

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022184Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 22, 2008
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-184
Supplement#	
Applicant	Allergan
Date of Submission	July 2, 2007
PDUFA Goal Date	May 3, 2008
Proprietary Name / Established (USAN) names	Lumigan (bimatoprost ophthalmic solution) 0.01%
Dosage forms / Strength	ophthalmic solution
Proposed Indication(s)	reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension
Recommended:	Approval

1. Introduction

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.

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).

The application demonstrated that bimatoprost 0.01% lowered IOP by approximately 5-7 mmHg; this amount is not only clinically meaningful but is greater than many currently marketed products. The drug product was not equivalent to Lumigan 0.03% in IOP-lowering efficacy as measured by mean IOP. The difference in mean IOP between bimatoprost 0.01% and Lumigan 0.03% 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.¹

¹ 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 types of adverse events seen were consistent with the known adverse event profile of Lumigan 0.03%. 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 0.03% arm. While the exact safety profile of bimatoprost 0.01% cannot be determined based on the results of a single trial submitted, these lower concentration products would be expected to at worst have a profile similar to the currently marketed Lumigan 0.03%.

Based on the known safety profile of Lumigan 0.03% and the IOP lowering effect of both bimatoprost 0.01% and 0.0125% in the submitted clinical trial, the risk/benefit profile for both products is favorable. Since it is favorable to expose patients to the lowest effective dose, bimatoprost 0.01% was recommended for approval by the reviewing Medical Officer.

NDA 22-184 is recommended for approval for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. The labeling for the bimatoprost 0.01% should indicate that it is not equivalent to Lumigan 0.03% in its ability to lower intraocular pressure. A combined package insert for both products, Lumigan 0.01% and Lumigan 0.03%, is recommended.

2. Background

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.

Bimatoprost is a synthetic prostaglandin analog 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%.

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.

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.

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.

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 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. CMC

DRUG SUBSTANCE:

Bimatoprost is a synthetic prostaglandin analog with ocular hypotensive activity. Bimatoprost drug substance to be used in the proposed formulation (0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution) is the same drug substance submitted and approved via the original NDA 21-275 for Lumigan (bimatoprost ophthalmic solution, 0.03%). For the chemistry, manufacturing, and controls (CMC) information for the bimatoprost drug substance, reference is made to NDA 21-275.

DRUG PRODUCT:

The 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution was developed from the Lumigan 0.03% product platform with modifications to the levels of the drug substance, bimatoprost, the preservative, benzalkonium chloride, and the tonicity agent, sodium chloride. No new ingredients have been added. Lumigan 0.03% is manufactured by Allergan under approved NDA 21-275.

As with Lumigan 0.03%, the proposed drug product is a clear, colorless, isotonic, sterile solution containing 0.01% (w/v) bimatoprost as the active ingredient and 0.02% (w/v) benzalkonium chloride as the preservative. The inactive ingredients include sodium chloride, dibasic sodium phosphate (b)(4), citric acid (b)(4), and purified water. The solution pH is adjusted to (b)(4) using either (b)(4) sodium hydroxide or (b)(4) hydrochloric acid. Except for the drug substance, all ingredients are USP/Ph Eur, NF/Ph Eur or USP compendial grade materials.

As stated above, all ingredients are identical to those used in the Lumigan 0.03% formulation. The currently proposed formulation of bimatoprost is essentially equivalent to Lumigan 0.03% except for the following small composition differences for the currently proposed drug product versus Lumigan 0.03%: a lower bimatoprost concentration (0.01% versus 0.03%), increased BAK (200 ppm versus 50 ppm), and decreased sodium chloride for isotonicity (b)(4)

DRUG PRODUCT COMPOSITION:

From the original CMC review, page 17.

Table 3.2.P.1-1 List of Components and Quantitative Composition

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)	(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.

REGULATORY SPECIFICATIONS:

From the original CMC review, page 30:

Test	Release acceptance criteria	Regulatory acceptance criteria	Method reference
Bimatoprost (AGN 192024)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

4. Nonclinical Pharmacology/Toxicology

Systemic and ocular toxicology studies were submitted in NDA 21-275 for the original Lumigan 0.03% formulation. Additional ocular toxicity studies with higher concentrations of BAK and lower concentrations of bimatoprost were performed to support the current NDA. Formulations containing 200 ppm BAK (including vehicle) administered twice daily for one month to New Zealand White rabbits were associated with minimal to moderate ocular findings including conjunctival congestion, epithelial degeneration/regeneration, and corneal stromal edema. Single daily doses of 0.01% bimatoprost containing 200 ppm BAK (as in the formulation proposed for marketing) were not associated with any gross or microscopic ocular changes in Dutch-Belted rabbits when administered daily for 6 months.

In monkeys and humans, chronic treatment with bimatoprost is associated with increased pigmentation of the iris and periocular tissues. Increased thickness and pigmentation of eyelashes has also been observed in these species.

Monkeys have demonstrated widening of the palpebral fissure and increased prominence of ocular sulci following ocular or intravenous treatment with bimatoprost.

Findings in mice (elevated RBC parameters, thymic lymphoid proliferation, increased vaginal acute inflammatory cells) and rats (testicular degeneration, adrenal cortical vacuolation, increased AST/ALT) after repeated oral dosing from 28 days-13 weeks were not observed at clinically relevant doses (rodent blood AUCs \geq 150-fold higher than that achieved following recommended clinical ocular doses). Ovarian findings (increased ovarian weight, prominently vacuolated corpora lutea) observed in rats beginning at doses about 30-fold higher than those achieved after ocular dosing in humans were not seen in other species including mice, monkeys, rabbits, and dogs. Bimatoprost is believed to have a species-specific effect on the luteal cycle in rats, delaying luteal regression. In naïve rats, PG F_{2 α} (in concert with other endogenous compounds) is involved in luteal cycling.

CARCINOGENICITY:

Oral rodent carcinogenicity studies were conducted to support NDA 21-275. There was no evidence of tumorigenic potential in mice and rats given bimatoprost by daily oral gavage for 2 years at doses up to 2 mg/kg/day and 1 mg/kg/day, respectively. These doses are 192 and 291 times higher than human exposure based on AUC levels in blood.

REPRODUCTIVE TOXICOLOGY:

A complete battery of reproductive and developmental toxicity studies was conducted to support NDA 21-275. Lumigan 0.03% has been assigned Pregnancy Category C. Bimatoprost did not impair the fertility of male or female rats given at doses up to 0.6 mg/kg/day (about 100 times human exposure based on blood AUC after Lumigan 0.03% administration). Bimatoprost induced late abortions and early delivery following oral administration to mice and rats at 0.3 or 0.6 mg/kg (systemic exposures approximately 30 and 100 times greater than those observed in humans using ocular bimatoprost). In rodents,

prostaglandins and their analogues are known to induce abortion mediated by their ovarian luteolytic effects; this mechanism is not relevant to humans. In humans, prostaglandins can cause the uterus to contract, but bimatoprost does not cause contraction of human uterine muscle. In a peri/post-natal study in rats, bimatoprost doses of 0.3 mg/kg (approximately 40-fold greater than those observed in humans after Lumigan 0.03% administration) were associated with reduced gestation length, late resorptions, fetal death, and postnatal mortality. The offspring of these bimatoprost-treated dams had lower preweaning body weights and had reproductive impairments. F1 animals reared to maturity had reduced mating performance compared to controls and pregnant females had reduced body weight gains.

Due to species specificity and the much greater systemic exposure of the mice and rats in toxicity studies compared to humans treated with ocular bimatoprost, the reproductive toxicity of bimatoprost in rodents is unlikely to be clinically relevant.

5. Clinical Pharmacology/Biopharmaceutics

The pharmacokinetics of bimatoprost in humans following the administration of Lumigan 0.03% has been characterized in four PK studies and by sparse PK sampling of patients with glaucoma or ocular hypertension in two Phase 3 studies. The data from these studies were previously submitted with NDA 21-275 (see Clinical Pharmacology review dated 18 September 2000). No additional clinical pharmacology studies have been conducted with the proposed 0.01% formulation.

Allergan requested a waiver of the in vivo bioavailability requirement for bimatoprost ophthalmic solution, 0.01%, as set forth in 21 CFR 320.22. As the concentration of bimatoprost has been reduced from 0.03% to 0.01% in the new formulation, it is believed that the systemic exposure of bimatoprost will not exceed that observed following the administration of Lumigan 0.03%. The systemic exposure of bimatoprost was negligible following the ocular administration of Lumigan 0.03% at the recommended dose to healthy subjects and patients. In healthy subjects, blood concentrations of bimatoprost were below the lower limit of quantitation (0.025 ng/mL) within 1 to 1.5 hours post-dose following 14 days of Lumigan 0.03% administration (1 drop once daily to both eyes). Mean C_{max} and AUC_{0-t} values on Day 14 were 0.082 ng/mL and 0.096 ng•h/mL, respectively. Bimatoprost blood concentrations in patients with glaucoma or ocular hypertension were similar to those observed in healthy subjects, with no systemic accumulation observed over time.

Allergan's request for a waiver of the requirement for submission of evidence of in vivo bioavailability was granted, based on the expected low systemic exposure of bimatoprost following ophthalmic administration of bimatoprost ophthalmic solution, 0.01%.

6. Sterility Assurance

No endotoxin specification for the final product was provided with the original submission. An information request (see below) was transmitted to Allergan on 14 February 2008 requesting that a bacterial endotoxin specification of NLT (b)(4) be submitted:

The drug product should have an endotoxin limit and a validated endotoxin test method should be part of the drug product specifications. The suggested limit is NMT (b)(4). Endotoxin testing should also be performed at release and expiry on stability samples.

Allergan responded to the deficiency in a 14 April 2008 amendment. Allergan validated a kinetic chromogenic endotoxin test method (Kinetic-QCL, Cambrex) for the drug product according to the acceptance criteria in USP <85>. The product had to be diluted (b)(4) to achieve acceptable endotoxin recovery. The lysate sensitivity was (b)(4), resulting in a limit of detection in the drug product of (b)(4).

Allergan then performed endotoxin testing on three primary registration lots and three commercial validation lots of the drug product. (b)(4)

Allergan is proposing to perform endotoxin testing at release and on stability (at expiry) on a “Record Only” basis. They will also commit to implementing the necessary process and raw material controls to achieve the lowest possible endotoxin specification for the drug product. Allergan states that they expect this process to take from 6-12 months.

The Product Quality Microbiology Reviewer recommends that a prior approval supplement containing the proposed endotoxin specification (test method and acceptance criteria), a summary of the endotoxin test method validation and the proposed process and raw material endotoxin controls be submitted within 12 months of the approval date. Allergan should also perform endotoxin testing on the drug product on a “for information only” basis until an endotoxin specification has been approved (see the Product Quality Microbiology Review dated 17 April 2008).

7. Clinical/Statistical - Efficacy

Table of Clinical Studies

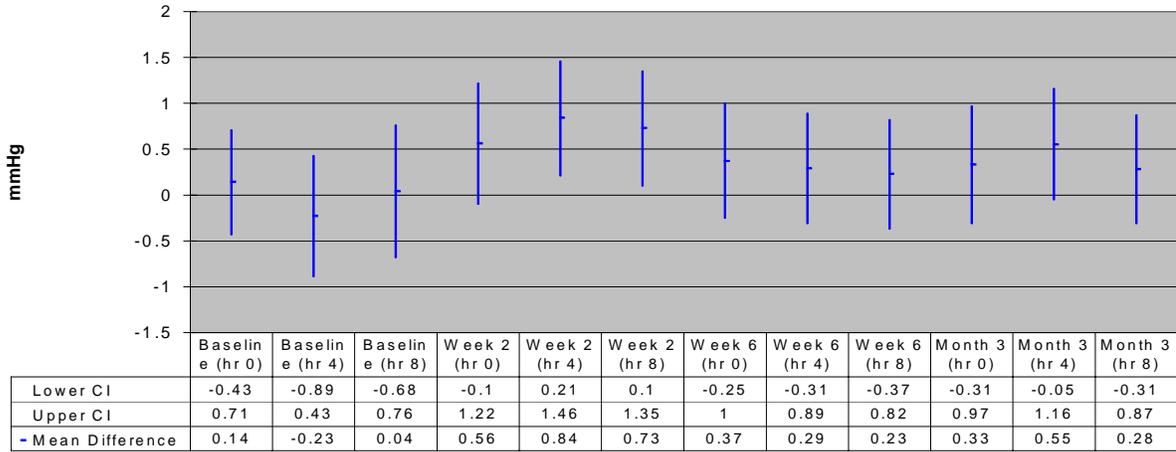
Study/Report No.	Phase	Population (ITT)	Key Features
192024-020	2	OHT or glaucoma (N = 188)	Bimatoprost 0.01% BID, 0.015% BID, 0.02% QD, 0.025% QD compared to LUMIGAN [®] (all with 50 ppm BAK) and Timolol 0.5% Double-masked, 6-arm parallel-group Twice-daily: study medication morning and evening Once-daily: 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](#)

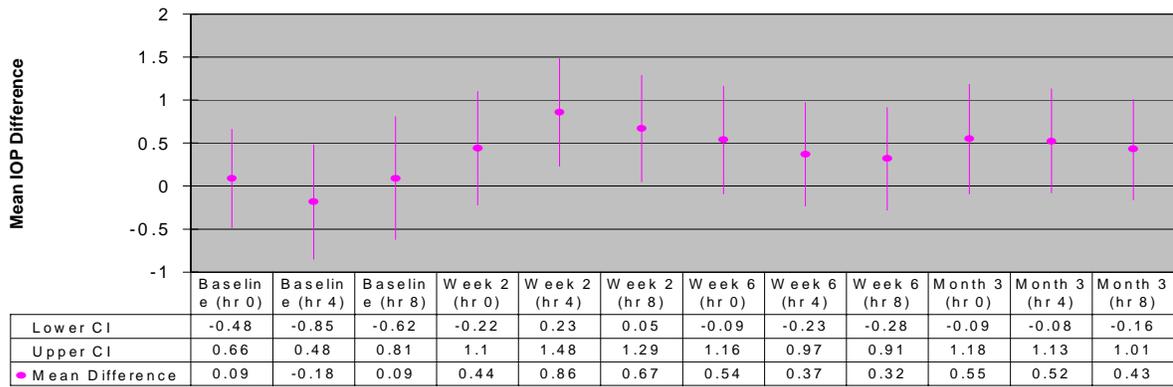
a Phase 2 Study, 192024-020, was not part of the clinical development program for Bim 0.01% but provides supportive efficacy and safety data for the choice of bimatoprost concentrations in Studies 192024-030 and 192024-031.

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 0.03%. Allergan 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 by the Medical Officer due to differing formulations and limited patient exposure.

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



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



See the Medical Officer's review, pages 17 and 20, dated 14 April 2008.

For the comparison between bimatoprost 0.01% and Lumigan 0.03%, at all the time points, the 2-sided 95% CI for the group difference was within 1.5 mm Hg. At 5/9 time points (Hours 0, 4 and 8 at Week 2 Visit, and Hour 0 at Week 6 Visit, and Hour 4 at Month 3 Visit), the upper limit of the 2-sided 95% CI for the group difference was at or above 1.0 mm Hg. At 2/9 time points (Hours 4 and 8 at Week 2 Visit), the lower limit of the 2-sided 95% CI for the group difference was above zero. At all the post baseline time points, the average IOP in the bimatoprost 0.01% group was higher than the one in the Lumigan 0.03% group.

For the comparison between bimatoprost 0.0125% and Lumigan 0.03%, at all the time points, the 2-sided 95% CI for the group difference was within 1.5 mm Hg. At 7/9 time points (Hours 0, 4, and 8 at Week 2 Visit, Hour 0 at Week 6 Visit, Hours 0, 4, and 8 at Month 3 Visit), the upper limit of the 2-sided 95% CI for the group difference was above 1.0 mm Hg. At 2/9 time points (Hours 4 and 8 at Week 2 Visit), the lower limit of the 2-sided 95% CI for the group difference was above zero. At all the post baseline time points, the average IOP in the bimatoprost 0.0125% group was higher than the one in the Lumigan 0.03% group.

Using an equivalency margin of 1.0 mg Hg, study 192024-031 failed to demonstrate equivalency of efficacy of bimatoprost 0.01% or bimatoprost 0.0125% to Lumigan 0.03% in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension at a majority of the post baseline time points. See Statistical Review dated 18 April 2008, page 20.

**Mean Intraocular Pressure (mm Hg) (ITT with LOCF)
 Comparison with LUMIGAN® Test of Non-inferiority at 1.5 mm Hg Margin**

Visit	Timepoint	Mean Intraocular Pressure (mm Hg)	
		Bim 0.01% / LUMIGAN® N = 185/187	Bim 0.0125% / LUMIGAN® N = 186/187
Week 2	Hour 0 Difference ^a (95% CI ^b)	17.8 / 17.3 0.56 (-0.10 to 1.22)	17.7 / 17.3 0.44 (-0.22 to 1.10)
	Hour 4 Difference ^a (95% CI ^b)	17.1 / 16.3 0.84 (0.21 to 1.46)	17.1 / 16.3 0.86 (0.23 to 1.48)
	Hour 8 Difference ^a (95% CI ^b)	16.9 / 16.2 0.73 (0.10 to 1.35)	16.9 / 16.2 0.67 (0.05 to 1.29)
Week 6	Hour 0 Difference ^a (95% CI ^b)	17.6 / 17.2 0.37 (-0.25 to 1.00)	17.8 / 17.2 0.54 (-0.09 to 1.16)
	Hour 4 Difference ^a (95% CI ^b)	16.8 / 16.5 0.29 (-0.31 to 0.89)	16.8 / 16.5 0.37 (-0.23 to 0.97)

	Hour 8	Difference ^a (95% CI ^b)	16.7 / 16.4 0.23 (-0.37 to 0.82)	16.8 / 16.4 0.32 (-0.28 to 0.91)
Month 3	Hour 0	Difference ^a (95% CI ^b)	17.3 / 17.0 0.33 (-0.31 to 0.97)	17.6 / 17.0 0.55 (-0.09 to 1.18)
	Hour 4	Difference ^a (95% CI ^b)	16.7 / 16.1 0.55 (-0.05 to 1.16)	16.6 / 16.1 0.52 (-0.08 to 1.13)
	Hour 8	Difference ^a (95% CI ^b)	16.4 / 16.2 0.28 (-0.31 to 0.87)	16.6 / 16.2 0.43 (-0.16 to 1.01)

^a Calculated as test formulation minus LUMIGAN®; a negative value favored the test formulation.

^b 95% confidence interval for between-treatment difference based on the one-way ANOVA model with fixed effect of treatment.

Data source: Sponsor's CSR Table 11.4-4.

8. Safety

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 0.03%. 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 0.03% arm. However, there is no confirmatory trial that replicates these results. Additionally, there was a separate section of the Case Report Form for reporting hyperemia; this separate section led to hyperemia being reported as a pharmacological event instead of an adverse event. While Division of Scientific Investigations (DSI) audit cites this as possibly underreporting some adverse events, the Review Division does not believe interpretation of the reported events is confounded. See Section 11 of this review.

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.

See the following tables from the Medical Officer's review, Section 7.3.3

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%)

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

9. Advisory Committee Meeting

Not applicable; this product is a non-NME.

10. Pediatrics

Allergan 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 principal unanswered questions with respect to bimatoprost in pediatric patients relate to the long term safety, i.e. skin and iris pigmentation and eyelash growth. While five year safety data is already known and considered sufficient for the elderly population in which elevated intraocular pressure is more commonly seen, it is not sufficient for a pediatric

population. A long term study in pediatric patients would require at least 20 years of follow-up.

11. Other Relevant Regulatory Issues

A Division of Scientific Investigations (DSI) audit was requested. This inspection audited one study, Study #192024-031-00 at two domestic sites, those of Investigators #2078 and #3761. The data from the #2078 site are considered acceptable in support of the respective indication. However, the safety data at the #3761 site were considered incomplete. At the #3761 site, the major finding was related to under-reporting of adverse events in 5 subjects (see the DSI consult dated 5 March 2008). There was a separate section of the Case Report Form in this trial for reporting hyperemia; this separate section led to hyperemia being reported as a pharmacological event instead of an adverse event. While the DSI audit cites this as possibly underreporting some adverse events, the Review Division does not believe interpretation of the reported events is confounded.

Allergan 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 the results of the study were impacted by any financial payments.

A consult was requested from the Office of Surveillance and Epidemiology regarding a trade name review for the proposed name “Lumigan RC.” They recommended managing the proposed product under the existing product name, Lumigan, with an educational program to increase awareness among the practitioners of the new strength.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed Allergan’s proposed product labeling (PI) for this application submitted to the Agency on 2 July 2007. Their suggestions regarding the Highlights section of the labeling and adverse reactions have been incorporated in the revised labeling.

12. Labeling

NDA 22-184 is recommended for approval for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension with the labeling submitted by Allergan on 29 April 2008 and found in this Cross-Discipline Team Leader Review (see Appendix 1).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 22-184 is recommended for approval for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. The labeling for the bimatoprost 0.01% should indicate that it is not equivalent to Lumigan 0.03% in its ability to lower intraocular pressure. A combined package insert for both products, Lumigan 0.01% and Lumigan 0.03%, is recommended.

The labeling submitted by Allergan on 29 April 2008 and found in this Cross-Discipline Team Leader Review (see Appendix 1) is acceptable for approval.

RISK BENEFIT ASSESSMENT:

The application demonstrated that bimatoprost 0.01% lowered IOP by approximately 5-7 mmHg; this amount is not only clinically meaningful but is greater than many currently marketed products. The drug product was not equivalent to Lumigan 0.03% in IOP-lowering efficacy as measured by mean IOP. The difference in mean IOP between bimatoprost 0.01% and Lumigan 0.03% 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.

The application supports the safety of bimatoprost 0.01% in the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. 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 0.03%. 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 0.03% arm. However, there is no confirmatory trial that replicates these results.

Clinical, CMC, Pharmacology/Toxicology, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

The Statistical review states that study 031 failed to demonstrate equivalency of efficacy of bimatoprost 0.01% or bimatoprost 0.0125% to Lumigan 0.03% in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

Appendix 1

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

**This is a representation of an electronic record that was signed electronically and
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/s/

William Boyd
5/1/2008 04:16:45 PM
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