CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-369

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 12, 2008
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA#	22-369
Applicant	Allergan, Inc.
Date of Submission	June 26, 2008
PDUFA Goal Date	December 27, 2008
Proprietary Name / Established (USAN) names	Latisse (bimatoprost ophthalmic solution) 0.03%
Dosage forms / Strength	ophthalmic solution
Proposed Indication(s)	To improve the prominence of natural eyelashes as measured by increases in growth, fullness and darkness
Recommended:	Approval

1. Introduction

Bimatoprost, the active moiety, is an efficacious ocular hypotensive agent that selectively mimics the effects of naturally occurring prostaglandins. NDA 21-275, Lumigan (bimatoprost ophthalmic solution) 0.03% was first approved in the United States in March 2001 for the reduction of intraocular pressure in patients with glaucoma or ocular hypertension.

There are four prostaglandin / prostaglandin analogue drug products which have been approved for the reduction of intraocular pressure in patients with glaucoma and ocular hypertension. As a class of drugs, the prostaglandin analogues have reported some degree of increased eyelash growth as an adverse event in their respective NDA submissions.

The applicant has developed bimatoprost ophthalmic solution, 0.03% for this new ophthalmic indication, "to improve the prominence of natural eyelashes as measured by increases in growth, fullness and darkness."

2. Background

Bimatoprost is an efficacious ocular hypotensive agent which was first approved for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension in March 2001 (NDA 21-275, Lumigan (bimatoprost ophthalmic solution, 0.03%). The mechanisms of action by which bimatoprost reduces intraocular pressure are believed to be by increasing aqueous humor outflow through the trabecular meshwork and by enhancing uveoscleral outflow.

In the initial NDA submission [21-275], increased eyelash growth was observed as an adverse event in the clinical trials of bimatoprost 0.03% ophthalmic solution used once daily. In two active-controlled Phase 3 studies, eyelash growth was reported as an adverse event after 3 months of treatment in 17.9% and 25.6% of patients receiving bimatoprost 0.03% ophthalmic solution once daily. The proportion of subjects reporting eyelash growth increased after 6 and 12 months of treatment. In a proof-of-concept study evaluating the effect of bimatoprost 0.03% on eyelash growth, color, and thickness, bimatoprost was shown to be effective as measured by subjects' assessment of change from baseline. At the end of the 3-month treatment period, 81% (13/16) of subjects who completed the study reported their overall eyelash appearance to be "much improved," and 19% of subjects reported their overall eyelash appearance to be "improved." Lumigan (bimatoprost ophthalmic solution) 0.03% and Latisse (bimatoprost ophthalmic solution) 0.03% studied in this NDA are the same formulation in the same bottle.

The exact mechanism of action by which bimatoprost causes eyelash growth is unknown; bimatoprost-induced eyelash enhancement is believed to occur by 3 mechanisms: by prolonging the growth phase of the hair cycle resulting in longer length; by stimulating the resting follicles resulting in thicker/fuller lashes; and by increasing melanin synthesis resulting in darker hair pigmentation.

3. CMC

From the CMC Review dated December 15, 2008:

Bimatoprost ophthalmic solution 0.03% is proposed to be applied to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying sterile disposable applicators. Bimatoprost is structurally similar to other approved prostaglandins but differs from some in having an amide group in the chemical structure. The proposed drug product is a clear, isotonic, colorless, sterile solution. The same solution was approved in NDA 21-275 under the trade name Lumigan for lowering intraocular pressure (IOP) when instilled directly to the eye in patients with elevated IOP. This CMC review covers only those sections in which the 2 drug products (NDA 21-275 and NDA 22-369) differ from each other.

One change made in the primary packaging component is a disposable sterile applicator required for the administration of bimatoprost solution to the skin of the upper eyelid margin. The approved solution is administered by a dropper.

The container closure system for the sterile applicator is a [redacted] tray with a [redacted] lid. The applicators are sterilized using a [redacted]. The secondary packaging is a retail paperboard unit carton containing six sterile applicator packages with 10 applicators per package for a total of 60 applicators (a one month supply). The sterile, single-use per eye disposable applicator is

b(4)

intended to apply bimatoprost solution 0.03% to the upper eyelid margin. It comprises ——— handle with an attached tuft made from multiple ——— ——— The tuft is configured to optimize product application to the upper eyelid margin. b(4)

The CMC Review dated December 15, 2008, identifies the proposed cap color as —, not turquoise. — was proposed in the original NDA submission dated June 26, 2008. In a subsequent submission to the NDA on September 29, 2008, Allergan changed the proposed cap color from — to turquoise (same as currently marketed Lumigan): b(4)

> 2.3.P.7.1 Container Closure System for 0.03% bimatoprost solution The container closure system for the 0.03% bimatoprost solution of TRADENAME drug product is the same as LUMIGAN. The primary container closure system is a white bottle, white tip, and turquoise cap.

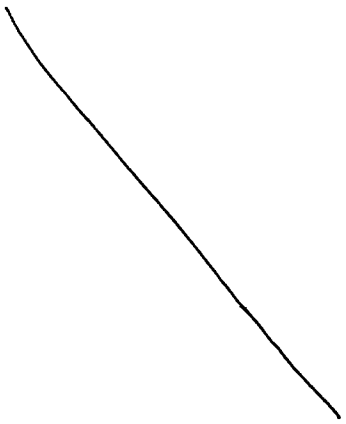
From a CMC Memo dated December 19, 2008:

The acceptability of the manufacturing facilities was the remaining CMC issue that needed to be resolved before approval of NDA 22-369.

The EES report now shows an Overall Recommendation of Acceptable (Dated Dec 19, 2008), so this NDA is recommended for approval from the CMC perspective.

DRUG SUBSTANCE SPECIFICATIONS

From the CMC Review dated December 15, 2008:



b(4)

1 Page(s) Withheld

X Trade Secret / Confidential (b4)

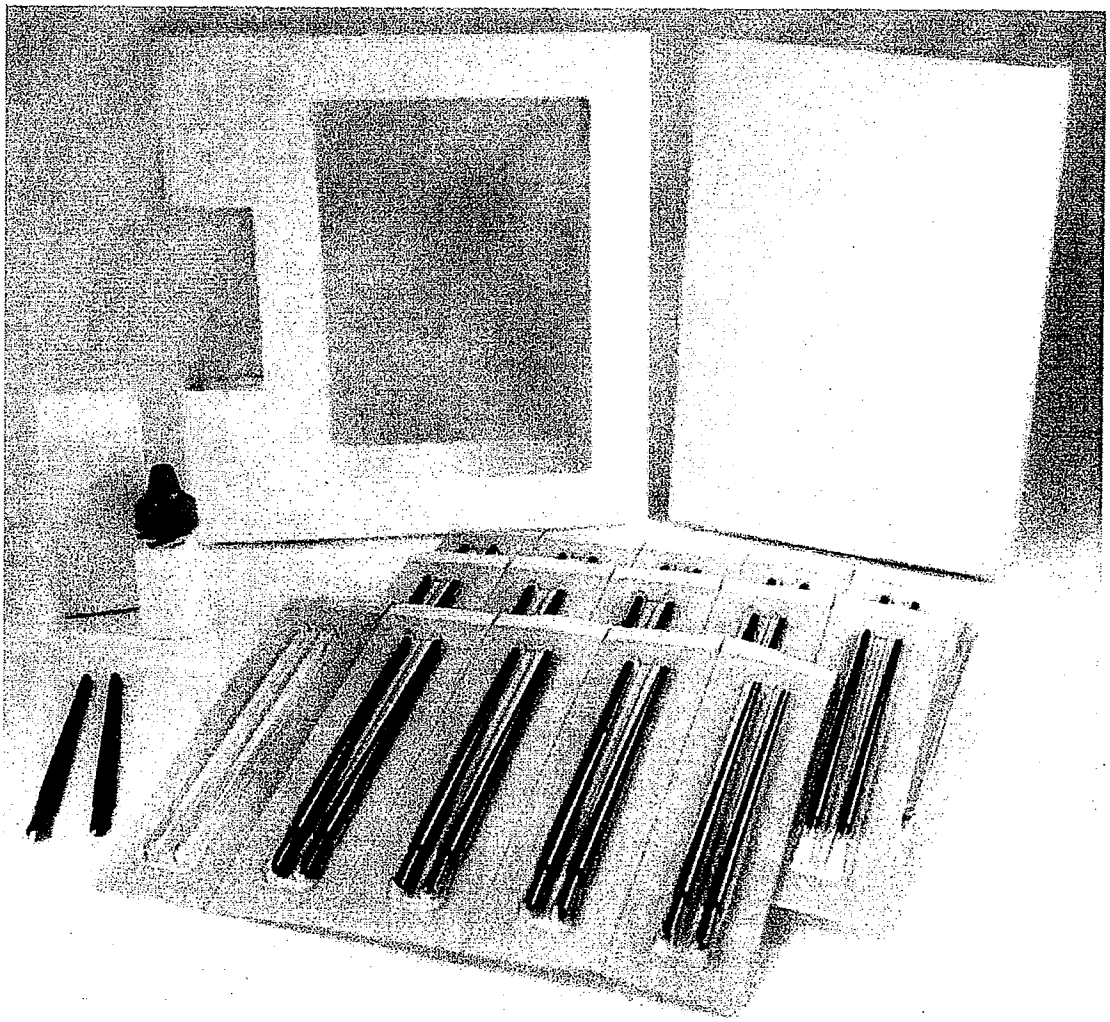
_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Cross Discipline TL Review- 1

PROPOSED PACKAGING:



4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology Review dated August 1, 2008:

NDA 21-275 for Lumigan belongs to Allergan and the nonclinical studies conducted to support the development and approval of that product are also appropriate to support the current NDA via cross-reference. Thus, the current NDA 22-369 does not require a

pharmacology/toxicology review. The sponsor did not need additional nonclinical studies to support the current NDA. The sponsor included a brief report (Effect of Bimatoprost (Lumigan) on the Eyelashes of Mice, Report No. BIO-07-630) for a nonGLP study on the effects of 0.03% bimatoprost on eyelash growth in C57BL/6 mice. According the report (which contained no raw data), bimatoprost increased the thickness and length of short and medium length (but not long) eyelashes and increased the number of eyelash follicles with 2 hairs but did not increase the number of follicles. The NDA also contains reports of a single dose dermal absorption study in mice using an alcoholic gel formulation of bimatoprost (Report No. PK-04-157) as well as a predictive multiple dose PK analysis based on data from that dermal absorption study (Report No. PK-08-038). The gel formulation is not being marketed.

The pharmacologist has no objection to the approval of NDA 22-369 for 0.03% bimatoprost solution for eyelash enhancement. The label contains the appropriate cautions to users of this product including the potential for ocular effects and increased pigmentation of skin or iris. The product appears reasonably safe if used as directed. Many portions of the label for the eyelash enhancement solution will be the same as that for Lumigan, including the *Carcinogenesis, Mutagenesis, Impairment of Fertility* and *Pregnancy* sections. This is appropriate and acceptable. The reviewer has no additional label recommendations.

The application is recommended for approval by the Pharmacology/Toxicology Reviewer.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review dated November 3, 2008:

In support of the NDA, the Sponsor submitted the results of a Phase 3 safety and efficacy study. No new clinical pharmacology data are submitted by the Sponsor. As the drug product, dose and dosing frequency are unchanged, the Sponsor is granted a waiver of the requirement to provide evidence of in vivo bioavailability based on 21 CFR 320.22(b)(1). Given the dose and route of administration (application to the upper eyelid), systemic exposure of bimatoprost is expected to be clinically negligible.

There are no recommended changes to the Sponsor's proposed label.

The application is recommended for approval by the Clinical Pharmacology Reviewer.

6. Sterility Assurance

From the Product Quality Microbiology Review dated December 8, 2008:

There are no changes in the previously approved manufacturing process for 0.03% bimatoprost solution [NDA 21-275] except that the newly designated product would be used for external application. An external applicator kit is provided.

The container closure system for the 0.03% bimatoprost solution of TRADENAME drug product is the same as Lumigan. The secondary container closure consists of the same paperboard unit carton and insert that are currently used. The bottles, tips, and caps are b(4)
— — using a validated process. The requalification report for the
— process for containers and closures was adequate for a —
(validation report VFR-SPQS-630).

The container closure system for the sterile applicator is a —
— tray with a — lid. The applicator packs are sterilized using a b(4)
validated — The initial — sterilization dose setting for
— applicators were determined in conformance with ISO 11137-2:2006.

The application is recommended for approval by the Product Quality Microbiology Reviewer.

The original submission contained neither a proposal for endotoxin data collection nor a proposed specification for endotoxin level testing. In a correspondence dated December 16, 2008, — See this review, Section 13.

7. Clinical/Statistical - Efficacy

Description of Clinical Efficacy Studies for Eyelash Growth

Study No.	Study Design	Main Entry Criteria	Study Objectives	# Pts Treated, Treatment	Duration of Treatment	Key Results
Controlled Studies Pertinent to the Claimed Indication						
192024-032	Phase 3 multicenter, double-masked, randomized, vehicle-controlled parallel-group study	Healthy adult subjects with no active ocular disease and with baseline overall eyelash prominence of minimal or moderate based on the 4-point Global Eyelash Assessment Scale	To evaluate the safety and efficacy of bimatoprost solution 0.03% once daily compared with vehicle in increasing overall eyelash prominence following topical administration to the upper eyelid margins	278 randomized 137 bimatoprost 141 vehicle Bimatoprost or vehicle applied once daily to the upper eyelid margins using a single-use-per-eye applicator	16 weeks (treatment period) followed by a 4-week posttreatment follow-up period	By the end of the treatment period, a statistically significantly higher percentage of subjects in the bimatoprost group compared with the vehicle group experienced improved eyelash prominence, length, thickness/fullness, and darkness ($p<0.0001$). Statistically significant differences between the 2 treatment groups were observed as early as week 4 for length and week 8 for prominence, thickness, and darkness; these differences were statistically significant at all subsequent time points. Bimatoprost solution 0.03% was well-tolerated.
Uncontrolled Clinical Studies						

Study No.	Study Design	Main Entry Criteria	Study Objectives	# Pts Treated, Treatment	Duration of Treatment	Key Results
192024-MA001	Investigator-sponsored open-label proof-of-concept study	Healthy adult females with no history of prior use of bimatoprost and no active ocular disease.	To assess the safety and efficacy of bimatoprost 0.03% to grow longer, darker, and thicker eyelashes with application to the eyelash root margin	28 subjects All subjects applied bimatoprost once daily to the upper eyelid margins using a sponge-tipped applicator	12 weeks (treatment period) followed by a 4-week posttreatment follow-up period	At the end of the 12-week treatment period, among those 16 respondents who answered the question 81% (13/16) and 19% (3/16) of subjects reported their eyelashes to be "much improved" or "improved," respectively. Most subjects reported that they had noticed growth or darkening of their eyelashes by week 8 (month 2) of the study. Bimatoprost 0.03% was well-tolerated.
Validation Study						
192024-033	Single-center, randomized study	Healthy adult subjects who did not have permanent eye makeup or eyelash implants	To evaluate the inter-rater (ratings of the same subjects by different raters) and intra-rater (ratings of the same subjects by the same rater at 2 different time points) reliability of the Global Eyelash Assessment Scale with photnumeric guide to assess overall eyelash prominence.	68 subjects enrolled. Investigational study drug was not administered in this study	No treatment was administered during this 1-day study	There was a "substantial" degree of agreement within raters (i.e., intra-rater reliability) when assessing overall eyelash prominence at 2 different time points. The degree of agreement amongst raters (i.e., inter-rater reliability) was deemed "almost perfect." The Global Eyelash Assessment Scale with photonumeric guide can be considered to be a reliable instrument in grading overall eyelash prominence.

CONTROLLED STUDIES PERTINENT TO THE CLAIMED INDICATION

192024-MA001

Clinical study 192024-MA001 was performed during the clinical development program. This study's objective was to evaluate the efficacy of bimatoprost 0.03% in promoting the growth of natural eyelashes. This was a prospective, open-label, pilot, and proof-of-concept study of healthy female subjects who desired longer, thicker, darker natural eyelashes. In this study, bimatoprost (Lumigan [bimatoprost ophthalmic solution] 0.03%), applied once daily to the upper eyelid margins of healthy female subjects was a safe, well-tolerated, and effective treatment for the enhancement of eyelash growth, with the majority of subjects reporting "improvement" as early as 4 weeks after starting treatment, and 81% of subjects reporting "much improvement" following 12 weeks of treatment.

This study was a multicenter (16 sites), randomized, double-masked, parallel group, vehicle-controlled study to evaluate the safety and efficacy of bimatoprost 0.03% solution to increase overall eyelash prominence following dermal application to the upper eyelid margins. This study consisted of 8 visits: screening (day -14 to -1); baseline (day 1); week 1; months 1, 2, 3, and 4 (or early exit); and month 5 (post-treatment follow-up). Treatment was initiated on day 1 and concluded at month 4 (week 16), after which there was a post-treatment follow-up period lasting 1 month.

192024-032

192024-032 was a multicenter (16 sites), randomized, double-masked, parallel group, vehicle-controlled study to evaluate the safety and efficacy of bimatoprost 0.03% solution to increase overall eyelash prominence following dermal application to the upper eyelid margins. This study consisted of 8 visits: screening (day -14 to -1); baseline (day 1); week 1; months 1, 2, 3, and 4 (or early exit); and month 5 (post-treatment follow-up). Treatment was initiated on day 1 and concluded at month 4 (week 16), after which there was a post-treatment follow-up period lasting 1 month.

Primary Efficacy Measurement

The primary efficacy measurement for this study was the subject's overall (i.e., both eyes scored together, superior and frontal views) eyelash prominence at month 4 (week 16) as measured by the investigator using the GEA scale. The GEA is a 4-point scale with a photonumeric guide which uses the following scores.

GEA Score	Description of Eyelash Prominence
1	Minimal (includes everything up to minimal [includes worst possible/none]) Corresponding to photoguide grade 1 frontal and superior views
2	Moderate Corresponding to photoguide grade 2 frontal and superior views
3	Marked Corresponding to photoguide grade 3 frontal and superior views
4	Very Marked (includes very marked and above [includes best possible]) Corresponding to photoguide grade 4 frontal and superior views

Primary Efficacy Variable

The primary efficacy variable was the change in GEA score from the baseline measurement to the month 4 (week 16) measurement. A clinical success was defined as at least a 1-grade increase from baseline.

Table 6.1.4-1 [from M.O. review]
Number (%) of Subjects with At Least a 1-Grade Increase from Baseline in GEA, Treatment and Post-treatment Periods (ITT Population)

Visit [a]	Bimatoprost 0.03% (N=137)	Vehicle (N=141)	p-value [b]
Week 1	7/137 (5)	3/141 (2)	0.2124 [c]
Week 4	20/137 (15)	11/141 (8)	0.0719
Week 8	69/137 (50)	21/141 (15)	<0.0001
Week 12	95/137 (70)	28/141 (20)	<0.0001
Week 16 (Primary Endpoint)	**107/137 (78)**	**26/141 (18)**	**<0.0001**
Week 20	103/131 (79)	27/126 (21)	<0.0001

a LOCF was performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.
b P-values are based on Pearson's chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of <5.
c Fisher's exact test was performed.

A secondary analysis of the primary efficacy variable was the percentage of subjects who experienced at least a 2-grade increase from baseline on the GEA scale.

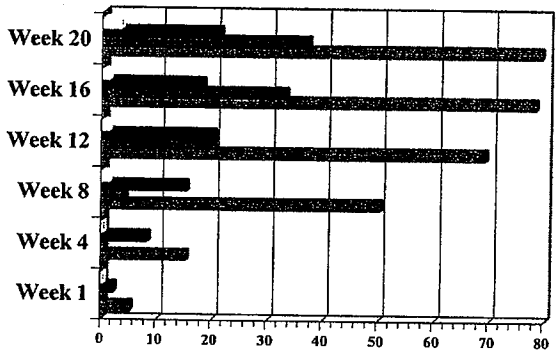
Table 6.1.4-2 [from M.O. review]
Number (%) of Subjects with At Least a 2-Grade Increase from Baseline in GEA, Treatment and Post-treatment Periods (ITT Population)

Visit [a]	Bimatoprost 0.03% (N=137)	Vehicle (N=141)	p-value [b]
Week 1	0/137 (0.0)	0/141 (0.0)	N/A
Week 4	0/137 (0.0)	0/141 (0.0)	N/A
Week 8	5/137 (3.6)	1/141 (0.7)	0.1164 [c]
Week 12	28/137 (20.4)	1/141 (0.7)	<0.0001
Week 16 (Primary Endpoint)	**45/137 (32.8)**	**2/141 (1.4)**	**<0.0001**
Week 20	49/131 (37.4)	4/126 (3.2)	<0.0001

a LOCF was performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.
b P-values are based on Pearson's chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of <5.
c Fisher's exact test was performed.

Chart 6.1.4-1 [from M.O. review]

Percentage of Subjects With at Least a 1- or 2-Grade Increase From Baseline in GEA for Treatment and Post-Treatment Periods (ITT Population)



	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20
2-Grade Vehicle	0	0	1	1	1	3
1-Grade Vehicle	2	8	15	20	18	21
2-Grade Bimatoprost	0	0	4	20	33	37
1-Grade Bimatoprost	5	15	50	69	78	79

The subjects in the bimatoprost 0.03% group experienced statistically significantly higher rates of improved eyelash prominence at Week 16, as defined by a $\geq$ 1-grade increase on the GEA scale, compared to subjects in the vehicle group ($p < 0.0001$).

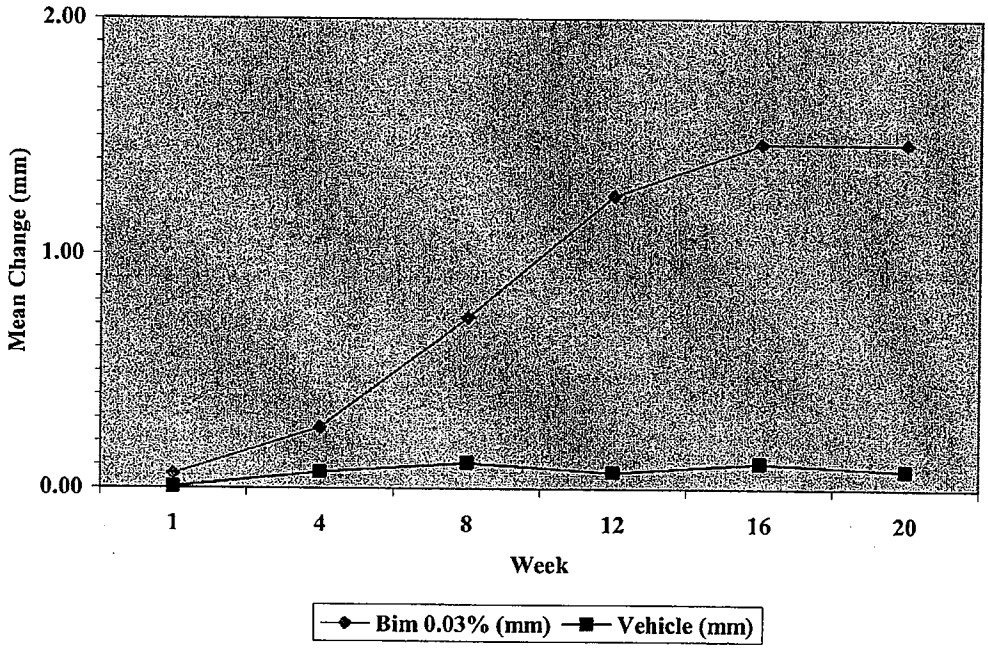
The treatment group differences in the number of subjects with a $\geq$ 1-grade increase on the GEA scale in eyelash prominence achieved statistical significance at Week 8. By week 12, a statistically significantly higher percentage of subjects in the bimatoprost group compared with the vehicle group experienced a $\geq$ 2-grade increase from baseline in GEA score.

Secondary Efficacy Measurements

Secondary efficacy measurements collected in this study included eyelash length, progressive eyelash thickness/fullness, and eyelash darkness (intensity), each determined by image analysis of digital eyelash photographs (superior view) across both eyes.

Chart 6.1.5-1 [from M.O. review]

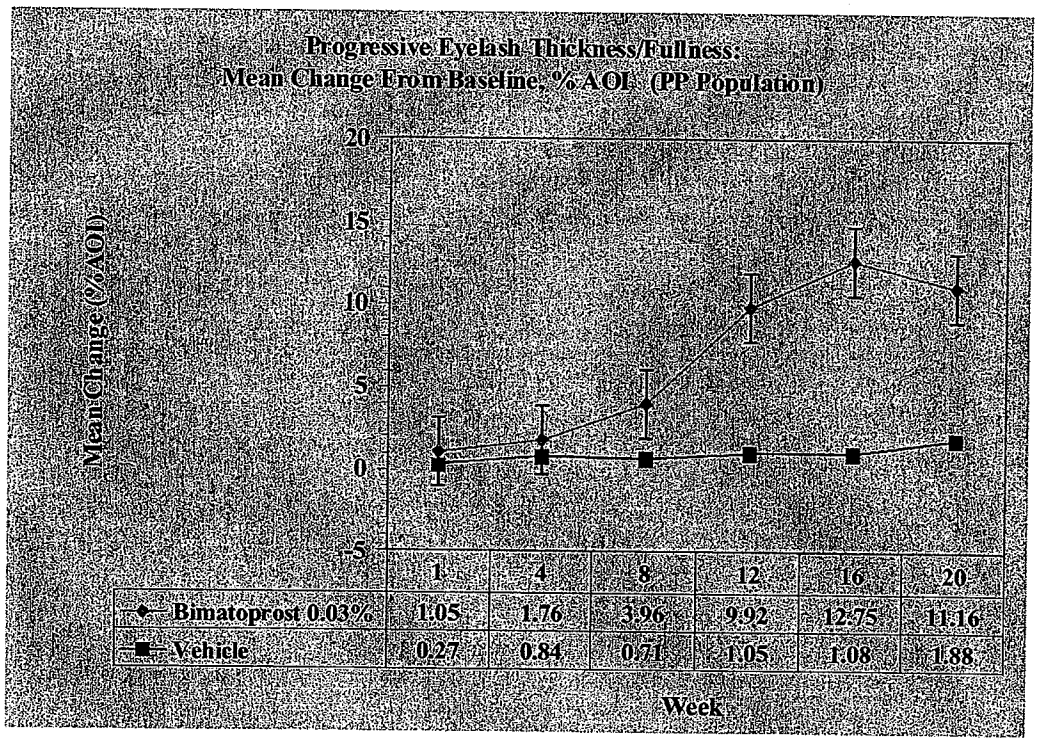
Eyelash Length: Mean Change from Baseline (PP Population)



The first secondary endpoint measured eyelash growth in terms of the overall change from baseline in eyelash length, as measured in pixels within the full area of interest (AOI) by week 16. The applicant found that 1 pixel was approximately equal to 0.0273 to 0.0274 mm. The eyelash length is also, therefore, analyzed in terms of millimeters.

At the week 16 endpoint, the bimatoprost and vehicle groups had experienced mean changes from baseline of 1.4 mm and 0.1mm. This difference was statistically significant with $p<0.0001$.

Chart 6.1.5-2 [from M.O. review]

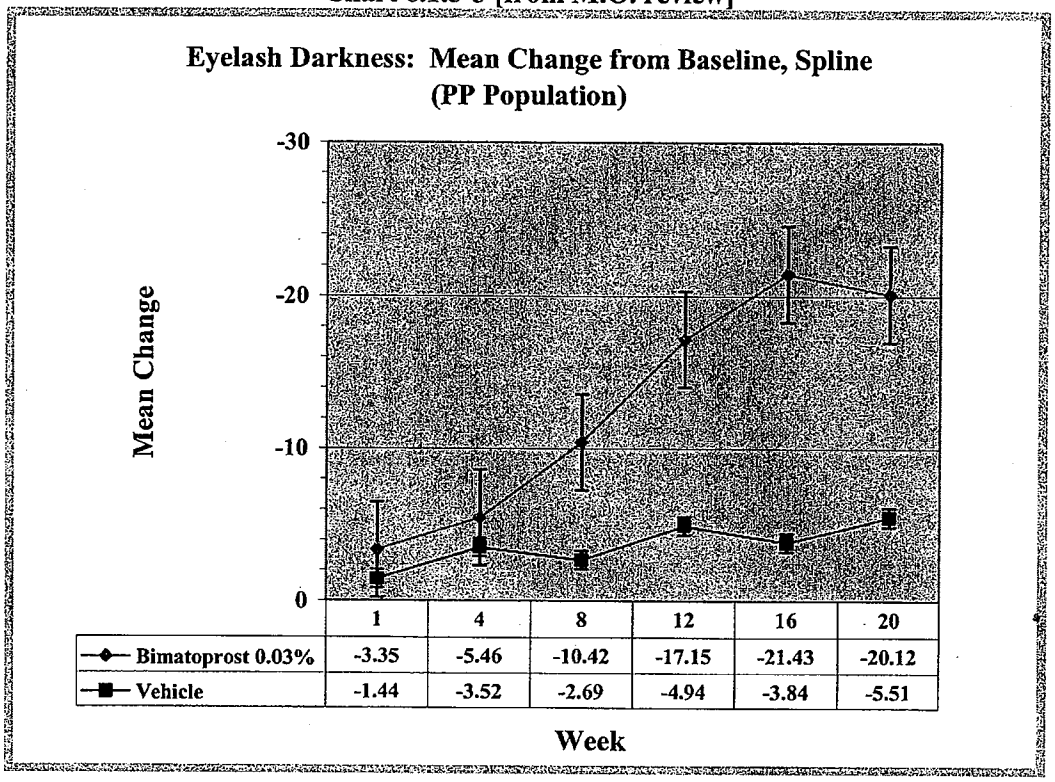


The second secondary endpoint to be analyzed was the overall change from baseline in progressive eyelash thickness/fullness by week 16, as measured by the average number of pixels within 3 preset areas of the area of interest (AOI).

At the week 16 endpoint, the bimatoprost and vehicle groups had experienced mean increases in progressive eyelash thickness/fullness of 11.16 mm and 1.88 mm, respectively. This difference was statistically significant with $p<0.0001$. These increases correspond to a percentage change from baseline of 106.00% for the bimatoprost group and 11.68% for the vehicle group.

When analyzed in terms of mm^2, the mean change from baseline to week 16 was 0.71 mm^2 for the bimatoprost group and 0.06 mm^2 vehicle group, respectively ($p<0.0001$).

Chart 6.1.5-3 [from M.O. review]



	1	4	8	12	16	20
Bimatoprost 0.03%	-3.35	-5.46	-10.42	-17.15	-21.43	-20.12
Vehicle	-1.44	-3.52	-2.69	-4.94	-3.84	-5.51

The third secondary endpoint was overall change from baseline in eyelash darkness/intensity at week 16, as measured within the spline. As the mean intensity of each pixel blob was interpreted on an 8-bit grayscale in the range of 0 (black) to 255 (white), a result with a negative value was representative of eyelash darkening.

At the week 16 endpoint, the bimatoprost group showed a statistically significantly greater degree of eyelash darkening compared to vehicle as shown by mean changes from baseline of -20.12 (bimatoprost) and -5.51 (vehicle) ($p<0.0001$). These results correspond to a percentage increase in darkness of 18% and 3% at week 16 for the bimatoprost and vehicle groups, respectively ($p<0.0001$).

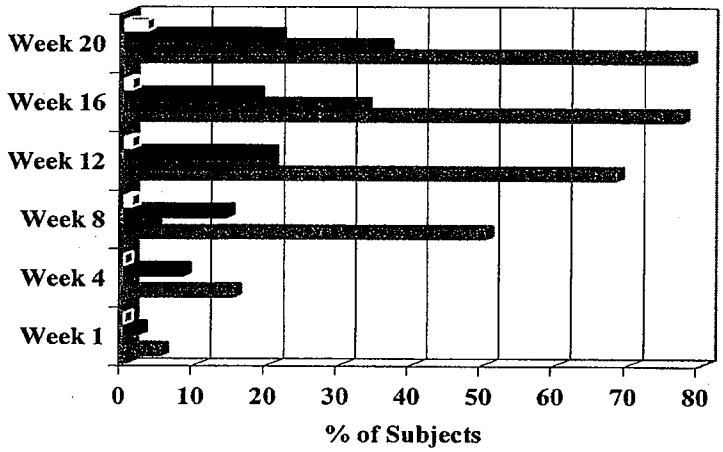
Sensitivity Analyses

The effects of increased eyelash prominence, length, thickness/fullness, and darkness elicited through the once-daily dermal application of bimatoprost 0.03% solution to the upper eyelid margins for 16 weeks was also statistically significant when a more statistically conservative Bonferroni correction was applied ($p < 0.01$ [0.05/5]).

A sensitivity analysis on the primary efficacy endpoint in which missing values were treated as treatment failures was performed.

Chart 6.1.10.1-1 [from M.O. review]

Percentage of Subjects with At Least a 1- or 2-Grade Increase From Baseline in GEA
Sensitivity Analysis - Missing Values Treated as Treatment Failures
(ITT Population)



	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20
2 Gr Vehicle	0	0	1	1	1	3
1 Gr Vehicle	2	8	14	20	18	21
2 Gr Bimatoprost	0	0	4	20	33	36
1 Gr Bimatoprost	5	15	50	68	77	78

When missing values were treated as treatment failures, there were no differences in the results of the primary analysis. The subjects in the bimatoprost 0.03% group experienced statistically significantly higher rates of improved eyelash prominence at the week 16 endpoint, as defined by a $\geq$ 1-grade increase on the GEA scale, compared to subjects in the vehicle group ($p < 0.0001$).

192024-032 Efficacy Conclusions
The subjects in the bimatoprost 0.03% group experienced statistically significantly higher rates of improved eyelash prominence at Week 16, as defined by a ≥ 1-grade increase on the GEA scale, compared to subjects in the vehicle group ($p < 0.0001$).

The effects of increased eyelash prominence, length, thickness/fullness, and darkness elicited through once-daily dermal application of bimatoprost 0.03% solution to the upper eyelid margins for 16 weeks is maintained to a statistically significant degree for at least 4 weeks after discontinuation of use.

VALIDATION STUDY

192024-033
Allergan developed the Global Eyelash Assessment (GEA) score as an objective measure for use as the primary efficacy variable in this clinical study. In order to validate the GEA, 192024-033 was conducted with the objective to evaluate the inter- and intra-rater reliability of the Global Eyelash (GEA) Scale with photonumeric guide.

One response measure was evaluated in this study: overall eyelash prominence as assessed by the GEA scale with photonumeric guide. The scale consisted of 4 categories (1 = minimal, 2 = moderate, 3 = marked, 4 = very marked). The primary efficacy analyses were the agreement between raters (inter-rater reliability) and within raters (intra-rater reliability) based on the GEA scores.

Intra-rater Results
The overall weighted Kappa statistic was 0.772. The overall unweighted Kappa statistic was 0.674. There were indications ($p=0.086$ and 0.035 for the weighted and unweighted Kappa statistic, respectively) that Kappa values were not homogenous among raters. This is due to the one rater whose intra-rater reliability was deemed to be "moderate." Excluding this rater, the p-values were 0.729 and 0.741 for the weighted and unweighted Kappa, respectively, indicating homogeneity amongst the 6 raters.

Inter-rater Results
The Kendall statistics were 0.862, 0.852, and 0.855 for evaluation 1, evaluation 2, and overall, respectively. The p-values for the Kendall statistics were < 0.001. When the data from the outlier rater was excluded from the analysis, the Kendall statistics were 0.877, 0.850, and 0.869 for evaluation 1, evaluation 2, and overall, respectively.

One rater appeared to be an outlier with lower Kappa values than the other raters. Sensitivity analyses in which data from this rater was excluded demonstrated that the overall conclusions were the same for both the intra- and inter-rater reliability.

192024-033 Validation Conclusions
Using the GEA scale with photonumeric guide to assess overall eyelash prominence, there was substantial degree of agreement within raters (i.e., intra-rater reliability, the degree of agreement amongst the raters in scoring eyelash prominence using the GEA scale was deemed "almost perfect" by the applicant. Therefore, the GEA scale with photonumeric guide can be considered to be a reliable instrument in grading overall eyelash prominence.

See the Medical Officer's original review, Section 6.1.

8. Safety

EXPOSURE

In Allergan-sponsored clinical studies of any phase, 5848 patients and healthy volunteers have been exposed to bimatoprost, resulting in approximately 3461 patient-years of exposure (10 patient-years in healthy volunteers and 3451 patient-years in glaucomatous patients). Since the initial product launch of Lumigan in 2001, the exposure to bimatoprost has been estimated to be approximately 9 million patient-years worldwide with 5 million patient-years in the United States alone.

Table 7.1.1-1 Exposure to Bimatoprost in Key Studies of IOP Reduction and Eyelash Growth [from M.O. review]

Study	Number of Patients/Subjects (Bimatoprost Group)	Duration of treatment	Comparator(s)
Phase 3 Studies of Lumigan (bimatoprost ophthalmic solution) 0.03%			
192024-008	240 (bimatoprost QD) 240 (bimatoprost BID)	12 months	Timolol
192024-009	234 (bimatoprost QD) 243 (bimatoprost BID)	12 months	Timolol
Phase 3 Studies of bimatoprost 0.03%/timolol 0.5% ophthalmic solution			
192024-018T [a]	261 (bimatoprost plus timolol) 129 (bimatoprost alone)	12 months	Timolol alone
192024-021T [a]	272 (bimatoprost plus timolol) 136 (bimatoprost alone)	12 months	Timolol alone
Studies of Lumigan in the Published Literature			
Noecker, et al (2003)	133	6 months	Latanoprost plus timolol
Manni et al (2004)	28	6 months	Latanoprost
Phase 4 Marketing Study of Lumigan			
MA-LUMO1 [b]	131	3 months	Travoprost
Studies of Bimatoprost for Eyelash Growth			
192024-MA001	28	3 months	None
192024-032	137	4 months	Vehicle

a Brandt, et al., 2008; data on file at Allergan
b Data on file at Allergan

The total dose of bimatoprost delivered with topical application to the upper eyelid margins for the enhancement of eyelash growth is much lower than the dose of bimatoprost for the treatment of elevated IOP. In the use of bimatoprost for the treatment of elevated IOP, a drop of bimatoprost ophthalmic solution is instilled directly into the eye leading not only to eye exposure but also eyelid skin and eyelash exposure via a bathing of the eyelid margin and eyelashes in the bimatoprost solution. The applicator was designed to deliver a fraction of a 1-drop bimatoprost dose directly to the target treatment area. With a single application, approximately 5% of the dose for the treatment of elevated IOP is delivered to the upper eyelid margin (Allergan Technical Memo PD-M-08-111).

POSTMARKETING EXPERIENCE

There is no post-marketing experience with bimatoprost ophthalmic solution for this indication or route of administration.

Post-marketing experience for the drug product marketed as Lumigan (bimatoprost ophthalmic solution) 0.03% is presented below. The applicant reports approximately 8.8 million patient years of Lumigan exposure. Global postmarketing experience includes 2410 case reports and 5033 adverse event reports:

Adverse Event	Number of reports
Conjunctival and ocular hyperemia	596
Eye Irritation	358
Skin hyperpigmentation	285
Eye pain	211
Growth of eyelashes	189
Eye pruritus	171
Headache	130
Vision blurred	119
Eyelid pruritus	75
Eyelid erythema	75

The most frequent adverse reactions reported with Lumigan are similar to those reported in the clinical studies submitted in this NDA.

LATISSE SIGNIFICANT ADVERSE EVENTS

Table 7.3.4-1 Adverse Events Reported by Greater than 1% of Subjects Treatment and Post-treatment Periods Combined (Safety Population) in 192024-032 [from M.O. review]

System Organ Class / Preferred Term	Bimatoprost 0.03% (N=137)	Vehicle (N=141)
OVERALL	55 (40.1)	41 (29.1)
EYE DISORDERS		
Eye Pruritus	5 (3.6)	1 (0.7)
Conjunctival hyperemia	5 (3.6)	0 (0.0)
Pinguecula	3 (2.2)	3 (2.1)
Eye irritation	3 (2.2)	2 (1.4)
Dry Eye	3 (2.2)	1 (0.7)
Erythema of eyelid	3 (2.2)	1 (0.7)
Eyelids pruritus	1 (0.7)	2 (1.4)
Conjunctival hemorrhage	0 (0.0)	2 (1.4)
IMMUNE SYSTEM DISORDERS		
Seasonal allergy	2 (1.5)	0 (0.0)
INFECTIONS AND INFESTATIONS		
Upper respiratory tract infection	2 (1.5)	5 (3.5)
Sinusitis	2 (1.5)	2 (1.4)
Influenza	2 (1.5)	0 (0.0)
Urinary tract infection	1 (0.7)	2 (1.4)
BENIGN AND MALIGNANT NEOPLASMS		
Blepharal papilloma	2 (1.5)	0 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Skin hyperpigmentation	4 (2.9)	1 (0.7)
Dermatitis contact	2 (1.5)	0 (0.0)

Note: All adverse events are represented, regardless of relationship to treatment.
Note: Within each system organ class, preferred terms are sorted by descending order of frequencies of treatment groups from left to right. Within each preferred term, a subject is counted at most once.

Conjunctival hyperemia was the only preferred term that was reported by a statistically significantly higher percentage of subjects in the bimatoprost group compared with the vehicle group.

Skin hyperpigmentation of the ocular adnexa was reported by 2.9% (4/137) and 0.7% (1/141) of subjects in the bimatoprost and vehicle groups, respectively. This difference was not statistically significant ($p = 0.209$). Each incidence was reported as mild in severity. One subject reported resolution of hyperpigmentation during the post-treatment period and 1 subject reported resolution in post-exit communication with the investigational site (data on file).

LATISSE COMMON ADVERSE EVENTS

Table 7.4.1-1 Adverse Events Reported by Greater than 1% of Subjects Treatment and Post-treatment Periods Combined (Safety Population) in 192024-032 [from M.O. review]

System Organ Class / Preferred Term	Bimatoprost 0.03% (N=137)	Vehicle (N=141)
OVERALL	55 (40.1)	41 (29.1)
EYE DISORDERS		
Eye Pruritus	5 (3.6)	1 (0.7)
Conjunctival hyperemia	5 (3.6)	0 (0.0)
Pinguecula	3 (2.2)	3 (2.1)
Eye irritation	3 (2.2)	2 (1.4)
Dry Eye	3 (2.2)	1 (0.7)
Erythema of eyelid	3 (2.2)	1 (0.7)
Eyelids pruritus	1 (0.7)	2 (1.4)
Conjunctival hemorrhage	0 (0.0)	2 (1.4)
IMMUNE SYSTEM DISORDERS		
Seasonal allergy	2 (1.5)	0 (0.0)
INFECTIONS AND INFESTATIONS		
Upper respiratory tract infection	2 (1.5)	5 (3.5)
Sinusitis	2 (1.5)	2 (1.4)
Influenza	2 (1.5)	0 (0.0)
Urinary tract infection	1 (0.7)	2 (1.4)
BENIGN AND MALIGNANT NEOPLASMS		
Blepharal papilloma	2 (1.5)	0 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Skin hyperpigmentation	4 (2.9)	1 (0.7)
Dermatitis contact	2 (1.5)	0 (0.0)

Note: All adverse events are represented, regardless of relationship to treatment.
Note: Within each system organ class, preferred terms are sorted by descending order of frequencies of treatment groups from left to right. Within each preferred term, a subject is counted at most once.

Conjunctival hyperemia was the only preferred term that was reported by a statistically significantly higher percentage of subjects in the bimatoprost group compared with the vehicle group.

LATISSE DEATHS AND NONFATAL SERIOUS ADVERSE EVENTS

No deaths occurred during the course of Study 192024-032.

A total of three subjects (1 bimatoprost, 2 vehicle) reported serious adverse events during the course of the study.

- Subject 10010-1035 (bimatoprost) was diagnosed with squamous cell carcinoma of the skin (on back)
- Subject 11302-1102 (vehicle) was diagnosed with lymphoma during the treatment period
- Subject 10011-1277 (vehicle) was diagnosed with recurrent metastatic breast cancer during the post-treatment period.

LATISSE DROPOUTS AND/OR DISCONTINUATIONS

Four subjects in each treatment group discontinued the study (192024-032) due to an adverse event. The adverse events that led to study discontinuation by the 4 subjects in the vehicle group were lymphoma, eyelid erythema, conjunctival hemorrhage (all mild or moderate severity), and low IOP (severe). The adverse events that led to study discontinuation by the four subjects in the bimatoprost group were eczema, dry eye, eye inflammation, and contact dermatitis, all of which were of mild or moderate severity.

Subject 10005-1159 discontinued study medication on day 16 on the advice of her private ophthalmologist due to suspected post-cataract cystoid macular edema (CME).

Subject 10012-1125 reported the adverse event of xerostomia at day 34 of the study. The subject discontinued use of the study treatment but remained in the study for follow-up through month 5/ study exit.

See the Medical Officer's original review, Section 7.1.

DEMOGRAPHICS OF TARGET POPULATIONS

Table 6.1.2-1 Demographics and Baseline Characteristics (ITT Population) in 192024-032 [from M.O. review]

	Bimatoprost 0.03% N=137	Vehicle N=141	Total N=278	p-value [a]
Age (years)				***0.904***
Mean	49.9	49.7	49.8	
SD	11.67	11.27	11.45	
Median	50.0	50.0	50.0	
Min, Max	22, 77	22, 78	22, 78	
< 45, N (%)	44 (32.1)	43 (30.5)	87 (31.3)	
45 to 65, N (%)	82 (59.9)	88 (62.4)	170 (61.2)	
> 65, N (%)	11 (8.0)	10 (7.1)	21 (7.6)	
Sex, N (%)				***0.499***
Male	3 (2.2)	5 (3.5)	8 (2.9)	
Female	134 (97.8)	136 (96.5)	270 (97.1)	
Race, N (%)				***0.566 [b]***
Caucasian	109 (79.6)	116 (82.3)	225 (80.9)	
Black	0 (0.0)	1 (0.7)	1 (0.4)	
Asian	18 (13.1)	16 (11.3)	34 (12.2)	
Hispanic	6 (4.4)	5 (3.5)	11 (4.0)	
Other	4 (2.9)	3 (2.1)	7 (2.5)	
Iris Color, N (%)				***0.677***
Dark [c]	53 (38.7)	58 (41.1)	111 (39.9)	
Light [c]	84 (61.3)	83 (58.9)	167 (60.1)	
GEA Score, N (%)				***0.675***
Minimal (1)	29 (21.2)	27 (19.1)	56 (20.1)	
Moderate (2)	108 (78.8)	114 (80.9)	222 (79.9)	
Marked (3)	0 (0.0)	0 (0.0)	0 (0.0)	
Very Marked (4)	0 (0.0)	0 (0.0)	0 (0.0)	

a For continuous variables, a 1-way ANOVA model was used. For categorical variables, Pearson's chi-square test was used or Fisher's exact test (if ≥ 25% of the expected cell count is < 5).
b P-value for race is for Caucasian vs. non-Caucasian
c Light irides included the colors blue, blue-gray, blue/gray-brown, green, green-brown, hazel, and other, and dark irides included the colors brown, dark brown, and black.

There were significantly more women than men enrolled in 192024-032. Men were not excluded or limited from the study participation. The study population demographics are likely reflective of the population that will use the product for this indication.

Sixteen African American subjects were screened for enrollment. One subject was randomized to the study in the vehicle group. The applicant suggested that many of these patients failed screening due to an inability to obtain and/or analyze acceptable digital image photographs.

An adequate safety database in men and African Americans has been established for bimatoprost ophthalmic solution 0.03% with Lumigan (bimatoprost ophthalmic solution)

0.03% [NDA 21-275]. However, Non-Caucasians were under-represented in the 192024-032.study (i.e., 79.6% of the treated subjects were Caucasian, 13% Asian, 4.4% Hispanic and 0.0% black). In a correspondence dated December 16, 2008, Allergan, Inc. proposes a postmarketing commitment to address this issue. See this review, Section 13.

INTRAOCULAR PRESSURE CHANGES WITH LATISSE

Since Lumigan is approved for the treatment of elevated IOP in patients diagnosed with glaucoma or ocular hypertension, IOP measurements were performed as a part of the overall safety assessment in 192024-032. Whereas statistically significant differences in mean IOP reduction were observed between the bimatoprost and vehicle treatment groups at weeks 1 through 16, the magnitude of this reduction was small and was not clinically meaningful, with the difference between the groups ranging from 0.5 to 0.9 mm Hg.

Intraocular Pressure (mm Hg): Change From Baseline by Visit (Study 192024-032) [from DODAC Briefing Package]

	Per Subject			Per Eye		
Visit	Bimatoprost 0.03% (N = 137)	Vehicle (N = 141)	P-value[a]	Bimatoprost 0.03% (N = 137)	Vehicle (N = 141)	P-value[a]
Screening, N	137	141	0.885	274	282	0.840
Mean	14.505	14.457		14.51	14.46	
SD	2.7576	2.7710		2.790	2.807	
Median	14.250	14.500		14.00	14.50	
Min, Max	8.25, 20.00	8.25, 19.75		8.0, 20.0	8.0, 20	
Week 1, N	130	128	0.044	260	256	0.007
Mean	-1.040	-0.543		-1.04	-0.54	
SD	1.8669	2.0730		2.001	2.159	
Median	-1.000	-0.500		-1.00	-0.50	
Min, Max	-7.25, 4.50	-7.25, 5.00		-8.5, 5.0	-7.5, 6.0	
Within-group p-value[b]	< 0.001	0.004		< 0.001	< 0.001	
Week 4, N	130	128	0.004	260	256	< 0.001
Mean	-1.285	-0.439		-1.28	-0.44	
SD	2.4053	2.2642		2.508	2.353	
Median	-1.250	-0.250		-1.25	-0.50	
Min, Max	-7.25, 6.00	-7.50, 6.00		-8.5, 6.5	-7.5, 6.0	
Within-group p-value[b]	< 0.001	0.030		< 0.001	0.003	
Week 8, N	126	122	0.006	252	244	< 0.001
Mean	-1.377	-0.605		-1.38	-0.60	
SD	2.0559	2.3682		2.144	2.445	
Median	-1.250	-0.500		-1.00	-0.50	
Min, Max	-6.50, 2.75	-8.75, 5.50		-7.0, 3.5	-11.0, 6.5	
Within-group p-value[b]	< 0.001	0.006		< 0.001	< 0.001	
Week 12, N	126	119	0.002	252	238	< 0.001
Mean	-1.540	-0.643		-1.54	-0.64	
SD	2.1994	2.2442		2.262	2.322	
Median	-1.500	-0.500		-1.25	-0.50	
Min, Max	-6.25, 3.25	-9.25, 5.50		-7.0, 3.5	-9.5, 7.0	
Within-group p-value[b]	< 0.001	0.002		< 0.001	< 0.001	
Week 16, N	126	125	0.056	252	250	0.009
Mean	-1.250	-0.724		-1.25	-0.72	
SD	2.1024	2.2365		2.195	2.317	
Median	-1.500	-0.500		-1.50	-0.50	
Min, Max	-6.75, 5.25	-9.25, 5.00		-7.5, 6.0	-10.0, 5.0	
Within-group p-value[b]	< 0.001	< 0.001		< 0.001	< 0.001	
Week 20, N	131	126	0.255	262	252	0.118
Mean	-0.668	-0.349		-0.67	-0.35	
SD	2.1529	2.3292		2.220	2.395	
Median	-0.500	-0.500		-0.50	-0.50	
Min, Max	-7.50, 5.00	-6.75, 6.00		-7.5, 5.0	-7.0, 6.0	
Within-group p-value[b]	< 0.001	0.095		< 0.001	0.021	

Source: CSR 192024-032
a A 1-way ANOVA was performed to evaluate the difference among/between treatment groups.
b Paired t-tests were used to test for mean shifts from baseline within treatment groups.

9. Advisory Committee Meeting

The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration met on December 5, 2008 at the Hilton Washington/Rockville 1750 Rockville Pike, Rockville, Maryland. Michael X. Repka, M.D., chaired the meeting. There were approximately 60 in attendance.

Attendance:
Dermatologic and Ophthalmic Drugs Advisory Committee Members present (voting):
Mary A. Majumder, J.D., Ph.D.
Temporary Voting Members:
Natalie Afshari, M.D., FACS ; Warren B. Bilker, Ph.D.; William G. Gates, M.D.; Philip Lavin, Ph.D.; Marijean M. Miller, M.D.; Michael X. Repka, M.D.; M. Roy Wilson, M.D., M.S.; Paula Cofer (Patient Representative)
Industry Representative (non-voting):
Ellen Strahlman, M.D., M.H.Sc
FDA Participants (non-voting):
Edward M. Cox, M.D., MPH; Wiley Chambers, M.D.; Martin Nevitt, M.D., M.P.H.; Rhea Lloyd, M.D.
Open Public Hearing Speaker:
Brandel France deBravo (National Research Center for Women and Families)

The following questions were posed to the Committee.

1. Do you think the benefits outweigh the risks for Latisse (bimatoprost ophthalmic solution) 0.03% for the treatment of hypotrichosis of the eyelashes?

After discussion, the committee agreed that safety and efficacy was demonstrated by the data presented. The committee vote on Question 1 was: Yes: 9, No: 0, Abstain: 0.

2. If not, what additional studies should be performed?

No discussion or comments

3. If yes, should any additional Phase 4 studies be performed?

After discussion, the committee was divided on this issue. The Committee vote on Question 3 was: Yes: 5 No: 3 Abstain: 1.

Committee members who were not in favor of performing Phase 4 studies viewed that there was sufficient data available with Lumigan not to require Phase 4 studies with bimatoprost 0.03% for eyelash growth. Suggestions were made to perform risk management programs or establish a tracking program in pediatric age groups and people of color in lieu of performing Phase 4 studies.

Committee members who were in favor of performing Phase 4 studies made the following recommendations:

- Studies in children and adolescents
- Studies including patients in disease states (i.e., autoimmune disease or on chemotherapy for cancer)
- Studies including patients of various ethnicities
- Lower lash studies

4. Do you have any suggestions concerning the labeling of the product?

After discussion, individual committee members recommended the labeling include the following:

- Continued use is necessary
- Wording of ocular pigmentation risk in layman's terms
- Information on side effects and drug interactions
- A description of conditions that should require prior evaluation by an ophthalmologist
- Language to include Lumigan has been tested in children although this product to date has not been tested.

10. Pediatrics

Safety and efficacy of Latisse in pediatric patients has not been studied, although as reported at the Advisory Committee meeting, there is extensive use of Lumigan in pediatric patients. Based on the mechanism of action of bimatoprost in eyelash growth and the fact that external ocular development is generally complete by age 3-6, the expected effect on lashes would be similar to that in adults. Pediatric studies are being deferred under PREA because the application is otherwise ready for approval in adults. The pediatric plan calls for the study listed in Allergan's December 16, 2008, commitment to conduct a post-marketing study of Latisse in pediatric subjects as described below:

A controlled trial of at least ——— with Latisse (bimatoprost ophthalmic solution) 0.03% in ——— pediatric subjects less than 18 years of age with hypotrichosis ——— b(4)

Protocol Submission: November 30, 2009
Study Start: June 30, 2010
Final Report Submission: December 31, 2012.

11. Other Relevant Regulatory Issues

Per the Statistical Review and Evaluation completed by the Office of Biostatistics on November 7, 2008, there were no major statistical issues identified for this submission. For the submitted pivotal study C-192024-032, bimatoprost ophthalmic solution 0.03% was statistically superior to vehicle in eyelash prominence using the global eyelash assessment (GEA) scale; bimatoprost ophthalmic solution 0.03% was also statistically superior to vehicle in the three secondary efficacy variables: change from baseline in eyelash length, in progressive eyelash thickness/fullness, and in eyelash darkness/intensity.

A Division of Scientific Investigations (DSI) audit was requested. The sites requested for inspection are the domestic centers that were among the highest enrollers in the study 192024-032. Three clinical investigator inspections were completed for this NDA. Based on the results of these inspections, the study appears to have been conducted adequately and the data in support of the NDA appear reliable. No regulatory violations were noted for Dr. Werschler or Dr. Smith. Although regulatory violations were noted and Form FDA 483 was issued to Dr. Yoelin, the nature of the violations makes it unlikely that they significantly affect overall reliability of safety and efficacy data from this site. These observations were for: Failing to utilize updated source documents specifically provided by the Sponsor that had been revised to include sections for recordation of vitreous exams. Failing to report intraocular pressure assessments that were not completed within the specified +/- 2 hour visit time frame (specified in newsletters to the sites) to the sponsor for 3 subjects. Failing to report all out-of-window visits to the sponsor as protocol deviations. Dr. Yoelin has provided a written response to the observations, dated November 7, 2008, and the data derived from Dr. Yoelin's site after review are considered acceptable.

Allergan, Inc. 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 "Latisse." The results of the Proprietary Name Risk Assessment found that the proposed name, Latisse, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Latisse, for this product.

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 26 June 2008.

12. Labeling

NDA 22-369 is recommended for approval for the treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness with the labeling submitted by Allergan, Inc. on 18 December 2008 and found in this Cross-Discipline Team Leader Review (see Appendix 1).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 22-369 is recommended for approval for the treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness.

The labeling submitted by Allergan, Inc. on 18 December 2008 and found in this Cross-Discipline Team Leader Review (see Appendix 1) is acceptable for approval.

The postmarket commitments are listed below are acceptable. The postmarket commitment to study pediatric patients is considered a postmarket requirement.

In a December 16, 2008, submission, Allergan, Inc. commits:

- b(4)

In a December 16, 2008, submission, Allergan, Inc. commits to:

- A four month randomized, controlled comparative study of Latisse (bimatoprost ophthalmic solution) 0.03% versus vehicle in at least 50 African American subjects b(4)

  Protocol Submission: September 30, 2009
  Study Start: May 31, 2010
  Final Report Submission: December 31, 2011

- A controlled trial of at ı with Latisse (bimatoprost ophthalmic solution) 0.03% in ediatric subjects less than 18 years of age with hypotrichosis b(4)

Protocol Submission: November 30, 2009
Study Start: June 30, 2010

Final Report Submission: December 31, 2012.

RISK BENEFIT ASSESSMENT:
Findings from Study 192024-032 together with studies submitted in NDA 21-275 provide adequate evidence of safety and efficacy for bimatoprost ophthalmic solution in the QD dosing regimen for the treatment of hypotrichosis of the eyelashes. Overall findings from these studies include analysis of 'the percentage of subjects with at least a 1-grade increase from baseline on the Global Eyelash Assessment scale'. This endpoint was found to be clinically relevant and statistically significant in Study 192024-032. The applicant also submitted a study to validate the GEA scale (Study 192024-033).

Study 192024-032 also showed significance in three key secondary endpoints which measured the overall change from baseline by week 16 after QD dosing in three different measures: eyelash length, progressive eyelash thickness/fullness, and eyelash darkness/intensity. These endpoints were considered clinically relevant and statistically significant. Based on the FDA recommended primary and secondary analysis results and other considerations, there was adequate overall evidence presented for the QD regimen as an effective treatment in subjects with hypotrichosis of the eyelashes.

The application supports the safety of Latisse (bimatoprost ophthalmic solution) 0.03% for the treatment of hypotrichosis of the eyelashes. The safety of bimatoprost ophthalmic solution 0.03% for the treatment of elevated intraocular pressure was demonstrated in NDA 21-275 Lumigan (bimatoprost ophthalmic solution) 0.03%. Overall, Latisse (bimatoprost ophthalmic solution) 0.03% was safe and well tolerated in Study 192024-032. Reactions most frequently associated with bimatoprost ophthalmic solution include eye pruritus, conjunctival hyperemia, skin hyperpigmentation, eye irritation, dry eye and erythema of the eyelid.

The total dose of bimatoprost delivered with topical application to the upper eyelid margins for the enhancement of eyelash growth is much lower than the dose of bimatoprost for the treatment of elevated IOP.

The potential for bimatoprost-related effects on intraocular pressure, iris and eyelid pigmentation, and hair growth outside the treatment area can be adequately described in the prescribing information. See Appendix 1 this review.

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

Appendix 1

The following labeling was submitted by Allergan on December 18, 2008.

9 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Cross Discipline TL Review- 2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

William Boyd
12/19/2008 06:23:37 PM
MEDICAL OFFICER

Wiley Chambers
12/23/2008 09:00:27 PM
MEDICAL OFFICER