CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22369
Drug Name:	Bimatoprost 0.03% ophthalmic solution
Indication(s):	Improve the prominence of natural eyelashes
Applicant:	Allergan
Submitted Date:	06/27/2007
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Review Priority:	Priority
Biometrics Division:	DBIV
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Keywords: superiority

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this NDA submission, the sponsor seeks approval of bimatoprost ophthalmic solution 0.03% once daily for eyelash growth. For this submission, the sponsor submitted one pivotal study: study C-192024-032. This study is a multicenter, double-masked, randomized, vehicle-controlled study to evaluate the safety and efficacy of bimatoprost ophthalmic solution 0.03% once daily compared with vehicle in increasing overall eyelash prominence following dermal administration to the upper eyelid margin.

Based on the review of the data, bimatoprost ophthalmic solution 0.03% is statistically superior to vehicle in eyelash prominence using the global eyelash assessment (GEA) scale.

1.2 Brief Overview of Clinical Studies

This submission contains one efficacy/safety study.

Study C-192024-032 is a multicenter, double-masked, randomized, vehicle-controlled study to evaluate the safety and efficacy of bimatoprost ophthalmic solution 0.03% 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 (posttreatment follow-up). Treatment was initiated on day 1 and concluded at month 4 (week 16), after which there was a posttreatment follow-up period lasting 1 month.

The primary clinical hypothesis tested in this study was that bimatoprost ophthalmic solution 0.03% solution is more effective than vehicle in increasing overall eyelash prominence as measured by the difference between the 2 groups in the proportion of subjects at month 4 (week 16) with at least a 1-grade increase from baseline in the 4-point global eyelash assessment (GEA) score.

2. INTRODUCTION

2.1 Indication

Bimatoprost is the active ingredient in the marketed product LUMIGAN® (bimatoprost ophthalmic solution 0.03%, NDA 21275). LUMIGAN® has been marketed in the US since March 2001. The indication for LUMIGAN® is for the reduction of elevated intraocular pressure in patients with open-angel glaucoma or ocular hypertension (IOP).

In 2 active-controlled phase 3 studies for IOP indication, 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 (Studies 192024-008 and 192024-009, respectively) (Table 1). The proportion of subjects reporting eyelash growth continued to increase after 6 and 12 months of treatment.

Table 1: Number (%) of Patients Reporting Eyelash Growth as an Adverse Event During Clinical Trials of Lumigan® (Bimatoprost 0.03% Ophthalmic Solution) for IOP Indication

	Bimatoprost 0.03% QD	Bimatoprost 0.03% BID	Timolol[1] 0.5% QD
Study 192024-008	N=240	N=240	N=122
3 month eyelash growth	43 (17.9%)	74 (30.8%)	2 (1.6%)
6 month eyelash growth	75 (31.3%)	104 (43.3%)	4 (3.3%)
12 month eyelash growth	87 (36.3%)	120 (50.0%)	6 (4.9%)
Study 192024-009	N=234	N=243	N=119
3 month eyelash growth	60 (25.6%)	82 (33.7%)	2 (1.7%)
6 month eyelash growth	94 (40.2%)	130 (53.5%)	5 (4.2%)
12 month eyelash growth	115 (49.1%)	139 (57.2%)	6 (5.0%)

[1] Timolol was the active comparator in clinical trials of Lumigan®
From Sponsor's Table 7-1 on Page 26 of Clinical Study Report

Because of the seemingly large percentage of patients reporting eyelash growth as adverse events in the registration trials for Lumigan® IOP indication, the Sponsor conducted one pivotal study C-192024-032 in seek of approval for the indication of eyelash growth for bimatoprost 0.03% ophthalmic solution.

2.2 Data Sources

The Sponsor's study reports for study C-192024-032 available on the EDR at \\CDSESUB1\EVSPROD\N22369\0000.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This submission contains one efficacy/safety study C-192024-032. The primary objective of this study was to evaluate the safety and efficacy of bimatoprost 0.03% solution once daily compared with vehicle in increasing overall eyelash prominence following dermal administration to the upper eyelid margins. In addition to the assessment of overall eyelash prominence, this study assessed elements that may contribute to the finding of enhanced prominence—increases in eyelash length, thickness/fullness, and darkness—by means of digital image analysis. This study also assessed changes in subject satisfaction in overall eyelash appearance following treatment with bimatoprost versus vehicle.

3.1.1 Study Design and Endpoints

Study C-192024-032 was a multi-center, randomized, double-masked, parallel-group, vehicle-controlled clinical trial. 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 (posttreatment 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.

The primary efficacy measure is the overall eyelash prominence which is measured using the following 4-point Global Eyelash Assessment (GEA) scale with the aid of the photonumeric guide:
1: Minimal (includes everything up to minimal; i.e. includes worst possible/none); Corresponding to photoguide Grade 1 frontal views and superior views.
2: Moderate; Corresponding to photoguide Grade 2 frontal views and superior views.
3: Marked; Corresponding to photoguide Grade 3 frontal views and superior views.
4: Very Marked (includes very marked and above; i.e. includes best possible); Corresponding to photoguide Grade 4 frontal views and superior views.

The key inclusion criteria were: male or female, at least 18 years of age; screening and baseline GEA score of a 1 or 2; best-corrected visual acuity score equivalent to a Snellen acuity of 20/100 or better in each eye, using a logarithmic acuity chart for testing at 100 feet; IOP $\leq$ 20 mm Hg in each eye; standardized eyelash photographs at the screening visit of acceptable quality for image analysis as verified by [redacted] b(4)

The key exclusion criteria were: subjects had any uncontrolled systemic disease; without visible lashes; with asymmetrical eyelashes; with any known disease or abnormality of the lids, lashes, ocular surface, or lacrimal duct system; with known or suspected trichotillomania disorder; any ocular pathology in either eye that may have interfered with the ability to obtain accurate IOP readings; contraindications to pupil dilation; active ocular disease (eg, glaucoma, uveitis, ocular infections, chronic blepharitis, or severe dry eye); myopia, strabismus, and cataracts were allowed provided other study criteria were met; any ocular surgery; any permanent eyeliner within 5 years; eyelash implant of any kind; any eyelash tint or dye application within 2 months of study entry; any eyelash extension application within 3 months of study entry; any use of eyelash growth products within 6 months of study entry; treatments that may affect hair growth within 6 months prior to study entry; any subjects requiring IOP-lowering eye drops or any other eye drop medications, lubricants or artificial tears at baseline, or anticipated use of these treatments during the study; known allergy or sensitivity to the study medication, its components, or the eye make-up remover provided; subjects with macular edema or those who were aphakic, pseudophakic with a torn posterior lens capsule, or subjects who had known risk factors for macular edema; females who were pregnant, nursing, or planning a pregnancy during the study or who were of childbearing potential and not using a reliable method of contraception.

There were three analysis populations: intent-to-treat (ITT) population, per-protocol (PP) population, and safety population. ITT population consists of all randomized subjects, regardless of whether or not treatment is received or administered. The ITT set is the primary efficacy

analysis set. PP population consists of subjects who have no major deviations from the protocol during their participation in the trial. The PP set is considered as secondary efficacy analysis set. Safety population consists of all randomized subjects who received study medication.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

3.1.2.1 Patient Disposition

The summary of subject disposition is shown in Table 2.

A total of 409 subjects were screened for the study, and 278 (68.0%) of these subjects were enrolled. Of the 278 enrolled subjects, 137 subjects were randomized to treatment with bimatoprost 0.03% and 141 to vehicle. A total of 257 subjects (92.4%) completed the study, including 131 subjects (95.6%) in the bimatoprost 0.03% group and 126 subjects (89.4%) in the vehicle group. The most common reason for discontinuation was adverse event. Masking was not broken for any subject at the time of discontinuation.

Table 2: Subject Disposition for the Treatment and Posttreatment Periods (ITT Population)

	Bimatoprost 0.03%	Vehicle	Total
Treatment Period			
Enrolled[1]	137	141	278
Completed	131 (95.6%)	126 (89.4%)	257 (92.4%)
Discontinued	6 (4.4%)	15 (10.6%)	21 (7.6%)
Adverse Event	4 (2.9%)	4 (2.8%)	8 (2.9%)
Lack of Efficacy	0	0	0
Pregnancy	0	0	0
Lost to Follow-up	0	3 (2.1%)	3 (1.1%)
Personal Reason	1 (0.7%)	4 (2.8%)	5 (1.8%)
Protocol Violation	0	2 (1.4%)	2 (0.7%)
Other	1 (0.7%)	2 (1.4%)	3 (1.1%)
Posttreatment Period[2]			
Enrolled	131	126	257
Completed	131 (100%)	126 (100%)	257 (100%)
Discontinued	0	0	0

[1] Includes all randomized subjects

[2] Includes all randomized subjects who entered the posttreatment period

3.1.2.2 Baseline Characteristics

The summary of patients' baseline characteristics is shown in Table 3. There was no marked difference in the baseline demographic characteristics among the two treatment groups.

Table 3: Demographics and Baseline Characteristics (ITT Population)

		Azithromycin (N=137)		Vehicle (N=141)		Total (N=278)	
		n	(%)	n	(%)	n	(%)
Gender	**Male**	3	(2.2)	5	(3.5)	8	(2.9)
	Female	134	(97.8)	136	(96.5)	270	(97.1)
Age	**MEAN**		49.9		49.7		49.8
	SD		11.67		11.27		11.45
	MEDIAN		50.0		50.0		50.0
	RANGE		22 to 77		22 to 78		22 to 78
	<45	44	(32.1)	43	(30.5)	87	(31.3)
	45 to 65	82	(59.9)	88	(62.4)	170	(61.2)
	>65	11	(8.0)	10	(7.1)	21	(7.6)
Race	**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	**Dark**	53	(38.7)	58	(41.1)	111	(39.9)
	Light	84	(61.3)	83	(58.9)	167	(60.1)
GEA Score	**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)

3.1.3 Statistical Methodologies

Primary Efficacy Endpoint

The primary efficacy measurement collected during this study was overall eyelash prominence measured using the GEA scale with photonumeric guide (1 [minimal], 2 [moderate], 3 [marked], 4 [very marked], corresponding to frontal and superior eyelash views). GEA scores were assigned based on overall eyelash prominence across both eyes. For the primary efficacy endpoint, a clinical response was defined as at least a 1-grade increase in the GEA score from baseline at month 4. In addition, the percentage of subjects in each treatment group who experienced an improvement in overall eyelash prominence by 2 or more grades on the GEA scale was evaluated.

Primary Hypothesis

The primary null hypothesis is that bimatoprost 0.03% and vehicle are equally effective as measured by the proportion of subjects with at least a 1 grade increase from baseline.
The alternative hypothesis is that the two treatments are not equally effective as measured by the proportion of subjects with at least a 1 grade increase from baseline.

A two-sided p-value less than or equal to 0.05 will be considered to be statistically significant.

Secondary Efficacy Variables
Upper eyelash length, thickness, and darkness (intensity) data will be calculated based on the digital image analysis (DIA) of the eyelash photographs of the superior view.

The main secondary variables are the following:

1. upper eyelash length (pixel count, change from baseline)
2. *average* progressive upper eyelash thickness (percent of detected eyelash thickness to AOI (based on pixel count), change from baseline)
3. upper eyelash darkness (darkness (0 – 255 units) within the spline, change from baseline)

Controlling Type 1 Error Rate for Secondary Efficacy Variables
To control the type 1 error rate for multiple secondary endpoints, a serial gatekeeping approach will be used with the following order of importance for the secondary variables at Week 16 (Month 4):

1. upper eyelash length (pixel count, change from baseline)
2. *average* progressive upper eyelash thickness (percent of detected eyelash thickness to AOI, change from baseline)
3. upper eyelash darkness (darkness (0 – 255 units) within the spline, change from baseline)

In other words, upper eyelash length will be tested first at $\alpha = 0.05$ level. The *average* progressive upper eyelash thickness will be tested at $\alpha = 0.05$ level only if the p-value from the test of eyelash length is ≤ 0.05. Upper eyelash darkness (intensity) will then be tested at $\alpha = 0.05$ level only if both p-values from the test of upper eyelash length and the test of *average* progressive upper eyelash thickness are ≤ 0.05.

Method of Analysis
The number and percent of subjects in each GEA category will be summarized by treatment group and visit utilizing by a frequency table.

The proportion of subjects with at least a 1-grade increase from baseline will be summarized by a frequency table and analyzed by the Pearson's chi-square test for two-by-two tables at each visit.

Eyelash length change from baseline in *pixels, average* progressive upper eyelash thickness change from baseline, and upper eyelash darkness change from baseline will be analyzed by the Wilcoxon rank-sum test.

3.1.4 Results and Conclusions

3.1.4.1 Primary Efficacy Endpoint

The efficacy results of proportion of subjects with at least a 1 grade increase from baseline in GEA at Week 16 are presents in the following table

Table 4: Number (%) of Subjects with at Least a 1-Grade Increase from Baseline in GEA (ITT Population)

	Bimatoprost 0.03% n/N (%)	**Vehicle** n/N (%)	**p-value**	**Difference (95% CI)**
Week 16	107/137 (78.1)	26/141 (18.4)	<0.0001	59.7% (50.2%, 69.1%)

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. The results for this analysis are presented in the following table

Table 5: Number (%) of Subjects with at Least a 2-Grade Increase from Baseline in GEA (ITT Population)

	Bimatoprost 0.03% n/N (%)	**Vehicle** n/N (%)	**Difference 95% CI**
Week 16	45/137 (32.8)	2/141 (1.4)	31.4% (23.3%, 39.5%)

Statistical Reviewer's Comments:

Based on these results, bimatoprost ophthalmic solution 0.03% is statistically superior to vehicle in eyelash prominence using the global eyelash assessment (GEA) scale.

3.1.4.2 Secondary Efficacy Variables

The first secondary endpoint measured eyelash growth in terms of the overall change from baseline in eyelash length by week 16, as measured in pixels within the full AOI. Table 6 presents the results for overall change in eyelash length in units of pixels and mm at week 16.

Table 6: Eyelash Length: Change from Baseline at Week 16 (ITT Population)

	Pixels			Millimeters		
	Bimatoprost 0.03% (N=137)	**Vehicle** (N=141)	p-value	**Bimatoprost 0.03%** (N=137)	**Vehicle** (N=141)	p-value
Week 16	51.63	4.19	<0.0001	1.39	0.11	<0.0001

The second secondary endpoint was 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 AOI. Table 7 presents the results for overall change in eyelash thickness/fullness in units of pixels at week 16.

Table 7: Average Progressive Eyelash Thickness/Fullness: Change from Baseline at Week 16 (ITT Population)

	Pixels		
	Bimatoprost 0.03% (N=137)	**Vehicle** (N=141)	p-value
Week 16	12.21	1.10	<0.0001

The third secondary endpoint was overall change from baseline in eyelash darkness/intensity at week 16, as measured within the spline. Table 8 presents the results for overall change in eyelash darkness/intensity in units of pixels at week 16.

Table 8: Eyelash Darkness Within the Spline: Change from Baseline at Week 16 (ITT Population)

	Pixels		
	Bimatoprost 0.03% (N=137)	**Vehicle** (N=141)	p-value
Week 16	-20.15	-3.57	<0.0001

Statistical Reviewer's Comments:
Based on these results, bimatoprost ophthalmic solution 0.03% is statistically superior to vehicle in the three secondary efficacy variables.

3.2 Evaluation of Safety

The following table is a brief summary of AEs for study C-192024-032.

Table 9: Number (%) of Adverse Events Reported by Greater Than 1% of Subjects, Treatment and Posttreatment Periods Combined (Safety Population)

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 hyperaemia	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 haemorrhage	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)

Please see the review of the medical officer for more details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The following table summarized the subgroup analyses on various subpopulations of study participants who achieved the primary efficacy endpoint of a 1-grade increase in GEA score by week 16.

Table 10 Analyses of Outcomes by gender, age, and race (ITT Population)

	Bimatoprost 0.03% (A) (N=137) Observed Response		**Vehicle (B) (N=141) Observed Response**		**Observed Differences (A-B)**
	n/N	%	n/N	%	%
Gender					
Male	2/3	66.7	2/5	40.0	26.7
Female	105/134	78.4	24/136	17.6	60.8
Age					
< 45 years	29/44	65.9	8/43	18.6	47.3
45 to 65 years	68/82	82.9	17/88	19.3	63.6
> 65 years	10/11	90.0	1/10	10.0	80.0
Race					
Caucasian	88/109	80.7	16/116	13.8	66.9
Black	0/0	0.0	1/1	100.0	-100.0
Asian	13/18	72.2	5/16	31.3	40.9
Hispanic	3/6	50.0	2/5	40.0	10.0
Other	3/4	75.0	2/3	66.7	8.3

N = Number of ITT patients in each treatment group.
n/N = Number of ITT patients with a favorable assessment / number of ITT patients with assessment.

Statistical Reviewer's Comments:

Overall, there were no major issues identified in the subgroups with respect to age, gender and race.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are no major statistical issues identified for this submission.

5.2 Conclusions and Recommendations

For the submitted pivotal study C-192024-032, bimatoprost ophthalmic solution 0.03% is statistically superior to vehicle in eyelash prominence using the global eyelash assessment (GEA) scale; bimatoprost ophthalmic solution 0.03% is 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.

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