

**Division of Anti-Infective and  
Ophthalmology Products  
Advisory Committee Meeting  
Latisse (bimatoprost ophthalmic  
solution) 0.03%**

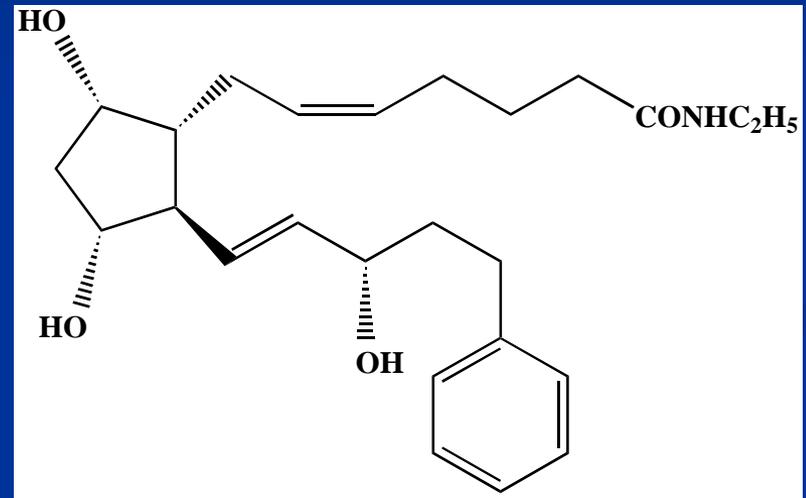
Rhea A. Lloyd, MD  
US Food and Drug Administration  
Medical Officer  
December 5, 2008

# Applicant Information

Applicant: Allergan, Inc.  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, CA 92623

# Introduction and Background

- Bimatoprost ((Z)-7-[(1R, 2R, 3R, 5S)-3, 5-dihydroxy-2-[(1E, 3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]- N-ethyl-5-heptenamide) is a prostamide, a synthetic structural prostaglandin analog that selectively mimics the effects of the naturally occurring substances.
- Bimatoprost ophthalmic solution was previously approved in March 2001, NDA 21-275 Lumigan, for the reduction of intraocular pressure in patients with OAG or OH.



# Applicant Proposed Indication

- To improve the prominence of natural eyelashes as measured by increases in growth, fullness and darkness.

# Drug Information

- Proposed Proprietary Name: **Latisse**
- Established name: bimatoprost ophthalmic solution
- NDA Drug Classification: P (**Priority designation** because this is **first drug product with the proposed indication** to improve the prominence of natural eyelashes as measured by increases in growth, fullness and darkness.)
- Pharmacologic Category: prostaglandin analog
- Dosage Form and Route of Administration: topical ophthalmic solution

# Clinical Studies for Ophthalmic Indications for bimatoprost ophthalmic solution

- *NDA 21-275, Lumigan, For the reduction in elevated intraocular pressure in patients with glaucoma or ocular hypertension.*
  - **Dose-Ranging** – Studies 192024-001, -002, -003, and -004 – Single and multicenter, double-masked, randomized, parallel group, active and inactive controlled
  - **Safety and Efficacy** – Studies 192024-008 and -009 – Multicenter, double-masked, randomized, parallel group active controlled
  - Approved March 2001.

# Clinical Studies for Ophthalmic Indications for bimatoprost ophthalmic solution

- *NDA 22-369, Latisse, For the treatment of hypotrichosis of the eyelashes*
  - Study 192024-MA001 – Proof of Concept - open-label, safety and efficacy trial
  - Study 192024-033 – Validation Study of the Global Eyelash Assessment Scale - single-center, randomized study evaluating the inter-rater and intra-rater reliability of the with photonic guide to assess overall eyelash prominence.
  - Study 192024-032 – Safety and Efficacy - double-masked, randomized, vehicle-controlled clinical trial

# Study 192024-032

## Supporting Bimatoprost Safety and Efficacy for the Proposed Indication

- To evaluate the safety and efficacy of bimatoprost ophthalmic solution 0.03% applied once daily compared with vehicle

# Study 192024-032

## Supporting Bimatoprost Safety and Efficacy for the Proposed Indication

- Multicenter (16 sites), randomized, double-masked, parallel group, vehicle-controlled study
- Subjects were instructed to apply one drop of study medication to a disposable single-use-per-eye applicator and brush along the upper eyelid margin only once daily in the evening.

# Key Inclusion Criteria

- $\geq 18$  years of age, dissatisfied with their overall eyelash prominence
- Provide written informed consent and authorization obtained prior to any study-related procedures
- Screening and baseline GEA score of 1 or 2
- BCVA equivalent to Snellen 20/100 or better in each eye
- IOP  $\leq 20$  mmHg in each eye
- Acceptable quality standardized eyelash photographs at screening for image analysis
- Ability to follow study instructions and willingness to complete all required procedures and visits.

# Exclusion Criteria

- Any uncontrolled systemic disease
- Without visible or asymmetric lashes
- Any known disease or abnormality of the lids, lashes, ocular surface, or lacrimal duct system
- Known or suspected trichotillomania disorder
- Any ocular pathology which would preclude accurate IOP readings
- Contraindications to pupil dilation
- Any active ocular disease
- Any ocular surgery during the 3 months prior to study entry or anticipated during the study
- Subjects unwilling or unable to remove CLs prior to study medication application and keep lenses out for 30 minutes.
- Any permanent eyeliner within 5 years
- Eyelash implants of any kind

# Exclusion Criteria

- 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
- Concurrent treatment with any prostaglandin or prostamide (ocular or systemic)
- 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
- Known allergy of sensitivity to the study medication, its components, or the eye make-up remover provided
- Subjects with macular edema or known risk factors for macular edema, or aphakic / pseudophakic with torn PC
- Women who were pregnant, nursing, or planning a pregnancy or of childbearing potential and not using reliable method of birth control.
- Current enrollment in an investigational study or within past 30 days
- Any condition or situation which, in the investigator's opinion, may have put the subject at risk, confounded study results or interfered with subject's participation

# Study 192024-032

## Supporting Bimatoprost Safety and Efficacy for the Proposed Indication

- First dose the evening of Day 1.
- Dosing once daily in evening through Month 4.
- Follow-up visits at Months 1, 2, and 3.
- **Primary Efficacy Endpoint**
  - Treatment end at Week 16 (Month 4)
- No dosing Month 4 – Month 5.
- Post-treatment visit, Week 20 (Month 5).

# Allergan Global Eyelash Assessment Photonumeric Guide (GEA)

- Global Eyelash Assessment Scale (GEA) –
  - A **static assessment** of **overall bilateral upper eyelash** prominence based on the actual appearance on the day of evaluation.
  - **4-point ordinal scale** including a brief description of each measure accompanied by representative photographs

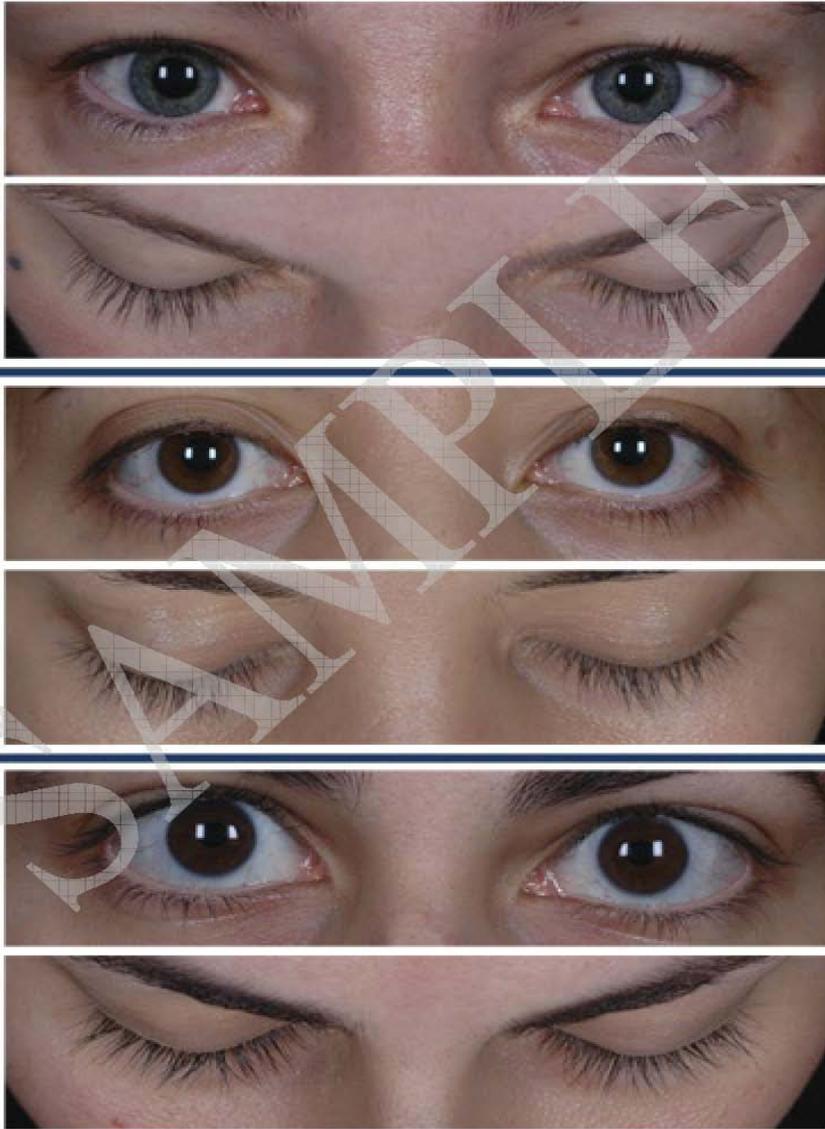
**Grade 1**



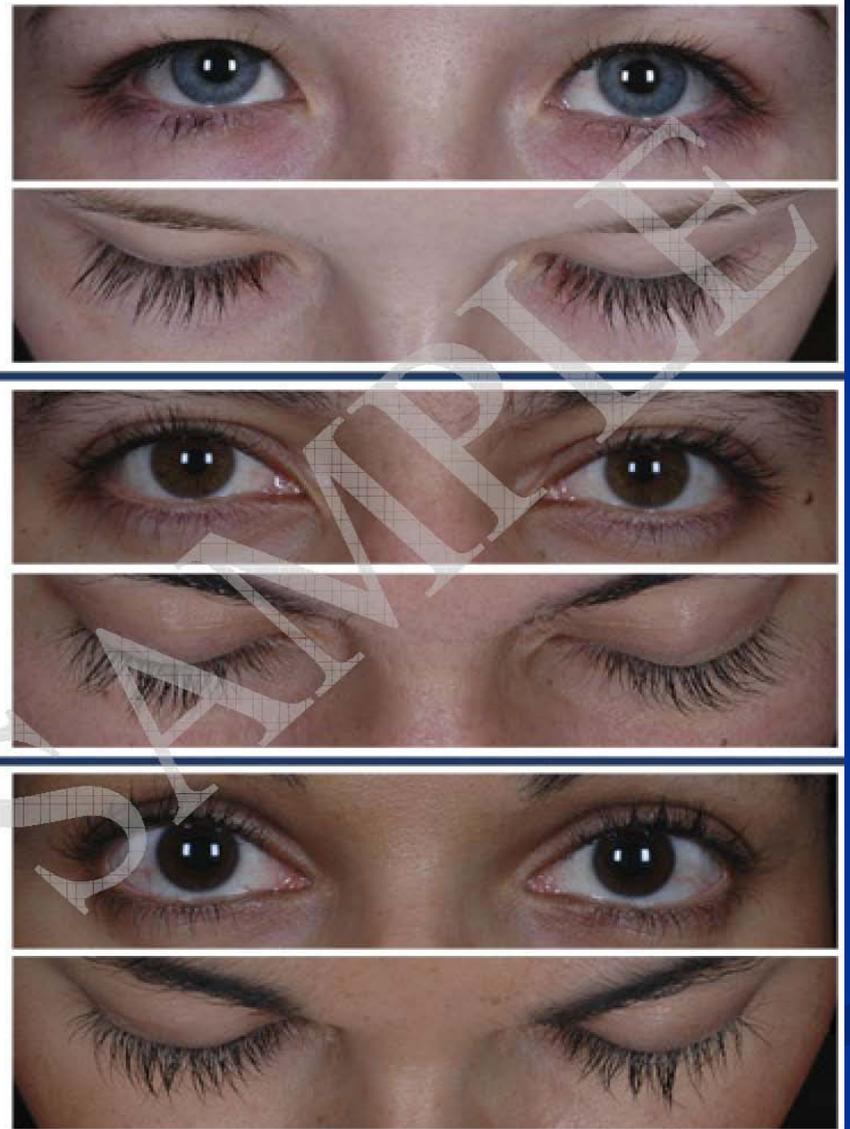
**Grade 2**



**Grade 3**



**Grade 4**



# Protocol Defined Analysis Populations

- Intent to Treat (ITT) population-All randomized subjects, regardless of whether or not treatment was received or administered.
- Per Protocol (PP) population-All randomized subjects who had no major deviation from the protocol during their participation in the trial.
- Safety population – All subjects who received 1 or more doses of study medication. If a subject was given the wrong study medication, the analysis of subject's data was based on the actual treatment received.

# Demographics and Baseline Characteristics (ITT Population)

	<b>Bimatoprost 0.03% N=137</b>	<b>Vehicle N=141</b>	<b>p-value <sup>a</sup></b>
<b><i>Age (years)</i></b>			<b><i>0.904</i></b>
Mean	49.9	49.7	
SD	11.67	11.27	
Median	50.0	50.0	
Min, Max	22, 77	22, 78	
< 45, N (%)	44 (32.1)	43 (30.5)	
45 to 65, N (%)	82 (59.9)	88 (62.4)	
> 65, N (%)	11 (8.0)	10 (7.1)	
<b><i>Sex, N (%)</i></b>			<b><i>0.499</i></b>
Male	3 (2.2)	5 (3.5)	
Female	134 (97.8)	136 (96.5)	
<b><i>Race, N (%)</i></b>			<b><i>0.566 <sup>b</sup></i></b>
Caucasian	109 (79.6)	116 (82.3)	
Black	0 (0.0)	1 (0.7)	
Asian	18 (13.1)	16 (11.3)	
Hispanic	6 (4.4)	5 (3.5)	
Other	4 (2.9)	3 (2.1)	
<b><i>Iris Color, N (%)</i></b>			<b><i>0.677</i></b>
Dark <sup>c</sup>	53 (38.7)	58 (41.1)	
Light <sup>c</sup>	84 (61.3)	83 (58.9)	
<b><i>GEA Score, N (%)</i></b>			<b><i>0.675</i></b>
Minimal (1)	29 (21.2)	27 (19.1)	
Moderate (2)	108 (78.8)	114 (80.9)	
Marked (3)	0 (0.0)	0 (0.0)	
Very Marked (4)	0 (0.0)	0 (0.0)	

# Subjects Discontinued from Treatment or Study Safety Population

	Bimatoprost 0.03% N=137	Vehicle N=141
Completed Study	131 (95.6%)	126 (89.4%)
Total Discontinued	6	15
Adverse event	4	5
Lack of efficacy	0	0
Lost to f/u	0	3
Subject decision	1	4
Protocol violation	0	2
Withdrawal of consent	1	0
Sponsor Request	0	2

# Analysis Populations

	<b>Bimatoprost</b> <b>N=137</b>	<b>Vehicle</b> <b>N=141</b>	<b>Total</b> <b>N=278</b>
<b>ITT</b>	<b>137</b>	<b>141</b>	<b>278</b>
<b>Safety Population</b>	<b>137</b>	<b>141</b>	<b>278</b>
<b>PP Population</b>	<b>131</b>	<b>126</b>	<b>257</b>

# Subjects Discontinued from Treatment or Study

## Safety Population

Reason for Discontinuation	Treatment	Investigator Number	Patient Number
AE – Dry eyes	Bimatoprost 0.03%	10007	1314
AE – Intraocular inflammation, mild; possible CME	Bimatoprost 0.03%	10005	1159
AE – Irritation / Dermatitis	Bimatoprost 0.03%	10010	1065
AE – Mild eczematous change	Bimatoprost 0.03%	11302	1072
AE – Eyelid erythema	Vehicle	10013	1399
AE – Intraocular pressure decreased	Vehicle	11301	1098
AE – Lymphoma	Vehicle	11302	1102
AE – Subconjunctival hemorrhage	Vehicle	10010	1263
AE - Xerostomia	Vehicle	10012	1125
Lost to follow-up	Vehicle	10002	1113
Lost to follow-up	Vehicle	10009	1366
Lost to follow-up	Vehicle	10012	1233
Protocol violation – Canfield photos could not be analyzed	Vehicle	10010	1230
Protocol violation – Non-Compliance	Vehicle	11302	1104
Sponsor request – Possible conflict of interest (Study coordinator)	Vehicle	10014	1271
Sponsor request – Possible conflict of interest (Spouse of Study coordinator)	Vehicle	10014	1287
Subject decision	Bimatoprost 0.03%	10008	1014
Subject decision	Vehicle	10013	1228
Subject decision	Vehicle	10014	1261
Subject decision	Vehicle	10004	1217
Subject decision	Vehicle	10004	1388
Withdrawal of consent	Bimatoprost 0.03%	10011	1142

# Primary Efficacy Variable

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

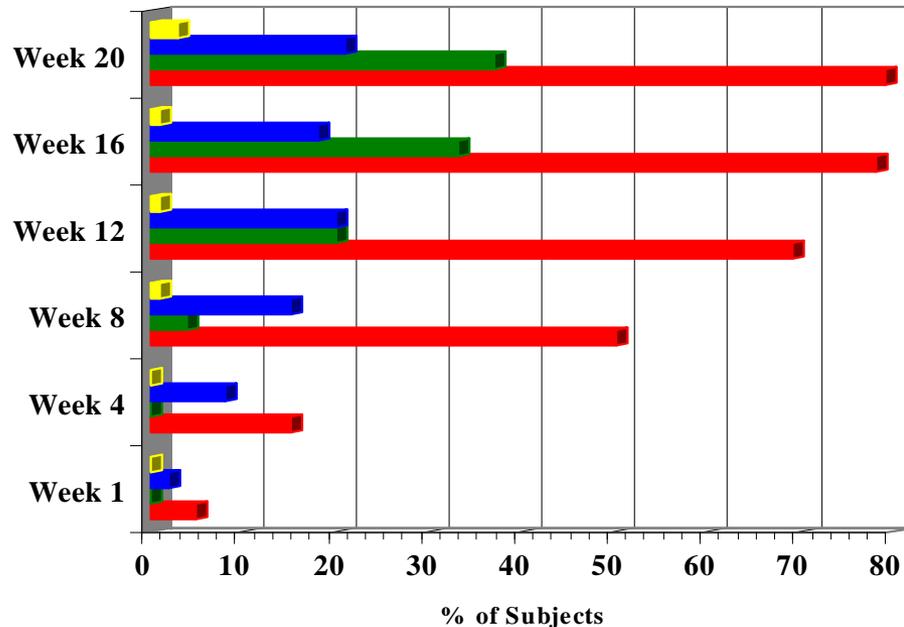
## Number (%) of Subjects with a $\geq 1$ -Grade Increase from Baseline in GEA, Treatment and Post-treatment Periods (ITT Population)

Visit	Bimatoprost 0.03% N=137	Vehicle N=141	P value
Week 1	7 (5%)	3 (2%)	0.2124
Week 4	20 (15%)	11 (8%)	0.0719
Week 8	69 (50%)	21 (15%)	<0.0001
Week 12	95 (70%)	28 (20%)	<0.0001
<b>Week 16 Primary Endpoint</b>	<b>107 (78%)</b>	<b>26 (18%)</b>	<b>&lt;0.0001</b>
Week 20	103 (79%)	27 (21%)	<0.0001

## Number (%) of Subjects with a $\geq 2$ -Grade Increase from Baseline in GEA, Treatment and Post-treatment Periods (ITT Population)

Visit <sup>a</sup>	Bimatoprost 0.03% N=137	Vehicle N=141	P value <sup>b</sup>
Week 1	0 (0%)	0 (0%)	N/A
Week 4	0 (0%)	0 (0%)	N/A
Week 8	5 (3.6%)	1 (0.7%)	0.1164 <sup>c</sup>
Week 12	28 (20%)	1 (0.7%)	<0.0001
<b>Week 16 Primary Endpoint</b>	<b>45 (33%)</b>	<b>2 (1%)</b>	<b>&lt;0.0001</b>
Week 20	49 (37%)	4 (3.2%)	<0.0001

# Percentage of Subjects with $\geq 1$ - 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

# Secondary Efficacy Endpoints

- Eyelash length
- Progressive Eyelash Thickness/Fullness
- Overall Eyelash Darkness/Intensity

# Secondary Efficacy Endpoints

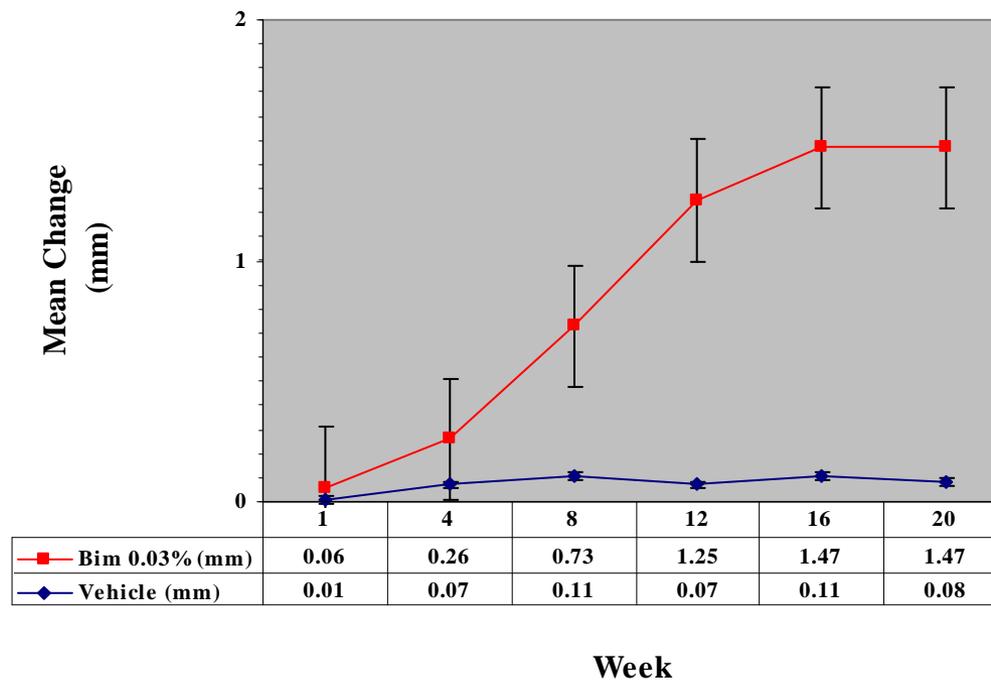
- Determined by image analysis of digital eyelash photographs (superior view) across both eyes.

# Secondary Efficacy Endpoints – Eyelash Length

- Upper eyelash length was measured within a defined eyelash boundary for each eye – the full area of interest (AOI)
- AOI was divided into a series of 25 vertical pixel segments.
- Maximum upper eyelash length - defined as the maximum height of each segment
- Measured in pixels and millimeters

# Analysis of Secondary Endpoints- Eyelash Length: Mean Change from Baseline (PP Population)

**Eyelash Length: Mean Change From Baseline (PP Population)**

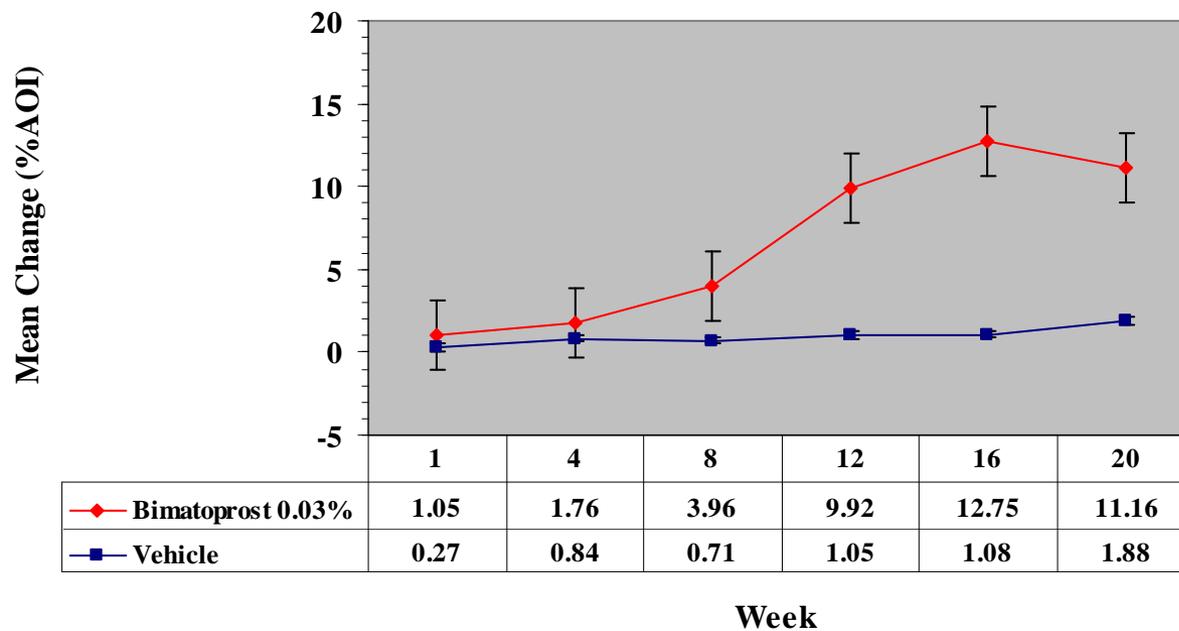


# Secondary Efficacy Endpoints – Progressive Eyelash Thickness / Fullness

- Upper eyelash thickness/fullness was measured within 3 preset rectangular areas (proximal, medial, and distal, each 300 x 25 pixels) at fixed distances from a standardized point on the eyelid margin
- For each superior-view image, the number of pixels representing the upper eyelashes was counted within each preset rectangular area.
- Assessed across both eyes – an average of the 3 rectangular areas, individually for the 3 areas (proximal, medial, distal), within the full AOI, and within the spline (a narrow area approximately 5 pixels wide, bisecting the AOI).
- Measurement in mm<sup>2</sup>

# Analysis of Secondary Endpoints- Progressive Eyelash Thickness/Fullness

**Progressive Eyelash Thickness/Fullness:  
Mean Change From Baseline, % AOI (PP Population)**

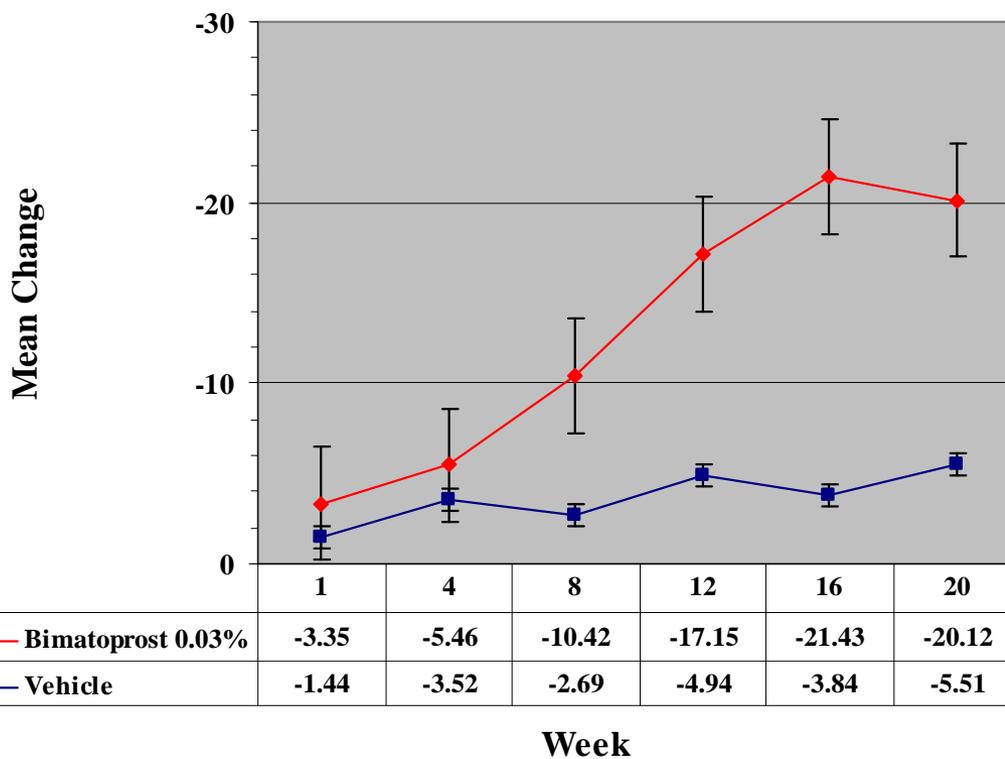


# Secondary Efficacy Endpoints – Overall Eyelash Darkness/Intensity

- Upper eyelash darkness was determined by lash intensity of the upper eyelash area within the spline.
- Darkness (intensity) of each pixel blob was reported as a mean intensity of the red, green, and blue scale.
- Mean intensity of each pixel blob was then interpreted on an 8-bit image gray scale on the continuum of 0 (black) and 255 (white)
- Mean lash intensity = average intensities of all pixel blobs
- Calculated within the full AOI and within the spline

# Analysis of Secondary Endpoints- Overall Eyelash Darkness / Intensity

**Eyelash Darkness: Mean Change from Baseline, Spline  
(PP Population)**



# Integrated Review of Safety

- Exposure data for bimatoprost ophthalmic solution
  - 2 Phase 3 trials in support of Lumigan
  - Phase 4 Lumigan marketing study
  - Lumigan Post-marketing data
  - Published literature studies of Lumigan
  - 2 trials for Eyelash Growth.

# Integrated Review of Safety

- Bimatoprost, alone or in combination, has been evaluated in over 1500 patients for over one year when applied directly to the eye.
- Worst case scenario for application to the eyelid.

# Integrated Review of Safety

## ■ Lumigan Phase 3 Studies

- 192024-008: 240 QD and 240 BID; 12 month duration
- 192024-009: 234 QD and 243 BID; 12 month duration

## ■ Bimatoprost 0.03% / timolol 0.5% Phase 3 Studies

- 192024-018T<sup>1</sup>: 261 (bimatoprost + timolol), 129 (bimatoprost alone)
- 192024-021T<sup>1</sup>: 272 (bimatoprost + timolol), 136 (bimatoprost alone)
- Each study 12 month duration

## ■ Lumigan Studies in the Published Literature

- Noecker, et al. (2003): 133 (bimatoprost), 6 months duration
- Manni, et al. (2004): 28 (bimatoprost), 6 months duration

<sup>1</sup> Brandt, et al., 2008; Allergan data on file

# Integrated Review of Safety

- **Lumigan Phase 4 Marketing Study**
  - MA-LUMO1<sup>2</sup>: 131 (bimatoprost), 3 months duration
- **Bimatoprost Studies for Eyelash Growth**
  - 192024-MA001: 28 (bimatoprost), 3 months duration
  - 192024-032: 137 (bimatoprost), 4 months

<sup>2</sup> Data on file at Allergan.

# Integrated Review of Safety

Study 192024-032 Bimatoprost for Eyelash Growth

- 137 subjects on bimatoprost
  - Median duration of treatment exposure
    - Bimatoprost – 113 days
    - Vehicle – 112 days
  - Majority of subjects exposed for at least 16 weeks
    - Bimatoprost – 73%
    - Vehicle – 60%

# Major Safety Results

## Study 192024-032 Bimatoprost for Eyelash Growth

- Deaths – None
- Nonfatal Serious Adverse Events
  - Bimatoprost:
    - Squamous cell carcinoma of skin (back)
  - Vehicle:
    - Lymphoma,
    - Recurrent metastatic breast cancer

# Major Safety Results

## Study 192024-032 Bimatoprost for Eyelash Growth

### ■ Study Discontinuation

- Bimatoprost group:
  - eczema,
  - dry eye,
  - eye inflammation,
  - contact dermatitis
- Vehicle group:
  - lymphoma,
  - eyelid erythema,
  - conjunctival hemorrhage, and
  - low IOP

### ■ Treatment Discontinuation

- Bimatoprost group:
  - Possible post-cataract CME
- Vehicle group:
  - Xerostomia

# Adverse Events Reported by Greater than 1% of Subjects Treatment and Post-treatment Periods Combined (Safety Population)

System Organ Class / Preferred Term	Bimatoprost 0.03% (N=137)	Vehicle (N=141)
<b>OVERALL</b>	55 (40.1)	41 (29.1)
<b>EYE DISORDERS</b>		
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)
<b>IMMUNE SYSTEM DISORDERS</b>		
Seasonal allergy	2 (1.5)	0 (0.0)
<b>INFECTIONS AND INFESTATIONS</b>		
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)
<b>BENIGN AND MALIGNANT NEOPLASMS</b>		
Blepharal papilloma	2 (1.5)	0 (0.0)
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>		
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.

# Post-marketing Experience - Lumigan

MedDRA Preferred Terms	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

- 2410 case reports
- 5033 adverse events

# Questions for the Advisory Committee

- Do you think the benefits outweigh the risks for Latisse (bimatoprost ophthalmic solution) 0.03% for the treatment of hypotrichosis of the eyelashes?
- If not, what additional studies should be performed?
- If yes, should any additional Phase 4 studies be performed?
- Do you have any suggestions concerning the labeling of the product?

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Rhea A. Lloyd, MD  
US Food and Drug Administration  
Medical Officer  
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