Study 659)



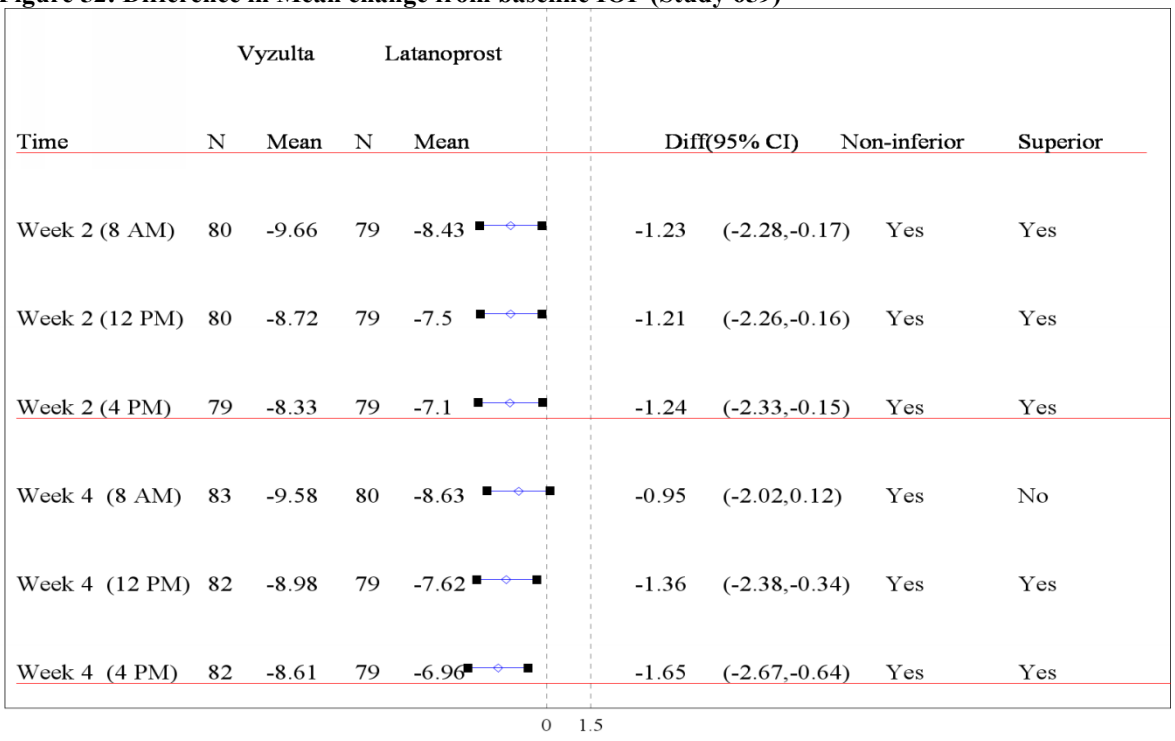
Source: Reviewer's Analysis. Observed data only

Figure 51: Difference in Mean IOP (Study 659)



Source: Reviewer's Analysis. Observed data only

Figure 52: Difference in Mean change from baseline IOP (Study 659)



Source: Reviewer's Analysis. Observed data only

6.4 Summary results: Study 803

This was a randomized, single-center, open-label, 2-period, 8-week study with a crossover at 4 weeks. There were 2 treatment sequences in this study: treatment sequence AB included Vyzulta QD for Period 1 and timolol maleate 0.5% BID (active control) for Period 2; Treatment sequence BA included timolol for Period 1 and Vyzulta for Period 2. The primary objective of this study was to compare the effect of Vyzulta dosed QD with timolol dosed BID in reducing diurnal IOP measured over a 24-hour period in subjects with OAG or OHT. The primary efficacy endpoint for this study was the supine IOP in the study eye after 4 weeks of treatment (Visit 4 [Week 4] and Visit 5 [Week 8]). A total of 25 subjects were randomized to the two treatment sequences (12 in AB and 13 in BA). The mean baseline values ranged between 23 and 27 mm Hg.

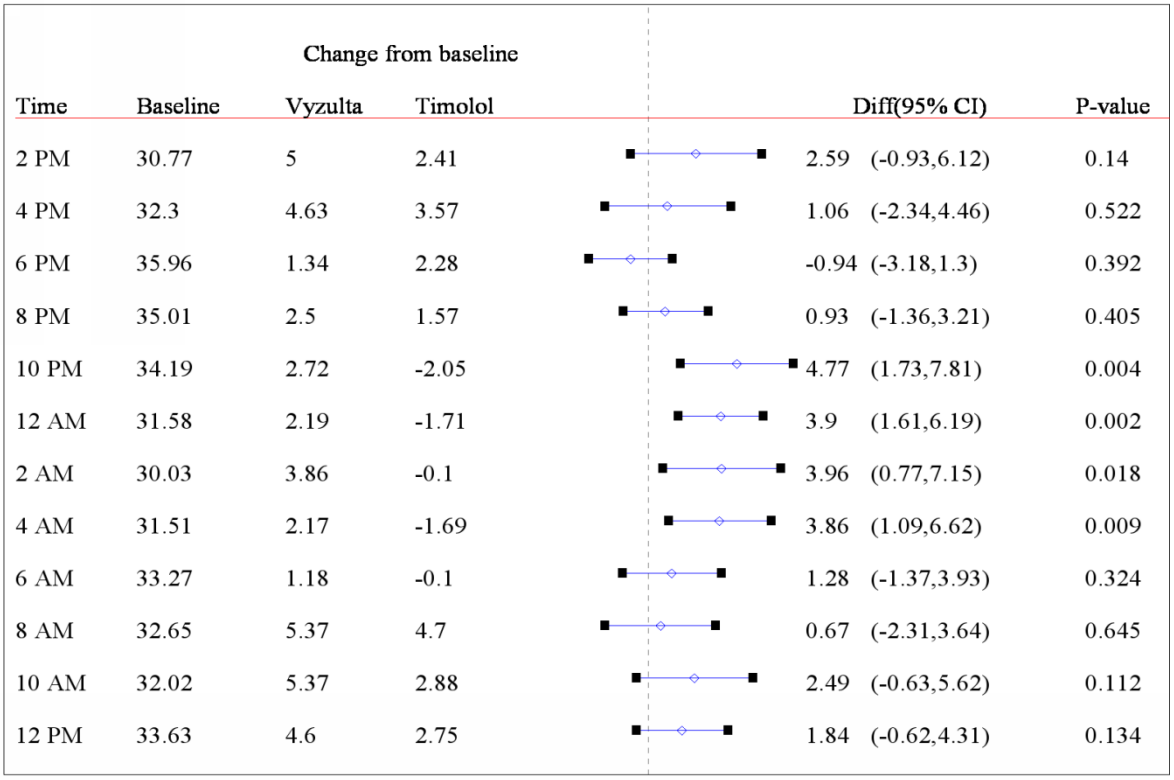
The primary efficacy analysis was conducted on all randomized and treated subjects with baseline and at least one post baseline IOP (ITT) using the mixed effects model for repeated measures. The model included fixed effects for baseline, treatment, time (relative to 1st IOP assessment), period, baseline-by-time and treatment-by-time interactions and a random subject effect. The least squares mean difference for treatment and 95% confidence interval was derived from this model. Based on the above model, the applicant reported the mean IOP in the Vyzulta and Timolol arms respectively as 21.77 mm Hg and 23.55 mm Hg leading to a treatment difference of -1.78 (95% CI -2.38, 1.12). The reviewer also summarized the change from baseline supine IOP and the change from baseline Ocular Perfusion Pressure over the 24 period. The results are presented in Figure 53 and Figure 54. The Vyzulta arm had consistently higher supine IOP reduction and higher increase in perfusion pressure from baseline compared to Timolol. With respect safety, there was only one ocular adverse event reported for the Vyzulta arm compared to three in the Timolol arm.

Figure 53: Mean Change from Baseline supine IOP (Study 803)

		Change from baseline			
Time	Baseline	Vyzulta	Timolol	Diff(95% CI)	P-value
2 PM	26.65	-4.9	-3.7	-1.2 (-3.06,0.66)	0.171
4 PM	25.5	-4.35	-3.05	-1.3 (-3.78,1.18)	0.261
6 PM	23.55	-3.15	-1.75	-1.4 (-3.07,0.27)	0.089
8 PM	22.7	-3	-1.65	-1.35 (-2.78,0.08)	0.061
10 PM	22.7	-1.9	0.95	-2.85 (-5.06,-0.64)	0.018
12 AM	23.1	-0.6	1.25	-1.85 (-4.17,0.47)	0.103
2 AM	23.5	-0.85	1.6	-2.45 (-5.35,0.45)	0.086
4 AM	23.75	-1.7	2.1	-3.8 (-6.5,-1.1)	0.012
6 AM	25.55	-3.05	-1.3	-1.75 (-4.8,1.3)	0.222
8 AM	25.75	-5.2	-2.8	-2.4 (-4.15,-0.65)	0.013
10 AM	25.05	-4.5	-2.95	-1.55 (-4.56,1.46)	0.269
12 PM	25.05	-5	-2.45	-2.55 (-4.47,-0.63)	0.016

Source: Reviewer's Analysis. Observed data only

Figure 54: Mean Change from Baseline Ocular Perfusion Pressure (Study 803)



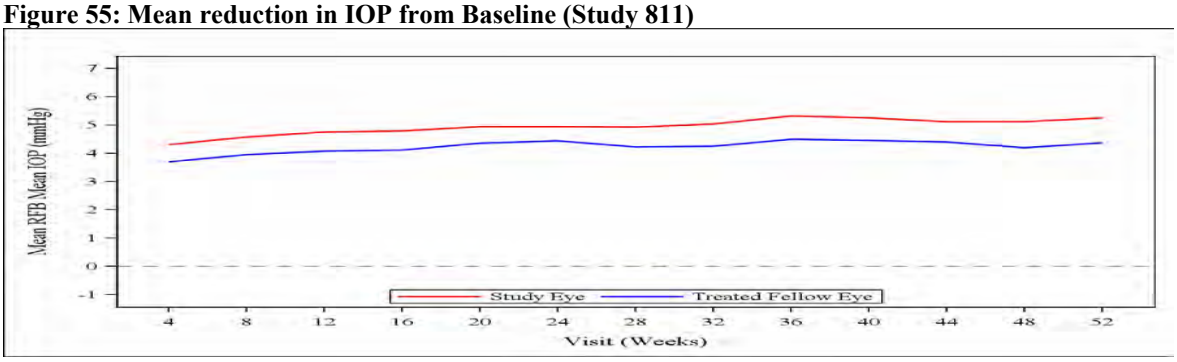
	Change from baseline			
Time	Baseline	Vyzulta	Timolol	Diff(95% CI) P-value
2 PM	30.77	5	2.41	2.59 (-0.93,6.12) 0.14
4 PM	32.3	4.63	3.57	1.06 (-2.34,4.46) 0.522
6 PM	35.96	1.34	2.28	-0.94 (-3.18,1.3) 0.392
8 PM	35.01	2.5	1.57	0.93 (-1.36,3.21) 0.405
10 PM	34.19	2.72	-2.05	4.77 (1.73,7.81) 0.004
12 AM	31.58	2.19	-1.71	3.9 (1.61,6.19) 0.002
2 AM	30.03	3.86	-0.1	3.96 (0.77,7.15) 0.018
4 AM	31.51	2.17	-1.69	3.86 (1.09,6.62) 0.009
6 AM	33.27	1.18	-0.1	1.28 (-1.37,3.93) 0.324
8 AM	32.65	5.37	4.7	0.67 (-2.31,3.64) 0.645
10 AM	32.02	5.37	2.88	2.49 (-0.63,5.62) 0.112
12 PM	33.63	4.6	2.75	1.84 (-0.62,4.31) 0.134

Source: Reviewer's Analysis. Observed data only

6.5 Summary results: Study 811

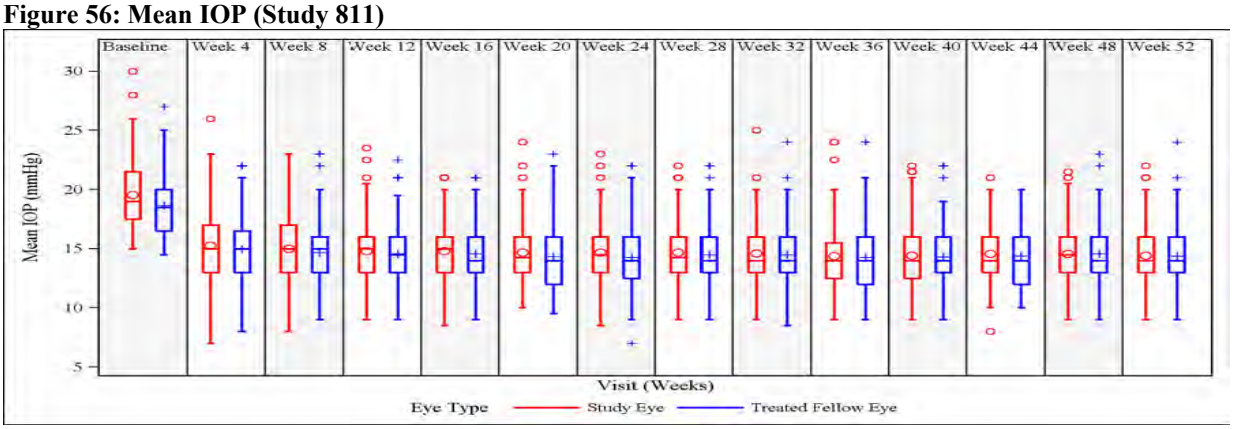
This was a single-arm, multicenter, open-label study designed to evaluate the long-term safety of Vyzulta. A total of 130 subjects were exposed to Vyzulta. The mean duration of exposure was 351.5 days (range of 28 to 371 days). The median duration of exposure was 364.0 days. The majority of subjects (92.3%) completed at least 364 days of study treatment. The efficacy endpoint was the absolute change from baseline IOP. The plots of the mean reduction in IOP and the mean IOP over time for the study eye and the treated fellow eye are presented in Figure 55 and Figure 56 respectively. The mean baseline IOP was 19.56 mmHg for the study eye and 18.65 mmHg for the treated fellow eye. For the study eye, a reduction from baseline in IOP of 15.26 which amount to a 22.0% reduction was achieved by Week 4. There was a consistent reduction in IOP over the entire period of the study. Similarly, for the treated fellow eye, an IOP reduction of 14.96 which amounted to a 19.8% reduction from baseline was achieved at Week 4.

Figure 55: Mean reduction in IOP from Baseline (Study 811)



Source Figure 11-1 of the applicant's study report

Figure 56: Mean IOP (Study 811)



Source: Figure 11-2 of the applicant's study report

With respect to safety, 76 (58.5%) of the 130 subjects experienced at least 1 ocular adverse event in the study eye, and 62 (47.7%) subjects experienced at least ocular AE in the study eye. Additionally, 67 (51.5%) of the 130 subjects experienced at least 1 non ocular AE. No deaths were reported in this study. Eight subjects experienced non ocular serious adverse events.

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/s/

ABEL T ESHETE
04/22/2016

YAN WANG
04/22/2016
I concur with the overall conclusion.

DIONNE L PRICE
04/22/2016
Concur with overall conclusion of efficacy/safety.