Dermatologic and Ophthalmic Drugs Advisory Committee Briefing Document

Title:	Bimatoprost Solution 0.03% for the Improvement of Natural Eyelash Prominence
NDA Number:	22-369
Product Name:	Bimatoprost solution 0.03%
Drug Substance:	Bimatoprost
Indication:	To improve the prominence of natural eyelashes as measured by increases in growth (length), fullness (thickness), and darkness (intensity)
Sponsor:	Allergan, Inc. 2525 Dupont Drive Irvine, California 92623-9534 Telephone (714) 246-4500
Meeting Date:	December 5, 2008

ADVISORY COMMITTEE BRIEFING MATERIALS:
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1. Executive Summary

Bimatoprost solution 0.03% has been shown to be safe and effective for the following proposed indication:

> Bimatoprost solution 0.03% is indicated to improve the prominence of natural eyelashes as measured by increases in growth (length), fullness (thickness), and darkness (intensity).

The proposed dosing regimen is one application nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying sterile single-use-per-eye disposable applicators. The proposed packaging and instructions for use are included in Appendix 9.1.

Introduction

Bimatoprost is a synthetic prostaglandin $F_{2\alpha}$ analog, developed by Allergan, Inc. and widely used as an ophthalmic preparation (bimatoprost ophthalmic solution 0.03%) for the treatment of ocular hypertension and open-angle glaucoma. Initial approval of bimatoprost ophthalmic solution 0.03% in this indication came from the United States Food and Drug Administration (FDA) in March 2001 and it is currently approved for the treatment of elevated intraocular pressure (IOP) in more than 80 countries worldwide, with approximately 9 million patient-years of exposure worldwide. Initially in clinical studies and later in broad scale use, it became apparent that bimatoprost increases the growth of eyelashes. Based on this observation and after amassing a large safety database on bimatoprost, Allergan developed a clinical program in consultation with the FDA to prospectively assess in a controlled manner the safety and efficacy of bimatoprost solution 0.03% for the improvement of eyelash prominence, length, thickness, and darkness in a healthy adult population.

Since this is an aesthetic indication, Allergan's development program was focused on safety. While it was clear that, through contact with eyelids and eyelashes, bimatoprost administered as an eyedrop increased eyelash growth, the intent of the development program for the new, aesthetic indication was to minimize drug exposure and enhance the tolerability of the drug to the extent possible to achieve the desired efficacy outcome.

Bimatoprost for eyelash growth (bimatoprost solution 0.03%) (referred to in this document as BEG) and bimatoprost for the treatment of glaucoma (bimatoprost ophthalmic solution 0.03%, marketed as LUMIGAN®) contain the same active product ingredient, in the same

formulation (sterile sodium chloride solution in purified water preserved with benzalkonium chloride), at the same concentration (0.03%). Both are applied topically; directly to the eye(s) for the treatment of glaucoma and directly to the upper eyelid margins using a sterile, single-use-per-eye applicator for eyelash growth. Application to the upper eyelid margin via the applicator for eyelash growth delivers approximately 5% of the volume of the drop administered for the treatment of glaucoma.

The safety of bimatoprost is well established, with a large clinical safety database as well as 7 years of postmarketing pharmacovigilance data. Since the proposed product BEG contains the same active product ingredient, at the same concentration and formulation as bimatoprost for the treatment of glaucoma, and since both are topically applied, the clinical development program for the treatment of glaucoma provides important support for the safety and efficacy of the new drug application (NDA) currently under review.

In the clinical development of bimatoprost, 5848 patients and healthy volunteers participated in 33 clinical studies spanning 13 years, including 6 long-term studies (≥1 year duration) involving 1,409 patients. Clinical studies have included both once daily (QD) and twice daily (BID) dosing regimens. The clinical program for bimatoprost for the treatment of glaucoma includes 2 pivotal phase 3 studies, in which eyelash growth was spontaneously reported as an adverse event. Growth of eyelashes was reported by 36.3% and 49.1% of patients treated once daily with bimatoprost ophthalmic solution 0.03% for 1 year (192024-008 and -009, respectively), rates that were statistically significantly higher than those reported by the active comparator (timolol) group (4.9% and 5.0% for 192024-008 and -009, respectively; $p < 0.001$). Indeed, this effect on eyelashes has been formally acknowledged in the LUMIGAN® package insert (Appendix 9.2), indicating that bimatoprost may gradually change eyelashes with regard to increased length, thickness, pigmentation, and number of eyelashes. Similarly, the postmarketing safety experience in 9 million patient-years of exposure with bimatoprost the treatment of glaucoma is directly relevant to the eyelash growth indication and indicates that the postmarketing safety profile is similar to that observed in the clinical studies.

Clinical Development Program

Based on the observation of a market need for safe and effective products for enhancing eyelash length, thickness and pigmentation, and once a large safety database had been amassed, Allergan embarked on a clinical development program for an indication of eyelash growth. The clinical development program was guided by discussion with FDA after

numerous clinical studies and years of postmarketing experience demonstrated a well-characterized and acceptable safety profile.

Allergan first considered obtaining an indication for eyelash growth with bimatoprost topically applied to the eye. However, to better target drug delivery, direct application of the drug to the base of the upper eyelid margins using a single-use-per-eye applicator was utilized. An open-label, investigator-sponsored clinical study demonstrated both efficacy and optimized safety with direct application of the reduced amount of bimatoprost to the base of the eyelashes. The efficacy of bimatoprost in growing eyelashes was demonstrated in both phase 3 clinical studies of bimatoprost for the treatment of glaucoma. Based upon review of the extensive safety database for bimatoprost for the treatment of glaucoma, including 2 pivotal studies and additional clinical data as well as postmarketing surveillance and the data from the open label study, FDA requested 1 additional pivotal confirmatory study prospectively assessing the safety and efficacy of bimatoprost for the indication of eyelash growth and stated that this would be sufficient to support the filing of an NDA for bimatoprost solution 0.03% for eyelash growth.

The NDA for bimatoprost for the treatment of glaucoma was comprised of 9 phase 1 and 2 studies and 2 pivotal phase 3 studies conducted over a period of 5 years, including 1219 patient exposures to bimatoprost.

Since its approval by FDA in March 2001 and subsequent approval in over 80 additional countries, it is estimated that bimatoprost ophthalmic solution 0.03% has 9 million patient-years of exposure worldwide with 5 million patient-years of exposure in the United States (Allergan Pharmacovigilance, 2008; data on file). The adverse events are predictable, dose-related, and, with the possible exception of iris hyperpigmentation, reversible upon discontinuation. The clinical data along with the postmarketing surveillance data demonstrate bimatoprost 0.03% has a good safety profile when applied daily as a topical ophthalmic solution.

In addition to the extensive database supporting the safety of bimatoprost 0.03%, the clinical development program for bimatoprost for eyelash growth (BEG) includes 3 additional clinical studies: an open-label investigator-initiated study, a study (192024-033) to test the reliability and reproducibility of a scale created by Allergan to evaluate global eyelash prominence (PRO measures and digital image analysis methodology for the assessment of length, thickness, and darkness were also refined during this study), and a study (192024-032, the pivotal phase 3 study) to assess the safety and efficacy of bimatoprost solution

0.03% applied topically to the upper eyelid margins for the enhancement of eyelash growth. An investigator-initiated, open-label, proof-of-concept study preceded these studies. This study provided evidence of effectiveness for eyelash growth when bimatoprost ophthalmic solution 0.03% was applied topically with an applicator to the upper eyelid margins of healthy adults, a much lower exposure compared to the instillation of a drop of bimatoprost directly into the eye for the treatment of glaucoma. Throughout the development program, patient reported outcome (PRO) measures were developed, refined, and validated; these measures were also collected in Study 192024-032.

The phase 3 study 192024-032 evaluated the safety and efficacy of bimatoprost solution 0.03% compared with vehicle in increasing overall eyelash prominence (primary endpoint), length, thickness, and darkness (secondary endpoints), as well as PRO measures following once-daily topical administration to the upper eyelid margins using a single-use-per-eye disposable brush. The study consisted of a 16-week treatment period followed by a 4-week posttreatment follow-up period.

Safety Results

The safety of bimatoprost solution 0.03% has been well characterized. Adverse events reported during the pivotal BEG study were similar to those reported during the clinical development program for the treatment of glaucoma and were largely localized to the treatment area. It is clear that when bimatoprost is instilled as an eyedrop, it bathes the eyelid margin and eyelashes, and this exposure yields a side effect of eyelash growth. The amount of bimatoprost solution 0.03% delivered to the upper eyelid margin skin with the applicator was, on average, approximately 5% of that delivered by the indicated 1-drop dose for the treatment of glaucoma (Allergan Technical Memo PD M 08 111). As would be expected with the considerably lower drug exposure and application solely to the upper eyelid margins used in BEG (compared with the direct instillation of eye drops in the bimatoprost studies for the treatment of glaucoma), the observed adverse events with BEG were milder in severity, had a much lower rate of occurrence, and resulted in a low rate of discontinuation from the study equal to that of the vehicle.

The adverse events that were most commonly reported by subjects in the bimatoprost-treated group in the pivotal BEG study were non-serious, cosmetic in nature, reversible with cessation of treatment, and predictable based on the known pharmacology of the drug and the prior clinical and postmarketing experience with bimatoprost for the treatment of glaucoma. Consistent with the lower level of exposure compared with bimatoprost for the treatment of glaucoma, individual adverse events were reported less frequently and were milder in

severity. The following adverse events were observed: eye pruritus (5/137, 3.6%), conjunctival hyperemia (5/137 3.6%), skin hyperpigmentation (4/137, 2.9%), pinguecula (3/137, 2.2%), eye irritation (3/137, 2.2%), dry eye (3/137, 2.2%), and erythema of eyelid (3/137, 2.2%). Only 4 of 137 subjects in the bimatoprost group and 4 of 141 subjects in the vehicle group discontinued from the study due to an adverse event. Conjunctival hyperemia was the only adverse event reported at a statistically significantly higher rate than vehicle (3.6% versus 0.0%, $p = 0.028$); however, the incidence of conjunctival hyperemia after 4-months of treatment in the pivotal BEG study was much lower than that observed in studies of bimatoprost for the treatment of glaucoma, in which bimatoprost was instilled directly into the eye as a topical ophthalmic (38.7% [358/926] to 52.6% [254/483] for QD and BID administration, respectively, after 4 months of treatment in glaucoma studies).

Efficacy Results

Bimatoprost solution 0.03% was found to be highly effective on multiple and concordant measures of efficacy as assessed through a physician global assessment of prominence, a digital analysis of photographs to technologically assess the individual components of prominence (length, thickness, and darkness), and a PRO questionnaire to assess efficacy from the subject's point of view with an emphasis on satisfaction. All of the objectives of the pivotal study were successfully achieved: by the end of the treatment period of the BEG study, bimatoprost-treated subjects experienced greater improvements than vehicle-treated subjects in the measurements of eyelash prominence, length, thickness, and darkness ($p < 0.0001$ for each endpoint) and had statistically significantly greater increases in patient satisfaction on all PRO measures ($p < 0.0439$).

A statistically significantly higher percentage of subjects in the bimatoprost group compared with the vehicle group experienced improvements from baseline to week 16 (end of treatment period) in their overall eyelash prominence (defined as at least a 1-grade increase on the 4-point Global Eyelash Assessment [GEA] scale [Appendix 9.3]), length, thickness, and darkness ($p < 0.0001$ for each endpoint). In addition to the efficacy observed at week 16—defined *a priori* as the primary time point—statistically significant differences between the bimatoprost group and vehicle group were first observed at week 8 for the primary endpoint of eyelash prominence, at week 4 for the secondary endpoint of eyelash length, and at week 8 for the secondary endpoints of eyelash thickness and darkness. For all endpoints, the difference between the 2 groups became progressively more pronounced with continued treatment and was highly statistically significant at all subsequent time points during the treatment period. The effects of improved eyelash prominence, length, thickness,

and darkness continued to be evident to be statistically significant in the bimatoprost group as compared to vehicle through the 1-month posttreatment follow-up period.

In the evaluation of PROs, subjects in the bimatoprost group as compared with the vehicle group had statistically significantly greater increases in patient satisfaction on all PRO measures ($p<0.0001$) and reported a statistically significantly higher level of satisfaction with their eyelashes in terms of the physical attributes of their eyelashes (ie, satisfaction with eyelashes in terms of length, fullness, and overall satisfaction), the subjective attributes of their eyelashes (ie, satisfaction with eyelashes as they relate to feelings of confidence, professionalism, and attractiveness), and the daily routine of making their eyelashes presentable. Bimatoprost-treated subjects who responded to treatment (based on the GEA scale) were more satisfied with their eyelashes than both bimatoprost-treated nonresponders and vehicle-treated subjects, and the PRO results demonstrated concordance with efficacy results in that the greater the improvement on GEA scale or in length of eyelash growth, the greater their satisfaction. These concordant results across multiple measures of eyelash growth (physician, photographic, and patient reported) indicate that the eyelash growth experienced by subjects in the bimatoprost group was statistically and clinically meaningful to subjects.

Conclusions

Bimatoprost solution 0.03%, applied topically to the upper eyelid margins at a substantially lower dose than topical ophthalmic administration, is safe and effective in improving the prominence of natural eyelashes as measured by increases in growth (length), fullness (thickness), and darkness (intensity). It also enhances patients' satisfaction with their eyelashes. If approved, this product will be the first eyelash enhancement product to be developed under FDA guidance and manufactured under good manufacturing practices, safely satisfying a desired aesthetic need in the marketplace. Given the substantial clinical and postmarketing safety data with bimatoprost ophthalmic solution and the positive results from the pivotal study for bimatoprost for eyelash growth, Allergan believes that bimatoprost solution 0.03%, used under physician supervision, can provide patients with clinically meaningful benefits with minimal risk. As a prescription drug product with an approved label and risk minimization plan, prescribers and patients would be assured of the safety and efficacy of BEG, which cannot be similarly confirmed for some over the counter or unapproved eyelash treatments.

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2. Development Rationale

2.1 Regulatory History

Based upon the observation of a market need for safe and effective products for enhancing eyelash growth, Allergan approached FDA to determine an appropriate development program for bimatoprost solution for the indication of enhanced eyelash growth. Based upon review of the extensive safety database for bimatoprost for the treatment of glaucoma, including 2 pivotal studies and additional clinical study data as well as postmarketing surveillance data, FDA requested 1 additional pivotal confirmatory study prospectively assessing the safety and efficacy of bimatoprost for the indication of eyelash growth and stated that this would be sufficient to support the filing of an NDA for bimatoprost solution 0.03% for eyelash growth. FDA also stated that no additional nonclinical studies were required, based on the extensive nonclinical research that had been performed in support of the original LUMIGAN® NDA (eg, carcinogenicity testing, reproductive and developmental toxicity, chronic systemic and ocular toxicology in multiple species) (**Table 10–1**). These nonclinical data for bimatoprost demonstrate that drug exposure is high in the eyelid after topical ophthalmic administration and therefore the safety of topical application of bimatoprost to the upper eyelid margins is strongly supported by the extensive nonclinical and clinical safety testing of bimatoprost.

For the pivotal BEG study, Allergan and FDA agreed that the primary efficacy analysis would be the comparison of the proportion of subjects in the bimatoprost and vehicle groups with at least a 1-grade increase on a static 4-point investigator-rated scale of global eyelash prominence from baseline to week 16 (end of treatment period).

2.2 Background

Bimatoprost is a synthetic prostaglandin $F_{2\alpha}$ analog, which exerts its action by selectively mimicking the effects of naturally occurring prostamides (Woodward et al, 2001). Bimatoprost ophthalmic solution 0.03% (LUMIGAN®) was first approved in the United States in 2001 and is currently approved in over 80 countries worldwide as an ocular hypotensive agent for the treatment of ocular hypertension and open-angle glaucoma. The pharmacological activity of bimatoprost and prostaglandins is well characterized in the literature (Hollo, 2007). The side effect profile of these compounds is related to known mechanisms, such as vasodilation (leading to hyperemia and hair growth) (Chen, 2005) and melanogenesis (leading to darker lashes, eyelid skin pigmentation, and sometimes iris pigmentation changes) (Kapur et al, 2005). These compounds have been consistently

reported to be systemically safe (Hollo, 2007). Most of the side effects are local, mild in severity, and reversible with cessation of treatment.

Increased eyelash growth has been reported as a side effect following the use of all topical ophthalmic prostaglandins, including latanoprost (Xalatan®, Pfizer), travoprost (Travatan®, Alcon), and the prostaglandin $F_{2\alpha}$ analog bimatoprost (LUMIGAN®, Allergan). Bimatoprost, used topically as an ocular hypotensive agent, has been associated with a higher incidence of eyelash growth as a side effect than latanoprost (Manni et al, 2004 and Noecker et al, 2005) and travoprost (Allergan data on file). While the precise molecular pathway remains unknown, bimatoprost-induced eyelash enhancement is believed to occur by 3 mechanisms, as follows: by prolonging the growth phase of the hair cycle resulting in longer length; by stimulating the resting follicles resulting in thicker/fuller lashes; and by increasing melanin synthesis resulting in darker hair pigmentation (Johnstone and Albert, 2002 and Sasaki et al, 2005).

During the clinical development program for glaucoma, eyelash growth was spontaneously reported as an adverse event in patients receiving bimatoprost 0.03% as a topical ophthalmic solution. In the 2 active-control phase 3 pivotal studies of similar design that evaluated bimatoprost in patients with glaucoma, "growth of eyelashes" was reported as an adverse event statistically significantly more frequently in the bimatoprost-treated groups compared with the active comparator (timolol) group ($p < 0.001$) (Table 2–1). Following 3 months of treatment, eyelash growth was reported by a higher proportion of patients treated with bimatoprost ophthalmic solution 0.03% (17.9% and 25.6%) compared with timolol-treated patients (1.6% and 1.7%) (Studies 192024-008 and -009, respectively). The proportion of bimatoprost-treated patients in these studies reporting eyelash growth increased to 31.3% and 40.2% after 6 months (compared to 3.3% and 4.2% in with timolol) and even further after 12 months (36.3% and 49.1% in the bimatoprost groups compared to 4.9% and 5.0% in the timolol groups, respectively for Studies 192024-008 and -009).

Further supporting the bimatoprost's effect on eyelash growth, this drug effect has been formally acknowledged in the LUMIGAN® package insert (Appendix 9.2), indicating that LUMIGAN® may gradually change eyelashes with regard to increased length, thickness, pigmentation, and number of eyelashes. Since the March 2001 US approval of LUMIGAN®, 189 adverse events of "growth of eyelashes" have been reported.

Table 2–1 Number (%) of Patients Reporting Eyelash Growth as an Adverse Event During Clinical Studies of LUMIGAN® (bimatoprost ophthalmic solution) 0.03% (Studies 192024-008 and 192024-009)

	Bimatoprost 0.03% QD	Bimatoprost 0.03% BID	Timolol[a] 0.5% QD	Among Group P-values
Study 008	N = 240	N = 240	N = 122	
3 months	43 (17.9%)	74 (30.8%)	2 (1.6%)	< 0.001
6 months	75 (31.3%)	104 (43.3%)	4 (3.3%)	< 0.001
12 months	87 (36.3%)	120 (50.0%)	6 (4.9%)	< 0.001
Study 009	N = 234	N = 243	N = 119	
3 months	60 (25.6%)	82 (33.7%)	2 (1.7%)	< 0.001
6 months	94 (40.2%)	130 (53.5%)	5 (4.2%)	< 0.001
12 months	115 (49.1%)	139 (57.2%)	6 (5.0%)	< 0.001

QD = once daily; BID = twice daily
a Timolol was the active comparator in clinical studies of Lumigan® (bimatoprost ophthalmic solution) 0.03%.

As shown in Table 2–1, subjects treated twice daily with bimatoprost reported the adverse event of eyelash growth more frequently than subjects who were treated once daily. This trend of higher incidence in the twice-daily treatment group was also observed in rates of overall adverse events and ocular adverse events. As the safety of the patient is of paramount concern, the once-daily administration was chosen for the prospective study evaluating the safety and efficacy of bimatoprost for the indication of eyelash growth. Furthermore, a 4-month treatment period was chosen for the pivotal BEG study because a typical hair growth cycle is 4 to 6 months in duration (Johnstone and Albert, 2002; Elder, 1997), and 4 months was determined to be a sufficient period for an effect on eyelashes to be observed based on an open-label investigator-initiated study of bimatoprost applied topically to the eyelid magin for eyelash growth..

2.3 Product Relevance

The current NDA under review is for a product that is intended to offer a predominantly aesthetic benefit. Nonetheless, aesthetic drug products are widely used and recognized for their ability to positively affect the user's feeling of attractiveness and hence his or her feelings of confidence, self-esteem, and well-being (Pruzinski, 1993). Numerous other drugs are currently FDA-approved for aesthetic benefits only (eg, Rogaine®) and have been used safely and effectively for years.

Focus group research conducted by Allergan indicates that both patients and physicians recognize the importance of attractiveness as it relates to eyes and eyelashes. Specifically, eyes play an important role in social communication and bright, distinct eyes are thought to make a good first impression and reflect personality. Patients stated that their eyelashes, when enhanced with mascara, make them feel more confident, attractive, and polished. On day 1 of the pivotal BEG study, prior to any treatment, subjects answered several PRO questions. Their answers indicated that they were unsatisfied with their eyelashes overall and interested in improving the length, fullness, darkness, and number of their eyelashes. Physicians participating in the focus group discussions, including dermatologists, plastic surgeons, and ophthalmologists, reported that successful cosmetic procedures to enhance eyelashes improve patients' self-confidence and overall sense of well-being. Physicians report a lack of safe and effective aesthetic solutions for eyelash enhancement—with permanent makeup, eyelash weaves, and hair transplants cited as the primary aesthetic medicine options—and a desire for other approaches. The development of a product to safely fill this need has generated strong interest from the dermatologists, plastic surgeons, and ophthalmologists who participated in the focus group discussions (data on file at Allergan).

The indication sought for bimatoprost solution 0.03% is to improve the prominence of natural eyelashes as measured by increases in growth (length), fullness (thickness), and darkness (intensity). While there are currently no FDA-approved eyelash enhancement products, unregulated products do exist in the marketplace. They are often formulated using prostaglandin-analog active ingredients, which have not been evaluated clinically for safety, have not been developed under FDA guidance, and lack FDA-approved patient instructions and guidance. This product, if approved, will be the first FDA-approved eyelash enhancement product to be developed under FDA guidance and would be accompanied by an approved product insert. Allergan will also provide education to physicians and patients on proper use and an ongoing analysis of safety through pharmacovigilance.

3. Summary of Safety

3.1 Extent of Exposure

3.1.1 Patient Exposure to Bimatoprost

In Allergan-sponsored clinical studies of any phase, 5848 patients and healthy volunteers have been exposed to bimatoprost, resulting in approximately 3461 patient-years of exposure (10 patient-years in healthy volunteers and 3451 patient-years in glaucomatous patients) (Table 10–2). Since the initial product launch of LUMIGAN® in 2001, the exposure to bimatoprost has been estimated to be approximately 9 million patient-years worldwide with 5 million patient-years in the United States alone.

3.1.2 Topical Ophthalmic Exposure Versus Topical BEG Exposure to Skin

The total dose of bimatoprost delivered with topical application to the upper eyelid margins for the enhancement of eyelash growth is much lower than the dose of bimatoprost for the treatment of glaucoma. In the use of bimatoprost for the treatmeant of glaucoma, a drop of bimatoprost ophthalmic solution is instilled directly into the eye leading not only to eye exposure but also eyelid skin and eyelash exposure via a bathing of the eyelid margin and eyelashes in the bimatoprost solution.

The BEG applicator was designed to deliver a fraction of a 1-drop bimatoprost dose directly to the target treatment area. With a single BEG application, approximately 5% of the dose for the treatment of glaucoma is delivered to the upper eyelid margin (Allergan Technical Memo PD-M-08-111). The subsequent absorption of bimatoprost from the eyelid surface into the ocular tissues and the body is expected to be incomplete due to the protective skin barrier and due to the small surface area upon which the dose is applied (Dugard, 1986; Dugard and Scott, 1984; Steiling et al, 2001; Trommer and Neubert, 2006).

Systemic exposure was measured after a 1-drop administration of bimatoprost ophthalmic solution 0.03% to both eyes of 15 healthy subjects once daily for 2 weeks using a state-of-the-art sensitive Liquid Chromatography Coupled with Mass Spectroscopy (LCMS) method during the development of bimatoprost ophthalmic solution 0.03%. The mean C_{max} values were similar on days 7 and 14 at approximately 0.08 ng/mL, which was approximately 3 times the lower limit of quantitation of the LCMS method (Studies 192024-006 and PK-98-119). Because the BEG applicator only transfers a small fraction of the bimatoprost

dose onto each eyelid margin (approximately 5%), the systemic exposure of bimatoprost from the BEG application would not have been measurable using this sensitive method.

Systemic, ocular, and eyelid exposures to bimatoprost after ophthalmic administration of 1 drop of LUMIGAN® have been demonstrated to be safe through extensive nonclinical (**Table 10–1**) and clinical studies and by 7 years of postmarketing surveillance. Specific to eyelid tissues, nonclinical pharmacokinetic research shows that a substantial portion of the ophthalmic bimatoprost dose is absorbed by the eyelid tissues (Studies PK-96-014, PK-97-036, PK-97-032, PK-97-013 and PK-98-003). Because of this, the safety of the BEG dose is well supported by extensive safety data from nonclinical, clinical, and postmarketing experience with bimatoprost for the treatment of glaucoma.

3.2 Safety Profile of Bimatoprost 0.03%

The overall safety profile of bimatoprost for eyelash growth is principally supported by data from 33 clinical studies (representing 3461 patient-years of exposure) and by more than 7 years of postmarketing experience with bimatoprost for the treatment of glaucoma (representing approximately 9 million patient-years of exposure). The following is a discussion of the safety profile of bimatoprost as observed in the following data sets:

- The pivotal BEG study
- The integrated safety data collected from 6 key long-term studies of bimatoprost for the treatment of glaucoma
- Postmarketing reports of bimatoprost use in glaucomatous patients

This integrated database provides long-term safety data across all relevant demographics.

The key long-term glaucoma studies of bimatoprost in this discussion of safety are the 2 pivotal phase 3 clinical studies of bimatoprost for the treatment of glaucoma (Studies 192024-008 and -009), a 3-year extension of the pivotal glaucoma studies (Study 192024-014), and 3 phase 3 clinical studies that compared LUMIGAN® with other exploratory formulations containing bimatoprost (Study 192024-031, -018T and -021T) (Table 3–1). Safety data from these 6 clinical studies were pooled and analyzed as a representation of the safety profile of bimatoprost because they were all masked, randomized, controlled, phase 3 studies, all contained at least 1 treatment group who received bimatoprost 0.03%, and all were at least 12 months in duration. The bimatoprost 0.03% treatment arms included in these

studies received 1 drop of bimatoprost ophthalmic solution 0.03% in each eye once daily (QD) for up to 4 years or twice daily (BID) for up to 2 years. Studies 192024-008, -009, and -014 included an active comparator group who received timolol ophthalmic solution 0.5% BID for up to 4 years.

Table 3–1 Overview of Key Bimatoprost Studies for the Treatment of Glaucoma Included in the Integrated Safety Database

Study Number	Number of Patients Enrolled in Each Group			Length of Study	Mean (Range) Age
	Bimatoprost 0.03% QD	Bimatoprost 0.03% BID	Comparator Group(s)		
192024-008	240	240	122	12 months	60.7 (22–90)
192024-009	234	243	119	12 months	62.4 (26–92)
192024-014[a]	167	131	81	36 months	62.1 (32–91)
192024-018T	129	–	391[b]	12 months	59.4 (22–91)
192024-021T	136	–	405[b]	12 months	62.4 (24–90)
192024-031	187	–	374[c]	12 months	63.5 (23–94)

a Study 192024-014 was a 3 year extension of the -008 and -009 studies; all patients enrolled in this study had completed 12 months of bimatoprost treatment.
b In Studies 192024-018T and -021T, there were 2 comparator groups: one received timolol and one received an exploratory bimatoprost formulation
c In Study 192024-031, 2 comparator groups received different exploratory bimatoprost formulations.

The studies of bimatoprost for the indications of eyelash growth and glaucoma have some similarities and differences, which are important to be aware of when reviewing the safety data collected from each. The studies were similar in design. Both had a treatment group that received bimatoprost once daily and both used the same concentration (0.03%) and formulation of bimatoprost. While the patient population in the glaucoma studies was generally older compared with the BEG population, the 2 populations overlap in terms of their ages. In both development programs, the majority of subjects were between the ages of 45 and 65 years. An important difference between the glaucoma and BEG programs was that in the glaucoma studies, patients were treated with a larger dose, applying it directly to the eye and bathing the surrounding eyelid margins (with typical application of an eyedrop), whereas in the pivotal BEG study, subjects applied a small amount of the product to a targeted treatment area on the upper eyelid margins. Thus the safety data in the glaucoma database should reasonably be considered as the safety profile of a much higher dose (a 20-[QD] to 40-fold [BID] increase). As would be expected with higher doses, side effects were reported more frequently in the glaucoma studies than are likely when bimatoprost is applied topically to the eyelid margin via an applicator for eyelash growth.

3.2.1 Study Populations in Bimatoprost Studies

The following sections (3.2.1.1 and 3.2.1.2) describe the demographics of the study populations in both clinical programs.

3.2.1.1 Bimatoprost for Eyelash Growth Study

In the pivotal BEG study, the 2 treatment groups were comparable at baseline, with no statistically significant demographic differences (**Table 10–3**). Overall, the mean (range) age of the subjects was 49.8 (22–78) years. The majority of the population was female (97.1%) and Caucasian (80.9%). The majority of subjects had light irides (60.1%). As per inclusion criteria, all enrolled subjects had a baseline GEA score of 1 (20.1%) or 2 (79.9%), with a similar distribution of GEA scores in both treatment groups at baseline. As per the protocol inclusion criteria, no subjects in either treatment group had baseline GEA scores of 3 (marked) or 4 (very marked). Because digital image analysis was performed as part of the efficacy evaluation of this study, subjects were excluded if their screening photographs were unable to be digitally analyzed. The unintended impact of this exclusion criterion was that subjects with darker skin tones were not enrolled in large numbers because the contrast between the eyelashes and skin was not enough for the technology to be utilized. A total of 53 non-Caucasians were enrolled. Out of 16 black subjects who were screened for the pivotal BEG study, only 1 black subject was enrolled, randomized to treatment with vehicle. While this is a limitation of the BEG study, the larger numbers of non-Caucasians enrolled (356/1409 25.3%) in the higher exposure glaucoma studies provides relevant insight into the safety profile that would be expected in this population, and at a higher dose.

In the investigator-initiated, open-label, proof-of-concept study that preceded the Allergan-sponsored development of BEG, all 28 subjects were female. The mean (range) age was 48.9 (32–73) years. The majority of subjects were Caucasian (96.4%); 1 subject was Asian. More subjects had brown irides than any other color (39.3%).

3.2.1.2 Glaucoma Studies

In the 6 key long-term glaucoma studies in patients with elevated IOP, the mean age of the patients was 61.5, 61.6, and 60.6 years (range 22 to 94) for the bimatoprost QD, BID, and timolol BID groups, respectively. Of the bimatoprost-treated patients enrolled in these studies, 9.9% were under the age of 45 years, 48.1% were between the ages of 45 and 65 years, and 42.0% were over the age of 65. Approximately half of the population was female (53.8% and 51.6% in the QD and BID groups, respectively), Caucasian (74.8% in the QD and BID groups), and approximately half had light irides (51.1% and 53.6% for the

bimatoprost QD and BID groups respectively) (**Table 10–4**). In total, 356 non-Caucasian patients were enrolled in these glaucoma studies, representing 25.3% of the total enrolled population, representing a substantive safety exposure database of non-Caucasians, exposed at much higher applied doses than in the BEG indication.

3.2.2 Adverse Events in Bimatoprost Pivotal Studies

The majority of adverse events reported during the long-term studies of bimatoprost for glaucoma started within the first 4 months of treatment. For this reason, adverse events occurring during the 4-month treatment period of the BEG study and the first 4 months of the long-term studies in glaucoma are a reliable indicator of the overall safety profile of BEG. Further evidence of the long-term safety of bimatoprost is demonstrated by 12- and 48-month data from the studies in glaucoma, which had not only a longer duration of treatment, but used a substantially higher applied dose of bimatoprost.

3.2.2.1 Bimatoprost for Eyelash Growth Pivotal Study

In the pivotal BEG study (Study 192024-032), 40.1% (55/137) of subjects in the bimatoprost group and 29.1% (41/141) of subjects in the vehicle group reported at least 1 adverse event, a difference that approached statistical significance ($p = 0.052$). The majority of adverse events were reported as mild in severity. Not unexpectedly, the most commonly affected system organ class was the eye, reported by 20.4% and 11.3% of subjects in the bimatoprost and vehicle groups, respectively ($p = 0.038$). The most commonly reported individual adverse events are displayed in Table 3–2. Conjunctival hyperemia, a very common adverse event with bimatoprost for the treatment of glaucoma, was the only adverse event to be reported by a statistically significantly higher number of subjects in the bimatoprost group compared with the vehicle group ($p = 0.028$).

Table 3–2 Number (%) of Subjects Reporting Adverse Events, Reported by >2% of Subjects in the Study of Bimatoprost for Eyelash Growth (Study 192024-032)

System Organ Class/Preferred Term	Bimatoprost (N = 137)	Vehicle (N = 141)
EYE DISORDERS		
Eye pruritus	5 (3.6)	1 (0.7)
Conjunctival hyperaemia[a]	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)
INFECTIONS AND INFESTATIONS		
Upper respiratory tract infection	2 (1.5)	5 (3.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Skin hyperpigmentation	4 (2.9)	1 (0.7)

Note: Adverse event data from Study 192024-032 were coded using MedDRA.
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.
a Conjunctival hyperaemia 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 (p = 0.028).

Adverse events that were considered by the investigator to be related to treatment were reported by 16.1% (22/137) and 7.1% (10/141) of subjects in the bimatoprost and vehicle groups, respectively (p = 0.019). The adverse events reported during the pivotal BEG study were predictable based on the known pharmacology of bimatoprost (Section 2.2), but were less severe and less common in comparison to the adverse events reported by subjects using the higher dose of bimatoprost for the treatment of glaucoma studies (Section 3.2.2.2).

PRO data show that, in general, the experience of adverse events which were mostly mild, reversible, and did not lead to discontinuation, did not impact subjects' assessment of overall satisfaction. Only 4 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 4 subjects in the bimatoprost group were eczema, dry eye, eye inflammation, and contact dermatitis, all of which were of mild or moderate severity. All were ongoing at the time of discontinuation, with the exception of contact dermatitis, which had resolved without sequelae. The adverse event of eye inflammation was considered by the investigator to be unrelated to treatment. Three subjects experienced serious adverse

events (1 bimatoprost subject [squamous cell carcinoma of the skin on the back] and 2 vehicle subjects [lymphoma and recurrent metastatic breast cancer); none were considered by the investigator to be related to treatment. No subjects died during the study.

Given that LUMIGAN® is approved for the treatment of glaucoma in patients diagnosed with glaucoma or ocular hypertension, IOP measurements were performed as a part of the overall safety assessment in this study (**Table 10–5**). Whereas statistically significant differences in mean IOP reduction were observed between the BEG and vehicle treatment groups at weeks 1 through 16, the magnitude of this reduction was small and was not clinically meaningful, with the difference between the groups ranging from 0.5 to 0.9 mm Hg. To put this in perspective, the average range of IOPs (maximum IOP minus minimum IOP) from baseline through week 16 was 3.9 mm Hg in the BEG group and 3.7 mm Hg in the vehicle group and, in general, IOPs in healthy subjects can vary by 3–5 mm Hg even over the course of 1 day (Drance, 1960; Liu et al, 2005).

In the investigator-initiated, open-label, proof-of-concept study that preceded the Allergan-sponsored development of BEG, the most commonly reported adverse event was "redness." Due to limited data collection, these data were able to be coded using a regulatory dictionary (ie, MedDRA), overall adverse event rates were not able to be calculated. No subjects discontinued from this study due to adverse events. Hyperemia was not noted on biomicroscopy for any subject at any time. There were no IOP-related adverse events. Mean changes from baseline in IOP were less than 1 mm Hg at any time point and were not considered to be clinically meaningful.

3.2.2.2 Glaucoma Studies

In the 6 key long-term glaucoma studies, 1409 patients were randomized to treatment with bimatoprost 0.03%. Of these, 926 patients were treated QD with bimatoprost 0.03% (Studies 192024-008, -009, -014, -018T, -021T, and -031) and 483 were treated BID with bimatoprost 0.03% (Studies 192024-008 ,-009, and -014)..

Since the BEG study had a 4-month treatment period, the safety results of the glaucoma studies were analyzed at the 4-month time point in order to facilitate a side-by-side comparison of the 2 treatment groups (adverse events occurring within the first 4 months in the BEG study and glaucoma studies). While the results were recorded for both treatment groups (bimatoprost QD and BID), the treatment group of principal interest is the bimatoprost QD group, since this was the dosing interval used in the BEG study.

Comparison of Adverse Events at the 4-month Time Point

Overall, adverse events (regardless of causality) were reported at the 4-month time point by 74.9% of patients treated with bimatoprost QD, and a higher rate of 89.0% was observed in patients treated with bimatoprost BID. The majority of adverse events were mild in severity. For the QD and BID treatment groups, respectively, 59.3% and 83.9% of patients experienced an adverse event that was considered by the investigator to be related to treatment, and 58.6% and 82.6% experienced an ocular adverse event, again demonstrating the higher rate of adverse events with BID administration. The most commonly reported adverse events at the 4-month time point are displayed in Table 3–3.

Table 3–3 Number (%) Patients Reporting Adverse Events in Studies of Bimatoprost for Eyelash Growth and the Treatment of Glaucoma

	Bimatoprost 0.03% QD for Eyelash Growth	Bimatoprost 0.03% QD for the Treatment of Glaucoma[a]		
	4 months	4 months	12 months	48 months
	N = 137	N = 926	N = 926	N =926
Overall	51 (37.2)	694 (74.9)	803 (86.7)	817 (88.2)
EYE DISORDERS				
Overall	27 (19.7)	543 (58.6)	661 (71.4)	678 (73.2)
Conjunctival hyperemia	5 (3.6)	358 (38.7)	405 (43.7)	413 (44.6)
Growth of eyelashes	3 (2.2)	115 (12.4)	188 (20.3)	195 (21.1)
Eye pruritus	5 (3.6)	84 (9.1)	99 (10.7)	103 (11.1)
Eye irritation	3 (2.2)	45 (4.9)	54 (5.8)	59 (6.4)
SKIN AND SUBCUTANEOUS TISSUE				
Skin hyperpigmentation	4 (2.9)	42 (4.5)	60 (6.5)	64 (6.9)
Hypertrichosis	N/A	33 (3.6)	47 (5.1)	50 (5.4)

N/A = not applicable.
Note: All adverse events were coded using MedDRA. All adverse events are represented regardless of causality.
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.
Note: The preferred terms included in this table are those that were reported at month 12 by greater than 5% of patients in the bimatoprost 0.03% QD treatment group in the 6 glaucoma studies.
Note: As eyelash growth was collected as a measure of efficacy in the study for eyelash growth, it was not collected as an adverse event.
a Six long-term bimatoprost studies of glaucoma are included; Studies 192024-008, -009, -014, -018T, -021T, and -031 were included. See Section 3.2.

As would be expected with the reduced exposure with the BEG administration compared with administration for the treatment of glaucoma, adverse events at the 4-month time point were reported by a lower percentage of patients in the BEG treatment group compared to the glaucoma treatment groups. Overall adverse events were reported 2 times more frequently in

the glaucoma group compared to the BEG treatment group. Ocular adverse events were reported approximately 3 times more frequently in the glaucoma treatment group compared to the BEG treatment group. With the exception of growth of eyelashes, which was not collected as an adverse event in the pivotal BEG study, all of the most common adverse events in the key bimatoprost studies were reported more frequently by subjects in the glaucoma treatment group than in the BEG treatment group. The individual adverse event of conjunctival hyperemia was reported over 10 times more frequently in the glaucoma treatment group compared with the BEG treatment group. The particularly large difference observed in the 2 study groups is likely due to the much lower ocular exposure with BEG administration compared to the direct instillation of eyedrops into the eye.

In the BEG pivotal study, subjects were treated for 4 months, whereas the glaucoma studies lasted 12 to 48 months. Therefore, it is important to note that, overall, the individual adverse events (preferred terms) reported by subjects at the 4-month time point in the glaucoma studies did not differ greatly from those reported at the 12-month time point in these studies, indicating that very few new adverse events would be expected with longer-term BEG treatment. As would be expected with longer exposure, the incidents of adverse events increased from the 4- to 12-month time point, however, the rates did not increase substantially with long-term (48-month) use. Overall, the adverse events were predictable based on the known pharmacology and prior clinical and postmarketing experience of bimatoprost, as discussed in Sections 2.2 and 3.2.3.

Specific adverse events that would be relevant to an aesthetic indication in eyelash growth were reported at a low incidence at the 4-month time point in the glaucoma studies. These events include iris hyperpigmentation, skin hyperpigmentation, eyelid erythema, and abnormal hair growth. For the QD and BID groups respectively, iris hyperpigmentation was reported by 0.5% and 0.8% of patients; skin hyperpigmentation was reported by 4.5% and 7.7% of patients, eyelid erythema was reported by 2.9% and 2.9% of patients, and abnormal hair growth was reported by 0.4% and 1.0% of patients.

Long-term Adverse Events in Intraocular Pressure Studies

In addition to the 4-month data, cumulative adverse event data were analyzed at the 12-month time point for the 6 long-term glaucoma studies of bimatoprost (**Table 10–6**). The results from these analyses demonstrate that long-term bimatoprost use at higher exposures than BEG administration does not result in any unpredictable or serious adverse events that would render it unsafe for use in an aesthetic indication.

Overall for these studies at the 12-month time point, adverse events (regardless of causality) were reported for a total of 86.7% of patients treated with bimatoprost QD, and a higher reporting rate of 95.2% was observed in patients treated with bimatoprost BID. For the QD and BID treatment groups, respectively, 68.7% and 91.3% of patients experienced an adverse event that was considered by the investigator to be related to treatment, and 71.4% and 89.9% experienced an ocular adverse event, again demonstrating the higher rate of adverse events with BID administration. Overall, adverse events were predominantly mild in severity. The most common adverse event across all 6 studies was conjunctival hyperemia, reported by 43.7% and 56.9% of patients in the QD and BID treatment groups, respectively.

Discontinuations due to Adverse Events

In total for the bimatoprost-treatment groups for the entire duration of all studies, 166 out of 1409 patients (11.8%) had discontinued prior to the end of the studies due to adverse events (9.5% and 14.7% of subjects in the QD and BID groups, respectively). In the timolol group, 27 out of 504 patients (5.4%) discontinued due to adverse events. In the bimatoprost QD treatment group, 50 patients discontinued due to ocular adverse events and 51 patients due to non-ocular events. In the bimatoprost BID group, 57 patients discontinued due to ocular adverse events and 30 patients due to non-ocular events. In the timolol group, 5 patients discontinued due to ocular adverse events and 22 patients due to non-ocular adverse events. The adverse event most commonly associated with early discontinuation from the studies was conjunctival hyperemia, which caused discontinuation by 32 (3.5%), 27 (5.6%), and 1 (0.2%) patients in the bimatoprost QD, BID, and timolol groups, respectively.

Serious Adverse Events and Deaths

The vast majority of serious adverse events reported during these studies were non-ocular and were not considered by the investigator to be related to treatment. In total for these studies, only 2 serious adverse events were considered by the investigator to be possibly related to the study treatment: 1 case of chest pain, experienced by a 62-year old female bimatoprost-treated patient (duration 2 days) and 1 case of bilateral corneal decompensation which did not resolve, experienced by an 83-year old female timolol-treated patient. Serious adverse events of the eye were reported by only 2 patients in any bimatoprost treatment group (retinal vein occlusion and macular hole; neither were considered by the investigator to be related to treatment) and 1 patient in the timolol group (corneal decompensation, which was considered by the investigator to be possibly related to treatment). In total (including events that were considered by the investigator to be unrelated to treatment), serious adverse

events were reported for a similar number of patients in the bimatoprost groups compared with the active comparator (timolol) group: 103 (11.1%) patients receiving bimatoprost QD, 51 (10.6%) patients receiving bimatoprost BID, and 47 (9.3%) patients receiving timolol.

During these studies, 4 patients in the bimatoprost QD treatment group died (2 myocardial infarctions, 1 stroke, and 1 car accident) and 3 patients in the timolol BID group died (1 cardiac arrest and 2 myocardial infarction). None of these adverse events were considered by the investigator to be related to study treatment.

Overall, the key long-term glaucoma studies of bimatoprost ophthalmic solution 0.03% characterize a safe drug with a favorable benefit-risk profile. In the 7 years since its initial approval by FDA, the postmarketing data continue to support it as a safe and well-tolerated drug.

3.2.3 Postmarketing Experience

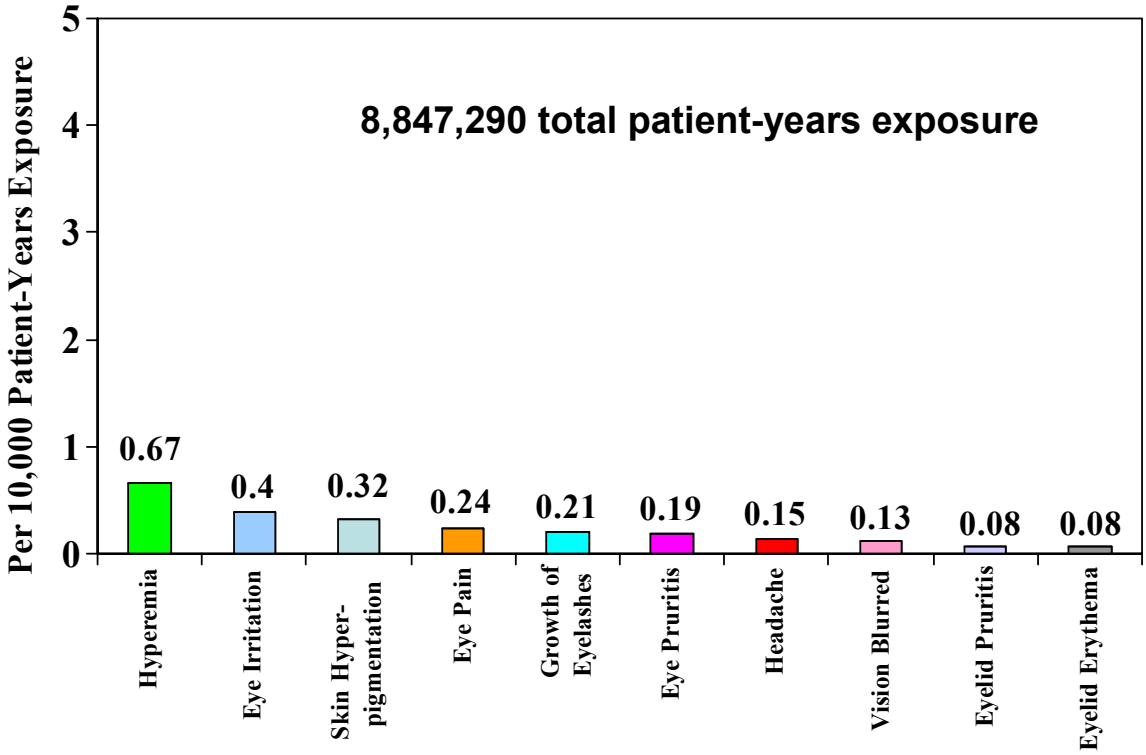
The overall safety profile of bimatoprost in human clinical use has been well-characterized by continuous clinical development since 1995 and postmarketing experience since 2001. Numerous clinical studies have been performed and reported to worldwide regulatory agencies on the efficacy and safety of bimatoprost for the treatment of glaucoma in association with clinical development activities. Routine safety surveillance and reporting of postmarketing safety data has also been performed throughout the lifecycle of LUMIGAN®.

In the global safety database, from the initial product approval (March 16, 2001) through August 31, 2008, there have been a total of 2410 case reports involving 5033 adverse events reported for LUMIGAN®. The 10 most commonly reported MedDRA (Medical Dictionary for Regulatory Activities) preferred terms in decreasing order of occurrence were: conjunctival and ocular hyperemia (incidence of both MedDRA terms combined) (596), eye irritation (358), skin hyperpigmentation (includes some events coded to skin discoloration (285), eye pain (211), growth of eyelashes (189), eye pruritus (171), headache (130), vision blurred (119), eyelid pruritis (75), and eyelid erythema (75). Compared to the total amount of LUMIGAN® exposure, the incidence of these events was low (Figure 3–1). The majority of events (95%) were not serious.

It is important to note that these events have been observed in patients who were applying a full 1-drop dose of LUMIGAN® to the eye(s), which bathes both the ocular surface and the surrounding eyelid skin. For BEG, as stated previously, bimatoprost exposure is substantially

reduced (Section 3.1.2). Based upon the lower exposure with BEG administration, far fewer adverse events are anticipated with this mode of administration.

Figure 3–1 Top 10 Events Compared to Total Postmarketing Exposure for LUMIGAN®



Note: Hyperemia includes ocular and conjunctival.
Note: Rates are calculated for all adverse events in the global safety database from March 2001 through August 2008.

Most of the commonly reported adverse events listed above are described in the product label, indicating that they are predictable based upon knowledge of bimatoprost. As part of routine and enhanced pharmacovigilance activities (Section 7), Allergan will continue to effectively monitor the safety profile of the product.

4. Summary of Efficacy

Bimatoprost solution 0.03% was found to be highly effective on multiple and concordant measures of efficacy as assessed through a physician global assessment of prominence, a digital analysis of photographs to technologically assess the individual components of prominence (length, thickness, and darkness), and a PRO questionnaire to assess efficacy from the subject's point of view with an emphasis on satisfaction. All of the objectives of the pivotal study were successfully achieved: by the end of the treatment period of the BEG study, bimatoprost-treated subjects experienced greater improvements than vehicle-treated subjects in the measurements of eyelash prominence, length, thickness, and darkness ($p < 0.0001$ for each endpoint) and had statistically significantly greater increases in patient satisfaction on all PRO measures ($p < 0.0439$).

Table 4–1 presents a summary of the results of the pivotal BEG study. All primary and secondary efficacy endpoints were met, with subjects in the bimatoprost group experiencing statistically significantly higher rates of improved eyelash prominence (defined by a $\geq$ 1-grade increase on the GEA scale [primary endpoint] and for an additional analysis requested by FDA, defined by the more stringent $\geq$ 2-grade increase on the GEA scale), eyelash length, thickness/fullness, and darkness, as compared to vehicle at week 16 ($p < 0.0001$ for all). The between-group p-values were also statistically significant when the more statistically conservative Bonferroni correction was applied to test each of these 5 pairwise comparisons separately. Only a p-value of less than 0.01 (0.05/5) would provide evidence of a treatment effect; the between-group p-value for each of these 5 endpoints at week 16 was < 0.0001. A detailed discussion of all efficacy results from this study is presented in Section 4.2.

Table 4–1 Efficacy Results From Pivotal Study of Bimatoprost for Eyelash Growth: Change From Baseline to Week 16 for all Efficacy Endpoints (Study 192024-032)

Endpoint	Bimatoprost (N = 137)	Vehicle (N = 141)	P-value
Primary Endpoint			
Improvement in Prominence[a] by ≥ 1-grade, N (%)	107 (78.1)	26 (18.4)	< 0.0001
Improvement in Prominence[a] by ≥ 2-grades, N (%)	45 (32.8)	2 (1.4)	< 0.0001
Secondary Endpoints[b]			
Percent Improvement in Length	25%	2%	< 0.0001
Percent Improvement in Thickness	106%	12%	< 0.0001
Percent Improvement in Darkness	18%	3%	< 0.0001

Note: Week 16 was the primary time point for the evaluation of efficacy.
a A ≥ 1-grade increase from baseline on the Global Eyelash Assessment scale was the primary efficacy endpoint. A ≥2-grade increase was a secondary analysis of the primary endpoint.
b The secondary endpoints of eyelash length, thickness, and darkness were measured using digital image analysis of superior-view photographs taken at each study visit.

In the investigator-initiated, open-label, proof-of-concept study that preceded the Allergan-sponsored development of BEG, 28 healthy female subjects were enrolled. Effectiveness was measured through subject responses to PRO questionnaires. At the end of the 12-week treatment period of this study, all respondents (N = 16) reported that their eyelashes were "improved" or "much improved." Of these 16 subjects, all had noticed eyelash changes starting at least by month 3, with 25% (4/16) reporting changes starting by month 1 and 56% (9/16) reporting changes in their eyelashes starting by month 2.

4.1 Efficacy Endpoints

The following section is a description of the efficacy endpoints and statistical methods used in the pivotal BEG study. The efficacy results are presented in Section 4.2. Efficacy was evaluated in 3 different manners: a physician global assessment of prominence, a digital analysis of photographs to technologically assess the individual components of prominence (length, thickness, and darkness), and a PRO questionnaire to assess efficacy from the subject's point of view with an emphasis on satisfaction. By assessing efficacy from these 3 distinct vantage points, it was felt that if concordance was found across all endpoints, the results would be reliable and clinically meaningful.

4.1.1 Primary Efficacy Endpoint: Eyelash Prominence

The primary efficacy endpoint measured in the pivotal BEG study was overall eyelash prominence at the end of the 16-week treatment period, as assessed by the investigator using the GEA Scale with photonumeric guide (Appendix 9.3).

Development of the GEA Scale With Photonumeric Guide

The GEA Scale is a 4-point ordinal scale of overall eyelash prominence (1 [minimal], 2 [moderate], 3 [marked], and 4 [very marked]), and was developed by Allergan to be used as an assessment tool in this clinical development program. The photonumeric guide is a collection of photos of superior and frontal views of eyelashes that correspond to each of the 4 GEA categories; it is used to aid investigators in assigning GEA scores to study participants. The development of the photonumeric guide started with the collection of 400 subject photos, which were rated by 5 physicians using the GEA scores of "minimal," "moderate," "marked," or "very marked." The differences between categories on the GEA scale were meant to reflect readily apparent and clinically different amounts of eyelash prominence. Based on statistical correlation analyses, 16 photos in each GEA grade were selected for further review. Ten additional physicians scored these 64 photos and this exercise resulted in the selection of 12 photos for each GEA grade. The resulting GEA Photonumeric Guide book was evaluated in Study 192024-033, which tested its inter-rater (ratings of the same subjects by different raters) and intra-rater (ratings of the same subjects by the same rater at different time points) reliability. A total of 68 healthy men and women aged 19 to 64 years were enrolled in this study, with approximately even distribution within the 4 GEA categories. Seven raters, all physicians, assessed each of the 68 subjects 2 times at least 1 hour apart. Using the photonumeric guide, the investigator evaluated eyelash prominence based on live frontal and superior assessments of the subject's eyelashes across both eyes and rated their prominence as minimal, moderate, marked, or very marked. The inter- and intra-rater reliability of the GEA Scale was calculated based upon the agreement of the scores assigned to each subject during the study. Weighted and unweighted Kappa statistics (for intra-rater results) and Kendall's coefficient of concordance (for inter-rater results) were calculated. There was a substantial degree of intra-rater agreement, shown by an overall weighted Kappa statistic of 0.772 and an unweighted Kappa statistic of 0.674 ($p < 0.001$). With respect to inter-rater reliability, the Kendall statistics were 0.862, 0.852, and 0.855 respectively for evaluation 1, evaluation 2, and overall ($p < 0.001$), showing the degree of agreement among the raters in scoring eyelash prominence using the GEA Scale to be almost perfect. Based upon the results of this study, it was concluded that the GEA Scale

with photonumeric guide is a reliable and reproducible assessment tool for the measurement of overall eyelash prominence (Allergan data on file).

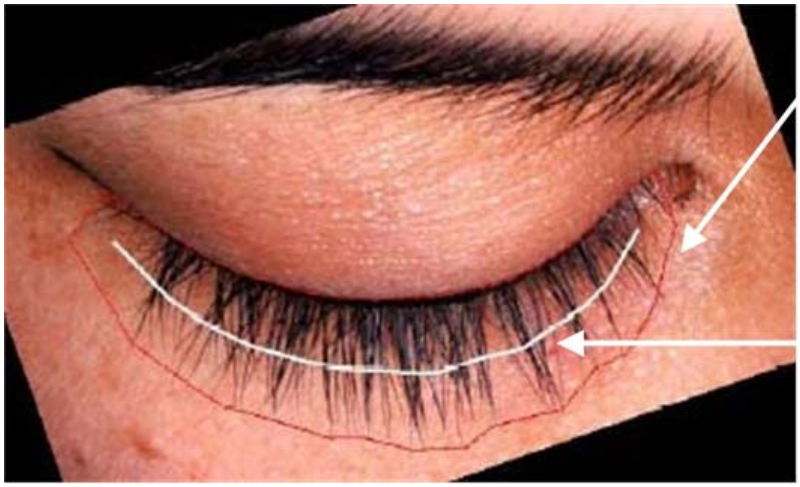
In the pivotal study evaluating the safety and efficacy of BEG (Study 192024-032), each subject's eyelashes were evaluated by the investigator once per visit across both eyes, using live frontal and superior views to determine the GEA category of eyelash prominence. The primary efficacy variable was a 1-grade improvement on the 4-point GEA scale from baseline to the end of the 16-week treatment period. This endpoint was analyzed using Pearson's chi-square test for 2-by-2 tables.

4.1.2 Secondary Efficacy Endpoints: Eyelash Length, Thickness, and Darkness

In addition to the improvement in overall eyelash prominence, the pivotal program evaluated elements that may contribute to the finding of enhanced prominence—increases in eyelash length, thickness, and darkness—by means of digital image analysis. These secondary endpoints were technologically evaluated in terms of change from baseline in overall eyelash length (measured in pixels), progressive eyelash thickness/fullness (measured in pixels), and eyelash darkness (measured in intensity units). Digital image analysis is a photographic process developed and validated by Canfield Scientific Inc (Fairfield, New Jersey). The validation study performed by Canfield evaluated the inter- and intra-rater reliability and reproducibility of the measurements produced by digital image analysis of eyelashes. Two analysts evaluated 60 photos a total of 4 separate times, each time at least 1 day apart. The results of this study showed the digital image analysis process to be reliable and reproducible.

Upper eyelash length was measured within a defined eyelash boundary for each eye, known as the area of interest (AOI, Figure 4–1). Canfield Scientific's computer software divided the full AOI image into a series of 25 vertical pixel segments. Within each segment, the maximum length of each segment was measured in pixels. The mean number of pixels over all segments was computed for each digital image across both eyes.

Figure 4–1 Definition of the Area of Interest and Spline for Digital Image Analyses



Upper eyelash thickness/fullness was measured within 3 preset areas (proximal, medial, and distal, each 300 x 25 pixels) within the AOI. For each superior-view image, the number of pixels representing the upper eyelashes within each area was reported as a percentage of the total number of the pixels within the full AOI. Eyelash thickness/fullness was assessed across both eyes as an average of the 3 preset areas.

Upper eyelash darkness was determined by lash intensity within a narrow area bisecting the full AOI called the spline (Figure 4–1). The darkness of each continuous collection of adjacent pixels was reported as mean intensity on the red, green, and blue scale, and then interpreted on an 8-bit image grayscale on a continuum of 0 (black) to 255 (white). The mean lash intensity was the average intensities of all pixel collections and was a measure of upper eyelash darkness.

Analyses of all 3 secondary efficacy endpoints were based on the average of the measurements from the left and right images. Data were summarized by descriptive statistics (ie, mean, standard deviation, median, minimum, and maximum) and analyzed using the Wilcoxon rank-sum test. To control the type 1 error rate at 0.05 for secondary efficacy variables, a serial gatekeeping procedure was used in which eyelash length was tested first, thickness was tested second if length was significant, and darkness was tested last if thickness was significant.

4.1.3 Patient-reported Outcomes Endpoints

In addition to the primary and secondary efficacy endpoints, the pivotal BEG study assessed changes in subject satisfaction with physical and subjective attributes of eyelashes following treatment with bimatoprost versus vehicle using a PRO questionnaire. PRO endpoints are of particular importance in this clinical development program, as a patient's perception of need and the satisfactory fulfillment of that need (ie, do patients derive a meaningful benefit from the product?) is a cornerstone in the development of aesthetic products.

The PRO questionnaire was a static measurement of satisfaction and was administered at every study visit in order to assess changes over time in subjects' satisfaction with their eyelashes (Appendix 9.4). This 23-item PRO tool is the first questionnaire developed to assess eyelash-related satisfaction. It was developed over a period of more than 2 years based on the FDA's Draft Guidance. Phase 1 involved the investigator-initiated proof-of-concept study, conducted in 29 healthy volunteers who applied bimatoprost ophthalmic solution 0.03% to their upper eyelid margins once daily for 12 weeks. Phase 2 involved 4 focus group discussions involving 32 women ranging from 20 to 70 years in age. In the focus groups, subjects gave open responses to personal eyelash satisfaction questions and an eyelashes outcomes pilot questionnaire was administered. Subjects provided feedback on this questionnaire, which resulted in refinement of the structure and content of the questionnaire. This modified version of the questionnaire then underwent psychometric validation and a scoring algorithm was developed.

Satisfaction with eyelashes was assessed by analysis of the change from baseline for 23 individual items and by analyses of 3 domains, which assessed the subjects' satisfaction with physical attributes of eyelashes (length, thickness, and overall satisfaction), satisfaction with subjective attributes of eyelashes (as related to feelings of confidence, professionalism, and attractiveness), and satisfaction with daily routine (as related to the amount of time spent on making eyelashes presentable). Additionally, analyses were conducted to determine the correlation between improvements in eyelash prominence (a 0-, 1-, 2-, or 3-grade improvement on GEA) and length and improvements in satisfaction in terms of a single question ("Overall, how satisfied are you with your eyelashes?"). Ordinal and continuous data from the PRO questionnaires were summarized by descriptive statistics and analyzed using the Wilcoxon rank-sum test.

4.2 Efficacy Results

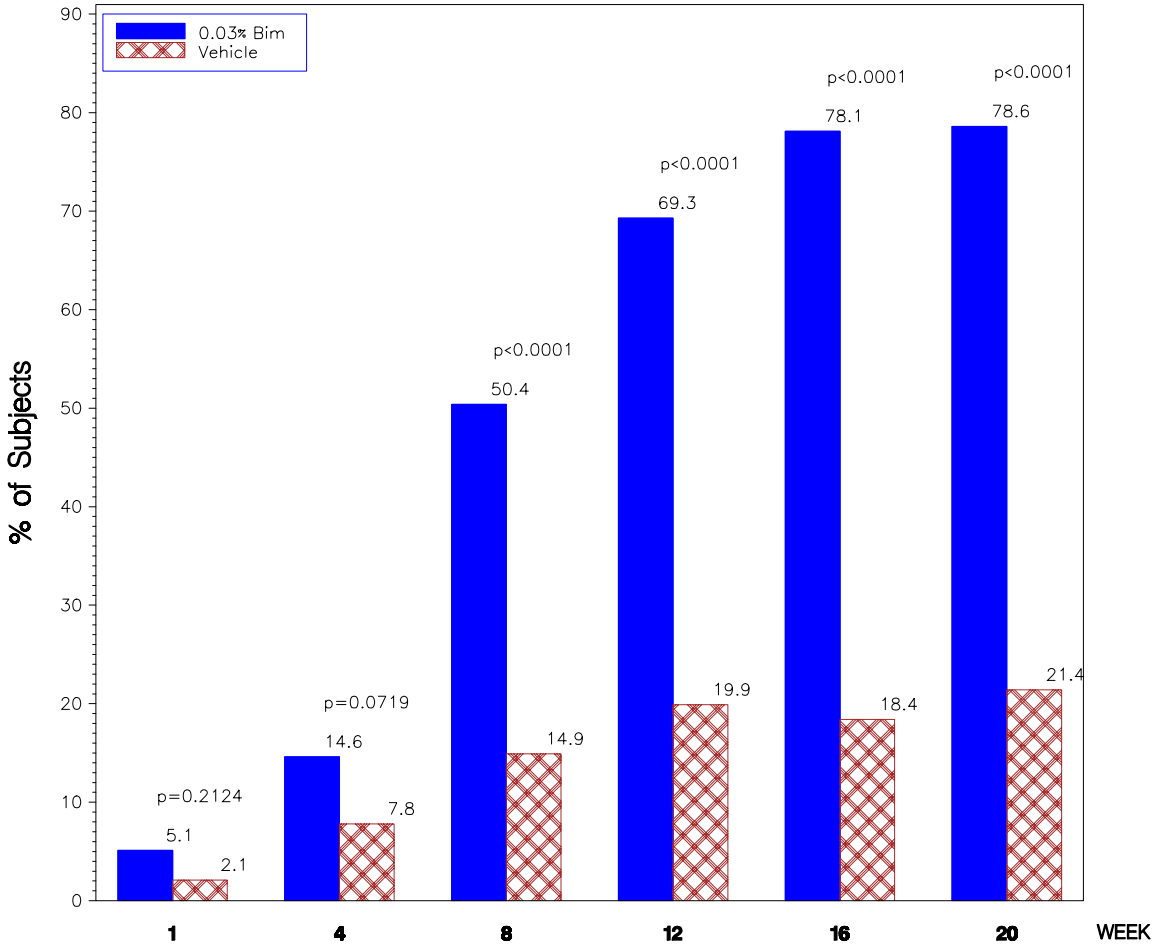
4.2.1 Primary Efficacy Endpoint: Eyelash Prominence

The primary efficacy endpoint for the pivotal BEG study was at least a 1-grade increase from baseline to week 16 on the GEA scale. Additional analyses performed on the GEA score data included analyses of subjects who experienced at least a 2-grade increases from baseline (performed at the request of FDA), of subjects who experienced a 3-grade increase from baseline, the change in distribution of GEA scores over the course of the study, and a subgroup analysis of nonresponders. The results of these analyses are discussed in the following sections.

Increase in Eyelash Prominence by at Least 1 Grade on the GEA Scale (Primary Endpoint)

Using the 4-point GEA Scale as a measurement of overall eyelash prominence, 78.1% of subjects in the bimatoprost group compared with 18.4% of subjects in the vehicle group experienced at least a 1-grade increase on the 4-point GEA scale from baseline in their overall eyelash prominence reported by the investigator at the end of the 16-week treatment period, a difference that was highly statistically significant ($p < 0.0001$, **Table 10–7**). The difference between the 2 groups trended towards favoring bimatoprost at weeks 1 and 4, and first became statistically significant by week 8 (Figure 4–2). The difference between the treatment groups became progressively more pronounced with continued treatment and was highly statistically significant at all subsequent time points during the treatment and posttreatment periods ($p < 0.0001$). Photos of subjects in the bimatoprost and vehicle groups who experienced a 1-grade change from baseline in eyelash prominence are provided in **Figure 10–1** and **Figure 10–2**.

Figure 4–2 **Percentage of Subjects With at Least a 1-Grade Increase From Baseline in GEA Score on the 4-Point GEA Scale (Study 192024-032)**



Note: Week 16 was the end of the treatment period in Study 192024-032.

Increase in Eyelash Prominence by at Least 2 Grades on the GEA Scale

At the request of FDA, an additional, more stringent analysis was performed for those subjects who experienced at least a 2-grade increase on the 4-point GEA Scale. At the end of the treatment period (week 16), 32.8% of subjects in the bimatoprost group compared with 1.4% of subjects in the vehicle group experienced at least a 2-grade increase from baseline, a difference that was statistically significant ($p < 0.0001$, **Table 10–8**). The difference between the 2 groups first became statistically significant by week 12 and the difference became progressively more pronounced and was statistically significant at all subsequent time points during the treatment and posttreatment periods ($p < 0.0001$). Photos of subjects treated with bimatoprost and vehicle who experienced a 2-grade change from baseline in eyelash prominence are provided in **Figure 10–3** and **Figure 10–4**.

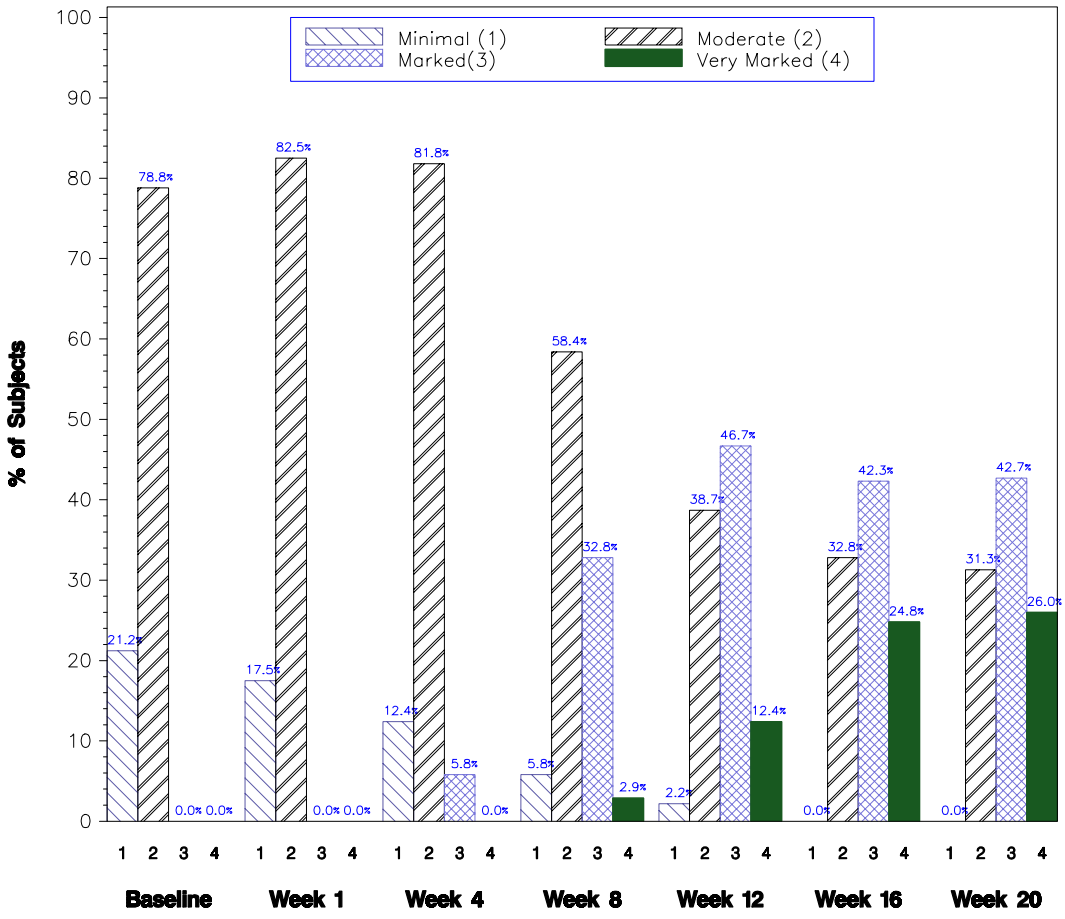
Increase in Eyelash Prominence by 3 Grades on the GEA Scale

Overall, 3 subjects (3/137, 2.2%) in the bimatoprost group and no subjects in the vehicle group experienced a 3-grade increase on the GEA scale at week 16. The maximum change in eyelash prominence that the GEA scale is capable of detecting is a 3-grade change. Only the 20% of enrolled subjects who were a "minimal" GEA grade at baseline could possibly have increased 3 grades (ie, change from baseline GEA scores of 1 [minimal] to 4 [very marked]). Among those 29 bimatoprost-treated subjects who experienced at least a 1-grade increase from baseline, 3 subjects (10.3%) experienced a 3-grade change at week 16. Photos of a bimatoprost-treated subject who experienced a 3-grade change from baseline in eyelash prominence are provided in **Figure 10–5**.

Distribution of GEA Score by Study Visit

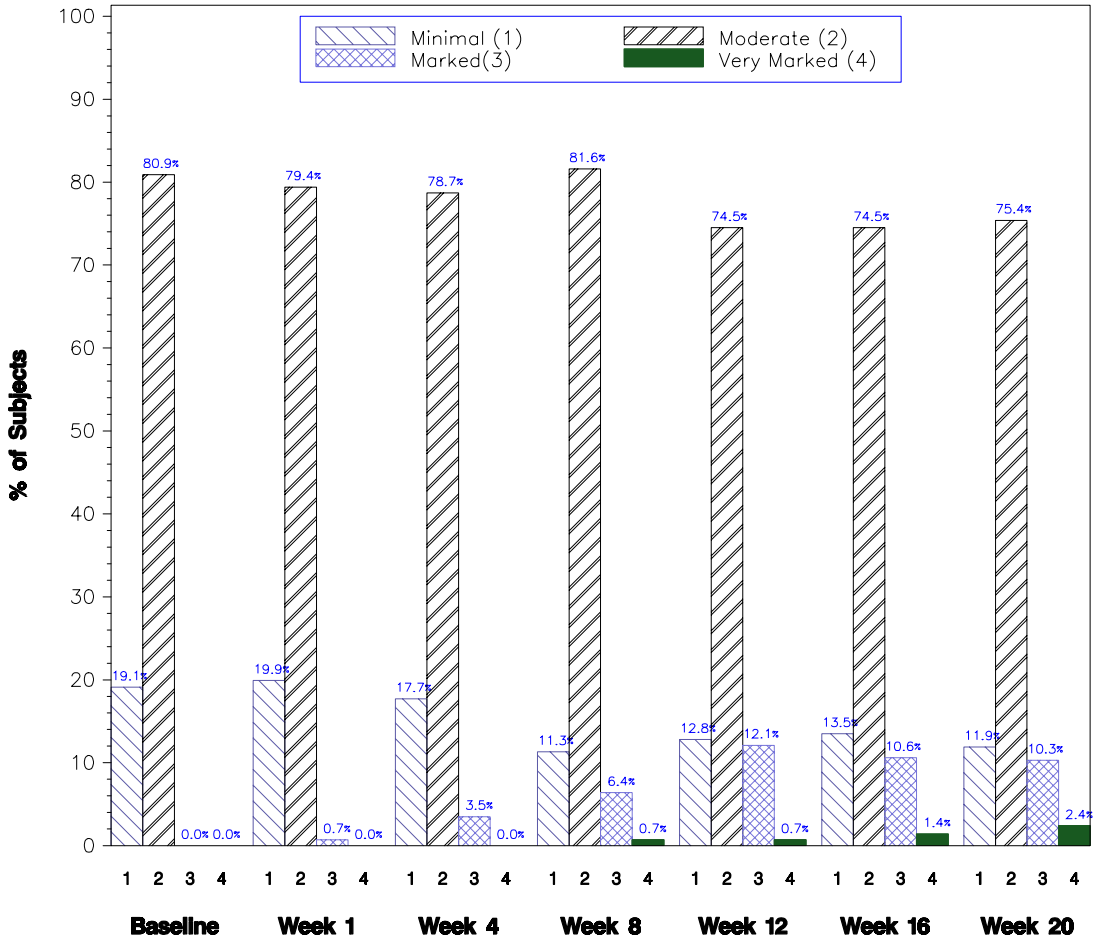
At baseline, both the bimatoprost and vehicle treatment groups had a similar distribution of GEA scores: approximately 20% had a GEA score of 1 (minimal) and approximately 80% had a GEA score of 2 (moderate) (**Table 10–3**). By week 16, 100% of the 29 subjects in the bimatoprost group who had a baseline GEA score of 1 (minimal) had improved by at least 1 grade (**Table 10–9**, Figure 4–3). By week 16, the percentage of subjects in the bimatoprost and vehicle groups rated as having a GEA score of 3 (marked) or 4 (very marked) was 67.2% (92/137) and 12.1% (17/141), respectively (Figure 4–3 and Figure 4–4). The percentage of bimatoprost-treated subjects in these categories (GEA scores of 3 or 4) was maintained through the 1-month posttreatment period (68.7%, 90/131).

Figure 4–3 Percentage of Subjects in Each GEA Grade by Study Visit, Bimatoprost Group (Study 192024-032)



Note: Week 16 was the end of the treatment period in Study 192024-032.
GEA = Global Eyelash Assessment Scale

Figure 4–4 **Percentage of Subjects in Each GEA Grade by Study Visit, Vehicle Group (Study 192024-032)**



Note: Week 16 was the end of the treatment period in Study 192024-032.
GEA = Global Eyelash Assessment Scale

Nonresponders on the GEA Scale

Because the GEA scale is a gross measure of all 3 components of prominence (length, thickness, and darkness) on a 4-point scale, it is expected that digital image technology might detect more subtle changes in the individual components of prominence through the precise measurement of length, thickness, and darkness in small units such as pixels and intensity units. A subgroup analysis was performed to evaluate the change in length, thickness, and darkness by digital image analysis for those subjects who, at week 16, were nonresponders to treatment. A nonresponder was defined as a subject who did not improve by 1 grade on the GEA scale from baseline to week 16.

Nonresponders in the bimatoprost group exhibited a greater mean change from baseline compared with nonresponders in the vehicle group in the technologically assessed endpoints of eyelash length, thickness, and darkness (**Table 10–10**). This suggests that even in the 21.9% of bimatoprost-treated subjects who, in the opinion of the investigator, did not improve in terms of overall prominence, the individual components were moving in the direction of improved prominence. Photos of bimatoprost- and vehicle-treated nonresponders are provided in **Figure 10–6** and **Figure 10–7**.

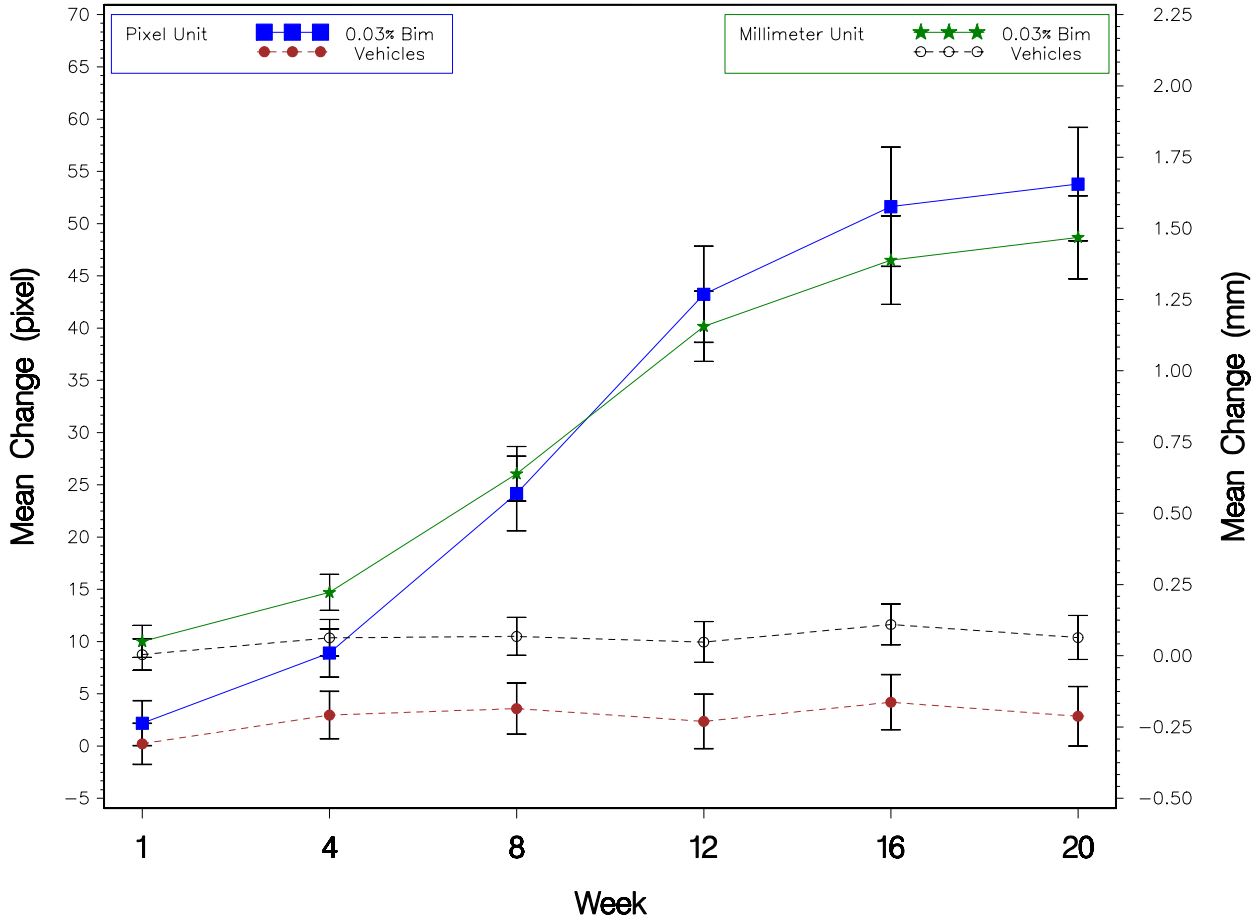
4.2.2 Secondary Efficacy Endpoints: Eyelash Length, Thickness, and Darkness

Eyelash Length

At the end of the 16-week treatment period, the bimatoprost and vehicle groups had experienced mean changes in eyelash length of 51.63 and 4.19 pixels, respectively, a difference in eyelash growth that was statistically significant ($p < 0.0001$, **Table 10–11**) Analyzed separately in terms of millimeters (mm), the mean increase in eyelash length from baseline was 1.39 mm and 0.11 mm for the bimatoprost and vehicle groups, respectively, a difference that was also statistically significant ($p < 0.0001$, **Table 10–11**). The mean baseline eyelash lengths of the bimatoprost and vehicle groups were 5.79 mm and 5.71 mm, respectively; these results correspond to a percentage change in eyelash length of 25% (bimatoprost) and 2% (vehicle) ($p < 0.0001$). Photos of subjects who most closely represent the mean measurements of length at baseline and week 16 for both treatment groups are provided in **Figure 10–8**.

Growth of eyelashes was first observed in terms of both pixels and mm at week 1 with the bimatoprost group experiencing a greater change from baseline in eyelash length than vehicle (Figure 4–5). By week 4, the difference between the 2 treatment groups had reached statistical significance, with greater increases in eyelash length observed in the bimatoprost group compared with vehicle. The difference between the treatment groups became progressively more pronounced at each subsequent visit: the vehicle group did not experience clinically meaningful changes from one visit to the next, while the bimatoprost group experienced progressive eyelash lengthening. The difference between the groups for change from baseline in eyelash length was statistically significant at every study visit from week 4 through the end of the treatment and posttreatment periods ($p < 0.0001$).

Figure 4–5 Eyelash Length: Mean Change From Baseline (Study 192024-032)



Note: Mean±2*SE.

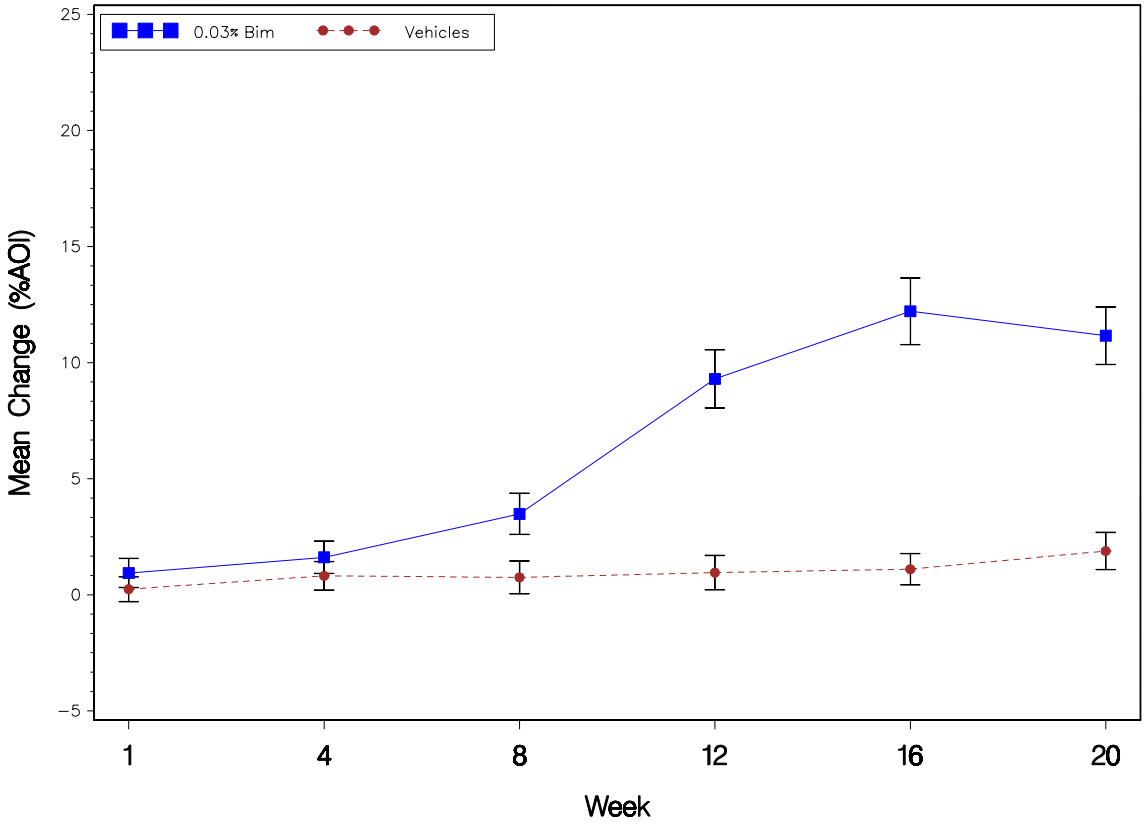
Note: Week 16 was the end of the treatment period in Study 192024-032.

Eyelash Thickness

At the end of the 16-week treatment period, the bimatoprost and vehicle groups had experienced mean increases in progressive eyelash thickness/fullness of 12.21 and 1.10 % AOI in pixels, respectively, a difference that was statistically significant ($p < 0.0001$, **Table 10–12**). These results correspond to a percentage increase from baseline of 106% (bimatoprost) and 12% (vehicle) ($p < 0.0001$). Photos of subjects who most closely represent the mean measurements of thickness at baseline and week 16 for both treatment groups are provided in **Figure 10–9**.

Progressive improvements in eyelash thickness/fullness were first observed at week 1 with greater improvements noted in the bimatoprost group than in the vehicle group (Figure 4–6). By week 8, the difference in eyelash thickness/fullness between the 2 treatment groups had reached statistical significance, with thicker, fuller eyelashes observed in the bimatoprost group compared with vehicle. As with eyelash length, the difference between the 2 treatment groups became more pronounced at each subsequent visit: the vehicle group did not experience clinically meaningful changes from one visit to the next, while the bimatoprost group experienced progressive eyelash thickening. The difference between the groups in change from baseline in eyelash thickness/fullness was statistically significant at every study visit from week 8 through the end of the treatment and posttreatment periods ($p < 0.0001$).

Figure 4–6 Progressive Eyelash Thickness/Fullness: Mean Change From Baseline (Study 192024-032)



Note: Mean±2*SE.

Note: Week 16 was the end of the treatment period in Study 192024-032.

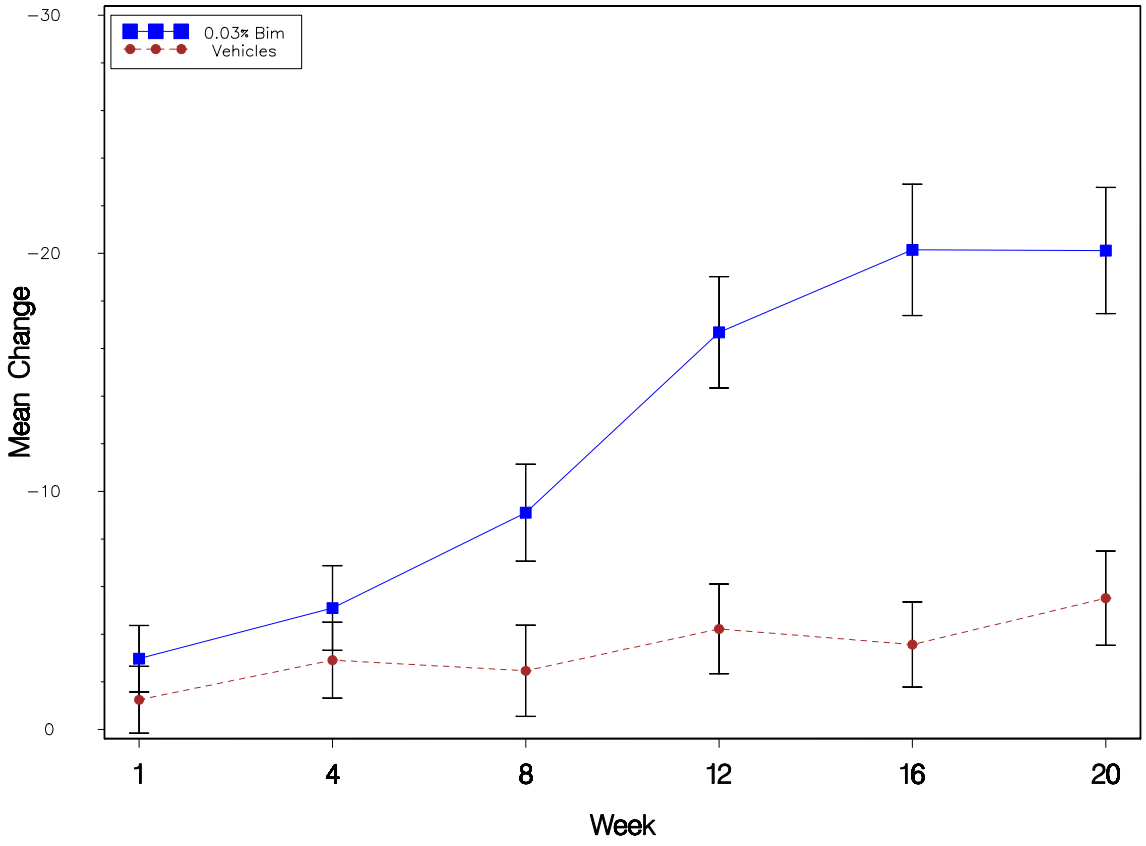
Eyelash Darkness

At the end of the 16-week treatment period, the bimatoprost group showed a statistically significantly greater degree of eyelash darkening compared to vehicle as shown by mean changes from baseline of -20.15 intensity units (bimatoprost) and -3.57 intensity units (vehicle) ($p < 0.0001$, **Table 10–13**). These results correspond to 18% darker eyelashes in the bimatoprost group and 3% darker eyelashes in the vehicle group as compared to baseline, a difference that was statistically significant between the 2 treatment groups ($p < 0.0001$, **Table 10–13**). Photos of subjects who most closely represent the mean measurements of thickness at baseline and week 16 for both treatment groups are provided in **Figure 10–10**.

Eyelash darkening was first noted starting at week 1, with statistically significantly more darkening occurring in the bimatoprost group compared with vehicle (Figure 4–7). A

significant difference between the 2 treatment groups was detected again at week 8 showing darker, more intense eyelashes in the bimatoprost group compared with vehicle. As with eyelash length and thickness, the difference between the 2 treatment groups became progressively more pronounced at each subsequent visit: the vehicle group did not experience clinically meaningful changes from one visit to the next, while the bimatoprost group experienced progressive eyelash darkening. The difference between the groups in change from baseline in eyelash darkness was statistically significant at every study visit from week 8 through the end of the treatment and posttreatment periods ($p < 0.0001$).

Figure 4–7 Eyelash Darkness: Mean Change From Baseline (Study 192024-032)



Note: Week 16 was the end of the treatment period in Study 192024-032.
Note: As the mean intensity of each continuous collection of pixels was interpreted on a grayscale in the range of 0 (black) to 255 (white), a result with a negative change from baseline value was representative of eyelash darkening.

4.2.3 Patient-reported Outcomes

Analysis of Individual Items and Domains

The results for all 23 individual PRO items (Appendix **9.4**) and all 3 domains (ie, satisfaction with physical and subjective eyelash attributes, and satisfaction with daily routine) were statistically significantly different between treatment groups, with a greater mean increase from baseline in subject satisfaction observed in the bimatoprost group compared with the vehicle group. All of these results were statistically significantly different favoring bimatoprost over vehicle by the primary time point of week 16 (end of treatment period). Of particular interest, the results for the single item that asked subjects to rate their overall satisfaction with their eyelashes were statistically significant in favor of bimatoprost over vehicle at week 8 and remained so through the end of the study (week 20).

Analysis of Overall Satisfaction with Eyelashes by Treatment Response

An analysis was performed in order to correlate subjects' changes in satisfaction with the change in their eyelash prominence and length. Table 4–2 summarizes the satisfaction levels of subjects in both treatment groups at the end of the 16-week treatment period. The 5 possible responses to the question "Overall, how satisfied are you with your eyelashes?" were separated into 3 categories: "very satisfied/satisfied," "neutral," and "dissatisfied/very dissatisfied." At week 16, 65% of subjects in the bimatoprost treatment group reported satisfaction with the study treatment compared to only 18.4% of subjects in the vehicle group.

Table 4–2 Number (%) of Subjects in Each Response Category at Week 16 for the Single Item Evaluating Overall Satisfaction With Eyelashes in PRO Questionnaire (Study 192024-032)

	Bimatoprost 0.03% N = 137	Vehicle N = 141
Very satisfied or satisfied	89 (65.0)	26 (18.4)
Neutral	26 (19.0)	39 (27.7)
Dissatisfied or very dissatisfied	22 (16.0)	76 (53.9)

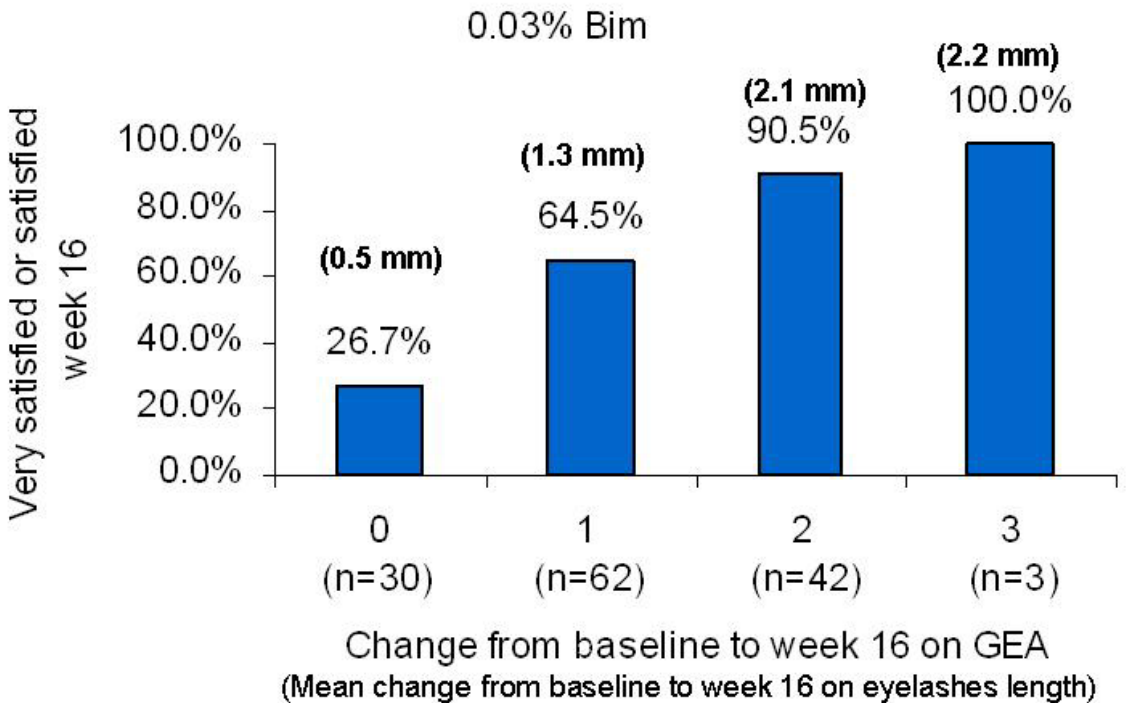
Note: Week 16 was the end of the treatment period in Study 192024-032.

More detailed analyses of PRO responses were performed for subjects who experienced changes of 0, 1, 2, and 3 grades on the GEA scale and for subjects who experienced increases in eyelash length grouped into 9 different categories (0 mm of change, >0 to ≤0.5 mm, >0.5

mm to ≤1 mm, >1 mm to ≤1.5 mm, >1.5 mm to ≤2.0 mm, >2.0 mm to ≤2.5 mm, >2.5 mm to ≤3.0 mm, >3.0 mm to ≤3.5 mm, and >3.5 mm to ≤4.0 mm).

Figure 4–8 illustrates the increasing levels of satisfaction for subjects who experienced greater changes in prominence and length. All 3 subjects who experienced the maximum increase of 3 grades on the GEA scale reported satisfaction with their eyelashes. Of the 42 subjects who experienced a 2-grade increase from baseline on the GEA scale, 90.5% reported satisfaction with their eyelashes. Of the 62 subjects who experienced a 1-grade increase from baseline GEA score, 64% reported satisfaction with their eyelashes at the end of the 16-week treatment period. The mean increases in eyelash length experienced by subjects who increased from baseline by 0-, 1-, 2-, or 3-grades on the GEA scale were 0.5 mm, 1.3 mm, 2.1 mm, and 2.2 mm, respectively, indicating concordance between increases in eyelash length and increased prominence. These results indicate that improvements of eyelash prominence as demonstrated by 1-, 2-, or 3-grade increases on the GEA scale and increases in length of approximately 1.3 mm (mean change in the pivotal BEG study was 1.39 mm) were perceived as clinically meaningful aesthetic benefits by a large proportion of the subjects who experienced this change.

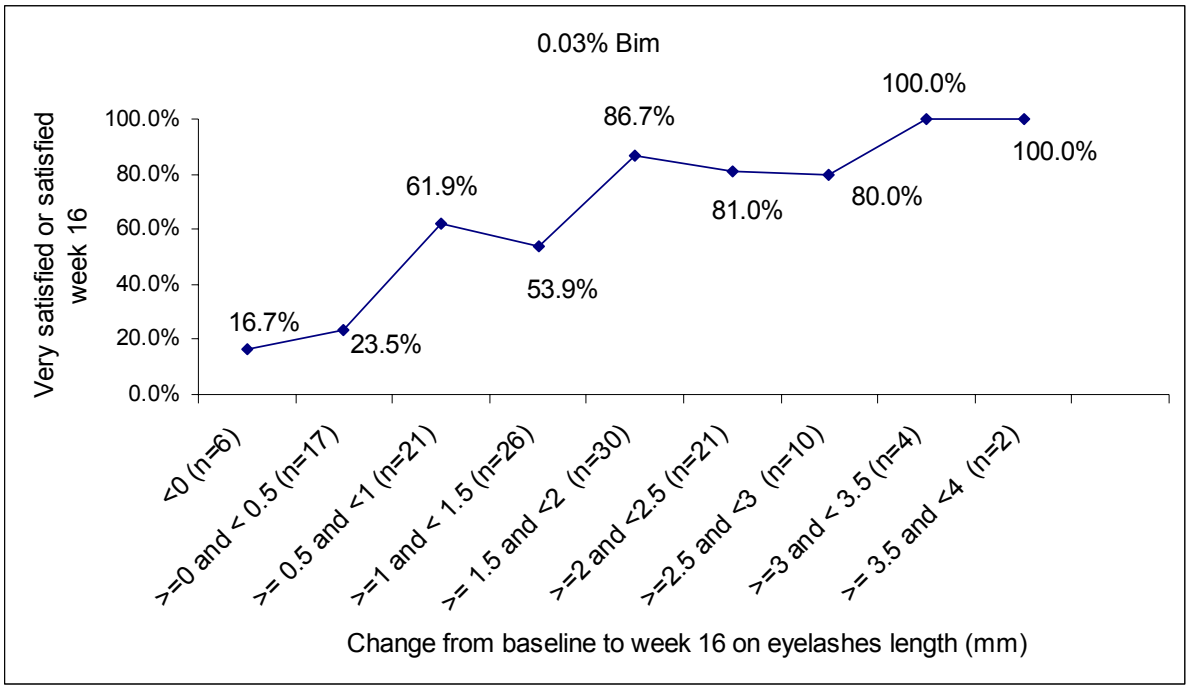
Figure 4–8 **Percentage of Bimatoprost-Treated Subjects Reporting Satisfaction With Eyelashes at Week 16, by 0-, 1-, 2-, and 3-Grades of GEA Improvement From Baseline to Week 16 and Corresponding Changes in Eyelash Length (Study 192024-032)**



Note: Mean eyelash length at baseline was 5.79 mm and 5.71 mm in the bimatoprost and vehicle groups, respectively. Mean change from baseline to week 16 was 1.39 mm and 0.11 mm for the bimatoprost and vehicle treatment groups, respectively.
Note: All subjects in Study 192024-032 had baseline GEA scores of 1 (minimal) or 2 (moderate). Week 16 was the end of the treatment period.

Figure 4–9 illustrates that subjects who experienced increasingly greater amounts of change from baseline in eyelash length reported increasingly greater levels of satisfaction. The majority (76.3%) of subjects who experienced at least 1 mm of eyelash growth reported that they were satisfied or very satisfied with their eyelashes overall. These results indicate that improvements of eyelash length of at least 1 mm were perceived as clinically meaningful benefits by a large proportion of the subjects who experienced this change. In the pivotal BEG study, the mean change from baseline to week 16 in eyelash length for the bimatoprost group was 1.39 mm.

Figure 4–9 **Percentage of Bimatoprost-Treated Subjects Reporting Satisfaction With Eyelashes at Week 16, by Category of Changes in Eyelash Length (Study 192024-032)**



5. Safety and Efficacy of BEG in Subgroups

Post hoc analyses were conducted to assess the safety and efficacy of BEG based on demographic subgroups of age and ethnicity. The pivotal BEG study, the 6 key long-term glaucoma studies, and the pivotal glaucoma studies were used for these analyses.

5.1 Safety and Efficacy by Age Group

5.1.1 Safety by Age Group

An analysis of adverse events by age group (< 45, 45 to 65, and > 65 years of age) were conducted for patients receiving bimatoprost in the pivotal BEG study (at the 4 month time point) and in the long-term glaucoma studies (at the 4- and 12-month time points) (Table 5–1). The 6 preferred terms included in this analysis were the most commonly reported adverse events at the 12-month time point by subjects in the bimatoprost QD group during the long-term glaucoma studies. With the exception of conjunctival hyperemia, which was reported by a higher incidence of younger patients, the proportion of these adverse events were similar across the 3 age categories evaluated.

Table 5–1 Number (%) of Patients Reporting Key Adverse Events in Bimatoprost Studies of Eyelash Growth and Glaucoma, by Age Group

	Bimatoprost 0.03% for Eyelash Growth QD 4 months	Bimatoprost 0.03% for Treatment of Glaucoma[a] QD 4 months	Bimatoprost 0.03% for Treatment of Glaucoma[a] QD 12 months
< 45 years	N = 44	N = 85	N = 85
Conjunctival hyperemia	2 (4.5)	42 (49.4)	44 (51.8)
Eye pruritus	2 (4.5)	8 (9.4)	10 (11.8)
Eye irritation	0 (0.0)	4 (4.7)	6 (7.1)
Erythema of eyelid	0 (0.0)	0 (0.0)	1 (1.2)
Skin hyperpigmentation	3 (6.8)	4 (4.7)	8 (9.4)
Foreign body sensation in eye	0 (0.0)	1 (1.2)	1 (1.2)
45 to 65 years	N = 82	N = 459	N = 459
Conjunctival hyperemia	3 (3.7)	187 (40.7)	211 (46.0)
Eye pruritus	3 (3.7)	41 (8.9)	46 (10.0)
Eye irritation	3 (3.7)	21 (4.6)	26 (5.7)
Erythema of eyelid	3 (3.7)	14 (3.1)	18 (3.9)
Skin hyperpigmentation	1 (1.2)	27 (5.9)	33 (7.2)
Foreign body sensation in eye	0 (0.0)	14 (3.1)	15 (3.3)
> 65 years	N = 11	N = 382	N = 382
Conjunctival hyperemia	0 (0.0)	130 (34.0)	151 (39.5)
Eye pruritus	0 (0.0)	35 (9.2)	43 (11.3)
Eye irritation	0 (0.0)	21 (5.5)	23 (16.0)
Erythema of eyelid	0 (0.0)	13 (3.4)	19 (5.0)
Skin hyperpigmentation	0 (0.0)	11 (2.9)	19 (5.0)
Foreign body sensation in eye	0 (0.0)	15 (3.9)	25 (6.5)

QD = once daily; BID = twice daily; IOP = intraocular pressure; N/A = not applicable
Note: Adverse events were coded using MedDRA. All adverse events are represented, regardless of causality.
Note: Within each system organ class, preferred terms are sorted by descending order of frequencies by treatment groups from left to right. Within each preferred term, a subject is counted at most once.
Note: The 6 preferred terms included in this table are those that were most commonly reported at the 12-month time point by subjects in the bimatoprost QD group during the glaucoma studies. The preferred term "growth of eyelashes" was excluded from this table because it was collected as an efficacy endpoint in the pivotal BEG study.

a Pooled analysis of Studies 192024-008, -009, -014, -018T, -021T, and -031.

5.1.2 Efficacy by Age Group

For each of the 3 age groups in this subgroup analysis (< 45, 45 to 65, and >65 years), statistically significant differences in efficacy between the bimatoprost and vehicle treatment groups were observed (Table 5–2). The > 65 age group had the highest proportion of subjects (90.9%) experiencing improvements in eyelash prominence.

Table 5–2 Number (%) of Subjects Experiencing at Least a 1-Grade Increase on the GEA Scale From Baseline to Week 16, by Age Group (Study 192024-032)

	Bimatoprost 0.03% N = 137	Vehicle N = 141	P-value[a]
< 45 years	29/44 (65.9)	8/43 (18.6)	< 0.0001
45 to 65 years	68/82 (82.9)	17/88 (19.3)	< 0.0001
> 65 years	10/11 (90.9)	1/10 (10.0)	0.0003[b]

Note: Week 16 was the end of the treatment period in Study 192024-032.
a P-value are based on Pearson chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of < 5.
b Fisher's exact test is performed.

5.2 Safety and Efficacy by Ethnic Group

5.2.1 Safety by Ethnic Group

An analysis of adverse events by ethnicity was conducted for patients receiving bimatoprost the pivotal BEG study (at the 4 month time point) and the long-term glaucoma studies (at the 4- and 12-month time points) (Table 5–3). With the exception of a higher incidence of conjunctival hyperemia reported by non-Caucasians compared with Caucasians, the proportion of patients reporting these individual adverse events were comparable based on race.

Table 5–3 Number (%) of Bimatoprost-Treated Patients Reporting Key Adverse Events in the Bimatoprost Studies of Eyelash Growth and Glaucoma, by Ethnic Group

	Bimatoprost 0.03% for Eyelash Growth QD 4 months	Bimatoprost 0.03% for Treatment of Glaucoma[a] QD 4 months	Bimatoprost 0.03% for Treatment of Glaucoma[a] QD 12 months
Caucasian	N = 109	N = 682	N = 682
Conjunctival hyperemia	4 (3.7)	248 (36.4)	289 (42.4)
Eye pruritus	4 (3.7)	60 (8.8)	70 (10.3)
Eye irritation	2 (1.8)	35 (5.1)	42 (6.2)
Erythema of eyelid	2 (1.8)	26 (3.8)	36 (5.3)
Skin hyperpigmentation	1 (0.9)	32 (4.7)	44 (6.5)
Foreign body sensation in eyes	0 (0.0)	27 (4.0)	37 (5.4)
Black	N = 0	N = 156	N = 156
Conjunctival hyperemia	N/A	64 (41.0)	66 (42.3)
Eye pruritus	N/A	15 (9.6)	19 (12.2)
Eye irritation	N/A	6 (3.8)	6 (3.8)
Erythema of eyelid	N/A	1 (0.6)	1 (0.6)
Skin hyperpigmentation	N/A	6 (3.8)	12 (7.7)
Foreign body sensation in eyes	N/A	3 (1.9)	4 (2.6)
Asian	N = 18	N = 13	N = 13
Conjunctival hyperemia	0 (0.0)	13 (100.0)	13 (100.0)
Eye pruritus	1 (5.6)	2 (15.4)	2 (15.4)
Eye irritation	0 (0.0)	1 (7.7)	1 (7.7)
Erythema of eyelid	0 (0.0)	0 (0.0)	0 (0.0)
Skin hyperpigmentation	2 (11.1)	1 (7.7)	1 (7.7)
Foreign body sensation in eyes	0 (0.0)	0 (0.0)	0 (0.0)
Hispanic	N = 6	N = 71	N = 71
Conjunctival hyperemia	0 (0.0)	31 (43.7)	35 (49.3)
Eye pruritus	0 (0.0)	5 (7.0)	6 (8.5)
Eye irritation	1 (16.7)	3 (4.2)	5 (7.0)
Erythema of eyelid	0 (0.0)	0 (0.0)	1 (1.4)
Skin hyperpigmentation	0 (0.0)	2 (2.8)	2 (2.8)
Foreign body sensation in eyes	0 (0.0)	0 (0.0)	0 (0.0)
Other	N = 4	N = 4	N = 4
Conjunctival hyperemia	1 (25.0)	2 (50.0)	2 (50.0)
Eye pruritus	0 (0.0)	2 (50.0)	2 (50.0)
Eye irritation	0 (0.0)	0 (0.0)	0 (0.0)
Erythema of eyelid	0 (0.0)	0 (0.0)	0 (0.0)
Skin hyperpigmentation	1 (25.0)	1 (25.0)	1 (25.0)
Foreign body sensation in eyes	0 (0.0)	0 (0.0)	0 (0.0)

QD = once daily; BID = twice daily; N/A = not applicable
Note: Adverse events were coded using MedDRA. All adverse events are represented, regardless of causality.
Note: Within each system organ class, preferred terms are sorted by descending order of frequencies by treatment groups from left to right. Within each preferred term, a subject is counted at most once.
a Pooled analysis from Studies 192024-008, -009, -014, -018T, -021T, and -031.

5.2.2 Efficacy by Ethnic Group

In the pivotal BEG study, a statistically significantly higher proportion of Caucasian and Asian bimatoprost-treated subjects experienced at least a 1-grade increase from baseline in GEA score compared with Caucasian and Asian vehicle-treated subjects (Table 5–4). Enrollment of small numbers of black and Hispanic subjects (due to the digital image analysis exclusion criterion [see Section **3.2.1.1**]) made it difficult to draw meaningful statistical conclusions for those populations.

Table 5–4 Number (%) of Subjects Experiencing at Least a 1-grade Increase on GEA Score From Baseline to Week 16, by Ethnic Group (Study 192024-032)

	Bimatoprost 0.03% N = 137	Vehicle N = 141	P-value[a]
Caucasian	88/109 (80.7)	16/116 (13.8)	< 0.0001
Black	0/0 (0.0)	1/1 (100.0)	N/A
Asian	13/18 (72.2)	5/16 (31.3)	0.0169
Hispanic	3/6 (50.0)	2/5 (40.0)	> 0.9999[b]
Other	3/4 (75.0)	2/3 (66.7)	> 0.9999[b]

N/A = Not applicable
a P-value are based on Pearson chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of < 5.
b Fisher's exact test is performed.

Table 5–5 summarizes the incidence of eyelash growth reported as an adverse event by different ethnic groups during the pivotal glaucoma studies. While eyelash growth was not prospectively assessed as an efficacy measure during the pivotal glaucoma studies, the incidence of eyelash growth reported as an adverse event does provide evidence of bimatoprost's effect on eyelash growth across different ethnic groups. Black and Hispanic patients treated QD with bimatoprost ophthalmic solution 0.03% for 12 months reported "growth of eyelashes" at rates of 30.2% and 31.6%, respectively (pooled analysis of Studies 192024-008 and -009). By comparison, 36.6% of Caucasian patients treated with bimatoprost QD reported eyelash growth, indicating similar rates of eyelash growth among all ethnic subgroups in the pivotal glaucoma studies. The incidence of eyelash growth increased slightly in each group with BID administration.

Table 5–5 Number (%) of Patients Reporting Growth of Eyelashes as an Adverse Event in the 12-Month Pivotal Glaucoma Studies, by Ethnic Subgroup (Studies 192024-008 and -009)

	Bimatoprost 0.03% QD	Bimatoprost 0.03% BID
Caucasian	133/363 (36.6)	182/371 (49.1)
Black	26/86 (30.2)	25/82 (30.5)
Asian	3/6 (50.0)	7/13 (53.8)
Hispanic	6/19 (31.6)	5/15 (33.3)
Other[a]	0 (0.0)	1/2 (50.0)

a "Other" races included Portuguese and Native American.

6. Benefit-Risk Assessment

6.1 Risks

The safety of bimatoprost for the enhancement of eyelash growth has been demonstrated by the favorable adverse event profile observed in the pivotal BEG study. In the pivotal BEG study, bimatoprost solution 0.03% was applied topically to the upper eyelid margins of healthy adult subjects, at a dose approximately 5% of that of a 1-drop dose of bimatoprost for the treatment of glaucoma. As would be expected with the considerably lower exposure from BEG administration as compared with direct instillation of bimatoprost to the eye, adverse events reported during the pivotal BEG study occurred at a low frequency and were largely mild in severity, cosmetic in nature, and reversible. Adverse events did not usually lead to discontinuation from the study. Importantly, patient satisfaction with bimatoprost treatment was generally not impacted by the experience of an adverse event of the types that were seen in this study. As shown in Table 6–1, 72.5% of bimatoprost-treated subjects who experienced any adverse event during the pivotal BEG study still reported satisfaction (i.e, being satisfied or very satisfied) with their eyelashes at the end of the treatment period. In terms of the mean change from baseline in scoring of overall satisfaction with eyelashes, bimatoprost-treated subjects who experienced an adverse event reported improved satisfaction with their eyelashes compared to baseline by more than 2 points on a 5-point scale (possible answers were very dissatisfied, dissatisfied, neutral, satisfied, and very satisfied). This indicates that the experience of an adverse event did not impact the subjects' perception of a benefit from bimatoprost.

Table 6–1 Impact of the Experience of an Adverse Event on Patient Reported Outcomes (Study 192024-032)

	Bimatoprost Solution 0.03% for Eyelash Growth	
	Subjects Reporting Adverse Event(s)	Subjects Not Reporting Adverse Event(s)
Subjects feeling satisfied or very satisfied at Week 16[a], N (%)	37/51 (72.5)	52/86 (60.5)
Change from baseline to week 16 on overall satisfaction[b], Mean (SD)	-2.04 (1.33)	-1.80 (1.21)

SD = standard deviation
a Week 16 marked the end of the treatment period in the pivotal BEG study (192024-032).
b The question, "Overall, how satisfied are you with your eyelashes?" was item #4 on the PRO questionnaire. Subjects answered the question using a 5-point scale; possible answers were very dissatisfied, dissatisfied, neutral, satisfied, or very satisfied. A negative change from baseline indicated an increase in satisfaction.

Certain "class effects" commonly associated with prostaglandin $F_{2\alpha}$ analogs, such as skin hyperpigmentation, hair growth outside the treatment area, hyperemia, and iris hyperpigmentation, were reported in the BEG study by very few subjects. With few exceptions (3 subjects reporting skin hyperpigmentation and 1 subject reporting errant hair growth outside the treatment area), all of these events reported by bimatoprost-treated subjects had resolved prior to the end of the study. IOP reduction, while statistically significantly different between the bimatoprost and vehicle groups, was minimal (ie, less than 1 mm Hg difference in mean IOP changes from baseline between the 2 treatment groups at any time point during the study) and thus, was not clinically significant.

6.2 Benefits

BEG is an aesthetic product. Therefore, its benefits must be considered first from the point of view of the patient. The benefits of bimatoprost solution 0.03% have been clearly demonstrated in the pivotal BEG study, not only through the clinical measurements of prominence (through physican-graded live assessment), and length, thickness, and darkness (through digital image analysis), but by the greater increases in satisfaction reported by subjects in the bimatoprost group versus the vehicle group. PRO data indicate that, compared with vehicle-treated subjects, subjects in the bimatoprost group were significantly more satisfied with the physical (eg, length, fullness) and subjective (eg, confidence, attractiveness) attributes of their eyelashes, as well as with their eyelashes overall. These results clearly show that the benefits of bimatoprost for eyelash growth are not only noticeable through the statistical interpretation of clinical measurements but are noticeable and appreciated by the persons who use the product. In line with these PRO results, quantitative improvements in eyelashes were demonstrated in the pivotal BEG study by the

significant efficacy of bimatoprost compared with vehicle in the clinical measurements of prominence, length, thickness, and darkness. By the end of the 16-week treatment period, 78.1% of subjects in the bimatoprost group had experienced improved eyelash prominence compared with only 18.4% of subjects in the vehicle group. Subjects in the bimatoprost group had experienced percentage increases in eyelash length, thickness, and darkness of 25%, 106%, and 18%, respectively, while subjects in the vehicle group experienced only 2%, 12%, and 3% increases in eyelash length, thickness, and darkness, respectively.

6.3 Benefit-Risk Summary

The overall benefit-risk assessment of bimatoprost for eyelash growth is favorable due to the fact that risks are minimal and the aesthetic benefits are well-demonstrated and meaningful. The following points summarize the favorable benefit-risk profile.

- There is a substantial history of safe use of bimatoprost for the treatment of glaucoma in multiethnic populations around the world, with an estimated 3461 patient-years of clinical exposures (including 440 patient-years of exposure in non-Caucasians) and 9 million patient-years of postmarketing exposures, at higher total drug exposures than when it is used topically for eyelash growth.

- The safety profile demonstrated in the pivotal BEG study was favorable when considered alone, but also when compared to the safety profile of bimatoprost for the treatment of glaucoma, which delivers bimatoprost at far greater levels than BEG. The observed risks in both of these clinical programs were low.

- Adverse events reported during the pivotal BEG study occurred at a low frequency and were largely mild in severity, cosmetic in nature, and reversible. Adverse events did not usually lead to discontinuation from the study and PRO data indicate that adverse events did not impact subjects' overall levels of satisfaction.

- Bimatoprost-treated subjects in the pivotal BEG study experienced substantial benefits. Bimatoprost solution 0.03% not only enhanced the overall prominence, length, thickness, and darkness of their eyelashes to a noticeable and significant degree, but also increased their level of satisfaction with their eyelashes in terms of physical attributes and in terms their feelings of confidence, attractiveness, and professionalism. The efficacy results demonstrated concordance with one another and with patient satisfaction.

- Allergan is committed to further assessing and verifying the safety profile of BEG through enhanced pharmacovigilance activities and appropriate risk communication and risk minimization efforts.

7. Risk Management Plan

Allergan proposes the following pharmacovigilance and risk minimization activities, with final plans to be agreed with FDA, in order to maximize the benefit and minimize the risk of BEG use in the postmarketing setting. The following is not intended to be an exhaustive list, but rather targets key issues, including potential ocular effects, long-term safety, use in non-Caucasians, potential off-label use and potential pregnancy exposures.

7.1 Potential Risks

7.1.1 Ocular Effects

Bimatoprost ophthalmic solution 0.03% lowers IOP when applied as a topical ophthalmic in patients with elevated IOP. Thus, if BEG solution gets into the eye, there is potential for a reduction in IOP. In the pivotal BEG study, which enrolled healthy subjects with normal IOP, statistically significant differences in mean IOP reduction were observed between the BEG and vehicle treatment groups; however, the magnitude of the reduction was not clinically meaningful (Section 3.2.2).

Co-administration of BEG solution (applied on the skin at the base of the upper eyelid margin) along with prostaglandin $F_{2\alpha}$ analogs, including LUMIGAN® (instilled in the eye for elevated IOP) has not been studied. In ocular hypertension studies of bimatoprost, it has been shown that exposure to the eye with more than 1 dose of bimatoprost daily may decrease the IOP-lowering effect. Therefore, BEG solution should be used with caution in patients with known risk factors for IOP changes. Patients using prostaglandin products concomitantly should be closely monitored for changes to their IOP.

BEG solution should also be used with caution in patients with active intraocular inflammation (eg, uveitis) because the inflammation may be exacerbated. There is a very low risk for any of these conditions in BEG-treated patients due to the low incidence of this adverse event in the glaucoma studies (< 1%) and due to the lower exposure with lid margin application.

Cosmetic products used on or around the eye may increase the risk of ocular infection. In a study conducted by Thomas and Barton (1978)—the only published epidemiological study identified in a literature search on this topic—it was found that 25% of all studied eye makeup contained viable microbes and that the most frequently contaminated product was mascara (37% positivity rate). The incidence of cosmetic-associated eye infections in the study was 7.1%. BEG is an aesthetic product formulated with preservative and is packaged with sterile, single use applicators, with the goal of minimizing the risk of ocular infection.

7.1.2 Long-term Safety

Eyelash changes are usually reversible upon discontinuation of treatment, thus continuous use is necessary to sustain the effects of eyelash enhancement. The long-term safety of bimatoprost has been demonstrated by up to 48 months of exposure in the glaucoma population (Study 192024-014). Exposure in the eyelash growth target population has been studied through 4 months.

7.1.3 Use in Blacks, Asians, and Other Ethnic Groups

Non-Caucasians were under-represented in the pivotal BEG study (ie, 79.6% of the treated subjects were Caucasian, 13% Asian, 4.4% Hispanic and 0.0% black). However, there is significant experience in non-Caucasians within the key long-term (>1 year) glaucoma studies. In fact, the long-term clinical studies studied 356 non-Caucasian patients (of which, 238 were black) with a total of 440.6 patient-years of exposure this shows the similar incidence of eyelash growth reported as an adverse event by different ethnic groups during the pivotal glaucoma studies. The safety profile was also similar across racial groups.

7.1.4 Potential off-label use

Areas of potential off-label use include use of the product 1) on other areas of the body (eg, lower lid, eyebrows, scalp), 2) by adolescents, 3) more than once per day, and 4) in women of childbearing potential.

Use on Other Areas of the Body

Off-label use of bimatoprost solution 0.03% on other parts of the body may occur. Application to large surface areas is not recommended. Due to the 3 mL fill size of the product, it will be impractical to use on larger body surface areas such as the scalp. In addition, the formulation is not well suited for penetration of the scalp. The bimatoprost 0.03% aqueous formulation (LUMIGAN®) was developed for ophthalmic use without consideration to optimizing the skin delivery of the active drug molecule. At the eyelid margin, the keratinized epithelium of the eyelid skin changes its character to become

nonkeratinized stratified squamous epithelium (Records, 1979). The nonkeratinized epithelium favors drug penetration without requiring vehicle ingredients used in typical dermatological formulations to optimize skin delivery. The scalp skin is highly keratinized and presents a significant barrier to penetration; it is highly likely that the current aqueous solution will not provide sufficient delivery of the active drug to the scalp hair follicles, resulting in poor or no efficacy.

Adolescents

Despite barriers of access to BEG and the compliance required in order to see an initial benefit (ie, daily applications over the course of several weeks are often needed to experience an effect), some off-label use in adolescents may occur. BEG is labeled for adult use only and has not been studied or approved for use in children under 18 years of age. Studies on treatment compliance in acne, a condition that can have a devastating effect on self esteem and social relationships, indicate that compliance rates among adolescents generally do not exceed 50%. For instance, the compliance rate in students using non-prescription benzoyl peroxide for acne for 10 weeks was 49% (Flanders et al, 1984), the compliance rate for students taking an unspecified acne medication at a college health services center was 12.5% (Parsons et al., 1980), and in another study of students, the compliance rate was 28.5% where regularly scheduled physician office visits were required (McEvoy et al, 2003).

Ocular and visual development in children generally approaches adult levels by 13 years of age. Significant ocular and visual development takes place during the first 2 years of life with the remainder of growth occurring in two stages, between 2–5 and 5–13 years of age (Fledelius and Christensen, 1996; Wright and Spiegel, 1999; Weingeist et al., 1999; Isenberg, 1994). IOP tends to be lower in children but increases with age and approaches adult levels by age 12 (Sihota et al., 2006). Though safety and efficacy of bimatoprost in pediatric patients has not been studied, there are several published studies on latanoprost (a prostaglandin) used in a pediatric population. In these studies, side effects have been reported as infrequent and mild (Enyedi and Freedman, 2002; Enyedi et al., 1999; Ravinet et al., 2003; Urban et al., 2004; Ong et al., 2003). Enyedi et al. (1999) prospectively followed 57 eyes of 48 pediatric patients for a total of 394 patient-months on latanoprost, with an average of 7 (range 1–19) months of latanoprost treatment per eye and reported that ocular side-effects in children were infrequent and mild. Reported side effects included transient conjunctival redness (2 patients), unspecified irritation (1 patient), possible sleep disturbance (1 patient), and possibly increased eyelash thickness and pigmentation (1 patient) (Enyedi and Freedman, 2002).

Should adolescents nevertheless use BEG off-label, it is anticipated that, based on the mechanism of action of bimatoprost in eyelash growth (ie. bimaotprost prolongs anagen and stimulates transition from telogen back to anagen) and the fact that ocular development is generally complete by adolescence, the benefit-risk profile would be similar to adults.

Higher than labeled application (eg, more than 1 application per day)

Proposed labeling recommends that BEG is applied once daily; however, there remains some potential that patients will use multiple applications daily thinking that they may achieve an earlier and/or more pronounced effect. The total dose of bimatoprost delivered to the eyelid margin of one eye when used according to the proposed package instructions is approximately 5% of the dose that is delivered to one eye by a 1-drop dose of bimatoprost ophthalmic solution. Bimatoprost ophthalmic solution has been shown to be safe and well-tolerated in clinical studies (evaluating both QD and BID administration) and postmarketing data. Thus, even if multiple daily applications do occur, exposure is expected to remain low and pose no associated safety concerns.

Women of Childbearing Potential

Pregnancy Exposure

In reproductive toxicity studies, late-gestational abortion, early delivery, and shortened gestation periods observed in high dose groups were likely related to exaggerated pharmacological effects of bimatoprost or a specific metabolite. The abortions are considered to be rodent-specific effects secondary to the ovarian luteolytic effect of prostaglandin analogs in these species. These effects were observed at systemic levels (C_{max}) of bimatoprost that were at least 120-fold greater than those in humans after ocular dosing. Prostaglandins exert abortifacient activity in humans by direct contractile effects on the uterus. Bimatoprost is not uterotonic in humans, and the specific metabolite is not detected in human females treated with bimatoprost ophthalmic drops. No embryo/fetal effects of malformations were apparent in the rodent reproductive toxicity studies. High exposure margins, species-specific metabolism and exaggerated pharmacological effects of bimatoprost in rodents indicate that the risk for abortion or abnormal fetal development in humans with this use is negligible.

Three pregnancies have been exposed to bimatoprost in the postmarketing setting. Normal birth resulted in 1 case, 1 case resulted in a spontaneous abortion at 9 weeks gestation, and for 1 case, the outcome is still unknown. The patient who reported a spontaneous abortion

was a 36 year old female who was switched from bimatoprost to betaxolol when she was 7 weeks pregnant. There is no indication that bimatoprost has an adverse effect on pregnancy.

There was 1 exposed pregnancy reported during the posttreatment period of the pivotal BEG study. The subject gave birth via cesarean section on June 10, 2008 to a normal female child with no complications reported.

Concomitant Use of Bimatoprost Solution and Oral Contraceptives
The effect of bimatoprost treatment on hepatic drug-metabolizing enzymes has been investigated in rats and monkeys following 1 month of daily intravenous administration at systemic drug exposures at least 4,000 times greater than those seen in humans following once daily ophthalmic administration. Bimatoprost was found to have no significant effect on any of the hepatic microsomal enzyme activities in cynomolgus monkeys. In female rats, an increase in the activity of UDP-glucuronosyl transferase was observed. In male rats, the only finding was a marginal reduction in the rate of testosterone 16β – hydroxylation. Neither of these observations is expected to have any clinically significant consequences in humans (Study PK-99-100).

7.2 Pharmacovigilance Plan

Allergan is a global, multi-specialty pharmaceutical company with a long history in prescription eye care and aesthetic products and as such, has the required systems in place throughout the company to collect, monitor, evaluate and report adverse events associated with our products in order to help ensure their safe and appropriate use. Aggregate safety reports and risk management plans are also created, managed, and maintained in compliance with all current regulations.

7.2.1 Routine Pharmacovigilance Practices

The potential risks listed above will be monitored in the postmarketing setting through a number of pharmacovigilance activities, resulting in the collection and evaluation of additional safety data. Allergan's pharmacovigilance systems are designed to systematically collect adverse events from multiple sources and to conduct real-time periodic medical assessments of single and aggregate cases to identify potential safety signals. The detection and evaluation of changes in reporting frequency of adverse events and changes in overall adverse event patterns that are suggestive of new potential safety concerns enables the company to develop and implement appropriate risk management strategies.

Pharmacovigilance activities are already utilized to monitor spontaneous adverse event reporting of bimatoprost in the postmarketing setting. These include:

- Adverse event collection and single case processing in a centralized and validated company safety database (Argus).
    - Collection of spontaneous adverse event reports and clinical serious adverse events in a centralized and validated company safety database (Argus).
    - Performance of real-time medical review and assessment to identify important single cases and conduct of appropriate follow-up to obtain relevant medical information.
    - Preparation and submission to health authorities, including the FDA, of all Expedited Reports and other reports of interest within specified time frames.
    - A "Sentinel Events List" is maintained for all products or product families. This list is utilized by global and regional pharmacovigilance staff and highlights particular events, regardless of seriousness or listedness, that may be more likely to require additional action by Allergan, depending on the nature the reports and/or reporting trends. Sentinel events may be internally identified or are of particular interest to individual regulatory authorities. Pigmentation changes are already part of the sentinel events list for bimatoprost for glaucoma, and will continue to be followed for bimatoprost solution 0.03% for eyelash growth as well.

- Aggregate Reports
    - Health Authority Specified Reports: Aggregate reports are prepared and submitted to health authorities as required by regulations. These include Periodic Safety Update Reports (PSURs), New Drug Application Periodic Adverse Drug Experience Reports (NDA PADER), Annual Safety Reports and other reports as required.
    - Ad-hoc or Interim Reports on Specified Topics as Requested or Agreed: Ad-hoc reports are prepared upon identification of a potential safety issue and/or upon request by a regulatory agency or other healthcare customer.
    - Other Summary Reports: This includes relevant safety information from clinical, epidemiology and external data sources.

- Safety surveillance and signal detection
    - Signals can also be recognized via numerous other routes including individual case safety reports, published literature, PSURs, regulatory authority questions, aggregate review of clinical study AEs, and other sources. As with other signals, these are triaged and evaluated as per the process below.
    - A signal may trigger additional risk evaluation (ie, a cumulative data review or an epidemiologic or clinical study) and may prompt risk minimization activities such as changes to the reference safety information (and thereby labeling changes) or other activities.
    - The signal detection and evaluation processes are led by Allergan's safety physicians. The signal detection process includes both qualitative and quantitative methods. Signal detection and evaluation activities are conducted on a scheduled basis for each product/product family and are also performed if a possible signal is detected.
    - Bi-weekly physician meetings are conducted to review the adverse event reporting experience of the previous period (both serious and non-serious events) and to present, discuss, and follow-up on cases of interest. Such meetings may also be held on an as-needed basis by the product's risk management team.
    - In order to supplement and facilitate qualitative medical analysis, quantitative methods of signal detection are employed on Allergan's global safety database on a scheduled basis. This includes the method of disproportionality analysis known as the Proportional Reporting Ratio, as applied to both individual MedDRA PTs and groups of events. Scheduled reports may also evaluate all occurrences of specific adverse events over a given time interval. These reports are reviewed by safety physicians to look for emerging signals and any unusual AEs. In addition, other sources of data may be analyzed or evaluated, eg, literature reviews, regulatory databases (eg, FDA AERS), epidemiological studies, to provide additional context. Any significant findings are reported to the regulatory authorities.

7.2.2 Additional Pharmacovigilance Activities Specific to Bimatoprost

Allergan is proposing the following additional activities to enhance and expedite the acquisition of safety information specifically for bimatoprost.

- Targeted questionnaire(s) to be used by Allergan's adverse event case-processing group at point of data collection to enhance the quality and completeness of data obtained through spontaneous reporting. Specifically, the following issues will be addressed in the Targeted Questionnaire:
    - Distinguishing among the bimatoprost products (eg, bimatoprost for glaucoma vs. BEG) with respect to the actual product used
    - The reason the patient was using the product (eg, glaucoma vs. eyelash growth)
    - How the product was obtained (eg, with a prescription; specialty of prescriber; from a friend or relative)
    - Patient demographics, including age and race
    - Relevant co-morbidities (eg, active eye disease) and concomitant medications (eg, other prostaglandin analogues)
    - Whether the patient had been seen by an ophthalmologist before starting the product
    - How the product was utilized (eg, topical ophthalmic or dermatologic application, number of applications per day, whether sterile applicators were used as indicated; duration of use)
    - Whether patients had received and read product materials in advance of starting treatment
    - Additional data, including pregnancy outcome, will be collected for all pregnancy exposures
- A periodic internal advisory board will be convened every 6 months for the first 2 years post-approval to review and evaluate aggregate pharmacovigilance data

- Submission of enhanced periodic safety reports, including the advisory board evaluation and/or enhanced aggregate analyses of BEG pharmacovigilance data as needed

7.3 Risk Minimization Activities

Allergan is committed to implementing measures that will inform and educate both physicians and patients. The fact that BEG will be a prescription drug helps to assure physicians and patients of the efficacy and safety of BEG, which cannot be similarly confirmed for some over-the-counter and unapproved eyelash treatments. Risk minimization activities proposed for BEG include both labeling and education for prescribers and patients.

To help ensure safe and effective use of BEG, conditions under which the drug can be used safely and effectively will be clearly described in the labeling for this product (ie, product package insert, patient package insert, and packaging). Samples of relevant excerpts from the proposed label are listed in Table 7–1.

Table 7–1 Summary of Proposed Labeling

Risk Management Issue	Labeling Information
Potential ocular effects, including decreased intraocular pressure, inflammation, and macular edema	Patients using these products concomitantly should be closely monitored for changes to their intraocular pressure. **(Section 5.2; Section 17.3; Section 17.6)** BEG solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated. **(Section 5.5)** BEG should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. **(Section 5.6)**
Potential off-label use	BEG (bimatoprost solution) 0.03% should only be applied to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying sterile, disposable applicators. **(Section 5.1; Section 17.1)** Safety and effectiveness in pediatric patients have not been established **(Section 8.4)**
Use in blacks, Asians, and other racial groups	Patients who receive treatment with BEG should be informed of the possibility of increased pigmentation **(Section 5.3; Section 17.4)**

In addition, product design elements have been incorporated in order to minimize risk:

Sterile applicators
BEG will be packaged with sterile, single-use applicators intended to help minimize the risk of ocular infection. Also important is that the applicators help to minimize exposure by enabling targeted placement of the drug to the upper lash line. The BEG clinical study demonstrated that this lower exposure leads to a lower incidence of adverse events compared to the topical ophthalmic application in glaucoma.

Formulation includes preservative
The BEG formulation includes a preservative, also intended to minimize risk of ocular infection. Unpreserved cosmetic products have been associated with higher infection risk (Thomas and Barton, 1978).

As an extension to labeling (product package insert, packaging), Allergan is also planning prescriber and patient education in the standard materials/aids provided to prescribers and patients at launch. The goal of this education and outreach effort is to inform healthcare practitioners and patients about conditions of appropriate use of BEG. Targeted key messages will include:

- Educating non-ophthalmologists on the importance of:
    - When it is important for the patient to be evaluated and/or monitored by an ophthalmologist
    - Potential ocular effects of BEG
    - Appropriate patient selection
    - Appropriate patient counselling, including the need for patients using BEG concomitantly with another prostaglandin analogue product to be monitored for any IOP effects

- Educating all prescribers on the importance of using the product as indicated:
    - BEG is labeled for adult use only and has not been studied or approved for use in children < 18 years of age)
    - BEG is labeled for use on the upper eyelid only
    - Appropriate patient selection (ie, identifying potentially higher-risk patients who require ophthalmologist supervision)

- Counsel patients on:
    - Potential ocular effects, including iris and skin hyperpigmentation
    - Appropriate product use, including the use of the sterile applicators
    - When to seek physician advice
    - Which patients should be treated under ophthalmologist supervision

Allergan is committed to ensuring the safe and appropriate use of our products via appropriate pharmacovigilance and risk minimization and communication, as agreed with FDA.

8. Conclusions

Bimatoprost solution 0.03%, applied topically to the upper eyelid margins, has been conclusively shown to be safe and effective in improving the prominence of natural eyelashes as measured by increases in growth (length), fullness (thickness), and darkness (intensity), thus providing a key benefit desired by consumers. The safety database for bimatoprost is substantial, with clinical study exposure to bimatoprost estimated at 3461 patient-years and worldwide postmarketing exposure estimated at 9 million patient-years. Bimatoprost ophthalmic solution 0.03% has been used safely and successfully for over 7 years in a large multi-ethnic population around the world. The pivotal study for bimatoprost for eyelash growth confirmed the highly favorable safety profile that was expected for bimatoprost 0.03% when applied topically to the upper eyelid margins at a dose approximately 5% of the indicated 1-drop dose for the treatment of glaucoma. In addition to the favorable safety profile demonstrated in the pivotal BEG study, excellent efficacy was observed for all endpoints, with differences between bimatoprost and vehicle reaching high statistical significance for the measurements of eyelash prominence, length, thickness, and darkness ($p < 0.0001$ for each endpoint at the primary time point). The primary and secondary efficacy endpoints showed concordance with each other and with the PRO measures. Patient-reported outcomes results clearly showed that the benefits of bimatoprost for eyelash growth are not only noticeable through the statistical interpretation of clinical measurements, but are noticeable and appreciated by the persons who use the product.

Given the long history of clinical and postmarketing safety with bimatoprost ophthalmic solution and the positive results from the pivotal study for bimatoprost for eyelash growth, Allergan believes that bimatoprost solution 0.03% can provide meaningful aesthetic benefit to the patients who use it while posing minimal risk. If approved, this product will be the first eyelash enhancement product to be developed under FDA guidance and manufactured

under good manufacturing practices. Furthermore, the launch of this product with comprehensive labeling for use under physician supervision and a risk minimization plan including enhanced pharmacovigilance, will further ensure the safe use of the product in the marketplace and allow patient access to a highly desired aesthetic benefit.

9. Appendices

9.1 Proposed Packaging and Instructions for Use

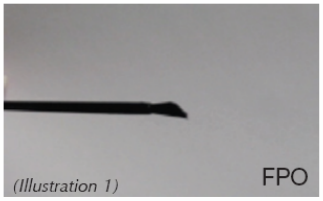
Figure 9–1 Proposed Packaging

Figure 9–2 Proposed Instructions for Use

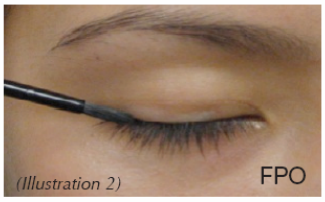
INTRODUCING TRADENAME™
(bimatoprost solution) 0.03%

Instructions for use once a day in the evening:

1. Start by ensuring your face is clean, makeup and contact lenses are removed, and any other facial care products have been applied.
2. Remove an applicator from its tray. Then, holding the sterile applicator horizontally, apply one drop of **TRADENAME**™ to the area of the applicator closest to the tip but not on the tip (see Illustration 1).



3. Then immediately draw the applicator carefully across the skin of the upper eyelid at the base of the eyelashes (where the eyelashes meet the skin) going from the inner part of your eyelash line to the outer part (see Illustration 2). This area should feel evenly and lightly moist without runoff.
4. Blot any excess solution beyond the eyelid margin.



5. Dispose of the applicator after one use. Repeat for opposite eyelid margin using a new sterile applicator. This helps minimize any potential for contamination from one eyelid to another.

DO NOT APPLY on your eye or to the lower eyelid. Use **ONLY** the sterile applicators supplied with **TRADENAME**™ to apply the product. If you miss a dose, don't try to "catch up." Just apply **TRADENAME**™ solution the next evening.

Do not allow the tip of the bottle or applicator to contact surrounding structures, fingers, or any other unintended surface in order to avoid contamination by common bacteria known to cause infections.

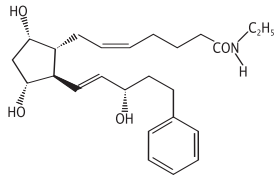
Contact lenses should be removed prior to application of **TRADENAME**™ and may be reinserted 15 minutes following its administration.

9.2 LUMIGAN® Product Information

LUMIGAN®
(bimatoprost ophthalmic solution) 0.03%

DESCRIPTION

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is $C_{25}H_{37}NO_4$. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. **LUMIGAN®** is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

Contains: Active: bimatoprost 0.3 mg/mL; **Preservative:** Benzalkonium chloride 0.05 mg/mL; **Inactives:** Sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics:

Absorption:

After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hr}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

Distribution:

Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism:

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination:

Following an intravenous dose of radiolabeled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:

In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.03% once daily (in the evening) was 7-8 mmHg.

Results of dosing for up to five years with products in this drug class showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment for the majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris pigmentation throughout the five years of the study. Observation of increased iris pigmentation did not affect the incidence, nature or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, **LUMIGAN®** had no adverse effect on liver function over 48 months.

INDICATIONS AND USAGE

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, and growth of eyelashes. Pigmentation is expected to increase as long as **LUMIGAN®** is administered. After discontinuation of **LUMIGAN®** pigmentation of the iris is likely to be permanent while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The effects of increased pigmentation beyond 5 years are not known.

PRECAUTIONS

General: LUMIGAN® (bimatoprost ophthalmic solution) 0.03% may gradually increase the pigmentation of the iris. The eye color change is due to increased melanin content in the stromal melanocytes of the iris rather than to an increase in the number of melanocytes. This change may not be noticeable for several months to years (see **WARNINGS**). Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN®** can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent.

Eyelid skin darkening, which may be reversible upon discontinuation of the treatment has been reported in association with the use of **LUMIGAN®**.

LUMIGAN® may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

LUMIGAN® has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PRECAUTIONS,** Information for Patients).

Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration (see **PRECAUTIONS,** Information for Patients).

Information for Patients: (see **WARNINGS** and **PRECAUTIONS**): Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®**.

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®**. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

Patients should be advised that **LUMIGAN®** contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of fertility: Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1mg/kg/day respectively (approximately 192 times and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure based on blood AUC levels).

Pregnancy: Teratogenic effects: *Pregnancy Category C.* In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the intended human exposure based on blood AUC levels.

At doses 41 times the intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: It is not known whether **LUMIGAN®** is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

In clinical trials, the most frequent events associated with the use of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.03% occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1 to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1 to 5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthenia and hirsutism.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** (bimatoprost ophthalmic solution) 0.03% occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m^2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN®** for a 10 kg child.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.03% should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.

LUMIGAN® may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is supplied sterile in opaque white low density polyethylene ophthalmic dispenser bottles and tips with turquoise polystyrene caps in the following sizes:

2.5 mL fill in 5 mL container - NDC 0023-9187-03
5 mL fill in 10 mL container - NDC 0023-9187-05
7.5 mL fill in 10 mL container - NDC 0023-9187-07

Storage: LUMIGAN® should be stored in the original container at 2º to 25ºC (36º to 77ºF).

Rx only
Revised September 2006

US Patent 5,688,819 and 6,403,649

9106X Re-order: 4961310
Based on 71669US11T

ALLERGAN®

9.3 Global Eyelash Assessment (GEA) Scale with Photonumeric Guide

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 uses a 4-point ordinal scale which includes a brief description of each measure accompanied by representative photographs. This scale provides 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 will be 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.

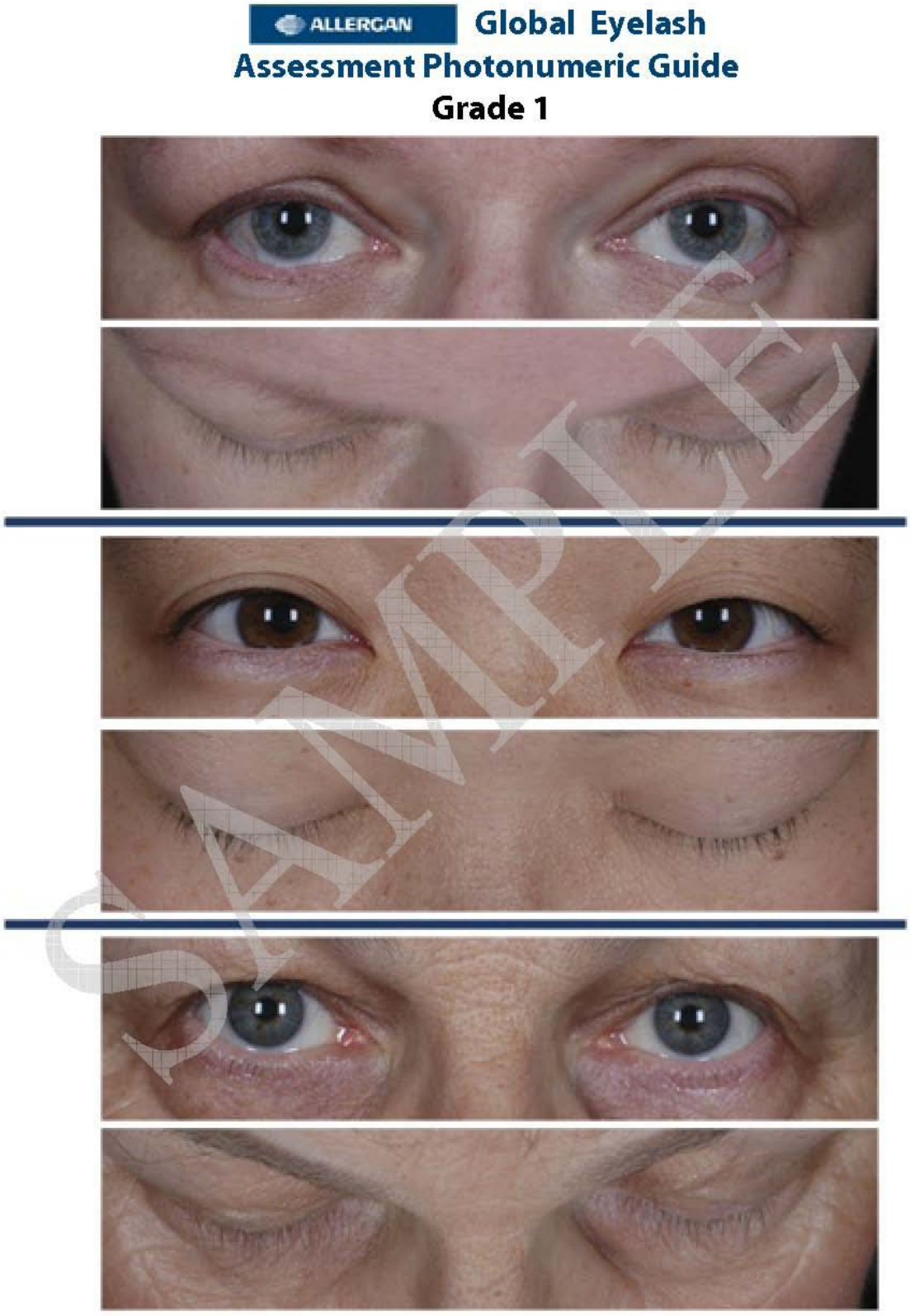
2. **Moderate:** Corresponding to photoguide Grade 2 frontal views and superior view.

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.

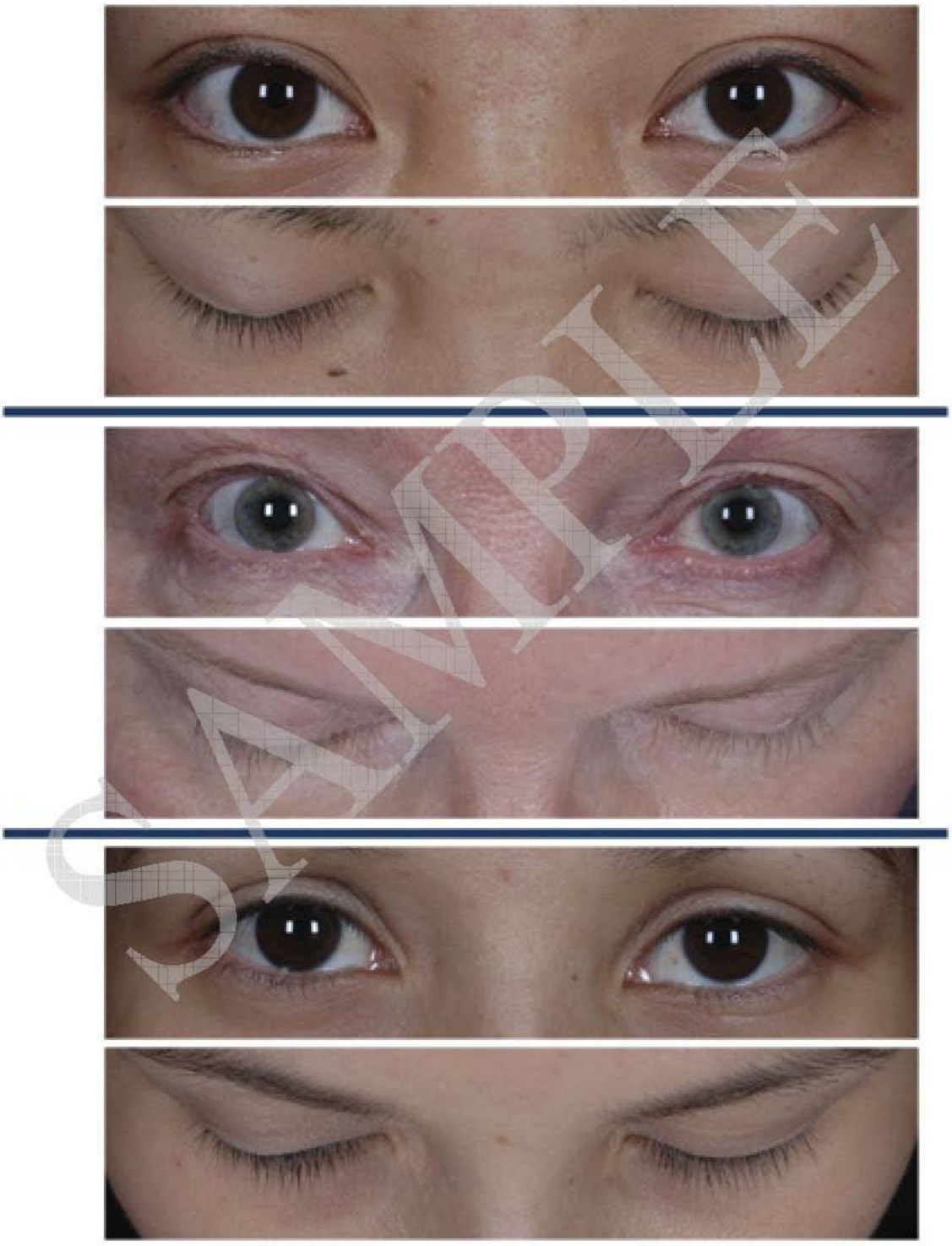
In determining the appropriate GEA score, the rater should evaluate overall eyelash prominence, including elements of length, fullness, and color of both upper eyelashes. Length should be considered the most important feature.

The following pages will serve as the photonumeric 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).


ALLERGAN
Global Eyelash
Assessment Photonumeric Guide
Grade 1
SAMPLE

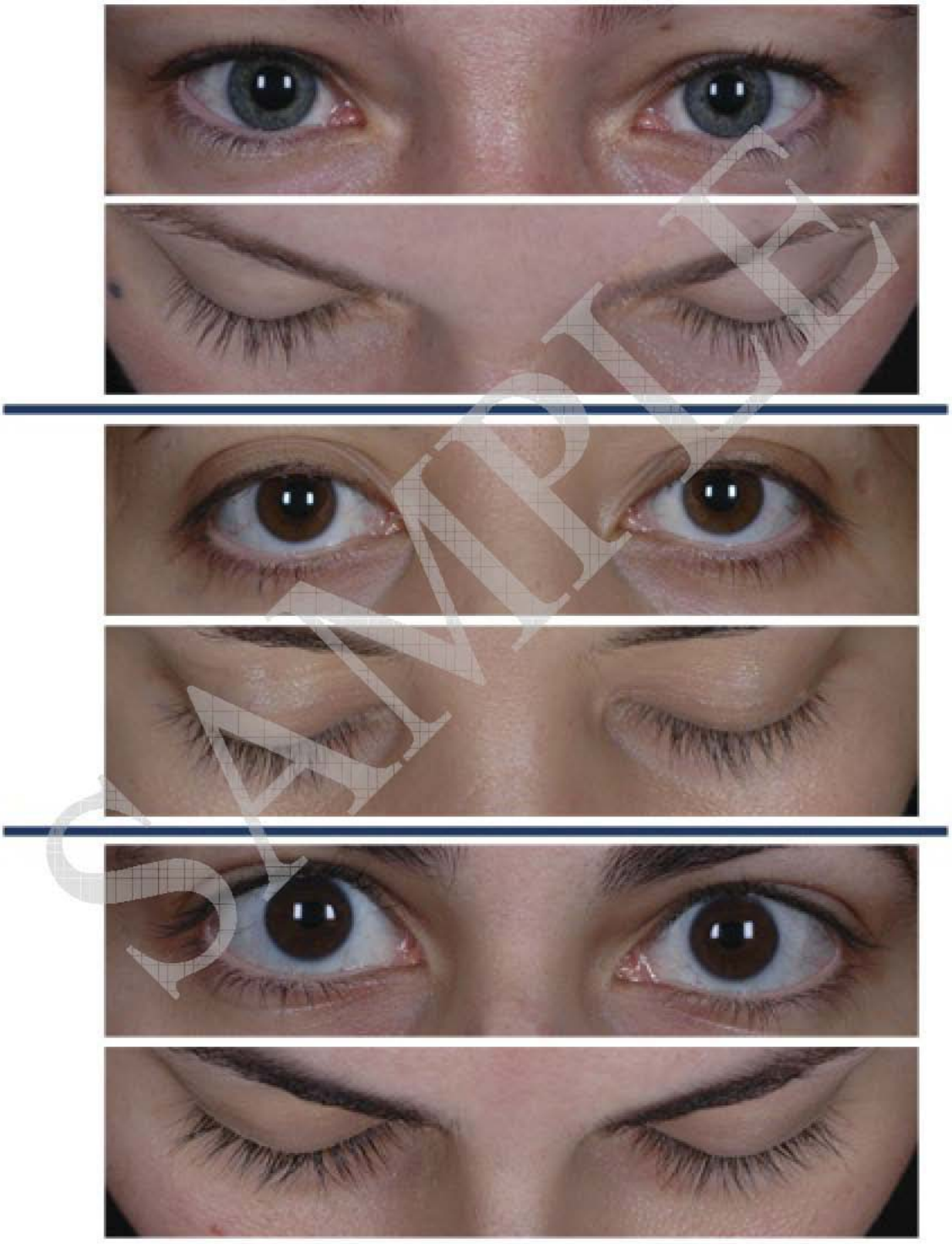
ALLERGAN **Global Eyelash Assessment Photonumeric Guide**

Grade 2



ALLERGAN **Global Eyelash Assessment Photonumeric Guide**

Grade 3



ALLERGAN **Global Eyelash Assessment Photonumeric Guide**

Grade 4

9.4 Patient Reported Outcomes Questionnaire

Please answer questions 1 -8 assuming without mascara.

1. How satisfied are you with the length of your eyelashes?
   - ❒ Very satisfied
   - ❒ Satisfied
   - ❒ Neutral
   - ❒ Unsatisfied
   - ❒ Very unsatisfied

2. How satisfied are you with the fullness/thickness of your eyelashes?
   - ❒ Very satisfied
   - ❒ Satisfied
   - ❒ Neutral
   - ❒ Unsatisfied
   - ❒ Very unsatisfied

3. How satisfied are you with the darkness of your eyelashes?
   - ❒ Very satisfied
   - ❒ Satisfied
   - ❒ Neutral
   - ❒ Unsatisfied
   - ❒ Very unsatisfied

4. OVERALL, how satisfied are you with your eyelashes?
   - ❒ Very satisfied
   - ❒ Satisfied
   - ❒ Neutral
   - ❒ Unsatisfied
   - ❒ Very unsatisfied

5. How often do others give you compliments about your eyelashes?
   - ❒ Very Frequently
   - ❒ Frequently
   - ❒ Sometimes/occasionally
   - ❒ Almost never
   - ❒ Never

6. Rate your eyelash length.
   - ❒ Very long
   - ❒ Long
   - ❒ Medium
   - ❒ Short
   - ❒ Very short

7. Rate your eyelash fullness/thickness.
   - ❒ Very full/thick
   - ❒ Full/thick
   - ❒ Medium
   - ❒ Thin
   - ❒ Very thin

8. Rate your overall eyelash color.
   - ❒ Very dark
   - ❒ Dark
   - ❒ Medium
   - ❒ Light
   - ❒ Very light

9. I am bothered with the amount of time I spend applying mascara to my eyelashes.
   - ❒ Very much agree
   - ❒ Agree
   - ❒ Neutral
   - ❒ Disagree
   - ❒ Very much disagree

10. I am bothered with the amount of time I spend removing mascara off of my eyelashes.
    - ❒ Very much agree
    - ❒ Agree
    - ❒ Neutral
    - ❒ Disagree
    - ❒ Very much disagree

11. It is a hassle to spend time in making my eyelashes presentable everyday.
    - ❒ Very much agree
    - ❒ Agree
    - ❒ Neutral
    - ❒ Disagree
    - ❒ Very much disagree

12. On my days off, I can go out in public without putting on mascara.
    - ❒ Very much agree
    - ❒ Agree
    - ❒ Neutral
    - ❒ Disagree
    - ❒ Very much disagree

13. I worry about my mascara smearing.
    - ❒ Very much agree
    - ❒ Agree
    - ❒ Neutral
    - ❒ Disagree
    - ❒ Very much disagree

For Questions 14-23, state how much you agree with the following statements.

	How much do you agree with the following statements?	**Very much agree**	**Agree**	**Neutral**	**Disagree**	**Very much disagree**
14.	Without wearing mascara my eyelashes make my eyes look tired.					
15.	Without wearing mascara my eyelashes look naturally attractive.					
16.	Without wearing mascara my eyelashes make me feel confident in my looks.					
17.	Without wearing mascara my eyelashes make me feel confident about going out in public.					
18.	Without wearing mascara my eyelashes make me feel confident about my professional appearance.					
19.	Without wearing mascara my eyelashes make me feel attractive.					
20.	Without wearing mascara my eyelashes look healthy.					
21.	Without wearing mascara my eyelashes make my eyes look vibrant.					
22.	Without wearing mascara my eyelashes look full.					
23.	Without wearing mascara my eyelashes make me feel beautiful.					

10. Tables and Figures

Table 10–1 Nonclinical Toxicology Program of Bimatoprost

Study Type	Species	Duration	Dose and Frequency
Repeat Dose Ocular	Rabbit (NZW)	1 month	0.001%, 35 μL, QID
	Rabbit (DB)	1 month	0.03%, 35 μL, BID
	Rabbit (DB)	6 month	0.1%, 35 μL, BID
	Dog	1 month	0.001% or 0.01%, 35 μL, QID
	Monkey	52 weeks	0.03%, 35 μL, QD or BID 0.1%, 35 μL, BID
Repeat Dose Oral	Mice	1 month	0, 8, 16 mg/kg/day
	Mice	90-day	0, 4, 8, 16 mg/kg/day
	Rats	1 month	0, 4, 16 mg/kg/day
	Rats	90 days	0, 0.1, 0.3, 4, 8 mg/kg/day
	Rats	52 weeks	0, 0.1, 0.3 mg/kg/day
Repeat Dose Intravenous	Rats	1 month	0, 0.3, 1.0 mg/kg/day
	Monkey	1 month	0, 1.0 mg/kg/day
	Monkey	17 weeks	0, 0.01, 1.0 mg/kg/day
Embryo/Fetal Development	Mice	GD 6-15	0, 0.1, 0.3, 0.6 mg/kg/day
	Rat	GD 7-17	0, 0.3, 0.6 mg/kg/day
Fertility/General Reproduction	Rat	As per guidelines	0, 0.6 mg/kg/day
Peri/postnatal Development	Rat	GD7 – LD20	0, 0.05, 0.1, 0.3 mg/kg/day
Genotoxicity	Bacterial (Ames)	-	As per guidelines
	Cell assay	-	As per guidelines
	Mice	1-day	up to 20 mg/kg
Carcinogenicity	Mice	2 year	0, 0.3, 1.0, 2.0 mg/kg/day
	Rat	2 year	0, 0.1, 0.3, 1.0 mg/kg/day
Contact hypersensitivity	Guinea pigs	-	Up to 2mg/mL (0.2%)

GD: gestation day; LD: lactation day

Table 10–2 Exposure to Bimatoprost in Allergan-Sponsored Studies

Study	Population[a]	Duration	Patients in Bimatoprost Treatment Group(s)	Patients in Comparator Treatment Group(s)
192024-001	Patients	5.5 days	36	24
192024-002	Patients	28 days	60	40
192024-003	Patients	1 month	16	16
192024-004	Patients	1 month	42	64
192024-006	Volunteers	2 weeks	15	0
192024-007	Volunteers	2 weeks	15	0
192024-008	Patients	12 months	480	122
192024-009	Patients	12 months	477	119
192024-010	Patients	3 months	119	113
192024-011	Volunteers	4 days	27	27
192024-012	Volunteers	7 days	45	0
192024-013	Patients	3 months	90	87
192024-014	Patients	First 12 months	298[b]	81
	Patients	Second 12 months	140[b]	43
	Patients	Third 12 months	117[b]	35
192024-015	Patients	4 months	88	88
192024-016	Patients	28 days	38	77
192024-017	Patients	2 months	78	77
192024-018T[a]	Patients	12 months	390	130
192024-019	Patients	6 months	133	136
192024-020	Patients	1 month	156	32
192024-021T[a]	Patients	12 months	408	133
192024-023	Patients	14 days	167	0
192024-024	Patients	2 weeks	73	38
192024-026T	Patients	1 month	445	0
192024-028	Volunteers	4 days	196	6
192024-030	Patients	5 days	498	0
192024-031	Patients	12 months	561	0
192024-032	Volunteers	4 months	137	141
192024-035	Patients	4 weeks	150	71
192024-501[c]	Patients	3 months	299	138
192024-502[c]	Patients	12 months	190	95
192024-503T[c]	Volunteers	1 month	36	18
192024-504T[c]	Patients	12 weeks	303	155
192024-505[c]	Volunteers	2 weeks	80	10

Note: Unless otherwise specified, all studies were conducted in the United States and/or Canada.

a "Patients" had been diagnosed with ocular hypertension or open angle glaucoma prior to enrollment into the study. "Volunteers" were normal, healthy volunteers as defined by each protocol.

b Study 192024-014 was an extension of Studies -008 and -009; therefore, while these patient numbers were used for the calculation of patient-years, they were not used for the calculation of total number of patients exposed to bimatoprost, since they had been counted in the numbers of patients treated in Studies -008 and -009.

c These studies were conducted in the European Union.

Table 10–3 Demographics and Baseline Characteristics of Subjects Enrolled in the Pivotal Study for Bimatoprost for Eyelash Growth (Study 192024-032)

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

Source: CSR 192024-032

a For continuous variables, a 1-way ANOVA model was used. For categorical variables, Pearson's chi-square test was used or Fisher's exact test (if ≥ 25% of the expected cell count is <5).

b P-value for race is for Caucasian versus non-Caucasian.

c Light irides included the colors blue, blue-gray, blue/gray-brown, gray, green, green-brown, hazel, and other, and dark irides included the colors brown, dark brown, and black.

Table 10–4 Demographics and Baseline Characteristics of Patients Enrolled in the Long-term Studies of Bimatoprost for Glaucoma

	Bimatoprost 0.03% QD N = 926	Bimatoprost 0.03% BID N = 483	Timolol 0.5% BID N = 504
Age (years)			
Mean	61.5	61.6	60.6
SD	12.32	12.00	11.70
Median	63.0	63.0	62.0
Min, Max	22, 94	32, 91	22, 85
< 45, N (%)	85 (9.2)	54 (11.2)	43 (8.5)
45 to 65, N (%)	459 (49.6)	218 (45.1)	268 (53.2)
>65, N (%)	382 (41.3)	211 (43.7)	193 (38.3)
Sex, N (%)			
Male	428 (46.2)	234 (48.4)	224 (44.4)
Female	498 (53.8)	249 (51.6)	280 (55.6)
Race, N (%)			
Caucasian	682 (73.7)	371 (76.8)	369 (73.2)
Black	156 (16.8)	82 (17.0)	91 (18.1)
Asian	13 (1.4)	13 (2.7)	10 (2.0)
Hispanic	71 (7.7)	15 (3.1)	32 (6.3)
Other	4 (0.4)	2 (0.4)	2 (0.4)
Iris Color, N (%)			
Dark[a]	453 (48.9)	223 (46.2)	256 (50.8)
Light[a]	473 (51.1)	260 (53.8)	248 (49.2)

Note: Pooled analysis of Studies 192024-008, -009, -014, -018T, -021T, and -031

a Light iris colors included the colors blue, blue-gray, blue-gray-brown, gray, green, green-brown, hazel, and "other." Dark iris colors included the colors brown, dark brown, and black.

Table 10–5 Intraocular Pressure (mm Hg): Change From Baseline by Visit, (Study 192024-032)

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

Source: CSR 192024-032

a A 1-way ANOVA was performed to evaluate the difference among/between treatment groups.

b Paired t-tests were used to test for mean shifts from baseline within treatment groups.

Table 10–6 Number (%) of Patients Reporting Adverse Events During the First 12 Months, ≥ 5% of Patients in Bimatoprost 0.03% Treatment Groups of the Long-term Glaucoma Studies

SYSTEM ORGAN CLASS Preferred Term	Bimatoprost 0.03% QD N = 926	Bimatoprost 0.03% BID N = 483	Timolol 0.5% BID N = 504
Overall	803 (86.7)	460 (95.2)	379 (75.2)
EYE DISORDERS			
Overall	661 (71.4)	434 (89.9)	208 (41.3)
Conjunctival hyperaemia	405 (43.7)	275 (56.9)	60 (11.9)
Growth of eyelashes	188 (20.3)	224 (46.4)	15 (3.0)
Eye pruritis	99 (10.7)	78 (16.1)	14 (2.8)
Eye irritation	54 (5.8)	42 (8.7)	28 (5.6)
Dry eye	48 (5.2)	50 (10.4)	10 (2.0)
Foreign body sensation in eye	41 (4.4)	47 (9.7)	6 (1.2)
Eye pain	33 (3.6)	55 (11.4)	15 (3.0)
Vision blurred	35 (3.8)	33 (7.0)	17 (3.4)
Photophobia	18 (1.9)	33 (6.8)	3 (0.6)
Eyelash discolouration	15 (1.6)	25 (5.2)	1 (0.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Overall	142 (15.3)	120 (24.8)	27 (5.4)
Skin hyperpigmentation	60 (6.5)	58 (12.0)	2 (0.4)
Hypertrichosis	47 (5.1)	44 (19.1)	0 (0.0)
VASCULAR DISORDERS			
Overall	43 (4.6)	38 (7.9)	28 (5.6)
Hypertension	35 (3.8)	30 (6.2)	26 (5.2)

Source: Studies 192024-008, -009, -014, 018T, -021T, and -031.
QD = once daily; BID = twice daily
Note: Adverse events were coded using MedDRA. All adverse events are represented, regardless of causality.
Note: Within each system organ class, preferred terms are sorted by descending order of frequencies by treatment groups from left to right. Within each preferred term, a subject is counted at most once.
a Adverse events reported in this table are those preferred terms that were reported by greater than 5% of subjects in the bimatoprost 0.03% QD and BID groups.

Table 10–7 Number (%) of Subjects With at Least a 1-Grade Increase From Baseline in GEA Score on the 4-Point GEA Scale (Study 192024-032)

Visit[a]	Bimatoprost 0.03% (N = 137)	Vehicle (N = 141)	P-value[b]
Week 1	7/137 (5.1)	3/141 (2.1)	0.2124[c]
Week 4	20/137 (14.6)	11/141 (7.8)	0.0719
Week 8	69/137 (50.4)	21/141 (14.9)	< 0.0001
Week 12	95/137 (69.3)	28/141 (19.9)	< 0.0001
Week 16 (Primary Endpoint)	107/137 (78.1)	26/141 (18.4)	< 0.0001
Week 20	103/131 (78.6)	27/126 (21.4)	< 0.0001

Note: Week 16 was the end of the treatment period in Study 192024-032.
Note: Summaries of week 1 through 16 pertain to the ITT population in the treatment period and week 20 the posttreatment period
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.

Table 10–8 Number (%) of Subjects With at Least a 2-Grade Increase From Baseline in GEA Score on the 4-Point GEA Scale (Study 192024-032)

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

N/A: not applicable
Note: Week 16 was the end of the treatment period in Study 192024-032.
a LOCF was performed for weeks 4 through 16; 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.

Table 10–9 Number (%) of Subjects in Each Global Eyelash Assessment Scale Grade by Study Visit (Study 192024-032)

Visit/ GEA Grade	Bimatoprost 0.03% (N = 137)	Vehicle (N = 141)	Total (N = 278)
Baseline, N	137	141	278
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
Very Marked (4)	0	0	0
Week 1, N	137	141	278
Minimal (1)	24 (17.5)	28 (19.9)	52 (18.7)
Moderate (2)	113 (82.5)	112 (79.4)	225 (80.9)
Marked (3)	0	1 (0.7)	1 (0.4)
Very Marked (4)	0	0	0
Week 4, N	137	141	278
Minimal (1)	17 (12.4)	25 (17.7)	42 (15.1)
Moderate (2)	112 (81.8)	111 (78.7)	223 (80.2)
Marked (3)	8 (5.8)	5 (3.5)	13 (4.7)
Very Marked (4)	0	0	0
Week 8, N	137	141	278
Minimal (1)	8 (5.8)	16 (11.3)	24 (8.6)
Moderate (2)	80 (58.4)	115 (81.6)	195 (70.1)
Marked (3)	45 (32.8)	9 (6.4)	54 (19.4)
Very Marked (4)	4 (2.9)	1 (0.7)	5 (1.8)
Week 12, N	137	141	278
Minimal (1)	3 (2.2)	18 (12.8)	21 (7.6)
Moderate (2)	53 (38.7)	105 (74.5)	158 (56.8)
Marked (3)	64 (46.7)	17 (12.1)	81 (29.1)
Very Marked (4)	17 (12.4)	1 (0.7)	18 (6.5)
Week 16, N	137	141	278
Minimal (1)	0	19 (13.5)	19 (6.8)
Moderate (2)	45 (32.8)	105 (74.5)	150 (54.0)
Marked (3)	58 (42.3)	15 (10.6)	73 (26.3)
Very Marked (4)	34 (24.8)	2 (1.4)	36 (12.9)
Week 20, N	131	126	257
Minimal (1)	0	15 (11.9)	15 (5.8)
Moderate (2)	41 (31.3)	95 (75.4)	136 (52.9)
Marked (3)	56 (42.7)	13 (10.3)	69 (26.8)
Very Marked (4)	34 (26.0)	3 (2.4)	37 (14.4)

Source: CSR 192024-032
Note: Summaries of day 1 through week 16 pertain to the treatment period and week 20 pertains to the posttreatment period.
LOCF was performed on weeks 1 to 16. Week 20 analysis was based on observed cases only.

Table 10–10 Mean (SD) Change From Baseline to Week 16 in Secondary Endpoints, Treatment Responders and Nonresponders (Study 192024-032)

Secondary Efficacy Variable	Bimatoprost 0.03%		Vehicle	
	Responder (N = 107)	Nonresponder (N = 30)	Responder (N = 26)	Nonresponder (N = 115)
Length, pixels	61.32 (29.131)	17.06 (23.138)`	9.28 (16.076)	3.04 (15.391)
Thickness, % AOI in pixels	14.39 (7.771)	4.53 (5.478)	2.42 (3.830)	0.80 (3.974)
Darkness, intensity units	-24.00 (15.03)	-6.66 (11.723)	-4.38 (7.992)	-3.39 (10.989)

SD = standard deviation; AOI = area of interest
Note: A responder is defined as a subject with at least a 1-grade increase from baseline in GEA score at week 16. LOCF is performed on week 16.
Note: A negative change from baseline value in intensity units is representative of eyelash darkening

Table 10–11 Eyelash Length: Mean (SD) Change from Baseline at Each Follow-up Visit (Study 192024-032)

Visit[a]	Pixels			Millimeters		
	Bimatoprost 0.03%	Vehicle	P-value[b]	Bimatoprost 0.03%	Vehicle	P-value[b]
Day 1 (Baseline)	211.48 (29.725)	208.53 (30.175)	0.4387	5.79 (0.815)	5.71 (0.814)	0.4265
Week 1	2.19 (12.564)	0.22 (11.668)	0.2130	0.05 (0.327)	0.00 (0.327)	0.3717
Week 4	8.90 (13.501)	2.97 (13.498)	0.0006	0.22 (0.731)	0.06 (0.382)	0.0010
Week 8	24.18 (20.896)	3.59 (14.528)	< 0.0001	0.64 (0.559)	0.07 (0.396)	< 0.0001
Week 12	43.24 (26.886)	2.36 (15.482)	< 0.0001	1.16 (0.722)	0.05 (0.425)	< 0.0001
Week 16	51.63 (33.363)	4.19 (15.650)	< 0.0001	1.39 (0.908)	0.11 (0.425)	< 0.0001
Week 20	53.78 (30.919)	2.85 (15.958)	< 0.0001	1.47 (0.831)	0.06 (0.431)	< 0.0001

SD = Standard deviation
Note: Week 16 was the end of the treatment period in Study 192024-032.
Note: Summaries of day 1 through week 16 pertain to the treatment period (bimatoprost N = 137; vehicle N = 141) and week 20 pertains to the posttreatment period (bimatoprost N = 130; vehicle N = 125)
a LOCF is performed on weeks 1 through 16. Week 20 (posttreatment) analysis is based on observed cases.
b P-values are based on the Wilcoxon rank-sum test.

Table 10–12 Progressive Eyelash Thickness/Fullness: Mean (SD) Change From Baseline at Each Visit (Study 192024-032)

	% AOI in Pixels			Percent Change		
Visit[a]	Bimatoprost 0.03%	Vehicle	P-value[b]	Bimatoprost 0.03%	Vehicle	P-value[b]
Day 1 (Baseline)	16.16 (8.089)	16.66 (7.787)	0.4106	-	-	-
Week 1	0.94 (3.651)	0.24 (3.161)	0.2315	9.86 (29.784)	5.07 (25.310)	0.3205
Week 4	1.62 (4.031)	0.81 (3.639)	0.0914	15.79 (32.933)	9.35 (30.775)	0.0747
Week 8	3.48 (5.148)	0.75 (4.189)	< 0.0001	34.60 (56.087)	10.11 (31.282)	0.0004
Week 12	9.30 (7.328)	0.95 (4.398)	< 0.0001	82.19 (88.095)	10.21 (33.360)	< 0.0001
Week 16	12.21 (8.381)	1.10 (3.984)	< 0.0001	106.00 (107.470)	11.68 (30.772)	< 0.0001
Week 20	11.16 (7.501)	1.88 (4.470)	< 0.0001	100.17 (97.827)	18.77 (48.349)	< 0.0001

SD = Standard deviation
Note: Week 16 was the end of the treatment period in Study 192024-032.
Note: Summaries of day 1 through week 16 pertain to the treatment period (bimatoprost N = 136; vehicle N = 140) and week 20 pertains to the posttreatment period (bimatoprost N = 129; vehicle N = 125)
a LOCF is performed on weeks 1 through 16. Week 20 (posttreatment) analysis is based on observed cases.
b P-values are based on the Wilcoxon rank-sum test.

Table 10–13 Eyelash Darkness: Mean (SD) Change From Baseline at Each Follow-up Visit (Study 192024-032)

	Units (0 to 255)			Percent Change		
Visit[a]	Bimatoprost 0.03%	Vehicle	P-value[b]	Bimatoprost 0.03%	Vehicle	P-value[b]
Day 1 (Baseline)	105.67 (20.349)	102.82 (18.161)	0.1999	-	-	-
Week 1	-2.97 (8.102)	-1.25 (8.233)	0.0427	-2.50 (7.932)	-0.84 (7.762)	0.0501
Week 4	-5.10 (10.327)	-2.91 (9.363)	0.0779	-4.29 (9.336)	-2.44 (8.630)	0.0814
Week 8	-9.11 (11.824)	-2.46 (11.249)	< 0.0001	-8.10 (10.317)	-1.85 (10.561)	< 0.0001
Week 12	-16.68 (13.585)	-4.22 (11.073)	< 0.0001	-15.11 (11.737)	-3.61 (10.689)	< 0.0001
Week 16	-20.15 (16.051)	-3.57 (10.491)	< 0.0001	-18.19 (13.613)	-2.96 (10.166)	< 0.0001
Week 20	-20.12 (14.943)	-5.51 (10.789)	< 0.0001	-17.97 (12.532)	-4.85 (9.896)	< 0.0001

SD = Standard deviation
Note: Week 16 was the end of the treatment period in Study 192024-032.
Note: Summaries of day 1 through week 16 pertain to the treatment period (bimatoprost N = 135; vehicle N = 138) and week 20 pertains to the posttreatment period (bimatoprost N = 127; vehicle N = 119).
Note: A result with a negative change from baseline value was representative of eyelash darkening.
a LOCF is performed on weeks 1 through 16. Week 20 (posttreatment) analysis is based on observed cases.
b P-values are based on the Wilcoxon rank-sum test.

Table 10–14 Mean (SD) Change From Baseline to Week 16 in PRO Results, Treatment Responders and Nonresponders (Study 192024-032)

PRO Endpoint	Bimatoprost 0.03%			Vehicle		
	Responder (N = 107)	Nonresponder (N = 30)	P-value	Responder (N = 26)	Nonresponder (N = 115)	P-value
Individual Item #4: Overall Satisfaction with Eyelashes	-2.21 (1.099)	-0.73 (1.081)	<0.0001	-1.23 (1.275)	-0.58 (0.991)	0.0069
Domain 1[a]: Satisfaction with Physical Attributes of Eyelashes	-13.72 (6.448)	-4.67 (5.927)	<0.0001	-8.50 (7.474)	-3.67 (5.448)	0.0009
Domain 2[b]: Satisfaction with Subjective Attributes of Eyelashes	-9.80 (7.682)	-3.73 (5.564)	< 0.0001	-5.88 (9.132)	-3.17 (5.937)	0.2405

SD = standard deviation

Note: A responder is defined as a subject with at least a 1-grade increase from baseline in GEA score at week 16. LOCF is performed on week 16.

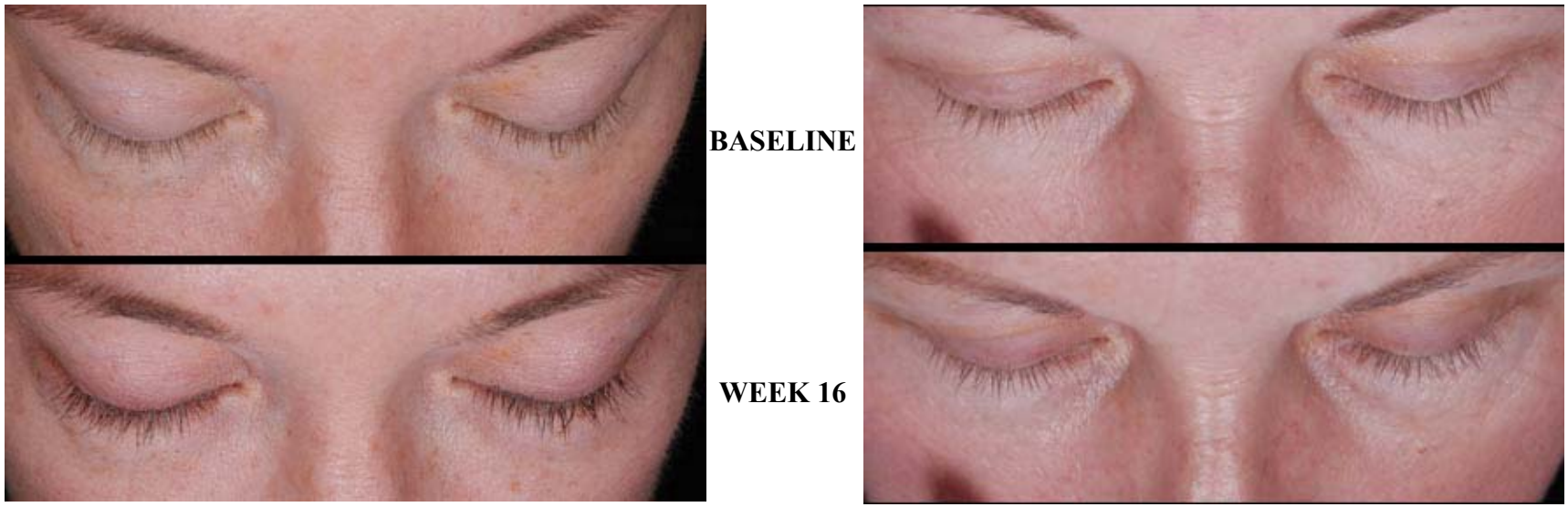
Note: A negative value in change from baseline of PRO responses for item 4 and domains 1 and 2 indicates an increase in satisfaction. PRO responses were collected using a 5-point scale, with 1 indicating highest satisfaction and 5 indicating lowest satisfaction.

a Domain 1 was comprised of questions 1, 2, 3, 4, 6, 7, 8, and 22 (8 questions total) in PRO questionnaire #1.

b Domain 2 was comprised of questions 5, 14, 15, 16, 17, 18, 19, 20, 21, and 23 (10 questions total) in PRO questionnaire #1.

Figure 10–1 Examples of a 1-grade Change From Baseline to Week 16 in GEA Score, From Baseline GEA Score of 1 (Minimal) to 2 (Moderate)

BIMATOPROST **VEHICLE**

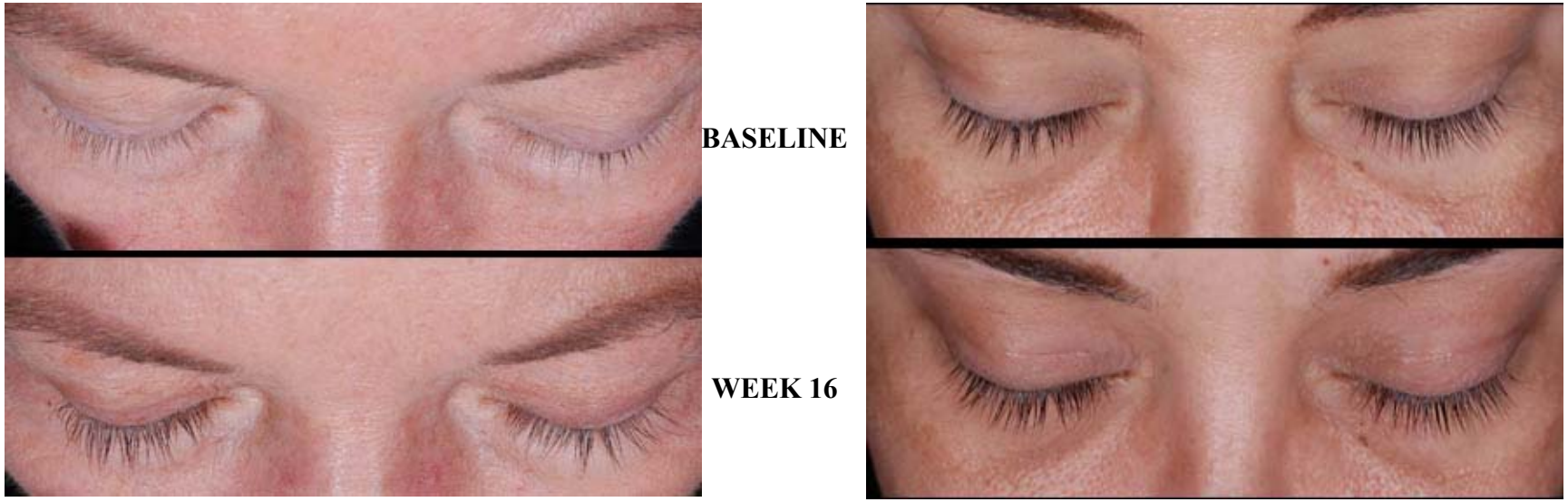


Top: Subject 10010-1091 (**bimatoprost**) at baseline, GEA Score 1
Bottom: Subject 10010-1091 (**bimatoprost**) at week 16, GEA Score 2

Top: Subject 10012-1041 (**vehicle**) at baseline, GEA Score 1
Bottom: Subject 10012-1041 (**vehicle**) at week 16, GEA Score 2

Figure 10–2 Examples of a 1-grade Change From Baseline to Week 16 in GEA Score, From Baseline GEA Score of 2 (Moderate) to 3 (Marked)

BIMATOPROST **VEHICLE**



Top: Subject 11302-1220 (**bimatoprost**) baseline (GEA Score 2)
Bottom: Subject 11302-1220 (**bimatoprost**) week 16 (GEA Score 3)

Top: Subject 10005-1248 (**vehicle**) at baseline (GEA Score 2)
Bottom: Subject 10005-1248 (**vehicle**) at week 16 (GEA Score 3)

Figure 10–3 Example of a 2-grade Change From Baseline to Week 16 in GEA Score, From Baseline GEA Score of 1 (Minimal) to 3 (Marked)

BIMATOPROST

BASELINE

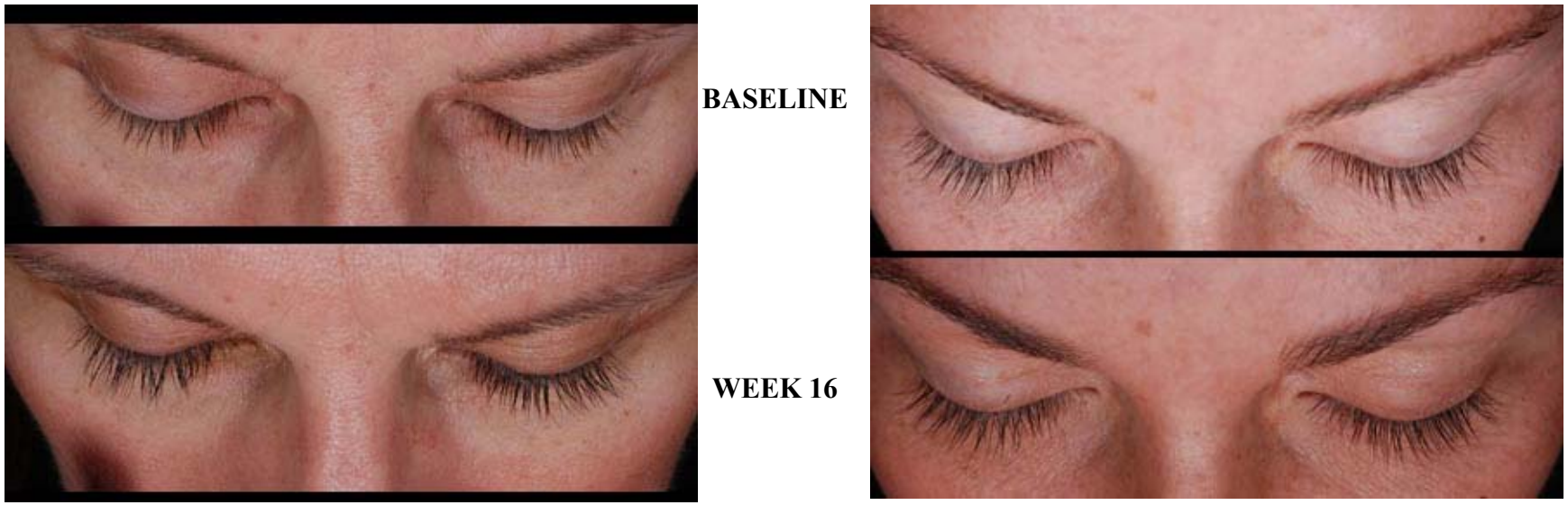
WEEK 16

Top: Subject 10006-1105 (**bimatoprost**) baseline (GEA Score 1)
Bottom: Subject 110006-1105 (**bimatoprost**) week 16 (GEA Score 3)

Note: As no vehicle-treated subject experienced a 2-grade change from a GEA score of 1 baseline to a GEA score of 3 at week 16, only a bimatoprost-treated subject is displayed.

Figure 10–4 Examples of a 2-grade Change From Baseline to Week 16 in GEA Score, From Baseline GEA Score of 2 (Moderate) to 4 (Very Marked)

BIMATOPROST **VEHICLE**



Top: Subject 10011-1284 (**bimatoprost**) baseline (GEA Score 2)
Bottom: Subject 10011-1284 (**bimatoprost**) week 16 (GEA Score 4)

Top: Subject 10004-1047 (**vehicle**) baseline (GEA Score 2)
Bottom: Subject 10004-1047 (**vehicle**) week 16 (GEA Score 4)

Figure 10–5 Example of a 3-grade Change From Baseline to Week 16 in GEA Score, From Baseline GEA Score of 1 (Minimal) to 4 (Very Marked)

BIMATOPROST

BASELINE

WEEK 16

Top: Subject 10014-1311 (**bimatoprost**) baseline (GEA Score 1)
Bottom: Subject 10014-1311 (**bimatoprost**) week 16 (GEA Score 4)

Note: No vehicle-treated subjects experienced a 3-grade change from baseline to week 16, therefore, only a bimatoprost-treated subject is displayed.

Figure 10–6 Example of a 0-grade Change From Baseline to Week 16 in GEA Score (Baseline and Week-16 GEA Score of 1 [Minimal])

VEHICLE

BASELINE

WEEK 16

Top: Subject 10001-1140 (**vehicle**) baseline (GEA Score of 1)
Bottom: Subject 10001-1140 (**vehicle**) week 16 (GEA Score of 1)

Note: All subjects in the bimatoprost group who had baseline GEA scores of 1 (minimal) improved by at least 1-grade on the GEA scale at week 16; therefore, no bimatoprost-treated subject is included in this figure.

Figure 10–7 Examples of a 0-grade Change From Baseline to Week 16 in GEA Score (Baseline and Week-16 GEA Score of 2 [Moderate])

BIMATOPROST **VEHICLE**

Top: Subject 10001-1310 (**bimatoprost**) baseline (GEA Score 2)
Bottom: Subject 10001-1310 (**bimatoprost**) week 16 (GEA Score 2)

Top: Subject 10001-1053 (**vehicle**) baseline (GEA Score 2)
Bottom: Subject 10001-1053 (**vehicle**) week 16 (GEA Score 2)

Figure 10–8 Photos for the bimatoprost- and vehicle-treated subjects who most closely represented the mean change in length from baseline to week 16

BIMATOPROST **VEHICLE**

BASELINE

WEEK 16

Top: Subject 11301-1196 (bimatoprost) at baseline (211.3 pixels)
Bottom: Subject 11301-1196 (bimatoprost) at week 16 (263.8 pixels)

Note: Mean baseline length in the bimatoprost group was 211.48 pixels. Mean week-16 length in the bimatoprost group was 263.11 pixels.

Top: Subject 10013-1135 (vehicle) at baseline (202.9 pixels)
Bottom: Subject 10013-1135 (vehicle) at week 16 (207.8 pixels)

Note: Mean baseline length in the vehicle group was 208.53 pixels. Mean week-16 length in the vehicle group was 212.72 pixels.

Figure 10–9 Photos for the bimatoprost- and vehicle-treated subjects who most closely represented the mean change in thickness from baseline to week 16

BIMATOPROST

BASELINE

WEEK 16

Top: Subject 10001-1257 (bimatoprost) at baseline (15.5% AOI in pixels)
Bottom: Subject 10001-1257 (bimatoprost) at week 16 (28.8% AOI in pixels)

Note: Mean baseline thickness in the bimatoprost group was 16.16% AOI in pixels. Mean week-16 thickness in the bimatoprost group was 28.37% AOI in pixels.

VEHICLE

Top: Subject 11302-1239 (vehicle) at baseline (16.7% AOI in pixels)
Bottom: Subject 11302-1239 (vehicle) at week 16 (18.2% AOI in pixels)

Note: Mean baseline thickness in the vehicle group was 16.66% AOI in pixels. Mean week-16 thickness in the vehicle group was 17.76% AOI in pixels.

Figure 10–10 Photos for the bimatoprost-treated subject who most closely represents the mean change in darkness from baseline to week 16

BIMATOPROST **VEHICLE**

BASELINE

WEEK 16

Top: Subject 10012-1127 (bimatoprost) at baseline (107.3 intensity units)
Bottom: Subject 10012-1127 (bimatoprost) at week 16 (86.1 intensity units)

Note: Mean baseline darkness in the bimatoprost group was 105.67 intensity units. Mean week-16 darkness in the bimatoprost group was 85.52 intensity units.

Top: Subject 10013-1201 (vehicle) at baseline (97.9 intensity units)
Bottom: Subject 10013-1201 (vehicle) at week 16 (91.6 intensity units)

Note: Mean baseline darkness in the vehicle group was 102.82 intensity units. Mean week-16 darkness in the vehicle group was 99.25 intensity units.

11. Reference List

Chen J, Dinh T, Woodward DF, et al. Bimatoprost: mechanism of ocular surface hyperemia associated with topical therapy. Cardiovascular Drug Reviews. 2005;23:231-246.

Drance SM. The significance of the diurnal tension variations in normal and glaucomatous eyes. Arch Ophthalmol 1960;64:314-322.

Dugard PH. Absorption through the skin: theory, in vitro techniques and their applications. Fd Chem Toxic 1986;24:749-753.

Dugard PH and Scott RC. Absorption through skin. In: Baden, HP (Ed), Chemotherapy of Psoriasis. Pergamon Press, 1984, Oxford, pp 125-144.

Elder MJ. Anatomy and physiology of eyelash follicles: relevance to lash ablation procedures. Ophthal Plast Recons 1997;13(1):21-25.

Enyedi, LB, Freedman, SF, Buckley, EG. The effectiveness of latanoprost for the treatment of pediatric glaucoma. J AAPOS 1999;3:33-39.

Enyedi, LB, Freedman, SF. Latanoprost for the treatment of pediatric glaucoma. Surv.Ophthalmol 2002;47(Suppl 1):S129-S132.

Flanders P, McNamara JR. Prediction of compliance with an over the counter acne medication. J Psychol 1984;118:31–35.

Fledelius HC, Christensen AC. Reappraisal of the human ocular growth curve in fetal life, infancy, and early childhood. Br J Ophthalmol 1996 Oct;80(10):918-21.

Hollo G. The side effects of the prostaglandin analogues. Expert Opin Drug Saf 2007;6(1):45.52.

Isenberg SJ. The eye in infancy. 2nd edition. St. Louis: Mosby; 1994.

Johnstone MA, Albert DM. Prostaglandin-induced hair growth. Surv Ophthalmol 2002;47(Suppl 1);S185-S202.

Kapur R, Osmanovic S, Toyran S, Edward DP. Bimatoprost-induced periocular skin hyperpigmentation: histopathological study. Arch Ophthalmol 2005;123:1541-6.

Liu JH, Sit AJ, Weinreb RN. Variation of 24-hour intraocular pressure in healthy individuals. Ophthalmology 2005;112:1670-5.

LUMIGAN [package insert]. Irvine, California; Allergan, Inc.; 2006.

Manni G, Centofanti M, Parravano M, Oddone F, Bucci M. A 6-month randomized clinical study of bimatoprost 0.03% versus the association of timolol 0.5% and latanoprost 0.005% in glaucomatous patients. *Arch Clin Exp Ophthalmol* 2004;242:767-770.

McEvoy B, Nydegger R, Williams G. Factors related to patient compliance in the treatment of acne vulgaris. Int J Dermatol 2003;42:274-280.

Noecker RS, Dirks MS, Choplin NT, Bernstein P, Batoosingh AL, Whitcup SM. A six-month randomized clinical study comparing intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *Am J Ophthalmol* 2003;135:55-63.

Ong T, Chia A, Nischal KK. Latanoprost in port wine stain related paediatric glaucoma Br J Ophthalmol 2003;87:1091-3.

Parsons RJ, Wright ND, Wilson LS. Evaluation of patients'compliance with medical practitioners' prescriptions: University Health Center experience. J Am College Health Assoc 1980;28:342–345.

Pruzinski T. Psychological Factors in Cosmetic Plastic Surgery: Recent Developments in Patient Care. Plast Surg Nurs 1993;13(2):64-71.

Ravinet E, Mermoud A, Brignoli R. Four years later: a clinical update on latanoprost. Eur J Ophthalmol 2003;13:162-175.

Records RE. Eyebrows and Eyelids. Physiology of the Human Eye and Visual Systems. Records RE. (ed). Hagerstown, MD: Harper & Row; 1979.

Sasaki S, Hozumi Y, Kondo S. Influence of prostaglandin F2a and its analogues on hair regrowth and follicular melanogenesis in a murine model. Exp Dermatol 2005;14:323-8.

Sihota R., Tuli D., Dada T., Gupta V, Sachdeva MM. Distribution and determinants of intraocular pressure in a normal pediatric population. J Pediatr Ophthalmol Strabismus 2006;43:14-18.

Steiling W, Kreutz J, Hofer H. Percutaneous penetration/dermal absorption of hair dyes in vitro. Toxicol in Vitro 2001;15:565-570.

Trommer H, Neubert RHH. Overcoming the stratum corneum: the modulation of skin penetration. Skin Pharmacol Physiol 2006;19:106-121.

Urban B, Bakunowicz-Lazarczyk A, Mrugacz M, Ozieblo-Kupczyk M. The effectiveness of latanoprost for the treatment of pediatric glaucoma. Klin Oczna 2004;106:243-4.

Weingeist TA, Liesegang TJ, Grand G. Pediatric Ophthalmology and Strabismus. Basic and Clinical Science Course 1999-2000, American Academy of Ophthalmology. p163-5.

Woodward DF, Krauss AH-P, Chen J, et al. The pharmacology of bimatoprost (Lumigan™). Surv Ophthalmol 2001;45:S337-S345.

Wright KW, Spiegel PH. Pediatric Ophthalmology and Strabismus: The Requisites in Ophthalmology. New York: Mosby; 1999.

12. List of Abbreviations and Definitions of Terms

AOI	area of interest; the specific area on a digital image that includes all eyelashes for a given eye
BEG	bimatoprost for eyelash growth
BID	twice daily
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
FDA	United States Food and Drug Administration
GEA	Global Eyelash Assessment Scale
GMP	Good Manufacturing Practices
IOP	intraocular pressure
LOCF	last observation carried forward
LUMIGAN®	bimatoprost ophthalmic solution 0.03%
MedDRA	Medical Dictionary for Regulatory Activities
mm	millimeters
mm Hg	millimeters of mercury
NDA	new drug application
NDA PADER	New Drug Application Periodic Adverse Event Experience Reports
pixel	picture element; the smallest discrete component of a digital image
PRO	patient-reported outcomes
PSUR	periodic safety update report
QD	once daily
SOC	system organ class
spline	a narrow area approximately 5 pixels wide, bisecting the AOI (area of interest) on a digital image
WHO	World Health Organization