CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	211911
Priority or Standard	Standard
Submit Date(s)	May 6, 2019
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Division/Office	Division of Ophthalmology
Reviewer Name(s)	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	February 18, 2020
Established/Proper Name	Bimatoprost implant
(Proposed) Trade Name	Durysta
Applicant	Allergan, Inc.
Dosage Form(s)	Ophthalmic implant
Applicant Proposed Dosing Regimen(s)	Ophthalmic implant administered intracamerally (b) (4)
Applicant Proposed Indication(s)/Population(s)	Reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT) in patients 18 years or older

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Durysta (bimatoprost implant) is a biodegradable, sustained-release, preservative-free bimatoprost implant that is preloaded into a single-use applicator for administration into the anterior chamber (AC). The implant is designed to provide (b) (4) sustained release of bimatoprost to the AC of the eye (b) (4) for the reduction of intraocular pressure (IOP). The proposed indication is for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension in patients 18 years or older. Throughout this review, the product is alternately referred to as Durysta, Bimatoprost SR, and bimatoprost intracameral implant.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Durysta (bimatoprost implant) has been shown to be effective for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension in patients 18 years or older based on two adequate and well controlled clinical trials (Studies 192024-91 and 192024-092). Bimatoprost SR 15 mcg and 10 mcg were not inferior to timolol BID dosing.

1.3. Benefit-Risk Assessment

The data contained in this submission establishes the efficacy of Bimatoprost SR 10 mcg given as an intracameral injection (b) (4) providing a significant lowering of intraocular pressure in patients elevated IOP in patients with open-angle glaucoma or ocular hypertension. Studies #192024-091 and #192024-92 demonstrate that the IOP lowering ability of Bimatoprost SR was not inferior to the amount of IOP lowering achieved by timolol maleate ophthalmic solution 0.5%, dosed BID.

The safety profile of Bimatoprost SR is similar to other marketed topical prostaglandin analogues with the exception of an increased risk of corneal endothelial cell loss (38%). After corneal endothelial cell loss, the most common ocular adverse events are conjunctival/ocular hyperemia (27%) and foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, eye irritation, dry eye, intraocular pressure increase, and vision blurred (5 - 10%).

The benefit/risk of Bimatoprost SR for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension is limited based on this NDA to a single administration per eye. The increased risk of corneal endothelial cell loss limits the use to only the 10 mcg product and only to a single administration. Bimatoprost SR should be contraindicated in patients with corneal endothelial cell dystrophy (e.g. Fuch's Dystrophy) given its increased risk of corneal endothelial cell loss and should be used with caution in patients with limited corneal endothelial cell reserve. Repeat injections are not supported by the submitted data. Further investigations will be needed to identify circumstances in which a second implant can be administered to an individual eye.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factor is elevated intraocular pressure (IOP).	Lowering intraocular pressure is currently the accepted standard for preserving visual function in patients with elevated intraocular pressure.
Current Treatment Options	• There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues. These products must be administered at least once per day.	Compliance with topical ophthalmic drop administration is a significant problem leading to inadequate treatment. (b) (4)
Benefit	• Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. The primary efficacy endpoint was mean IOP measured at multiple time points for studies #192024-091 and #192024-92.	Studies #192024-091 and #192024-92 demonstrated that Bimatoprost SR 15 mcg and 10 mcg were non-inferior to the active-control, timolol maleate ophthalmic solution 0.5% and lowered intraocular pressure by a clinically significant amount.
Risk and Risk Management	• The risk for using this drug is consistent with currently U.S. marketed prostaglandin analogues with the exception of increased loss of corneal endothelial cells. There is significant corneal endothelial cell loss with the use of the 15 mcg product and with repeat injections of either product. • No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events. Should the applicant wish to pursue labeling which provides for additional cycles of implantation, they would need to submit new clinical study results demonstrating no significant endothelial cell loss after at least three implantations.	The safety database contained in this application established the safety of Bimatoprost SR intracameral injection administered once. Repeat injections are not supported by the submitted data. The 10mcg implant consistently demonstrates a better safety profile. Routine monitoring and reporting of all adverse events are adequate.

2. Therapeutic Context

2.1. Analysis of Condition

Elevated intraocular pressure (IOP), if untreated will result in damage to the nerve fiber layer of the eye and subsequent loss of visual fields.

2.2. Analysis of Current Treatment Options

There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Pharmacologic Class	Trademark	Active Ingredient
Alpha-2 agonist	Alphagan	Brimonidine tartrate
Beta-adrenergic antagonist	Betoptic	Betaxolol hydrochloride
Beta-adrenergic antagonist	Ocupress	Carteolol hydrochloride
Beta-adrenergic antagonist	Betagan	Levobutanol hydrochloride
Beta-adrenergic antagonist	Optipranolol	Metipranolol
Beta-adrenergic antagonist	Betimol	Timolol hemihydrate
Beta-adrenergic antagonist	Timoptic, Timoptic XE, Istalol	Timolol maleate
Carbonic anhydrase inhibitor	Diamox	Acetazolamide
Carbonic anhydrase inhibitor	Neptazane	Methazolamide
Carbonic anhydrase inhibitor	Azopt	Brinzolamide
Carbonic anhydrase inhibitor	Trusopt	Dorzolamide
Cholinergic agonist	Pilocarpine HS, Isoptocarpine	Pilocarpine hydrochloride
Prostaglandin analog	Lumigan	Bimatoprost
Prostaglandin analog	Xalatan	Latanoprost
Prostaglandin analog	Travatan, Izba	Travoprost
Prostaglandin analog	Zioptan	Tafluprost
Rho kinase inhibitor	Rhopressa	Netarsudil
Other	Rescula	Unoprostone isopropyl

In addition, there are multiple combinations of the active ingredients listed above.

2.3 Availability of Proposed Active Ingredient in the United

The active ingredient of the bimatoprost intracameral implant is the bimatoprost drug substance which was originally developed by Allergan and approved as Lumigan ophthalmic solution for topical administration in 2001.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

NDA 211911, Durysta (bimatoprost implant) is submitted via the 505(b)(1) regulatory pathway and cross references the applicant's previously approved NDAs, NDA 21-275 Lumigan 0.03% (bimatoprost ophthalmic solution 0.03%) and NDA 22-184 Lumigan 0.01% (bimatoprost ophthalmic solution 0.01%), approved in the Unites States in March 2001 and August 2010, respectively.

3.2. Summary of Presubmission/Submission Regulatory Activity

In July 2010, IND 108324 for bimatoprost SR (sustained release) was submitted to the FDA with the target indication of lowering IOP in patients with glaucoma or OHT. Two adequate and well controlled studies designed to support the initial marketing application (Studies 192024-91 and 192024-092) were initiated in late 2014.

An End-of-Phase 2 meeting was held in February 2014 to obtain feedback on the proposed clinical study designs as well as nonclinical and clinical programs to support registration. In the meeting, Allergan reached agreement on the Phase 3 study design including the population, primary efficacy endpoints and analyses, safety assessments, and study duration. These agreements were incorporated into the protocols for Studies 192024-091 and 192024-092. To establish substantial evidence of efficacy, 2 Phase 3 noninferiority studies against topical timolol twice daily as the comparator was deemed acceptable.

Following the End-of-Phase 2 meeting, a Special Protocol Assessment Request of clinical protocol and statistical analysis plan for Study 192024-091 was submitted in May 2014. Acceptance of the comparator, study duration, primary efficacy time period and analysis, and method for handling missing data was obtained.

In November 2014, the FDA provided confirmation of their agreement on the initial Pediatric Study Plan for Bimatoprost SR. The plan requested a waiver of the requirement to perform pediatric studies in glaucoma patients from 0 to 14 years of age based on evidence strongly

suggesting that the drug would be ineffective, or unsafe due to repeated anesthesia that would be needed to administer the product. The plan also requested a waiver of the requirement to perform pediatric studies in glaucoma patients from > 14 to 17 years of age based on evidence that necessary studies would be impossible or highly impracticable because patients are geographically dispersed.

The statistical analysis plans for Studies 192024-091 and 192024-092 were submitted for review and comment in June 2016. The FDA indicated that a claim of superiority would need to show a clinically and statistically significant difference in favor of Bimatoprost SR at all 6 timepoints measured in the primary efficacy analysis. The final analysis plan for Study 192024-091, also representative of the identical plan for Study 192024-092, was submitted to IND 108324 on 24 April 2018.

In January 2018, a Type C written response from FDA confirmed no objection to the reduction in sample size of an ongoing Phase 3 study based on either masked discontinuation rate or masked IOP variability that was lower than originally assumed. Allergan subsequently amended the protocol for Study 192024-092, reducing the sample size to 540 patients while preserving the original statistical power.

A pre-NDA meeting (NDA 211911) was held in December 2018, wherein agreement was obtained regarding the format and content of the US marketing application. Agreement was also obtained on the information to be included in the Day 120 Safety Update.

3.3. Foreign Regulatory Actions and Marketing History

Bimatoprost SR has not been licensed or marketed in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No issues were identified in the review of the clinical portion of the NDA to suggest a problem with data integrity. Routine clinical inspections were requested from OSI.

4.2. Product Quality

DURYSTA is an intracameral biodegradable implant containing (b) (4) 10 mcg bimatoprost in the NOVADUR® solid polymer sustained-release drug delivery system (DDS). DURYSTA is

preloaded into a single-use, DDS applicator to facilitate injection of the rod-shaped implant directly into the anterior chamber of the eye. The components of the implant are bimatoprost drug substance and polymers poly (D,L-lactide), poly (D,L-lactide-co-glycolide), and polyethylene glycol. The chemical name for bimatoprost is (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide, and its molecular weight is 415.57.

Both Phase 3 trials studied a Bimatoprost 15 mg and 10 mg sustained release dose. The applicant has proposed marketing only the Bimatoprost SR 10 mg dose.

Components and Quantitative Composition of Bimatoprost SR 10mcg implant

Component	Function	Quality Standard	Concentration	
			% w/w	µg/Dose
Bimatoprost	Drug substance	In-house[a]	(b) (4)	10
(b) (4) Poly (D,L-lactide)	(b) (4)	In-house		(b) (4)
(b) (4) Poly (D,L-lactide-co-glycolide)		In-house		
(b) (4) Poly (D,L-lactide) Acid End		In-house		
Polyethylene Glycol 3350		USP		
		Total	100	

a Per Type II DMF (b) (4)
b (b) (4)

4.3. Clinical Microbiology

Not applicable. The drug product is not an antimicrobial.

4.4. Nonclinical Pharmacology/Toxicology

Carcinogenesis

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses up to 2 mg/kg/day and 1 mg/kg/day respectively for 104 weeks (approximately 3100 and 1700 times, respectively, the maximum human exposure [based on plasma Cmax levels; blood-to-plasma partition ratio of 0.858]).

Mutagenesis
Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the in vivo mouse micronucleus tests.

Impairment of Fertility
Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 1800 times the maximum human exposure [based on plasma Cmax levels; blood-to-plasma partition ratio of 0.858]).

4.5. Clinical Pharmacology

Bimatoprost, a prostaglandin analog, is a synthetic structural analog of prostaglandin with ocular hypotensive activity. Bimatoprost is believed to lower IOP in humans by increasing outflow of aqueous humor through both the trabecular meshwork (conventional) and uveoscleral routes (unconventional).

Pharmacokinetics

Absorption
After a single administration of DURYSTA, bimatoprost concentrations systemically were below the lower limit of quantitation (0.001-0.005 ng/mL) in the majority of patients. The maximum bimatoprost concentration observed in any patient was 0.00224 ng/mL. There was no accumulation of bimatoprost upon repeat administration of DURYSTA. Bimatoprost acid concentrations were below the lower limit of quantitation (0.01-0.05 ng/mL) in all patients.

Distribution
Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism
Bimatoprost is not extensively metabolized in human eyes and remains the major circulating species in the blood once it reaches the systemic circulation following ocular administration. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites. Bimatoprost was found to have no significant effect on any of the hepatic microsomal enzyme activities in cynomolgus monkeys.

Elimination
Following an intravenous dose of radiolabeled bimatoprost (3.12 mcg/kg) to six healthy subjects, the mean maximum blood concentration of total radioactivity was 14.5 ng·eq/mL.

Total radioactivity was eliminated from the body with a half-life of 1.74 hours. The maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. Blood concentrations of the C-1 acid metabolite were much lower than those of bimatoprost, reaching a peak of 0.12 ng/mL. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The table below lists the two clinical studies (192024-091 and 192024-092) that were reviewed to evaluate safety and efficacy of Bimatoprost SR implant.

Study	Design	Key Entry Criteria	Planned Number of subjects	Duration
192024-091	Multicenter, Randomized, Parallel group, Patient and Investigator masked	Iridocorneal inferior angle ≥Shaffer Grade 3 on gonioscopy, peripheral AC depth by Van Herick examination ≥1/2 corneal thickness, Hour 0 IOP ≥22mmHg and ≤32mmHg, Hour 2 IOP ≥19mmHg and ≤32mmHg	200 Bimatoprost SR 10 µg 200 Bimatoprost SR 15 µg 200 Timolol 0.5% drops	Approx 20 months
192024-092	Same as -091	Same as -091	170 Bimatoprost SR 10 µg 170 Bimatoprost SR 15 µg 170 Timolol 0.5% drops	Same as -091

5.2. Review Strategy

The efficacy of DURYSTA, for the proposed indication was based on the review of the 2 randomized, double-masked studies listed in Section 5.1.

The following is a list of investigators and the number of subjects enrolled in the two clinical studies (192024-091 and 192024-092). Given over 100 sites enrolled subjects in each clinical trial only those sites enrolling 10 or more subjects are listed:

List and Description of Investigators 192024-091

Principal Investigator	Site Address	Subjects Enrolled (N)
Jitendra Swarup, M.D.	Elizabeth City, NC	10
Joseph Martel, M.D.	Rancho Cordova, CA	19
Louis Alpern, M.D.	El Paso, TX	21
Thomas Walters, M.D.	Austin, TX	36

Paul Hartman, M.D.	Rochester, NY	17
Jacob Brubaker, M.D.	Sacramento, CA	12
Charles Crane, M.D.	South Orange, NJ	11
Sherif El-Harazi, M.D.	Glendale, CA	16
Richard Evans, M.D.	San Antonio, TX	30
Ronald Frenkel, M.D.	Stuart, FL	14
Don Perez Ortiz, M.D.	Tampa, FL	10
Fiaz Zaman, M.D.	Houston, TX	12
Douglas Day, M.D.	Roswell, GA	18
Andrew Camp, M.D.	La Jolla, CA	15
Max Kim, M.D.	Phoenix, AZ	15
William Haynes, M.D.	Asheville, NC	10
Gary Jerkins, M.D.	Nashville, TN	11
Jeffrey Levenson, M.D.	Jacksonville, FL	12
Harvey UY, M.D.	Makati City, Phillipines	13
Krystyna Raczynska, M.D.	Gdansk, Poland	11
Slawomir Zalewski, M.D.	Olsztyn, Poland	10

List and Description of Investigators 192024-092

Principal Investigator	**Site Address**	**Subjects Enrolled (N)**
James Branch, M.D.	Winston Salem, NC	20
William Christie, M.D.	Cranberry Township, PA	11
Damien Goldberg, M.D.	Torrance, CA	13
Christopher Lin, M.D.	Redding, CA	10
Zachary Segal, M.D.	Miami, FL	13
Frank Cotter, M.D.	Roanoke, VA	11
David Wirta, M.D.	Newport Beach, CA	36
Michael Depenbusch, M.D.	Chandler, AZ	18
Pankajkumar Shah, M.D.	Mission, TX	22
Sebastian Heersink, M.D.	Dothan, AL	10
Lance Bergstrom, M.D.	Fargo, ND	22
Shailesh Gupta, M.D.	Weston, FL	13
Gabriel Bercovich, M.D.	Argentina	11
Federico Furno Sola	Argentina	14
Juan Camilo Parra Restrepo, M.D.	Colombia	10

Reviewer's comment:
No one site in either trial drove the overall results of the clinical trials.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. The Efficacy and Safety of Bimatoprost SR in Patients with Open-angle Glaucoma or Ocular Hypertension

6.1.1. Study Design

Overview and Objective

To evaluate the intraocular pressure (IOP)-lowering efficacy and safety of 2 dose strengths of Bimatoprost SR in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) after initial and repeated administration

Trial Design

Structure: Phase 3, multicenter, randomized, masked, parallel-group comparison (2 dose strengths of Bimatoprost SR versus active control), repeat administration

Duration: Approximately 22 months, consisting of screening of up to 28 days before washout, washout period of up to 42 days before initial administration of study medication, 52-week treatment period, plus 8 months extended follow-up

Study Treatment Groups: Bimatoprost SR dose groups: 10 µg and 15 µg

Control: Timolol eye drops plus Sham needleless procedure (that involves touching the eye at the area of insertion with a needleless applicator).

Dosage/Dose Regimen: Patients will receive 1 of 2 dose strengths of Bimatoprost SR or Control treatment in the study eye on Day 1 (with repeat administration of the same dose strength or Sham at Week 16 and Week 32). Bimatoprost SR-treated patients will receive intracameral administration of Bimatoprost SR in the study eye using a prefilled applicator. Timolol vehicle eye drops will be used twice daily (BID; in the morning and evening) to mask the treatment of patients receiving Bimatoprost SR in the study eye. The fellow eye will receive a Sham needleless procedure (hereafter called Sham administration or Sham administration procedure) plus topical timolol eye drops, BID. Control group patients will receive a Sham administration plus timolol in both eyes. All patients will be masked to their treatment group.

Study Endpoints

At least 1 dose strength (10 µg or 15 µg) of Bimatoprost SR will have an IOP-lowering effect that is noninferior to that of topically administered timolol maleate 0.5% (hereafter referred to as timolol) eye drops in patients with OAG or OHT following single and repeat administration at Hours 0 and 2, Weeks 2, 6 and 12.

Bimatoprost SR administered intracamerally in dose strengths of 10 µg or 15 µg will have an acceptable safety.

Statistical Analysis Plan

The intent-to-treat population (ITT) is defined as all randomized patients and will be used for demographic and efficacy analyses. The per protocol (PP) population will consist of the subset of the ITT population with no protocol deviations affecting the primary efficacy analysis and will be used to confirm the primary efficacy analysis.

The primary efficacy variable is study eye time-matched IOP change from baseline. Mean IOP change from baseline will be compared between each Bimatoprost SR dose strength and timolol for each hour (Hours 0 and 2) using the ITT population at multiple timepoints

Reviewer's Comment:
These time points capture the peak and trough times of timolol maleate (i.e., 2 hours after dosing).

6.1.2. Study Results

Compliance with Good Clinical Practices

The studies were conducted under Good Clinical Practices.

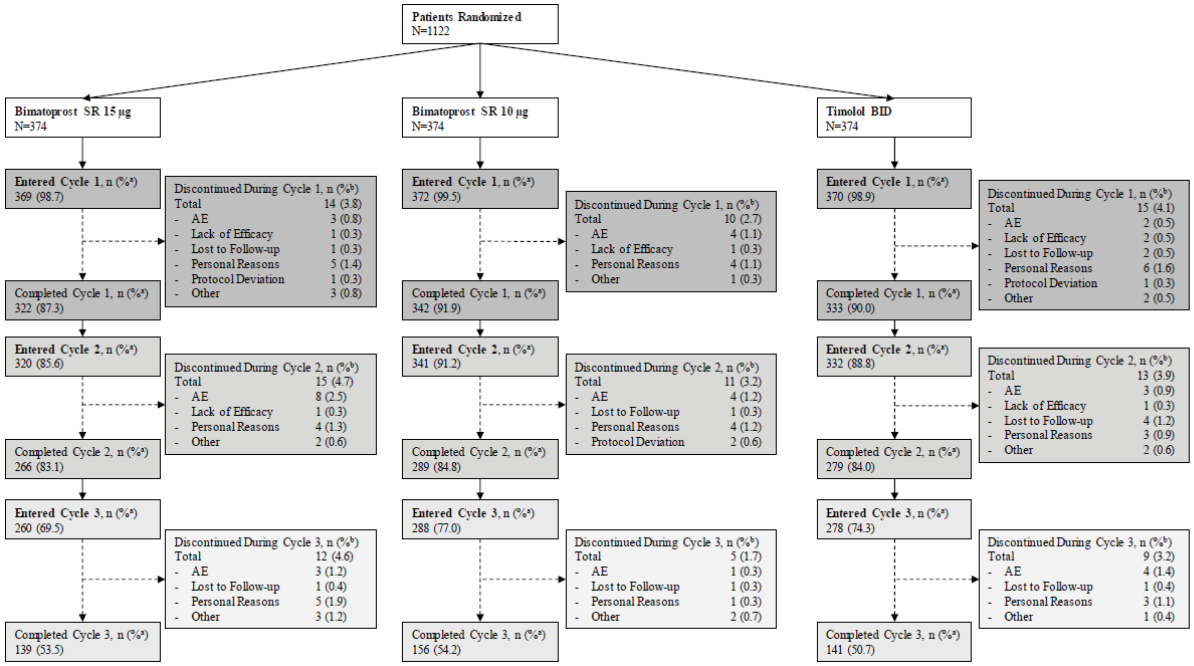
Financial Disclosure

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

Patient Disposition and Primary Reason for Discontinuation

Summary of Patient Disposition (Studies 192024-091 and 192024-92, Pooled, ITT Population)



These studies are still ongoing; disposition is based on data available at the time of the primary database lock (Week 12).
a Denominator = Number of patients in the treatment group
b Denominator = Number of patients in the treatment group who entered treatment cycle.

Protocol Violations/Deviations

As noted within above chart of Summary of Patient Disposition there were less than 1% Protocol deviations in any group.

Table of Demographic Characteristics

Parameter	Study 192024-091			Study192024-092			Pooled Studies 192024-091 and -092			
	Bim SR 15 µg (N = 198)	Bim SR 10 µg (N = 198)	Tim BID (N = 198)	Bim SR 15 µg (N = 176)	Bim SR 10 µg (N = 176)	Tim BID (N = 176)	Bim SR 15 µg (N = 374)	Bim SR 10 µg (N = 374)	Tim BID (N = 374)	Total (N = 1122)
Age (years)										
Mean (SD)	62.5 (13.0)	62.6 (11.5)	62.5 (11.0)	63.8 (10.7)	62.5 (12.7)	61.4 (12.4)	63.1 (12.0)	62.6 (12.1)	62.0 (11.7)	62.6 (11.9)
Min, Max	25, 92	23, 88	24, 88	24, 85	23, 88	19, 90	24, 92	23, 88	19, 90	19, 92
Age Group, n (%)										
< 45	17 (8.6)	12 (6.1)	11 (5.6)	8 (4.5)	15 (8.5)	16 (9.1)	25 (6.7)	27 (7.2)	27 (7.2)	79 (7.0)
≥ 45 and ≤ 65	88 (44.4)	102 (51.5)	109 (55.1)	86 (48.9)	81 (46.0)	94 (53.4)	174 (46.5)	183 (48.9)	203 (54.3)	560 (49.9)
> 65	93 (47.0)	84 (42.4)	78 (39.4)	82 (46.6)	80 (45.5)	66 (37.5)	175 (46.8)	164 (43.9)	144 (38.5)	483 (43.0)
Sex, n (%)										
Male	102 (51.5)	112 (56.6)	92 (46.5)	85 (48.3)	86 (48.9)	88 (50.0)	187 (50.0)	198 (52.9)	180 (48.1)	565 (50.4)
Female	96 (48.5)	86 (43.4)	106 (53.5)	91 (51.7)	90 (51.1)	88 (50.0)	187 (50.0)	176 (47.1)	194 (51.9)	557 (49.6)
Race, n (%)										
White	122 (61.6)	123 (62.1)	130 (65.7)	116 (65.9)	115 (65.3)	104 (59.1)	238 (63.6)	238 (63.6)	234 (62.6)	710 (63.3)
Black or African American	30 (15.2)	31 (15.7)	21 (10.6)	19 (10.8)	20 (11.4)	36 (20.5)	49 (13.1)	51 (13.6)	57 (15.2)	157 (14.0)
Asian	12 (6.1)	17 (8.6)	16 (8.1)	6 (3.4)	11 (6.3)	13 (7.4)	18 (4.8)	28 (7.5)	29 (7.8)	75 (6.7)
Hispanic	27 (13.6)	23 (11.6)	25 (12.6)	27 (15.3)	22 (12.5)	21 (11.9)	54 (14.4)	45 (12.0)	46 (12.3)	145 (12.9)
Other	6 (3.0)	4 (2.0)	5 (2.5)	8 (4.5)	8 (4.5)	2 (1.1)	14 (3.7)	12 (3.2)	7 (1.9)	33 (2.9)
Not Reported	1 (0.5)	0	1 (0.5)	0	0	0	1 (0.3)	0	1 (0.3)	2 (0.2)
Race group, n (%)										
White	122 (61.6)	123 (62.1)	130 (65.7)	116 (65.9)	115 (65.3)	104 (59.1)	238 (63.6)	238 (63.6)	234 (62.6)	710 (63.3)
Non-White	75 (37.9)	75 (37.9)	67 (33.8)	60 (34.1)	61 (34.7)	72 (40.9)	135 (36.1)	136 (36.4)	139 (37.2)	410 (36.5)
Not Reported	1 (0.5)	0	1 (0.5)	0	0	0	1 (0.3)	0	1 (0.3)	2 (0.2)

Source: Module 5.3.5.1, CSR Study 192024-091, Table 10-3, CSR Study 192024-092, Table 10-3; and ISE Table 2-1.1

Other Baseline and Disease Characteristics

Parameter	Study 192024-091			Study192024-092			Pooled Studies 192024-091 and -092			
	Bim SR 15 µg (N = 198)	Bim SR 10 µg (N = 198)	Tim BID (N = 198)	Bim SR 15 µg (N = 176)	Bim SR 10 µg (N = 176)	Tim BID (N = 176)	Bim SR 15 µg (N = 374)	Bim SR 10 µg (N = 374)	Tim BID (N = 374)	Total (N = 1122)
Iris Color, n (%)										
Monochromic	160 (80.8)	165 (83.3)	157 (79.3)	133 (75.6)	147 (83.5)	145 (82.4)	293 (78.3)	312 (83.4)	302 (80.7)	907 (80.8)
Heterochromic - Peripupillary	29 (14.6)	24 (12.1)	27 (13.6)	26 (14.8)	20 (11.4)	20 (11.4)	55 (14.7)	44 (11.8)	47 (12.6)	146 (13.0)
Heterochromic - Diffuse	9 (4.5)	9 (4.5)	14 (7.1)	16 (9.1)	7 (4.0)	9 (5.1)	25 (6.7)	16 (4.3)	23 (6.1)	64 (5.7)
Missing	0	0	0	1 (0.6)	2 (1.1)	2 (1.1)	1 (0.3)	2 (0.5)	2 (0.5)	5 (0.4)
Diagnosis, n (%)										
OHT	41 (20.7)	35 (17.7)	41 (20.7)	49 (27.8)	41 (23.3)	45 (25.6)	90 (24.1)	76 (20.3)	86 (23.0)	252 (22.5)
OAG										
Primary	153 (77.3)	159 (80.3)	152 (76.8)	118 (67.0)	131 (74.4)	125 (71.0)	271 (72.5)	290 (77.5)	277 (74.1)	838 (74.7)
Pseudoexfoliation	1 (0.5)	1 (0.5)	1 (0.5)	2 (1.1)	1 (0.6)	2 (1.1)	3 (0.8)	2 (0.5)	3 (0.8)	8 (0.7)
Pigmentary	3 (1.5)	3 (1.5)	4 (2.0)	7 (4.0)	3 (1.7)	4 (2.3)	10 (2.7)	6 (1.6)	8 (2.1)	24 (2.1)
Hour 0 IOP, n (%)										
≤ 25mm Hg	135 (68.2)	132 (66.7)	136 (68.7)	130 (73.9)	132 (75.0)	130 (73.9)	265 (70.9)	264 (70.6)	266 (71.1)	795 (70.9)
>25 mm Hg	63 (31.8)	66 (33.3)	62 (31.3)	46 (26.1)	44 (25.0)	45 (25.6)	109 (29.1)	110 (29.4)	107 (28.6)	326 (29.1)
Missing	0	0	0	0	0	1 (0.6)	0	0	1 (0.3)	1 (0.1)
CECD (cells/mm^2)										
Mean	2452.5	2472.9	2455.3	2487.7	2434.2	2469.2	2469.1	2454.7	2461.8	2461.9
(SD)	(349.4)	(342.1)	(306.4)	(301.9)	(310.8)	(352.4)	(327.9)	(327.9)	(328.5)	(327.9)
Min, Max	1802, 3373	1540, 3396	1423, 3419	1811, 3719	1824, 3215	1698, 3643	1802, 3719	1540, 3396	1423, 3643	1423, 3719
Lens status, n (%)										
Phakic	131 (66.2)	152 (76.8)	144 (72.7)	142 (80.7)	135 (76.7)	135 (76.7)	273 (73.0)	287 (76.7)	279 (74.6)	839 (74.8)
Pseudophakic	67 (33.8)	46 (23.2)	54 (27.3)	34 (19.3)	41 (23.3)	41 (23.3)	101 (27.0)	87 (23.3)	95 (25.4)	283 (25.2)
Iridocorneal angle MIF (µm)										
Mean	495.1	476.8	470.4	448.9	467.8	474.9	473.3	472.6	472.5	472.8
(SD)	(133.1)	(135.7)	(132.2)	(142.0)	(131.6)	(137.5)	(139.1)	(133.7)	(134.5)	(135.7)
Min, Max	220, 720	120, 720	100, 720	20, 720	140, 720	100, 720	20, 720	120, 720	100, 720	20, 720

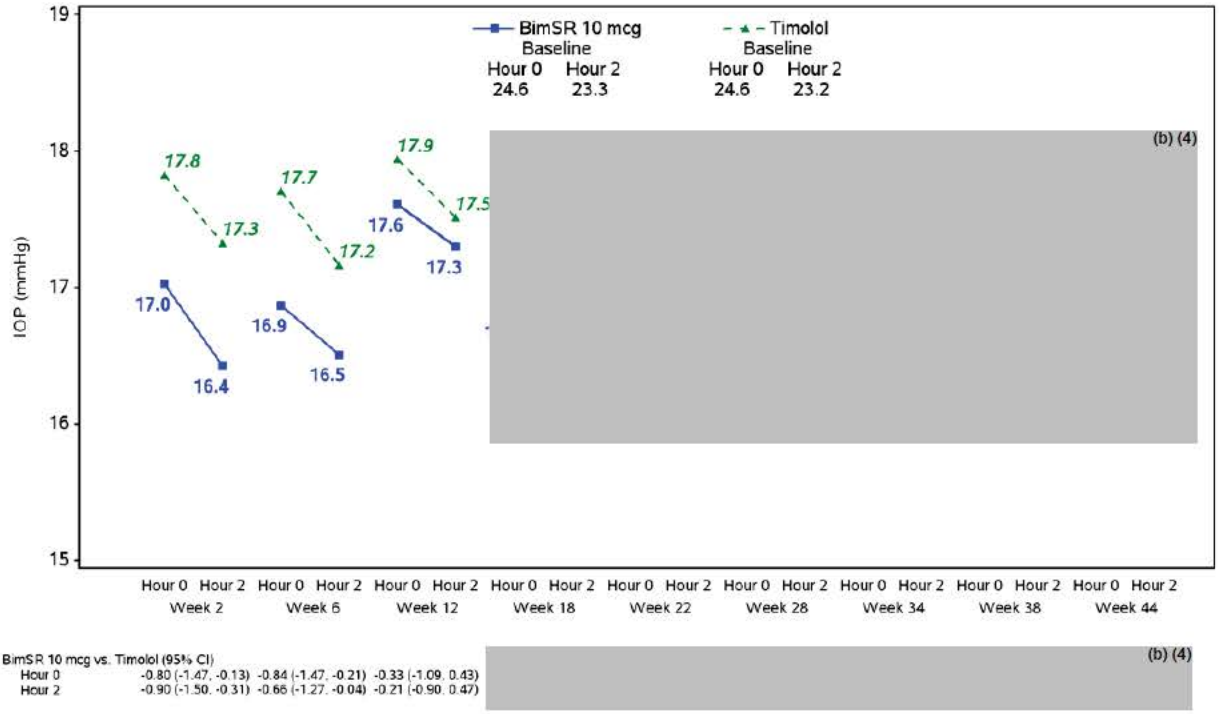
Source: Module 5.3.5.1 CSR Study 192024-091, Table 10-4, CSR Study 192024-092, Table 10-4, and ISE Table 2-2.1

Treatment Compliance

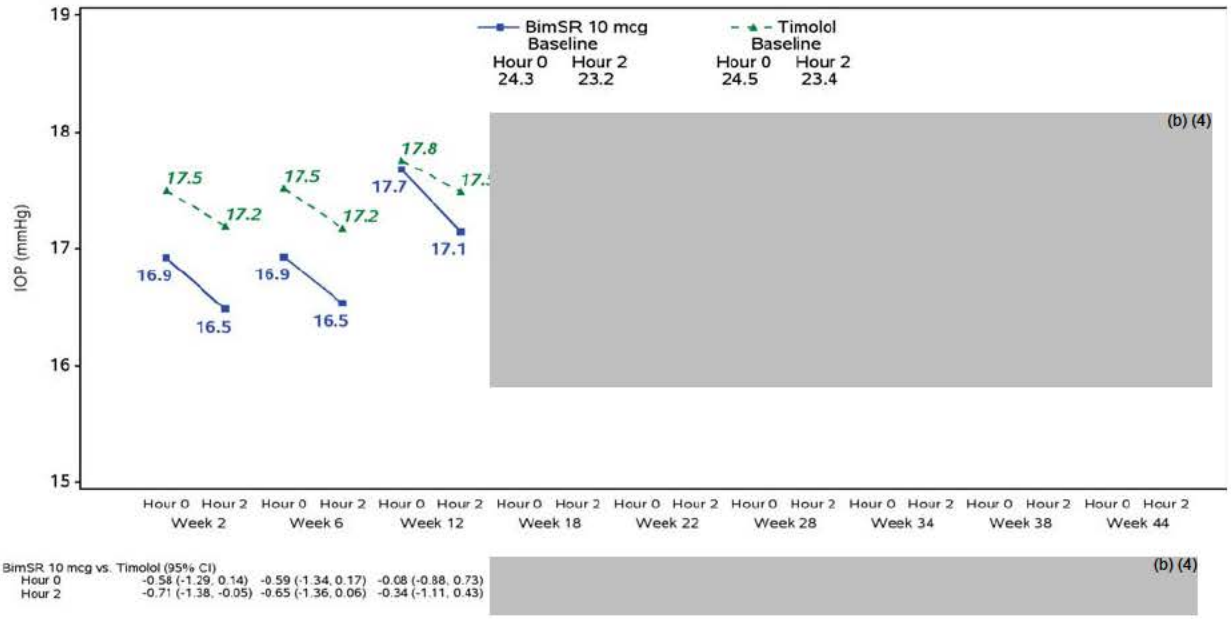
Subjects were treated with an intracameral injection of sustained release of bimatoprost. Therefore, upon treatment the subjects' treatment compliance was not an issue.

Efficacy Results – Primary Endpoint

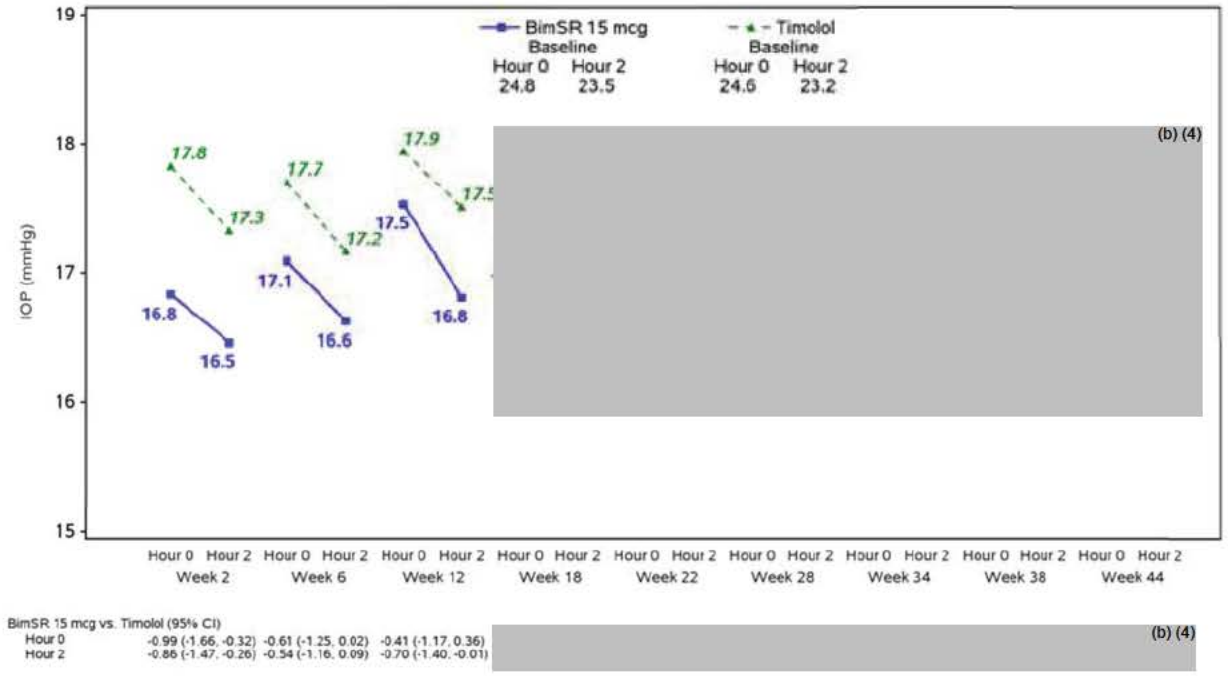
Study 1: 192024-91 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP – Bimatoprost SR 10 mcg versus Timolol 0.5% BID



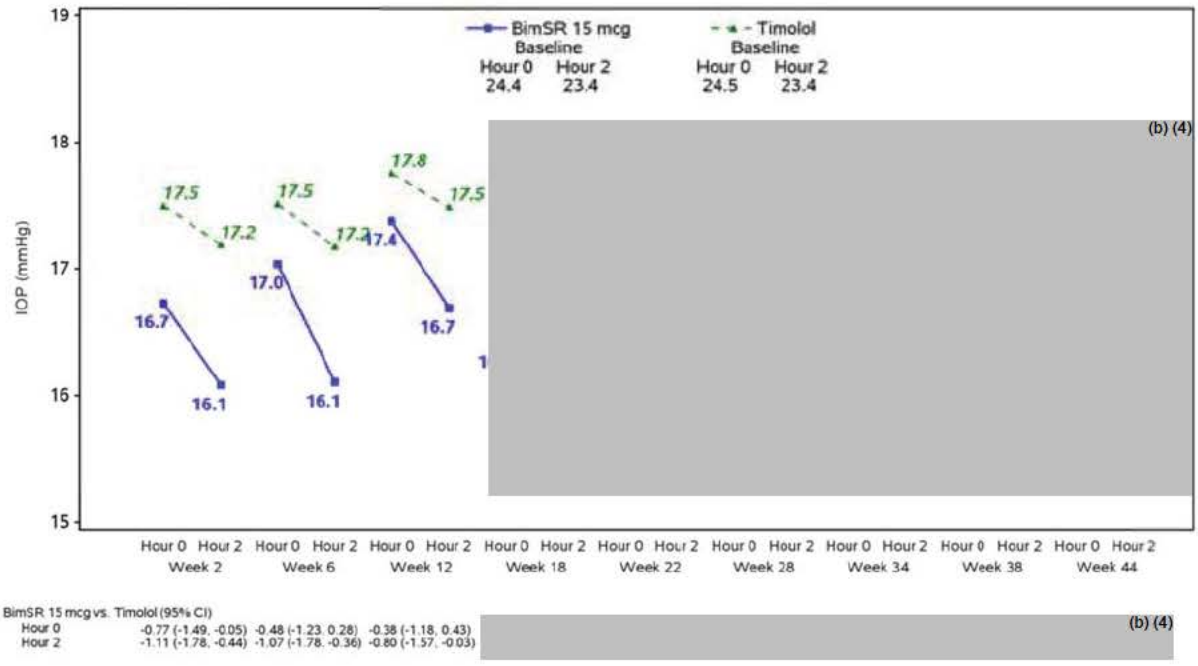
Study 2: 192024-92 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP – Bimatoprost SR 10 mcg versus Timolol 0.5% BID



Study 1: 192024-91 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP – Bimatoprost SR 15 mcg versus Timolol 0.5% BID



Study 2: 192024-92 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP – Bimatoprost SR 15 mcg versus Timolol 0.5% BID



Both Bimatoprost SR 15 mcg and 10 mcg dose strengths were considered to be clinically noninferior to timolol based on the prespecified definition for noninferiority (upper limit of the 95% CI ≤ 1.5 mm Hg for each of the 6 primary timepoints [Hours 0 and 2 at Weeks 2, 6, and 12) and (upper limit of the 95% CI ≤ 1.0 mm Hg for majority of the 6 primary timepoints).

Reviewer's Comment:
Baseline mean IOP of the two treatment groups for both trials are similar. The mean IOP for Bimatoprost SR and timolol 0.5% are similar for both trials at all time points measured. Bimatoprost SR was not inferior compared to timolol BID dosing.

IOP (mm Hg) Baseline and Change from Baseline in Study Eye at Weeks 2, 6, and 12 for Cycle 1 (Studies 192024-091 and 192024-092, Pooled, ITT Population)

			192024-091			192024-092		
Visit	Hour		Bim 15	Bim 10	Tim	Bim 15	Bim 10	Tim
			N=198	N=198	N=198	N=176	N=176	N=176
Baseline	0	N	197	198	198	176	176	175
		Mean	24.8	24.6	24.6	24.4	24.3	24.5
		Std	2.8	2.7	2.6	2.5	2.4	2.5
	2	N	197	198	198	176	175	175
		Mean	23.6	23.3	23.2	23.4	23.2	23.4
		Std	3.1	3.1	2.9	2.8	2.8	3.1
Week 2	0	N	190	196	196	170	172	171
		Mean Change	-7.9	-7.6	-6.2	-7.9	-7.6	-7.2
		Difference	-1.0	-0.8		-0.8	-0.6	
		95% CI	-1.7,-0.3	-1.5,-0.1		-1.5,-0.1	-1.3,0.1	
	2	N	190	196	196	170	171	171
		Mean Change	-7.4	-7.2	-6.2	-7.7	-7.3	-6.7
		Difference	-0.9	-0.9		-1.1	-0.7	
		95% CI	-1.5,-0.3	-1.5,-0.3		-1.8,-0.4	-1.4,-0.1	
Week 6	0	N	187	197	194	171	171	167
		Mean Change	-7.7	-7.8	-7.0	-7.6	-7.6	-7.3
		Difference	-0.6	-0.8		-0.5	-0.6	
		95% CI	-1.3,-0.0	-1.5,-0.2		-1.2,0.3	-1.3,0.2	
	2	N	186	197	193	171	170	167
		Mean Change	-7.2	-7.1	-6.4	-7.7	-7.2	-6.7
		Difference	-0.5	-0.7		-1.1	-0.7	
		95% CI	-1.2,0.1	-1.3,-0.0		-1.8,-0.4	-1.4,-0.3	
Week 12	0	N	185	192	191	168	169	165
		Mean Change	-7.2	-7.0	-6.7	-7.2	-6.9	-7.0
		Difference	-0.4	-0.3		-0.4	-0.1	
		95% CI	-1.2,0.4	-1.1,0.4		-1.2,0.4	-0.9,0.7	
	2	N	183	192	191	168	168	165
		Mean Change	-7.1	-6.3	-6.1	-7.1	-6.6	-6.4
		Difference	-0.7	-0.2		-0.8	-0.3	
		95% CI	-1.4,-0.0	-0.9,0.5		-1.6,0.0	-1.1,0.4	

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoint analyses are exploratory. The Applicant does not plan to make labeling claims based on pre-specified secondary and other endpoints.

Dose/Dose Response

Both trials studied a Bimatoprost 15 mg and 10 mg sustained release dose. The applicant has proposed marketing only the Bimatoprost SR 10 mg dose.

Durability of Response

The mean IOP reduction does not extend over the full four month evaluation periods in many patients even though portions of the implant are still visible in the angle. Although still effective at Week 12, a reduction in efficacy was being to be noticed at Week 12.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Clinically significant reduction of intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy products to treat ocular hypertension. The primary efficacy endpoint for studies 192024-91 and 192024-92 were the same. The primary endpoint was mean IOP measured at hours 0 and 2 (weeks 2, 6 and 12) when compared to Timolol dosed BID which was intended to capture the peak and trough of Timolol dosed BID daily.

7.1.2. Subpopulations

The amount of reduction in IOP was consistent across all relevant subpopulations including age, sex, race/ethnicity, and geographic region.

8. Review of Safety

8.1. Safety Review Approach

Safety was evaluated in Studies 192024-091 and 192024-92 which were two multicenter, randomized, parallel-group, patient- and efficacy evaluator-masked, active-controlled 20-month (including 8-month extended follow-up) studies of Bimatoprost SR compared to

twice daily topical timolol 0.5% drops, in patients with OAG or OHT.

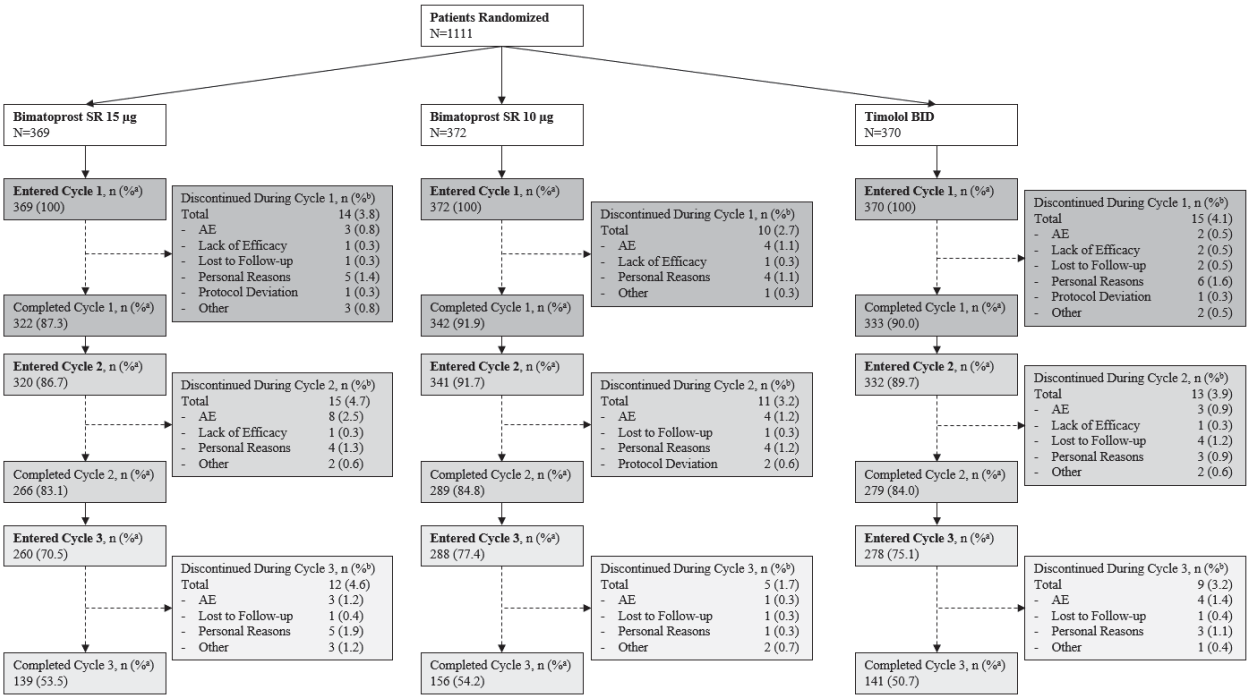
The pooled safety data from Studies 192024-091 and 192024-092 were summarized using 2 analysis sets:

- Analysis Set 1 comprising all patients in the safety population
- Analysis Set 2 comprising all patients in the safety population in the safety population with long term exposure (≥ 350 days in total study duration) and also had 3 implants/Sham administrations

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Summary of Patient Disposition (Pooled 091 and 092 Phase 3 Studies, Analysis 1)



a Denominator = Number of patients in the treatment group.
b Denominator = Number of patients within the treatment group who entered the treatment cycle.
These studies are still ongoing; disposition is based on data available at the time of primary database lock (Week 12).
Source: ISS Table 1-1.1

Summary of Duration of Exposure (Pooled 091 and 092 Phase 3 Studies, Analysis 1)

Study Duration (DAYS)	BimSR 15µg N=369	BimSR 10µg N=374	Tim BID N=370
Mean (SD)	424 (185.4)	431 (185.0)	413 (188.0)
Median	481	486	459
Q1, Q3	266, 600	267, 602	239, 598
Min, Max	8, 662	17, 715	16, 657

Study duration = Date of study exit - Day 1 administration date + 1. If the date of exit is missing, the date of the last visit will be used.
Source: ISS Table 3-1.1

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat. The safety population included primarily subjects with open-angle glaucoma or ocular hypertension.

8.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

The safety parameters for these studies included the following non-ocular safety parameters: non-ocular AEs, clinical laboratory values, vital signs, physical examinations, and recorded cases of pregnancy. Ocular safety parameters included ocular AEs, implant/Sham assessment, visual acuity, visual field examination, macroscopic iris color assessment, macroscopic conjunctival hyperemia assessment, biomicroscopic examination, lens assessment, optic disc examination, dilated ophthalmoscopic examination, gonioscopy assessment, OCT, specular microscopy, pachymetry, and AS-OCT.

8.3.3. Routine Clinical Tests

The routine clinical testing to evaluate safety concerns for Bimatoprost SR was adequately addressed in the design and conduct of the clinical trials.

8.4. Safety Results

8.4.1. Deaths

There have been 3 patient deaths reported in these studies to date; 2 deaths in the Bimatoprost SR 15 µg group (cause of death was reported as left middle cerebral artery cerebrovascular accident due to atrial fibrillation and hypertension for 1 patient, and complications from bowel obstruction with torsion, which resulted in cardiac arrest for the other patient) and 1 death in the timolol group (cause of death was reported as head injury from a fall). None of the patient deaths were considered to be related to study treatment or procedures.

8.4.2. Serious Adverse Events

Ocular Serious AEs: Number (%) of Patients by System Organ Class and Preferred Term in Descending Incidence (Pooled 091 and 092 Phase 3 Studies, Analysis Set 1)

	Study Eye			Fellow Eye
Preferred Term	BimSR 15 ug (N=369) n (%)	BimSR 10 ug (N=372) n (%)	Tim BID (N=370) n (%)	All Patients (N=1111) n (%)
Any term	18 (4.9)	11 (3.0)	0	1 (0.1)
Corneal endothelial cell loss	14 (3.8)	5 (1.3)	0	0
Corneal oedema	4 (1.1)	2 (0.5)	0	0
Macular oedema	1 (0.3)	1 (0.3)	0	0
VIth nerve paralysis	1 (0.3)	1 (0.3)	0	0
Iridocyclitis	1 (0.3)	0	0	0
Product administered at inappropriate site	1 (0.3)	0	0	0
Retinal tear	0	1 (0.3)	0	1 (0.1)
Corneal decompensation	0	1 (0.3)	0	0
Corneal touch	0	1 (0.3)	0	0
Ulcerative keratitis	0	1 (0.3)	0	0
Uveitis	0	1 (0.3)	0	0
Visual impairment	0	1 (0.3)	0	0

AE dictionary: MedDRA Version 21.0
Ocular AEs are AEs that are marked as 'ocular' on AE eCRF form.
Patients are counted only once within each preferred term.
Source: ISS Table 4-11.1

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Ocular AEs Leading to Study Discontinuations: Number (%) of Patients by System Organ Class and Preferred Term in Descending Incidence (Pooled 091 and 092 Phase 3 Studies, Analysis Set 1)

	Study Eye			Fellow Eye
System Organ Class Preferred Term	BimSR 15 ug (N=369) n (%)	BimSR 10 ug (N=372) n (%)	Tim BID (N=370) n (%)	All Patients (N=1111) n (%)
Any term	20 (5.4)	5 (1.3)	3 (0.8)	5 (0.5)
Eye disorders	14 (3.8)	4 (1.1)	2 (0.5)	1 (0.1)
Corneal oedema	5 (1.4)	3 (0.8)	0	0
Corneal endothelial cell loss	4 (1.1)	1 (0.3)	0	0
Conjunctival hyperaemia	3 (0.8)	0	0	0
Corneal touch	2 (0.5)	2 (0.5)	0	0
Corneal disorder	1 (0.3)	1 (0.3)	0	0
Cataract	1 (0.3)	0	1 (0.3)	1 (0.1)
Corneal decompensation	1 (0.3)	0	0	0
Corneal opacity	1 (0.3)	0	0	0
Eye pain	1 (0.3)	0	0	0
Iritis	1 (0.3)	0	0	0
Conjunctival oedema	0	1 (0.3)	0	0
Macular oedema	0	1 (0.3)	0	0
Uveitis	0	1 (0.3)	0	0
Vitreal cells	0	1 (0.3)	0	0
Optic disc haemorrhage	0	0	1 (0.3)	0
Immune system disorders	0	0	0	1 (0.1)
Drug hypersensitivity	0	0	0	1 (0.1)
Infections and infestations	2 (0.5)	0	1 (0.3)	2 (0.2)
Conjunctivitis viral	1 (0.3)	0	0	1 (0.1)
Keratouveitis	1 (0.3)	0	0	0
Conjunctivitis	0	0	1 (0.3)	1 (0.1)
Injury, poisoning and procedural complications	0	1 (0.3)	0	0
Product administered at inappropriate site	0	1 (0.3)	0	0
Nervous system disorders	0	0	0	1 (0.1)
Visual field defect	0	0	0	1 (0.1)
Product issues	1 (0.3)	0	0	0
Device dislocation	1 (0.3)	0	0	0
Surgical and medical procedures	5 (1.4)	0	0	0
Drug delivery device implantation	5 (1.4)	0	0	0

AE dictionary: MedDRA Version 21.0
Ocular AEs are AEs that are marked as 'ocular' on AE eCRF form.
Patients are counted only once within each preferred term.
Source: ISS Table 4-12.1

8.4.4. Significant Adverse Events

Ocular AEs Leading to Implant Removal: Number (%) of Patients by System Organ Class and Preferred Term in Descending Incidence (Pooled 091 and 092 Phase 3 Studies, Analysis Set 1)

	Study Eye	
Preferred Term	BimSR 15 ug (N=369) n (%)	BimSR 10 ug (N=372) n (%)
Any term	27 (7.3)	10 (2.7)
Corneal endothelial cell loss	11 (3.0)	3 (0.8)
Corneal oedema	10 (2.7)	4 (1.1)
Corneal touch	4 (1.1)	2 (0.5)
Product administered at inappropriate site	1 (0.3)	2 (0.5)
Corneal decompensation	1 (0.3)	1 (0.3)
Corneal degeneration	1 (0.3)	1 (0.3)
Corneal disorder	1 (0.3)	1 (0.3)
Uveitis	1 (0.3)	1 (0.3)
Conjunctival hyperaemia	1 (0.3)	0
Corneal abrasion	1 (0.3)	0
Eye pain	1 (0.3)	0
Iridocyclitis	1 (0.3)	0
Iritis	1 (0.3)	0
Keratopathy	1 (0.3)	0
Keratouveitis	1 (0.3)	0
Macular oedema	0	1 (0.3)
Visual impairment	0	1 (0.3)

AE dictionary: MedDRA Version 21.0
Ocular AEs are AEs that are marked as 'ocular' on AE eCRF form.
Patients are counted only once within each preferred term.
Source: ISS Table 4-14.1

Across the pooled Phase 3 studies, ocular TEAEs leading to implant removal were reported in 7.3% (27/369) of study eyes in the Bimatoprost SR 15 mcg group and 2.7% (10/372) of study eyes in the Bimatoprost SR 10 mcg group. The most frequently reported TEAEs leading to implant removal were corneal endothelial cell loss, corneal edema, corneal touch, and product administered at inappropriate site. All other TEAEs leading to implant removal were reported by only 1 study eye per treatment group.

Ocular AEs Leading to Implant Removal: Number (%) of Patients by System Organ Class and Preferred Term in Descending Incidence (Pooled 091 and 092 Phase 3 Studies, Analysis Set 2)

	Study Eye	
Preferred Term	BimSR 15 ug (N=217) n (%)	BimSR 10 ug (N=234) n (%)
Entire Study, n [1]	217	234
Any term	14 (6.5)	4 (1.7)
Corneal endothelial cell loss	8 (3.7)	2 (0.9)
Corneal oedema	6 (2.8)	2 (0.9)
Corneal touch	1 (0.5)	1 (0.4)
Product administered at inappropriate site	1 (0.5)	0
Uveitis	1 (0.5)	0
Corneal degeneration	0	1 (0.4)
Cycle 1, n [1]	217	234
Any term	0	0
Cycle 2, n [1]	217	234
Any term	2 (0.9)	0
Corneal endothelial cell loss	2 (0.9)	0
Cycle 3, n [1]	217	234
Any term	10 (4.6)	4 (1.7)
Corneal endothelial cell loss	6 (2.8)	2 (0.9)
Corneal oedema	4 (1.8)	2 (0.9)
Corneal touch	1 (0.5)	1 (0.4)
Product administered at inappropriate site	1 (0.5)	0
Corneal degeneration	0	1 (0.4)
Extended Safety Follow-Up, n [1]	196	212
Any term	4 (2.0)	1 (0.5)
Corneal oedema	2 (1.0)	0
Corneal endothelial cell loss	1 (0.5)	1 (0.5)
Uveitis	1 (0.5)	0

AE dictionary: MedDRA Version 21.0
Ocular AEs are AEs that are marked as 'ocular' on AE eCRF form.
Patients are counted only once within each preferred term.
Source: ISS Table 4-14.2

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAEs: Number (%) Reported in ≥ 2% of Patients in any Treatment Group by System Organ Class and Preferred Term in Descending Incidence
(Pooled 091 and 092 Phase 3 Studies, Analysis Set 1)

System Organ Class Preferred Term	BimSR 15 ug (N=369) n (%)	BimSR 10 ug (N=372) n (%)	Tim BID (N=370) n (%)	Total (N=1111) n (%)
Any term	297 (80.5)	286 (76.9)	240 (64.9)	823 (74.1)
Eye disorders	262 (71.0)	227 (61.0)	162 (43.8)	651 (58.6)
Conjunctival hyperaemia	140 (37.9)	101 (27.2)	64 (17.3)	305 (27.5)
Corneal endothelial cell loss	51 (13.8)	19 (5.1)	1 (0.3)	71 (6.4)
Eye pain	50 (13.6)	38 (10.2)	20 (5.4)	108 (9.7)
Foreign body sensation in eyes	47 (12.7)	40 (10.8)	14 (3.8)	101 (9.1)
Eye irritation	38 (10.3)	28 (7.5)	30 (8.1)	96 (8.6)
Photophobia	33 (8.9)	32 (8.6)	4 (1.1)	69 (6.2)
Dry eye	32 (8.7)	27 (7.3)	15 (4.1)	74 (6.7)
Conjunctival haemorrhage	30 (8.1)	34 (9.1)	29 (7.8)	93 (8.4)
Corneal oedema	29 (7.9)	8 (2.2)	2 (0.5)	39 (3.5)
Iritis	28 (7.6)	18 (4.8)	1 (0.3)	47 (4.2)
Punctate keratitis	26 (7.0)	19 (5.1)	19 (5.1)	64 (5.8)
Lacrimation increased	22 (6.0)	15 (4.0)	12 (3.2)	49 (4.4)
Vision blurred	19 (5.1)	21 (5.6)	10 (2.7)	50 (4.5)
Anterior chamber cell	19 (5.1)	15 (4.0)	1 (0.3)	35 (3.2)
Ocular discomfort	18 (4.9)	8 (2.2)	3 (0.8)	29 (2.6)
Visual acuity reduced	11 (3.0)	5 (1.3)	0	16 (1.4)
Iris adhesions	9 (2.4)	9 (2.4)	4 (1.1)	22 (2.0)
Corneal opacity	8 (2.2)	3 (0.8)	2 (0.5)	13 (1.2)
Eyelid oedema	7 (1.9)	3 (0.8)	9 (2.4)	19 (1.7)
Blepharitis	5 (1.4)	11 (3.0)	5 (1.4)	21 (1.9)
Vitreous floaters	3 (0.8)	9 (2.4)	3 (0.8)	15 (1.4)
Gastrointestinal disorders	33 (8.9)	22 (5.9)	27 (7.3)	82 (7.4)
General disorders and administration site conditions	11 (3.0)	9 (2.4)	10 (2.7)	30 (2.7)
Immune system disorders	5 (1.4)	10 (2.7)	4 (1.1)	19 (1.7)
Infections and infestations	101 (27.4)	91 (24.5)	83 (22.4)	275 (24.8)
Nasopharyngitis	20 (5.4)	21 (5.6)	21 (5.7)	62 (5.6)
Influenza	12 (3.3)	11 (3.0)	9 (2.4)	32 (2.9)
Upper respiratory tract infection	11 (3.0)	9 (2.4)	9 (2.4)	29 (2.6)
Sinusitis	9 (2.4)	8 (2.2)	6 (1.6)	23 (2.1)
Bronchitis	8 (2.2)	8 (2.2)	8 (2.2)	24 (2.2)
Conjunctivitis	8 (2.2)	7 (1.9)	4 (1.1)	19 (1.7)
Injury, poisoning and procedural complications	36 (9.8)	45 (12.1)	38 (10.3)	119 (10.7)
Corneal abrasion	8 (2.2)	8 (2.2)	6 (1.6)	22 (2.0)
Aqueous humour leakage	6 (1.6)	8 (2.2)	0	14 (1.3)
Fall	2 (0.5)	5 (1.3)	10 (2.7)	17 (1.5)
Investigations	37 (10.0)	42 (11.3)	21 (5.7)	100 (9.0)
Intraocular pressure increased	22 (6.0)	27 (7.3)	9 (2.4)	58 (5.2)
Metabolism and nutrition disorders	16 (4.3)	15 (4.0)	11 (3.0)	42 (3.8)
Musculoskeletal and connective tissue disorders	44 (11.9)	35 (9.4)	42 (11.4)	121 (10.9)
Arthralgia	6 (1.6)	3 (0.8)	10 (2.7)	19 (1.7)
Back pain	4 (1.1)	8 (2.2)	10 (2.7)	22 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (3.0)	10 (2.7)	8 (2.2)	29 (2.6)
Nervous system disorders	33 (8.9)	41 (11.0)	29 (7.8)	103 (9.3)
Headache	15 (4.1)	19 (5.1)	11 (3.0)	45 (4.1)
Visual field defect	4 (1.1)	9 (2.4)	4 (1.1)	17 (1.5)
Product issues	8 (2.2)	6 (1.6)	0	14 (1.3)
Device dislocation	8 (2.2)	2 (0.5)	0	10 (0.9)
Psychiatric disorders	14 (3.8)	12 (3.2)	4 (1.1)	30 (2.7)
Respiratory, thoracic and mediastinal disorders	26 (7.0)	30 (8.1)	14 (3.8)	70 (6.3)
Cough	6 (1.6)	10 (2.7)	3 (0.8)	19 (1.7)
Surgical and medical procedures	8 (2.2)	2 (0.5)	0	10 (0.9)
Drug delivery device implantation	8 (2.2)	2 (0.5)	0	10 (0.9)
Vascular disorders	25 (6.8)	23 (6.2)	19 (5.1)	67 (6.0)
Hypertension	21 (5.7)	17 (4.6)	12 (3.2)	50 (4.5)

AE dictionary: MedDRA Version 21.0
[M] Adverse events specific to male; [F] Adverse events specific to female.
For sex-specific TEAEs, percentages are relative to the number of patients of the appropriate sex.
TEAE = Treatment-emergent adverse event.
Patients are counted only once within each category.
Source: ISS Table 4-2.1

8.4.6. Vital Signs

Changes from baseline in vital signs were small and similar across treatment groups. Mean changes from baseline in systolic blood pressure were ≤ 3.4 mmHg. Mean changes from baseline in diastolic blood pressure were ≤ 2.5 mmHg. Mean changes from baseline in body temperature were ≤ 0.123°C. Mean changes from baseline in pulse rate were ≤ 3.8 bpm.

8.5. Analysis of Submission-Specific Safety Issues

Corneal endothelial density (CECD) using specular microscopy was a special safety study performed during the clinical development program. Specular microscopy was assessed by a central reader.

The number of study eyes or pooled fellow eyes with a categorical percent loss from baseline in CECD is provided in the following table. Overall mean percent loss in CECD was greatest in the study eyes of the Bimatoprost SR 15 mcg group and was higher in the study eyes of the Bimatoprost SR 10 mcg group compared to the study eyes of the timolol group. Corneal endothelial cell density loss of ≥ 10% was observed across all study eye and fellow eye groups and was most frequently observed in the Bimatoprost 15 mcg group. This finding is likely within the error of measurement. Corneal endothelial cell density loss of ≥ 20% was most frequently observed in the study eyes of the Bimatoprost 15 mcg group, and incidence increased in Cycles 2, 3, and the extended safety follow-up compared to Cycle 1. Corneal endothelial cell loss of ≥ 20% was not observed in the study eyes of the Bimatoprost 10 mcg or timolol groups during Cycle 1. Corneal endothelial cell loss of ≥ 20% was observed from Cycle 2 onwards in study eyes of the Bimatoprost 10 mcg, though the frequency was lower than in study eyes of the Bimatoprost 15 mcg group.

Specular Microscopy: Number (%) of Patient Eyes Categorical Changes in Endothelial Cell Density (Pooled 091 and 092 Phase 3 Studies, Analysis Set 1)

Visit		Study Eye: BimSR 15 ug (N=369)	Study Eye: BimSR 10 ug (N=372)	Study Eye: Tim BID (N=370)	Fellow Eye All Patient (N=1111)
At any visit	n	364	367	369	1100
	Changes within 200 cells/mm2 [1]	242 (66.5)	293 (79.8)	328 (88.9)	994 (90.4)
	>= 10% Loss	102 (28.0)	48 (13.1)	17 (4.6)	39 (3.5)
	>= 20% Loss	66 (18.1)	23 (6.3)	2 (0.5)	2 (0.2)
	>= 30% Loss	50 (13.7)	17 (4.6)	0	0
	>= 40% Loss	42 (11.5)	12 (3.3)	0	0
	>= 50% Loss	38 (10.4)	7 (1.9)	0	0
Week 12/ Cycle 1 Week 12	n	345	350	345	1041
	Changes within 200 cells/mm2	323 (93.6)	332 (94.9)	323 (93.6)	992 (95.3)
	>= 10% Loss	16 (4.6)	3 (0.9)	7 (2.0)	15 (1.4)
	>= 20% Loss	7 (2.0)	0	0	0
	>= 30% Loss	4 (1.2)	0	0	0
	>= 40% Loss	2 (0.6)	0	0	0
	>= 50% Loss	0	0	0	0
Week 28/ Cycle 2 Week 12	n	276	293	295	864
	Changes within 200 cells/mm2	238 (86.2)	270 (92.2)	274 (92.9)	828 (95.8)
	>= 10% Loss	30 (10.9)	14 (4.8)	9 (3.1)	15 (1.7)
	>= 20% Loss	16 (5.8)	5 (1.7)	0	1 (0.1)
	>= 30% Loss	9 (3.3)	4 (1.4)	0	0
	>= 40% Loss	6 (2.2)	3 (1.0)	0	0
	>= 50% Loss	5 (1.8)	3 (1.0)	0	0
Week 44/ Cycle 3 Week 12	n	222	237	233	694
	Changes within 200 cells/mm2	168 (75.7)	211 (89.0)	220 (94.4)	666 (96.0)
	>= 10% Loss	39 (17.6)	21 (8.9)	6 (2.6)	9 (1.3)
	>= 20% Loss	27 (12.2)	9 (3.8)	0	0
	>= 30% Loss	21 (9.5)	4 (1.7)	0	0
	>= 40% Loss	16 (7.2)	4 (1.7)	0	0
	>= 50% Loss	13 (5.9)	2 (0.8)	0	0
Week 52/ Cycle 3 Week 20	n	203	222	216	642
	Changes within 200 cells/mm2	141 (69.5)	200 (90.1)	205 (94.9)	619 (96.4)
	>= 10% Loss	57 (28.1)	19 (8.6)	5 (2.3)	7 (1.1)
	>= 20% Loss	33 (16.3)	8 (3.6)	2 (0.9)	0
	>= 30% Loss	24 (11.8)	4 (1.8)	0	0
	>= 40% Loss	22 (10.8)	1 (0.5)	0	0
	>= 50% Loss	20 (9.9)	1 (0.5)	0	0
Month 20	n	136	152	139	428
	Changes within 200 cells/mm2	74 (54.4)	117 (77.0)	135 (97.1)	397 (92.8)
	>= 10% Loss	52 (38.2)	23 (15.1)	1 (0.7)	9 (2.1)
	>= 20% Loss	33 (24.3)	11 (7.2)	0	1 (0.2)
	>= 30% Loss	25 (18.4)	9 (5.9)	0	0
	>= 40% Loss	21 (15.4)	5 (3.3)	0	0
	>= 50% Loss	19 (14.0)	1 (0.7)	0	0

[1] A patient with CECD changes from baseline within 200 cells/mm2 across all visits in the entire study.
n is the number of patients who had cell density assessment during respective visit, and will be used as the denominators for percentage calculation.
Source: ISS Table 5-10.1

As a risk mitigation measure in Study 192024-091 and 192024-092, patients that received Bimatoprost SR and experienced a significant adverse reaction, including central corneal endothelial cell decrease, could have the implant removed at the discretion of the investigator. As described in the study procedure manual, removal of the implants would be accomplished by the routine surgical procedure of anterior chamber washout, with or without use of viscoelastic material.

Across the pooled Phase 3 studies, ocular TEAEs leading to implant removal were reported in 7.3% (27/369) of study eyes in the Bimatoprost SR 15 mcg group and 2.7% (10/372) of study eyes in the Bimatoprost SR 10 mcg group. The most frequently reported TEAEs leading to implant removal were corneal endothelial cell loss, corneal edema, corneal touch, and product

administered at inappropriate site. All other TEAEs leading to implant removal were reported by only 1 study eye per treatment group.

Subsequent Corneal Endothelial Surgeries

Allergan is aware of 3 treated patients that subsequently had one or more corneal endothelial surgeries. Of these 3 patients, corneal endothelial surgeries were reported in 2 (0.5%) patients receiving the 15 mcg dose strength and 1 (0.3%) patient receiving the 10 mcg dose strength:

- Patient (b) (6), Study 192024-091 – Bimatoprost SR 15 mcg
- Patient , Study 192024-091 – Bimatoprost SR 15 mcg
- Patient , Study 192024-091 – Bimatoprost SR 10 mcg

Reviewer's comments:

After reviewing the newly submitted safety data, Clinical has determined that we will recommend approval of only a single implantation of Durysta 10 mcg due to the adverse event of endothelial cell loss seen with repeat Durysta implantations.

The etiology of the of the corneal endothelial cell loss is unclear. The loss is seen with both the 10 mcg and 15 mcg with repeat injections in subjects with a range of baseline cell counts. It is possible the loss is to due retained sustained-release polymer from the drug delivery system.

Should the applicant wish to pursue labeling which provides for additional cycles of implantation, they would need to submit clinical study results demonstrating ≤ 20% baseline endothelial cell loss after three implantations in ≤ 1% of subjects.

Bimatoprost SR should be contraindicated in patients with corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy) given its increased risk of corneal endothelial cell loss and should be used with caution in patients with limited corneal endothelial cell reserve.

8.6. Safety Analyses by Demographic Subgroups

The incidence of some AEs was numerically higher in the older age group categories compared with the youngest age group. This was evident for corneal endothelial cell loss and corneal edema, particularly the Bimatoprost 15 µg group. The incidence of TEAEs leading to implant removal in the Bimatoprost 15 µg group was higher in patients >65 years old (9.2% [16/173]) compared to patients 45 to 65 years old (6.4% [11/171]) and patients < 45 years old (0%). This trend was not evident in the Bimatoprost 10 µg group. The incidence of ocular TEAEs leading to study discontinuation for the Bimatoprost SR 15 µg group were 8.0% (2/25) for patients aged < 45 years, 5.3% (9/171) for patients aged 45 to ≤65 years, and 5.2% (9/173) for patients aged >65 years. For the Bimatoprost SR 10 µg group, the incidences were: 0 patients (<45 years), 2.2% (4/182) (45 to ≤65 years), and 0.6% (1/163) (>65 years).

Overall, the distribution of AEs across treatment groups was generally similar in males and females. Overall, the distribution of AEs across treatment groups was generally similar across race categories.

8.7. Specific Safety Studies/Clinical Trials

Refer to Section 8.5.

120 Day Safety Update Report

The 120 Day Safety Update was submitted on August 28, 2019, to NDA 211911 / Sequence 0006.

In summary, the 120 Day Safety Update Report does not introduce any new or unexpected safety concerns that were not identified in the original submission.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There is no data to suggest that bimatoprost has any tumorigenic potential.

8.8.2. Human Reproduction and Pregnancy

There have been no reported cases of pregnancy in any clinical study of Bimatoprost SR. There are no adequate and well-controlled studies of Bimatoprost SR or LUMIGAN (bimatoprost ophthalmic solutions) administration in pregnant women. There is no increase in the risk of major birth defects or miscarriages based on LUMIGAN postmarketing experience.

8.8.3. Pediatrics and Assessment of Effects on Growth

Durysta has an agreed PSP with a full waiver for all pediatric age groups. The endothelial cell loss seen with the product in the submitted clinical trials makes it unacceptable for use in children. The product was reviewed at the Pediatric Regulatory Committee on 1/28/20.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose and drug abuse are unlikely as Bimatoprost SR is an intracameral injection administered into the eye by a physician. No information is available on Bimatoprost SR withdrawal or rebound in humans.

8.9. Safety in the Post-market Setting and prior approvals of the molecular entity

Bimatoprost SR has not been licensed or marketed in any country. It contains the same active ingredient as LUMIGAN ophthalmic solutions.

LUMIGAN 0.03% is currently licensed and marketed in more than 80 countries; LUMIGAN 0.03% PF is currently licensed and marketed in more than 20 countries; LUMIGAN 0.01% is licensed and marketed in more than 40 countries. Inclusive of LUMIGAN 0.03%, LUMIGAN PF 0.03%, and LUMIGAN 0.01%, there have been over 17 years of post-marketing pharmacovigilance data constituting over 29 million patient-years of exposure to bimatoprost for IOP lowering worldwide.

The following adverse reactions have been identified during post-marketing use of LUMIGAN 0.03%: deepened lid sulcus (enophthalmos), erythema (periorbital), eyelid edema, macular edema, hair growth abnormal, nausea, dizziness and headache, asthma, exacerbation of asthma, dyspnea, and hypertension. The following adverse reactions have been identified during post-marketing use of LUMIGAN 0.01%: eye pain, vision blurred, headache, asthma, exacerbation of asthma, dyspnea, macular edema, iris hyperpigmentation, blepharal pigmentation, lid sulcus deepened, dry eye, eye discharge, eye edema, eyelid edema, foreign body sensation in eyes, and lacrimation increased. Hypersensitivity reactions with symptoms and signs of eye allergy and allergic dermatitis have been identified for all LUMIGAN formulations.

8.9.1. Expectations on Safety for the molecular entity

Bimatoprost is a prostaglandin analogue. Prostaglandin associated safety issues are described in current class labeling. The safety issues identified in class labeling include increased eyelash, iris and periocular pigmentation, eyelash growth and intraocular inflammation. Information regarding these safety concerns is presented in the recommended labeling.

8.9.2. Additional Safety Issues From Other Disciplines

There are no specific safety concerns from other disciplines.

8.10. Integrated Assessment of Safety

The safety profile of Bimatoprost SR is similar to other marketed prostaglandin analogues with the additional risk of corneal endothelial cell loss. After reviewing the newly submitted safety data, Clinical has determined that we will recommend approval of only a single implantation of Durysta 10 mcg due to the adverse event of endothelial cell loss seen with repeat Durysta implantations.

The etiology of the of the corneal endothelial cell loss is unclear. The loss is seen with both the 10 mcg and 15 mcg with repeat injections in subjects with a range of baseline cell counts. It is possible the loss is to due retained sustained-release polymer from the drug delivery system.

Should the applicant wish to pursue labeling which provides for additional cycles of implantation, they would need to submit clinical study results demonstrating ≤ 20% baseline endothelial cell loss after three implantations in ≤ 1% of subjects.

Bimatoprost SR should be contraindicated in patients with corneal endothelial cell dystrophy (e.g. Fuch's Dystrophy) given its increased risk of corneal endothelial cell loss and should be used with caution in patients with limited corneal endothelial cell reserve.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was required or convened for this NDA. There are multiple prostaglandin analogue drug products marketed in the United States.

10. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

11. Postmarketing Requirements and Commitments

(b) (4)

12. Appendices

12.1. References

An independent literature review was not conducted for this application.

12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 240		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): O		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in stock: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 227		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

12.3. Labeling

NDA 207795 is recommended for approval with the labeling revisions found in this review.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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