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/BLA #:	NDA 22369
Supplement #:	010
Drug Name:	LATISSE® (bimatoprost ophthalmic solution 0.03%)
Indication(s):	Treat hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness
Applicant:	Allergan
Date(s):	Submitted: 03/04/2014 PDUFA date: 09/20/2014
Review Priority:	Pediatric supplement
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Keywords: pediatric, hypotrichosis of the eyelashes, subgroup

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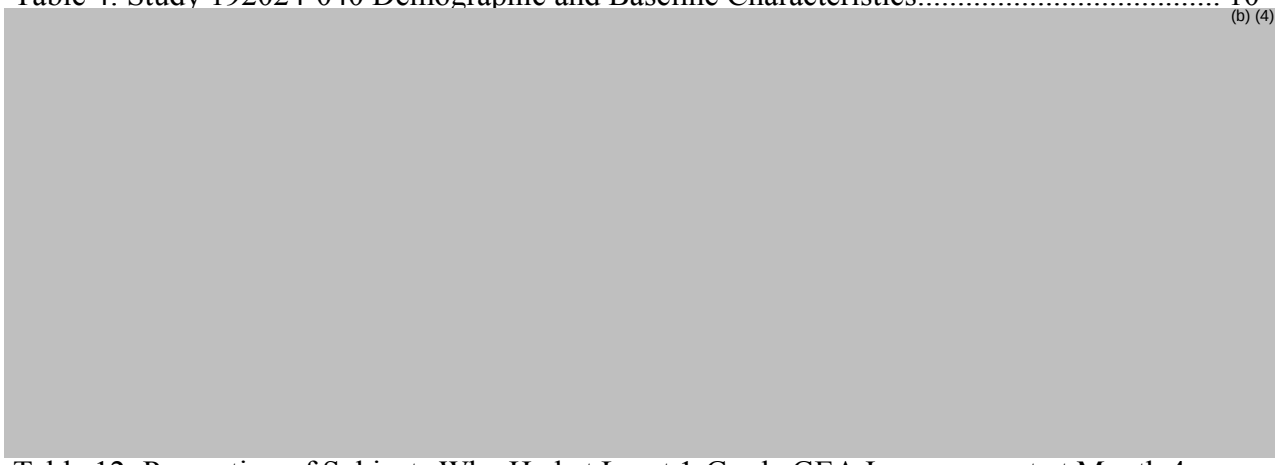
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1 EXECUTIVE SUMMARY

Bimatoprost ophthalmic solution 0.03% (LUMIGAN®) was first approved in March 2001 by the United States Food and Drug Administration (FDA) for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. In December 2008, LATISSE® (bimatoprost ophthalmic solution 0.03%) was approved by FDA for the treatment of hypotrichosis (inadequate or not enough lashes) of the eyelashes by increasing their growth including length, thickness, and darkness. This supplement New Drug Application (sNDA) included the results from a pediatric study (192024-400) for the safety and efficacy of bimatoprost ophthalmic solution 0.03% in the treatment of hypotrichosis of the eyelashes for pediatric subjects. This submission intends to fulfill the pediatric study request under the Pediatric Research Equity Act (PREA) (21 U.S.C.355c) as a post-marketing requirement. Furthermore, based on the clinical data, the applicant proposed revised labeling for LATISSE®.

Study 192024-040 was a multi-center, randomized, vehicle-controlled, double-masked clinical study to investigate the safety and efficacy of bimatoprost solution 0.03% compared with vehicle in pediatric subjects, when applied once-daily bilaterally for four months to the upper eyelid margins. By etiology, there were three different subgroups of pediatric subjects enrolled in this study:

1) Five to 17 years old pediatric subjects who had post chemotherapy eyelash hypotrichosis;
2) Five to 17 years old pediatric subjects with alopecia areata;
3) Fifteen to 17 years old non-medical need adolescent subjects (also known as healthy adolescents in this review).

Seventy-one subjects were randomized at eight sites in the US and Brazil: 48 to the bimatoprost group and 23 to the vehicle group. Except one subject in the bimatoprost group, all other subjects completed the study (70/71 [98.6%]). Among these 71 subjects, 40 (56.3%) were healthy adolescents; 15 (21.1%) were pediatric subjects with alopecia areata; and 16 (22.5%) were pediatric subjects who had post chemotherapy eyelash hypotrichosis.

The applicant-defined primary efficacy endpoint was the proportion of treatment responders at Month 4 visit. Treatment responders were defined as subjects who had at least a 1-grade increase (i.e., improvement) from baseline in Global Eyelash Assessment (GEA) score. GEA score is a clinician's assessment of the overall bilateral eyelash prominence based on the 4-point scale (1 = minimal, 2 = moderate, 3 = marked and 4 = very marked).

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- *Section 8.4 Pediatric Use, updating the paragraph as "Use of LATISSE®* (b) (4)

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Bimatoprost is a synthetic prostaglandin analog. Bimatoprost ophthalmic solution 0.03% (LUMIGAN®) was approved in March 2001 by FDA for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. In December 2008, LATISSE® (bimatoprost ophthalmic solution) 0.03% was approved by FDA for the treatment of

hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness.

2.1.2 History of Drug Development

In the approval letter issued by FDA in December 2008, the applicant was required to conduct a study evaluating the safety and efficacy of LATISSE in the pediatric population as a post-marketing study commitment, mandated under Section 2 of the PREA.

In accordance with the PREA request, the applicant conducted Study 192024-040 to evaluate the safety and efficacy of bimatoprost ophthalmic solution 0.3% in pediatric subjects with hypotrichosis of the eyelashes. The statistical reviewer was not aware of any discussion between the applicant and the Agency regarding the clinical trial design for this pediatric study.

2.1.3 Studies Reviewed

One pediatric study (Study 192024-040) was submitted in this sNDA. Key information of this study is presented in the following table.

Table 1: Key Information for Study 192024-040

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
192024-040	*multicenter, double-masked, randomized, vehicle-controlled, parallel-group study*	*One drop of study treatment once every night to each of the upper eyelid margin for four months*	*One month follow-up after the 4-month treatment period*	*bimatoprost: 48* *Vehicle: 23*	*Three different etiology subgroups:* *1) Post-chemotherapy pediatric subjects (5 to 17 years old)* *2) Pediatric subjects (5 to 17 years old) with alopecia areata* *3) Non-medical need adolescent subjects (15 to 17 years old)*

Source: Statistical Reviewer's Summary

2.2 Data Sources

The data sources for this review mainly came from the applicant's study report for Study 192024-040. The study report is available at: \\Cdsesub1\evsprod\NDA022369\0067\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eyelash-growth\5351-stud-rep-contr\192024-040

The applicant submitted SAS datasets electronically; the datasets are available at: \\Cdsesub1\evsprod\NDA022369\0079\m5\datasets\192024-040

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were in good quality with definition of each variable. Results of the primary efficacy endpoint can be reproduced by the statistical reviewer with minor data manipulation. The final statistical analysis plan (SAPs) for the study was submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 192024-040 was a multi-center, randomized, vehicle-controlled, double-masked clinical study to investigate the safety and efficacy of bimatoprost solution 0.03% compared with vehicle in pediatric subjects, when applied once-daily bilaterally to the upper eyelid margins for four months.

Initially, the study planned to only enroll pediatric subjects with hypotrichosis of the eyelashes due to recently completed chemotherapy treatment because according to the applicant, chemotherapy-induced hair loss (including hypotrichosis of the eyelashes) was expected to be of most clinical relevance in a pediatric population. However, due to continued difficulty enrolling this specific population, the applicant expanded the enrollment to a much broader pediatric population, which included medical-need pediatric subjects with hypotrichosis of the eyelashes due to alopecia areata as well as nonmedical-need adolescent subjects. Therefore, by etiology, three different subgroups of pediatric subjects were enrolled in this study:

1) Five to 17 years old pediatric subjects who had post chemotherapy eyelash hypotrichosis;
2) Five to 17 years old pediatric subjects with alopecia areata;
3) Fifteen to 17 years old non-medical need adolescent subjects.

Eligible pediatric subjects were randomized to receive bimatoprost or vehicle in a 2:1 ratio. Randomization was stratified by age group (5 to 11 versus 12 to 17 years). The key inclusion criterion for all three subgroups was that enrolled subjects must had a Global Eyelash Assessment (GEA) score of 1 (minimal), 2 (moderate), or 3 (marked). GEA score is a clinician's assessment of the overall bilateral eyelash prominence based on the 4-point scale (1 = minimal, 2 = moderate, 3 = marked and 4 = very marked).

The study duration was 5 months, which included 4-month treatment period and a 1-month post treatment follow-up period. The scheduled visits for evaluating safety and efficacy were: screening (day -14 to day -1), baseline (day 1) (or combined into a single screening/baseline visit), week 1 (telephone follow-up), and months 1, 2, 3, 4, and 5 (see Table below).

The applicant-defined primary efficacy endpoint was the proportion of treatment responders at month 4 visit. Treatment responders were defined as subjects who had at least a 1-grade increase (i.e., improvement) from baseline in GEA.

Secondary efficacy endpoints were eyelash characteristics as assessed by digital image analysis which included upper eyelash length in millimeters (mm), average progressive eyelash thickness in mm^2, and eyelash darkness in intensity units.

The safety variables included study treatment exposure, AEs, biomicroscopy, ophthalmoscopy (dilated), intraocular pressure (IOP), iris color assessment, best-corrected visual acuity (BCVA), physical examination, physical measurement (weight and height), vital signs (pulse rate and blood pressure [systolic/diastolic]), and urine pregnancy test.

Table 2: Schedule of Assessments

	Combined Screening/ Baseline[a] (Day 1)	Separate Screening[a] (Day -14 to Day -1)	Separate Baseline[a] (Day 1)	Telephone Visit (Week 1) (± 2 days)	Month 1 (± 7 days)	Month 2 (± 7 days)	Month 3 (± 7 days)	Month 4 /Early Term (± 7 days)	Month 5/ Posttreat. Follow-Up (± 7 days)
Parental Consent/Minor Assent/Authorization	X	X							
Inclusion/Exclusion Criteria	X	X	X						
Medical History	X	X	X						
Physical Examination	X[b]	X[b]			X	X	X	X[b]	X
Vital Signs	X	X			X	X	X	X	X
Pregnancy Test (Urine)[c]	X	X	X					X	X
Patient Reported Outcome (PRO) ages 12-17	X		X		X	X	X	X	X
Global Eyelash Assessment (GEA)[d, e, f]	X	X	X		X	X	X	X	X
Standardized Eyelash Photography[e]	X	X	X[g]		X	X	X	X	X
Ophthalmic History	X	X[j]							
Best Corrected Visual Acuity[h, i]	X	X[j]			X			X	
Iris Color Assessment[f, i]	X	X[j]			X			X	
Biomicroscopy	X	X[j]			X			X	
Intraocular Pressure (IOP)[h, i]	X	X[j]			X			X	
Ophthalmoscopy[i]	X	X[j]						X	
Dispense (D)/Return (R) Study Drug	D		D		R+D	R+D	R+D	R	
Serious Medical Events	X[k]	X	X[k]						
Adverse Events	X[k]		X[k]	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Concurrent Procedures	X		X	X	X	X	X	X	X

Term = termination; Posttreat. = posttreatment

a Screening and baseline may have been combined. Procedures in the baseline column were to be performed at baseline (day 1) if they occurred on a separate day than screening.
b Physical examination included height and weight at screening (or combined screening/baseline) and month 4/early termination.
c For females of childbearing potential, was to be completed prior to dispensing study medication at day 1 visit. Pregnancy testing could have occurred at any visit at the investigator's discretion.
d For postchemotherapy subjects, if GEA score was 1, a separate additional data point was collected to assess whether the subject had approximately 10 or fewer visible eyelash hairs per eye.
e Subjects were to have removed all eye makeup at least 15 minutes prior to GEA and photography to ensure eyelashes were dry. At screening, baseline (if applicable), and month 4/early exit, photographs were to be taken when pupils were not dilated.
f GEA and iris color assessment were to be evaluated by the same investigator at each visit. If this was not possible, there was to be an overlap in evaluation by both investigators.
g Photography was to be collected at baseline in the event that photographs were not successfully collected at screening.
h According to the discretion of the ophthalmologist, IOP measurements may have been collected using either a Goldmann or Tono-Pen applanation tonometer and best-corrected visual acuity could have been assessed using a logarithmic letter chart or LEA symbol chart.
i Ophthalmoscopy was to be performed following visual acuity, iris color assessment, and IOP reading, so mydriatics were to be instilled after these procedures.
j The initial ophthalmology examinations were to be performed at the screening visit or any time between screening and randomization.
k Serious medical events were collected prior to study entry (ie, randomization in IVRS/IWRS); after study entry, adverse events were collected.

Source: Table 9-1 of applicant's Study 192024-040 report.

3.2.2 Statistical Methodologies

The applicant-defined primary efficacy endpoint was the proportion of treatment responders at Month 4 visit. Treatment responders were defined as subjects who had at least a 1-grade increase (i.e., improvement) from baseline in GEA.

The primary endpoint was evaluated using the intent-to-treat (ITT) population with missing data imputed using the last observation carried forward (LOCF) method. The ITT population included all randomized subjects. The proportion of treatment responders at month 4 was summarized by treatment groups; and the treatment groups were compared using Cochran-Mantel-Haenszel (CMH) test stratified by age group. The point estimate for the treatment difference and its corresponding 95% confidence interval (CI) were calculated and reported.

In addition, the applicant also analyzed the proportion of treatment responders at months 1, 2, 3, and 5 based on ITT analysis set using the same method as the primary efficacy endpoint. Also, proportion of subjects who had at least 2-grade improvement from baseline in GEA score were analyzed (inclusive of subjects with baseline GEA scores of 1 or 2 only). Similarly, proportion of subjects who had 3-grade improvement from baseline in GEA score were analyzed (inclusive of subjects with baseline GEA scores of 1 only).

Other than stated that the planned sample size for this study was determined empirically to assess the safety profile in a population with different etiologies, the applicant did not provide any power calculation for the chosen sample size.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Seventy-one subjects were randomized in this study: 48 to the bimatoprost group and 23 to the vehicle group. Except one subject in the bimatoprost group, all other subjects completed the study (70/71 [98.6%]). The one subject in the bimatoprost group (2.1%, 1/48) discontinued the study treatment and the study due to an adverse event of exacerbation of eczema of the face, which was deemed by the investigator as not related to treatment.

Table 3: Study 192024-040 Subject Disposition

	Bim 0.03% (N=48) n (%)	**Vehicle (N=23) n (%)**	**Total (N=71) n (%)**
Number of Subjects Randomized	48 (100.0%)	23 (100.0%)	71 (100.0%)
Number of Subjects Receiving Study Treatment	48 (100.0%)	23 (100.0%)	71 (100.0%)
Number of Subjects Completed Study	47 (97.9%)	23 (100.0%)	70 (98.6%)
Reason for Study Discontinuation			
Adverse Event	1 (2.1%)	0	1 (1.4%)

[a] Bim 0.03% refers to bimatoprost ophthalmic solution 0.03% in all the tables throughout this review.
Source: Table 10-1 of Study 192024-040 report.

All randomized subjects (N=71) were included in both the safety population and the ITT population. Among these 71 subjects, 40 (56.3%) were healthy adolescents; 15 (21.1%) were pediatric subjects with alopecia areata; and 16 (22.5%) were subjects who had post chemotherapy eyelash hypotrichosis.

As presented in the following table, demographics and ocular baseline characteristics were generally consistent between the two treatment groups.

Table 4: Study 192024-040 Demographic and Baseline Characteristics

Characteristics	Bim 0.03% (N=48)	Vehicle (N=23)	Total (N=71)
	n (%)	n (%)	n (%)
Gender			
Male	11 (22.9%)	7 (30.4%)	18 (25.4%)
Female	37 (77.1%)	16 (69.6%)	53 (74.6%)
Age			
Mean (Std)	14.5 (2.97)	14.6 (2.59)	14.5 (2.83)
Median	15.0	16.0	15.0
Min, Max	5, 17	8, 17	5, 17
5 – 11	6 (12.5%)	3 (13.0%)	9 (12.7%)
12 – 17	42 (87.5%)	20 (87.0%)	62 (87.3%)
Race			
White/Caucasian	31 (64.6%)	15 (65.2%)	46 (64.8%)
Black/African American	0 (0.0%)	3 (13.0%)	3 (4.2%)
Asian	2 (4.2%)	0 (0.0%)	2 (2.8%)
Hispanic	12 (25.0%)	5 (21.7%)	17 (23.9%)
Other	3 (6.3%)	0 (0.0%)	3 (4.2%)
GEA Score			
Minimal (GEA=1)	10 (20.8%)	9 (39.1%)	19 (26.8%)
Moderate (GEA=2)	11 (22.9%)	1 (4.3%)	12 (16.9%)
Marked (GEA=3)	27 (56.3%)	13 (56.5%)	40 (56.3%)
Very Marked (GEA=4)	0	0	0
Etiology			
Postchemotherapy Pediatric	13 (27.1%)	3 (13.0%)	16 (22.5%)
Alopecia Areata Pediatric	9 (18.8%)	6 (26.1%)	15 (21.1%)
Healthy Adolescent	26 (54.2%)	14 (60.9%)	40 (56.3%)

Source: Table 14.1-3.1 of Study 192024-040 report.

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3.3 Evaluation of Safety

For the bimatoprost group, 35.4% (17/48) subjects had at least one adverse event (AE) reported; and for the vehicle group, 43.5% (10/23) subjects had at least one adverse event reported. Treatment-related AEs were reported for 16.7% (8/48) of subjects in the bimatoprost group and no subjects (0/23) in the vehicle group. Among these treatment-related AEs, two subjects had conjunctivitis.

There were no severe or serious AEs and no death during the study. One nonmedical-need adolescent subject in the bimatoprost group discontinued study treatment and the study due to exacerbation of eczema of the face, which was considered unrelated to treatment by the study investigator.

Please refer to the review of the medical reviewer for details of the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

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5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

By etiology, there were three different subgroups of pediatric subjects enrolled in this study:

1) Five to 17 years old pediatric subjects who had post chemotherapy eyelash hypotrichosis;
2) Five to 17 years old pediatric subjects with alopecia areata;
3) Fifteen to 17 years old non-medical need (healthy) adolescent subjects.

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Table 12: Proportion of Subjects Who Had at Least 1-Grade GEA Improvement at Month 4 (ITT)

Month 4	Bim 0.03%	Vehicle	p-value[a]	Difference (95% CI)
(b) (4)				
Post Chemotherapy Pediatrics	11/13 (84.6%)	3/3 (100.0%)		-15.4% (-35.0%, 4.2%)[b]
Alopecia Areata Pediatrics	4/9 (44.4%)	2/6 (33.3%)		11.1% (-38.7%, 60.9%)[b]
Healthy Adolescent	19/26 (73.1%)	1/14 (7.1%)		63.2% (41.4%, 85.1%)[b]

[a] P-value for between-group comparison is based on Cochran-Mantel-Haenszel test stratified by age group (5-11 versus 12-17 years). Difference and 95 % CI based on Mantel-Haenszel method stratified by age group using Greenland and Robins' 1985 formula.
[b] Difference and 95 % CI based on Chi-Square test.
Source: Tables 11-2 and 14.5-12 of Study 192024-040 report.

5.3 Conclusions and Recommendations

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5.4 Labeling Recommendations

Based on the study results, the applicant proposes to revise the package insert by updating the labeling as follows:

- (b) (4)
- *Section 8.4 Pediatric Use, updating the paragraph as "Use of LATISSE®* (b) (4) "


(b) (4)

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/s/

YUNFAN DENG
08/05/2014

YAN WANG
08/05/2014
I concur.