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APPLICATION NUMBER:

022184Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 22-184
Submission Number	001
Submission Code	SE5
Letter Date	July 2, 2007
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Reviewer Name	Jennifer Harris, M.D.
Review Completion Date	02/28/2008
Established Name	bimatoprost ophthalmic solution
(Proposed) Trade Name	Lumigan RC
Therapeutic Class	prostaglandin analog
Applicant	Allergan
Priority Designation	S
Formulation	ophthalmic solution
Dosing Regimen	one drop a day
Indication	reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension
Intended Population	adult patients with open-angle glaucoma or ocular hypertension

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Bimatoprost 0.01% is recommended for approval for the (b) (4) *of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.*

1.2 Risk Benefit Assessment

The purpose of this development program was to create a new formulation of bimatoprost that would maintain the IOP-lowering efficacy achieved with Lumigan and improve the overall safety profile and ocular surface tolerability. Bimatoprost 0.01% was developed from the marketed product Lumigan (bimatoprost ophthalmic solution) 0.03%, 50 ppm benzalkonium chloride (BAK) with modifications to the levels of both the active substance, bimatoprost, and the preservative, BAK (and decreased sodium chloride for isotonicity).

Results from the phase 3 study 192024-31 submitted in the NDA demonstrated that bimatoprost 0.01% and 0.0125 lowered IOP by approximately 5-7 mmHg; however, neither drug was equivalent to Lumigan in IOP-lowering efficacy as measured by mean IOP. The difference in mean IOP between bimatoprost 0.01% and Lumigan was within 1.5mmHg at all post-baseline timepoints; however, the majority of timepoints were not within 1 mmHg as stipulated in the Division's definition for establishing equivalency. Bimatoprost 0.0125% yielded similar results.

Overall, bimatoprost 0.01% and 0.0125% were safe and well tolerated. The types of adverse events seen were consistent with the known adverse event profile of Lumigan. There were less ocular adverse events reported in the bimatoprost 0.01% (47.6% vs. 62%) and 0.0125% (48.9% vs. 62%) arms compared to the Lumigan arm. However, there is no confirmatory trial that replicates these results. Additionally, there was underreporting in adverse events, specifically, hyperemia, periorbital hyperpigmentaiton and eyelash growth noted during an investigation at one of the study sites. While this underreporting was distributed across the treatment groups and did not favor any one treatment group, it confounds the interpretation of the reported events.

Approximately three times as many subjects discontinued the study due to ocular adverse events in the Lumigan group compared to bimatoprost 0.01% (6.4% vs. 2.2%) and approximately twice as many compared to bimatoprost 0.0125% (6.4% vs. 3.2%). However, more subjects discontinued the study due to non-ocular adverse events in the bimatoprost 0.01% arm compared to the Lumigan (2.7% vs. 1.6%) and bimatoprost 0.0125% (2.7% vs. 1.1%) arms.

Approximately twice as many subjects in the Lumigan group discontinued due to ocular irritation symptoms (i.e. hyperemia, pruritus, irritation) compared to either the bimatoprost 0.01% group or the bimatoprost 0.0125% group. The safety data also suggests that the number of subjects with mild/moderate/severe hyperemia in the Lumigan group is numerically higher all

timepoints in the study compared to bimatoprost 0.01% and for the majority of timepoints compared to bimatoprost 0.0125%. Also, the number of subjects that worsened by at least one severity grade in ocular hyperemia was numerically higher in the Lumigan group compared to bimatoprost 0.01% and 0.0125% for the majority of timepoints.

Although, neither bimatoprost 0.01% nor bimatoprost 0.0125% demonstrated equivalence to Lumigan in the submitted trial, both lower IOP by approximately 5 – 7 mmHg from baseline (26-29%). This amount is not only clinically meaningful but is greater than many currently marketed products. While the exact safety profile of bimatoprost 0.01% or 0.0125% cannot be determined based on the results of a single trial submitted, these lower concentration products would at worst have a profile similar to the currently marketed Lumigan. Based on the known safety profile of Lumigan and the IOP lowering effect of both bimatoprost 0.01% and 0.0125%, the risk/benefit profile for both products is favorable. Since it is favorable to expose patients to the lowest effective dose, bimatoprost 0.01% is recommended for approval.

1.3 Recommendations for Postmarketing Risk Management Activities

N/A – there are no recommendations for postmarketing actions required for this product. Routine Pharmacovigilance activities are sufficient to monitor the safety profile of the product.

1.4 Recommendations for other Post Marketing Study Commitments

N/A – there are no recommended phase 4 commitments for this product.

2 Introduction and Regulatory Background

2.1 Product Information

Bimatoprost 0.01% was developed from the marketed product Lumigan (bimatoprost ophthalmic solution) 0.03%, 50 ppm benzalkonium chloride (BAK) with modifications to the levels of both the active substance, bimatoprost, and the preservative, BAK (and decreased sodium chloride for isotonicity). Lumigan (bimatoprost ophthalmic solution) 0.03% has been approved in the United States (US) since March 2001. Bimatoprost ophthalmic solution is a member of the class of prostaglandin analogs.

The purpose of this development program was to create a new formulation of bimatoprost that would maintain the IOP-lowering efficacy achieved with Lumigan and improve the overall safety profile and, in particular, ocular surface tolerability.

A clinical development program was conducted to evaluate the efficacy and safety of 0.01% bimatoprost/200 ppm BAK Ophthalmic Solution for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (OHT).

2.2 Tables of Currently Available Treatments for Proposed Indications

There are in excess of twenty products currently approved for the treatment/reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (OHT). These products are members of various drug classes with the majority being beta adrenergic blockers, carbonic anhydrase inhibitors and prostaglandin analogues.

Bimatoprost is a synthetic prostaglandin analogues affecting outflow by both the uveoscleral and the trabecular meshwork routes. There are currently four products within this class of drugs approved for this indication. They include bimatoprost ophthalmic solution 0.03%, travoprost ophthalmic solution 0.004%, latanoprost ophthalmic solution 0.005% and unoprostone isopropyl ophthalmic solution 0.15%.

2.3 Availability of Proposed Active Ingredient in the United States

Bimatoprost 0.01% will be manufactured at (b) (4). This is the is the same manufacturer of bimatoprost drug substance used for the currently marketed LUMIGAN®(bimatoprost ophthalmic solution) 0.03%.

2.4 Important Safety Issues With Consideration to Related Drugs

Safety issues related topical prostaglandin-like products include skin and iris pigmentation and eyelash growth. All of the effects with respect to iris pigmentation, lid pigmentation and lash growth appear to be due to the same mechanisms of action of all of the prostaglandin-like products. Long term studies in this class of drugs have concluded that these changes do not appear to result in any serious safety consequences.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

At an End-of-Phase 2 meeting with the Division of Anti-Infective and Ophthalmology Products (August 19, 2005), it was agreed that Allergan could file an NDA for a lower strength bimatoprost ophthalmic solution based on a single Phase 3 clinical study. Study 192024-031 was designed to show equivalence of either investigational formulation of bimatoprost (0.01% or 0.0125% with 200 ppm BAK) to Lumigan.

2.6 Other Relevant Background Information

Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications.

For equivalence trials, efficacy is attained if the difference in mean IOP between treatment groups is within ±1.50 mm Hg at all post-baseline timepoints; and within ±1.00 mm Hg at the majority of post-baseline timepoints. This requirement for equivalence has been consistently used for the approval of several IOP lowering products for approximately twenty years.

The primary efficacy variable for this trial was the IOP change from baseline at each scheduled follow-up timepoint. However, the primary efficacy endpoint for the US FDA HFD-520 review as stated in the protocol was mean IOP measured at all timepoints. The primary between-group comparisons were of bimatoprost 0.01% versus Lumigan and bimatoprost 0.0125% versus Lumigan.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI audits were conducted at two sites for study 192024-031: Site #2078 (Monte Dirks, MD) and site #3761 (Jason Bacharach, MD). The study data from Site 2078 was considered reliable and adequate to support the proposed indication. The safety data from site #3761 raises the issue of whether an expected pharmacologic effect recorded in the case report form must also be recorded as an adverse event. The clinical investigator at this site failed to report nine occurrences in five subjects of subject-reported redness of the eye as adverse events. The investigator also failed to report an occurrence of subject-reported periorbital darkening as an adverse event for two subjects and self-reported eyelash growth for two subjects.

3.2 Compliance with Good Clinical Practices

This study was conducted in accordance with Institutional Review Board (IRB) regulations (US 21 Code of Federal Regulations [CFR] Part 56.103). This protocol was conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, e.g., the International Conference on Harmonization (ICH) guideline for GCP.

The study was performed in compliance with informed consent regulations (US 21 CFR Part 50, Subpart B), with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) topic E6, and with Electronic Signatures Regulations (21CFR Part11). The study was discussed with the patient, and those wishing to participate gave informed consent and Authorization for Use and Release of Health and Research Study Information prior to any study related procedures or change in treatment.

3.3 Financial Disclosures

Allergan has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for bimatoprost ophthalmic solution. There are three investigators who participated in the phase 3 safety and efficacy trial who have disclosed financial ties to the sponsor. (b) (6) receives research support; (b) (6) is a consultant; and (b) (6) receives grant support for studies and fellowship training. A review of these arrangements do not raise questions about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

List of Components and Quantitative Composition of 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution

Component	Concentration (% w/v)	Concentration (mg/mL)	Reference of Quality Standard	Function
Bimatoprost	0.01	0.1	In-house standard	Drug Substance
Benzalkonium Chloride [a]	0.02	0.2	NF/Ph Eur	Preservative
Dibasic Sodium Phosphate (b) (4)		(b) (4)	USP	(b) (4)
Citric Acid (b) (4)			USP/Ph Eur	
Sodium Chloride			USP/Ph Eur	
Hydrochloric Acid [b]			NF/Ph Eur	
Sodium Hydroxide [b]			NF/Ph Eur	
Purified Water			USP/Ph Eur	

a (b) (4)

b Pharmaceutical grade hydrochloric acid and sodium hydroxide are prepared into appropriate normality for pH adjustments.

Composition of Test Formulations of Bimatoprost in Phase 2 and 3 Clinical Trials

Ingredients	Concentration (% w/v)												
	Study 192024-020					Study 192024-030					Study 192024-031		
	Lumigan® 9106X	9243X	9464X	9465X	9466X	Lumigan® 9106X	9668X	9669X	9673X	9670X	Lumigan® 9106X	9668X	9721X
Bimatoprost (AGN 192024)	0.03	0.01	0.015	0.020	0.025	0.03	0.01	0.015	0.015	0.02	0.03	0.01	0.0125
Benzalkonium Chloride	0.005	0.005	0.005	0.005	0.005	0.005	0.02	0.02	0.02	0.02	0.005	0.02	0.02
Dibasic Sodium Phosphate (b) (4)	(b) (4)												
(b) (4) Citric Acid													
Sodium Chloride													
Edetate Disodium													
Sodium Hydroxide or Hydrochloric Acid	(b) (4)												
Purified Water	(b) (4)												

Note: See chemistry review for detailed review.

4.2 Clinical Microbiology

N/A – this product is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

See pharm/tox review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Bimatoprost is a synthetic prostaglaindin analogue that stimulates prostaglaindin -sensitive receptors to produce its biological activity. Bimatoprost is a structural analog of prostaglandin F_{2a} (PGF_{2a}). Bimatoprost appears to mimic the activity of prostaglaindin F_{2a}, a substance that is biosynthetically derived from anandamide by a pathway that involves cyclooxygenase 2 (COX-2). This pathway, named the prostamide pathway, leads to the biosynthesis of novel lipid amides that lower IOP. Bimatoprost reduces IOP in humans by increasing aqueous humor outflow through the trabecular meshwork and enhancing uveoscleral outflow.

4.4.2 Pharmacodynamics

N/A - The pharmacodynamics of bimatoprost is well established and no new clinical pharmacology studies were performed for this submission.

4.4.3 Pharmacokinetics

The pharmacokinetics of bimatoprost has been well characterized in humans following ocular administration of Lumigan (bimatoprost ophthalmic solution) 0.03%. Since the concentration of the active substance has been reduced 3-fold, the systemic drug exposure of bimatoprost is not expected to increase with the new bimatoprost formulation compared with Lumigan. It was agreed with the FDA that it would not be necessary to conduct any pharmacokinetic studies with the new formulation in healthy subjects or in glaucoma patients for this NDA.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study/Report No.	Phase	Population (ITT)	Key Features
192024-020	2	OHT or glaucoma (N = 188)	Bimatoprost 0.01% BID, 0.015% BID, 0.02% QD, 0.025% QD compared to LUMIGAN® (all with **50 ppm BAK**) and Timolol 0.5% Double-masked, 6-arm parallel-group Twice-daily: study medication morning and evening Once-daily: vehicle morning, study medication evening 1-month primary analysis
192024-030	2	OHT or glaucoma (N = 249)	Bimatoprost 0.01% QD, 0.015% QD, 0.015% QD/EDTA, 0.02% QD (all with **200 ppm BAK**) compared to LUMIGAN® (with **50 ppm BAK**) Double-masked, paired-eye Once-daily, morning dosing, one eye test formulation, the other eye LUMIGAN® 5-day
192024-031	3	OHT or glaucoma (N = 561)	Bimatoprost 0.01% QD, 0.0125% QD (with **200 ppm BAK**) compared to LUMIGAN® (with **50 ppm BAK**) Double-masked, 3-arm parallel-group Once-daily, evening dosing 3-month primary analysis period followed by 9-month masked extension

Source: Reports 192024-020, 192024-030 and 192024-031

a Phase 2 Study, 192024-020, was not part of the clinical development program for Bim 0.01% but provides supportive efficacy and safety data for the choice of bimatoprost concentrations in Studies 192024-030 and 192024-031.

5.2 Review Strategy

The efficacy for this product is based on a single Phase 3 clinical study (192024-031). The safety was evaluated based on results of this phase 3 study as well as what is known about the adverse effects associated with the use of this class of drugs. The results of the two phase 2 studies were not reviewed in the same depth due to differing formulations and limited patient exposure.

5.3 Discussion of Individual Studies

The safety and efficacy for this product is based on a single phase 3 clinical study. Study 192024-031 was designed to show equivalence of either investigational formulation of bimatoprost (0.01% or 0.0125% with 200 ppm BAK) to Lumigan. The sponsor also submitted the results from pilot phase 2 studies that were conducted during development to determine the optimum dose and formulation to carry into phase 3 testing. The results of the two phase 2 studies were not reviewed to the same depth due to differing formulations and limited patient exposure.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication for the new bimatoprost formulation is the same indication as for Lumigan: Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

Study Design

The study was a 3-month (plus 9-month, masked extension), multicenter, double-masked, randomized, parallel group, active-controlled comparison of the safety and efficacy of bimatoprost 0.01% and bimatoprost 0.0125% once-daily compared with Lumigan once-daily in patients with chronic glaucoma or ocular hypertension (OHT).

Patients were stratified into 1 of 6 groups based on baseline [day 0, hour 0] IOP and prestudy central corneal thickness (CCT) averaged from both eyes. The 6 strata were derived from 2 IOP categories (IOP ≤ 25 mm Hg or IOP > 25 mm Hg) and 3 CCT categories (CCT < 555 microns, CCT 555-600 microns, or CCT > 600 microns). Within each stratum, each patient was randomly assigned to either bimatoprost 0.01% once-daily, bimatoprost 0.0125% once-daily or Lumigan once-daily in an even allocation (1:1:1).

There were 8 visits: Prestudy followed by a washout period of up to 6 weeks, Baseline, Weeks 2 and 6, and Months 3, 6, 9 and 12. Patients were instructed to instill one drop of study medication in each eye every evening for 12 months. All visits except the Prestudy and Month 9 visits consisted of 3 diurnal timepoints [hour 0 (07:00 – 09:00), hour 4, and hour 8]. The Prestudy visit had 1 timepoint (at any time during the day) and the Month 9 visit had Hour 0 and Hour 4 timepoints only.

For this report, data were analyzed after all patients completed the Month 3 visit or exited the study prior to Month 3. The 3-month analyses are considered primary. In addition, an analysis on all 12-month data will be performed as a safety and efficacy update.

The primary efficacy variable was the change from baseline in IOP, at each post-baseline timepoint. The primary efficacy endpoint for the US FDA HFD-520 review was mean IOP measured at all timepoints.

Investigators Study 192024031

Investigator	Number	Location	Number of Subjects
Kenneth Sall	2707	Artesia, CA	52
Jason Bacharach	3761	Petaluma, CA	39
Eugene Protzko	3507	Bel Air, MD	32
David Wirta	3276	Newport Beach, CA	48
Michael Tepedino	3212	High Point, NC	39
Jeff Lozier	2981	San Diego, CA	33
Monte Dirks	2078	Rapid City, SD	30
Thomas Walters	1634	Austin, TX	24
David Cooke	2232	St. Joseph, MI	31
Richard Evans	2975	San Antonia, TX	23
Robert Williams	2710	Louisville, KY	25
Richard Sturm	1587	Lynbrook, NY	22
Jeffrey Whitsett	3185	Houston, TX	16
Allen Beck	2999	Atlanta, GA	9
Steven Simmons	1655	Slingerlands, NY/Pittsburgh, PA	13
Louis Cantor	2117	Indianapolis, IN	9
William Davitt	3809	El Paso, TX	5
Howard Schenker	2429	Rochester, NY	21
Harvey DuBiner	2450	Morrow, GA	13
Frank Mares	0671	Albuquerque, NM	7
Alfred Solish	0202	Pasadena, CA	10
Donald McCormack	1942	Boulder, CO	7
Robert Shields	1724	Denver, CO	6
Michael Rotberg	2037	Charlotte, NC	16
Richard Lewis	0526	Sacramento, CA	7
Arash Mansouri	3764	Fredericksburg, VA	5
Robert Foerster	0207	Colorado Springs, CO	4
Jay Katz	1960	Philadelphia, PA	5
Mark Juzych	4566	Detroit, MI	3
David Brodstein	3283	Ogden, UT	5
John Cohen	1176	Cincinnati, OH	1
George Cioffi	2855	Portland, OR	1

Inclusion Criteria

The following were requirements for entry into the study:

1. Male or female, at least 18 years of age and of legal age of consent
2. Patient had either OHT, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy/iridectomy, pseudoexfoliative glaucoma, or pigmentary glaucoma in each eye
3. Baseline: A best-corrected visual acuity score equivalent to a Snellen acuity of 20/100 or better in each eye, using a logarithmic visual acuity chart for testing at 10 feet (3 meters)
4. Baseline: Patient had been appropriately washed out of all IOP-lowering medications

5. Baseline (day 0, hour 0): IOP of ≥ 22 mm Hg and ≤ 34 mm Hg in both eyes with asymmetry of IOP not greater than 5 mm Hg between the eyes
6. Patient required bilateral IOP-lowering therapy
7. Patient's IOP was likely to be controlled on monotherapy
8. Baseline: Negative urine pregnancy test for females of childbearing potential prior to randomization
9. Written informed consent obtained prior to any study procedures
10. Written Authorization for Use and Release of Health and Research Study Information obtained prior to any study procedures
11. Patient was able and willing to follow study instructions and likely to complete all required visits

Exclusion Criteria

The following were criteria for exclusion from participating in the study:

1. Uncontrolled systemic disease
2. Females who were pregnant, nursing, or planning a pregnancy or who were of childbearing potential and not using a reliable method of contraception
3. Intermittent use of oral or injectable steroids within 21 days prior to the baseline visit or anticipated use within 21 days prior to a follow-up study visit or any use of topical ophthalmic steroids
4. Known allergy or hypersensitivity to the study medication or its components
5. Allergy or contraindication to the use of fluorescein
6. Recent (within previous 2 months) or anticipated alteration of existing chronic systemic treatment or introduction of treatment with agents which could have a substantial effect on IOP (including, but not necessarily limited to, systemic adrenergic agents including beta-adrenergic blocking agents, e.g., propranolol, metoprolol, nadolol, timolol, and atenolol), substantial interactions with study medications, or interaction with study outcomes
7. Active ocular disease (e.g., uveitis, ocular infections, chronic blepharitis, or severe dry eye), that in the opinion of the investigator would interfere with the interpretation of the study data. Stable myopia, strabismus, and cataracts were allowed provided other inclusion/exclusion criteria were met
8. Corneal or other ocular abnormalities that would preclude accurate readings with an applanation tonometer, including severe astigmatism
9. Required chronic use of ocular medications during the study other than the study medication. Intermittent use of artificial tear products were allowed, but not within 24 hours of a scheduled visit. Intermittent use of ocular decongestants or antihistamines was allowed, but not within 2 weeks of a scheduled visit
10. History of recurrent ocular seasonal allergies within the past 2 years
11. Baseline (day 0, hour 0): Significant ocular surface findings (e.g., hyperemia or irritation equal to +1 (mild) or greater) in either eye found on gross macroscopic hyperemia or slit-lamp examination
12. Patient's IOP was previously uncontrolled on bimatoprost monotherapy
13. History of severe ocular trauma or history of laser, intraocular, or filtering surgery within 3 months prior to baseline, or refractive surgery at any time

14. Visual field loss which in the opinion of the investigator is functionally significant or evidence of progressive visual field loss within the last year
15. Patients with corneal grafts
16. Contraindication to pupil dilation
17. Anticipated wearing of contact lenses during the study (use of soft lenses should have been discontinued at least 2 days prior to baseline, and use of rigid gas permeable (RGP) or hard contact lenses should have been discontinued at least one week prior to baseline)
18. Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to baseline
19. Patient had a condition or was in a situation which, in the investigator's opinion, may have put the patient at a significant risk, may have confounded study results, or may have interfered significantly with the patient's participation in the study

Study Schedule - Study 192024-031

Visit	PSa	Baseline Day 0		Week 2		Week 6		Month 3		Month 6		Month 9		Month 12/ Early Exitl	
Timepoints[b]		H0	H4/ H8	H0	H4/ H8	H0	H4/ H8	H0	H4/ H8	H0	H4/ H8	H0	H4	H0	H4/ H8
Patient ICF and Auth	X														
History / Demographics[c]	X														
Health Outcomes[d]								X		X				X	
BP and PR	X	X		X		X		X		X		X		X	
Macroscopic (gross) Hyperemia Grading	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Iris Color Assessment		X						X		X				X	
Visual Acuity	X	X		X		X		X		X		X		X	
Visual Field	X[e]	X[f]						X[f]		X[f]				X[f]	
Biomicroscopy	X	X		X		X		X		X		X		X	
IOP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Corneal Pachymetry[g]	X														
Ophthalmoscopy	X								X[h]		X[h]				X[h]
Urine Pregnancy Test[i]		X						X		X				X	
Serious Medical Events[j]	X	X													
Adverse Events			X	X		X		X		X		X		X	
Dispense Study Medication		X[k]						X		X		X			

Abbreviations: PS = Prestudy; H = Hour; BP = Blood Pressure; PR = Pulse Rate; IOP = Intraocular Pressure; ICF = Informed Consent Form; Auth = Authorization;

a. Patients on IOP-lowering medications must washout those medications prior to the baseline visit. The prestudy visit should occur between 2 and 50 days prior to the baseline visit.

b. Timepoints: Hour 0 = should occur between 07:00 and 09:00 at all visits. All patients should have their visits at approximately the same time of day during the study; H4, H8 = 4 hours and 8 hours from the time of Hour 0 IOP evaluation, respectively.

c. Patient histories include ophthalmic, medical, and medication. Demographic information includes date of birth, iris color, height and weight.

d. Health Outcome measures include patient-reported outcomes and physician-reported outcomes.

e. Prestudy visual field is not required if a reliable visual field (per protocol) is on file within 6 months prior to the prestudy visit.

f. The baseline visual field may be performed within 1 week prior to the visit or at the visit. The month 3, month 6, and month 12 visual fields may be performed within 1 week of the visit or at the visit.

g. Corneal pachymetry may be performed within 3 months of the prestudy visit as long as the method of collection is per protocol.

h. Ophthalmoscopy exam should be completed at hour 8 only after all other measurements are completed.

i. Urine pregnancy test will be performed for females of childbearing potential.

j. Serious Medical Events will be collected between the time informed consent is signed and randomization at the baseline visit.

k. Study medication will be dispensed after study entry criteria are met. Use the IVRS or IWRS system to randomize the patient and obtain their study medication kit number. The first dose of study medication will be taken by the patient in the evening of the baseline (day 0) visit day.

l. For patients who exit the study early, at a minimum all Hour 0 procedures should be completed plus ophthalmoscopy at the Early Exit visit.

6.1.1 Methods

The efficacy of bimatoprost 0.01% is based on a single Phase 3 clinical study (study 192024-031) which was designed and conducted by the Sponsor to show equivalence of either investigational formulation of bimatoprost (0.01% or 0.0125% with 200 ppm BAK) to Lumigan.

The primary efficacy variable for this trial was the IOP change from baseline at each scheduled follow-up timepoint. However, the primary efficacy endpoint for the US FDA HFD-520 review as stated in the protocol was mean IOP measured at all timepoints. The primary between-group comparisons were of bimatoprost 0.01% versus Lumigan and bimatoprost 0.0125% versus Lumigan

Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. IOP is a surrogate end point for potential visual function loss.

For equivalence trials efficacy is attained if the difference in mean IOP between treatment groups is within ±1.50 mm Hg at all post-baseline timepoints; and within ±1.00 mm Hg at the majority of post-baseline timepoints. This regulatory requirement for equivalence has been consistently used for the approval of several IOP lowering products over many years.

6.1.2 Demographics

Study 192024-031 - Demographics

	Bim 0.01% N = 186	Bim 0.0125% N = 188	LUMIGAN® N = 187	TOTAL N = 561	p-value
Mean age (range) years	61.6 (25-86)	64.7 (40-93)	64.2 (23-94)	63.5 (23-94)	0.019
Sex					
male	79 (42.5%)	72 (38.3%)	89 (47.6%)	240 (42.8%)	0.190
female	107 (57.5%)	116 (61.7%)	98 (52.4%)	321 (57.2%)	
Race					
black	28 (15.1%)	25 (13.3%)	23 (12.3%)	76 (13.5%)	0.734
non-black	158 (84.9%)	163 (86.7%)	164 (87.7%)	485 (86.5%)	
Iris color					
light	90 (48.4%)	96 (51.1%)	98 (52.4%)	284 (50.6%)	0.732
dark	96 (51.6%)	92 (48.9%)	89 (47.6%)	277 (49.4%)	
Mean central corneal thickness (µm)	559.6	560.3	561.3		
Ophthalmic dx glaucoma	94 (50.5%)	102 (54.3%)	94 (50.3%)		
Ophthalmic dx OHT	91 (48.9%)	84 (44.7%)	87 (46.5%)		
Ophthalmic dx glaucoma/OHT	1 (0.5%)	2 (1.1%)	6 (3.2%)		

6.1.3 Patient Disposition

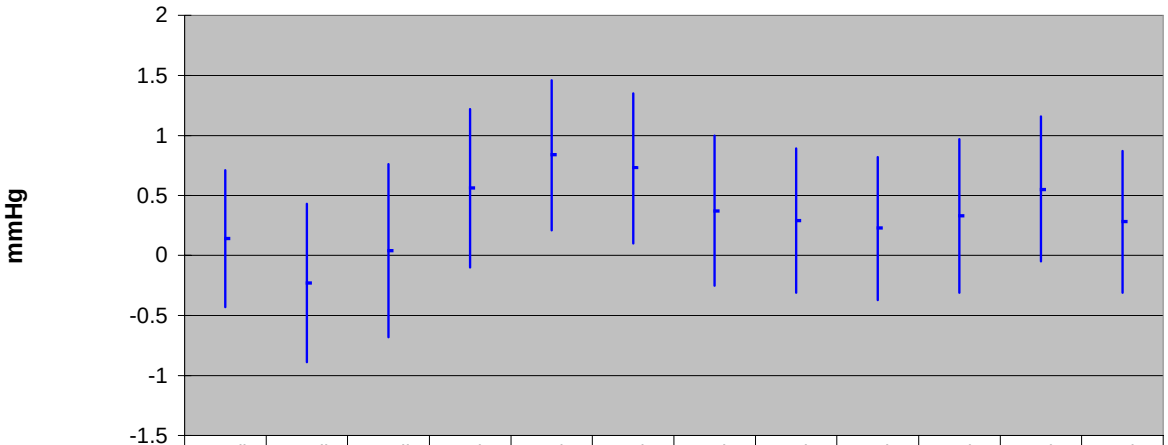
Study 192024-031 – Patient Disposition

	0.01% bimatoprost	0.0125% bimatoprost	Lumigan

Enrolled	186	188	187
Completed	171 (91.9%	171 (91%)	162 (86.6%)
Discontinued	15 (8.1%)	17 (9.0%)	25 (13.4%)

6.1.4 Analysis of Primary Endpoint(s)

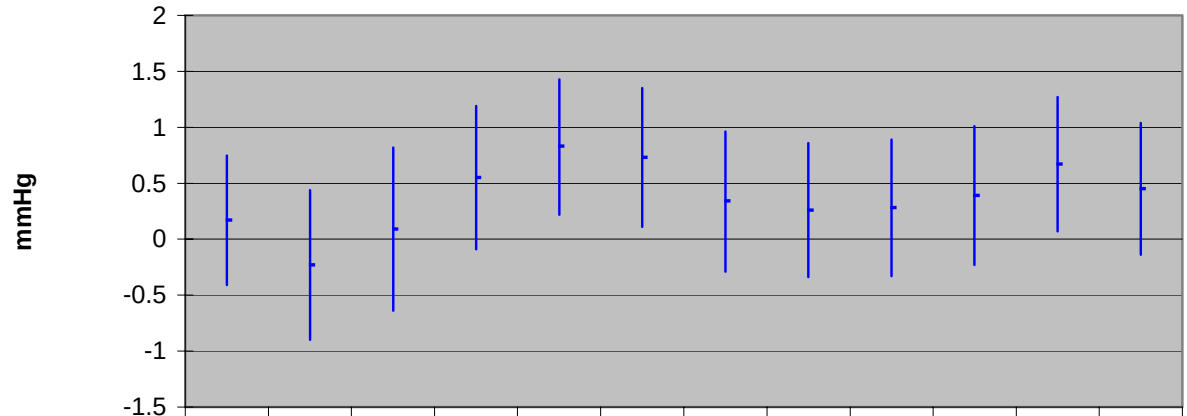
Mean IOP Difference Bimatoprost 0.01% - Lumigan (ITT LOCF- 95% Confidence Interval) - Study 192024-031



	Baseline (hr 0)	Baseline (hr 4)	Baseline (hr 8)	Week 2 (hr 0)	Week 2 (hr 4)	Week 2 (hr 8)	Week 6 (hr 0)	Week 6 (hr 4)	Week 6 (hr 8)	Month 3 (hr 0)	Month 3 (hr 4)	Month 3 (hr 8)
Lower CI	-0.43	-0.89	-0.68	-0.1	0.21	0.1	-0.25	-0.31	-0.37	-0.31	-0.05	-0.31
Upper CI	0.71	0.43	0.76	1.22	1.46	1.35	1	0.89	0.82	0.97	1.16	0.87
- Mean Difference	0.14	-0.23	0.04	0.56	0.84	0.73	0.37	0.29	0.23	0.33	0.55	0.28

Reviewer's Comments: *The 95% confidence interval of the mean difference in IOP between Lumigan and bimatoprost 0.01% is within 1.5mmHg for all timepoints measured. However,only 5/9 of the timepoints are within 1mmHg. The point estimates favor Lumigan by approximately 0.5 mmHg for all post baseline timepoints.*

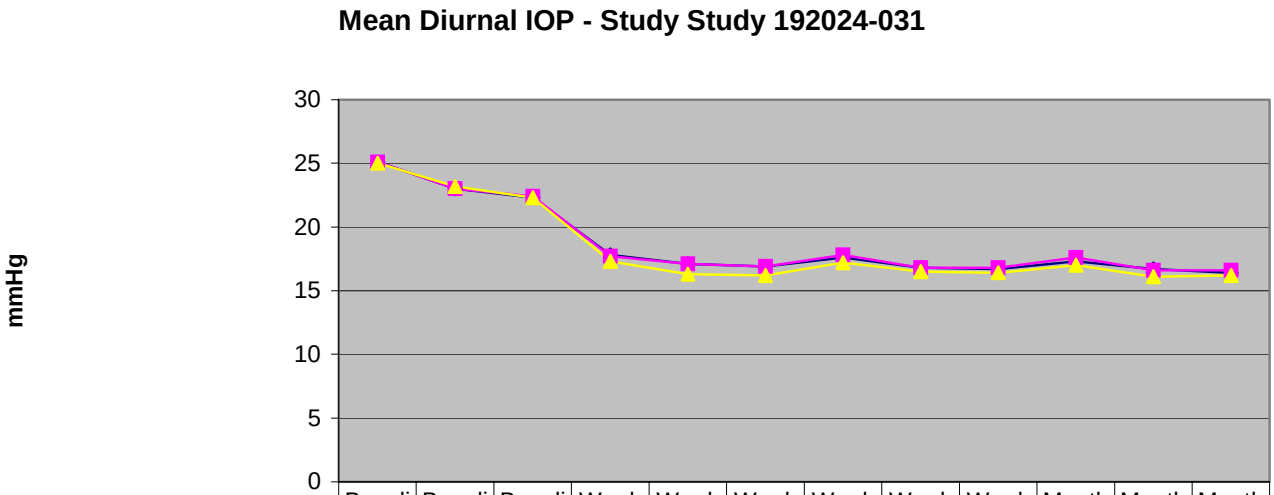
Mean Difference Bimatoprost 0.01% - Lumigan (PP - 95% Confidence Interval) - Study 192024-031



	Baseline (hr 0)	Baseline (hr 4)	Baseline (hr 8)	Week 2 (hr 0)	Week 2 (hr 4)	Week 2 (hr 8)	Week 6 (hr 0)	Week 6 (hr 4)	Week 6 (hr 8)	Month 3 (hr 0)	Month 3 (hr 4)	Month 3 (hr 8)
Lower CI	-0.41	-0.9	-0.64	-0.09	0.22	0.11	-0.29	-0.34	-0.33	-0.23	0.07	-0.14
Upper CI	0.75	0.44	0.82	1.19	1.43	1.35	0.96	0.86	0.89	1.01	1.27	1.04
Mean Difference	0.17	-0.23	0.09	0.55	0.83	0.73	0.34	0.26	0.28	0.39	0.67	0.45

Reviewer's Comments: *The PP population analysis is consistent with the ITT-LOCF results except 6 out of 9 of the confidence intervals are not within 1 mmHg.*

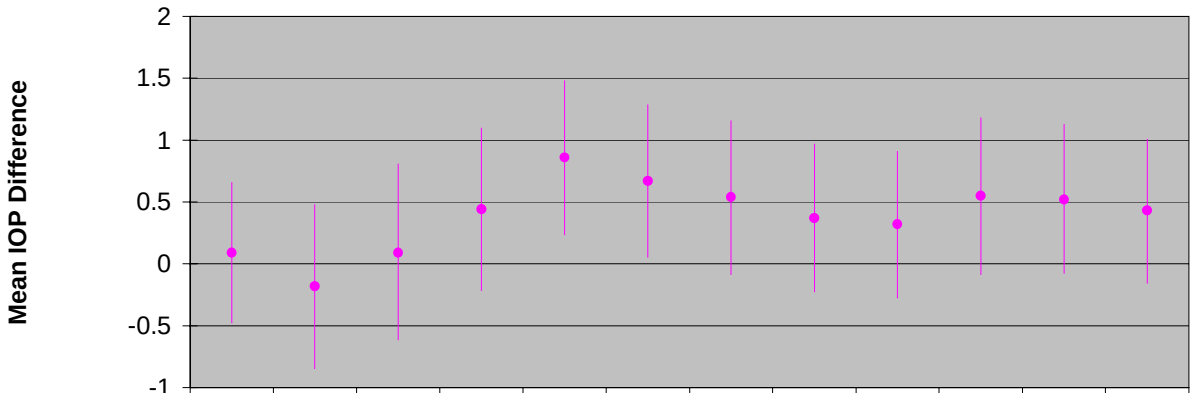
6.1.5 Analysis of Secondary Endpoints(s)



	Baseline (hr 0)	Baseline (hr 4)	Baseline (hr 8)	Week 2 (hr 0)	Week 2 (hr 4)	Week 2 (hr 8)	Week 6 (hr 0)	Week 6 (hr 4)	Week 6 (hr 8)	Month 3 (hr 0)	Month 3 (hr 4)	Month 3 (hr 8)
0.01% bimatoprost	25.1	23	22.3	17.8	17.1	16.9	17.6	16.8	16.7	17.3	16.7	16.4
0.0125% bimatoprost	25.1	23	22.4	17.7	17.1	16.9	17.8	16.8	16.8	17.6	16.6	16.6
Lumigan	25	23.2	22.3	17.3	16.3	16.2	17.2	16.5	16.4	17	16.1	16.2

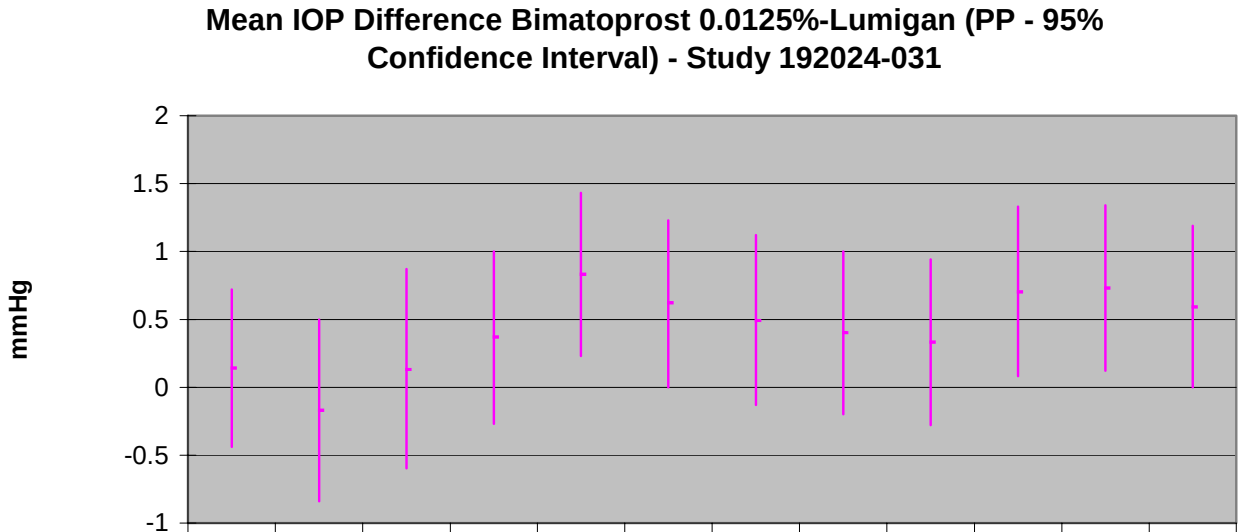
Reviewer's Comments: *Lumigan, bimatoprost 0.01% and 0.0125% have similar IOP lowering ability throughout the trial. All treatments lower IOP by approximately 26%-29% percent from baseline.*

Mean IOP Difference Bimatoprost 0.0125% - Lumigan (ITT LOCF- 95% Confidence Interval) - Study 192024-031



	Baseline (hr 0)	Baseline (hr 4)	Baseline (hr 8)	Week 2 (hr 0)	Week 2 (hr 4)	Week 2 (hr 8)	Week 6 (hr 0)	Week 6 (hr 4)	Week 6 (hr 8)	Month 3 (hr 0)	Month 3 (hr 4)	Month 3 (hr 8)
Lower CI	-0.48	-0.85	-0.62	-0.22	0.23	0.05	-0.09	-0.23	-0.28	-0.09	-0.08	-0.16
Upper CI	0.66	0.48	0.81	1.1	1.48	1.29	1.16	0.97	0.91	1.18	1.13	1.01
Mean Difference	0.09	-0.18	0.09	0.44	0.86	0.67	0.54	0.37	0.32	0.55	0.52	0.43

Reviewer's Comments: *The 95% confidence interval of the mean difference in IOP between Lumigan and bimatoprost 0.01% is within 1.5mmHg for all timepoints measured. However, the majority of timepoints are not within 1mmHg. This does not meet the definition of equivalency. The point estimates favor Lumigan by approximately 0.5 mmHg for all post baseline timepoints.*



	Baseline (hr 0)	Baseline (hr 4)	Baseline (hr 8)	Week 2 (hr 0)	Week 2 (hr 4)	Week 2 (hr 8)	Week 6 (hr 0)	Week 6 (hr 4)	Week 6 (hr 8)	Month 3 (hr 0)	Month 3 (hr 4)	Month 3 (hr 8)
Lower CI	-0.44	-0.84	-0.6	-0.27	0.23	0	-0.13	-0.2	-0.28	0.08	0.12	0
Upper CI	0.72	0.5	0.87	1	1.43	1.23	1.12	1	0.94	1.33	1.34	1.19
Mean Difference	0.14	-0.17	0.13	0.37	0.83	0.62	0.49	0.4	0.33	0.7	0.73	0.59

Reviewer's Comments: *The PP population analysis is consistent with the ITT-LOCF results.*

6.1.6 Other Endpoints

See section 6.1.5.

6.1.7 Subpopulations

IOP data was analyzed by subpopulations based on age, sex, race and iris color. Overall, there were no clinically significant differences in the effectiveness of bimatoprost 0.01%, bimatoprost 0.0125% and Lumigan in the different subpopulations.

The sponsor has requested a full waiver for pediatric studies for all pediatric age groups (neonates, infants, children, and adolescents) from birth to 16 years of age. The sponsor based this request on the premise that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Once-daily dosing was considered the correct dosing frequency for the new formulation of bimatoprost as this is the dosing frequency for Lumigan. The once-daily regimen was supported by studies conducted with bimatoprost 0.03%, which demonstrated that bimatoprost 0.03% administered once-daily was safe and effective in lowering IOP. In addition, an evening dose is recommended to achieve greatest IOP-lowering at the times when IOP is at its highest.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Bimatoprost 0.01% maintained consistent IOP lowering effect throughout the duration of the phase 3 study. There was no loss of IOP lowering effect seen. Lumigan (bimatoprost ophthalmic solution) 0.03% which has been marketed since 2000 has not demonstrated any tolerance effects.

6.1.10 Additional Efficacy Issues/Analyses

N/A – there are no additional efficacy issues to address

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The safety of this product is based on the 12 month results of study192024-031 in conjunction with what is known about the adverse effects associated with the use of this class of drugs. Standard safety measurements were selected to evaluate those parameters associated with the use of topical ocular medications. Additional assessments were conducted to evaluate possible systemic side effects and effects associated the use of this class of drugs. Safety assessments included the following: visual acuity, visual field, biomicroscopy, ophthalmoscopy, iris color change, blood pressure, pulse, hyperemia and pregnancy.

7.1.2 Adequacy of Data

The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

N/A – data pooling is not applicable to this application. The safety of this product is based on the 12 month results of a single phase 3 study: 192024-031 in conjunction with what is known about the adverse effects associated with the use of this class of drugs.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 561 patients enrolled in study 192024-031 were randomized to study treatment: 186 patients to bimatoprost 0.01%, 188 to bimatoprost 0.0125% and 187 to Lumigan. One patient randomized to bimatoprost 0.01% was excluded from the safety analysis because this patient was inadvertently randomized despite failing the screening criteria and was subsequently discontinued from the study without receiving any study medication.

Subjects in study 192024-031 received bimatoprost 0.01%, bimatoprost 0.0125% or Lumigan once-daily in the study eye.

Number of Patients Exposed to Study Treatment - Study 192024-031

Timepoint	Bim 0.01% (N = 185)	Bim 0.0125% (N = 188)	LUMIGAN® (N = 187)
At least 1 day	185 (100.0%)	188 (100.0%)	187 (100.0%)
At least 29 days	180 (97.3%)	185 (98.4%)	181 (96.8%)
At least 57 days	179 (96.8%)	183 (97.3%)	178 (95.2%)
At least 138 days	175 (94.6%)	176 (93.6%)	170 (90.9%)
At least 229 days	174 (94.1%)	173 (92.0%)	167 (89.3%)
At least 320 days	171 (92.4%)	172 (91.5%)	163 (87.2%)

Source: Table 14.3-2

7.2.2 Explorations for Dose Response

Bimatoprost 0.01% was developed from the marketed product Lumigan (bimatoprost ophthalmic solution) 0.03% with 50 ppm benzalkonium chloride (BAK) with modifications to the levels of both the active substance, bimatoprost, and the preservative, BAK (and decreased sodium chloride for isotonicity).

Study 192024-002 evaluated nonpreserved bimatoprost ophthalmic solutions at the 0.003%, 0.01% and 0.03% concentrations and demonstrated that the ocular hypotensive effect of bimatoprost was dose-related. In another Phase 2 Study, 192024-020, further reductions in mean IOP were achieved with bimatoprost concentrations ranging from 0.01% to 0.025% by the addition of 50 ppm BAK.

In Study 192024-030, bimatoprost 0.01% (200 ppm BAK) showed non-clinically meaningful differences in IOP-lowering and improved ocular safety/tolerability compared to Lumigan and was chosen for the Phase 3 study. Bimatoprost 0.015% also showed comparable results to Lumigan but had a similar incidence of ocular adverse events.

Therefore, together with bimatoprost 0.01%, a concentration between 0.01% and 0.015% (i.e. bimatoprost 0.0125%) was selected for evaluation in the Phase 3 Study, 192024-031.

7.2.3 Special Animal and/or In Vitro Testing

See pharm/tox review.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

The pharmocokinetics and pharmacodynamics of bimatoprost is well established and no new clinical pharmacology studies were performed for this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Safety issues related topical prostaglandin-like products include skin and iris pigmentation and eyelash growth. These were adequately evaluated in this trial with the use of digital photography and biomicroscopy.

7.3 Major Safety Results

7.3.1 Deaths

One death (Patient 3212-33019) was reported during the 3-month study period. An additional 2 deaths occurred during the 9-month extension period (Patients 2707-32334 and 2232-30840). These deaths were due to serious adverse events that were non-ocular and not considered to be treatment related.

Treatment Group	Patient Number	Age, Race, Sex	SAE (Preferred Term) Leading to Death	Days at Onset of SAE[a]
Bim 0.01%	2232-30840	77-year-old Black male	Lung neoplasm malignant	227
Bim 0.0125%	2707-32334	65-year-old Caucasian female	Cerebral haemorrhage	252
Bim 0.0125%	3212-33019	65-year-old Caucasian female	Myocardial infarction	82

Source: Listing 14.3.2

a Day at onset relative to first dosing on Day 0

7.3.2 Nonfatal Serious Adverse Events

A total of 42 patients reported serious adverse events for the 12 month trial duration. All of the serious adverse events were non-ocular and not considered to be related to study treatment.

Serious Adverse Events - Study 192024-031

Treatment Group	Patient Number	SAE (Preferred Term)	Severity	Days at Onset[a]
Bim 0.01%	1634-33111	Ovarian cancer	Moderate	223
	1655-32706	Vertigo	Severe	56
	1942-31906	Bronchioloalveolar carcinoma	Severe	212
	2078-31003	Bladder cancer	Severe	244
	2078-31013	Ligament rupture	Severe	96
	2078-31028	Appendicitis perforated	Severe	144
	2232-30828	Joint dislocation	Severe	264
	2232-30840	Lung neoplasm malignant[b]	Severe	227
	2710-33304	Atrial fibrillation	Moderate	141
	2710-33331	Arteriosclerosis coronary artery	Moderate	118
		Cardiac failure congestive	Moderate	118
		Abdominal pain	Mild	107
		Cholecystitis chronic	Moderate	225
	2981-31626	Bronchitis, bacterial	Moderate	278
	2999-30105	Proteinuria	Mild	258
	3212-33012	Neck pain	Moderate	38
		Supraventricular tachycardia	Moderate	38
		Headache	Moderate	38
	3276-33409	Cerebrovascular accident	Moderate	341
	3276-33425	Cardiac failure congestive	Moderate	332
	3761-30013	Traumatic brain injury	Severe	101
	3809-30904	Cholecystitis infective	Severe	243
		Subdiaphragmatic abscess	Severe	254
Bim 0.0125%	0202-32809	Carotid artery stenosis	Severe	172
	2232-30804	Endometrial cancer	Severe	5
	2232-30825	Coronary artery disease	Moderate	12
		Myocardial infarction	Severe	296

Treatment Group	Patient Number	SAE (Preferred Term)	Severity	Days at Onset[a]
	2429-32403	Pneumonia	Severe	39
	2450-31118	Cellulitis	Severe	307
	2707-32334	Cerebral haemorrhage[b]	Severe	252
	2707-32349	Osteoarthritis	Severe	289
	2710-33309	Osteoarthritis	Moderate	99
	2710-33334	Osteoarthritis	Moderate	27
	2981-31628	Uterine prolapse	Moderate	60
	3212-33019	Myocardial infarction[b]	Severe	82
LUMIGAN®	1587-32921	Diabetes mellitus	Moderate	41
	1655-32719	Acute coronary syndrome	Severe	263
	1960-33606	Chest pain	Moderate	221
	2037-32213	Upper gastrointestinal haemorrhage	Severe	270
	2037-32215	Coronary artery disease	Severe	107
		Haematuria	Severe	170
	2232-30802	Osteoarthritis	Mild	55
	2232-30813	Abdominal hernia	Severe	21
	2707-32365	Ovarian cancer	Severe	176
	2710-33305	Osteoarthritis	Moderate	145
	2975-31213	Lumbar spinal stenosis	Moderate	326
		Spinal compression fracture	Moderate	326
	2981-31623	Arthritis	Moderate	67
	2981-31624	Chronic obstructive pulmonary disease	Moderate	361
	2981-31630	Dehydration	Severe	67
	3764-31702	Renal artery stenosis	Moderate	102
		Hypertension	Mild	92
		Intermittent claudication	Mild	Not reported

Source: Listings 14.3.2 and 16.2.7-1

a Day at onset relative to first dosing on Day 0

b This serious adverse event lead to the patient's death.

7.3.3 Dropouts and/or Discontinuations

Overall Profile of Dropouts - Study 192024-031

	0.01% bimatoprost	0.0125% bimatoprost	Lumigan
Enrolled	186	188	187
Completed	171 (91.9%	171 (91%)	162 (86.6%)
Discontinued	15 (8.1%)	17 (9.0%)	25 (13.4%)
Adverse Event	8 (4.4%)	8 (4.3%)	14 (7.5%)
Ocular	4 (2.2%)	6 (3.2%)	12 (6.4%)
Non-Ocular	5 (2.7%)	2 (1.1%)	3 (1.6%)
Lost to Follow Up	2 (1.1%)	5 (2.7%)	4 (2.1%)
Personal Reasons	1 (0.5%)	1 (0.5%)	1 (0.5%)
Protocol Violation	0	1 (0.5%)	3 (1.6%)
Other	4 (2.2%)	2 (1.1%)	3 (1.6%)

Reviewer Comments: *Approximately three times as many subjects discontinued the study due to ocular adverse events in the Lumigan group compared to bimatoprost 0.01% and approximately twice as many compared to bimatoprost 0.0125%. More subjects discontinued the study due to non-ocular adverse events in the bimatoprost 0.01% arm compared to the Lumigan and bimatoprost 0.0125% arms.*

Overall Profile of Adverse Events

	Bimatoprost 0.01% N=185	Bimatoprost 0.0125% N=188	Lumigan N=187
Adverse events	121(65.4%)	125 (66.5%)	145 (77.5%)
Ocular	88 (47.6%)	92 (48.9%)	116 (62%)
Non-ocular	80 (43.2%)	69 (36.7%)	77 (41.2%)
SAEs	17 (9.2%)	11 (5.9%)	14 (7.5%)
Discontinuation due to AEs	8 (4.3%)	8 (4.3%)	14 (7.5%)
Deaths	1 (0.5%)	2 (1.1%)	0

Patients Discontinued from Study - Study 192024-031

Subject	Treatment	Age/Sex. Race	Treatment Exposure	Reason For Discontinuation
0207-31304	Bimatoprost 0.01%	71/F/C	5	Burning on instillation, headache, blurred vision, nausea
1634-33111	Bimatoprost 0.01%	66/F/C	243	Ovarian cancer
1724-32607	Bimatoprost 0.01%	67/M/C	14	Conjunctival hyperemia, eye

				pruritus
3276-33422	Bimatoprost 0.01%	61/F/C	5	Conjunctival hyperemia
3276-33446	Bimatoprost 0.01%	70/F/C	120	Conjunctival hyperemia
1942-31906	Bimatoprost 0.01%	72/M/C	246	Bronchial/alveola carcinoma
2232-30840	Bimatoprost 0.01%	77/M/B	85	Lung cancer
2981-31626	Bimatoprost 0.01%	69/F/C	278	Bacterial bronchitis
3185-33203	Bimatoprost 0.01%	80/F/C	14	Lost to Follow-up
3507-32123	Bimatoprost 0.01%	45/F/C	91	Lost to Follow-up
3212-33007	Bimatoprost 0.01%	52/F/C	189	IOP too high
3761-30035	Bimatoprost 0.01%	83/F/C	10	Lack of efficacy
2707-32302	Bimatoprost 0.01%	64/F/C	91	Personal Reasons
3761-30029	Bimatoprost 0.01%	55/M/B	46	Patient moved out of state
3276-33442	Bimatoprost 0.01%	59/M/C	.	Patient was inadvertently entered. Was a screen failure
0202-32809	Bimatoprost 0.0125%	79/M/C	176	Personal Reasons
0671-31805	Bimatoprost 0.0125%	66/M/C	240	Uncontrolled IOP
3212-33054	Bimatoprost 0.0125%	64/F/H	95	Uncontrolled IOP
2710-33313	Bimatoprost 0.0125%	93/M/C	91	Lack of efficacy
1587-32908	Bimatoprost 0.0125%	70/M/C	1	Protocol Violation
1634-33121	Bimatoprost 0.0125%	67/F/C	146	Eye irritation
3761-30003	Bimatoprost 0.0125%	62/F/H	333	Eye pruritus
2981-31621	Bimatoprost 0.0125%	83/F/C	131	Ocular discomfort
2429-32401	Bimatoprost 0.0125%	58/F/C	64	Conjunctival hyperemia
2707-32334	Bimatoprost 0.0125%	65/F/C	92	Cerebral hemorrhage
2707-32361	Bimatoprost 0.0125%	43/F/H	84	Lost to Follow-up
2707-32366	Bimatoprost 0.0125%	47/M/H	84	Lost to Follow-up
3185-33205	Bimatoprost 0.0125%	74/F/C	14	Lost to Follow-up
3212-33009	Bimatoprost 0.0125%	56/F/B	42	Lost to Follow-up
3212-33020	Bimatoprost 0.0125%	66/M/B	14	Lost to Follow-up
3212-33001	Bimatoprost 0.0125%	74/M/C	148	maculopathy
3212-33019	Bimatoprost 0.0125%	65/F/C	56	Myocardial infarction
1942-31901	Lumigan	52/F/C	14	Protocol Violation
2037-32206	Lumigan	72/M/C	42	Protocol Violation
3507-32129	Lumigan	63/F/C	13	Protocol Violation
1960-33601	Lumigan	62/F/C	100	Hair growth, periorbital darkening, increased iris hyperpigmentation
3276-33440	Lumigan	39/M/O	91	Periorbital darkening,
2037-32210	Lumigan	74/M/B	238	Uncontrolled IOP
2037-32213	Lumigan	78/F/B	115	Lost to Follow-up
2037-32217	Lumigan	42/M/B	107	Lost to Follow-up
2707-32348	Lumigan	50/F/H	112	Lost to Follow-up
2707-32364	Lumigan	43/F/H	84	Lost to Follow-up
2037-32223	Lumigan	61/F/C	272	Conjunctival hyperemia
2078-31018	Lumigan	56/M/C	159	Conjunctival hyperemia, eye irritation
2429-32407	Lumigan	58/F/C	100	Conjunctival hyperemia,
2429-32420	Lumigan	75/M/C	3	Conjunctival hyperemia

3761-30022	Lumigan	32/M/H	10	Conjunctival hyperemia, eye pruritus
3276-33419	Lumigan	74/F/C	173	Eye pruritus
3276-33449	Lumigan	65/F/H	21	Eye pruritus
2078-31025	Lumigan	71/M/C	5	Allergic reaction,
2707-32310	Lumigan	65/F/H	52	Retinal vein occlusion,
2707-32365	Lumigan	67/F/H	84	Ovarian cancer
3276-33434	Lumigan	69/F/C	287	Dysguesia
2078-31002	Lumigan	46/M/C	261	Patient moved out of state
2707-32317	Lumigan	72/F/H	176	Personal Reasons
2707-32356	Lumigan	94/F/B	42	Patient withdrew consent
2981-31630	Lumigan	78/F/C	362	Patient withdrew consent

Reviewer's Comments: *Approximately twice as many subjects in the Lumigan group discontinued due to ocular irritation symptoms (i.e. hyperemia, pruritus, irritation) compared to either the bimatoprost 0.01% group or the bimatoprost 0.0125% group.*

7.3.4 Significant Adverse Events

Significant adverse events are considered those that resulted in patient death, were coded and SAE's or those that lead to participant discontinuation in the study. Refer to sections 7.3.1, 7.3.2 and 7.3.3 for discussion.

7.3.5 Submission Specific Primary Safety Concerns

N/A – there are no submission specific safety concerns. The safety issues contained in this submission are consistent with Lumigan and other topical prostaglandin –like drops.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Number (%) of Patients with Non-Ocular Adverse Events, Regardless of Causality, Reported by >1% of Patients in Any Treatment Group - Study 192024-031

SOC Preferred Term[a]	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187
All non-ocular events	80 (43.2%)	69 (36.7%)	77 (41.2%)
Blood and lymphatic system disorders			
Anaemia	3 (1.6%)	3 (1.6%)	1 (0.5%)
Cardiac disorders			
Cardiac failure congestive	3 (1.6%)	0 (0.0%)	0 (0.0%)
Coronary artery disease	0 (0.0%)	2 (1.1%)	1 (0.5%)
Myocardial infarction	0 (0.0%)	2 (1.1%)	0 (0.0%)
Endocrine disorders			
Hypothyroidism	4 (2.2%)	1 (0.5%)	1 (0.5%)
Gastrointestinal disorders			
Gastroesophageal reflux disease	6 (3.2%)	1 (0.5%)	1 (0.5%)
Nausea	3 (1.6%)	2 (1.1%)	1 (0.5%)
Toothache	2 (1.1%)	0 (0.0%)	0 (0.0%)
Constipation	0 (0.0%)	2 (1.1%)	1 (0.5%)
Gastric ulcer	0 (0.0%)	2 (1.1%)	0 (0.0%)
Diarrhoea	0 (0.0%)	1 (0.5%)	2 (1.1%)
General disorders and administration site conditions			
Oedema peripheral	3 (1.6%)	0 (0.0%)	2 (1.1%)
Chest pain	2 (1.1%)	0 (0.0%)	2 (1.1%)
Infections and infestations			
Upper respiratory tract infection	6 (3.2%)	4 (2.1%)	3 (1.6%)
Nasopharyngitis	5 (2.7%)	4 (2.1%)	4 (2.1%)
Pharyngitis streptococcal	3 (1.6%)	0 (0.0%)	0 (0.0%)
Influenza	2 (1.1%)	3 (1.6%)	1 (0.5%)
Bronchitis	2 (1.1%)	2 (1.1%)	0 (0.0%)
Urinary tract infection	2 (1.1%)	1 (0.5%)	2 (1.1%)
Sinusitis	1 (0.5%)	2 (1.1%)	2 (1.1%)
Diverticulitis	1 (0.5%)	2 (1.1%)	1 (0.5%)
Pneumonia	1 (0.5%)	2 (1.1%)	0 (0.0%)
Tooth abscess	0 (0.0%)	1 (0.5%)	2 (1.1%)

SOC Preferred Term[a]	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187
Injury, poisoning, and procedural complications			
Skin laceration	3 (1.6%)	1 (0.5%)	1 (0.5%)
Procedural pain	2 (1.1%)	1 (0.5%)	1 (0.5%)
Fall	2 (1.1%)	0 (0.0%)	2 (1.1%)
Contusion	1 (0.5%)	1 (0.5%)	2 (1.1%)
Metabolism and nutrition disorders			
Hypercholesterolaemia	5 (2.7%)	4 (2.1%)	5 (2.7%)
Diabetes mellitus	5 (2.7%)	4 (2.1%)	2 (1.1%)
Diabetes mellitus non-insulin-dependent	3 (1.6%)	0 (0.0%)	1 (0.5%)
Dyslipidaemia	2 (1.1%)	0 (0.0%)	0 (0.0%)
Dehydration	0 (0.0%)	0 (0.0%)	2 (1.1%)
Musculoskeletal and connective tissue disorders			
Muscle spasms	3 (1.6%)	2 (1.1%)	0 (0.0%)
Back pain	2 (1.1%)	3 (1.6%)	6 (3.2%)
Musculoskeletal pain	1 (0.5%)	0 (0.0%)	2 (1.1%)
Osteoarthritis	0 (0.0%)	3 (1.6%)	3 (1.6%)
Arthritis	0 (0.0%)[b]	2 (1.1%)	7 (3.7%)
Arthralgia	0 (0.0%)	2 (1.1%)	4 (2.1%)
Exostosis	0 (0.0%)	2 (1.1%)	0 (0.0%)
Osteoporosis	0 (0.0%)	0 (0.0%)	3 (1.6%)
Plantar fasciitis	0 (0.0%)	0 (0.0%)	2 (1.1%)
Nervous system disorders			
Dizziness	3 (1.6%)	3 (1.6%)	2 (1.1%)
Headache	3 (1.6%)	0 (0.0%)	3 (1.6%)
Altered state of consciousness	0 (0.0%)	0 (0.0%)	2 (1.1%)
Psychiatric disorders			
Depression	3 (1.6%)	1 (0.5%)	3 (1.6%)
Anxiety	1 (0.5%)	0 (0.0%)	2 (1.1%)
Renal and urinary disorders			
Nephrolithiasis	2 (1.1%)	1 (0.5%)	0 (0.0%)

SOC Preferred Term[a]	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187
Respiratory, thoracic, and mediastinal disorders			
Cough	2 (1.1%)	1 (0.5%)	1 (0.5%)
Asthma	2 (1.1%)	0 (0.0%)	3 (1.6%)
Dyspnoea	2 (1.1%)	0 (0.0%)	1 (0.5%)
Pharyngolaryngeal pain	0 (0.0%)	1 (0.5%)	2 (1.1%)
Chronic obstructive pulmonary disease	0 (0.0%)	0 (0.0%)	2 (1.1%)
Vascular disorders			
Hypertension	8 (4.3%)	12 (6.4%)	11 (5.9%)

Source: Tables 14.6-1.1 and 14.6-1.2

a Coding based on MedDRA version 9.1

b Bim 0.01% significantly less than LUMIGAN® (p = 0.015)

Number (%) of Patients with Ocular Adverse Events, Regardless of Causality, Reported by > 1% of Patients in Any Treatment Group - Study 192024-031

SOC Preferred Term[a]	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187
All ocular events	88 (47.6%)[b]	92 (48.9%)[c]	116 (62.0%)
Eye disorders			
Conjunctival hyperaemia	58 (31.4%)	50 (26.6%)[c]	73 (39.0%)
Erythema of eyelid	7 (3.8%)	6 (3.2%)	10 (5.3%)
Eye irritation	7 (3.8%)	5 (2.7%)	3 (1.6%)
Growth of eyelashes	7 (3.8%)	2 (1.1%)	6 (3.2%)
Conjunctival haemorrhage	5 (2.7%)	2 (1.1%)	1 (0.5%)
Vision blurred	5 (2.7%)	0 (0.0%)[d]	3 (1.6%)
Punctate keratitis	4 (2.2%)	6 (3.2%)	11 (5.9%)
Cataract	4 (2.2%)	5 (2.7%)	4 (2.1%)
Eye pruritus	4 (2.2%)	2 (1.1%)[c]	10 (5.3%)
Conjunctival oedema	3 (1.6%)	0 (0.0%)	1 (0.5%)
Visual acuity reduced	2 (1.1%)	8 (4.3%)	4 (2.1%)
Eye pain	2 (1.1%)	1 (0.5%)	2 (1.1%)
Eyelids pruritus	2 (1.1%)	1 (0.5%)	1 (0.5%)
Vitreous floaters	2 (1.1%)	1 (0.5%)	1 (0.5%)
Asthenopia	1 (0.5%)	1 (0.5%)	3 (1.6%)
Vitreous detachment	1 (0.5%)	1 (0.5%)	3 (1.6%)
Foreign body sensation in eyes	0 (0.0%)	5 (2.7%)	5 (2.7%)
Dry eye	0 (0.0%)	5 (2.7%)	3 (1.6%)
Blepharitis	0 (0.0%)	3 (1.6%)	3 (1.6%)
Abnormal sensation in eye	0 (0.0%)	2 (1.1%)	3 (1.6%)
Eye allergy	0 (0.0%)	2 (1.1%)	1 (0.5%)
Iris hyperpigmentation	0 (0.0%)	2 (1.1%)	1 (0.5%)
Maculopathy	0 (0.0%)	1 (0.5%)	2 (1.1%)
Scotoma	0 (0.0%)	1 (0.5%)	2 (1.1%)
Blepharitis allergic	0 (0.0%)	0 (0.0%)	3 (1.6%)
Corneal erosion	0 (0.0%)	0 (0.0%)	2 (1.1%)
Photophobia	0 (0.0%)	0 (0.0%)	2 (1.1%)
General disorders and administration site conditions			
Instillation site irritation	2 (1.1%)	3 (1.6%)	1 (0.5%)

Infections and infestations			
Hordeolum	1 (0.5%)	0 (0.0%)	2 (1.1%)
Investigations			
Intraocular pressure increased	0 (0.0%)	1 (0.5%)	3 (1.6%)
Nervous system disorders			
Visual field defect	1 (0.5%)	0 (0.0%)	2 (1.1%)
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation	5 (2.7%)	1 (0.5%)[c]	10 (5.3%)
Hypertrichosis	3 (1.6%)	3 (1.6%)	1 (0.5%)
Hair growth abnormal	0 (0.0%)	0 (0.0%)	2 (1.1%)

Source: Tables 14.3-3.1 and 14.3-3.2

a Coding based on MedDRA version 9.1
b Bim 0.01% significantly less than LUMIGAN® (p = 0.005)
c Bim 0.0125% significantly less than LUMIGAN® (p ≤ 0.018)
d Bim 0.0125% significantly less than Bim 0.01% (p = 0.029)

Reviewer's Comments: *Overall, there were less ocular adverse events reported in the bimatoprost 0.01% and 0.0125% arms compared to the Lumigan arm. However, since there is no confirmatory trial that replicates these results, the actual adverse event rate in the 0.01% and 0.0125% arms cannot be determined.*

7.4.2 Laboratory Findings

N/A – no clinical laboratory evaluations were performed for this study.

7.4.3 Vital Signs

Cardiovascular parameters were measured at baseline, week 2 and 6, and months 3, 6, 9 and 12. Pulse rate was measured while patients were at rest (seated) for at least 5 minutes. Systolic and diastolic blood pressure was measured in the same arm each time by a sphygmomanometer while patients were at rest (seated) for at least 5 minutes.

Baseline and Change from Baseline in Systolic Blood Pressure (mm Hg) (Safety Population) - Study 192024-031

		0.01% Bim (N=185)	0.0125% Bim (N=188)	Lumigan (N=187)	P-value[a]
Baseline					
	N	185	188	187	0.666
	Mean	134.5	135.4	133.8	
	SD	16.09	16.49	16.79	
	Median	132.0	134.0	132.0	
	Min	101	96	98	
	Max	186	193	181	
Week 2					
	N	181	185	181	0.114
	Mean	-1.4	-2.0	0.7	
	SD	12.64	13.34	12.90	
	Median	0.0	-2.0	0.0	
	Min	-35	-42	-32	
	Max	27	58	54	
	P-value[b]	0.139	0.042	0.469	
Week 6					
	N	179	185	180	0.373
	Mean	-1.7	-0.3	0.4	
	SD	13.01	12.96	16.62	
	Median	-1.0	0.0	1.0	
	Min	-48	-39	-49	
	Max	47	40	56	
	P-value[b]	0.089	0.734	0.730	
Month 3					
	N	179	179	176	0.124
	Mean	-3.4	-0.8	-0.7	
	SD	14.72	13.15	14.19	
	Median	-2.0	-2.0	0.0	
	Min	-44	-38	-50	
	Max	38	38	40	
	P-value[b]	0.002	0.405	0.535	

		0.01% Bim (N=185)	0.0125% Bim (N=188)	Lumigan (N=187)	P-value[a]
Month 6					
	N	175	175	170	0.992
	Mean	-1.4	-1.2	-1.2	
	SD	14.33	13.99	13.52	
	Median	-2.0	-1.0	0.0	
	Min	-37	-44	-51	
	Max	48	48	53	
	P-value[b]	0.207	0.262	0.240	
Month 9					
	N	172	170	165	0.400
	Mean	-1.6	-0.2	0.6	
	SD	14.01	15.38	16.36	
	Median	-1.5	0.0	0.0	
	Min	-56	-46	-44	
	Max	33	44	63	
	P-value[b]	0.129	0.870	0.648	
Month 12					
	N	171	171	162	0.301
	Mean	-3.0	-1.0	-0.5	
	SD	15.01	16.05	15.28	
	Median	-1.0	0.0	0.0	
	Min	-68	-47	-49	
	Max	40	44	44	
	P-value[b]	0.011	0.403	0.693	

[a] P-values for among-group comparison are based on the 1-way ANOVA model with fixed effects of treatment using the type III sum of squares.
[b] P-values for within-group analysis of changes from baseline are based on a paired t-test.

Reviewers Comments: *There were no statistically significant differences in systolic blood pressure among the treatment groups. Some statistically significant within group changes from baseline were observed but these were small and not considered clinically relevant.*

Baseline and Change from Baseline in Diastolic Blood Pressure (mm Hg) (Safety Population) - Study 192024-031

		0.01% Bim (N=185)	0.0125% Bim (N=188)	Lumigan (N=187)	P-value[a]
Baseline					
	N	185	188	187	0.063
	Mean	77.8	77.2	75.5	
	SD	9.14	10.13	9.24	
	Median	78.0	78.0	76.0	
	Min	56	42	48	
	Max	98	105	110	
Week 2					
	N	181	185	181	0.040
	Mean	-1.9	-1.1	0.2	
	SD	7.44	8.23	7.82	
	Median	-2.0	-2.0	0.0	
	Min	-23	-27	-29	
	Max	22	17	26	
	P-value[b]	<0.001	0.067	0.747	
Week 6					
	N	179	185	180	0.526
	Mean	-0.8	-0.3	0.2	
	SD	7.94	8.66	7.83	
	Median	0.0	0.0	0.0	
	Min	-22	-32	-21	
	Max	22	25	24	
	P-value[b]	0.199	0.672	0.718	
Month 3					
	N	179	179	176	0.173
	Mean	-2.0	-0.6	-0.7	
	SD	8.28	8.35	7.93	
	Median	-2.0	-1.0	0.0	
	Min	-37	-32	-30	
	Max	20	21	29	
	P-value[b]	0.001	0.367	0.244	

		0.01% Bim (N=185)	0.0125% Bim (N=188)	Lumigan (N=187)	P-value[a]
Month 6					
	N	175	175	170	0.139
	Mean	-1.5	-2.0	-0.2	
	SD	9.06	9.15	7.58	
	Median	-2.0	-2.0	0.0	
	Min	-40	-38	-26	
	Max	22	28	25	
	P-value[b]	0.025	0.004	0.679	
Month 9					
	N	172	170	165	0.641
	Mean	-1.4	-0.8	-0.5	
	SD	8.59	9.62	8.86	
	Median	-0.5	0.0	0.0	
	Min	-35	-38	-32	
	Max	20	22	21	
	P-value[b]	0.036	0.256	0.505	
Month 12					
	N	171	171	162	0.296
	Mean	-1.9	-0.6	-0.3	
	SD	9.40	10.58	7.93	
	Median	-1.0	0.0	0.0	
	Min	-30	-42	-20	
	Max	25	26	20	
	P-value[b]	0.011	0.427	0.580	

[a] P-values for among-group comparison are based on the 1-way ANOVA model with fixed effects of treatment using the type III sum of squares.
[b] P-values for within-group analysis of changes from baseline are based on a paired t-test.

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Baseline and Change from Baseline in Pulse Rate (bpm) (Safety Population) - Study 192024-031

		0.01% Bim (N=185)	0.0125% Bim (N=188)	Lumigan (N=187)	P-value[a]
Baseline					
	N	185	188	187	0.505
	Mean	71.1	71.9	70.8	
	SD	9.38	10.04	9.50	
	Median	71.0	72.0	71.0	
	Min	44	48	49	
	Max	93	104	102	
Week 2					
	N	181	185	181	0.340
	Mean	-0.0	0.3	-0.9	
	SD	6.48	8.43	8.78	
	Median	0.0	0.0	-1.0	
	Min	-22	-35	-32	
	Max	16	28	34	
	P-value[b]	0.963	0.651	0.169	
Week 6					
	N	179	185	180	0.903
	Mean	-0.5	-0.2	-0.2	
	SD	6.60	8.75	7.83	
	Median	0.0	0.0	0.0	
	Min	-25	-30	-20	
	Max	18	28	29	
	P-value[b]	0.320	0.814	0.739	
Month 3					
	N	179	179	176	0.309
	Mean	-0.1	-0.8	-1.4	
	SD	7.01	8.25	9.05	
	Median	0.0	0.0	0.0	
	Min	-19	-22	-32	
	Max	28	32	34	
	P-value[b]	0.907	0.219	0.044	

		0.01% Bim (N=185)	0.0125% Bim (N=188)	Lumigan (N=187)	P-value[a]
Month 6					
	N	175	175	170	0.982
	Mean	-0.2	0.1	-0.3	
	SD	8.52	8.40	9.27	
	Median	0.0	0.0	0.0	
	Min	-22	-33	-36	
	Max	28	24	29	
	P-value[b]	0.737	0.843	0.650	
Month 9					
	N	172	170	165	0.771
	Mean	0.5	0.5	1.1	
	SD	8.13	8.26	10.10	
	Median	0.0	0.0	0.0	
	Min	-28	-27	-32	
	Max	31	26	65	
	P-value[b]	0.437	0.464	0.172	
Month 12					
	N	171	171	162	0.503
	Mean	1.3	0.7	0.2	
	SD	8.41	8.38	9.61	
	Median	2.0	0.0	-0.5	
	Min	-24	-24	-32	
	Max	29	28	32	
	P-value[b]	0.039	0.295	0.775	

[a] P-values for among-group comparison are based on the 1-way ANOVA model with fixed effects of treatment using the type III sum of squares.
[b] P-values for within-group analysis of changes from baseline are based on a paired t-test.

Reviewers Comments: *No statistically significant mean changes from baseline or among-group differences were observed in pulse rate in any treatment group at any visit.*

7.4.4 Electrocardiograms (ECGs)

N/A –ECGs were not performed for this study

7.4.5 Special Safety Studies

Macroscopic Hyperemia

Macroscopic hyperemia (by gross inspection) was measured at 3 timepoints (hours 0, 4, and 8) at each scheduled visit except month 9 (hours 0 and 4 only. The following 5-point scale was used:

0	**None**	**Normal. May appear blanched to reddish-pink without perilimbal injection. Vessels of bulbar conjunctiva easily observed**
+0.5	**Trace**	**Minimal flush, reddish color predominantly confined to the bulbar conjunctiva**
+1	**Mild**	**A flush, reddish color predominantly confined to the bulbar conjunctiva**
+2	**Moderate**	**Bright red color of the bulbar conjunctiva**
+3	**Severe**	**Deep, bright diffused redness of the bulbar conjunctiva**

Number (%) of Patients with Mild/Moderate/Severe Macroscopic Hyperemia - Study 192024-031*

Visit	Timepoint	Bimatoprost 0.01% N=185	Bimatoprost 0.0125% N=188	Lumigan N=187
Week2	Hour0	47/185 (25.4%)	49/185 (26.5%)	68/187 (36.4%)
	Hour 4	44/182 (24.2%)	46/184 (25%)	59/185 (31.9%)
	Hour 8	40/182 (22%)	41/185 (22.2%)	53/185 (28.6%)
Week6	Hour0	57/179 (32.8%)	61/188 (32.5%)	78/181 (43%)
	Hour 4	48/179 (26.8%)	52/184 (28.3%)	67/181 (37%)
	Hour 8	49/179 (27.4%)	53/188 (28.2%)	69/181 (38%)
Month 3	Hour0	64/179 (35.8%)	54/182 (29.7%)	67/178 (37.6%)
	Hour 4	49/179 (27.4%)	50/181 (27.6%)	57/178 (32%)
	Hour 8	44/179 (24.6%)	43/181 (23.8%)	51/178 (28.7%)
Month 6	Hour0	50/176 (28.4%)	55/176 (31.3%)	62/187 (33.2%)
	Hour 4	44/176 (25%)	49/176 (27.8%)	59/172 (34.3%)
	Hour 8	39/176 (22.2%)	48/176 (27.3%)	55/172 (32%)
Month 9	Hour0	47/174 (27%)	50/171 (29.2%)	48/168 (28.6%)
	Hour 4	44/172 (25.6%)	49/170 (28.8%)	51/168 (30.4%)
Month 12	Hour0	61/171 (35.7%)	50/172 (29.1%)	63/162 (38.9%)
	Hour 4	53/170 (31.2%)	53/171 (31%)	57/162 (35.2%)
	Hour 8	49/171 (28.7%)	49/171 (28.7%)	46/162 (28.4%)

** note: subjects with trace hyperemia were not included in the calculation since approximately 1/3 to ½ had trace hyperemia at baseline.*

Reviewer's Comments: *The number of subjects with mild/moderate/severe hyperemia in the Lumigan group is numerically higher all timepoints in the study compared to bimatoprost 0.01% and for the majority of timepoints compared to bimatoprost 0.0125%. However, due to underreporting of adverse events and one of the investigational sites (see section 3.1), the exact rate of hyperemia in the trial cannot be determined.*

Number (%) of Patients with at least 1 Severity Grade Increase (Worsening) from Baseline in Macroscopic Hyperemia - Study 192024-031

Visit	Timepoint	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187
Week 2	Hour 0	21/184 (11.4%)[a]	27/185 (14.6%)	39/187 (20.9%)
	Hour 4	22/182 (12.1%)	26/184 (14.1%)	35/185 (18.9%)
	Hour 8	20/182 (11.0%)	19/185 (10.3%)	23/185 (12.4%)
Week 6	Hour 0	31/179 (17.3%)	34/185 (18.4%)	45/181 (24.9%)
	Hour 4	31/179 (17.3%)	29/184 (15.8%)	35/181 (19.3%)
	Hour 8	25/179 (14.0%)	25/184 (13.6%)	34/181 (18.8%)
Month 3	Hour 0	34/179 (19.0%)	33/182 (18.1%)	38/178 (21.3%)
	Hour 4	22/179 (12.3%)	28/181 (15.5%)	26/178 (14.6%)
	Hour 8	19/179 (10.6%)	24/181 (13.3%)	22/178 (12.4%)
Month 6	Hour 0	22/176 (12.5%)	33/176 (18.8%)	35/172 (20.3%)
	Hour 4	18/176 (10.2%)	27/176 (15.3%)	30/172 (17.4%)
	Hour 8	14/176 (8.0%)	28/176 (15.9%)	26/172 (15.1%)
Month 9	Hour 0	25/174 (14.4%)	29/171 (17.0%)	25/168 (14.9%)
	Hour 4	19/172 (11.0%)	27/170 (15.9%)	22/168 (13.1%)
Month 12	Hour 0	33/171 (19.3%)	29/172 (16.9%)	38/162 (23.5%)
	Hour 4	26/170 (15.3%)	31/171 (18.1%)	31/162 (19.1%)
	Hour 8	22/171 (12.9%)	29/171 (17.0%)	20/162 (12.3%)
Overall		86/185 (46.5%)	88/187 (47.1%)	102/187 (54.5%)

Source: Table 14.3-7

Note: Overall = Number (percent) of patients who had a severity grade increase from baseline of at least one severity grade in the follow-up visits.

a Bim 0.01% significantly lower rate of macroscopic hyperemia than LUMIGAN® (p = 0.014)

Reviewer's Comments: *The number subjects that worsened by at least one severity grade was numerically higher in the Lumigan group compared to bimatoprost 0.01% and 0.0125% for the majority of timepoints.*

Biomicroscopy and Ophthalmoscopy

The number and percent of patients with at least a 1 severity grade increase from baseline in any parameter assessed by biomicroscopy or ophthalmoscopy was evaluated. Observations were recorded using a 5-point grading scale: 0 = none, +0.5 = trace, +1 = mild, +2 = moderate, +3 = severe.

Number (%) of Patients with at Least One Severity Grade Increase from Baseline for Biomicroscopy and Ophthalmoscopy Findings with ≥ 5% Incidence

Finding	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187
Overall	102 (55.1%)	93 (49.5%)	113 (60.4%)
Conjunctival hyperaemia	76 (41.1%)	66 (35.1%)[a]	92 (49.2%)
Erythema of eyelid	7 (3.8%)	10 (5.3%)	10 (5.3%)
Cataract	6 (3.2%)	8 (4.3%)	15 (8.0%)
Punctate keratitis	5 (2.7%)	11 (5.9%)	11 (5.9%)

Visual Field/Visual Acuity/Cup/Disc Ratio Examination

There were not clinically significant changes in visual field, visual acuity or cup/disc ratio in any treatment group during the study.

Iris Color Assessment

Digital photographs were taken and Iris color was assessed using printed photographs. The investigator compared baseline (Day 0) to subsequent printed photographs (Month 3, Month 6, and Month 12) to determine whether there had been any changes in iris color pigmentation.

Only 1 patient in the Lumigan group and 2 patients in the bimatoprost 0.125% group were noted to have increased iris pigmentation during the 12 month treatment period.

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A – bimatoprost 0.01% and 0.0125% were both dosed one drop per day in the test eye. There was no variation in the dosing.

7.5.2 Time Dependency for Adverse Events

In comparing the 3-month adverse event profile to the 12-month data, there is an expected increase in the number of adverse events in each of the treatment groups. However, there were no new unexpected adverse events that suggest a duration related increased in risk in any of the treatment groups.

7.5.3 Drug-Demographic Interactions

Study 192024-031 was analyzed for ocular and non-ocular adverse events (all causality and treatment-related) in key patient subgroups defined by age, sex, race, and iris color. There was no apparent clinically relevant difference across age, race or gender groups in the incidence and type of adverse events among treatment groups.

7.5.4 Drug-Disease Interactions

Drug-Disease interactions were not studied for this submission. However, based on the information available regarding specific patient populations for Lumigan the following interactions are likely with the use of bimatoprost 0.01%.

Macular edema, including cystoid macular edema, has been uncommonly reported during treatment with Lumigan therefore bimatoprost 0.01% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Bimatoprost 0.01% has not been evaluated in patients with angle-closure, inflammatory or neovascular glaucoma. Bimatoprost 0.01% should be used with caution in patients with active intraocular inflammation (eg, uveitis). Bimatoprost 0.01% contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should therefore be removed prior to instillation of Bimatoprost 0.01% and may be reinserted 15 minutes following administration. Bimatoprost 0.01% was not formally studied in patients with renal or hepatic impairment. In patients enrolled on the long-term Lumigan studies who had a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, Lumigan had no adverse effect on liver function over 48 months.

7.5.5 Drug-Drug Interactions

No specific drug-drug or drug-food interaction studies were performed with bimatoprost 0.01%. Bimatoprost 0.01% is a topical drug with effects expected to be predominantly local. No interactions are anticipated, since systemic concentrations of bimatoprost are extremely low (< 0.2 ng/mL) following ocular dosing of Lumigan.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

The following information is available on the carcinogenicity of bimatoprost:

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

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

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate data for the use of bimatoprost 0.01% in pregnant women. The following information is available on the use of bimatoprost in pregnant or nursing women:

Studies in rodents produced species-specific abortion at systemic exposure levels 33 to 97 times that achieved in humans after ocular administration. No treatment-related developmental effects were observed (Lumigan, PI, 2006). At doses at least 41 times the intended human exposure based on blood area under the curve levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

Because animal reproductive studies are not always predictive of human response, bimatoprost 0.01% should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is unknown if bimatoprost is excreted in human milk; however, it is excreted in rat milk after intravenous administration. Because many drugs are excreted in human milk, caution should be exercised when bimatoprost 0.01% is administered to a nursing woman.

7.6.3 Pediatrics and Effect on Growth

Data on growth affects is not available. Safety studies in pediatric patient have not been conducted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no pharmacological evidence for any potential of drug abuse with bimatoprost eye drops. Bimatoprost does not belong to a class of compounds that has known abuse potential.

Withdrawal and rebound effects after discontinuation were not evaluated in the bimatoprost 0.01% studies.

Bimatoprost 0.01% is intended for topical use only. Due to the low systemic concentrations of bimatoprost after topical ophthalmic administration, the likelihood of systemic intoxication from topical overdose is remote. No cases of overdose with bimatoprost have been reported.

No information is available on overdosage of bimatoprost in humans. In oral mouse and rat studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 210 times higher than the accidental dose of 1 bottle of bimatoprost for a 10-kg child.

7.7 Additional Submissions

The results of the 120 Day Safety update have been incorporated throughout the review.

8 Postmarketing Experience

Bimatoprost 0.01% is presently not marketed and there are no post-marketing reports. Post-marketing reports received for Lumigan have not altered the risk-benefit profile.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

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

9.3 Advisory Committee Meeting

N/A – an advisory committee was not held for this product.

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/s/

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4/14/2008 04:21:08 PM
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