CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 211911
Supplement #:	0001
Drug Name:	Durysta™ (bimatoprost (b) (4) implant)
Indication(s):	For the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension
Applicant:	Allergan, Inc.
Date(s):	Submitted: 05/06/2019 Review Completion Goal Date: 01/28/2020 PDUFA Goal date: 03/06/2020
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Keywords: elevated intraocular pressure (IOP), non-inferiority

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1 EXECUTIVE SUMMARY

This NDA seeks approval of DURYSTA™ (referred to by the investigational name as Bimatoprost SR) for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Bimatoprost SR is a biodegradable, sustained-release, preservative-free bimatoprost implant (using the NOVADUR® drug delivery system [DDS®]) that is preloaded into a single-use applicator for administration into the anterior chamber (AC). The implant is designed to provide a (b) (4) sustained release of bimatoprost to the AC of the eye (b) (4) for the reduction of IOP. The biodegradable polymer matrix of Bimatoprost SR slowly degrades so that there is no need to remove the implant once the drug has been released. The components of the implant are the bimatoprost drug substance and polymers poly (D,Llactide), poly (D,L-lactide-co-glycolide), and polyethylene glycol. The drug substance, bimatoprost, was originally developed by Allergan and approved as LUMIGAN® ophthalmic solution (NDA 21-275 and NDA 22-184) for topical administration for the same indication.

The efficacy of Durysta was evaluated in two identically designed pivotal clinical trials: 192024-091 (also referred to as Study 091), and 192024-092 (also referred to as Study 092). Both studies were multicenter, randomized, masked, parallel-group, repeat-administration studies that evaluate the IOP-lowering efficacy and safety of 2 dose strengths of Bimatoprost SR (10 µg and 15 µg) versus control topical IOP-lowering treatment with timolol 0.5%, in patients with OAG or OHT. Retreatment were performed at 16-week intervals (a total of 3 administrations) to maintain. The active comparator timolol 0.5% was agreed upon by the clinical team at the design stage of both studies.

For both studies, the primary efficacy endpoint was the study eye IOP at Hours 0 and 2 at Weeks 2, 6, and 12. All Hour 0 IOP examinations were scheduled at 0800 ± 1 hour; and Hour 2 IOP examinations occurred 2 hours after the Hour 0 IOP exam. The protocol-defined success criteria for non-inferiority of each dose of Bimatoprost SR to timolol was that the upper limit of the 95% CIs around the difference in mean IOP values (Bimatoprost SR - timolol) was less than 1.5 mmHg at all six time points for Weeks 2, 6, and 12. Since the mean IOP changes from baseline may potentially form the basis for label claims and the efficacy conclusions are the same based on the results of these endpoints as those based on the primary efficacy endpoint, this statistical review also presents the results of mean IOP changes from baseline.

In Study 091, IOP reductions were observed in all three groups; mean IOP reduction from baseline ranged from 6.5 to 7.5 mmHg in the Bimatoprost SR 15 µg group, from 6.4 to 7.6 mmHg in the Bimatoprost SR 10 µg group, and from 6.1 to 6.8 mmHg in the timolol group. Both doses of Bimatoprost SR demonstrated non-inferiority to the active comparator timolol. The treatment differences between Bimatoprost SR 15 µg and timolol groups ranged from -0.4 mmHg to -1.0 mmHg; and met the non-inferiority criteria at all the six time points – the upper bounds of the 95% CIs for the difference in mean IOP values (Bimatoprost SR - timolol) were less than 1.5 mmHg. The treatment differences between Bimatoprost SR 10 µg and timolol groups ranged from -0.2 mmHg to -0.9 mmHg; also met the non-inferiority criteria at all the six time points.

In Study 092, IOP reductions were observed in all three groups; mean IOP reduction from baseline ranged from 6.6 to 7.6 mmHg in the Bimatoprost SR 15 µg group, from 6.3 to 7.8 mmHg in the Bimatoprost SR 10 µg group, and from 6.1 to 6.9 mmHg in the timolol group. Both doses of Bimatoprost SR demonstrated non-inferiority to the active comparator timolol. The treatment differences between Bimatoprost SR 15 µg and timolol groups ranged from -0.3 mmHg to -0.8 mmHg; and met the non-inferiority criteria at all the six time points. The treatment differences between Bimatoprost SR 10 µg and timolol groups ranged from -0.3 mmHg to -0.9 mmHg; and met the non-inferiority criteria at all the six time points.

In conclusion, the two pivotal studies demonstrated that both doses of Bimatoprost SR were efficacious in reducing elevated intraocular pressure.

There were more ocular related treatment emergent adverse events (TEAEs) leading to study drug discontinuation or regimen change in the Bimatoprost SR 15 µg group (7.8% [15/193] in Study 091 and 4.0% [7/176] in Study 092) than in the Bimatoprost SR 10 µg group (3.6% [7/197] in Study 091 and 1.1% [2/175] in Study 092) or in the timolol group (2.0% [4/197] in Study 091 and 1.2% [2/173] in Study 092). While subjects in Bimatoprost SR 10 µg group had similar mean IOP reduction as subjects in Bimatoprost SR 15 µg group, the ocular TEAEs leading to study drug discontinuation or regimen change in Bimatoprost SR 10 µg group were lower comparing with the in Bimatoprost SR 15 µg group and were slightly higher comparing with timolol. Therefore, the statistical reviewer recommends the approval of Bimatoprost SR 10 µg for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

Table 1: Study 091 and Study 092 Mean IOP and Mean IOP Change from Baseline (CFB) by Visit and Time

	Hour	Variable	BimSR 15µg (mmHG)	BimSR 10µg (mmHG)	Tim BID (mmHG)	BimSR 15µg vs. Tim BID Differences (95% CI)[1]	BimSR 10µg vs. Tim BID Differences (95% CI)[1]
Study 091							
			N=198	**N=198**	**N=198**		
Baseline	**0**	IOP	24.76	24.64	24.63	0.13 (-0.41, 0.68)	0.02 (-0.51, 0.54)
	2	IOP	23.55	23.29	23.19	0.36 (-0.24, 0.96)	0.10 (-0.50, 0.69)
Week 2	**0**	IOP	16.83	17.02	17.82	-0.99 (-1.66, -0.32)	-0.80 (-1.47, -0.13)
		CFB	-7.16	-6.97	-6.17		
	2	IOP	16.46	16.42	17.33	-0.86 (-1.47, -0.26)	-0.90 (-1.50, -0.31)
		CFB	-7.53	-7.57	-6.66		
Week 6	**0**	IOP	17.09	16.87	17.71	-0.61 (-1.25, 0.02)	-0.84 (-1.47, -0.21)
		CFB	-6.90	-7.12	-6.29		
	2	IOP	16.63	16.51	17.16	-0.54 (-1.16, 0.09)	-0.66 (-1.27, -0.04)
		CFB	-7.36	-7.48	-6.83		
Week 12	**0**	IOP	17.53	17.61	17.94	-0.41 (-1.17, 0.36)	-0.33 (-1.09, 0.43)
		CFB	-6.46	-6.38	-6.05		
	2	IOP	16.81	17.30	17.51	-0.70 (-1.40, -0.01)	-0.21 (-0.90, 0.47)
		CFB	-7.18	-6.69	-6.48		
Study 092							
			N=176	**N=176**	**N=176**		
Baseline	**0**	IOP	24.39	24.28	24.46	-0.07 (-0.59, 0.45)	-0.18 (-0.70, 0.34)
	2	IOP	23.41	23.24	23.43	-0.02 (-0.64, 0.59)	-0.19 (-0.81, 0.42)

Week 2	**0**	IOP	17.08	17.11	17.88	-0.80 (-1.48, -0.12)	-0.77 (-1.46, -0.09)
		CFB	-7.60	-7.57	-6.80		
	2	IOP	16.38	16.18	17.07	-0.69 (-1.30, -0.08)	-0.89 (-1.50, -0.28)
		CFB	-6.96	-7.16	-6.27		
Week 6	**0**	IOP	17.30	16.93	17.82	-0.51 (-1.18, 0.15)	-0.88 (-1.55, -0.22)
		CFB	-7.37	-7.75	-6.86		
	2	IOP	16.51	16.22	16.89	-0.38 (-1.01, 0.24)	-0.66 (-1.29, -0.04)
		CFB	-6.84	-7.12	-6.45		
Week 12	**0**	IOP	17.77	17.69	18.11	-0.34 (-1.11, 0.43)	-0.42 (-1.19, 0.35)
		CFB	-6.91	-6.98	-6.56		
	2	IOP	16.72	17.02	17.22	-0.50 (-1.20, 0.20)	-0.29 (-0.90, 0.50)
		CFB	-6.62	-6.32	-6.12		

CI = Confidence Interval

[1] Based on a mixed-effects model with repeated measures (MMRM) including IOP as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used in the MMRM model.

Source: Tables 11-2 and 11-3 of Study 091 Report; and Tables 11-2 and 11-3 of Study 092 Report.

Table 2: Summary of Ocular TEAEs Leading to Study Drug Discontinuation or Regimen Change for Study 091 and Study 092 (Safety Population)

	System Organ Class	BimSR 15µg n/N (%)	BimSR 10µg n/N (%)	Timolol n/N (%)
Study 091	**Ocular TEAEs**	15/193 (7.8)	7/197 (3.6)	4/197 (2.0)
Study 092	**Ocular TEAEs**	7/176 (4.0)	2/175 (1.1)	2/173 (1.2)

Source: Table 12-13 of Study 091 Report and Table 12-13 of Study 092 Report.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Glaucoma is a complicated disease that damages the eye's optic nerve, which is vital to good vision. If left untreated, the damage to the optic nerve will lead to progressive, irreversible vision loss, and eventually blindness. Primary open-angle glaucoma (POAG) is the most common form of glaucoma. Of the several causes for glaucoma, elevated intraocular pressure (IOP) is the most important risk factor in most glaucoma. Therefore, reducing IOP is crucial in managing disease progression in patients with POAG or OHT.

The drug substance of Bimatoprost SR, bimatoprost, was originally developed by the applicant and approved as LUMIGAN® ophthalmic solution (NDA 21-275 and NDA 22-184) for topical administration for the same indication. The investigational product Bimatoprost SR is sustained-release formulation of bimatoprost developed by the applicant (Allergan) to provide an ocular antihypertensive therapy that does not require daily patient self-administration.

The Bimatoprost SR implant is injected into the anterior chamber (AC) through clear cornea adjacent to the corneal limbus using the prefilled applicator. The biodegradable polymer matrix gradually degrades to carbon dioxide and water so that there is no need to remove the implant once the drug has been released. The applicant stated that the Bimatoprost SR implant used the pivotal clinical studies contains total preservative-free bimatoprost loads of 10 µg or 15 µg, providing a sustained release (as determined by in vitro studies) of bimatoprost over an approximate 3-month duration in the AC.

2.1.2 History of Drug Development

The applicant conducted all clinical studies for DURYSTA under IND 108324.

On May 13, 2014, the applicant requested for a special protocol assessment (SPA) for the clinical protocol entitled "*A Randomized, Multicenter, Parallel Group, 20-month Safety and Efficacy Study of Bimatoprost SR in Patients with Open-angle Glaucoma or Ocular hypertension*." In response to the applicant proposed primary efficacy analysis method using mixed effects model repeated measures (MMRM) approach, the statistical review team stated (excerpt taken from the SPA letter to the applicant):

> "*The mixed effects model repeated measures (MMRM) approach for the primary efficacy analysis is acceptable in principle. However, you need to specify the variance-covariance structure for the proposed model. In addition, please provide the SAS pseudo-codes for your primary efficacy analyses in your final protocol/statistical analysis plan."*

On June 6, 2016, the applicant submitted the statistical analysis plan for Study 091 (note: Study 092 was designed identically as Study 091). In this submission, the applicant specified that unstructured covariance matrix would be used for repeated measures on the same patient. The pseudo-SAS codes for the primary efficacy analysis was also included. Therefore, the statistical review team had no further comments for the proposed primary efficacy analysis.

2.1.3 Studies Reviewed

The efficacy of Durysta was evaluated in two identically designed pivotal Phase 3 clinical trials: Studies 192024-091 (also referred to as Study 091) and 192024-092 (also referred to as Study 092). Both studies had 3 treatment arms (Bimatoprost SR 15 µg, Bimatoprost SR 10 µg, and timolol BID).

Table 3: Summary of Efficacy Studies to be assessed in the Statistical Review

Study No	Design	Objective	Treatment Groups Randomized/Completed Cycle 1	Study Population
192024-091	Multi-center, randomized,	to evaluate the IOP-lowering efficacy and safety of two dose strengths (10 µg and 15 µg) of Bimatoprost SR in	Bimatoprost SR 10 µg / 197 Bimatoprost SR 15 µg / 193	Adult subjects with OAG or OHT in both eyes

	double-masked, parallel group, active-control 3-arm	patients with OAG or OHT after initial and repeated administrations.	Timolol / 197	
192024-092	Multi-center, randomized, double-masked, parallel group, active-control 3-arm	to evaluate the IOP-lowering efficacy and safety of two dose strengths (10 µg and 15 µg) of Bimatoprost SR in patients with OAG or OHT after initial and repeated administrations.	Bimatoprost SR 10 µg / 175 Bimatoprost SR 15 µg / 176 Timolol / 173	Adult subjects with OAG or OHT in both eyes

Source: Statistical Reviewer's Summary.

2.2 Data Sources

The data sources for this review mainly came from the applicant's study reports for studies 091, and 092. The study reports are available at the following locations:
\\cdsesub1\evsprod\NDA211911\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\glaucoma\5351-stud-rep-contr\192024-091
\\cdsesub1\evsprod\NDA211911\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\glaucoma\5351-stud-rep-contr\192024-092

The applicant submitted SAS datasets electronically; the datasets for the three studies are available respectively at:
\\cdsesub1\evsprod\NDA211911\0001\m5\datasets\192024-091
\\cdsesub1\evsprod\NDA211911\0001\m5\datasets\192024-092

The SAS program codes that were used to generate the results in the study reports are available respectively at:
\\cdsesub1\evsprod\NDA211911\0001\m5\datasets\192024-091\analysis\adam\programs
\\cdsesub1\evsprod\NDA211911\0001\m5\datasets\192024-092\analysis\adam\programs

The IOP assessments were included in the "adeff.xpt" dataset with variable names "AVAL" for IOP readings and "CHG" for IOP change from baseline. The treatment variable, given both as numeric (TRT01PN) and character (TRT01P), was also included in both the above datasets. The adverse events were included in the "adae.xpt" dataset.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were of good quality with definitions provided for each variable. Results of the primary and secondary efficacy endpoints can be reproduced by the statistical reviewer with minor data manipulation. The statistical reviewer's analyses were primarily based

on the analysis datasets. The final statistical analysis plans (SAPs) for the two pivotal studies were submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The two pivotal efficacy studies Study 091, and Study 092 were identically designed Phase 3 studies. Both studies were randomized, multi-center, active controlled, parallel-group, patient- and efficacy evaluator-masked, 20-month evaluation (52-week active treatment period with 8 months extended follow-up) of the safety and efficacy of Bimatoprost SR compared to timolol twice daily in adult patients with OAG or OHT. Due to the administration route difference between Bimatoprost SR and timolol, the site coordinator and designated staff were not masked to whether the patient received Bimatoprost SR or the Sham administration, but they were masked to the specific Bimatoprost SR dose strength that the patient receives. Furthermore, the patients and the evaluators of the primary endpoint (IOP) were masked to the treatment received.

Patients who were treated with IOP-lowering medication(s) in either eye at the time of Screening were required to washout of these medication(s) following completion of the screening procedures. The washout period was up to 42 days depending on the minimum washout required for each class of IOP-lowering medication as shown in the schedule below.

Table 4: Minimum Washout Period by Ophthalmic Medication Class

Ophthalmic Medications	Minimum Washout Period
Parasympathomimetics (eg, PILAGAN®, Carbachol, Pilocar®)	4 days
Carbonic anhydrase inhibitors (topical or systemic) (eg, Diamox, Trusopt®, Azopt®)	4 days
Sympathomimetics (eg, PROPINE®, Epifrin®)	14 days
Alpha-agonists (eg, ALPHAGAN® P, Iopidine®)	14 days
Beta-adrenergic blocking agents (eg, Timoptic®, BETAGAN®, Betoptic®, Betoptic-S®, Opti-Pranolol®, Ocupress®, Timoptic XE®)	28 days
Prostamides, prostaglandins, and PGAs, as well as combination products that include these medications (eg, LUMIGAN, Xalatan®, Travatan®, Rescula®, GANFORT®)	28 days
Combination therapy (eg, COMBIGAN® [28 days], Cosopt® [28 days], Simbrinza® [14 days])	Longest minimum duration of any component based on medication class

Source: Table 9-2 of Study 091 Report.

After washout, subjects were required to meet minimum IOP criteria while off ocular hypotensive medication at Baseline visit. The IOP enrollment requirement was based on the following entry criteria. Please also see Appendix 1 for key inclusion and exclusion criteria.

Table 5: IOP Entry Criteria (Studies 091, and 092)

Study Eye	Follow Eye
≥ 22 mmHg and ≤ 32 mmHg at 8:00 h ≥ 19 mmHg and ≤ 32 mmHg at 10:00 h	≤ 32 mmHg at 8:00 h ≤ 32 mmHg at 10:00 h

Source: Protocol for Studies 091 and 092.

Two Bimatoprost SR dose strengths (10 µg and 15 µg) were tested in this study. For patients in the Bimatoprost 10 µg and 15 µg groups, the study eye received an initial administration of Bimatoprost SR on Treatment Day 1, a second administration of Bimatoprost SR at 16 weeks following the first administration, and a third administration at 16 weeks following the second administration (i.e., 32 weeks after the initial administration). Vehicle eye drops were used twice daily to mask the treatment of patients receiving Bimatoprost SR in the study eye. The fellow eye also received Sham administrations on the administration visit days, plus topical timolol eye drops twice daily throughout the study. Control group patients received Sham administrations plus timolol in both eyes throughout the study. The following table presents the different treatment groups.

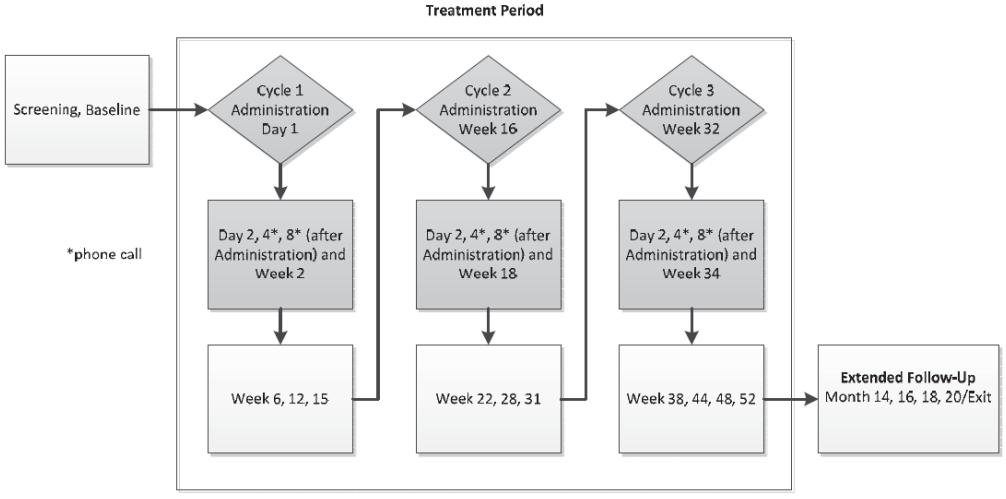
Table 6: Treatment Groups

Treatment	Study Eye Treatment	Fellow Eye Treatment
Bimatoprost SR 10 µg	Dose strength: 10 µg Eye drops: Vehicle BID	Sham administration procedure Eye drops: Timolol BID
Bimatoprost SR 15 µg	Dose strength: 15 µg Eye drops: Vehicle BID	Sham administration procedure Eye drops: Timolol BID
Control	Sham administration procedure Eye drops: Timolol BID	Sham administration procedure Eye drops: Timolol BID

Source: Table 9-1 of Study 091 Report.

Patients began self-administration of the study-provided eye drops in both eyes starting with the evening dose on the first Bimatoprost SR administration (Day 1) visit (at which they received Bimatoprost SR administration and/or Sham administration in each eye). Patients continued self-administration of study-provided eye drops in the morning (at 0800 ± 1 hour) and in the evening (at 2000 ± 1 hour) daily, approximately 12 hours apart. Patients administered their drops on the morning of a study visit; rather, drops were administered at the study site immediately after the Hour 0 IOP measurement. The study schema is illustrated in the following figure.

Figure 1: Study Schema



Source: Figure 9-1 of Study 091 Report.

After the start of study treatment on Day 1, all subjects had office visits at Week 2, Week 6, and Week 12, and Week 15 for safety and efficacy evaluation. At Weeks 16 and 32, patients were re-administered the Bimatoprost SR dose strength and/or Sham to which they were randomized, unless in the investigator's opinion it would not be in the best interest of the patient to re-administer Bimatoprost SR based on previous AEs or safety concerns.

The total duration of the study for each patient was approximately 22 months (screening duration of up to 28 days before washout, plus washout of up to 42 days before Baseline (of up to 3 days), followed by the first administration, the 52-week treatment period with two more Bimatoprost SR or Sham administration at Week 16 and 32, plus 8 months follow-up period. Please also refer to Appendix 1 for the schedule of assessments for both studies.

Table 7: Study Duration and Visits (Studies 091 and 092)

Baseline	IOP Assessment for Treatment Cycle 1	IOP Assessment for Treatment Cycle 2	IOP Assessment for Treatment Cycle 3	Extended Follow-up
Qualification (08:00, 10:00 h)	Day 1: at least one hour after the administration procedure Day 2 (08:00, 10:00 h) Week 2, 6, 12, and 15 (± 4 days) (08:00, 10:00 h)	Week 16 (-2 to + 4 days) Bimatoprost SR re-administration day: at least one hour after the administration procedure Week 16 + 1 day (08:00, 10:00 h) Week 18, 22, 28, and 31 (± 4 days) (08:00, 10:00 h)	Week 32 (-2 to + 4 days) Bimatoprost SR re-administration day: at least one hour after the administration procedure Week 32 + 1 day (08:00, 10:00 h) Week 34, 38, 44, and 48 (± 4 days) (08:00, 10:00 h) Week 52 (± 7 days) (08:00, 10:00 h)	Month 14 (± 14 days) (8:00, 10:00 h) Month 16 (± 14 days) (8:00, 10:00 h) Month 18 (± 14 days) (8:00, 10:00 h) Month 20/Exit (± 14 days) (8:00, 10:00 h)

Source: Protocol for Study 091; and Protocol for Study 092.

The applicant planned to follow patients who had received non-study IOP-lowering medication in only one eye for the duration of the study through the Month 20 visit. In addition, patients who have received non-study IOP-lowering medication in both eyes, or who do not complete an Administration Day visit, may discontinue the study 12 months after the last Bimatoprost SR or Sham administration at which time they should complete the Month 20/Exit visit procedures.

For both studies, the primary efficacy endpoint was the study eye IOP at each hour evaluated (Hours 0 and 2) at Weeks 2, 6, and 12. All Hour 0 IOP examinations were scheduled at 0800 ± 1 hour. As scheduling permitted, the patient had approximately the same Hour 0 time of day throughout the study. Hour 2 IOP examinations occurred 2 hours after the Hour 0 IOP exam.

The sample size estimations of both studies were based on the following assumptions:

- 0.05 two-sided level of significance for t-test at each of the 6 time points
- Standard deviation of 4.0 mmHg

- Treatment difference between Bimatoprost SR 10 µg and timolol is -0.25 mmHg and a common within-subject correlation of 0.6
- The IOP lowering effect of Bimatoprost SR 15 µg is better than that of Bimatoprost SR 10 µg by 0.25 mmHg
- 95% power to conclude non-inferiority of Bimatoprost SR 15 µg to timolol
- 81% power to conclude non-inferiority of Bimatoprost SR 10 µg to timolol

Based on the above assumption, the estimated sample size was approximately 180 subjects per arm (540 subjects total). Assuming a premature discontinuation rate of 10% within 12 weeks (before primary database lock), approximately 600 patients (200 per group) were planned to be enrolled into both studies.

3.2.2 Statistical Methodologies

For both studies, the null and alternative hypotheses for the comparison between a given Bimatoprost SR dose strength and timolol for each hour at each visit were:

- Null Hypothesis: the difference in mean IOP between the given Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) is > 1.5 mm Hg VS.
- Alternative Hypothesis: the difference in mean IOP between the given Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) is ≤ 1.5 mm Hg

A study would be considered a success if both H_{01} and H_{02} are rejected.

The protocol-defined success criteria for non-inferiority of each dose of Bimatoprost SR to timolol required that the upper limit of the 95% CIs around the difference in mean IOP values (Bimatoprost SR - timolol) was within 1.5 mmHg at all time points for Weeks 2, 6, and 12.

For both studies, there were three different analysis populations (also known as analysis sets) defined by the applicant:

- **Intent-to-Treat (ITT) population**, which included all randomized subjects. The ITT population was analyzed as randomized and the primary efficacy analyses of both studies were based on the ITT population.
- **Per-Protocol (PP) Population,** which was a subset of the ITT population who had the primary efficacy variable measured. IOP measures deemed being influenced by other medications would be excluded from PP analysis. The PP population was used to confirm the primary efficacy analyses.
- **Safety Population**, which included all randomized subjects who received at least one dose of study treatment. The safety population was analyzed as treated and used for the safety analyses.

The primary analysis of the primary outcome was based on a mixed-effects model with repeated measures (MMRM). The model included IOP time-matched change from baseline as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and

timepoint-by-baseline time-matched IOP interaction. Unstructured covariance matrix was used for repeated measures on the same patient. Within the framework of this model, the mean difference between each Bimatoprost SR dose strength and timolol (Bimatoprost SR minus timolol) and the corresponding 2-sided 95% confidence interval (CI) were calculated for each hour (Hours 0 and 2) at each visit. According to the applicant, to avoid confounding of efficacy data, IOP values obtained after initiating the use of non-study IOP-lowering medication or procedure in an eye were excluded from the calculation of the summary statistics and the statistical analyses for that eye, but raw values were presented in the listings.

A gatekeeping procedure were used to control the overall type I error rate at the 0.05 level. Bimatoprost SR 15 μg were tested against timolol first at each timepoint (Hours 0 and 2 at Weeks 2, 6, and 12) and then followed by the comparison between Bimatoprost SR 10 μg and timolol. The test for Bimatoprost SR 10 μg versus timolol for a given hour at a visit is valid only if the noninferiority of Bimatoprost SR 15 μg to timolol has been demonstrated for the given timepoint.

To evaluate the robustness of the primary analysis results, the applicant conducted various supportive analyses of the primary efficacy variables:

- PP population analysis – The analysis outlined for the primary efficacy analysis was repeated on the PP population.
- Time-matched LOCF analysis: Missing values were imputed by time-matched LOCF. At each visit/hour, the treatment difference and its 95% CI were based on least square means by using an ANCOVA model with IOP time-matched change from baseline as the response variable, treatment as a factor, and time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate.
- Multiple imputation implementation before performing ANCOVA analysis: Step 1: Intermittent missing values at each hour of Week 2, 6, and 12 were first imputed by treatment group using the MCMC method (defined as the MCMC step), resulting in data with a monotone pattern. Step 2: Multiple imputation by treatment group using linear regression with factors of demographics and baseline characteristics including but not limited to race group, sex, and lens status; and age, baseline IOP values at both Hour 0 and Hour 2 as covariates (defined as the regression step) was applied to the data obtained from the MCMC step. Step 2 immediately followed Step 1 and the entire procedure was repeated 25 times.

The statistical review also presented the results of analyzing mean IOP changes from baseline using the baseline IOP as covariate for the following reasons:

(1) At the subject level, the mean IOP change from baseline can be derived from the mean IOP and vice versa.
(2) At the population level, the treatment differences are the same for both endpoints.
(3) The 95% confidence intervals for the treatment differences are the same for both endpoints if the confidence intervals are obtained based on the covariate adjustment for baseline IOP.
(4) In Studies 091 and 092, the 95% confidence intervals for the treatment differences are similar for both endpoints regardless of the analysis methods.
(5) The mean IOP changes from baseline may form the basis for desired label claims.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Both studies are still ongoing, and not all patients have completed all cycles and/or the extended follow-up period. Study completers were defined as patients who received at least 1 administration and completed the extended safety follow-up visits. Entering a treatment cycle was defined as receiving the corresponding administration of that treatment cycle, and a completer of a treatment cycle was defined as a patient in a cycle who had either received the following cycle of administration or completed the safety follow-up visits (marked as "complete" in eCRF study exit form). The statistical review will focus on the efficacy results of Cycle 1 as the study reports for both studies were based on the available primary lock data collected through the date that the last patient enrolled completed the Month 3 (Week 12) visit (all the data up to February 19th, 2018).

3.2.3.1 Study 091

Five hundred and ninety-four (594) subjects were enrolled into the study, 198 patients in each treatment group. Among these 594 subjects, 587 (98.8%) received any dose of study treatment. Five patients (1 screen failure, 1 lost to follow-up, 1 due to personal reasons, 1 due to protocol deviation, 1 due to other reason [withdrawn due to randomization error]) in the Bimatoprost SR 15µg group, 1 patient (screen failure) in the Bimatoprost SR 10µg group, and 1 patient (screen failure) in the timolol group did not receive study treatment.

At the time of the database cutoff for the Week 12 primary analysis, 37.7% (224/594) of patients overall had completed the study and 11.8% (70/594) of patients had discontinued from the study. The most common reasons for discontinuing from the study were AEs (3.4%, 20 patients overall) and personal reasons (3.2%, 19 patients overall). Of the 20 patients who discontinued from the study due to AEs, 10 patients discontinued due to ocular AEs and due to non-ocular AEs. The remaining 50.5% (300) of patients are still ongoing in the study.

Of the 587 patients who entered Cycle 1, 91.7% (538) of patients completed Cycle 1 and 4.3% (25) of patients discontinued during Cycle 1. The most common reason for discontinuation during Cycle 1 was personal reasons (8 patients). Of the 5 patients who discontinued during Cycle 1 due to AEs, 3 were in the Bimatoprost SR 15 µg group (2 discontinued due to an ocular AE and 1 due to a non-ocular AE) and 2 were in the Bimatoprost SR 10 µg group (1 discontinued due to an ocular AE and 1 due to a non-ocular AE).

Of the 536 patients who entered Cycle 2, 81.9% (439) of patients completed Cycle 2 and 3.9% (21) of patients discontinued during Cycle 2. The most common reason for discontinuation during Cycle 2 was an AE. Of the 10 patients who discontinued during Cycle 2 due to AEs, 4 were in the Bimatoprost SR 15 µg group (3 discontinued due to an ocular AE and 1 due to a nonocular AE), 3 were in the Bimatoprost SR 10 µg group (all discontinued due to ocular AEs), and 3 were in the timolol group (1 discontinued due to an ocular AE and 2 due to non-ocular AEs).

Of the 438 patients who entered Cycle 3, 50.5% (221) of patients completed Cycle 3 and 3.9% (17) of patients discontinued during Cycle 3. The most common reasons for discontinuation during Cycle 3 were AE (5 patients), personal reasons (6 patients), and other (5 patients). Of the 5 patients who discontinued during Cycle 3 due to AEs, 2 were in the Bimatoprost SR 15 µg group (both discontinued due to a non-ocular AEs) and 3 were in the timolol group (all discontinued due to non-ocular AEs).

Overall, more patients in the Bimatoprost SR 15µg group discontinued at each cycle comparing with patients in both the Bimatoprost SR 10µg group and the placebo group.

Table 8: Study 091 Summary of Subjects' Disposition (ITT)

	BimSR 15 µg N=198 n (%)	**BimSR 10 µg N=198 n (%)**	**Tim BID N=198 n (%)**	**Overall N=594 n (%)**
Number of Subjects Randomized	198 (100)	198 (100)	198 (100)	594 (100)
Number of Subjects Treated	193 (97.5)	197 (99.5)	197 (99.5)	587 (98.8)
Number of Subjects Entered Cycle 1 [1]	193 (97.5)	197 (99.5)	197 (99.5)	587 (98.8)
Completed Cycle 1[2]	169 (87.6)	187 (94.9)	182 (92.4)	538 (91.7)
Discontinued During Cycle 1	12 (6.2)	5 (2.5)	8 (4.1)	25 (4.3)
Reasons for Discontinuation				
Adverse Events	3 (1.6)	2 (1.0)	0	5 (0.9)
Ocular	2 (1.0)	1 (0.5)	0	3 (0.5)
Non-Ocular	1 (0.5)	1 (0.5)	0	2 (0.3)
Lack of Efficacy	1 (0.5)	1 (0.5)	2 (1.0)	4 (0.7)
Lost to Follow-up	1 (0.5)	0	2 (1.0)	3 (0.5)
Personal Reasons	5 (2.6)	1 (0.5)	2 (1.0)	8 (1.4)
Protocol Deviation	0	0	1 (0.5)	1 (0.2)
Other	2 (1.0)	1 (0.5)	1 (0.5)	4 (0.7)
Number of Subjects Entered Cycle 2 [1]	169 (85.4)	186 (93.9)	181 (91.4)	536 (90.2)
Completed Cycle 2 [2]	137 (81.1)	155 (83.3)	147 (81.2)	439 (81.9)
Discontinued During Cycle 2	8 (4.7)	5 (2.7)	8 (4.4)	21 (3.9)
Reasons for Discontinuation				
Adverse Events	4 (2.4)	3 (1.6)	3 (1.7)	10 (1.9)
Ocular	3 (1.8)	3 (1.6)	1 (0.6)	7 (1.3)
Non-Ocular	1 (0.6)	0	2 (1.1)	3 (0.6)
Lack of Efficacy	1 (0.6)	0	1 (0.6)	2 (0.4)
Lost to Follow-up	0	1 (0.5)	1 (0.6)	2 (0.4)
Personal Reasons	2 (1.2)	1 (0.5)	1 (0.6)	4 (0.7)
Other	1 (0.6)	0	2 (1.1)	3 (0.6)
Number of Subjects Entered Cycle 3 [1]	136 (68.7)	155 (78.3)	147 (74.2)	438 (73.7)
Completed Cycle 3 [2]	71 (52.2)	80 (51.6)	70 (47.6)	221 (50.5)
Discontinued During Cycle 3	7 (5.1)	4 (2.6)	6 (4.1)	17 (3.9)
Reasons for Discontinuation				
Adverse Events	2 (1.5)	0	3 (2.0)	5 (1.1)
Ocular	0	0	0	0
Non-Ocular	2 (1.5)	0	3 (2.0)	5 (1.1)
Lost to Follow-up	0	1 (0.6)	0	1 (0.2)

Personal Reasons	3 (2.2)	1 (0.6)	2 (1.4)	6 (1.4)
Other	2 (1.5)	2 (1.3)	1 (0.7)	5 (1.1)
Number of Subjects Completed Study *	72 (36.4)	81 (40.9)	71 (35.9)	224 (37.7)
Number of Subjects Discontinued Study	32 (16.2)	15 (7.6)	23 (11.6)	70 (11.8)
Reasons for Discontinuation				
Screen Failure	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
Adverse Events	9 (4.5)	5 (2.5)	6 (3.0)	20 (3.4)
Ocular	5 (2.5)	4 (2.0)	1 (0.5)	10 (1.7)
Non-Ocular	4 (2.0)	1 (0.5)	5 (2.5)	10 (1.7)
Lack of Efficacy	2 (1.0)	1 (0.5)	3 (1.5)	6 (1.0)
Lost to Follow-up	2 (1.0)	2 (1.0)	3 (1.5)	7 (1.2)
Personal Reasons	11 (5.6)	3 (1.5)	5 (2.5)	10 (1.7)
Protocol Deviation	1 (0.5)	0	1 (0.5)	2 (0.3)
Other	6 (3.0)	3 (1.5)	4 (2.0)	13 (2.2)

[1] A participant is considered to have entered a cycle if the participant has received the corresponding injection for that cycle.
[2] The completers for each cycle are participants who received injection in the relevant cycle and completed the cycle by either receiving the following injection or completing the extended safety follow-up visits within the cycle.
* This is an ongoing study, and not all patients have completed all cycles and/or the extended follow-up period. Study completers are participants who received at least 1 injection and completed the extended safety follow-up visits.
Completion and discontinuation rates for each cycle were calculated based on the number of participants who entered each cycle.
Source: Table 10-1 of Study 091 Report.

A total of 594 patients (198 patients in each treatment group) were enrolled; all were included in the ITT population. The PP population consisted of the subset of patients in the ITT population who had received the randomized treatment in the study eye, with study eye baseline hour 0 IOP ≥ 20 mm Hg and at least one IOP measurement from the six primary efficacy timepoints. In the PP population, there were 192 patients in the Bimatoprost SR 15µg group, 197 patients in the Bimatoprost SR 10µg group, and 196 patients in the timolol group; a total of 9 patients were excluded from the PP population. The safety population consisted of all patients who received at least 1 dose of study treatment and included 193 patients in the Bimatoprost SR 15µg group, 197 patients in the Bimatoprost SR 10µg group, and 197 patients in the timolol group.

Table 9: Study 091 Summary of Study Population

	BimSR 15 µg N=198 n (%)	**BimSR 10 µg N=198 n (%)**	**Tim BID N=198 n (%)**	**Overall N=594 n (%)**
ITT	198	198	198	594
PP	192 (97.0)	197 (99.5)	196 (99.0)	585 (98.5)
Safety	193 (97.5)	197 (99.5)	197 (99.5)	587 (98.8)

Source: Table 10-2 of Study 091 Report.

As presented in the following table, in general, demographic and baseline characteristics were comparable among the treatment groups.

Table 10: Study 091 Demographic and Baseline Characteristics (ITT)

Characteristics	**BimSR 15 µg N=198**	**BimSR 10 µg N=198**	**Tim BID N=198**	**Overall N=594**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Study Eye Diagnosis				

Characteristics	BimSR 15 µg N=198	BimSR 10 µg N=198	Tim BID N=198	Overall N=594
	n (%)	n (%)	n (%)	n (%)
Ocular Hypertension (OHT)	41 (20.7)	35 (17.7)	41 (20.7)	117 (19.7)
Open Angle Glaucoma (OAG)	157 (79.3)	163 (82.3)	157 (79.3)	477 (80.3)
Primary	153 (77.3)	159 (80.3)	152 (76.8)	464 (78.1)
Pseudoexfoliation	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
Pigmentary	3 (1.5)	3 (1.5)	4 (2.0)	10 (1.7)
Gender				
Male	102 (51.5)	112 (56.6)	92 (46.5)	306 (51.5)
Female	96 (48.5)	86 (43.4)	106 (53.5)	288 (48.5)
Age				
Mean (Std)	62.5 (13.0)	62.6 (11.5)	62.5 (11.0)	62.5 (11.9)
Min, Max	25, 92	23, 88	24, 88	23, 92
Median	64.0	64.0	64.0	64.0
< 45	17 (8.6)	12 (6.1)	11 (5.6)	40 (6.7)
≥ 45 and ≤ 65	88 (44.4)	102 (51.5)	109 (55.1)	299 (50.3)
> 65	93 (47.0)	84 (42.4)	78 (39.4)	255 (42.9)
Race				
Asian	12 (6.1)	17 (8.6)	16 (8.1)	45 (7.6)
Black/African American	30 (15.2)	31 (15.7)	21 (10.6)	82 (13.8)
Hispanic	27 (13.6)	23 (11.6)	25 (12.6)	75 (12.6)
White	122 (61.6)	123 (62.1)	130 (65.7)	375 (63.1)
Other	6 (3.0)	4 (2.0)	5 (2.5)	15 (2.5)
Not Reported	1 (0.5)	0	1 (0.5)	2 (0.3)
Iris Color of Study Eye				
Blue/Grey/Green	52 (26.3)	49 (24.7)	60 (30.3)	161 (27.1)
Brown/Black	135 (68.2)	129 (65.2)	122 (61.6)	386 (65.0)
Hazel	8 (4.0)	11 (5.6)	13 (65.7)	32 (5.4)
Other	3 (1.5)	9 (4.5)	3 (1.5)	15 (2.5)
Hour 0 IOP				
≤ 25 mmHg	135 (68.2)	132 (66.7)	136 (68.7)	403 (67.8)
> 25 mmHg	63 (31.8)	66 (33.3)	62 (31.3)	191 (32.2)
Prior Hypotensive Therapy				
Prior IOP-Lowering Therapy	168 (84.8)	164 (82.8)	179 (90.4)	511 (86.0)
No Prior IOP-Lowering Therapy	30 (15.2)	34 (17.2)	19 (9.6)	83 (14.0)

Source: Tables 10-3 and 10-4 of Study 091 report.

3.2.3.2 Study 092

Five hundred and twenty-eight (528) subjects were enrolled into the study, 176 patients in each treatment group. Among these 528 subjects, 524 (99.2%) received any dose of study treatment. One patient (screen failure) in the Bimatoprost SR 10µg group and 3 patients (2 screen failures and 1 discontinued due to personal reasons) in the timolol group did not receive study treatment.

At the time of the database cutoff for the Week 12 primary analysis, 42.4% (224/528) of patients overall had completed the study and 8.5% (45/528) of patients have discontinued from the study. The most common reasons for discontinuing from the study were personal reasons (3.4%, 18 patients overall) and AEs (2.3%, 12 patients overall). Of the 12 patients who discontinued from the study due to AEs, 10 were due to ocular AEs and 2 were due to non-ocular AEs. The remaining 49.1% (259) of patients are still ongoing in the study

Of the 524 patients who entered Cycle 1, 87.6% (459) of patients completed Cycle 1 and 2.7% (14) of patients discontinued during Cycle 1. The most common reasons for discontinuation during Cycle 1 were personal reasons (7 patients) and AEs (4 patients). Of the 4 patients who discontinued during Cycle 1 due to AEs, 2 were in the Bimatoprost SR 10µg group (1 discontinued due to an ocular AE and 1 due to a non-ocular AE) and 2 were in the timolol group (both discontinued due to ocular AEs).

Of the 457 patients who entered Cycle 2, 86.4% (395) of patients completed Cycle 2 and 3.9% (18) of patients discontinued during Cycle 2. The most common reasons for discontinuation during Cycle 2 were personal reasons (7 patients) and AEs (5 patients). Of the 5 patients who discontinued during Cycle 2 due to AEs, 4 were in the Bimatoprost SR 15µg group and 1 was in the Bimatoprost SR 10µg group (all were discontinued due to ocular AEs).

Of the 388 patients who entered Cycle 3, 55.4% (215) of patients completed Cycle 3 and 2.3% (9) of patients discontinued during Cycle 3. The most common reasons for discontinuation during Cycle 3 were personal reasons (3 patients) and AEs (3 patients). Of the 3 patients who discontinued during Cycle 3 due to AEs, 1 was in the Bimatoprost SR 15µg group (discontinued due to an ocular AE), 1 was in the Bimatoprost SR 10µg group (discontinued due to a non-ocular AE), and 1 was in the timolol group (discontinued due to an ocular AE).

Table 11: Study 092 Summary of Subjects' Disposition

	BimSR 15 µg N=176 n (%)	**BimSR 10 µg N=176 n (%)**	**Tim BID N=176 n (%)**	**Overall N=528 n (%)**
Number of Subjects Randomized	176 (100)	176 (100)	176 (100)	528 (100)
Number of Subjects Treated	176 (100)	175 (99.4)	173 (98.3)	524 (99.2)
Number of Subjects Entered Cycle 1 [1]	176 (100)	175 (99.4)	173 (98.3)	524 (99.2)
Completed Cycle 1[2]	153 (86.9)	155 (88.6)	151 (87.3)	459 (87.6)
Discontinued During Cycle 1	2 (1.1)	5 (2.9)	7 (4.0)	14 (2.7)
Reasons for Discontinuation				
Adverse Events	0	2 (1.1)	2 (1.2)	4 (0.8)
Ocular	0	1 (0.6)	2 (1.2)	3 (0.6)
Non-Ocular	0	1 (0.6)	0	1 (0.2)
Lack of Efficacy	0	0	0	0
Lost to Follow-up	0	0	0	0
Personal Reasons	0	3 (1.7)	4 (2.3)	7 (1.3)
Protocol Deviation	1 (0.6)	0	0	1 (0.2)
Other	1 (0.6)	0	1 (0.6)	2 (0.4)
Number of Subjects Entered Cycle 2 [1]	151 (85.8)	155 (88.1)	151 (85.8)	457 (86.6)

Completed Cycle 2 [2]	129 (85.4)	134 (86.5)	132 (87.4)	395 (86.4)
Discontinued During Cycle 2	7 (4.6)	6 (3.9)	5 (3.3)	18 (3.9)
Reasons for Discontinuation				
Adverse Events	4 (2.6)	1 (0.6)	0	5 (1.1)
Ocular	4 (2.6)	1 (0.6)	0	5 (1.1)
Non-Ocular	0	0	0	0
Lost to Follow-up	0	0	3 (2.0)	3 (0.7)
Personal Reasons	2 (1.3)	3 (1.9)	2 (1.3)	7 (1.5)
Protocol Deviation	0	2 (1.3)	0	2 (0.4)
Other	1 (0.7)	0	0	1 (0.2)
Number of Subjects Entered Cycle 3 [1]	124 (70.5)	133 (75.6)	131 (74.4)	388 (73.5)
Completed Cycle 3 [2]	68 (54.8)	76 (57.1)	71 (54.2)	215 (55.4)
Discontinued During Cycle 3	5 (4.0)	1 (0.8)	3 (2.3)	9 (2.3)
Reasons for Discontinuation				
Adverse Events	1 (0.8)	1 (0.8)	1 (0.8)	3 (0.8)
Ocular	1 (0.8)	0	1 (0.8)	2 (0.5)
Non-Ocular	0	1 (0.8)	0	1 (0.3)
Lost to Follow-up	1 (0.8)	0	1 (0.8)	2 (0.5)
Personal Reasons	2 (1.6)	0	1 (0.8)	3 (0.8)
Other	1 (0.8)	0	0	1 (0.3)
Number of Subjects Completed Study *	75 (42.6)	77 (43.8)	72 (40.9)	224 (42.4)
Number of Subjects Discontinued Study	14 (8.0)	13 (7.4)	18 (10.2)	45 (8.5)
Reasons for Discontinuation				
Screen Failure	0	1 (0.6)	2 (1.1)	3 (0.6)
Adverse Events	5 (2.8)	4 (2.3)	3 (1.7)	12 (2.3)
Ocular	5 (2.8)	2 (1.1)	3 (1.7)	10 (1.9)
Non-Ocular	0	2 (1.1)	0	2 (0.4)
Lost to Follow-up	1 (0.6)	0	4 (2.3)	5 (0.9)
Personal Reasons	4 (2.3)	6 (3.4)	8 (4.5)	18 (3.4)
Protocol Deviation	1 (0.6)	2 (1.1)	0	3 (0.6)
Other	3 (1.7)	0	1 (0.6)	4 (0.8)

Source: Table 10-1 of Study 092 Report.

All 528 randomized subjects were included in the ITT population. The PP population consisted of the subset of patients in the ITT population who had received the randomized treatment in the study eye, with study eye baseline Hour 0 IOP ≥ 20 mm Hg and at least 1 IOP measurement from the six primary efficacy timepoints. In the PP population, there were 174 patients in the Bimatoprost SR 15 µg group, 173 patients in the Bimatoprost SR 10 µg group, and 171 patients in the timolol group; a total of 10 patients were excluded from the PP population. The safety population consisted of all patients who received at least 1 dose of study treatment and included 176 patients in the Bimatoprost SR 15 µg group, 175 patients in the Bimatoprost SR 10 µg group, and 173 patients in the timolol group.

Table 12: Study 092 Summary of Study Population

	BimSR 15 µg N=176 n (%)	**BimSR 10 µg N=176 n (%)**	**Tim BID N=176 n (%)**	**Overall N=528 n (%)**

ITT	176 (100)	176 (100)	176 (100)	528 (100)
PP	174 (98.9)	173 (98.3)	171 (97.2)	518 (98.1)
Safety	176 (100)	175 (99.4)	173 (98.3)	524 (99.2)

Source: Table 10-2 of Study 092 Report.

As presented in the following table, demographic and baseline characteristics were comparable among the treatment groups.

Table 13: Study 092 Demographic and Baseline Characteristics (ITT)

Characteristics	BimSR 15 µg N=176	BimSR 10 µg N=176	Tim BID N=176	Overall N=528
	n (%)	n (%)	n (%)	n (%)
Study Eye Diagnosis				
Ocular Hypertension (OHT)	49 (27.8)	41 (23.3)	45 (25.6)	135 (25.6)
Open Angle Glaucoma (OAG)	127 (72.2)	135 (76.7)	131 (74.4)	393 (74.4)
Primary	118 (67.0)	131 (74.4)	125 (71.0)	374 (70.8)
Pseudoexfoliation	2 (1.1)	1 (0.6)	2 (1.1)	5 (0.9)
Pigmentary	7 (4.0)	3 (1.7)	4 (2.3)	14 (2.7)
Gender				
Male	85 (48.3)	86 (48.9)	88 (50.0)	259 (49.1)
Female	91 (51.7)	90 (51.1)	88 (50.0)	269 (50.9)
Age				
Mean (Std)	63.8 (10.7)	62.5 (12.7)	61.4 (12.4)	62.6 (12.0)
Min, Max	24, 85	23, 88	19, 90	19, 90
Median	65.0	63.5	62.0	63.0
< 45	8 (4.5)	15 (8.5)	16 (9.1)	39 (7.4)
≥ 45 and ≤ 65	86 (48.9)	81 (46.0)	94 (53.4)	261 (49.4)
> 65	82 (46.6)	80 (45.5)	66 (37.5)	228 (43.2)
Race				
Asian	6 (3.4)	11 (6.3)	13 (7.4)	30 (5.7)
Black/African American	19 (10.8)	20 (11.4)	36 (20.5)	75 (14.2)
Hispanic	27 (15.3)	22 (12.5)	21 (11.9)	70 (13.3)
White	116 (65.9)	115 (65.3)	104 (59.1)	335 (63.4)
Other	8 (4.5)	8 (4.5)	2 (1.1)	18 (3.4)
Iris Color of Study Eye				
Blue/Grey/Green	42 (23.9)	43 (24.4)	37 (21.0)	122 (23.1)
Brown/Black	123 (69.9)	118 (67.0)	125 (71.0)	366 (69.3)
Hazel	6 (3.4)	7 (4.0)	9 (5.1)	22 (4.2)
Other	3 (1.7)	7 (4.0)	3 (1.7)	13 (2.5)
Hour 0 IOP				
≤ 25 mmHg	130 (73.9)	132 (75.0)	130 (73.9)	392 (74.2)
> 25 mmHg	46 (26.1)	44 (25.0)	45 (25.6)	135 (25.6)
Prior Hypotensive Therapy				
Prior IOP-Lowering Therapy	139 (79.0)	150 (85.2)	139 (79.0)	428 (81.7)
No Prior IOP-Lowering Therapy	37 (21.0)	26 (14.8)	37 (21.0)	100 (18.3)

Source: Tables 10-3 and 10-4 of Study 092 report.

3.2.4 Results and Conclusions

3.2.4.1 Study 091

The three treatment groups had comparable mean baseline IOP. The mean baseline IOP was in the range of 23.2 to 24.8 mmHg for the three treatment groups. From Week 2 to Week 12 of the Cycle 1 treatment period, mean IOP over time ranged from 16.4 to 17.6 mmHg for study eyes treated with Bimatoprost SR 15µg, 16.1 to 17.6 mmHg for Bimatoprost SR 10µg, and 16.7 to 17.9 mmHg for timolol across all 6 primary efficacy time points. At Week 15, mean IOP were 19.3, and 18.3 mmHg at Hour 0 and 2 respectively for study eyes treated with Bimatoprost SR 15µg; 18.9 and 18.0 mmHg for Bimatoprost SR 10µg; 17.8 and 17.1 mmHg for timolol.

IOP reductions were observed in all three groups starting from Week 2:

- From Week 2 to Week 12, mean IOP reduction from baseline ranged from 7.1 to 7.9 mmHg in the Bimatoprost SR 15µg, from 6.3 to 7.6 mmHg in the Bimatoprost SR 10µg, and from 6.1 to 6.8 mmHg in the timolol group. The observed mean IOP change from baseline in the Bimatoprost SR 15µg treatment group were slightly better than those in the Bimatoprost SR 10µg and in the timolol group.
- By Week 15, when the drug substance in the Bimatoprost SR implant had completely released, mean IOP reduction in both Bimatoprost SR 15µg and Bimatoprost SR 10µg groups was slightly less than the timolol group. Mean IOP reduction were -5.5, and -5.4 mmHg at Hour 0 and 2 respectively for study eyes treated with Bimatoprost SR 15µg; -5.6 and -5.3 mmHg for Bimatoprost SR 10µg; -6.7 and -6.0 mmHg for timolol.

The observed mean IOP and mean IOP change from baseline over time at each time point at presented in the following table and figure.

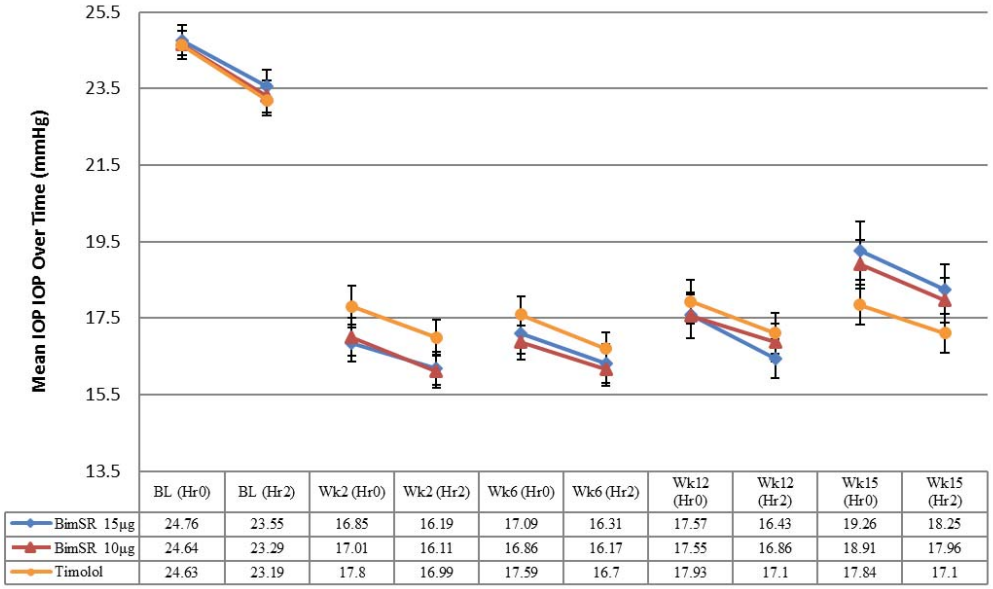
Table 14: Study 091 Mean IOP and Mean IOP Change from Baseline (CFB) over Time (ITT Observed)

	Hour		BimSR 15 µg N=198		BimSR 10 µg N=198		Tim BID N=198	
			n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	**0**	**IOP**	197	24.76 (2.85)	198	24.64 (2.67)	198	24.63 (2.63)
		CFB		n/a		n/a		n/a
	2	**IOP**	197	23.55 (3.13)	198	23.29 (3.09)	198	23.19 (2.93)
		CFB		n/a		n/a		n/a
Week 2	**0**	**IOP**	190	16.58 (3.36)	196	17.01 (3.58)	196	17.80 (3.86)
		CFB		-7.92 (3.52)		-7.63 (3.56)		-6.84 (3.51)
	2	**IOP**	190	16.19 (3.09)	196	16.11 (3.06)	196	16.99 (3.41)
		CFB		-7.36 (3.51)		-7.20 (3.70)		-6.24 (3.51)
Week 6	**0**	**IOP**	187	17.09 (3.59)	197	16.86 (3.23)	194	17.59 (3.43)
		CFB		-7.66 (3.57)		-7.77 (3.21)		-6.99 (3.44)
	2	**IOP**	187	16.31 (3.53)	197	16.17 (3.20)	193	16.70 (3.10)
		CFB		-7.23 (3.90)		-7.12 (3.42)		-6.40 (3.43)
Week 12	**0**	**IOP**	185	17.57 (4.15)	192	17.55(4.07)	191	17.93 (4.08)
		CFB		-7.19 (3.84)		-7.01 (3.63)		-6.69 (3.98)
	2	**IOP**	183	16.43 (3.50)	192	16.86 (3.52)	191	17.10 (3.71)
		CFB		-7.11 (3.70)		-6.33 (3.92)		-6.05 (4.00)

Week 15	**0**	**IOP**	176	19.26 (5.22)	186	18.91 (4.39)	182	17.84 (3.60)
		CFB		-5.47 (4.56)		-5.64 (3.97)		-6.67 (3.68)
	2	**IOP**	175	18.25 (4.34)	186	17.96 (4.09)	181	17.10 (3.49)
		CFB		-5.38 (4.11)		-5.27 (4.25)		-6.01 (3.89)

Source: Table 14.2-3.1 of Study 091 Report.

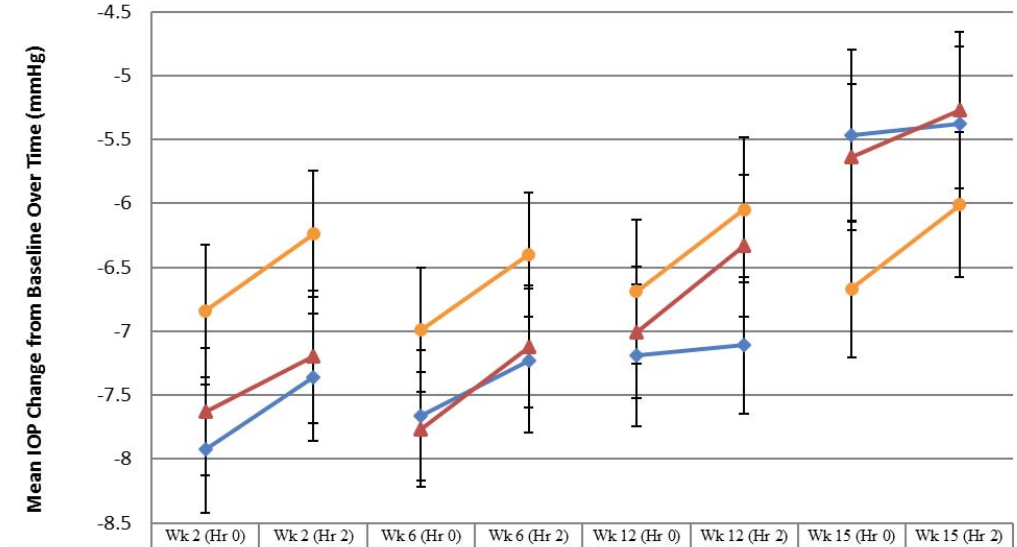
Figure 2: Study 091 Mean IOP over Time (ITT Observed)



	BL (Hr0)	BL (Hr2)	Wk2 (Hr0)	Wk2 (Hr2)	Wk6 (Hr0)	Wk6 (Hr2)	Wk12 (Hr0)	Wk12 (Hr2)	Wk15 (Hr0)	Wk15 (Hr2)
BimSR 15µg	24.76	23.55	16.85	16.19	17.09	16.31	17.57	16.43	19.26	18.25
BimSR 10µg	24.64	23.29	17.01	16.11	16.86	16.17	17.55	16.86	18.91	17.96
Timolol	24.63	23.19	17.8	16.99	17.59	16.7	17.93	17.1	17.84	17.1

* BL: Baseline; Hr: Hour; Wk: Week.
Source: Statistical Reviewer's graph based on Table 14.2-3.1 of Study 091 Report.

Figure 3: Study 091 Mean IOP Change from Baseline Over Time (ITT Observed)



	Wk 2 (Hr 0)	Wk 2 (Hr 2)	Wk 6 (Hr 0)	Wk 6 (Hr 2)	Wk 12 (Hr 0)	Wk 12 (Hr 2)	Wk 15 (Hr 0)	Wk 15 (Hr 2)
BimSR 15µg	-7.92	-7.36	-7.66	-7.23	-7.19	-7.11	-5.47	-5.38
BimSR 10µg	-7.63	-7.2	-7.77	-7.12	-7.01	-6.33	-5.64	-5.27
Timolol	-6.84	-6.24	-6.99	-6.4	-6.69	-6.05	-6.67	-6.01

* Hr: Hour; Wk: Week.
Source: Statistical Reviewer's graph based on Table 14.2-3.1 of Study 091 Report.

As demonstrated in the following table, both mean IOP and mean IOP change from baseline in the Bimatoprost SR 15µg group were similar to those in the timolol group; and the treatment differences met the pre-defined non-inferiority margin for all six time points – the upper limit of the 95% CIs of the treatment difference (Bimatoprost SR - timolol) was within 1.5 mmHg at all six time points for Weeks 2, 6, and 12. Mean IOP and mean IOP change from baseline in the Bimatoprost SR 10µg group were also similar to those in the timolol across the six time points up to Week 12; and these treatment differences met the pre-defined non-inferiority margin as well.

It is noted that by Week 15, timolol had higher IOP reduction effect compared with both Bimatoprost SR treatment groups at the two time points.

Table 15: Study 091 Results of Mixed-Effects Model with Repeated Measured (MMRM) for Mean IOP and Mean IOP Change from Baseline (mmHg) (CFB) by Visit and Time (ITT)

	Hour	Variable	BimSR 15µg N=198	BimSR 10µg N=198	Tim BID N=198	BimSR 15µg vs. Tim BID Differences (95% CI)[1]	BimSR 10µg vs. Tim BID Differences (95% CI)[1]
Baseline	**0**	IOP	24.76	24.64	24.63	0.13 (-0.41, 0.68)	0.02 (-0.51, 0.54)
	2	IOP	23.55	23.29	23.19	0.36 (-0.24, 0.96)	0.10 (-0.50, 0.69)
Week 2	**0**	IOP	16.83	17.02	17.82	-0.99 (-1.67, -0.32)	-0.80 (-1.47, -0.13)
		CFB	-7.16	-6.97	-6.17		
	2	IOP	16.46	16.42	17.33	-0.86 (-1.47, -0.26)	-0.90 (-1.50, -0.31)
		CFB	-7.53	-7.57	-6.66		
Week 6	**0**	IOP	17.09	16.87	17.71	-0.61 (-1.25, 0.02)	-0.84 (-1.47, -0.21)
		CFB	-6.90	-7.12	-6.29		
	2	IOP	16.63	16.51	17.16	-0.54 (-1.16, 0.09)	-0.66 (-1.27, -0.04)
		CFB	-7.36	-7.48	-6.83		
Week 12	**0**	IOP	17.53	17.61	17.94	-0.41 (-1.17, 0.36)	-0.33 (-1.09, 0.43)
		CFB	-6.46	-6.38	-6.05		
	2	IOP	16.81	17.30	17.51	-0.70 (-1.40, -0.01)	-0.21 (-0.90, 0.47)
		CFB	-7.18	-6.69	-6.48		
Week 15	**0**	IOP	19.21	19.07	18.02	1.19 (0.35, 2.03)	1.05 (0.22, 1.89)
		CFB	-4.77	-4.90	-5.96		
	2	IOP	18.59	18.54	17.67	0.92 (0.14, 1.70)	0.87 (0.10, 1.64)
		CFB	-5.40	-5.44	-6.32		

CI = Confidence Interval

[1] Based on a mixed-effects model with repeated measures (MMRM) including IOP as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used in the MMRM model.

Source: Tables 11-2 and 11-3 of Study 091 Report and Statistical Reviewer's Analysis for Week 15.

For the above primary efficacy analysis, a patient's IOP were treated as missing in efficacy analysis after initiation of non-study IOP lowering medications or procedure. The following table summarizes the cumulative number of patients in the ITT population by treatment group and visit within Cycle 1 who had the study eye IOP being treated as missing.

Table 16: Study 091 Summary of Patients with IOP Exclusion due to Use of Non-study IOP Lowering Medications or Procedures in Study Eye (ITT)

	BimSR 15 µg N=198 n (%)	BimSR 10 µg N=198 n (%)	Tim BID N=198 n (%)
Cycle 1 Week 2	3	0	1
Cycle 1 Week 6	4	0	2
Cycle 1 Week 12	5	2	2
Cycle 1 Week 15	7	5	5
By the end of Cycle 1	16	7	6

Source: Table 14.2-4.1 of Study 302 Report.

The applicant conducted sensitivity analysis for IOP at Weeks 2, 6, and 12 of Cycle 1 using ANCOVA model with LOCF Imputation for subjects who had missing observations. The results are presented in the following table.

Table 17: Study 091 Results of ANCOVA Model with LOCF Imputation for Missing Mean IOP and Mean IOP Change from Baseline (mmHg) (CFB) by Visit and Time (ITT)

	Hour	Variable	BimSR 15µg N=198	BimSR 10µg N=198	Tim BID N=198	BimSR 15µg vs. Tim BID Differences (95% CI)[1]	BimSR 10µg vs. Tim BID Differences (95% CI)[1]
Baseline	**0**	IOP	24.76	24.64	24.63	0.13 (-0.41, 0.68)	0.02 (-0.51, 0.54)
	2	IOP	23.55	23.29	23.19	0.36 (-0.24, 0.96)	0.10 (-0.50, 0.69)
Week 2	**0**	IOP	17.08	17.11	17.88	-0.80 (-1.48, -0.12)	-0.77 (-1.46, -0.09)
		CFB	-7.60	-7.57	-6.80	-0.80 (-1.48, -0.12)	-0.77 (-1.46, -0.09)
	2	IOP	16.38	16.18	17.07	-0.69 (-1.30, -0.08)	-0.89 (-1.50, -0.28)
		CFB	-6.96	-7.16	-6.27	-0.69 (-1.30, -0.08)	-0.89 (-1.50, -0.28)
Week 6	**0**	IOP	17.30	16.93	17.82	-0.51 (-1.18, 0.15)	-0.88 (-1.55, -0.22)
		CFB	-7.37	-7.75	-6.86	-0.51 (-1.18, 0.15)	-0.88 (-1.55, -0.22)
	2	IOP	16.51	16.22	16.89	-0.38 (-1.01, 0.24)	-0.66 (-1.29, -0.04)
		CFB	-6.84	-7.12	-6.45	-0.38 (-1.01, 0.24)	-0.66 (-1.29, -0.04)
Week 12	**0**	IOP	17.77	17.69	18.11	-0.34 (-1.11, 0.43)	-0.42 (-1.19, 0.35)
		CFB	-6.91	-6.98	-6.56	-0.34 (-1.11, 0.43)	-0.42 (-1.19, 0.35)
	2	IOP	16.72	17.02	17.22	-0.50 (-1.20, 0.20)	-0.29 (-0.90, 0.50)
		CFB	-6.62	-6.32	-6.12	-0.50 (-1.20, 0.20)	-0.29 (-0.90, 0.50)

Based on ANCOVA with IOP time-matched change from baseline as the response variable, treatment as a factor, and time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate. Estimated differences were based on least-squares means.
Source: Table 14.2-2.3 of Study 091 Report.

The statistical reviewer conducted sensitivity analysis for IOP at Weeks 2, 6, and 12 of Cycle 1 using ANCOVA model with baseline observations carried forward (BOCF) imputation for subjects who had missing observations. The analysis results are presented in the following table.

Table 18: Study 091 Results of ANCOVA Model with BOCF Imputation for Missing Mean IOP and Mean IOP Change from Baseline (mmHg) (CFB) by Visit and Time (ITT)

	Hour	Variable	BimSR 15µg N=198	BimSR 10µg N=198	Tim BID N=198	BimSR 15µg vs. Tim BID Differences (95% CI)[1]	BimSR 10µg vs. Tim BID Differences (95% CI)[1]
Baseline	**0**	IOP	24.76	24.64	24.63	0.13 (-0.41, 0.68)	0.02 (-0.51, 0.54)

	2	IOP	23.55	23.29	23.19	0.36 (-0.24, 0.96)	0.10 (-0.50, 0.69)
Week 2	**0**	IOP	17.08	17.11	17.88	-0.80 (-1.48, -0.12)	-0.77 (-1.46, -0.09)
		CFB	-7.60	-7.57	-6.80		
	2	IOP	16.37	16.18	17.07	-0.69 (-1.30, -0.08)	-0.89 (-1.50, -0.28)
		CFB	-6.96	-7.16	-6.27		
Week 6	**0**	IOP	17.44	16.93	17.80	-0.36 (-1.02, 0.30)	-0.87 (-1.53, -0.21)
		CFB	-7.23	-7.74	-6.87		
	2	IOP	16.62	16.23	17.02	-0.41 (-1.05, 0.24)	-0.79 (-1.44, -0.14)
		CFB	-6.70	-7.11	-6.33		
Week 12	**0**	IOP	17.95	17.87	18.21	-0.26 (-1.03, 0.51)	-0.34 (-1.11, 0.43)
		CFB	-6.73	-6.81	-6.47		
	2	IOP	16.85	17.17	17.42	-0.57 (-1.30, 0.15)	-0.25 (-0.98, 0.47)
		CFB	-6.49	-6.17	-5.92		

Based on ANCOVA with IOP time-matched change from baseline as the response variable, treatment as a factor, and time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate. Estimated differences were based on least-squares means.
Source: Statistical Reviewer's Analyses.

These supportive analyses conducted by the statistical reviewer and by the applicant yielded consistent results as the primary analysis.

3.2.4.2 Study 092

The three treatment groups had comparable mean baseline IOP. The mean baseline IOP was in the range of 23.2 to 24.8 mmHg for the three treatment groups. From Week 2 to Week 12 of the Cycle 1 treatment period, mean IOP over time ranged from 16.4 to 17.6 mmHg for study eyes treated with Bimatoprost SR 15µg, 16.1 to 17.6 mmHg for Bimatoprost SR 10µg, and 16.7 to 17.9 mmHg for timolol across all 6 time points. At Week 15, mean IOP over time were 18.5, and 17.9 mmHg at Hour 0 and 2 respectively for study eyes treated with Bimatoprost SR 15µg; 18.6 and 18.0 mmHg for Bimatoprost SR 10µg; 17.5 and 16.7 mmHg for timolol.

IOP reductions were observed in all three groups starting from Week 2:

- From Week 2 to Week 12, mean IOP reduction from baseline ranged from 7.1 to 7.9 mmHg in the Bimatoprost SR 15µg, from 6.3 to 7.6 mmHg in the Bimatoprost SR 10µg, and from 6.1 to 6.8 mmHg in the timolol group. The observed mean IOP change from baseline in the Bimatoprost SR 15µg treatment group were slightly better than those in the Bimatoprost SR 10µg and in the timolol group.
- By Week 15, about 3 weeks after the drug substance in the Bimatoprost SR implant had all released during the 3-month period after insertion, although there were still IOP reduction effects for both Bimatoprost SR groups, the mean IOP reduction in both Bimatoprost SR 15µg and Bimatoprost SR 10µg groups was slightly less than the timolol group. Mean IOP reduction were -6.0, and -5.5 mmHg at Hour 0 and 2 respectively for study eyes treated with Bimatoprost SR 15µg; -5.7 and -5.1 mmHg for Bimatoprost SR 10µg; -7.0 and -6.6 mmHg for timolol.

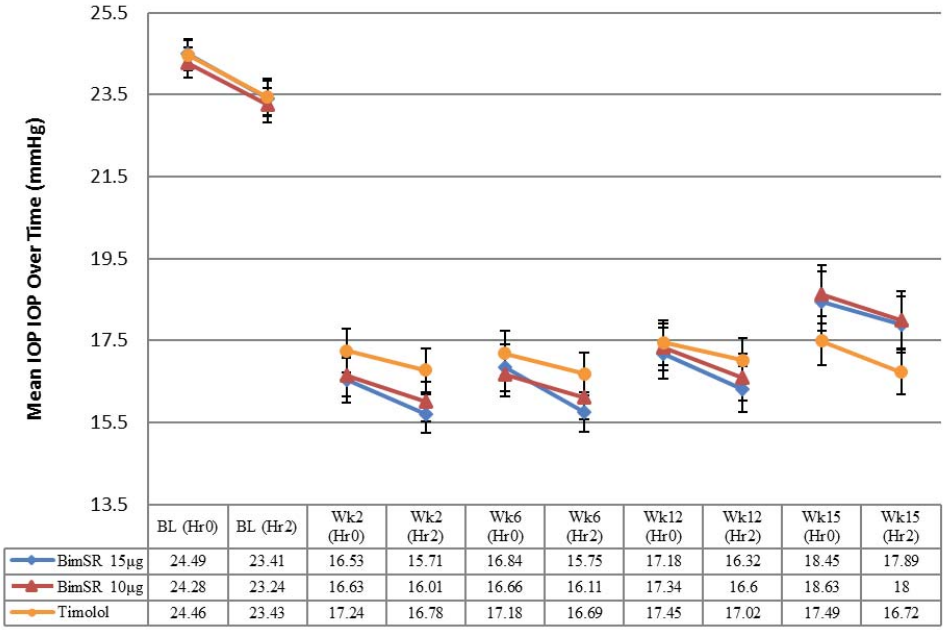
The observed mean IOP and mean IOP change from baseline over time at each time point at presented in the following table and figure.

Table 19: Study 092 Mean IOP and Mean IOP Change from Baseline (CFB) over Time (ITT Observed)

	Hour		BimSR 15 µg N=176		BimSR 10 µg N=176		Tim BID N=175	
			n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	**0**	**IOP**	176	24.39 (2.46)	176	24.28 (2.43)	175	24.46 (2.53)
		CFB		n/a		n/a		n/a
	2	**IOP**	176	23.41 (2.81)	175	23.24 (2.76)	175	23.43 (3.06)
		CFB		n/a		n/a		n/a
Week 2	**0**	**IOP**	170	16.53 (3.63)	172	16.63 (3.37)	172	17.24 (3.57)
		CFB		-7.88 (3.6)		-7.64 (3.71)		-7.17 (3.61)
	2	**IOP**	170	15.71 (3.16)	172	16.01 (3.20)	172	16.78 (3.56)
		CFB		-7.72 (3.26)		-7.25 (3.68)		-6.65 (3.82)
Week 6	**0**	**IOP**	171	16.84 (3.80)	171	16.66 (3.56)	168	17.18 (3.63)
		CFB		-7.58 (3.75)		-7.63 (3.63)		-7.26 (3.83)
	2	**IOP**	171	15.75 (3.26)	171	16.11 (3.60)	168	16.69 (3.44)
		CFB		-7.68 (3.75)		-7.63 (3.63)		-7.26 (3.83)
Week 12	**0**	**IOP**	168	17.18 (4.11)	169	17.34 (3.87)	166	17.45 (3.56)
		CFB		-7.21 (4.07)		-6.93 (3.99)		-6.99 (3.87)
	2	**IOP**	168	16.32 (3.68)	169	16.60 (3.76)	166	17.02 (3.46)
		CFB		-7.09 (3.82)		-6.59 (4.00)		-6.41 (4.17)
Week 15	**0**	**IOP**	153	18.45 (4.58)	152	18.63 (4.51)	149	17.49 (3.75)
		CFB		-5.96 (4.29)		-5.67 (4.23)		-6.95 (3.66)
	2	**IOP**	153	17.89 (4.33)	153	18.00 (4.35)	149	16.72 (3.41)
		CFB		-5.53 (4.26)		-5.10 (4.23)		-6.64 (3.87)

Source: Table 14.2-3.1 of Study 092 Report.

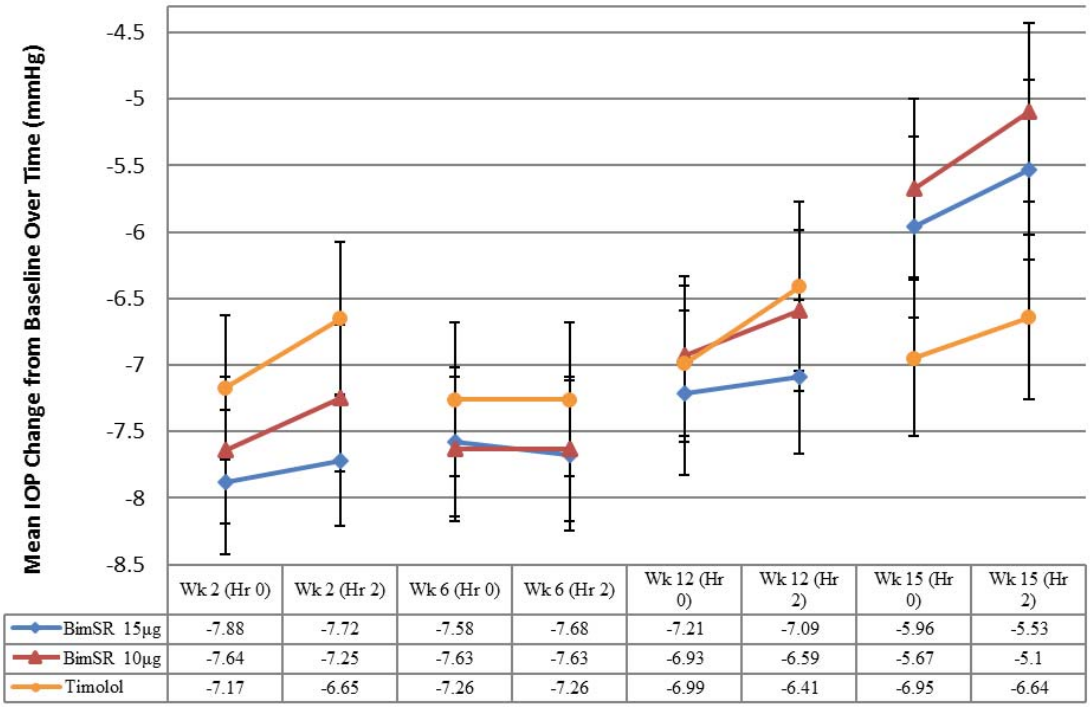
Figure 4: Study 092 Mean IOP over Time (ITT Observed)



	BL (Hr0)	BL (Hr2)	Wk2 (Hr0)	Wk2 (Hr2)	Wk6 (Hr0)	Wk6 (Hr2)	Wk12 (Hr0)	Wk12 (Hr2)	Wk15 (Hr0)	Wk15 (Hr2)
BimSR 15µg	24.49	23.41	16.53	15.71	16.84	15.75	17.18	16.32	18.45	17.89
BimSR 10µg	24.28	23.24	16.63	16.01	16.66	16.11	17.34	16.6	18.63	18
Timolol	24.46	23.43	17.24	16.78	17.18	16.69	17.45	17.02	17.49	16.72

* BL: Baseline; Hr: Hour; Wk: Week.
Source: Statistical Reviewer's graph based on Table 14.2-3.1 of Study 092 Report.

Figure 5: Study 092 Mean IOP Change from Baseline Over Time (ITT Observed)



	Wk 2 (Hr 0)	Wk 2 (Hr 2)	Wk 6 (Hr 0)	Wk 6 (Hr 2)	Wk 12 (Hr 0)	Wk 12 (Hr 2)	Wk 15 (Hr 0)	Wk 15 (Hr 2)
BimSR 15µg	-7.88	-7.72	-7.58	-7.68	-7.21	-7.09	-5.96	-5.53
BimSR 10µg	-7.64	-7.25	-7.63	-7.63	-6.93	-6.59	-5.67	-5.1
Timolol	-7.17	-6.65	-7.26	-7.26	-6.99	-6.41	-6.95	-6.64

* Hr: Hour; Wk: Week.
Source: Statistical Reviewer's graph based on Table 14.2-3.1 of Study 092 Report.

As demonstrated in the following table, both mean IOP and mean IOP change from baseline in the Bimatoprost SR 15µg group were similar to those in the timolol group; and the treatment differences met the pre-defined non-inferiority margin for all six time points – the upper limit of the 95% CIs of the treatment difference (Bimatoprost SR - timolol) was within 1.5 mmHg at all six time points for Weeks 2, 6, and 12. Mean IOP and mean IOP change from baseline in the Bimatoprost SR 10µg group were also similar to those in the timolol across the six time points up to Month 3; and these treatment differences met the pre-defined non-inferiority margin as well.

It is noted that by Week 15, timolol had higher IOP reduction effect compared with both Bimatoprost SR treatment groups at the two time points.

Table 20: Study 092 Results of Mixed-Effects Model with Repeated Measured (MMRM) for Mean IOP and Mean IOP Change from Baseline (mmHg) (CFB) by Visit and Time (ITT)

	Hour	Variable	BimSR 15µg N=176	BimSR 10µg N=176	Tim BID N=176	BimSR 15µg vs. Tim BID Differences (95% CI)[1]	BimSR 10µg vs. Tim BID Differences (95% CI)[1]
Baseline	**0**	IOP	24.39	24.28	24.46	-0.07 (-0.59, 0.45)	-0.18 (-0.70, 0.34)
	2	IOP	23.41	23.24	23.43	-0.02 (-0.64, 0.59)	-0.19 (-0.81, 0.42)
Week 2	**0**	IOP	16.73	16.92	17.50	-0.77 (-1.49, -0.05)	-0.58 (-12.9, 0.14)
		CFB	-7.13	-6.94	-6.36		
	2	IOP	16.08	16.48	17.19	-1.11 (-1.78, -0.44)	-0.71 (-1.38, -0.05)
		CFB	-7.78	-7.38	-6.67		

Week 6	**0**	IOP	17.04	16.93	17.52	-0.48 (-1.23, 0.28)	-0.59 (-1.34, 0.17)
		CFB	-6.82	-6.93	-6.34		
	2	IOP	16.11	16.53	17.18	-1.07 (-1.78, -0.36)	-0.65 (-1.36, 0.06)
		CFB	-7.75	-7.33	-6.68		
Week 12	**0**	IOP	17.38	17.68	17.76	-0.38 (-1.18, 0.43)	-0.08 (-0.88, 0.73)
		CFB	-6.48	-6.18	-6.10		
	2	IOP	16.69	17.15	17.49	-0.80 (-1.57, -0.03)	-0.34 (-1.11, 0.43)
		CFB	-7.17	-6.71	-6.37		
Week 15	**0**	IOP	18.48	18.86	17.81	0.67 (-0.22, 1.57)	1.05 (0.15, 1.94)
		CFB	-5.27	-4.99	-6.04		
	2	IOP	18.27	18.55	17.35	0.92 (0.06, 1.78)	1.20 (0.35, 2.06)
		CFB	-5.59	-5.30	-6.51		

CI = Confidence Interval

[1] Based on a mixed-effects model with repeated measures (MMRM) including IOP as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used in the MMRM model.

Source: Tables 11-2 and 11-3 of Study 092 Report and Statistical Reviewer's Analysis for Week 15.

For the above primary efficacy analysis, a patient's IOP were treated as missing in efficacy analysis after initiation of non-study IOP lowering medications or procedure. The following table summarizes the cumulative number of patients in the ITT population by treatment group and visit within Cycle 1 who had the study eye IOP being treated as missing.

Table 21: Study 092 Summary of Patients with IOP Exclusion due to Use of Non-study IOP Lowering Medications or Procedures in Study Eye (ITT)

	BimSR 15 µg N=176 n (%)	**BimSR 10 µg N=176 n (%)**	**Tim BID N=176 n (%)**
Cycle 1 Week 2	2	0	1
Cycle 1 Week 6	2	0	1
Cycle 1 Week 12	2	1	1
Cycle 1 Week 15	2	2	2
By the end of Cycle 1	7	3	2

Source: Table 14.2-4.1 of Study 092 Report.

The applicant conducted sensitivity analysis for IOP at Weeks 2, 6, and 12 of Cycle 1 using ANCOVA model with LOCF Imputation for subjects who had missing observations. The results are presented in the following table.

Table 22: Study 092 Results of ANCOVA Model with LOCF Imputation for Missing Mean IOP and Mean IOP Change from Baseline (mmHg) (CFB) by Visit and Time (ITT)

	Hour	**Variable**	**BimSR 15µg N=176**	**BimSR 10µg N=176**	**Tim BID N=176**	**BimSR 15µg vs. Tim BID Differences (95% CI)[1]**	**BimSR 10µg vs. Tim BID Differences (95% CI)[1]**
Baseline	**0**	IOP	24.39	24.28	24.46	-0.07 (-0.59, 0.45)	-0.18 (-0.70, 0.34)
	2	IOP	23.41	23.24	23.43	-0.02 (-0.64, 0.59)	-0.19 (-0.81, 0.42)
Week 2	**0**	IOP	16.77	16.85	17.41	-0.65 (-1.39, 0.10)	-0.56 (-1.31, 0.18)
		CFB	-7.61	-7.52	-6.96		
	2	IOP	15.94	16.20	16.91	-0.97 (-1.66, -0.28)	-0.71 (-1.40, -0.01)
		CFB	-7.42	-7.16	-6.46		

Week 6	**0**	IOP	16.97	16.82	17.42	-0.44 (-1.21, 0.32)	-0.60 (-13.6, 0.17)
		CFB	-7.40	-7.55	-6.96		
	2	IOP	15.88	16.23	16.95	-1.07 (-1.80, -0.33)	-0.71 (-1.45, 0.02)
		CFB	-7.48	-7.13	-6.42		
Week 12	**0**	IOP	17.26	17.52	17.67	-0.41 (-1.21, 0.40)	-0.15 (-0.95, 0.66)
		CFB	-7.00	-6.50	-7.00		
	2	IOP	16.38	16.78	17.22	-0.84 (-1.61, -0.06)	-0.44 (-1.21, 0.34)
		CFB	-6.98	-6.58	-6.15		

Based on ANCOVA with IOP time-matched change from baseline as the response variable, treatment as a factor, and time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate. Estimated differences were based on least-squares means.
Source: Table 14.2-2.3 of Study 092 Report.

The statistical reviewer conducted sensitivity analysis for IOP at Weeks 2, 6, and 12 of Cycle 1 using ANCOVA model with baseline observations carried forward (BOCF) imputation for subjects who had missing observations. The analysis results are presented in the following table.

Table 23: Study 092 Results of ANCOVA Model with BOCF Imputation for Missing Mean IOP and Mean IOP Change from Baseline (mmHg) (CFB) by Visit and Time (ITT)

	Hour	**Variable**	**BimSR 15µg N=176**	**BimSR 10µg N=176**	**Tim BID N=176**	**BimSR 15µg vs. Tim BID Differences (95% CI)[1]**	**BimSR 10µg vs. Tim BID Differences (95% CI)[1]**
Baseline	**0**	IOP	24.39	24.28	24.46	-0.07 (-0.59, 0.45)	-0.18 (-0.70, 0.34)
	2	IOP	23.41	23.24	23.43	-0.02 (-0.64, 0.59)	-0.19 (-0.81, 0.42)
Week 2	**0**	IOP	16.77	16.85	17.41	-0.65 (-1.39, 0.10)	-0.56 (-1.31, 0.18)
		CFB	-7.61	-7.52	-6.96		
	2	IOP	15.94	16.20	16.91	-0.97 (-1.66, -0.28)	-0.71 (-1.40, -0.01)
		CFB	-7.42	-7.16	-6.46		
Week 6	**0**	IOP	17.02	16.91	17.49	-0.47 (-1.25, 0.30)	-0.58 (-1.36, 0.19)
		CFB	-7.35	-7.47	-6.88		
	2	IOP	15.93	16.34	16.99	-1.06 (-1.80, -0.32)	-0.65 (-1.39, 0.09)
		CFB	-7.43	-7.02	-6.37		
Week 12	**0**	IOP	17.50	17.67	17.83	-0.32 (-1.15, 0.50)	-0.16 (-0.98, 0.67)
		CFB	-6.87	-6.70	-6.55		
	2	IOP	16.62	16.96	17.36	-0.74 (-1.53, 0.05)	-0.40 (-1.19, 0.39)
		CFB	-6.74	-6.40	-6.00		

Based on ANCOVA with IOP time-matched change from baseline as the response variable, treatment as a factor, and time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate. Estimated differences were based on least-squares means.
Source: Statistical Reviewer's Analysis.

These supportive analyses conducted by the statistical reviewer and by the applicant yielded consistent results as the primary analysis.

(b) (4)

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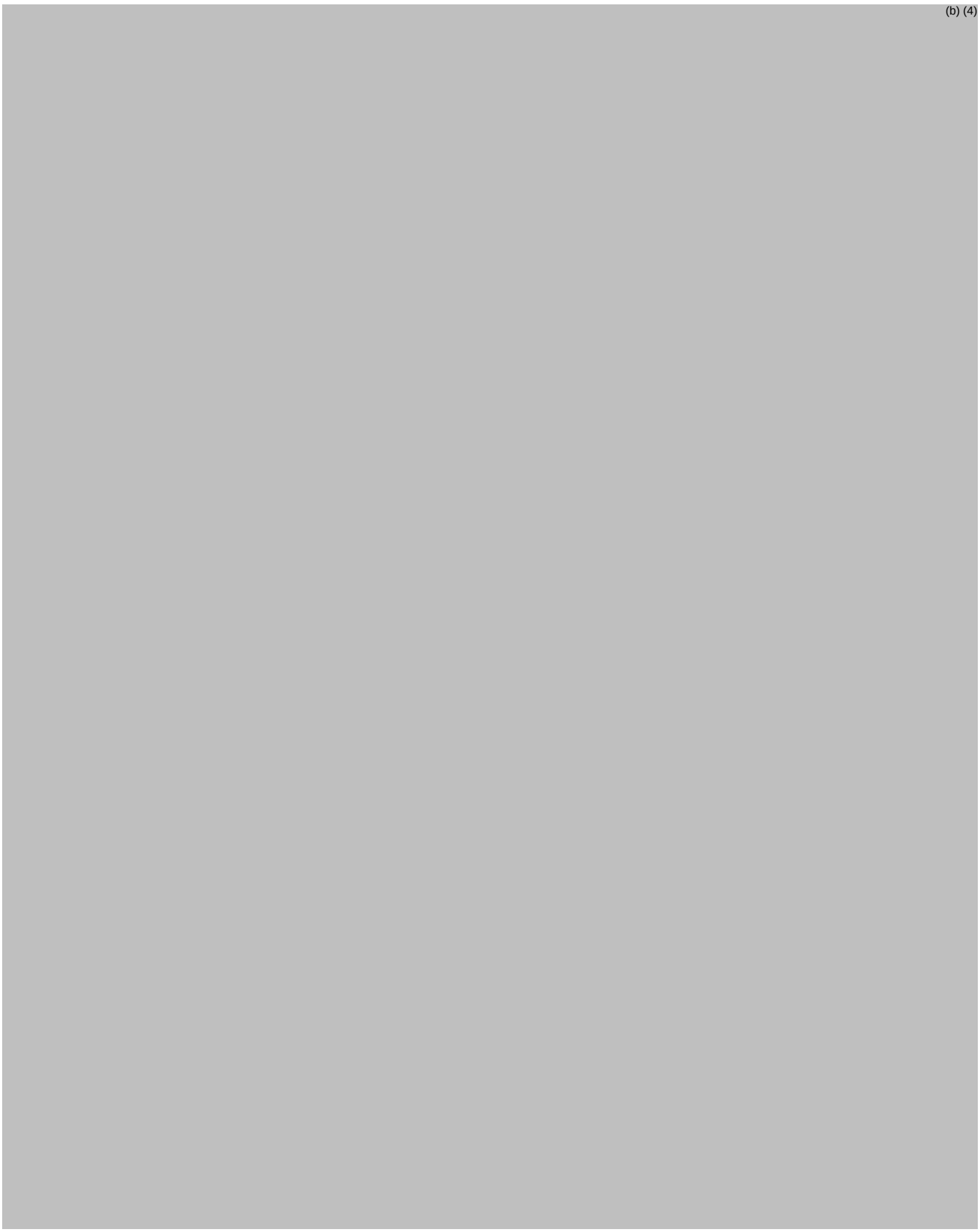
3.2.4.4 Time to Non-study IOP-lowering Medication or Procedure

The applicant also conducted exploratory analysis for time to non-study IOP medication or procedure. Patients in the timolol group continued to receive topical timolol twice daily; the time to non-study IOP-lowering treatments was evaluated with Bimatoprost SR based on the time from the third/last Sham administration.

The time to non-study IOP lowering medication or procedure after the 3rd injection was defined as the days from the 3rd injection date to the start day of the 1st time use of non-study IOP lowering medication or procedure in the study eye. However, the applicant didn't define clearly the criteria for using of non-study IOP lowering medication or procedure; it appeared to be at the treating investigator's discretion. The Kaplan-Meier curves for both studies are presented in the following figure.



study IOP lowering medication, the statistical reviewer considers this analysis exploratory in nature.

3.2.4.5 Conclusion

In conclusion, the two pivotal studies 091 and 092 demonstrated that both Bimatoprost SR treatment groups were efficacious in reducing elevated intraocular pressure. However, by the end of 4 months after the insertion of Bimatoprost SR implant, when the drug substance in the implant had all released, although there were still IOP reduction effects for both Bimatoprost SR groups, the mean IOP reduction in Bimatoprost SR 15µg and Bimatoprost SR 10µg groups was slightly less than the timolol group.

3.3 Evaluation of Safety

For each of the two studies (091 and 092), more subjects in Bimatoprost SR groups (15 µg and 10 µg) had AEs than subjects in the timolol group. The higher Bimatoprost SR dose group (15 µg) had most of the AEs among all three treatment groups; while the Bimatoprost SR 10 µg group had slightly less AEs than the 15 µg group but more than the timolol group. For both studies, the most common TEAEs were in the Eye Disorders SOC and included conjunctival hyperemia, conjunctival hemorrhage, corneal endothelial cell loss, eye irritation, eye pain, photophobia, and foreign body sensation in eyes.

Table 28: Study 091 Safety Analysis: Adverse Events Associated with ≥ 5.0% of Subjects in Any Treatment Group by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	BimSR 15µg N=198 n (%)	BimSR 10µg N=198 n (%)	Timolol N=198 n (%)
Congenital, familial and genetic disorders	5 (2.6)	0	2 (1.0)
Corneal dystrophy	5 (2.6)	0	1 (0.5)
Eye Disorders	135 (69.9)	128 (65.0)	92 (46.7)
Conjunctivital Hyperemia	71 (36.8)	58 (29.4)	46 (23.4)
Foreign Body Sensation in Eyes	30 (15.5)	22 (11.2)	12 (6.1)
Eye Pain	28 (14.5)	26 (13.2)	11 (5.6)
Eye Irritation	27 (14.0)	18 (9.1)	21 (10.7)
Photophobia	21 (10.9)	19 (9.6)	4 (2.0)
Iritis	19 (9.8)	10 (5.1)	1 (0.5)
Corneal endothelial cell loss	18 (9.3)	11 (5.6)	0
Dry eye	17 (8.8)	17 (8.6)	9 (4.6)
Punctate keratitis	16 (8.3)	11 (5.6)	13 (6.6)
Conjunctival hemorrhage	15 (7.8)	16 (8.1)	14 (7.1)
Lacrimation increased	13 (6.7)	10 (5.1)	11 (5.6)
Vision blurred	12 (6.2)	10 (5.1)	9 (4.6)
Corneal oedema	11 (5.7)	5 (2.5)	2 (1.0)
Anterior chamber cell	10 (5.2)	9 (4.6)	0

Infections and infestations	54 (28.0)	41 (20.8)	45 (22.8)
Nasopharyngitis	12 (6.2)	10 (5.1)	10 (5.1)
Investigations	15 (7.8)	24 (12.2)	12 (6.1)
Intraocular pressure increased	10 (5.2)	16 (8.1)	5 (2.5)

Source: Table 12-4 of Study 091 Report.

Table 29: Study 092 Safety Analysis: Adverse Events Associated with ≥ 5.0% of Subjects in Any Treatment Group by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	BimSR 15µg N=176 n (%)	BimSR 10µg N=176 n (%)	Timolol N=176 n (%)
Eye Disorders	127 (72.2)	99 (56.6)	70 (40.5)
Conjunctivital Hyperemia	69 (39.2)	43 (24.6)	18 (10.4)
Corneal endothelial cell loss	33 (18.8)	8 (4.6)	1 (0.6)
Eye Pain	22 (12.5)	12 (6.9)	9 (5.2)
Corneal oedema	18 (10.2)	3 (1.7)	0
Foreign Body Sensation in Eyes	17 (9.7)	18 (10.3)	2 (1.2)
Conjunctival hemorrhage	15 (8.5)	18 (10.3)	15 (8.7)
Dry eye	15 (8.5)	18 (10.3)	15 (8.7)
Photophobia	12 (6.8)	13 (7.4)	0
Eye Irritation	11 (6.3)	10 (5.7)	9 (5.2)
Punctate keratitis	10 (5.7)	8 (4.6)	6 (3.5)
Ocular discomfort	10 (5.7)	3 (1.7)	1 (0.6)
Iritis	9 (5.1)	8 (4.6)	0
Anterior chamber cell	9 (5.1)	6 (3.4)	1 (0.6)
Lacrimation increased	9 (5.1)	5 (2.9)	1 (0.6)
Vision blurred	7 (4.0)	11 (6.3)	1 (0.6)
Infections and infestations	22 (12.5)	18 (10.3)	9 (5.2)
Nasopharyngitis	8 (4.5)	11 (6.3)	11 (6.4)
Investigations	22 (12.5)	18 (10.3)	9 (5.2)
Intraocular pressure increased	12 (6.8)	11 (6.3)	4 (2.3)

Source: Table 12-4 of Study 092 Report.

In Study 091, there have been 3 reported deaths in the study to date. Two of the deaths occurred in the Bimatoprost SR 15 µg group and 1 death was in the timolol group:

- Patient (b) (6) in the Bimatoprost SR 15 µg group was a 90-year-old white male passed away due to complications from bowel obstruction with torsion, which resulted in cardiac arrest during Cycle 3. The investigator assessed the event as not related to the study medication.
- Patient (b) (6) in the Bimatoprost SR 15 µg was an 86-year-old white male passed away due to left middle cerebral artery cerebrovascular accident due to atrial fibrillation and hypertension during Cycle 3. The investigator assessed that the events were not related to the study drug.

- Patient (b) (6) was an 84-year-old white female in the timolol group. She passed away due to head injury from a fall reported as severe during Cycle 3. The investigator assessed that the events were not related to the study drug.

No deaths have occurred in Study 092 to date.

Please see the review of the medical reviewer for details of the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Subgroup analyses based on gender, race, and age were performed (see results in Appendix 3). In both studies, all the subgroup analyses results were similar to those seen for the overall population for each demographic subgroup.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for the two pivotal studies submitted.

The primary analysis of the primary outcome was based on a mixed-effects model with repeated measures (MMRM). Various supportive analyses were conducted to examine the robustness of the primary analysis results. All analysis results were supportive of the primary efficacy results, demonstrating non-inferiority of both doses of Bimatoprost SR (15 µg and 10 µg) to the active comparator timolol in Study 091 and Study 092.

5.2 Collective Evidence

In Study 091, IOP reductions were observed in all three groups. From Week 2 to Week 12, mean IOP reduction from baseline ranged from 6.5 to 7.5 mmHg in the Bimatoprost SR 15 µg group, from 6.4 to 7.6 mmHg in the Bimatoprost SR 10 µg group, and from 6.1 to 6.8 mmHg in the timolol group. Both doses of Bimatoprost SR demonstrated non-inferiority to the active comparator timolol. The treatment differences between Bimatoprost SR 15 µg and timolol groups ranged from -0.4 mmHg to -1.0 mmHg; and met the non-inferiority criteria at all the six time points. The treatment differences between Bimatoprost SR 10 µg and timolol groups ranged from -0.2 mmHg to -0.9 mmHg; and met the non-inferiority criteria at all the six time points.

In Study 092, IOP reductions were observed in all three groups. From Week 2 to Week 12, mean IOP reduction from baseline ranged from 6.6 to 7.6 mmHg in the Bimatoprost SR 15 µg group, from 6.3 to 7.8 mmHg in the Bimatoprost SR 10 µg group, and from 6.1 to 6.9 mmHg in the

timolol group. Both doses of Bimatoprost SR demonstrated non-inferiority to the active comparator timolol. The treatment differences between Bimatoprost SR 15 µg and timolol groups ranged from -0.3 mmHg to -0.8 mmHg; and met the non-inferiority criteria at all the six time points. The treatment differences between Bimatoprost SR 10 µg and timolol groups ranged from -0.3 mmHg to -0.9 mmHg; and met the non-inferiority criteria at all the six time points.

However, by the end of 4 months (Week 15) after the insertion of Bimatoprost SR implant, when the drug substance in the implant had all released, although there were still IOP reduction effects for both Bimatoprost SR groups, the mean IOP reduction in Bimatoprost SR 15µg and Bimatoprost SR 10µg groups was slightly less than the timolol group. The statistical reviewer recommends that the study label include the Week 15 IOP information to remind physicians to re-treat patients as the treatment effects diminishing with the wear-off of the drug substance 4 months after the implant insertion.

Table 30: Study 091 and Study 092 Mean IOP and Mean IOP Change from Baseline (CFB) by Visit and Time

	Hour	Variable	BimSR 15µg N=198	BimSR 10µg N=198	Tim BID N=198	BimSR 15µg vs. Tim BID Differences (95% CI)[1]	BimSR 10µg vs. Tim BID Differences (95% CI)[1]
Study 091							
Baseline	**0**	IOP	24.76	24.64	24.63	0.13 (-0.41, 0.68)	0.02 (-0.51, 0.54)
	2	IOP	23.55	23.29	23.19	0.36 (-0.24, 0.96)	0.10 (-0.50, 0.69)
Week 2	**0**	IOP	16.83	17.02	17.82	-0.99 (-1.66, -0.32)	-0.80 (-1.47, -0.13)
		CFB	-7.16	-6.97	-6.17		
	2	IOP	16.46	16.42	17.33	-0.86 (-1.47, -0.26)	-0.90 (-1.50, -0.31)
		CFB	-7.53	-7.57	-6.66		
Week 6	**0**	IOP	17.09	16.87	17.71	-0.61 (-1.25, 0.02)	-0.84 (-1.47, -0.21)
		CFB	-6.90	-7.12	-6.29		
	2	IOP	16.63	16.51	17.16	-0.54 (-1.16, 0.09)	-0.66 (-1.27, -0.04)
		CFB	-7.36	-7.48	-6.83		
Week 12	**0**	IOP	17.53	17.61	17.94	-0.41 (-1.17, 0.36)	-0.33 (-1.09, 0.43)
		CFB	-6.46	-6.38	-6.05		
	2	IOP	16.81	17.30	17.51	-0.70 (-1.40, -0.01)	-0.21 (-0.90, 0.47)
		CFB	-7.18	-6.69	-6.48		
Study 092							
Baseline	**0**	IOP	24.39	24.28	24.46	-0.07 (-0.59, 0.45)	-0.18 (-0.70, 0.34)
	2	IOP	23.41	23.24	23.43	-0.02 (-0.64, 0.59)	-0.19 (-0.81, 0.42)
Week 2	**0**	IOP	17.08	17.11	17.88	-0.80 (-1.48, -0.12)	-0.77 (-1.46, -0.09)
		CFB	-7.60	-7.57	-6.80		
	2	IOP	16.38	16.18	17.07	-0.69 (-1.30, -0.08)	-0.89 (-1.50, -0.28)
		CFB	-6.96	-7.16	-6.27		
Week 6	**0**	IOP	17.30	16.93	17.82	-0.51 (-1.18, 0.15)	-0.88 (-1.55, -0.22)
		CFB	-7.37	-7.75	-6.86		
	2	IOP	16.51	16.22	16.89	-0.38 (-1.01, 0.24)	-0.66 (-1.29, -0.04)
		CFB	-6.84	-7.12	-6.45		
Week 12	**0**	IOP	17.77	17.69	18.11	-0.34 (-1.11, 0.43)	-0.42 (-1.19, 0.35)
		CFB	-6.91	-6.98	-6.56		
	2	IOP	16.72	17.02	17.22	-0.50 (-1.20, 0.20)	-0.29 (-0.90, 0.50)
		CFB	-6.62	-6.32	-6.12		

CI = Confidence Interval

[1] Based on a mixed-effects model with repeated measures (MMRM) including IOP as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used in the MMRM model.
Source: Tables 11-2 and 11-3 of Study 091 Report; and Tables 11-2 and 11-3 of Study 092 Report.

While subjects in Bimatoprost SR 10 µg group had similar mean IOP reduction as subjects in Bimatoprost SR 15 µg group, there were less ocular AEs in Bimatoprost SR 10 µg group than in the Bimatoprost SR 15 µg group.

5.3 Conclusions and Recommendations

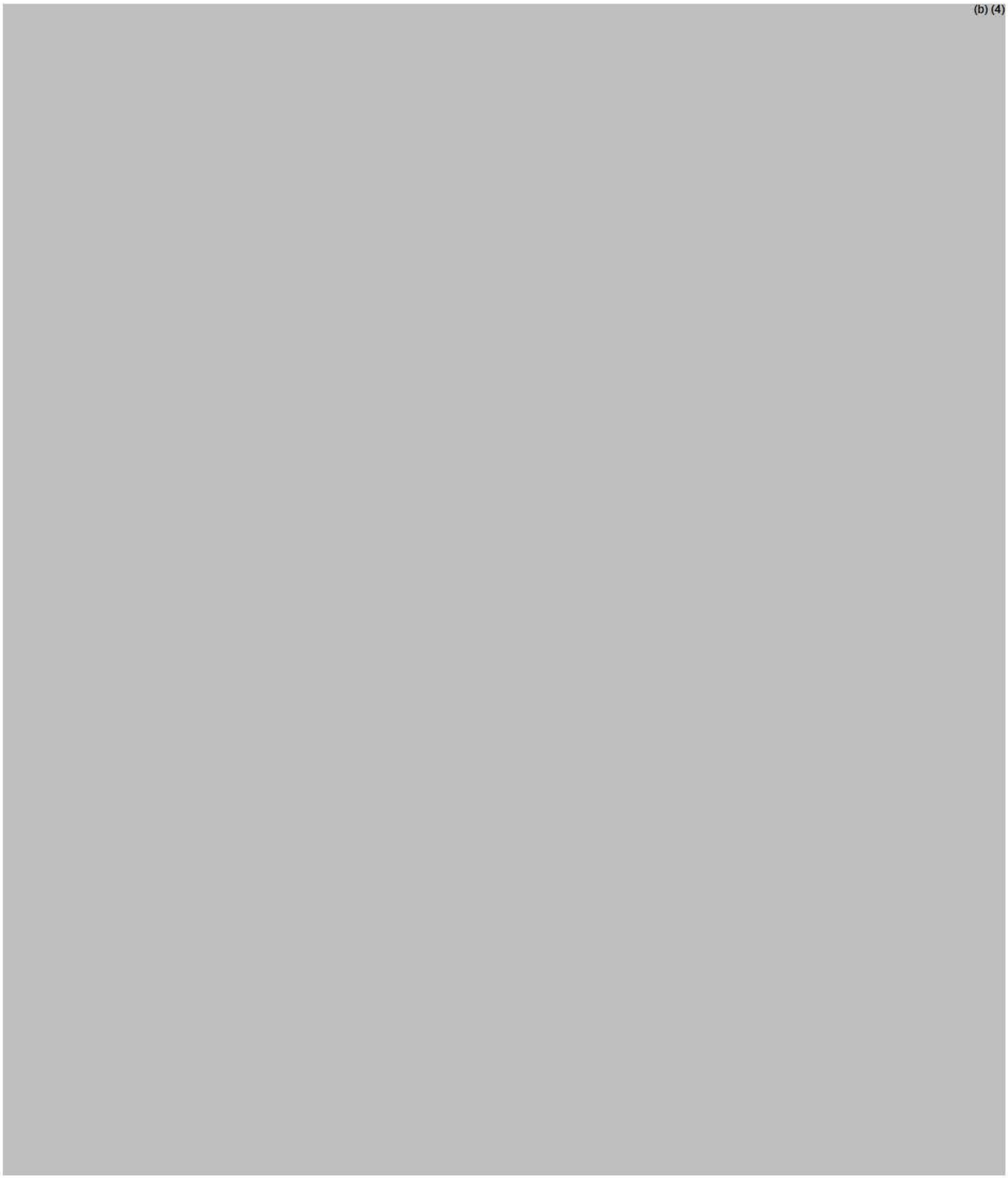
In conclusion, the two pivotal studies demonstrated that both doses of Bimatoprost SR (15 µg and 10 µg) were efficacious in reducing elevated intraocular pressure. As the lower dose group may have less safety concerns, the statistical reviewer recommended the approval of Bimatoprost SR 10 µg for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

5.4 Labeling Recommendations

In the NDA resubmission, the applicant's proposed label had the following text for the clinical studies section.

"Efficacy was evaluated in two multicenter, randomized, parallel-group, (b) (4) controlled 20-month (including 8-month extended follow-up) studies of DURYSTA compared to twice daily topical timolol 0.5% drops, in patients with OAG or OHT. DURYSTA (b) (4) demonstrated an IOP reduction of (b) (4) to 8 mmHg in patients with a mean baseline IOP of 24.5 mmHg (see Figures 3 and 4).

Figure 3: Study 1 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP



(b) (4)

As noted in this statistical review, by the end of 4 months (Week 15) after the insertion of Bimatoprost SR implant, when the drug substance in the implant had all released, although there were still IOP reduction effects for both Bimatoprost SR groups, the mean IOP reduction in Bimatoprost SR 15µg and Bimatoprost SR 10µg groups was slightly less than the timolol group. The statistical reviewer recommends that the clinical studies section include the Week 15 IOP information to remind physicians to re-treat patients as treatment effect diminishing with the wear-off of the drug substance of the implant. The statistical reviewer recommends that the clinical studies section be presented as follows:

"Efficacy was evaluated in two multicenter, randomized, parallel-group, (b) (4) controlled 20-month (including 8-month extended follow-up) studies of DURYSTA compared to twice daily topical timolol 0.5% drops, in patients with OAG or OHT. DURYSTA (b) (4) demonstrated an IOP reduction of up to 7.6 mmHg in patients with a mean baseline IOP of 24.6 mmHg (see Figures 3 and 4).

Figure 3: Study 1 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP

(b) (4)

Appendix 1: Inclusion and Exclusion Criteria and Schedule of Assessment

For both studies 091, and 092, the following were applicant-defined key inclusion and exclusion criteria.

Key Inclusion Criteria:

- 18 years of age or greater
- Diagnosis of either OAG (ie, primary, pseudoexfoliation, or pigmentary glaucoma) or OHT in each eye and both eyes required IOP-lowering treatment (Note: diagnosis did not have to be the same in both eyes)
- The patient was willing to withhold his/her IOP-lowering treatments according to the study requirements, and in the opinion of the investigator could have done so without significant risk. If patients could not have discontinued their currently prescribed therapy for up to 6 weeks to meet the washout period for study entry, the investigator could have switched the patient's medication to one that required a shorter washout interval during the washout of the original medication
- In the investigator's opinion, either eye could have been treated adequately with topical ophthalmic beta-blocker (eg, timolol) eye drops as the sole therapy
- In the investigator's opinion, either eye could have been treated adequately with topical prostamide, prostaglandin, or PGA (eg, LUMIGAN, Xalatan®, Travatan®) eye drops as the sole therapy
- At the Baseline visit:
    - Hour 0 IOP in the study eye of ≥ 22 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ≤ 32 mm Hg
    - Hour 2 IOP in the study eye of ≥ 19 mm Hg and ≤ 32 mm Hg, and in the fellow eye of ≤ 32 mm Hg
- The iridocorneal angle in the study eye must have been independently confirmed as being qualified by 2 ophthalmologists using the following criteria:
    - Shaffer Grade ≥ 3 on clinical gonioscopy of the inferior angle
    - Peripheral anterior chamber depth by Van Herick examination ≥ 1/2 corneal thickness

  Note: The independent eligibility assessments must have both agreed that the Shaffer grade was ≥ 3 and the Van Herick grade was ≥ 1/2 corneal thickness.
- Central CECD by specular microscopy:
    - At Screening, had a minimum endothelial cell density of 1800 cells/mm2 in at least 1 eye by automated analysis
    - By Baseline, final central endothelial cell density in both eyes was confirmed as being qualified by reading center assessment, with at least 1 eye qualified for inclusion as the study eye
- At the Baseline visit, had BCVA (Snellen equivalent, by manifest refraction) of 20/50 or better in the study eye and 20/100 or better in the fellow eye
- Able and willing to give signed informed consent and follow instructions.

Key Exclusion Criteria:

Ophthalmic

- In the investigator's opinion, the patient was nonresponsive to topical ophthalmic beta-blockers and/or topical prostamides, prostaglandins, or PGAs (eg, LUMIGAN, Xalatan, Travatan)
- History or evidence of a clinically relevant, substantial ocular trauma (eg, a traumatic cataract, traumatic angle recession, etc.) in the study eye
- Had any of the following surgical history:
    - History or evidence of complicated cataract surgery in the study eye: eg, surgery resulting in complicated lens placement (such as anterior chamber IOL, sulcus IOL, aphakia, etc.) or intraoperative complications (such as a posterior capsular tear [with or without vitreous loss], substantial iris trauma, etc.). Note: history of uncomplicated cataract surgery was not an exclusion.
    - History of phakic IOL insertion for refractive error correction in the study eye
- Intraocular surgery (including cataract surgery) and/or any ocular laser surgery within the 6 months prior to treatment (Day 1) in the study eye
- Had any history of corneal graft, including partial grafts (eg, DSEK, DMEK) in the study eye
- Incisional refractive surgery (eg, radial keratotomy), other than astigmatic keratotomy or limbal relaxing incisions in the study eye
- Corneal or other ocular abnormalities in either eye that could have precluded accurate readings with an applanation tonometer, AS- OCT, specular microscope, and/or a contact pachymeter, or could have confounded study results, eg, moderate to severe corneal dystrophy, including ABMD (ie, map-dot-fingerprint) and guttata. Mild ABMD or mild guttata were not exclusionary by clinical examination if, in the opinion of the investigator, the condition was stable and not likely to cause corneal changes during the course of the clinical study period.
- Active or recurrent ocular disease in either eye (eg, uveitis, ocular infection, chronic moderate to severe blepharitis or severe dry eye, ocular seasonal allergies) or sight threatening diseases (eg, neovascular AMD, diabetic macular edema) that, in the opinion of the investigator, could have placed the patient at a significant risk or interfered with the interpretation of the study data. Patients with slowly progressive eye diseases (ie, mild cataracts, non-neovascular AMD) could have been enrolled at the discretion of the investigator.
- In the study eye, any history of external ocular or intraocular malignancy, and/or any history of benign ocular neoplasia that, in the investigator's opinion, resulted in clinically significant ocular morbidity
- History of herpetic ocular diseases (including herpes simplex virus and varicella zoster virus) in the study eye
- The following ocular surface findings:
    - Bulbar conjunctival hyperemia on either macroscopic or slit-lamp examination, > +1(mild) in either eye at baseline

    - Active ocular surface findings other than bulbar conjunctival hyperemia, on either macroscopic or slit-lamp examination, > +1 (mild) at baseline in the study eye
- History of moderate or worse (≥ +2) bulbar conjunctival hyperemia due to marketed prostaglandin, prostamide, or PGA use in either eye
- Central corneal thickness of < 480 micrometers or > 620 micrometers in the study eye
- Anticipated need for any incisional or laser ocular surgery in either eye within the first 52 weeks of the study duration
- History of anatomically narrow angle that resulted in evidence of angle changes, or any history of closed angle glaucoma in either eye; historically narrow-angled patients whose angle had been opened by cataract surgery or peripheral iridotomy could have been eligible for enrollment if they had no evidence of angle abnormalities.
- History or evidence of a peripheral iridotomy/iridectomy in the inferior iris in the study eye
- Any history of trabeculectomy or other types of glaucoma surgery, including a glaucoma seton or aqueous bypass stents, in either eye
- History of laser trabeculoplasty within 6 months prior to Screening in the study eye
- PAS in the inferior iridocorneal angle on gonioscopic examination at Screening in either eye (limited PAS resulting from previous laser trabeculoplasty in the fellow eye were not exclusionary)
- Visual field loss in either eye that, in the opinion of the investigator, was functionally significant (eg, split fixation, field defect within the central 10 degrees that was visually significant or likely to cause central visual impairment upon progression) or showed evidence of progressive visual field loss within the year prior to baseline (2 visual fields were required for qualification, 1 performed within the 10 months prior to or at screening, and 1 performed at Baseline or during the washout period using the protocol-required testing method). The same test methodology was to be used for all historical and study-related examinations for a given patient.
- Evidence of macular edema on screening OCT evaluation or in medical history in either eye
- Use of any ocular corticosteroids from 2 months prior to the baseline exam or anticipated use during the study period in either eye, except for use of postoperative topical ocular corticosteroids from an administration day to Day 7 following an administration
- Anticipated use of other topical ocular medications in either eye

Systemic:

- Uncontrolled systemic disease
- Had a known allergy or sensitivity to any study medication or its components, any component of the delivery vehicle, procedure-related materials, or diagnostic agents used during the study (eg, topical anesthetic, dilating drops, fluorescein)
- Had contraindications to beta-blocker therapy, eg,
    - Reactive airway disease including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease

    - Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pacemaker, overt cardiac failure, or cardiogenic shock
- Anticipated use of oral, intramuscular, or intravenous corticosteroids from 2 months prior to the Baseline visit through Week 52
- Had a known history of bleeding disorder or prolonged bleeding after surgery (in the opinion of the investigator). Patients receiving pharmacologic blood thinners (eg, aspirin or Coumadin) could have been enrolled at the investigator's discretion.
- Female patients who were pregnant, nursing, or planning a pregnancy, or who were of childbearing potential and not using a reliable means of contraception during the study

Schedule of assessments for Studies 091 and 092 are presented in the following tables.

Table 31: Study 091 and Study 092 Schedule of Assessments from Screening through Treatment Day 1

	Screening	Washout[a]	Baseline[b]	Day 1 Administration Day
Visit Windows	up to 28 days[a]	up to 42 days	up to 3 days	
Informed Consent/Authorization	X			
Demographic Data	X			
Medical/Ophthalmic History	X		X	
Adverse Events	X		X	X
Concomitant Medications/Procedures	X		X	X
Physical Examination	X			
Vital Signs (at rest ≥ 5 min)	X		X	X
Pregnancy Test			X	
Blood and Urine Sample Collection[c]	X[c]			
Ocular exams in **bold** should be performed in the order shown.				
Pre-Hour 0 exams				
Macroscopic Conjunctival Hyperemia Assessment	OU		OU	
Manifest Refraction[d]	OU		OU	
BCVA[d]	OU		OU	
IOP Measurement Hour 0	OU		OU	
Non-contact exams (may perform in any order at any time before Hour 2 IOP)				
Macroscopic Iris Color Assessment[e]			OU	
Macroscopic Iris Color Photography[e]			OU	
Visual Field[f]	OU		OU	
Specular Microscopy[g]	OU			
AS-OCT	OU			
Biomicroscopy	OU		OU	SC/T[h]
IOP Measurement Hour 2	OU		OU	SC/T[h]

	Screening	Washout[a]	Baseline[b]	Day 1 Administration Day
Visit Windows	up to 28 days[a]	up to 42 days	up to 3 days	
Gonioscopy/Implant Assessment	OU[i]			
Contact Pachymetry (may be done any time after Hour 2 IOP)	OU			
Pupil Dilation (may perform post-dilation eye exams in any order)	OU		OU	
OCT of Macula	OU			
Dilated Ophthalmoscopy	OU		OU	
Optic Disc Examination	OU		OU	
Determination of Eligibility	X		X	X
IV/WRS	X			X[j]
Randomization				X
Bimatoprost SR/Sham Administration[k]				X

AS-OCT = anterior segment optical coherence tomography; BCVA = best-corrected visual acuity; IOP = intraocular pressure; OU = both eyes; IV/WRS = interactive voice/web response system; SC/T = patients with sickle cell disease or trait or other hemoglobinopathies; X = perform procedure. Shaded columns indicate administration and postadministration study visits. Hour 0 = 08:00 ± 1 hour. Hour 2 = Hour 0 + 2 hours (± 30 minutes).

[a] Washout may begin after screening procedures have been completed. Final reading center confirmation of central endothelial cell density should be received by the site by the Baseline visit.

[b] Baseline visit procedures, excluding IOP measurements (Hour 0 and Hour 2 must be performed in a single day), can be performed over a 3-day period. Perform pupil dilation/diagnostic procedures after the completion of the final IOP measurement or on another day. If, after initial washout, the IOP does not meet entry criteria and the investigator believes this is due to inadequate washout, additional washout up to a total of 42 days may be performed if time remains in the washout period.

[c] Blood and urine samples will be collected. Samples are collected only at Screening unless a retest is necessary.

[d] Manifest refraction will be used to provide a correction for BCVA testing. If there is a 2-line or more reduction in visual acuity from the last BCVA performed, a repeat manifest refraction in both eyes and BCVA will be performed.

[e] After Baseline, if iris color change is suspected additional iris color photographs will be taken.

[f] Two visual field tests are required prior to the administration procedure. The first can be performed up to 10 months prior to or at Screening, and the second during the washout period or at the Baseline visit, a minimum of 4 days apart. For a given patient, the same test methodology must be used for historical fields and throughout the study. If dilation is required to perform test (see Protocol Procedure Manual), test should be done following the final IOP measurement of the day.

[g] Final confirmation of the patient's central endothelial cell density by specular microscopy will be determined by the reading center.

[h] For SC/T only: Biomicroscopy and IOP in both eyes may be measured 4 hours after Bimatoprost SR or sham administration procedure at the investigator's discretion (see Section 8.4).

[i] At Screening only, gonioscopy will be performed by 2 ophthalmologists for independent eligibility assessment. Subsequent examinations will be performed by the study investigator only. Examination will also include, at selected sites only, gonioscopic photographs of both eyes in consenting patients at the indicated visits.

[j] After confirmation of eligibility on Day 1, IV/WRS is contacted for randomization. However, this contact for randomization may take place at the end of the Baseline day visit if needed.

[k] Administration Day activities will also include, at selected sites only, video recording of the administration procedure of both eyes in consenting patients.

Source: Table 2 of Study 091 Protocol.

Table 32: Study 091 and Study 092 Schedule of Assessments for Treatment Cycle 1 Day 2 through Week 12

	Day 2	Day 4 Phone	Day 8 Phone	Week 2	Week 6	Week 12
Visit Windows				± 4 days	± 4 days	± 4 days
Adverse Events[a]	X	X	X	X	X	X
Concomitant Medications/Procedures[a]	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 min)[a]	X			X	X	X
Ocular exams in **bold** should be performed in the order shown.						
Pre-Hour 0 exams (may perform in any order before Hour 0 IOP)						
Macroscopic Conjunctival Hyperemia Assessment	OU			OU	OU	OU
BCVA[b]	OU			OU	OU	OU
IOP Measurement Hour 0[c]	OU			OU	OU	OU
Non-contact exams (may perform in any order at any time before Hour 2 IOP)						
Macroscopic Iris Color Assessment[d]						OU
Manifest Refraction[b]						OU
Specular Microscopy						OU
Biomicroscopy	OU			OU	OU	OU
IOP Measurement Hour 2	OU			OU	OU	OU
Gonioscopy/Implant Assessment				OU[e]	OU	OU[e]
Contact Pachymetry (may be done any time after Hour 2 IOP)						OU
Pupil Dilation (may perform post-dilation eye exams in any order)						OU
Dilated Ophthalmoscopy						OU
Optic Disc Examination						OU
IV/WRS				X	X	X

BCVA = best-corrected visual acuity; IOP = intraocular pressure; OU = both eyes; IV/WRS = interactive voice/web response system; X = perform procedure. Shaded columns indicate administration and postadministration study visits. Hour 0 = 08:00 ± 1 hour. Hour 2 = Hour 0 + 2 hours (± 30 minutes).

[a] Adverse events should be collected prior to examinations being performed. Vital signs and concomitant medications/procedures may be performed at any time.

[b] Manifest refraction will be used to provide a correction for BCVA testing. If there is a 2-line or more reduction in visual acuity from the last BCVA performed, a repeat manifest refraction in both eyes and BCVA will be performed.

[c] The morning dose of study-provided eye drops will be administered immediately following the Hour 0 IOP measurement.

[d] After Baseline, if iris color change is suspected additional iris color photographs will be taken.

[e] The examination will also include, at selected sites only, gonioscopic photographs of both eyes in consenting patients at the indicated visits.

Source: Table 3 of Study 091 Protocol.

Table 33: Study 091 and Study 092 Schedule of Assessments for Treatment Period Week 15 through Week 28

	Week 15	Week 16 Administration Day	Cycle 2 Day 2	Cycle 2 Day 4 Phone	Cycle 2 Day 8 Phone	Week 18	Week 22	Week 28
Visit Windows	± 4 days	-2 / + 4 days				± 4 days	± 4 days	± 4 days
Adverse Events[a]	X	X	X	X	X	X	X	X
Concomitant Medications/Procedures[a]	X	X	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 min)[a]	X	X	X			X	X	X
Ocular exams in **bold** should be performed in the order shown.								
Pre-Hour 0 exams (may perform in any order before Hour 0 IOP)								
Macroscopic Conjunctival Hyperemia Assessment	OU		OU			OU	OU	OU
BCVA[b]	OU		OU			OU	OU	OU
IOP Measurement Hour 0[c]	OU		OU			OU	OU	OU
Non-contact exams (may perform in any order at any time before Hour 2 IOP)								
Macroscopic Iris Color Assessment[d]								OU
Visual Field[e]								OU
Specular Microscopy								OU
Biomicroscopy	OU	SC/T[f]	OU			OU	OU	OU
IOP Measurement Hour 2	OU	SC/T[f]	OU			OU	OU	OU
Gonioscopy/Implant Assessment	OU					OU[g]	OU	OU[g]
Contact Pachymetry (may be done any time after Hour 2 IOP)								OU
Pupil Dilation (may perform post-dilation eye exams in any order)								OU

	Week 15	Week 16 Administration Day	Cycle 2 Day 2	Cycle 2 Day 4 Phone	Cycle 2 Day 8 Phone	Week 18	Week 22	Week 28
Visit Windows	± 4 days	-2 / + 4 days				± 4 days	± 4 days	± 4 days
Dilated Ophthalmoscopy								OU
Optic Disc Examination								OU
IV/WRS	X	X[h]				X	X	X
Bimatoprost SR/Sham Administration[i]		X						

BCVA = best-corrected visual acuity; IOP = intraocular pressure; IV/WRS = interactive voice/web response system; OU = both eyes; SC/T = patients with sickle cell disease or trait or other hemoglobinopathies; X = perform procedure; Hour 0 = 08:00 ± 1 hour. Hour 2 = Hour 0 + 2 hours (± 30 minutes).
Shaded columns indicate visits that are not performed if a patient has received nonstudy IOP-lowering medication in both eyes prior to the Week 16 Administration Day.

[a] Adverse events should be collected prior to examinations being performed. Vital signs and concomitant medications/procedures may be performed at any time.
[b] Manifest refraction will be used to provide a correction for BCVA testing. If there is a 2-line or more reduction in visual acuity from the last BCVA performed, a repeat manifest refraction in both eyes and BCVA will be performed.
[c] The morning dose of study-provided eye drops will be administered immediately following the Hour 0 IOP measurement.
[d] If iris color change is suspected, additional iris color photographs will be taken.
[e] For a given patient, the same test methodology must be used throughout the study.
[f] For SC/T only, biomicroscopy and IOP in both eyes may be measured 4 hours after Bimatoprost SR or Sham administration procedure at the investigator's discretion (see Section 8.4).
[g] The examination will also include, at selected sites only, gonioscopic photographs of both eyes in consenting patients.
[h] IV/WRS is contacted to obtain administration kit number. However, this contact may take place 1 day prior to the Administration Day if needed.
[i] Administration Day activities will also include, at selected sites only, video recording of the administration procedure of both eyes in consenting patients.

Source: Table 4 of Study 091 Protocol.

Table 34: Study 091 and Study 092 Schedule of Assessments for Treatment Period Week 31 through Week 52

	Week 31	Week 32 Administration Day	Cycle 3 Day 2	Cycle 3 Day 4 Phone	Cycle 3 Day 8 Phone	Week 34	Week 38	Week 44	Week 48	Week 52
Visit Windows	± 4 days	-2 / + 4 days				± 4 days	± 4 days	± 4 days	± 4 days	± 7 days
Adverse Events[a]	X	X	X	X	X	X	X	X	X	X
Concomitant Medications/Procedures[a]	X	X	X	X	X	X	X	X	X	X
Vital Signs (at rest ≥ 5 min)[a]	X	X	X			X	X	X	X	X
Ocular exams in **bold** should be performed in the order shown.										
Pre-Hour 0 exams (may perform in any order before Hour 0 IOP)										
Macroscopic Conjunctival Hyperemia Assessment	OU		OU			OU	OU	OU	OU	OU
BCVA[b]	OU		OU			OU	OU	OU	OU	OU
IOP Measurement Hour 0[c]	OU		OU			OU	OU	OU	OU	OU
Non-contact exams (may perform in any order at any time before Hour 2 IOP)										
Macroscopic Iris Color Assessment[d]								OU		OU
Macroscopic Iris Color Photography[d]										OU
Manifest Refraction[b]										OU
Visual Field[e]										OU
Specular Microscopy								OU		OU
Biomicroscopy	OU	SC/T[f]	OU			OU	OU	OU	OU	OU
IOP Measurement Hour 2	OU	SC/T[f]	OU			OU	OU	OU	OU	OU
Gonioscopy/Implant Assessment	OU					OU[g]	OU	OU	OU[g]	OU[g]
Contact Pachymetry (may be done any time after Hour 2 IOP)								OU		OU
Pupil Dilation (may perform post-dilation eye exams in any								OU		OU

	Week 31	Week 32 Administration Day	Cycle 3 Day 2	Cycle 3 Day 4 Phone	Cycle 3 Day 8 Phone	Week 34	Week 38	Week 44	Week 48	Week 52
Visit Windows	± 4 days	-2 / + 4 days				± 4 days	± 4 days	± 4 days	± 4 days	± 7 days
order)										
OCT of Macula										OU
Dilated Ophthalmoscopy								OU		OU
Optic Disc Examination								OU		OU
IV/WRS	X	X[h]				X	X	X	X	X
Bimatoprost SR/Sham Administration[i]		X								

BCVA = best-corrected visual acuity; IOP = intraocular pressure; IV/WRS = interactive voice/web response system; OCT = optical coherence tomography; OU = both eyes; SC/T = patients with sickle cell disease or trait or other hemoglobinopathies; X = perform procedure; Hour 0 = 08:00 ± 1 hour. Hour 2 = Hour 0 + 2 hours (± 30 minutes).
Shaded columns indicate visits that are not performed if a patient has received nonstudy IOP-lowering medication in both eyes prior to the Week 32 Administration Day.

[a] Adverse events should be collected prior to examinations being performed. Vital signs and concomitant medications/procedures may be performed at any time.
[b] Manifest refraction will be used to provide a correction for BCVA testing. If there is a 2-line or more reduction in visual acuity from the last BCVA performed, a repeat manifest refraction in both eyes and BCVA will be performed.
[c] The morning dose of study-provided eye drops will be administered immediately following the Hour 0 IOP measurement.
[d] If iris color change is suspected, additional iris photographs will be taken. Iris color photographs will be taken at Week 52 in all patients.
[e] For a given patient, the same test methodology must be used throughout the study.
[f] For SC/T only, biomicroscopy and IOP in both eyes may be measured 4 hours after Bimatoprost SR or Sham administration procedure at the investigator's discretion (see Section 8.4).
[g] The examination will also include, at selected sites only, gonioscopic photographs of both eyes in consenting patients.
[h] IV/WRS is contacted to obtain administration kit number. However, this contact may take place 1 day prior to the Administration Day if needed.
[i] Administration Day activities will also include, at selected sites only, video recording of the administration procedure of both eyes in consenting patients.

Source: Table 5 of Study 091 Protocol.

Table 35: Study 091 and Study 092 Schedule of Assessments for Extended Follow Up Months 14, 16, 18, and 20

	Month 14[a]	Month 16	Month 18[a]	Month 20/Exit
Visit Windows	± 14 days	± 14 days	± 14 days	± 14 days
Adverse Events[b]	X	X	X	X
Concomitant Medications/Procedures[b]	X	X	X	X
Vital Signs (at rest ≥ 5 min)[b]	X	X	X	X
Pregnancy Test				X
Ocular exams in **bold** should be performed in the order shown.				
Pre-Hour 0 exams (may perform in any order before Hour 0 IOP)				
Macroscopic Conjunctival Hyperemia Assessment	OU	OU	OU	OU
BCVA[c]	OU	OU	OU	OU
IOP Measurement Hour 0[d]	OU	OU	OU	OU
Non-contact exams (may perform in any order at any time before Hour 2 IOP)				
Macroscopic Iris Color Assessment[e]		OU		OU
Macroscopic Iris Color Photography[e]				OU
Manifest Refraction[c]				OU
Visual Field[f]				OU
Specular Microscopy				OU
Biomicroscopy	OU	OU	OU	OU
IOP Measurement Hour 2	OU	OU	OU	OU
Gonioscopy/Implant Assessment	OU	OU[g]	OU	OU[g]
Contact Pachymetry (may be done any time after Hour 2 IOP)				OU
Pupil Dilation (may perform post-dilation eye exams in any order)				OU

	Month 14[a]	Month 16	Month 18[a]	Month 20/Exit
Visit Windows	± 14 days	± 14 days	± 14 days	± 14 days
OCT of Macula				OU
Dilated Ophthalmoscopy				OU
Optic Disc Examination				OU
IV/WRS	X	X	X	X

BCVA = best-corrected visual acuity; IOP = intraocular pressure; IV/WRS = interactive voice/web response system; OCT = optical coherence tomography; OU = both eyes; X = perform procedure; Hour 0 = 08:00 ± 1 hour. Hour 2 = Hour 0 + 2 hours (± 30 minutes).

[a] Patients who have received nonstudy IOP-lowering medication in both eyes before the time of the Month 14 visit are not required to attend the Month 14 or 18 visits unless the visit is 12 months after their last injection or Sham, at which time the patient may exit early and should complete all Month 20/Exit visit examinations. Patients who have received nonstudy IOP-lowering medication in both eyes by the time of the Month 16 visit are not required to attend the Month 18 visit, unless that visit is 12 months after their last injection or Sham, at which time the patient may exit early and should complete all Month 20/Exit visit examinations.

[b] Adverse events should be collected prior to examinations being performed. Vital signs and concomitant medications/procedures may be performed at any time.

[c] Manifest refraction will be used to provide a correction for visual acuity testing. If there is a 2-line or more reduction in visual acuity from the last BCVA performed, a repeat manifest refraction in both eyes and BCVA will be performed. Manifest refraction will be performed at Month 20/Exit in all patients.

[d] The morning dose of study-provided eye drops will be administered immediately following the Hour 0 IOP measurement.

[e] If iris color change is suspected, additional iris photographs will be taken. Iris color photographs will be taken at Month 20/Exit in all patients.

[f] For a given patient, the same test methodology must be used throughout the study.

[g] The examination will also include, at selected sites only, gonioscopic photographs of both eyes in consenting patients.

Source: Table 6 of Study 091 Protocol.

Appendix 2: Subgroup Analysis Results for Gender, Race, and Age

Table 36: Study 091 Mean IOP Subgroup Analyses by Gender, Age, and Race

Sub group			Mean IOP						Treatment Difference (95% CI)[1]	
			BimSR 15µg		BimSr 10µg		Tim BID		BimSR 15µg vs. Tim BID	BimSR 10µg vs. Tim BID
	WK	HR	N	IOP	N	IOP	N	IOP		
Gender										
Female	**2**	**0**	95	17.1	85	17.4	104	18.4	-1.3 (-2.3, -0.4)	-0.9 (-1.9, 0.0)
		2	95	16.7	85	16.8	104	17.7	-0.9 (-1.7, -0.1)	-0.8 (-1.7, 0.0)
Male	**2**	**0**	95	16.6	111	16.7	92	17.2	-0.6 (-1.5, 0.4)	-0.5 (-1.4, 0.5)
		2	95	16.2	111	16.2	92	17.0	-0.8 (-1.7, 0.1)	-0.8 (-1.7, 0.1)
Female	**6**	**0**	93	17.0	86	17.1	103	18.3	-1.4 (-2.2, -0.5)	-1.2 (-2.1, -0.4)
		2	92	16.5	86	16.6	102	17.7	-1.2 (-2.1, -0.4)	-1.1 (-2.0, -0.2)
Male	**6**	**0**	94	17.3	111	16.7	91	17.0	0.2 (-0.7, 1.2)	-0.3 (-1.2, 0.7)
		2	94	16.8	111	16.5	91	16.6	0.2 (-0.7, 1.1)	-0.1 (-1.0, 0.8)
Female	**12**	**0**	92	17.6	84	17.8	99	18.4	-0.8 (-1.9, 0.3)	-0.6 (-1.8, 0.5)
		2	90	17.0	84	17.3	99	17.9	-1.0 (-1.9, 0.0)	-0.6 (-1.6, 0.4)
Male	**12**	**0**	93	17.5	108	17.6	92	17.3	0.2 (-0.9, 1.2)	0.2 (-0.8, 1.3)
		2	93	16.7	108	17.4	92	17.1	-0.3 (-1.3, 0.7)	0.3 (-0.7, 1.3)
Age										
≤ 65	**2**	**0**	99	16.4	112	17.0	120	17.9	-1.3 (-2.3, -0.4)	-0.8 (-1.7, 0.1)
		2	99	16.1	112	16.3	120	17.3	-1.3 (-2.1, -0.4)	-1.0 (-1.8, -0.2)
> 65	**2**	**0**	91	17.3	84	17.1	76	17.9	-0.6 (-1.5, 0.4)	-0.8 (-1.8, 0.2)
		2	91	16.9	84	16.6	76	17.4	-0.4 (-1.3, 0.4)	-0.8 (-1.7, 0.1)
≤ 65	**6**	**0**	99	16.8	113	16.5	117	17.7	-0.9 (-1.7, 0.0)	-0.8 (-1.7, 0.0)
		2	98	16.1	113	17.9	117	17.3	-1.2 (-2.0, -0.4)	-0.8 (-1.6, 0.0)
> 65	**6**	**0**	88	17.4	84	16.9	77	17.7	-0.3 (-1.2, 0.7)	-0.8 (-1.8, 0.2)
		2	88	17.3	84	16.5	76	16.9	0.3 (-0.7, 1.3)	-0.4 (-1.4, 0.6)
≤ 65	**12**	**0**	98	17.2	109	17.3	115	17.9	-0.7 (-1.6, 0.2)	0.0 (-0.9, 0.9)
		2	97	16.6	109	17.8	115	17.6	-1.0 (-1.9, -0.1)	-0.2 (-1.1, 0.6)
> 65	**12**	**0**	87	18.1	83	17.3	76	18.0	0.1 (-1.2, 1.3)	-0.7 (-2.0, 0.6)
		2	86	17.1	83	17.3	76	17.4	-0.3 (-1.5, 0.8)	-0.2 (-1.4, 1.0)
Race										
White	**2**	**0**	118	17.1	122	17.3	128	17.9	-0.8 (-1.7, 0.0)	-0.6 (-1.4, 0.2)
		2	118	16.7	122	16.6	128	17.1	-0.5 (-1.2, 0.3)	-0.6 (-1.3, 0.3)

Other	**2**	**0**	72	16.4	74	16.6	68	17.7	-1.2 (-2.4, -0.1)	-1.1 (-2.2, 0.1)
		2	72	16.1	74	16.2	68	17.7	-1.5 (-2.6, -0.5)	-1.5 (-2.5, -0.4)
White	**6**	**0**	115	17.3	123	17.0	127	17.6	-0.3 (-1.0, 0.5)	-0.6 (-1.4, 0.1)
		2	114	16.7	123	16.5	126	17.0	-0.2 (-0.9, 0.6)	-0.5 (-1.2, 0.2)
Other	**6**	**0**	72	16.7	74	16.7	67	17.9	-1.2 (-2.4, -0.1)	-1.3 (-2.4, -0.1)
		2	72	16.3	74	16.6	67	17.5	-1.2 (-2.4, -0.1)	-1.0 (-2.1, 0.1)
White	**12**	**0**	114	17.5	121	17.6	124	17.9	-0.3 (-1.2, 0.6)	-0.2 (-1.1, 0.7)
		2	71	17.0	71	17.1	67	17.5	-0.5 (-1.4, 0.3)	-0.4 (-1.2, 0.4)
Other	**12**	**0**	113	17.6	121	17.6	124	18.3	-0.6 (-2.0, 0.8)	-0.7 (-2.1, 0.7)
		2	70	16.6	71	17.6	67	17.6	-0.9 (-2.2, 0.3)	0.1 (-1.2, 1.3)

[1] Based on a mixed-effects model with repeated measures (MMRM) including IOP as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used in the MMRM model.
Source: Statistical Reviewer's Analysis.

Table 37: Study 092 Mean IOP Subgroup Analyses by Gender, Age, and Race

Sub group			**Mean IOP**						**Treatment Difference (95% CI)[1]**	
			BimSR 15µg		**BimSr 10µg**		**Tim BID**		**BimSR 15µg vs. Tim BID**	**BimSR 10µg vs. Tim BID**
	WK	**HR**	**N**	**IOP**	**N**	**IOP**	**N**	**IOP**		
Gender										
Female	**2**	**0**	86	16.4	87	16.6	85	17.3	-1.0 (-2.0, 0.1)	-0.7 (-1.8, 0.3)
		2	86	15.9	87	16.5	85	17.1	-1.2 (-2.2, -0.3)	-0.6 (-1.6, 0.3)
Male	**2**	**0**	84	17.1	85	17.2	87	17.7	-0.6 (-1.6, 0.4)	-0.5 (-1.5, 0.5)
		2	84	16.2	85	16.4	87	17.3	-1.1 (-2.0, -0.1)	-0.9 (-1.8, 0.1)
Female	**6**	**0**	87	17.0	88	16.7	82	17.6	-0.6 (-1.7, 0.5)	-0.9 (-1.9, 0.2)
		2	87	16.0	88	16.4	82	17.3	-1.3 (-2.3, -0.3)	-0.9 (-1.9, 0.1)
Male	**6**	**0**	84	17.0	83	17.1	86	17.4	-0.4 (-1.5, 0.7)	-0.3 (1.4, 0.8)
		2	84	16.1	83	16.6	86	17.1	-0.9 (-2.0, 0.1)	-0.5 (-1.5, 0.5)
Female	**12**	**0**	86	17.0	86	17.2	82	18.2	-1.2 (-2.3, -0.1)	-1.0 (-2.1, 0.1)
		2	86	16.4	86	17.0	82	17.6	-1.2 (-2.3, -0.1)	-0.6 (-1.8, 0.5)
Male	**12**	**0**	82	17.8	83	18.1	84	17.4	0.3 (-0.8, 1.5)	0.7 (-0.5, 1.9)
		2	82	17.0	83	17.3	84	17.4	-0.5 (-1.5, 0.6)	-0.1 (-1.2, 0.9)
Age										
≤ 65	**2**	**0**	91	16.4	94	16.5	107	17.2	-0.8 (-1.8, 0.1)	-0.7 (-1.7, 0.2)
		2	91	15.6	94	16.2	107	16.8	-2.8 (-2.1, -0.4)	-0.6 (-1.5, 0.2)
> 65	**2**	**0**	79	17.2	78	17.5	65	18.0	-0.9 (-2.0, 0.2)	-0.6 (-1.6, 0.5)
		2	79	16.7	78	16.9	65	17.9	-1.2 (-2.3, -0.2)	-1.0 (-2.0, 0.1)
≤ 65	**6**	**0**	92	16.8	94	16.7	105	17.2	-0.8 (-1.5, 0.6)	-0.5 (-1.6, 0.5)
		2	92	15.7	94	16.4	105	16.8	-2.1 (-2.0, -0.1)	-0.4 (-1.4, 0.5)
> 65	**6**	**0**	79	17.4	77	17.3	63	18.1	-0.7 (-1.8, 0.4)	-0.8 (-1.9, 0.3)
		2	79	16.6	77	16.8	63	17.9	-1.3 (-2.4, -0.3)	-1.1 (-2.2, 0.0)
≤ 65	**12**	**0**	90	16.9	92	17.2	106	17.3	-0.4 (-1.5, 0.6)	-0.1 (-1.2, 0.9)
		2	90	16.2	92	16.7	106	17.2	-1.0 (-2.0, 0.0)	-0.5 (-1.5, 0.5)
> 65	**12**	**0**	78	18.0	77	18.4	60	18.5	-0.5 (-1.8, 0.7)	-0.1 (-1.4, 1.1)
		2	78	17.2	77	17.8	60	18.0	-0.8 (-2.0, 0.4)	-0.2 (-1.4, 1.0)
Race										
White	**2**	**0**	114	16.9	113	16.9	100	17.3	-0.5 (-1.4, 0.4)	-0.4 (-1.3, 0.5)
		2	114	16.2	113	16.6	100	17.2	-1.0 (-1.8, -0.1)	-0.6 (-1.5, 0.2)
Other	**2**	**0**	56	16.5	59	16.9	72	17.7	-1.3 (-2.5, -0.1)	-0.8 (-2.0, 0.4)
		2	56	15.8	59	16.3	72	17.2	-1.4 (-2.5, -0.3)	-0.9 (-2.0, 0.2)
White	**6**	**0**	113	17.5	112	16.9	98	17.6	-0.1 (-1.0, 0.8)	-0.7 (-1.6, 0.2)
		2	113	16.2	112	16.5	98	17.2	-1.0 (-1.9, -0.2)	-0.8 (-1.6, 0.1)
Other	**6**	**0**	58	16.2	59	17.1	70	17.4	-1.2 (-2.6, -0.2)	-0.4 (-1.7, 1.0)

White		**2**	58	15.9	59	16.6	70	17.0	-1.2 (-2.5, 0.1)	-0.4 (-1.7, 0.8)
	12	**0**	112	17.5	112	17.6	96	17.8	-0.3 (-1.3, 0.6)	-0.2 (-1.2, 0.8)
		2	56	16.9	57	17.0	70	17.5	-0.5 (-1.5, 0.4)	-0.4 (-1.4, 0.5)
Other	**12**	**0**	112	17.2	112	17.8	96	17.7	-0.4 (-1.9, 1.0)	0.1 (-1.3, 1.5)
		2	56	16.3	57	17.3	70	17.5	-1.3 (-2.6, 0.1)	-0.2 (-1.5, 1.1)

[1] Based on a mixed-effects model with repeated measures (MMRM) including IOP as the response variable and treatment, timepoint (Hours 0 and 2 at each visit of Weeks 2, 6, and 12), treatment-by-timepoint interaction and baseline IOP stratification as fixed factors, as well as time-matched baseline IOP (either Hour 0 or Hour 2 according to the response variable) as a covariate and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used in the MMRM model.
Source: Statistical Reviewer's Analysis.

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