

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-369**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

**Application Type** NDA  
**Submission Number** 22-369  
**Submission Code** Original

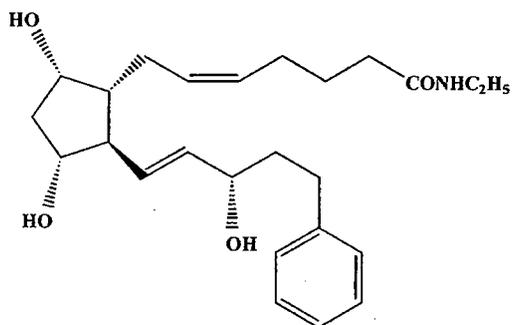
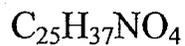
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**Reviewer Name** Rhea A. Lloyd, MD  
**Review Completion Date** 12/19/2008

**Established Name** bimatoprost ophthalmic solution,  
0.03%  
**(Proposed) Trade Name** Latisse  
**Therapeutic Class** Prostaglandin analogue  
**Applicant** Allergan, Inc.  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, CA 92623-9534

**Priority Designation** P

## Formulation



(Z)-7-[(1R, 2R, 3R, 5S)-3, 5-dihydroxy-2-[(1E, 3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]- N-ethyl-5-heptenamide

## Dosing Regimen

Apply topically once-daily to the upper eyelid margin

## Proposed Indication

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

## Intended Population

Individuals with hypotrichosis of the eyelashes

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

It is recommended that Latisse (bimatoprost ophthalmic solution) 0.03% be approved for the treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness based upon both the Agency's prior findings of safety and efficacy in the NDA 21-275 approved on March 2001 and the determination of safety and efficacy from the clinical trials submitted in this application and included in this review.

### **1.2 Risk Benefit Assessment**

Findings from Study 192024-032 together with studies submitted in NDA 21-275 provided adequate evidence of safety and efficacy for bimatoprost ophthalmic solution in the QD dosing regimen for the treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness. 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). This validation study is reviewed in Section 6.1.10.3 of this review.

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 by increasing their growth including length, thickness, and darkness. 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.

### **1.3 Recommendations for Postmarketing Risk Management Activities**

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

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

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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 \_\_\_\_\_ with Latisse (bimatoprost ophthalmic solution) 0.03% \_\_\_\_\_ 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.

#### 1.4 Recommendations for other Post Marketing Study Commitments

No other Phase 4 commitments are required.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Established Name	Bimatoprost Ophthalmic Solution, 0.03%
(Proposed) Trade Name	Latisse
Therapeutic Class	Prostaglandin analogue

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, 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 the NDA are the same drug product.

The exact mechanism of action by which bimatoprost causes eyelash growth is unknown.

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

There are no other products currently available for this proposed indication.

## **2.3 Availability of Proposed Active Ingredient in the United States**

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.

## **2.4 Important Safety Issues With Consideration to Related Drugs**

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.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

In December 2006, Allergan received written responses to questions submitted for the December 11, 2006, End-of-Phase 2 teleconference regarding IND 48,929 bimatoprost ophthalmic solution. The Division offered the following guidance for the clinical development of bimatoprost ophthalmic solution for this indication:

- It was not anticipated that additional toxicology studies would be required.
- An adequate and well controlled study with the proposed number of patients and demonstration of efficacy would be adequate to support filing of a new application or supplemental new drug application
- Clarifications regarding the statistical analysis plan were requested.

In December 2007, Allergan received written responses to questions submitted for the December 12, 2007, Pre-NDA teleconference concerning bimatoprost ophthalmic solution 0.03%.

## **2.6 Other Relevant Background Information**

There is no other relevant background information.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

Case Report Forms for all discontinued subjects in study 192024-032 were reviewed by this medical officer. No concerns were noted.

### **3.2 Compliance with Good Clinical Practices**

The clinical trials in this application and in the original NDA for bimatoprost, NDA 21-275, Lumigan (bimatoprost ophthalmic solution) 0.03% were conducted in accordance with good clinical trial practices.

### **3.3 Financial Disclosures**

The applicant 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 suggesting problems with the integrity of the submitted data.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

The application relies upon the Agency's findings of safety and efficacy for NDA 21-275, Lumigan (bimatoprost ophthalmic solution) 0.03% approved March 2001. The same drug formulation is used in Lumigan (bimatoprost ophthalmic solution) 0.03% and Latisse (bimatoprost ophthalmic solution) 0.03%.

### **4.2 Clinical Microbiology**

Not applicable.

### **4.3 Preclinical Pharmacology/Toxicology**

The application relies upon the Agency's findings of safety and efficacy for NDA 21-275, Lumigan (bimatoprost ophthalmic solution) 0.03% approved March 2001. The same drug formulation is used in Lumigan (bimatoprost ophthalmic solution) 0.03% and Latisse (bimatoprost ophthalmic solution) 0.03%.

### **4.4 Clinical Pharmacology**

#### **4.4.1 Mechanism of Action**

Bimatoprost is a synthetic structural prostaglandin analog that selectively mimics the effects of naturally occurring substances. Bimatoprost increases hair growth by increasing the length and thickness of medium and short eyelashes. It also increases the number of follicles containing two eyelashes. Although the precise mechanism of action is unknown the growth of eyelashes is believed to occur by increasing the percent of hairs in, and the duration of the anagen or growth phase.

#### **4.4.2 Pharmacodynamics**

The effects of prostanoid FP receptor agonists and bimatoprost on eyelashes were discovered during clinical evaluation of these drugs as topical ocular antihypertensive agents. The use of mouse eyelashes has permitted detailed evaluation of bimatoprost-induced hypertrichosis. This was accomplished by measuring the length and width of murine eyelashes by morphological examinations. Lumigan (bimatoprost ophthalmic solution) 0.03%, administered once daily for 14 days to mouse eyes produced a statistically significant increase in eyelash number. Morphological studies revealed that this was related to an increased incidence of eyelash follicles containing two hair shafts. After Lumigan treatment, 23% of follicles

contained two eyelashes compared to 12.7% in the untreated, contralateral eyes. Lumigan did not increase the number of eyelash follicles. Lumigan (bimatoprost ophthalmic solution) 0.03%, produced a thickening of medium and short mouse eyelashes whereas long eyelashes remained unaffected. Thickening occurred in addition to increased eyelash growth. No signs of inflammation, hyperplasia, or other unwanted manifestations were observed.

#### 4.4.3 Pharmacokinetics

The absorption, distribution, metabolism and elimination (ADME) of bimatoprost was extensively studied during the development of topical ocular bimatoprost for the treatment of open-angle glaucoma or ocular hypertension, and presented in submissions for Lumigan (bimatoprost ophthalmic solution) 0.03% (NDA 21-275). To support the clinical safety of bimatoprost, a number of nonclinical pharmacokinetic and toxicokinetic (TK) studies have been conducted. The scope of development included in vivo studies in mice, rats, rabbits, monkeys and humans and in vitro studies using animal and human tissues. A large number of the ADME studies and TK studies were conducted in compliance with Good Laboratory Practice (GLP) regulations.

The absorption, distribution, metabolism, and excretion characteristics of bimatoprost are well established following topical ocular administration of 0.03% bimatoprost. The ocular and systemic pharmacokinetics and toxicokinetics of bimatoprost following topical administration has been extensively evaluated in animals during the development of Lumigan 0.03% which is currently being used to treat patients with glaucoma and ocular hypertension. The ocular and systemic safety profile of bimatoprost is well established.

With this new indication, the dose and the formulation of bimatoprost would be the same as with Lumigan 0.03%. The safety of Lumigan 0.03% has been well established and supported by pharmacokinetic and toxicokinetic data. This safety data adequately supports application of bimatoprost 0.03% to the upper eyelid margin for the proposed indication of increased eyelash prominence in humans.

## 5 Sources of Clinical Data

All submitted clinical study reports, clinical protocols, and literature reports related to Study 192024-032 and Study 192024-033 were reviewed. This study was conducted in the United States under IND 48,929 and is evaluated in this Medical Officer's review.

The application was submitted in electronic CTD format. Modules 1, 2, and 5 were reviewed in depth.

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

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### 5.1 Tables of Clinical Studies

Table 5.1-1 Description of Clinical Efficacy and Safety Studies

Study No.	Study Design	Main Entry Criteria	Study Objectives	# Pts Treated/ Treatment	Duration of Treatment	Key Results
<i>Controlled Studies Pertinent to the Claimed Indication</i>						
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.
<i>Uncontrolled Clinical Studies</i>						

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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.
<b>Other Studies</b>						
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 photometric 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 photometric guide can be considered to be a reliable instrument in grading overall eyelash prominence.

**Reviewer's Comment:**

*Clinical studies 192024-032 and -033 are discussed within this Medical Officer's review.*

*Clinical study 192024-MA001 was also 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.*

## **5.2 Review Strategy**

The submitted clinical study reports, clinical protocols, and literature reports related to trial 192024-032 and Study 192024-033 were reviewed. The majority of the application was submitted in electronic CTD format. Modules 1, 2, and 5 were reviewed in depth.

## **5.3 Discussion of Individual Studies**

### **5.3.1 Study 192024-032: A Multicenter, Double-masked, Randomized, Parallel Study Assessing the Safety and Efficacy of Once-daily Application of Bimatoprost Solution Compared to Vehicle in Increasing Overall Eyelash Prominence.**

#### **Study Objective**

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 margins.

#### **Primary Hypothesis**

Bimatoprost ophthalmic solution 0.03% once daily is more effective than vehicle in increasing overall eyelash prominence as measured by the difference between the two groups in the incidence of subjects at Month 4 with at least a 1 grade increase from baseline in the 4-point Global Eyelash Assessment (GEA) score.

#### **Secondary Hypotheses**

- The efficacy of bimatoprost ophthalmic solution 0.03% once daily is superior to that of vehicle in increasing upper eyelash length as measured by digital image analysis.
- The efficacy of bimatoprost ophthalmic solution 0.03% once daily is superior to that of vehicle in increasing upper eyelash thickness as measured by digital image analysis.

- The efficacy of bimatoprost ophthalmic solution 0.03% once daily is superior to that of vehicle in darkening upper eyelashes as measured by digital image analysis.
- Bimatoprost ophthalmic solution 0.03% once daily has an acceptable safety profile.

### **Study Design**

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.

After randomization, the subject was instructed to carefully apply one drop of study medication to a disposable single-use-per-eye applicator and brush along the upper eyelid margin once daily in the evening. The subject was instructed not to apply study medication to the lower eyelash line. Study site personnel instructed the subjects in how to apply study medication using saline solution and subjects practiced under investigator supervision.

Subjects applied their first dose of study medication on the evening of Day 1. Each dose thereafter was applied every evening for 1 month. Subjects received a one month supply of study medication and applicators at Months 1, 2, and 3 for a total of 4 months of treatment. At each of the visits, the site called the IVRS or logged into the IWRS to obtain a new medication kit number to be dispensed to the subject.

Subjects were considered to have completed the study when all visit procedures were completed at month 5. Subjects were considered to have exited the study when the early exit visit was completed at any time prior to month 5 for any reason.

### **Global Eyelash Assessment Scale**

The Global Eyelash Assessment Scale (GEA) is a tool used for the static assessment of overall bilateral upper eyelash prominence. The GEA Scale developed by Allergan used a 4-point ordinal scale which included a brief description of each measure accompanied by representative photographs. (Global Eyelash Assessment Photographic Guide in Appendix 9.4) This scale provided for a static assessment of overall eyelash prominence, as eyelashes are assessed based on actual appearance on the day of evaluation, without relying on prior memory, perception, or assessment of change as compared to previous assessments.

Using the GEA, the overall eyelash prominence of the subject's bilateral upper eyelashes was assessed by the rater as being one of the following 4 assessments:

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 view.
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.

In determining the appropriate GEA score, the rater evaluated overall eyelash prominence, including elements of length, fullness, and color of both upper eyelashes. Length was considered the most important feature. The following pages will serve as the photonic guideline for the rater deriving this score. The photographic illustrations are provided as examples to help guide the rater in deriving the GEA score. The illustrations give examples of each scaled grade. The photographs are limited to two angles (frontal and superior).

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**Table 5.3.1-1 Table of Investigators**

Site No.	Principal Investigator Name (Number) and Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
11301	Alastair Carruthers, MD (1901) Carruthers Dermatology Centre 943 West Broadway, Suite 820 Vancouver, BC V5Z 4E1 Canada	—	26	1086-1087; 1092-1094; 1098-1099; 1103; 1107; 1111-1112; 1133; 1138; 1151; 1166; 1174; 1179; 1181; 1196; 1206
11302	Jean Carruthers, MD (1976) Carruthers Cosmetic Surgery, Inc. 943 West Broadway, Suite 740 Vancouver, BC V5Z 4E1 Canada	—	20	1066-1067; 1072- 1073; 1101-1102; 1104; 1109; 1152; 1171-1172; 1191; 1218-1220; 1234; 1236; 1239; 1242; 1245
10001	Joel Cohen, MD (8922) AboutSkin Dermatology and DermSurgery, PC 499 East Hampden, Suite 450 Englewood, CO 80113	—	20	1050; 1052-1053; 1056-1057; 1110; 1116; 1140; 1146; 1186; 1187; 1257; 1305; 1310; 1316; 1340; 1349; 1362; 1367; 1409
10002	Sue Ellen Cox, MD (3883) Aesthetic Solutions, PA 5821 Farrington Rd., Suite 101 Chapel Hill, NC 27517	—	19	1003-1005; 1007; 1009; 1011-1012; 1021-1027; 1113; 1118; 1150; 1215- 1216
10003	Doris J. Day, MD (8923) Day Cosmetic, Laser, & Comprehensive Dermatology 135 E. 71 <sup>st</sup> Street, Suite 1A New York, NY 10021	—	11	1048; 1114; 1153; 1285; 1304; 1319; 1329; 1339; 1371; 1375; 1401
10004	Lisa M. Donofrio, MD (3158) The Savin Center, PC 134 Park Street New Haven, CT 06511	—	8	1047; 1156; 1163; 1182; 1217; 1312; 1388; 1402
10005	Steven Fagien, MD (3819) 660 Glades Road, Suite 210 Boca Raton, FL 33431	—	17	1155; 1157-1160; 1175-1178; 1246; 1248; 1286; 1293; 1393; 1396; 1407- 1408

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Clinical Review  
 Rhea A. Lloyd, MD  
 NDA 22-369, Original  
 Latisse (bimatoprost ophthalmic solution 0.03%)

Site No.	Principal Investigator Name (Number) and Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
10006	Dee Anna Glaser, MD (3644) Saint Louis University Department of Dermatology 1755 S. Grand Blvd. St. Louis, MO 63104	_____	21	1075; 1077; 1105-1106; 1154; 1185; 1254-1255; 1276; 1289; 1302; 1323; 1333; 1337; 1342; 1345; 1348; 1370; 1380; 1398; 1400
10007	Richard Glogau, MD (1978) 350 Parnassus Ave., Suite 400 San Francisco, CA 94117	_____	6	1068; 1170; 1313-1314; 1320; 1335
10008	Derek Jones, MD (8924) Skin Care and Laser Physicians of Beverly Hills 9201 Sunset Blvd., Suite 602 Los Angeles, CA 90069		1	1014
10009	Gary Lask, MD (8925) ILR Dermatology 16260 Ventura Blvd., Suite 530 Encino, CA 91436	_____	5	1059; 1061; 1088; 1366; 1368
10012	Stacy Smith, MD (3187) Therapeutics Clinical Research 9025 Balboa Avenue, Suite 105 San Diego, CA 92123	_____	33	1002; 1015; 1018; 1020; 1031-1032; 1034; 1041; 1045-1046; 1108; 1119; 1125; 1127; 1169; 1173; 1189; 1223; 1226; 1250-1251; 1290; 1303; 1324; 1330; 1343; 1350; 1355; 1357-1359; 1372; 1386
10014	William P. Werschler, MD (2941) Premier Clinical Research 104 W. 5 <sup>th</sup> Ave., Suite 320 Spokane, WA 99204	_____	18	1258; 1260-1261; 1265-1266; 1268; 1271-1272; 1278-1279; 1281; 1287-1288; 1311; 1315; 1331; 1352; 1383
10013	David Wirta, MD (3276) Eye Research Foundation 1501 Superior Avenue, Suite 303 Newport Beach, CA 92663	None	36	1132; 1135; 1143-1144; 1147-1148; 1164; 1194; 1197-1201; 1207; 1209; 1211; 1214; 1228-1229; 1249; 1264; 1269; 1273; 1292; 1361; 1363; 1369; 1373-1374; 1376-1379; 1389; 1391; 1399

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Clinical Review  
 Rhea A. Lloyd, MD  
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 Latisse (bimatoprost ophthalmic solution 0.03%)

Site No	Principal Investigator Name (Number) and Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
10010	Jessica Wu, MD (8926) Pacific Dermatology 11600 Wilshire Blvd., Suite 322 Los Angeles, CA 90025	_____	19	1035; 1040; 1044; 1060; 1063; 1065; 1081-1083; 1091; 1096; 1115; 1222; 1230-1232; 1252; 1263; 1274
10011	Steven Yoelin, MD (8927) 355 Placentia, Suite 203 Newport Beach, CA 92663	None	24	1001; 1037-1039; 1070; 1124; 1139; 1142; 1180; 1241; 1253; 1259; 1277; 1283-1284; 1298- 1299; 1301; 1325; 1356; 1360; 1385; 1404-1405

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**Study Population**

Approximately 280 subjects were enrolled at 16 sites with an anticipated dropout rate of 15%. Each subject had to meet all of the following inclusion criteria and exclusion criteria.

**Inclusion Criteria**

1. Male or female, at least 18 years of age, dissatisfied with their overall eyelash prominence.
2. Written informed consent and authorization obtained prior to any study-related procedures
3. Screening and baseline GEA score of a 1 or 2
4. A 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 10 feet
5. IOP  $\leq$  20 mmHg in each eye
6. Standardized eyelash photographs at the screening visit of acceptable quality for image analysis as verified by \_\_\_\_\_
7. Ability to follow study instructions and willingness to complete all required procedures and visits

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**Exclusion Criteria**

1. Any uncontrolled systemic disease
2. Subjects without visible lashes
3. Subjects with asymmetrical eyelashes, including but not limited to unequal right and left and GEA scores
4. Subjects with any known disease or abnormality of the lids, lashes, ocular surface, or lacrimal duct system
5. Subjects with known or suspected trichotillomania disorder
6. Any ocular pathology in either eye that may have interfered with the ability to obtain accurate IOP readings
7. Contraindications to pupil dilation

8. Active ocular disease (e.g., glaucoma, uveitis, ocular infections, chronic blepharitis, or severe dry eye); myopia, strabismus, and cataracts were allowed provided other study criteria were met
9. Any ocular surgery (including laser, refractive, intraocular filtering surgery) during the 3 months prior to study entry or any anticipated need for ocular surgery for the duration of the study
10. Subjects unwilling or unable to remove contact lenses prior to study medication application in the evening and keep lenses out for 30 minutes
11. Any permanent eyeliner within 5 years
12. Eyelash implants of any kind
13. Any eyelash tint or dye application within 2 months of study entry
14. Any eyelash extension application within 3 months of study entry
15. Any use of eyelash growth products within 6 months of study entry
16. Concurrent treatment with any prostaglandin or prostamide (ocular or systemic)
17. Treatments that may affect hair growth (e.g., minoxidil, cancer chemotherapeutic agents, etc.) within 6 months prior to study entry
18. 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.
19. Known allergy or sensitivity to the study medication, its components, or the eye make-up remover provided
20. 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
21. 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
22. Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to study entry
23. Subject had a condition or was in a situation which, in the investigator's opinion, may have put the subject at significant risk, may have confounded the study results, or may have interfered significantly with the subject's participation in the study

#### **Treatments Administered**

Subjects applied 1 drop of study treatment (bimatoprost ophthalmic solution 0.03% or vehicle) to a disposable single-use-per-eye applicator and applied it to each upper eyelid margin once daily in the evening for 4 months.

#### **Identity of Investigational Products**

Bimatoprost ophthalmic solution 0.03% (Allergan formulation number 9105X, lot number 46097) contained 0.3 mg/mL of bimatoprost, sodium phosphate dibasic heptahydrate, sodium chloride, citric acid monohydrate, hydrochloric acid, sodium hydroxide, Benzalkonium chloride 0.005% and purified water.

Bimatoprost vehicle ophthalmic solution (Allergan formulation 9105X, lot number 12775A1) contained odium phosphate dibasic heptahydrate, sodium chloride, citric acid monohydrate, hydrochloric acid, sodium hydroxide, Benzalkonium chloride 0.005% and purified water.

### **Method of Assigning Subjects to Treatment Groups**

At the time of randomization, subjects were assigned in a 1:1 ratio to a treatment group through the use of an automated IVRS/IWRS. A randomization number was assigned by IVRS/IWRS to each subject sequentially according to the order of enrollment and the randomization scheme prepared by Allergan Biostatistics. That is, from the blocks of numbers assigned to the site, IVRS/IWRS assigned the next available randomization number to the subject at the time when the investigator requests randomization. The treatment group assignment was based on a 1:1 ratio of bimatoprost to vehicle for the overall study. The IVRS/IWRS reported a medication kit number for each subject. The site dispensed study medication based on the medication kit assigned and the kit number was recorded. Sites called the IVRS or logged onto the IWRS at day 1 and months 1, 2, and 3 to obtain study medication kit numbers in order to accurately dispense study medications at these visits. Treatment assignment remained the same throughout the 4-month treatment period.

### **Masking**

The study was double-masked. The investigator, the investigational staff, and the subjects were masked to which treatment each subject received. All treatments were identical in appearance and were supplied in identical-appearing bottles. If necessary for the safety and proper treatment of the subjects, the investigator was able to unmask the subject's treatment assignment in order to institute appropriate follow-up care. When possible, Allergan was to be notified before unmasking the study medication. The date and signature of the person breaking the code as well as the reason for breaking the code and any associated adverse events were to be recorded in the subject's source documentation. However, no treatments were unmasked during the study.

### **Instructions for the Subjects**

Subjects were instructed to remove all eye makeup prior to each office visit, at least 15 minutes prior to GEA evaluation. If a subject comes to a visit wearing makeup, makeup remover was provided. Subjects were also instructed to remove all facial jewelry including eyewear (glasses) for the GEA evaluations.

Subjects were instructed to carefully apply one drop of study medication to a disposable single-use-per-eye applicator and brush along the upper eyelid margin once daily in the evening. Subjects were instructed to not apply study medication to the lower eyelash line.

Subjects were instructed to dab or blot any excess study medication runoff on the area outside the upper eyelash margin with a tissue or other absorbent cloth.

Subjects were instructed to apply the treatment on a clean face after all makeup was removed and after any other facial care products were applied (e.g., lotion).

Since study medication should only be applied in the evening, if subjects wear contact lenses, they will be instructed to remove contact lenses before applying study medication and keep them out for at least 30 minutes. Subjects were to return all vials of study medication.

### Prior and Concomitant Therapy

The use of concurrent medications (prescription or over-the-counter) was recorded on the subject's CRF along with the reason the medication was taken. Therapy considered necessary for the subject's welfare was allowed at the discretion of the investigator.

Medications that were prohibited for the duration of the study included eyelash growth products, any treatment that may affect hair growth (e.g., minoxidil, cancer chemotherapeutic agents), and any treatment with an ocular or systemic prostaglandin or prostamides. The decision to administer a prohibited medication/treatment was done with the safety of the study participant as the primary consideration. When possible, Allergan was to be notified before the prohibited medication/treatment was administered.

### Efficacy Measurements

#### 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 photonic numeric 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

The GEA photoguide is included in Appendix 9.4 of this review.

#### 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.

#### 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. The digital image analysis was based on standardized equipment and subject preparation. Digital image analysis is a photographic process developed and performed by \_\_\_\_\_ The details regarding the processes are maintained by \_\_\_\_\_ The information describing software and technical processes of digital image analysis is maintained in standard operating procedures (SOPs) and work instruction manuals on file at \_\_\_\_\_

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Upper eyelash length was measured within a defined eyelash boundary for each eye, known as the full area of interest (AOI). For the digital image, the computer software divided the full AOI image into a series of 25 vertical pixel segments. Within each segment, the maximum upper eyelash length (defined as the maximum height of each segment) was measured in pixels. The mean number of pixels over all segments represented the upper eyelash length and was computed for each digital image across both eyes. Upper eyelash length was additionally measured in terms of millimeters (mm). The principal variable for eyelash length was change from baseline within the full AOI in pixels.

Upper eyelash thickness/fullness was measured within 3 preset rectangular areas (proximal, medial, and distal, each 300 x 25 pixels) positioned at fixed distances from a standardized point on the eyelash margin. For each superior-view image, the number of pixels representing the upper eyelashes was counted within each preset rectangular area. Eyelash thickness/fullness was assessed across both eyes as an average of the 3 rectangular areas (i.e., average progressive eyelash thickness), individually for the 3 areas (proximal, medial, and distal), within the full AOI, and within the spline (a narrow area approximately 5 pixels wide, bisecting the AOI). Upper eyelash thickness/fullness was additionally measured in terms of  $\text{mm}^2$ . The principal variable for eyelash thickness/fullness was change from baseline in average progressive eyelash thickness, expressed in pixels as percent of AOI.

Upper eyelash darkness was determined by lash intensity of the upper eyelash area within the spline. Darkness (intensity) of each pixel blob (a continuous collection of pixels that are touching) was reported as mean intensity of the red, green, and blue scale. The 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). The mean lash intensity was the average intensities of all pixel blobs and was a measure of upper eyelash darkness. Eyelash intensity was calculated within the full AOI and within the spline. The principal analysis variable for eyelash intensity was change from baseline within the spline.

### **Health Outcomes Measurement**

Four Patient Reported Outcome questionnaires were collected during this study.

PRO questionnaire 1, collected at every study visit, was a static measure of satisfaction with regard to subjects' eyelashes and the study treatment. Subjects were asked to answer using the 5-point scale presented for each question (e.g., very satisfied, satisfied, neutral, unsatisfied, very unsatisfied). Satisfaction was assessed by analysis of the change from baseline for 23 individual items and by analyses of 3 domains. Domain 1 (8 questions) assessed the subjects' satisfaction with physical attributes of eyelashes including length, fullness/thickness, and overall satisfaction with eyelashes. Domain 2 (10 questions) assessed subjects' satisfaction with subjective attributes of eyelashes such they relate to feelings of confidence, professionalism, and attractiveness. Domain 3 (5 questions) assessed subjects' satisfaction with their daily routine with regard to the amount of time spent on the application and removal of mascara, and the hassle of making eyelashes presentable. For questions within domains 1 and 2, a lower score represented higher satisfaction (i.e., the minimum score translated to "no impairment of life

quality” and the maximum score, “maximum impairment”); for domain 3, higher score represented higher satisfaction.

PRO questionnaire 2, collected only during the day 1 visit, asked the subjects which effects of eyelash enhancement were most valuable among eyelash length, fullness/thickness, darkness, and number of eyelashes. Subjects were asked to rate the importance of each using a 5-point scale (extremely important, important, neutral, not very important, not important at all).

PRO questionnaire 3, collected at the week 1 through month 4 visits, was a dynamic measure of change from baseline, based on subjects’ recollection of any perceived change in their feelings of satisfaction with their eyelashes and the study treatment. For the majority of questions, subjects were asked to answer using the provided 5-point scale (e.g., very much agree, agree, neutral, disagree, very much disagree).

PRO questionnaire 4, collected only during the month 5 visit, asked the subjects to rate their change in overall satisfaction with the appearance of their eyes, with their daily activities, and with their quality of life. Subjects were asked to check 1 box on a 15-point scale ranging from “a very great deal better” to “a very great deal worse.”

### **Safety Measurements**

Safety measurements collected during this study included adverse events, ophthalmic examination variables (iris color, IOP, visual acuity, biomicroscopy, and ophthalmoscopy), physical examination, vital signs, and pregnancy testing.

#### *Adverse Events*

During the screening period, after signing of the informed consent and entry into the study, any serious medical events were to be immediately reported to Allergan. Throughout the course of the study, all adverse events were monitored and documented on the appropriate CRF, including seriousness, severity, action taken, and relationship to study drug.

#### *Ophthalmic Examination Variables*

Iris color was recorded for each subject at every study visit. Iris color was grouped as light (blue, blue-gray, blue/gray-brown, green, green-brown, hazel, and other) and dark (brown and dark brown). If the “other” category contained black in the description, it was grouped as dark. IOP (measured at approximately the same time of day at each visit), visual acuity, and biomicroscopy data were collected at screening, week 1, and months 1, 2, 3, 4, and 5. Ophthalmoscopy (dilated) was performed at screening and month 4.

#### *Physical Examination*

Physical examination was performed for each subject at screening and month 4.

#### *Vital signs*

Vital signs (blood pressure and pulse rate) were collected for each subject at each visit.

*Pregnancy Screening*

Urine pregnancy tests were collected from all female subjects of childbearing potential at screening, day 1, and month 4. If a subject became pregnant during the study, the investigator was to notify Allergan immediately and the subject was to be discontinued from the study. The investigator was to notify the subject's physician that the subject had been treated with an investigational drug (bimatoprost or vehicle). The investigator was to follow the progress of the pregnancy and document the outcome, providing a copy of this documentation to Allergan.

**Appropriateness of Measurements**

The GEA scale with photonumeric guide was developed by Allergan and was determined to be a reliable and reproducible instrument in grading overall eyelash prominence (CSR 192024-033). The digital image analysis performed for the evaluation of eyelash length, thickness/fullness, and darkness was developed by \_\_\_\_\_ the safety measurements evaluated in this study are widely used in clinical studies.

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**Table 5.3.1-1 Schedule of Visits and Procedures**

	Screening (Day -14 to -1)	Baseline (Day 1)	Week 1	Month 1	Month 2	Month 3	Month 4/ Early Exit	Month 5
Consent / authorization	X							
Inclusion / exclusion criteria	X	X						
Medical history / ophthalmic history <sup>a</sup>	X	X						
Physical examination	X							
Pregnancy test (urine)	X	X						
Vital signs	X	X	X	X	X	X	X	X
Visual acuity <sup>b</sup>	X		X	X	X	X	X	X
Biomicroscopy	X		X	X	X	X	X	X
Intraocular pressure (IOP) measurement <sup>c</sup>	X		X	X	X	X	X	X
Ophthalmoscopy <sup>d</sup>	X						X	
Patient reported outcomes questionnaires <sup>e</sup>	X	X	X	X	X	X	X	X
Global eyelash assessment <sup>f</sup>	X	X	X	X	X	X	X	X
Standardized eyelash photography <sup>f</sup>	X	X	X	X	X	X	X	X
Dispensed study drug		X	X	X	X	X		
Serious medical events	X	X						
Adverse events		X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Concurrent procedures		X	X	X	X	X	X	X

a Subjects who reported any eye issues or discomfort at the day 1 visit were seen by an ophthalmologist for further procedures if necessary.  
 b Best corrected visual acuity with refraction.  
 c Was to be measured at approximately the same time of day as the screening visit for each subsequent visit.  
 d Ophthalmoscopy and lens assessments were performed following visual acuity and IOP reading; mydriatics were instilled after the IOP measurement.  
 e Was to be completed by the subject prior to conducting any other visit procedures.  
 f Subjects were to remove all eye makeup ≥ 15 minutes before procedure.

### **Statistical and Analytical Plans**

Continuous demographic variables were analyzed using parametric test (i.e., 2-sample t-test). Binary or ordinal demographic variables were analyzed by nonparametric methods (i.e., Pearson's chi-square test, Wilcoxon rank-sum test, etc). Ordinal and continuous PRO data were summarized by descriptive statistics and analyzed by the Wilcoxon rank-sum test.

Statistical tests were considered statistically significant if 2-sided p-value is  $\leq 0.05$ .

### **Analysis Populations**

Three analysis populations were utilized:

- Intent-to-treat (ITT) population (primary efficacy analysis population) consisted of all randomized subjects, regardless of whether or not treatment was received or administered.
- Per Protocol (PP) population (secondary efficacy analysis population) consisted of subjects who had no major deviation from the protocol during their participation in the trial; and
- Safety population consisted of all subjects who received 1 or more doses of study medication. If a subject was given the wrong study medication (other than the intended study medication as randomized), the analysis of the subject's data was based on the actual treatment received.

### **Primary Efficacy Analysis**

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). 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 (week 16). GEA scores were assigned by the investigator based on overall eyelash prominence across both eyes. If data were missing or not available for baseline (day 1), data from the screening visit were used as the baseline value. The proportion of subjects with at least a 1-grade increase from baseline was summarized by a frequency table and analyzed by the Pearson's chi-square test for 2-by-2 tables at each visit. The number and percentage of subjects in each GEA category were summarized by treatment group and visit by a frequency table. No test was performed for treatment-by-center interaction.

### **Secondary Efficacy Analysis**

#### ***Secondary Analysis of Primary Efficacy Endpoint***

The percentage of subjects in each treatment group who experienced at least a 2-grade increase from baseline in GEA score at each study visit was summarized by a frequency table and analyzed by the Pearson's chi-square test for 2-by-2 tables at each visit.

Mean change from baseline in GEA score was calculated for each treatment group at each study visit. Within-group comparisons were performed using a Wilcoxon signed-rank test for change from baseline. Between-group comparisons were performed using a Wilcoxon rank-sum test.

### ***Primary Analyses of Secondary Efficacy Endpoints***

For assessments of eyelash length, progressive eyelash thickness/fullness, and eyelash darkness (intensity) based on digital image analysis, analyses were based on the average of the measurements from both left and right upper eyelashes (from superior view images). The methods used to determine upper eyelash length, average progressive upper eyelash thickness/fullness, and upper eyelash darkness are described in the statistical analysis plan. For each of these variables, raw values at baseline and change from baseline at each visit were summarized. If baseline (day 1) data are unavailable or if there was a reshoot, then the screening visit digital image analysis data were imputed for the baseline (day 1) data. In the event that a subject's digital image was not able to be interpreted due to the presence of spectral noise, he or she was not included in the analysis population for that particular secondary endpoint. Within-group comparisons were performed using a Wilcoxon signed-rank test for change from baseline. Between-group comparisons were performed using a Wilcoxon rank-sum test. Missing data were imputed up to week 16 using the LOCF method.

### **Reviewer's Comment:**

*The original protocol stated that the secondary efficacy analysis population was the Per Protocol population with the last observation carried forward for missing values. The Division disagrees with using the LOCF method for a Per Protocol population. In the Division's analysis, the Per Protocol population used observed cases only.*

To control the type 1 error rate at 0.05 for multiple secondary efficacy variables, a serial gatekeeping procedure was used with the following order of importance for the secondary variables at month 4 (week 16):

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

### ***Sensitivity Analyses***

To test the robustness of the ITT with LOCF analysis for both the primary and secondary efficacy analyses, 2 sensitivity analyses were performed. First, efficacy analyses were performed on the PP population using observed data. Second, instead of LOCF, missing values were imputed with the median value of the subject's treatment group at each respective visit. In addition, for the primary endpoint of a 1-grade increase in GEA scale, a sensitivity analysis was performed where missing values were treated as treatment failures.

### ***Health Outcomes Analyses***

Four PRO questionnaires were collected during this study for the purpose of health outcomes analysis. Analyses of these data were based on the ITT population, with each question analyzed at baseline and follow-up visits (change from baseline). Within each treatment group, a Wilcoxon signed-rank test for change from baseline was performed. Between-group comparisons were performed using a Wilcoxon rank-sum test. Missing data for questionnaires 1 and 3 were imputed up to week 16 (month 4) using the LOCF method. There was no imputation

of data for questionnaires 2 and 4 because these were only collected during one study visit (questionnaire 2 at day 1 and questionnaire 3 at month 5).

**Reviewer's Comment:**

*The Health Outcomes data was not reviewed during this Priority review cycle. The submitted Patient Reported Outcome (PRO) questionnaires have been internally validated. To ensure that the submitted validation information meets the Agency's requirements for internal and external validation, an evaluation by the Study Endpoints and Labeling Division (SEALD) team will be necessary. A decision regarding PRO outcome labeling claims will be made after the SEALD team review is complete.*

**Safety Analysis**

Safety data (adverse events, ophthalmic examination variables, physical examination, and vital signs variables) were summarized by descriptive statistics and/or frequency tables and were analyzed by appropriate nonparametric statistical methods (Pearson's chi-square test, Wilcoxon rank sum test) and/or parametric tests (ANOVA, t-test). The safety analyses were based on the safety population. No data imputation for missing visits or values was performed.

***Exposure to Study Treatment***

Subjects' exposure to study treatment was characterized by summary statistics and no statistical comparisons were performed. The number of subjects who were exposed to study treatment for at least 1 day and at least 1, 4, 8, 12, and 16 weeks was presented in a frequency table.

***Adverse Events***

The Medical Dictionary for Regulatory Activities (MedDRA) was used to code all adverse events. Adverse events that continued with severity changes within a study period were tabulated using the maximum reported severity. The incidence of all adverse events and treatment-related adverse events were summarized by treatment group by primary system organ class (SOC) and preferred term; by primary SOC, preferred term and severity; and by primary SOC, preferred term, and severity with individual subject identification listed beneath each frequency. All adverse event data were summarized by treatment period (day 1 to month 4) and post-treatment period (month 5) in addition to a summary of all adverse events for the entire study (treatment and post-treatment periods together).

***Ophthalmic Examinations***

Iris color, visual acuity, IOP, and biomicroscopy measurements were collected at screening, week 1, and months 1, 2, 3, 4, and 5. Ophthalmoscopy measurements were collected at screening and month 4.

***IOP***

IOP measurements were collected twice for each eye. If the two measurements differed by more than 2 mmHg, a third measurement was taken on that eye. If two measurements were collected, the average of the two was recorded as the IOP for a particular eye; if a third measurement was collected, the median measurement was recorded as the IOP for that eye.

#### *Visual Acuity*

Best-corrected visual acuity was measured using a logarithmic visual acuity chart and was recorded in Snellen equivalent units on the case report forms.

#### *Biomicroscopy and Ophthalmoscopy*

Biomicroscopy and ophthalmoscopy data were collected using a 5-point scale (0 [none], 0.5 [trace], 1 [mild], 2 [moderate], 3 [severe]) for the following findings: lid/lashes (edema, erythema, hyperemia, other pathology), conjunctiva (edema, erythema, hyperemia, other pathology), cornea (edema, staining/erosion, other pathology), anterior chamber (cells, flare, other pathology), iris/pupil (other pathology), and lens (cataract).

#### *Physical Examinations*

Physical examinations were performed at the screening visit and at month 4 or early exit. Physical examination findings were summarized by a frequency table for each of these two visits.

#### *Vital Signs*

Vital signs collected during this study were blood pressure and pulse rate, collected at each visit. These data were summarized by descriptive statistics and analyzed by 1-way ANOVA. Analyses at post-baseline visits were based on change from baseline. Within-group changes from baseline were analyzed by the paired t-test. All analyses were based on observed cases and no data imputations were performed.

#### *Pregnancy Screening*

The results for the urine pregnancy tests are presented in a listing.

#### *Subgroup Analyses for Safety Variables*

All adverse events were summarized and analyzed by the following subgroups: age (<45, 45 to 65, and > 65 years), gender, and race (Caucasian and non-Caucasian). This was performed for both the treatment and post-treatment periods.

Analyses of IOP were stratified by three subgroups, according to baseline IOP (8 to 12 mmHg, > 12 to 15 mmHg, and > 15 mmHg). These ranges were determined by taking the bottom tercile, middle tercile, and the top tercile of baseline IOPs. The sampling unit was the "eye" (i.e., each subject contributed 2 data points). Within each of the subgroups, the number and percent of subjects with an IOP of  $\leq 6$  mmHg was summarized by treatment group and visit utilizing a frequency table and was analyzed by the Pearson's chi-square test or Fisher's exact tables for 2-by-2 tables for each visit. The sampling unit was the eye and not the subject. In addition, a scatterplot of baseline IOP versus final IOP for each treatment group was presented for the treatment period and post-treatment period.

#### *Drug Concentration Analysis*

No drug concentration analyses were planned or performed for this study.

### **Interim Analysis**

No interim analyses were planned or performed for this study.

### **Determination of Sample Size**

Sample size calculations were based on the following assumptions:

- Percent of subjects with a 1 grade increase from baseline in the GEA score for the vehicle group to be 20%
- Twenty percentage point difference between the treatment group and the vehicle group
- Pearson's chi-square test
- Two-sided type 1 error of 0.05

Based on the above assumptions, 110 subjects per group would have a statistical power of 90%. Adjusting for an anticipated 15% drop-out rate, 260 subjects were planned to be enrolled in the study. Sample size calculations were performed using the procedure PTT0-1 of the commercial software nQuery 6.01.

### **Changes in the Conduct of the Study or Planned Analyses**

The database was locked on 29 January 2008. Following the initial review of the safety data, a number of items were identified which required clarification (e.g., coding of a biomicroscopy finding, clarification of adverse event data). The database was unlocked on 04 March 2008, the issues were clarified and coded, and the database was relocked on 07 March 2008.

### **Changes to Analyses Prior to Database Lock**

Detailed plans for the statistical analysis of the study data were specified prior to the database lock and unmasking. The following key changes were made to the analysis plan after the finalization of the statistical analysis plan.

- A secondary analysis of the primary efficacy variable to examine the percentage of subjects who experienced at least a 2-grade increase from baseline in GEA score (based upon FDA feedback)
- Analysis of the percentage of subjects with at least a 1-grade improvement from baseline in GEA score, treating missing values as treatment failures (based upon FDA feedback)
- Analysis of change from baseline in IOP using the eye as the independent sampling unit

### **Changes to Analyses Following Database Lock**

The following additional analyses were made after database lock:

- A secondary analysis of the primary efficacy variable: mean change from baseline on the GEA scale by visit
- For eyelash length, summary statistics of unit conversion from pixel to mm by visit
- Correlation of change from baseline in each of the primary and secondary efficacy variables with change from baseline in 3 components of PRO questionnaire 1: a single-item (question 4, "overall satisfaction with eyelashes"), domain 1, and domain 2. The correlation analyses were conducted for both treatment groups for each study visit.

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Correlations were evaluated for statistical significance, proper direction, and strength using the Spearman rank correlation.

**Reviewer's Comment:**

*Because the drug product is a liquid, it was anticipated that the drug product would make contact with the eye despite the use of the applicator. The agency did not consider this inadvertent drug exposure, and subjects were not instructed to contact the investigator or take any other action if drug product made contact with the eye.*

*Any final labeling for the product would be expected to contain warnings/precautions similar to the Lumigan product which is dropped on the eye proper.*

## 6 Review of Efficacy

### Efficacy Summary

#### 6.1 Indication

The proposed indication is to improve the prominence of natural eyelashes as measured by increases in growth, fullness, and darkness.

##### 6.1.1 Methods

The submitted clinical study report, clinical protocol, and literature reports related to trial 192024-032 were analyzed in this efficacy review.

##### 6.1.2 Demographics

**Table 6.1.2-1 Demographics and Baseline Characteristics (ITT Population)**

	<b>Bimatoprost 0.03%</b> N=137	<b>Vehicle</b> N=141	<b>Total</b> N=278	<b>p-value<sup>a</sup></b>
<b>Age (years)</b>				<b>0.904</b>
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)	
<b>Sex, N (%)</b>				<b>0.499</b>
Male	3 (2.2)	5 (3.5)	8 (2.9)	
Female	134 (97.8)	136 (96.5)	270 (97.1)	
<b>Race, N (%)</b>				<b>0.566<sup>b</sup></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)	
<b>Iris Color, N (%)</b>				<b>0.677</b>
Dark <sup>c</sup>	53 (38.7)	58 (41.1)	111 (39.9)	
Light <sup>c</sup>	84 (61.3)	83 (58.9)	167 (60.1)	
<b>GEA Score, N (%)</b>				<b>0.675</b>
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)	

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- 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  $\geq 25\%$  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.

**Reviewer's Comment:**

*There were no significant differences in the treatment groups at baseline.*

*There were significantly more women than men enrolled in the study. 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.*

### 6.1.3 Patient Disposition

A total of 409 subjects were screened for the study and 278 subjects were enrolled. The Intent-to-Treat (ITT) and Safety populations each consisted of all 278 randomized subjects. The Per Protocol population included the 257 randomized subjects who were not discontinued from treatment or the study.

**Table 6.1.3 -1 Subject Disposition for the Treatment and Post-treatment Periods (ITT Population)**

	Bimatoprost 0.03%	Vehicle	Total
<b>Treatment Period</b>			
Enrolled <sup>a</sup>	137	141	278
Intent to Treat population	137	141	278
Safety population	137	141	278
Per Protocol population	131 (95.6)	126 (89.4)	257 (92.4)
Completed, N (%)	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 Reasons	1 (0.7)	4 (2.8)	5 (1.8)
Protocol Violations	0	2 (1.4)	2 (0.7)
Other	1 (0.7)	2 (1.4)	3 (1.1)
<b>Post treatment Period</b>			
Enrolled <sup>b</sup>	131	126	257
Completed, N (%)	131 (100.0)	126 (100.0)	257 (100.0)
Discontinued	0	0	0
Adverse Event	0	0	0
Lack of Efficacy	0	0	0
Pregnancy	0	0	0
Lost to Follow-up	0	0	0
Personal Reasons	0	0	0
Protocol Violations	0	0	0
Other	0	0	0

a Includes all randomized subjects. ITT and Safety populations

b Includes all randomized subjects who entered the post-treatment period.

**Reviewer's Comment:**

*Subject disposition during the treatment and post-treatment periods was the same for the Intent-to-Treat and Safety populations.*

*The Division disagrees with the applicant's use of the LOCF method for the Per Protocol population. In the Division's analysis, the Per Protocol population is of observed cases only.*

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*More than 95% of enrolled subjects completed the treatment period and 100% of enrolled subjects completed the post-treatment period.*

*The most common reason for discontinuation was adverse event in both treatment groups.*

**Table 6.1.3-2 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 – _____ 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

b(4)

**Reviewer’s Comment:**

*Four subjects in the bimatoprost group and five subjects in the vehicle group discontinued the study due to an adverse event.*

*Subject 10012-1125 reported xerostomia on day 34 of the study and discontinued study treatment (vehicle) at that time. Subject remained in the study through the month 5/study exit.*

*Subject 10005-1159 (Bimatoprost group) who was 9 months post-cataract surgery discontinued study treatment on day 16. The subject's private ophthalmologist noted possible cystoid macular edema and started treatment with Acular LS during a follow-up exam. Subject's best corrected visual acuity was 20/20. Investigator examined the subject 6 days later and did not note CME on ophthalmoscopy. Investigator discontinued the subject from the study.*

#### 6.1.4 Analysis of Primary Endpoint(s)

**Table 6.1.4-1**  
**Number (%) of Subjects with At Least a 1-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	7/137 (5)	3/141 (2)	0.2124 <sup>c</sup>
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
<b>Week 16 (Primary Endpoint)</b>	<b>107/137 (78)</b>	<b>26/141 (18)</b>	<b>&lt;0.0001</b>
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**  
**Number (%) of Subjects with At Least a 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	0/137 (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 <sup>c</sup>
Week 12	28/137 (20.4)	1/141 (0.7)	<0.0001
<b>Week 16 (Primary Endpoint)</b>	<b>45/137 (32.8)</b>	<b>2/141 (1.4)</b>	<b>&lt;0.0001</b>
Week 20	49/131 (37.4)	4/126 (3.2)	<0.0001

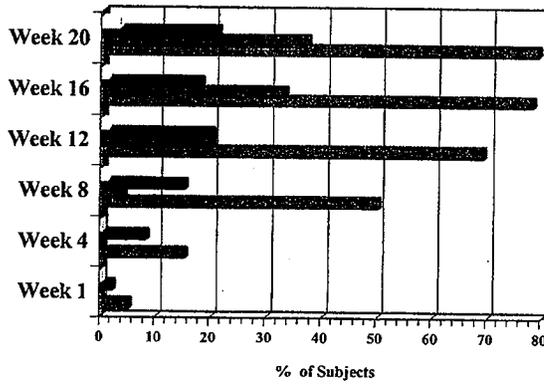
a LOCF was performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.

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**

**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

**Reviewer's Comment:**

*The clinical study met the primary efficacy endpoint. 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.*

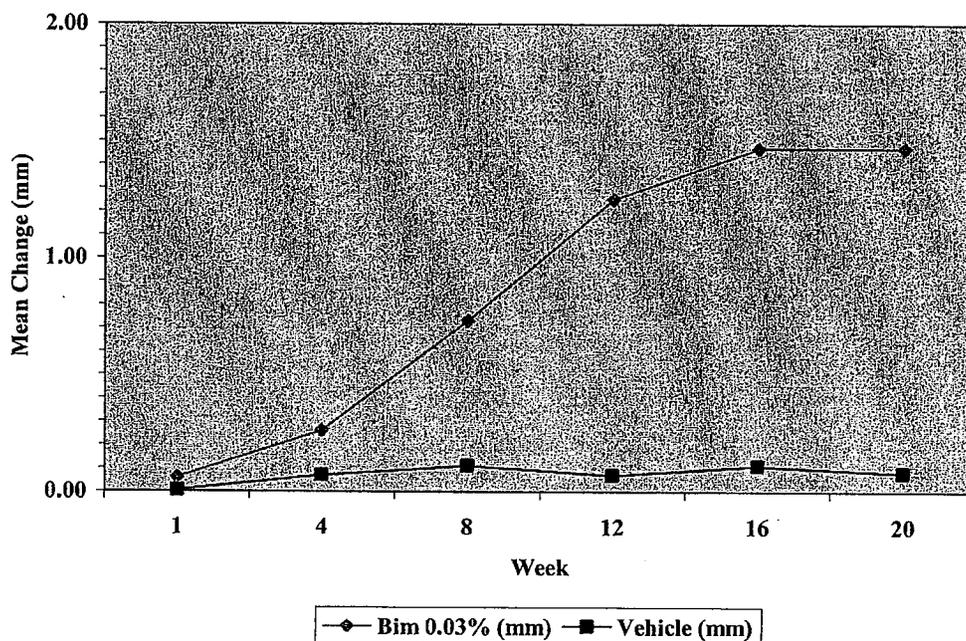
### 6.1.5 Analysis of Secondary Endpoints(s)

#### ***Eyelash Length***

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.

**Chart 6.1.5-1**

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



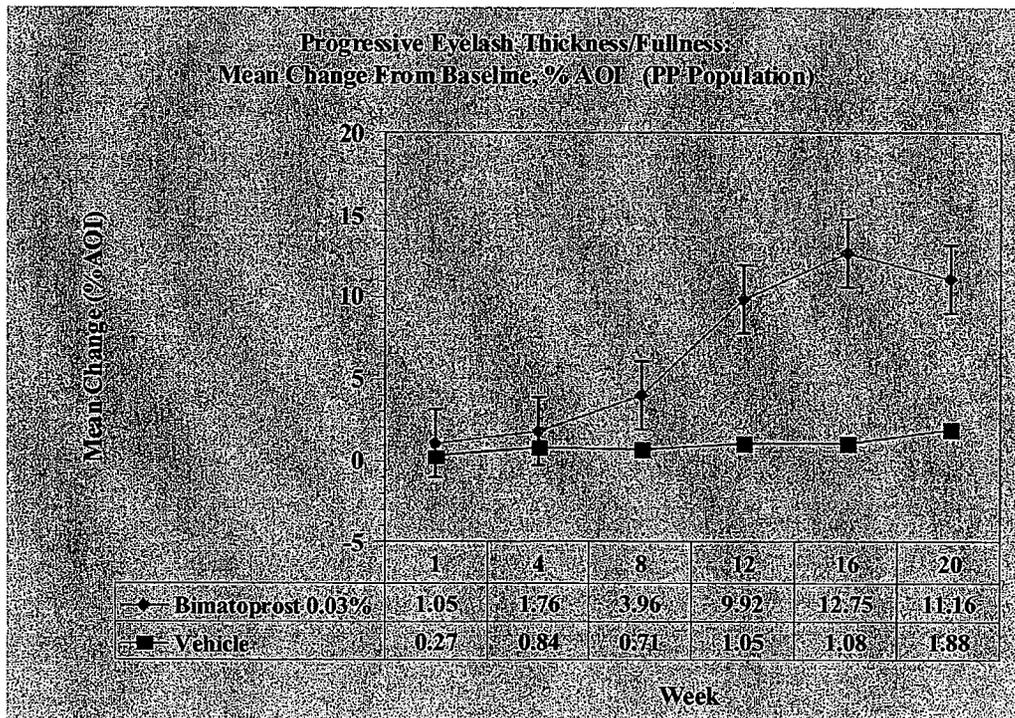
**Reviewer's Comment:**

*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  $p < 0.0001$ .*

**Progressive Eyelash Thickness/Fullness**

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).

**Chart 6.1.5-2**



**Reviewer's Comment:**

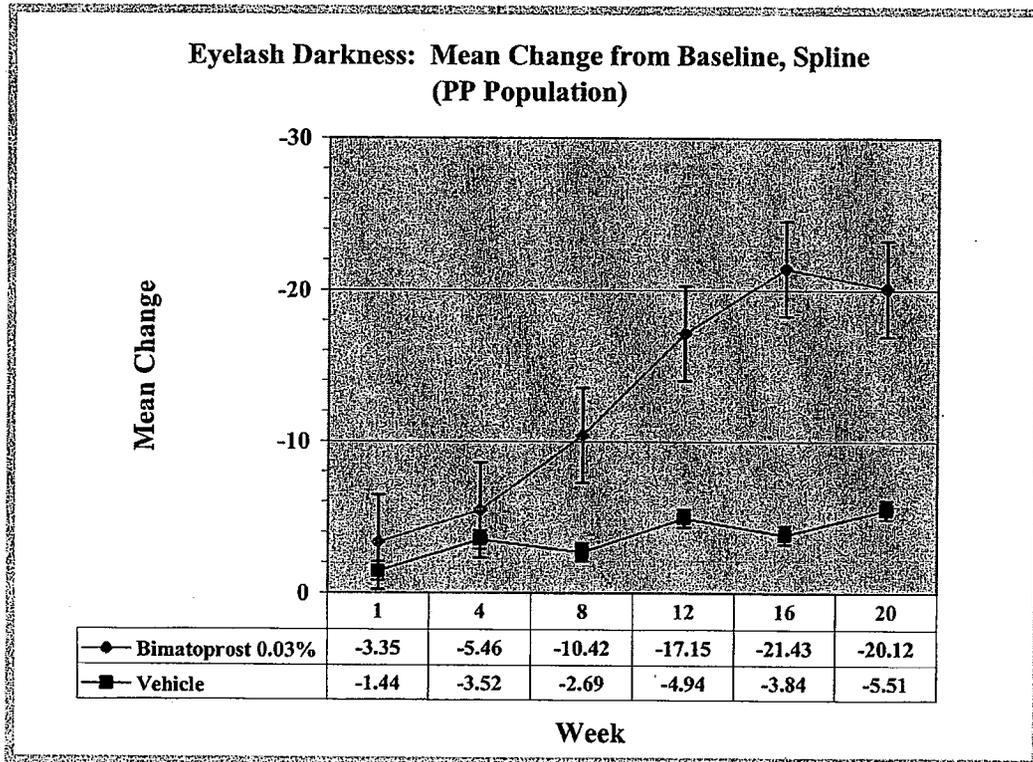
*At the week 16 endpoint, the bimatoprost and vehicle groups had experienced mean increases in progressive eyelash thickness/fullness of 11.16 mm and 1.88 mm, respectively. This difference was statistically significant with  $p < 0.0001$ . These increases correspond to a percentage change from baseline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

**Overall Eyelash Darkness/Intensity**

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.

**Chart 6.1.5-3**



**Reviewer’s Comment:**

*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 ( $p < 0.0001$ ).*

#### 6.1.6 Other Endpoints

There were no additional endpoints tested.

#### 6.1.7 Subpopulations

Subpopulation analyses were not performed.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

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.

## 6.1.10 Additional Efficacy Issues/Analyses

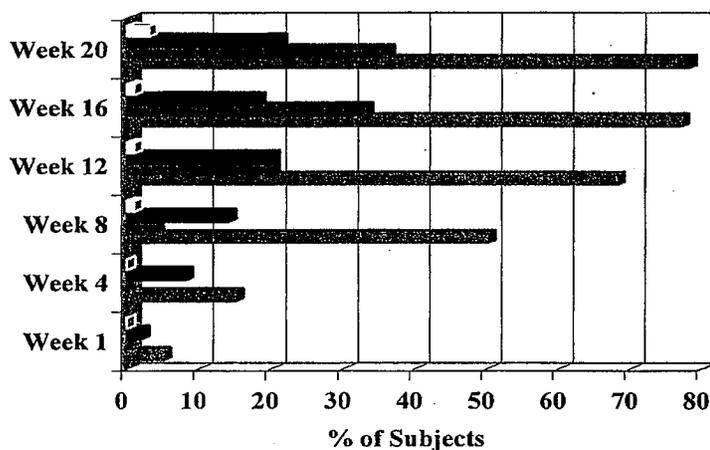
### 6.1.10.1 Sensitivity Analyses

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**

**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

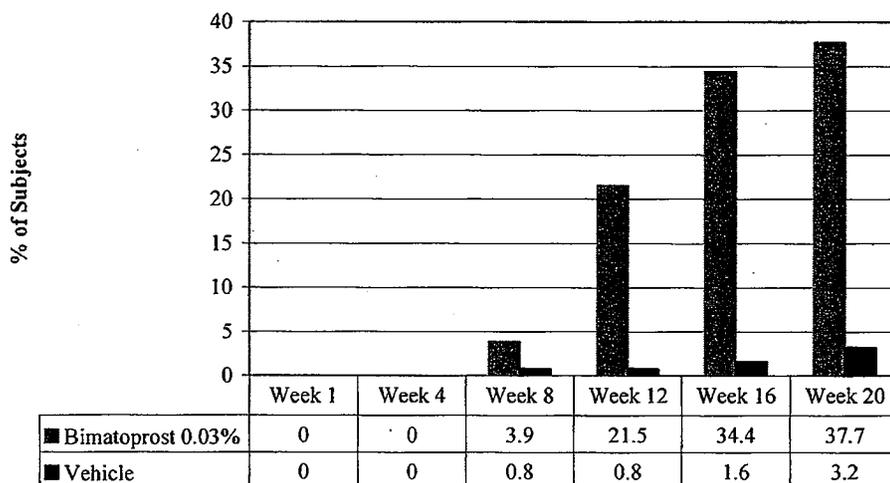
**Reviewer's Comment:**

*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 ( $p < 0.0001$ ).

**Chart 6.1.10.1-2**

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



**Reviewer’s Comment:**

*An analysis of the 2-grade change from baseline in GEA score using the PP population did not result in any meaningful differences compared with the original analysis using the ITT population.*

**6.1.10.2 Health Outcomes Analyses**

Four Patient Reported Outcome (PRO) questionnaires were collected during this study. The vast majority of results from all 4 PRO questionnaires were highly statistically significant favoring bimatoprost over vehicle following 12 weeks of treatment.

**Reviewer’s Comment:**

*The submitted Patient Reported Outcome (PRO) questionnaires have been internally validated. To ensure that the submitted validation information meets the Agency’s requirements for internal and external validation, an evaluation by the Study Endpoints and Labeling Division (SEALD) team will be necessary. A decision regarding PRO outcome labeling claims will be made after the SEALD team review is complete.*

Questionnaire 1 was collected at every study visit, was a static measure of satisfaction with regard to subjects' eyelashes and the study treatment.

**Table 6.1.10.2-1**  
**Statistical Significance of Results from Patient Reported Outcomes Questionnaire 1**  
**(ITT Population)**

Item Number	Measure	Time Period Significant (Favoring Bimatoprost)	P-value <sup>a</sup>
1	Satisfaction with length of eyelashes <sup>b</sup>	Weeks 8 to 20	≤ 0.0433
2	Satisfaction with fullness/thickness of eyelashes <sup>b</sup>	Weeks 12 to 20	< 0.0001
3	Satisfaction with darkness of eyelashes <sup>b</sup>	Weeks 12 to 20	≤ 0.0002
4	Satisfaction with eyelashes, overall <sup>b</sup>	Weeks 8 to 20	≤ 0.0063
5	Frequency of compliments from others about eyelashes <sup>c</sup>	Weeks 8 to 20	≤ 0.0206
6	Eyelash length rating <sup>b</sup>	Weeks 8 to 20	≤ 0.0433
7	Eyelash fullness/thickness rating <sup>b</sup>	Weeks 8 to 20	≤ 0.0064
8	Eyelash color rating <sup>b</sup>	Weeks 1, 4, 12 to 20	≤ 0.0439
9	Amount of time spent applying mascara is bothersome <sup>d</sup>	Weeks 8 to 20	≤ 0.0038
10	Amount of time spent removing mascara is bothersome <sup>d</sup>	Weeks 12 to 20	≤ 0.0125
11	Hassle to spend time making eyelashes presentable <sup>d</sup>	Weeks 12 to 20	≤ 0.0125
12	Able to go out in public without mascara <sup>d</sup>	Weeks 8 to 20	≤ 0.0429
13	Worry about mascara smearing <sup>d</sup>	Weeks 16 to 20	≤ 0.0316
14	Without mascara, eyes look tired <sup>c</sup>	Weeks 12 to 20	≤ 0.0189
15	Without mascara, eyelashes look naturally attractive <sup>c</sup>	Weeks 12 to 20	< 0.0001
16	Without mascara, feel confident <sup>c</sup>	Weeks 12 to 20	≤ 0.0020
17	Without mascara, feel confident going out in public	Weeks 12 to 20	≤ 0.0078
18	Without mascara, feel confident about professional appearance <sup>c</sup>	Weeks 12 to 20	≤ 0.0053
19	Without mascara, feel attractive <sup>c</sup>	Weeks 12 to 20	≤ 0.0125
20	Without mascara, eyelashes look healthy <sup>c</sup>	Weeks 8 to 20	≤ 0.0399
21	Without mascara, eyes look vibrant <sup>c</sup>	Weeks 12 to 20	≤ 0.0014
22	Without mascara, eyelashes look full <sup>b</sup>	Weeks 12 to 20	< 0.0002
23	Without mascara, feel beautiful <sup>c</sup>	Weeks 12 to 20	≤ 0.0039

Note: Summaries of day 1 through week 16 pertain to the treatment period and week 20 the post-treatment period

Note: LOCF is performed on weeks 1 through 16. Week 20 (post-treatment) analysis is based on observed cases.

a P-values are based on the Wilcoxon rank-sum test.

b Questions 1, 2, 3, 4, 6, 7, 8, and 22 comprised domain 1 (satisfaction with physical attributes of eyelashes)

c Questions 5, 14, 15, 16, 17, 18, 19, 20, 21, and 23 comprised domain 2 (satisfaction with subjective attributes of eyelashes)

d Questions 9, 10, 11, 12, and 13 comprised domain 3 (satisfaction with time spent in daily routine making eyelashes presentable)

**Reviewer's Comment:**

*The submitted Patient Reported Outcome (PRO) questionnaires have been internally validated. To ensure that the submitted validation information meets the Agency's requirements for internal and external validation, an evaluation by the Study Endpoints and Labeling Division (SEALD) team will be necessary. A decision regarding PRO outcome labeling claims will be made after the SEALD team review is complete.*

*Statistically significant differences in patient reported outcomes were maintained through the duration of the treatment and post-treatment periods of the study.*

*In Domain 1 (satisfaction with physical attributes of eyelashes) the bimatoprost group experienced a statistically significantly greater change from baseline compared with the vehicle group in their overall degree of satisfaction at week 1 and weeks 8 through 20.*

*For Domain 2 (satisfaction with eyelashes as they relate to feelings of confidence, professionalism, and attractiveness), the bimatoprost group experienced a statistically significantly greater change from baseline compared with vehicle in the overall degree of satisfaction at weeks 12 through 20.*

*For Domain 3 (satisfaction with the amount of time spent during subjects' daily routine to make their eyelashes presentable), the bimatoprost group experienced a statistically significantly greater change from baseline compared with vehicle in their overall degree of satisfaction, at weeks 16 and 20.*

A statistical analysis was conducted to detect a correlation between the change from baseline in each of the primary and secondary efficacy variables (GEA score and eyelash length, thickness/fullness, and darkness) with the change from baseline in subject satisfaction as measured by three components of PRO questionnaire 1. At week 16, statistically significant correlations were observed for the bimatoprost group between change in subject satisfaction with eyelashes as measured by PRO scores (single item, domain 1, domain 2) and change in each of the primary and secondary efficacy variables ( $p < 0.0001$  for all). That is, improvement in GEA score and increases in eyelash length, fullness, and darkness were associated with increased satisfaction with eyelashes for subjects in the bimatoprost group at week 16. For the vehicle group, the correlations at week 16 were considerably weaker than those for bimatoprost and, with few exceptions; the correlations were not statistically significant.

### 6.1.10.3 Validation Study for Global Eyelash Assessment Scale

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, the following study was conducted.

#### Study 192024-033: Single-center, Inter-rater and Intra-Rater Reliability of the Global Eyelash Assessment (GEA) Scale With Photonumeric Guide or Assessment of Overall Eyelash Prominence

Objective: To evaluate the inter- and intra-rater reliability of the Global Eyelash (GEA) Scale with photonumeric guide.

#### Overall Study Design

This was a single-center study designed 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 two different time points) reliability of the GEA scale with photonumeric guide to assess overall eyelash prominence. The GEA consists of 4 categories for assessment of overall eyelash prominence (1=minimal, 2=moderate, 3=marked, 4=very marked). At the screening visit, the subject's GEA score was assessed by a designated screening rater (i.e., the principal investigator) in order to insure inclusion of an appropriate representation of each of the four GEA categories within the population under evaluation. The designated screening rater did not rate subjects on day 1. In addition, each subject completed a patient-reported outcomes questionnaire at the screening visit. On day 1, each subject completed the patient-reported outcomes questionnaire again and was evaluated twice by seven raters. Raters determined the GEA scores using the GEA scale with photonumeric guide. On the same day, raters evaluated each subject two times at least one hour apart. Photographs of subject's eyelashes were taken (two views; frontal and superior) after the second GEA evaluation.

The clinical hypothesis for this study was the GEA scale with photonumeric guide is a reliable method for determining overall eyelash prominence as determined by inter- and intra-rater reliability.

Because this study was designed solely to evaluate the GEA scale with photonumeric guide, no investigational study drug was administered in this study.

#### Selection of Study Population

##### Inclusion Criteria

The following requirements for entry into the study:

1. Men or women at least 18 years of age
2. Able and willing to remove all eye makeup and facial jewelry at each visit.
3. Written informed consent and written authorization for use or release of health and research study information obtained

4. Ability to follow study instructions and willingness to complete all required study visits and procedures, including protocol-specified photography

**Exclusion Criteria**

The following were criteria for exclusion from participation in the study:

1. Subjects with permanent eye makeup or eyelash implants of any kind
2. Infection or disorder at the evaluation site that would prevent adequate assessment of eyelashes
3. Any eyelash tint or dye applications within 2 months prior to study entry
4. Any eyelash extension application within 3 months prior to study entry
5. Any planned facial cosmetic procedure that would interfere with the evaluation of eyelashes between the screening visit and the day 1 visit
6. Concurrent participation in another investigational drug or device study or participation in the 30 days immediately prior to study enrollment
7. Any condition or situation that in the investigator's opinion may put the subject at significant risk, confound the study results, or interfere significantly with the subject's participation in the study.

**Efficacy and Safety Variables**

**Response Measure**

One response measure was evaluated in this study: overall eyelash prominence as assessed by the GEA scale with photonic numeric 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.

**Safety Measures**

Medical events were collected from the screening visit through the completion of the day 1 visit. Since investigational study drug was not administered in this study, collection of adverse events was not applicable. In addition, evaluation of laboratory variables, vital signs, physical examinations, and other safety measures were not performed.

**Table 6.1.10.3-1 Schedule of Study Assessments**

	Screening (Day -21 to -1)	Day 1	
		Evaluation 1	Evaluation 2
Informed consent and medical history	X		
Removal of all eye makeup (at least 15 minutes prior to evaluation)	X	X	
GEA evaluation	X <sup>a</sup>	X	X
Standardized eyelash photography			X <sup>b</sup>
Patient reported outcomes questionnaire	X	X	
Medical events	X	X	X

a Conducted by an independent, designated screening rater who did not rate subjects on day 1

b Photographs taken after second GEA evaluation

## Statistical Methods

### Intra-Rater Reliability

Intra-rater agreement of the respective photonic guide for GEA was evaluated by weighted and unweighted Kappa statistics. For intra-rater agreement, unweighted and weighted Kappa statistics were calculated for each rater assessment agreement between the 2 measurements (i.e., evaluation 1 and evaluation 2). Overall intra-rater for both unweighted and weighted Kappa statistics for all raters combined in the study were estimated by using chi-square statistic. The hypothesis test was that the g underlining values (Kappa values for all the raters) were equal. Kappa statistics, along with the corresponding p-value and 2-sided 95% confidence interval, were computed and presented for each of the 7 raters and for overall. For the 95% confidence intervals, the normal approximation was used.

### Inter-rater Reliability

Inter-rater agreement of the respective photonic guide for the GEA was evaluated using Kendall's coefficient of concordance (W). Kendall's coefficient evaluates the degree of agreement among the 7 raters in rating eyelashes using the GEA scale along with the photoguide. Kendall's coefficient statistic along with the corresponding p-value and 2-sided 95% confidence interval were computed and presented for evaluation 1 and evaluation 2 on the day 1 visit and for overall. The overall statistic was based on the average of the scores of evaluations 1 and 2 rounded up to the nearest whole integer.

### Summary

Of the 79 subjects screened and assessed, 68 subjects were enrolled into the study, each of which completed this study. Ninety percent of the subjects were women, and the mean (SD) age was 40.6 (11.76) years (range: 19 to 64 years). Seventy-eight percent of subjects were Caucasian, 16% were Asian, 3% were Hispanic and 3% were of other races.

### Efficacy:

The GEA scores were approximately evenly distributed amongst the subjects participating in the study as prospectively defined in the protocol. The mean (SD) GEA score 2.4 (1.10) and the median was 2.0.

### *Intra-rater Results*

The intra-rater reliability was deemed to be "moderate" for one of the raters. The overall weighted Kappa statistic was 0.772, which is considered to be "substantial" agreement. Although the overall unweighted Kappa statistic (0.674) was less than the weighted Kappa statistic, the degree of agreement was still considered to be "substantial." 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.

Sponsor's Conclusion:

Using the GEA scale with photonic 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." In other words, in grading overall eyelash prominence on subjects using the GEA scale with the photonic guide, on average, there would be an "almost perfect" agreement amongst the rater's scores. Therefore, the GEA scale with photonic guide can be considered to be a reliable instrument in grading overall eyelash prominence.

**Reviewer's Comment:**

*The results of this validation study demonstrate that the GEA scale was an acceptable measure of eyelash appearance among the raters tested.*

## 7 Review of Safety

### Safety Summary

#### 7.1 Methods

##### 7.1.1 Clinical Studies Used to Evaluate Safety

In addition to the current clinical development program for eyelash growth, exposure data have been collected for bimatoprost solution 0.03%, the two phase 3 trials of bimatoprost 0.03%/timolol 0.5% ophthalmic solution, a phase 4 Lumigan marketing study, the published literature, and an investigator-sponsored proof-of-concept study in which subjects applied bimatoprost to their upper eyelid margins.

**Table 7.1.1-1 Exposure to Bimatoprost in Key Studies of IOP Reduction and Eyelash Growth**

Study	Number of Patients/Subjects (Bimatoprost Group)	Duration of treatment	Comparator(s)
<b>Phase 3 Studies of Lumigan (bimatoprost ophthalmic solution) 0.03%</b>			
192024-008	240 (bimatoprost QD) 240 (bimatoprost BID)	12 months	Timolol
192024-009	234 (bimatoprost QD) 243 (bimatoprost BID)	12 months	Timolol
<b>Phase 3 Studies of bimatoprost 0.03%/timolol 0.5% ophthalmic solution</b>			
192024-018T <sup>a</sup>	261 (bimatoprost plus timolol) 129 (bimatoprost alone)	12 months	Timolol alone
192024-021T <sup>a</sup>	272 (bimatoprost plus timolol) 136 (bimatoprost alone)	12 months	Timolol alone
<b>Studies of Lumigan in the Published Literature</b>			
Noecker, et al (2003)	133	6 months	Latanoprost plus timolol
Manni et al (2004)	28	6 months	Latanoprost
<b>Phase 4 Marketing Study of Lumigan</b>			
MA-LUMO1 <sup>b</sup>	131	3 months	Travoprost
<b>Studies of Bimatoprost for Eyelash Growth</b>			
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

### 7.1.2 Adequacy of Data

**Reviewer's Comment:**

*Bimatoprost, alone or in combination, has been evaluated in over 1500 patients for over one year when applied directly to the eye. This route of administration is considered a worst case for applications to the eyelid.*

*The safety and exposure database for the clinical development of bimatoprost ophthalmic solution 0.03% is adequate.*

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The median duration of treatment exposure was comparable between the two treatment groups: 113 days for the bimatoprost group and 112 days for the vehicle group. The majority of subjects in each treatment group were exposed to treatment for at least 16 weeks (73% [bimatoprost] and 59.6% [vehicle]). During the treatment periods, study treatment was applied topically to the upper eyelid margins once a day using a single-use-per-eye applicator.

### 7.2.2 Explorations for Dose Response

Studies to evaluate dose response in this indication were not conducted.

### 7.2.3 Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology review for details.

### 7.2.4 Routine Clinical Testing

Routine clinical testing and monitoring of study subject was adequate to elicit adverse events.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance and interaction were not performed due to the negligible systemic absorption of bimatoprost given by the intravitreal route of administration.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The routine clinical assessments, testing and monitoring of study subjects was adequate to elicit potential adverse events for similar drugs in the drug class.

### 7.3 Major Safety Results

The major safety results for Study 192024-032 are presented.

#### 7.3.1 Deaths

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

#### 7.3.2 Nonfatal Serious Adverse Events

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.

#### **Reviewer's Comment:**

*The nonfatal serious adverse events were not related to the study treatment, bimatoprost ophthalmic solution 0.03%.*

#### 7.3.3 Dropouts and/or Discontinuations

Four subjects in each treatment group discontinued the study 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.

### 7.3.4 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)**

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.

**Reviewer's Comment:**

*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. This finding is consistent with the safety profile of Lumigan (bimatoprost ophthalmic solution) 0.03%.*

*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). Two of these adverse events were ongoing as of March 2008.*

### 7.3.5 Submission Specific Primary Safety Concerns

The possibility of iris color change which has been reported with topical administration of bimatoprost ophthalmic solution 0.03% to the eye was investigated. No cases of iris color change were noted or reported during the clinical development of bimatoprost ophthalmic solution 0.03% for this indication.

## 7.4 Supportive Safety Results

### 7.4.1 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)**

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.

#### **Reviewer's Comment:**

*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. This finding is consistent with the safety profile of Lumigan (bimatoprost ophthalmic solution) 0.03%.*

#### 7.4.2 Laboratory Findings

Laboratory testing was not performed during the development program.

#### 7.4.3 Vital Signs

Vital signs were not assessed during the development program.

#### 7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed during the development program.

#### 7.4.5 Special Safety Studies

No special safety studies were performed.

#### 7.4.6 Immunogenicity

There have been no bimatoprost clinical studies performed and no post-marketing data suggests immunogenic potential.

### **7.5 Other Safety Explorations**

#### 7.5.1 Dose Dependency for Adverse Events

Studies to evaluate dose dependency in the occurrence of adverse events were not performed.

#### 7.5.2 Time Dependency for Adverse Events

Studies to evaluate time dependency in the occurrence of adverse events were not performed.

#### 7.5.3 Drug-Demographic Interactions

No studies investigating drug-demographic interactions were conducted.

#### 7.5.4 Drug-Disease Interactions

No studies of drug-disease interactions were conducted.

#### 7.5.5 Drug-Drug Interactions

No studies of drug-drug interactions were conducted.

## 7.6 Additional Safety Explorations

### 7.6.1 Human Carcinogenicity

There have been no bimatoprost clinical studies performed and no post-marketing data suggests tumorigenic potential.

### 7.6.2 Human Reproduction and Pregnancy Data

There have been no clinical studies in human reproduction or pregnancy performed. No clinical study or post-marketing data suggest an effect on human reproduction or pregnancy.

### 7.6.3 Pediatrics and Effect on Growth

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 \_\_\_\_\_ with Latisse (bimatoprost ophthalmic solution) 0.03% in \_\_\_\_\_ pediatric subjects less than 18 years of age with hypotrichosis \_\_\_\_\_

e.

b(4)

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

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence for the potential for overdose or potential for abuse with bimatoprost.

## 7.7 Additional Submissions

The Safety Update was submitted on October 24, 2008. Per Allergan:

There are no additional safety data from this study and Allergan is not conducting any other clinical studies at this time related to the proposed indication for this NDA with Latisse (bimatoprost ophthalmic solution) 0.03%.

## 8 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 as Lumigan (bimatoprost ophthalmic solution) 0.03% is presented here. 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

### Reviewer's Comment:

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

## 9 Appendices

### 9.1 Literature Review/References

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

## 9.2 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

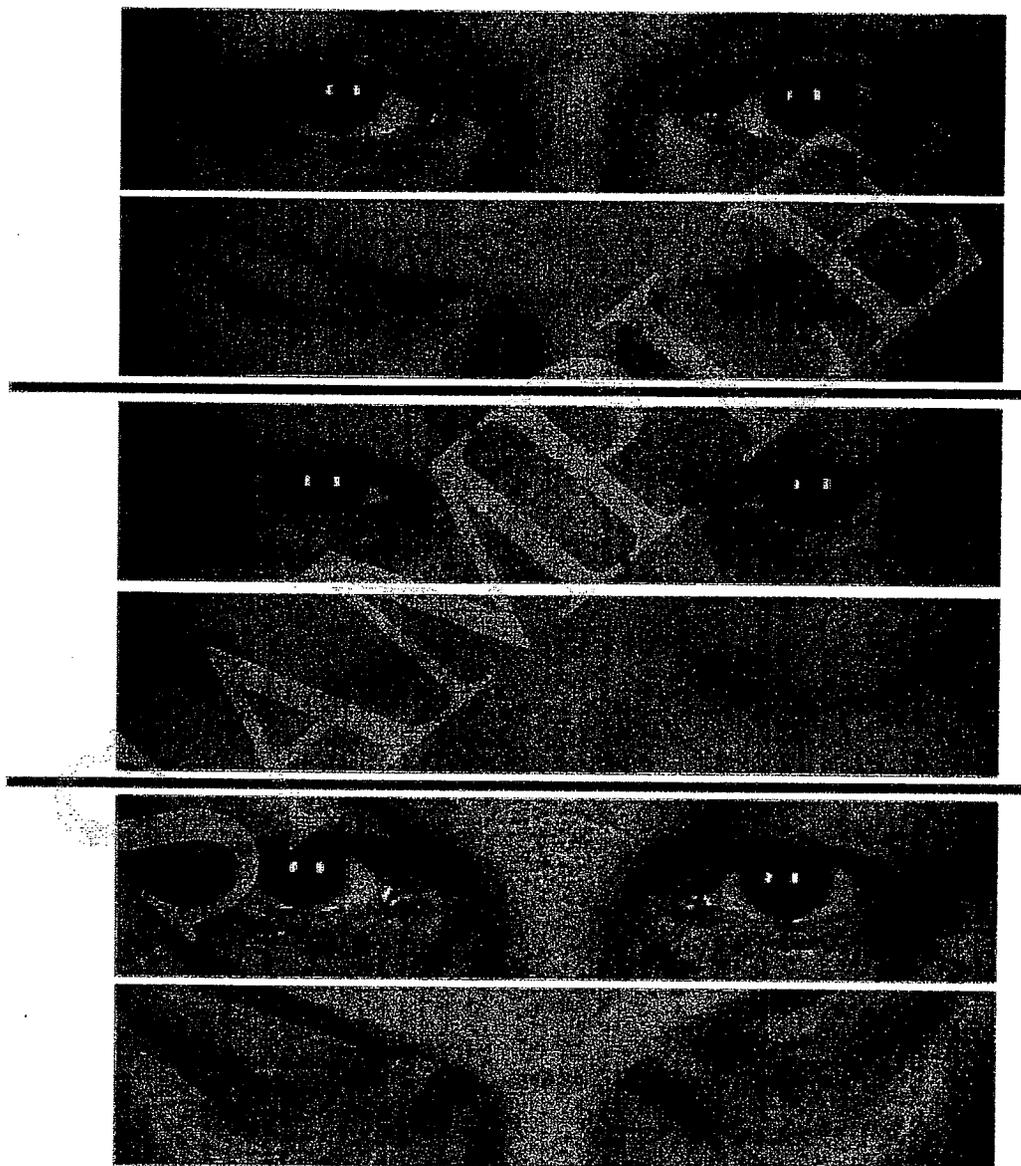
**4. Do you have any suggestions concerning the labeling of the product?**

After discussion, the committee 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

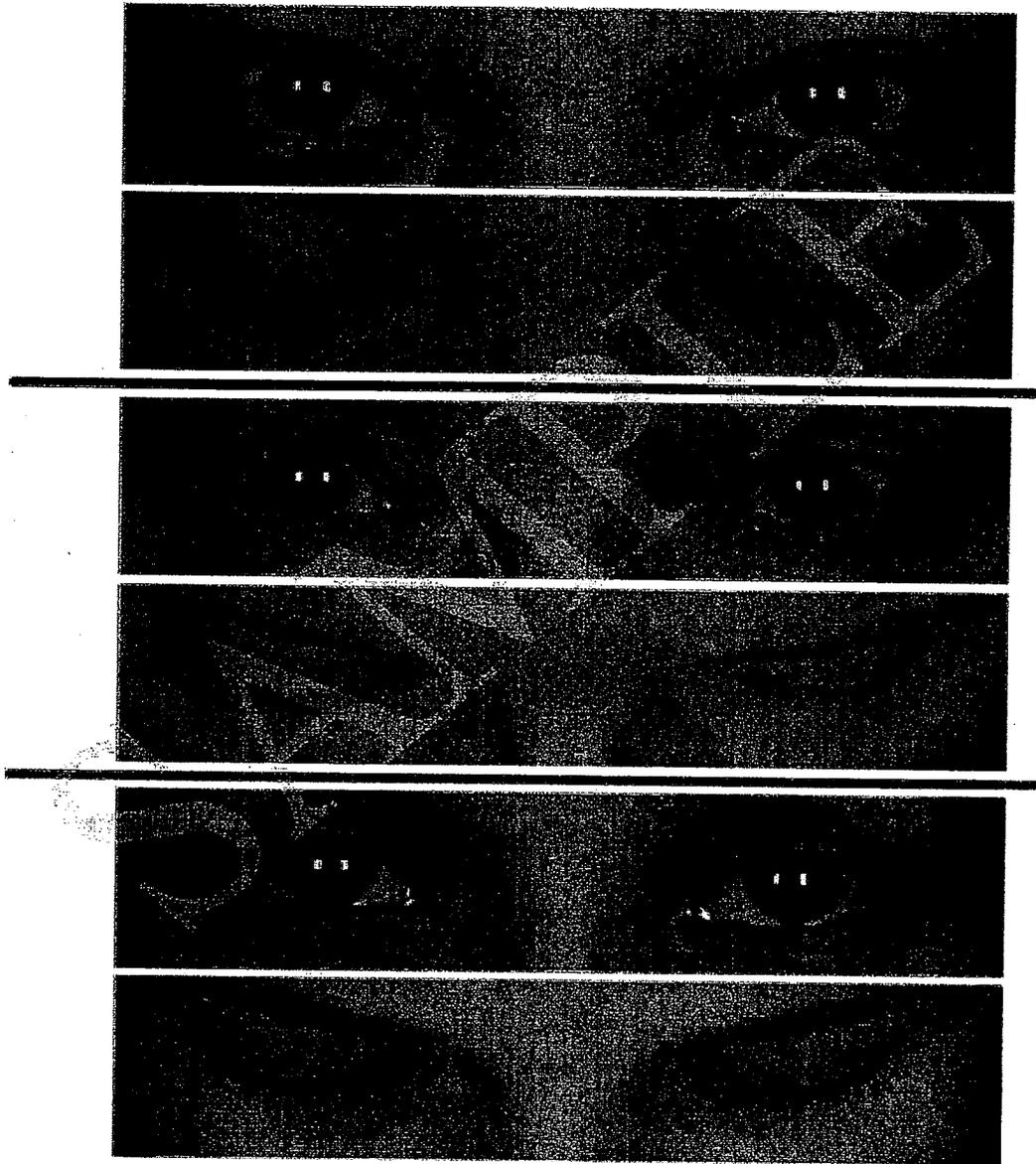
### 9.3 Global Eyelash Assessment Photonumeric Guide

 **Global Eyelash  
Assessment Photonumeric Guide  
Grade 1**



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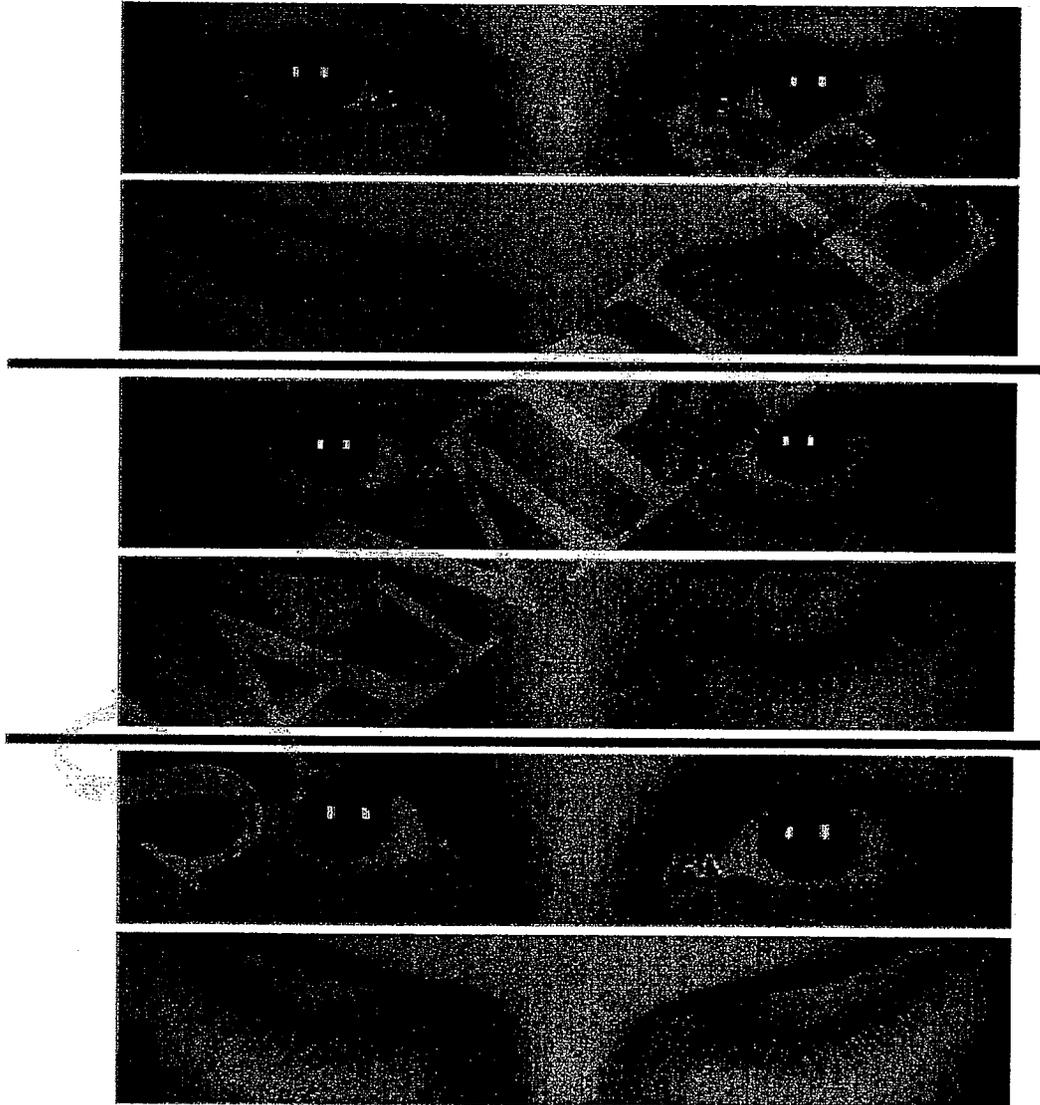
 **Global Eyelash  
Assessment Photonumeric Guide  
Grade 2**



Clinical Review  
Rhea A. Lloyd, MD  
NDA 22-369, Original  
Latisse (bimatoprost ophthalmic solution 0.03%)

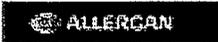
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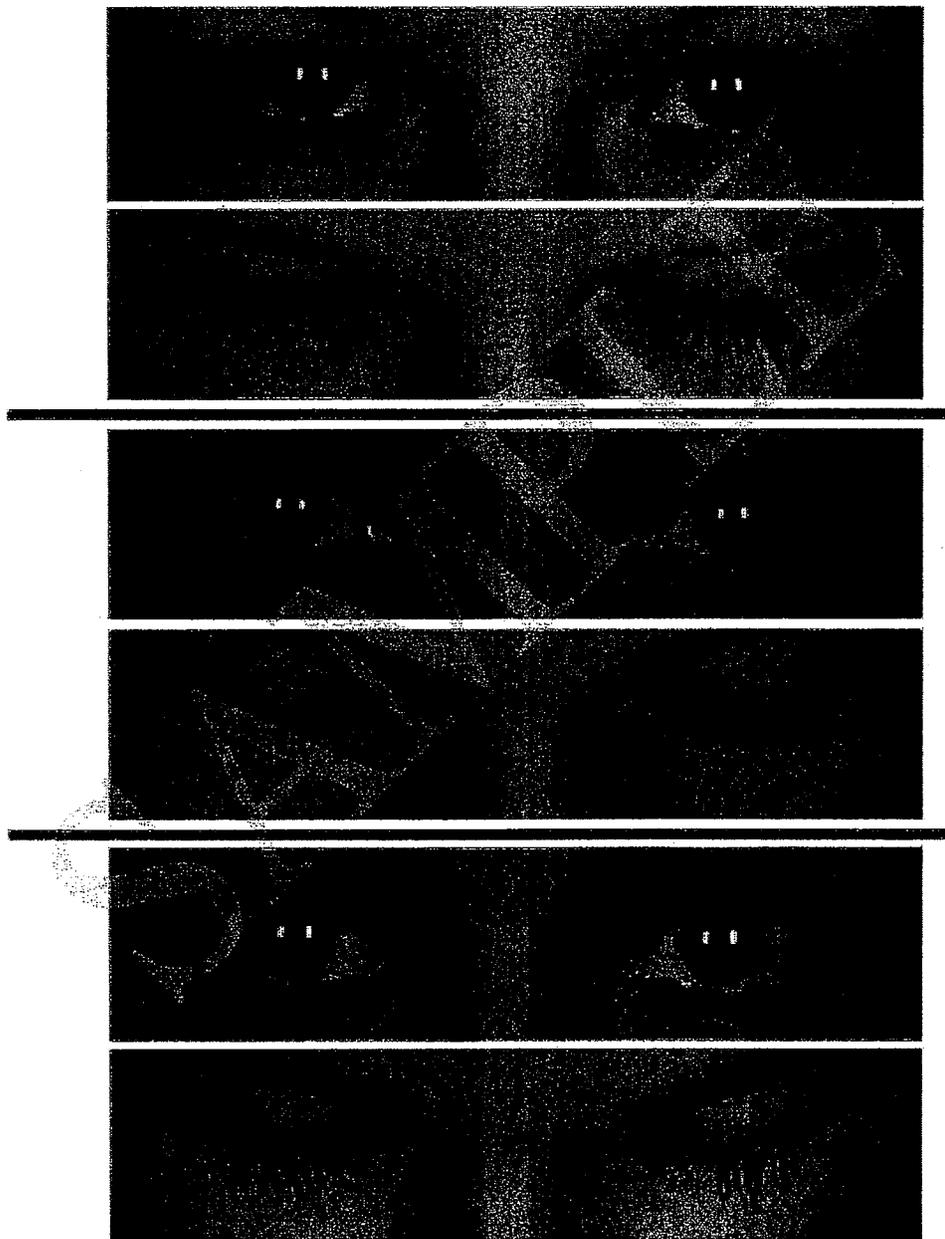
 **Global Eyelash  
Assessment Photonumeric Guide  
Grade 3**



Clinical Review  
Rhea A. Lloyd, MD  
NDA 22-369, Original  
Latisse (bimatoprost ophthalmic solution 0.03%)

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 **Global Eyelash  
Assessment Photonumeric Guide  
Grade 4**



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Rhea Lloyd  
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William Boyd  
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MEDICAL OFFICER