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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product: Durysta® (bimatoprost (b) (4) implant)
Indication: For the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT)
Applicant: Allergan Inc. (Irvine, CA)
Review Division: Division of Ophthalmology (DO)
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1 Executive Summary

1.1 Introduction

The Applicant has submitted a 505(b)1 NDA application for Durysta® (bimatoprost (b) (4) implant) for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension. The NDA is approvable from a Pharmacology/Toxicology perspective.

1.2 Brief Discussion of Nonclinical Findings

For systemic toxicology, safety pharmacology, genotoxicity assessment, and carcinogenicity studies, the Applicant relies on studies conducted for the approval of Lumigan (NDA 21-275), a topical formulation of bimatoprost, for which the Applicant has right of reference. The Applicant conducted primary pharmacology, ocular distribution and pharmacokinetics and ocular toxicology studies to support the new formulation and route of administration.

Pharmacology

- In normotensive cynomolgus monkeys, intracameral administration of the bimatoprost implant was most effective in reducing IOP compared to topical dosing.
- In hypertensive monkeys, following intracameral administration of the bimatoprost implant, mean IOP reduction from week 1 to month 3 was $22 \pm 5\%$.
- In normotensive Beagle dogs, intracameral administration of the implant resulted in a dose-related reduction in IOP over 3 months.
- In dogs, topical ocular administration of Lumigan® followed by administration of bimatoprost intracameral implant resulted in a biphasic effect on episcleral venous pressure (EVP). Initially, an increase in EVP relative to the untreated fellow eye was followed by a slow decline with lower pressures in the treated eye than the untreated fellow right eye.
- An additive ocular hypotensive effect was shown following administration of triple topical therapy and the bimatoprost intracameral implant in monkeys.
- In normotensive dogs following selective laser trabeculoplasty (SLT), the bimatoprost insert was equally efficacious in lowering intraocular pressure (IOP) in both SLT treated eyes and contralateral SLT naïve eyes.

Pharmacokinetics / Ocular Distribution

- In dogs, when compared to topical administration, the bimatoprost intracameral implant achieved higher intraocular exposure in target tissues while achieving lower exposure in extra-ocular structures such as the eyelid margin, bulbar conjunctiva and periorbital fat.

Toxicology

- The Applicant conducted ocular toxicity studies of at least 6 to 12 months duration in 2 species (Cynomolgus monkeys and Beagle dogs). In cynomolgus monkeys, only the “Generation 1” implant was studied, which is not the “Generation 2” formulation proposed for approval; however, given the similarity in formulations and the relevance of results, the results are reviewed below.
- In the cynomolgus monkey, corneal endothelial changes were observed at all implant sizes that were evaluated. The iridocorneal angle is narrower in monkeys than humans and therefore the implant often remained in contact with the corneal endothelium. It was hypothesized that chronic implant contact with the corneal endothelium may have contributed to injury. The bimatoprost implant is intended to immediately settle in the inferior anterior chamber (iridocorneal) angle following dosing in human patients, while avoiding contact with the corneal endothelium throughout the drug-release and implant-erosion processes.
- In the dog, 3 intracameral administrations of up to 20µg/left eye was not associated with adverse toxicity. In dogs receiving the bimatoprost implant, minimal Schwalbe’s line cell/limbal endothelial cell hypertrophy and/or Schwalbe’s line cell/limbal endothelial cell hyperplasia and subendothelial/sub-Schwalbe’s line cell fibrillar matrix deposition were reported.

1.3 Recommendations

1.3.1 Approvability

- The NDA is approvable from a Pharmacology/Toxicology perspective.

1.3.3 Labeling

1.3.3.1 Applicant’s Proposed Labeling (Sections 8, 12.1, and 13 only)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DURYSTA administration in pregnant women (b) (4)

Data

Animal Data

(b) (4)

(b) (4)

8.2 Lactation

Risk Summary

There is no information regarding the presence of bimatoprost in human milk, the effects on the breastfed infants, or the effects on milk production. 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 DURYSTA is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DURYSTA and any potential adverse effects on the breastfed child from DURYSTA.

8.4 Pediatric Use

Safety and effectiveness of DURYSTA in pediatric patients have not been established.

8.5 Geriatric Use

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

12.1 Mechanism of Action

Bimatoprost, a prostaglandin analog, is a synthetic structural analog of prostaglandin with ocular hypotensive activity. (b) (4)

Bimatoprost is believed to lower IOP in humans by increasing outflow of aqueous humor through both the trabecular meshwork (conventional) and uveoscleral routes (unconventional). (b) (4)

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses up to 2 mg/kg/day and 1 mg/kg/day respectively for 104 weeks (approximately 3100 and 1700 times, respectively, the maximum human exposure [based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858]).

Mutagenesis

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

Impairment of Fertility

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day ((b) (4) times the maximum human exposure [based on plasma $C_{\max}$ (b) (4); blood-to plasma partition ratio of 0.858]).

FDA Reviewer Labeling Recommendations:

8.1 Pregnancy Risk Summary There are no adequate and well-controlled studies of DURYSTA administration in pregnant women. (b) (4)	8.1 Pregnancy Risk Summary There are no adequate and well-controlled studies of DURYSTA® (bimatoprost (b) (4) implant) administration in pregnant women to inform a drug-associated risk. Oral administration of bimatoprost to pregnant rats and mice throughout organogenesis did not produce adverse maternal or fetal effects at clinically relevant exposures. Oral administration of bimatoprost to rats from the start of organogenesis to the end of lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant exposures [see <i>Animal Data</i>].
<u>Data</u> <i>Animal Data</i> (b) (4) (b) (4)	<u>Data</u> <i>Animal Data</i> <i>In an embryofetal development rat study, oral administration of bimatoprost to pregnant rats during organogenesis produced abortion at 0.6 mg/kg/day (1770-times the human systemic exposure to bimatoprost from DURYSTA®, based on C_{max} and a blood-to plasma partition ratio of 0.858). The No Observed Adverse Effect Level (NOAEL) for abortion was 0.3 mg/kg/day (estimated at 470-times the human systemic exposure to bimatoprost from DURYSTA®, based on C_{max}). No fetal abnormalities were</i>

(b) (4)	observed at doses up to 0.6 mg/kg/day. <i>In an embryofetal development mouse study, oral administration of bimatoprost to pregnant mice during organogenesis produced abortion and early delivery at 0.3 mg/kg/day (2240-times the human systemic exposure to bimatoprost from DURYSTA[®], based on plasma C_{max} level; blood-to plasma partition ratio of 0.858). The NOAEL for abortion and early delivery was 0.1 mg/kg/day (400-times the human systemic exposure to bimatoprost from DURYSTA[®], based on C_{max}). No fetal abnormalities were observed at doses up to 0.6 mg/kg/day (5200-times the human systemic exposure to bimatoprost from DURYSTA[®], based on C_{max}).</i> <i>In a pre/postnatal development study, oral administration of bimatoprost to pregnant rats from gestation day 7 through lactation resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 470-times the human systemic exposure to bimatoprost from DURYSTA[®], based plasma C_{max} and a blood-to plasma partition ratio of 0.858). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA[®], based on plasma C_{max}).</i>
8.2 Lactation Risk Summary There is no information regarding the presence of bimatoprost in human milk,	8.2 Lactation -No changes suggested.

the effects on the breastfed infants, or the effects on milk production. 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 DURYSTA is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DURYSTA and any potential adverse effects on the breastfed child from DURYSTA.	
12.1 Mechanism of Action Bimatoprost, a prostaglandin analog, is a synthetic structural analog of prostaglandin with ocular hypotensive activity. (b) (4) (b) (4) Bimatoprost is believed to lower IOP in humans by increasing outflow of aqueous humor through both the trabecular meshwork (conventional) and uveoscleral routes (unconventional). (b) (4) (b) (4) 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.	-No suggested changes (from Pharmacology/Toxicology perspective; defer to Clinical discipline regarding (b) (4)).
13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility <u>Carcinogenesis</u> Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses up to 2 mg/kg/day and 1 mg/kg/day respectively for 104 weeks (approximately 3100 and 1700 times, respectively, the maximum human	13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility No changes suggested.

exposure [based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858]).	
<u>Mutagenesis</u> Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the <i>in vivo</i> mouse micronucleus tests.	No changes suggested
<u>Impairment of Fertility</u> Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day ((b) (4) times the maximum human exposure [based on plasma C_{max} (b) (4); blood-to plasma partition ratio of 0.858]).	<u>Impairment of Fertility</u> <i>Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (1770-times the maximum human exposure, based on plasma C_{max}; blood-to plasma partition ratio of 0.858).</i>

2 Drug Information

2.1 Drug

CAS Registry Number (bimatoprost): 155206-00-1

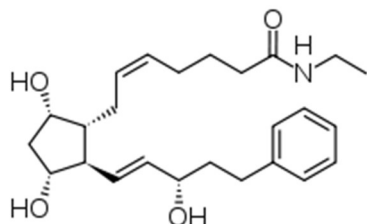
Generic Name: Bimatoprost intracameral insert

Code Name: Durysta®; bimatoprost SR; B737

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

Molecular Formula/Molecular Weight: $C_{25}H_{37}NO_4$ / 415.57 g/mol

Structure:



Pharmacologic Class: Prostaglandin analog

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 108,324
- NDA 022-184 (Lumigan ophthalmic solution, 0.01%)

2.3 Drug Formulation

Table 1. “Generation 2” formulation proposed for approval

Component	Function	Quality Standard	Concentration	
			% w/w	µg/Dose
Bimatoprost	Drug substance	In-house ^a	(b) (4)	10
(b) (4)		In-house	(b) (4)	
Poly (D,L-lactide)		In-house		
Poly (D,L-lactide-co-glycolide)		In-house		
Poly (D,L-lactide) Acid End		In-house		
Polyethylene Glycol 3350		USP		
Total			100	

a Per Type II DMF

b

2.4 Comments on Novel Excipients

All components of the formulation have not been previously qualified for intracameral administration. The Applicant has conducted toxicology studies both “Generation 1” and “Generation 2” formulations of the drug product. The “Generation 2” formulation is proposed for approval and the excipients are qualified by the intracameral toxicity studies reviewed below.

2.5 Comments on Impurities/Degradants of Concern

DS bimatoprost is referenced to DMF (b) (4). The impurity specifications proposed are similar to the RLDs the Applicant is referencing.

Table 2. Drug substance related impurities and specification proposed

Related compounds	
Individual unspecified impurity	NMT (b) (4) % w/w
(b) (4)	NMT (b) (4) % w/w
(b) (4)	NMT (b) (4) % w/w
(b) (4)	NMT (b) (4) % w/w
(b) (4)	NMT (b) (4) % w/w
(b) (4)	NMT (b) (4) % w/w
(b) (4)	NMT (b) (4) % w/w
Total impurities	NMT (b) (4) % w/w

Per *in vitro* data (see CMC Drug Product review), the highest release of DS from the insert occurs on Day 1 and was on average 7%. The highest release in the batches tested was (b) (4) %. Using that as a worst-case scenario ((b) (4) %), the amount of DS released from the 10ug insert would be (b) (4) ug. If the impurity is present at the proposed highest specification (b) (4)], then that corresponds to exposure to (b) (4) of the impurity on Day 1. This closely approximates the allowable exposure per day below the ICHQ3A established qualification limit (0.1%) for an immediate release product (0.1% of 10ug = 10 ng). This is the worst-case scenario based on the *in vitro* data. Additionally, elution of drug substance (and impurities) decreases over time following administration.

For this drug product, the highest proposed impurity specification would result in release of an amount of impurity that approximates the qualification threshold ((b) (4) ng vs 10 ng, respectively). On average, it would be lower. Therefore, the reviewer agrees with the Applicant's proposed specifications without qualification.

2.6 Proposed Clinical Population and Dosing Regimen

- Patients with open angle glaucoma (OAG) or ocular hypertension (OHT)
- The Applicant has proposed that the 10µg insert be administered by intracameral administration via applicator (b) (4)

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology

- BIO-09-785: A comparison of the ocular response to single dose intracameral and intravitreal 60µg bimatoprost DDS and QD topical Lumigan in monkeys

- BIO-09-787: Ocular pharmacology of intracameral single dose 30µg bimatoprost DDS in monkeys with unilateral ocular hypertension
- BIO-09-803: Ocular pharmacology of intracameral single dose bimatoprost DDS in dogs
- BIO-09-805: Optical coherence tomographic analysis of irido-corneal angle of dogs, monkeys and humans: a simulation study to examine the fit of indwelling implants for sustained release IOP control
- BIO 18-1218: Determination of the effect of bimatoprost on the episcleral venous pressure and intraocular pressure (IOP) following topical ocular administration of Lumigan and administration of bimatoprost via intracameral drug delivery system (IC DDS) to dogs
- BIO-18-1221: Additive ocular hypotensive effects of bimatoprost sustained-release intracameral implant on potent topical therapy in monkeys
- BIO-18-1224: IOP lowering efficacy of bimatoprost SR in dogs pre-treated with selective laser trabeculoplasty (SLT)

Pharmacokinetics

- PK11086-PK: Ocular pharmacokinetics of bimatoprost following a single intracameral injection of bimatoprost intracameral drug delivery system (IC DDS) in Beagle dogs
- PK14025-PK: Ocular pharmacokinetics of bimatoprost following 7 daily topical ophthalmic or a single intracameral drug delivery system (IC DDS) administration to female Beagle dog
- PK15022-PK: Ocular pharmacokinetics of bimatoprost following 7 daily topical ophthalmic administrations or a single bimatoprost SR administration to female aphakic Beagle dogs

Toxicology

- Study TX09051-TX: Bimatoprost (AGN-192024) IC DDS implant: A 6-month single dose intracameral ocular toxicity study in monkeys
- Study TX12102-TX: bimatoprost (AGN-192024) PF IC DDS: 18-month

3.2 Studies Not Reviewed

- BIO-11-920: Ocular evaluation of second generation intracameral bimatoprost DDS
- BIO-12-975: The effect of PLGA content in formulations of intracameral bimatoprost sustain release implants on ocular tolerability in cynomolgus monkeys
- BIO-15-1095: Ocular response to bimatoprost SR dosed in the posterior chamber in dogs – pilot study
- AN09047-BM: Partial validation of a bioanalytical method for the quantitation of AGN-192024 and AGN-191522 in monkey blood using liquid chromatography tandem mass spectrometry

- AN09060-BM: Partial validation of a bioanalytical method for the quantitation of AGN-192024 and AGN-191522 in dog blood using liquid chromatography tandem mass spectrometry
- AN13077-BM: Partial validation of a bioanalytical method for the quantitation of AGN-192024 and AGN-191522 in dog blood using liquid chromatography tandem mass spectrometry
- AN13080-BM: Stability of AGN-192024 and AGN-191522 in dog blood after storage in a standard freezer (-40°C to -10°C)
- PK-00-156: Stability of AGN-192024 and AGN-191522 in mouse, rat, rabbit, and monkey blood stored in acetonitrile: methanol at -20°C for up to 27 weeks
- PK09109-PK: Pharmacokinetics and pharmacodynamics of bimatoprost following a single intracameral injection of bimatoprost intracameral drug delivery system (IC DDS) in dogs
- Study TX09066-TX: Bimatoprost (AGN-192024) IC DDS implant: A 6-month single dose intracameral ocular toxicity study in dogs
 - *Reviewer's note: Generation 1 formulation*
- Study TX10016-TX: Bimatoprost (AGN-192024) PF IC DDS implant: 6-month single dose intracameral ocular toxicity study in dogs
 - *Reviewer's note: Generation 1 formulation*
- Study TX11076-TX: Bimatoprost (AGN-192024) IC DDS implant: 8- or 12-month single dose intracameral ocular toxicity study in dogs with a 4-month interim necropsy
 - *Reviewer's note: Non-GLP pilot study; not pivotal*
- Study TX12012-TX: bimatoprost (AGN-192024) PF IC DDS Implant: 7-month (two doses) intracameral ocular toxicity study in dogs with a 4-month observation period
 - *Reviewer's note: Non-GLP pilot study; not pivotal*
- Study TX12018-TX: Bimatoprost (AGN-192024) PF IC DDS: 7-month repeat dose (2X) intracameral ocular toxicity study in dogs
 - *Reviewer's note: Non-GLP pilot study; not pivotal*

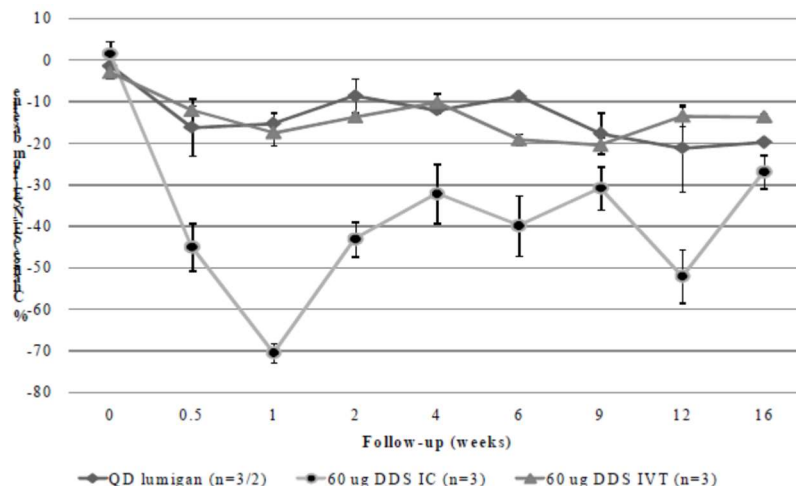
4 Pharmacology

4.1 Primary Pharmacology

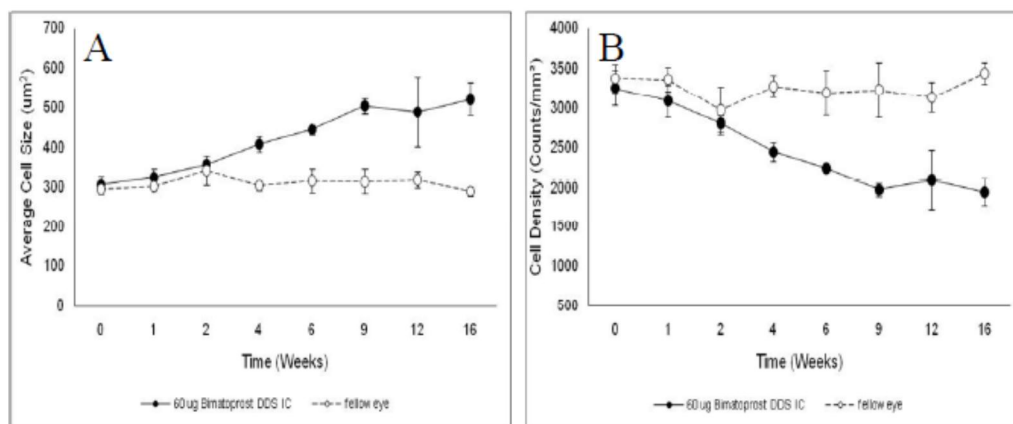
Study BIO-09-785: A comparison of the ocular response to single dose intracameral and intravitreal 60µg bimatoprost DDS and QD topical Lumigan in monkeys

- Normotensive cynomolgus monkeys (n=3/group) were dosed unilaterally with intravitreal (IVT) or intracameral (IC) Bimatoprost PF IC DDS implant [60 µg; (b) (4) inch ((b) (4) mm)] or treated with LUMIGAN® ophthalmic drops QD.
 - IOP, slit lamp biomicroscopy, corneal endothelial specular microscopy, anterior segment ocular coherence tomography (OCT), corneal topography, aqueous laser flare photometry, posterior segment OCT, retinal fluorescein angiography (FA), fundus photography and wide-angle vitreous photography were assessed periodically for 4-months.

- IOP reduction
 - Intracameral administration of the implant was most effective in reducing IOP with a 3-month mean reduction of $(-45 \pm 4\%)$.
 - IOP reduction was comparable for IVT and topical dosing with an $\sim 15\%$ reduction in IOP.

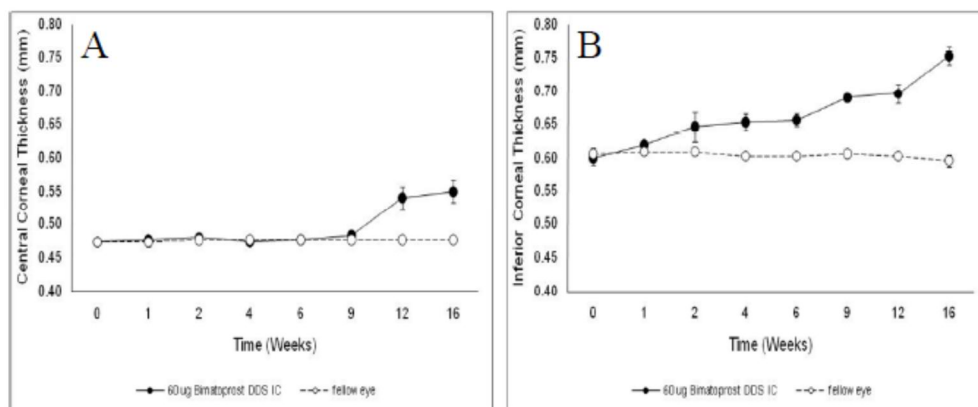


- Anterior chamber cell grading:
 - Following intracameral placement, at week 1, there were 2 to 3+ cells and flare associated with the injection procedure, and persistent trace cells up to 4 months.
 - There were no changes in cells and flare in either the topical or IVT groups over 4 months.
- Corneal endothelial cell density
 - There was a progressive decrease in and an increase in corneal thickness starting at week 1 with IC dosing; at 4 months central corneal endothelial cell density and inferior corneal thickness (in contact with the implant) changed by 40% ($3259 \pm 218 \text{ mm}^2$ to $1949 \pm 168 \text{ mm}^2$) and 25% ($0.6 \pm 0.01 \text{ mm}$ to $0.75 \pm 0.01 \text{ mm}$) respectively.



- There was no change in corneal integrity with either topical or IVT dosing.

- Corneal topography
 - There was no change in corneal topography in any of the groups.
- Corneal thickness
 - In animals treated with the intracameral insert, central cornea thickness increased at 12 weeks by ~60 μm , and inferior cornea thickness increased as early as 2 weeks by ~40 μm . The increase in cornea thickness at 4 months was ~150 μm .



- Other corneal observations
 - The inferior cornea was mildly opaque in all 3 eyes treated with IC Bimatoprost DDS by 4 weeks of follow-up.
- Iridial observations
 - No darkening of the iris was observed up to 4 months in any of the groups
- Retinal thickness / changes in vasculature
 - There was no change in foveal or peripapillary retinal thickness in any group, nor were there changes in retinal vascular caliber or angiographic leakage.
- Implant disposition
 - The implant was not located in the anterior chamber angle, but in the inferior mid-periphery of the anterior chamber in chronic with corneal endothelium and iris.
- Implant integrity
 - There was progressive swelling of the implant from week 1 to 4 months in both the IC and IVT groups up to 2.9-fold.

Study BIO-09-787: Ocular pharmacology of intracameral single dose 30 μg bimatoprost DDS in monkeys with unilateral ocular hypertension

- In hypertensive monkeys (circumferential argon laser induced to right eye only) eyes were administered either intracameral (IC) Bimatoprost PF IC DDS implant [30 μg ; (b) (4) inch ((b) (4) mm)] or a placebo implant.

- IOP, slit lamp biomicroscopy, corneal endothelial specular microscopy, anterior segment OCT, corneal topography, and aqueous laser flare photometry were assessed periodically until Month 6 following implant administration.
- Prior to intracameral administration, all hypertensive eyes were treated with topical LUMIGAN® QD for 5 days which decreased IOP by a mean of $22.4 \pm 3\%$ and was followed by a 5-week washout period.
- IOP reduction following intracameral administration
 - The mean IOP reduction from week 1 to month 3 was $22 \pm 5\%$.
 - Placebo DDS reduced IOP by $15 \pm 8\%$, over the same period.
- Central corneal endothelial cell density
 - There was a progressive and comparable decrease in both groups: 35% ($2682 \pm 298 \text{ mm}^2$ to $1744 \pm 91 \text{ mm}^2$) with bimatoprost implant and 28% ($1949 \pm 193 \text{ mm}^2$ to $1400 \pm 148 \text{ mm}^2$) with the placebo implant at 6 months.
- Inferior corneal thickness
 - Increased over time in both groups, with a 12% and 14% bimatoprost implant and placebo implant at 6 months, respectively.
- Corneal topography
 - There was no change in either group.
- Implant disposition
 - Both the active and placebo implants were located in inferior mid-periphery of the anterior chamber in chronic contact with the corneal endothelium and iris.
- Implant integrity
 - There was progressive swelling of both implants from 1 week to 6 months.

Study BIO-09-803: Ocular pharmacology of intracameral single dose bimatoprost DDS in dogs

- Normotensive Beagle dogs were administered a single intracameral implant containing various amounts of bimatoprost (placebo, 8, 12, 22, 30, 60 and 120 μg). Implants ranged in size from (b) (4) to (b) (4) inches. The 120 μg dose consisted of 2 implants ($2 \times 60 \mu\text{g}$).
- Assessments were made for 4 to 10 months following administration and included evaluation of IOP, pupil diameter, gross ocular observation, slit lamp biomicroscopy, gonioscopy, and corneal endothelial specular microscopy.
- IOP reduction
 - Dose-related reduction over 3 months for placebo, 8, 12, 22, 30, 60 and 120 μg were 12%, 17%, 20%, 23%, 24%, 35%, and 39% respectively.
 - By comparison, the peak IOP reduction of LUMIGAN® ophthalmic drops during three days of QD dosing in dogs was 27%.
 - The duration of action was also dose-related; IOP was reduced for ~2 months with the 8 μg , ~3 months with the 12 μg , ~4 months with the 22, 30 and 60 μg doses and >9 months with the 120 μg doses.
- Pupil diameter

- Miosis was present with all doses, except placebo.
- Slit lamp observations
 - Ocular surface hyperemia with the implant was different from LUMIGAN® ophthalmic drops. The implant only dilated outflow vessels; LUMIGAN® ophthalmic drops dilated both outflow vessels and conjunctival vessels. The 30 µg dose, with comparable IOP reduction to LUMIGAN® ophthalmic drops, had less ocular surface hyperemia.
 - There were very few instances of anterior chamber cells and flare, which never exceeded trace amounts.
- Corneal changes
 - There were no changes in corneal integrity (clarity, thickness, endothelial cell density) with doses ≤30 µg;
 - 60 and 120 µg showed a trend of endothelial cell density decrease at 4 and 6.5 months.
- Implant disposition
 - The implants settled in the inferior angle, were non-adherent to the trabecular meshwork, increased in size and became porous with smooth edges in as early as 3 months.

Study BIO-09-805: Optical coherence tomographic analysis of irido-corneal angle of dogs, monkeys and humans: a simulation study to examine the fit of indwelling implants for sustained release IOP control

- Optical coherence tomography (OCT) anterior segment scans of dogs (n=7), monkeys (n=7) and human volunteers (n=7) showed interspecies differences for anterior chamber (AC) angle anatomy (angle, angle recess area, angle opening distance) in the following ranked order: dogs>>humans>monkeys.
- This study used simulation to determine whether the anterior chamber can accommodate an implant with a specific diameter size.
- The study concluded that the AC angle anatomy of monkeys is too small to accommodate the proposed clinical implant, allowing it to come into constant contact with the corneal endothelium which eventually decompensates.
- The data also provides guidelines for patient selection for anterior segment DDS dosing. Patients with a grade 4 AC angle would be able to adequately accommodate the current (b) (4) gauge size DDS ((b) (4)) even if it swells in-vivo by 2-fold.

Study BIO 18-1218: Determination of the effect of bimatoprost on the episcleral venous pressure and intraocular pressure (IOP) following topical ocular administration of Lumigan and administration of bimatoprost via intracameral drug delivery system (IC DDS) to dogs

- This study assessed the effect of bimatoprost on the episcleral venous pressure (EVP) and intraocular pressure (IOP) in dogs following topical ocular administration of Lumigan® and administration of bimatoprost via Intracameral Drug Delivery System (IC DDS).

- For Phase 1 of the study, treated animals (n=7) were administered one drop of 0.03% Lumigan® to the left eye daily on Study Days 9 through 22, with the right eye untreated. IOP and EVP were measured on Study Days 1, 4, 8, 15, and 22. Other assessments included systemic blood pressure, slit lamp biomicroscopy and indirect ophthalmoscopy. Results showed that topical application of 0.03% bimatoprost ophthalmic solution (Lumigan®) in the left eye only from Study Days 9 to 22 resulted in the following:
 - mild (1+) conjunctival hyperemia
 - miotic pupil
 - reduced intraocular pressure [3.7 to 5.1 mm Hg (23 to 30%) compared to the untreated right eye and 2.9 to 3.4 mm Hg (19 to 23%) compared to the untreated left eye of animals of control animals
 - increased mean episcleral venous pressure [2.6 to 4.4 mm Hg (25 to 42%) in the Lumigan®-treated left eye versus the untreated control left eye.
- In Phase 2 of the study, animals previously dosed with Lumigan® were administered a 30-µg bimatoprost intracameral implant on Study Day 1. The right eye was untreated. Control animals received a sham injection. IOP and EVP were measured on Study Days 8, 11, 15, 22, 36, 49, and 65.
- Intracameral injection of the implant resulted in the following:
 - mild (1+) conjunctival hyperemia
 - miotic pupil
 - reduced intraocular pressure (2.8 to 5.3 mm Hg; 17 to 32%) compared to the untreated fellow eye
 - a biphasic effect on EVP, with the peak increase on Study Day 8 (3.2 mm Hg or 35% increase relative to the untreated fellow eye), and a slow decline thereafter with lower pressures in the treated eye than the untreated fellow right eye on Study Day 29
 - Further decline in EVP, with decreases of 1.9 to 2.6 mm Hg (23 to 27%) on Study Days 36, 49, and 65.
- For the sham injected eye, the following was noted:
 - mean EVP was lower in the treated eye than in the untreated fellow eye on Study Day 8 (8.6 versus. 9.8 mm Hg), suggesting that the conjunctival hyperemia following an intracameral injection is associated with reduced EVP
 - mean IOP in the sham injected left eye was lower than that in the treated eye by 1 mm HG or more only on Study Days 8, 11, and 15.

Study BIO-18-1221: Additive ocular hypotensive effects of bimatoprost sustained-release intracameral implant on potent topical therapy in monkeys

- This study assessed the additive effect on IOP of intracameral administration of the bimatoprost implant (20 µg) and triple topical treatment in normotensive cynomolgus monkeys (n=6)
 - Animals received triple topical treatment with fixed-combination dorzolamide 2%/timolol 0.5% BID, and latanoprost 0.005% QD) until week 5 when topical latanoprost was switched to topical bimatoprost 0.03% (Lumigan®) QD while dorzolamide/timolol BID was continued. At Week 8,

the intracameral implant was administered. At week 12, topical therapy was discontinued in all eyes after IOP measurement. The animals were then monitored for an additional 4 weeks.

- Intracameral administration of bimatoprost implant contributed to additive reduction of IOP when added to triple topical treatment
 - In monkeys treated with topical dorzolamide/timolol/latanoprost therapy, the average mean IOP decreased to 15.7 mmHg. When topical latanoprost was switched to topical bimatoprost, there was an additional decrease in average mean IOP to 14.5 mmHg.
 - Following intracameral administration of the implant, the average mean IOP decreased significantly to 10.8 mmHg
 - When topical therapy was discontinued, the IOP increased but the IOP in eyes treated with Bimatoprost SR remained below that of unmedicated eyes. Intracameral BimSR has IOP-lowering effects additive to those of topical bimatoprost, suggesting an additional mechanism of action with intracameral drug delivery.

Table 3. Mean intraocular pressure ($\pm$ standard error), mmHg

Time and Treatment	All Animals (n=6)	BimSR Added to Topical Triple Therapy (n=3)	No Implant Added to Topical Triple Therapy (n=3)
Baseline: prior to any treatment	19.8 $\pm$ 0.7	—	—
Week 1: 1 week after initiating topical dorzolamide/timolol/latanoprost triple therapy	15.8 $\pm$ 1.0*	—	—
Week 6: 1 week after switch to topical dorzolamine/timolol/bimatoprost triple therapy	14.8 $\pm$ 1.1*	—	—
Week 9: 1 week after addition of BimSR or no implant to topical dorzolamine/timolol/bimatoprost triple therapy	—	11.0 $\pm$ 0.5* [†]	14.5 $\pm$ 1.3*
Week 12: 4 weeks after addition of BimSR or no implant to topical dorzolamine/timolol/bimatoprost triple therapy	—	9.5 $\pm$ 0.6* [†]	14.5 $\pm$ 1.8*
Week 16: 4 weeks after all topical therapy stopped	—	16.5 $\pm$ 1.3* [†]	20.0 $\pm$ 1.5

* $P < 0.005$ vs baseline, [†] $P \leq 0.012$ vs no implant added to topical therapy, BimSR, bimatoprost sustained-release implant (bimatoprost SR)

Study BIO-18-1224: IOP lowering efficacy of bimatoprost SR in dogs pre-treated with selective laser trabeculoplasty (SLT)

- This study assessed the IOP lowering efficacy of the bimatoprost insert in normotensive dogs pre-treated with selective laser trabeculoplasty (SLT).
- Unilateral SLT reduced IOP by ~15% and returned to baseline within 6 to 10 weeks post SLT treatment. Bimatoprost SR (15 μ g) were intracamerally administered to both SLT treated and contralateral SLT naïve eyes.
- The bimatoprost insert was equally efficacious in lowering intraocular pressure (IOP) in both SLT treated eyes and contralateral SLT naïve eyes with mean peak decrease in IOP following Bimatoprost SR administration to the SLT treated eye

of $34.2\% \pm 2.8$ (6.7 ± 0.7 mmHg) and a mean peak decrease of $34.7\% \pm 1.7$ (6.8 ± 0.5 mmHg) in the contralateral, SLT naïve eye.

- The bimatoprost insert lowered IOP equally in eyes that responded to SLT (i.e., sustained decrease in IOP of ≥ 3 mmHg in the laser treated eye, $n=6$, mean peak IOP decrease following insert administration, $34.3\% \pm 4.2$) and eyes that did not respond to SLT treatment (i.e., decrease in IOP of < 3 mmHg in the SLT treated eye, $n=5$, mean peak IOP decrease following insert administration, $34.1\% \pm 2.7$).

5 Pharmacokinetics/ADME/Toxicokinetics

PK11086-PK: Ocular pharmacokinetics of bimatoprost following a single intracameral injection of bimatoprost intracameral drug delivery system (IC DDS) in Beagle dogs

This study assessed the ocular pharmacokinetics of bimatoprost (AGN-192024) following a single intracameral injection of the Durysta formulation in Beagle dogs ($n = 2/\text{group}$). Aqueous humor was collected at 1, 2, 4, 6, 8, 10, 12, and 14 weeks post-dose from each eye. Animals were euthanized at 14 weeks post-dose for collection of cornea, iris-ciliary body, choroid, retina, vitreous humor and remnant implant.

Ocular samples were quantified for AGN-192024 and AGN-191522 (bimatoprost acid) using a LC-MS/MS assay. Assay linearity for AGN-192024 and AGN-191522 was in the range of 0.1 – 100 ng/mL in aqueous humor. Analyte linearities in cornea, choroid, iris-ciliary body, vitreous humor and retina were in the range of 0.1 – 100 ng for both AGN-192024 and AGN-191522. Pharmacokinetic parameters for the proposed clinical formulation are summarized below:

Table 4. Pharmacokinetic parameters of bimatoprost and bimatoprost acid in aqueous humor following single dose administration

Pharmacokinetic parameter	Result
Bimatoprost	
$C_{\max}$ (ng/mL)	13.7 ± 2.3
$AUC_{0-\text{last}}$ (ng·weeks/mL)	53.6 ± 4.8
$T_{\max}$ (weeks)	8.00 ± 0.00
Bimatoprost acid	
$C_{\max}$ (ng/mL)	3.40 ± 0.57
$AUC_{0-\text{last}}$ (ng·weeks/mL)	13.4 ± 1.1
$T_{\max}$ (weeks)	8.00 ± 0.00

Table 5. Mean concentrations of bimatoprost in ocular tissues following single dose administration

Mean concentrations of bimatoprost in ocular tissues following single dose administration	
Cornea (ng/g)	4.62 ± 5.01
Iris-ciliary body (ng/g)	2.80 ± 2.94
Choroid (ng/g)	0.942 ± 1.63
Retina (ng/g)	BLQ (<0.2 ng/mL)
Vitreous humor (ng/mL)	BLQ (<0.2 ng/mL)

PK14025-PK: Ocular pharmacokinetics of bimatoprost following 7 daily topical ophthalmic or a single intracameral drug delivery system (IC DDS) administration to female Beagle dog

This study determined the ocular pharmacokinetics of bimatoprost and bimatoprost acid following either 7 days of topical ocular administration of LUMIGAN® 0.03% (bimatoprost ophthalmic solution 0.03%, once daily [QD]) or a single administration of Bimatoprost intracameral implant formulation similar in excipient content but different in drug substance content (15 µg bimatoprost; i.e. not 10 µg proposed for approval) to female beagle dogs.

For topical treatment, female dogs received a bilateral topical drop (~35 µL) of LUMIGAN 0.03% QD for 7 consecutive days (n=10). In a parallel group, dogs received bilateral Bimatoprost SR (15 µg) implants (n=14). At designated timepoints, cornea, aqueous humor, iris-ciliary body (ICB), upper and lower eyelid margin, bulbar conjunctiva, periorbital fat, retina (macula), and remnant dose implants were collected. Concentrations of bimatoprost and bimatoprost acid were measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS) and high-performance liquid chromatography (HPLC). Key pharmacokinetic parameters in ocular tissues are summarized in the table below. Results showed that the bimatoprost implant achieved much higher intraocular exposure in target tissues (cornea, AH, iris-ciliary body) compared to Lumigan 0.03% topical administration, while achieving much lower exposure in extra-ocular structures such as the eyelid margin, bulbar conjunctiva and periorbital fat.

Table 6. Pharmacokinetic parameters of bimatoprost in ocular tissues following daily topical once daily (QD) for 7 days administration of Lumigan 0.03% or administration of a single bimatoprost intracameral implant (15µg) to Beagle dogs

LUMIGAN 0.03% Once Daily (QD) for 7 Days					
Ocular Tissue	C_{max} (ng/mL or ng/g)		AUC_{0-tlast} (ng•hr/mL or ng•hr/g)		T_{max} (hr)
	Mean	SE	Mean	SE	
Cornea	2.90	1.70	15.5	4.8	9
Aqueous Humor	0.285	0.166	1.45	0.41	1
Iris-Ciliary Body	0.825	0.505	5.12	2.30	9
Upper Eyelid Margin	2100	410	8500	1510	2
Lower Eyelid Margin	1160	340	6220	1240	2
Bulbar Conjunctiva	75.4	21.9	517	107	9
Periorbital Fat	36.1	10.8	139	25.6	2
Retina (Macula)	BLQ	NC	NA	NA	NA
Bimatoprost SR (15 µg)					
Ocular Tissue	C_{max} (ng/mL or ng/g)		AUC_{0-tlast} (ng•day/mL or ng•day/g)		T_{max} (day)
	Mean	SE	Mean	SE	
Cornea	2980	530	93,800	14,900	52
Aqueous Humor	22.9	19.6	727	511	27
Iris-Ciliary Body	18,100	16,700	486,000	441,000	52
Upper Eyelid Margin	BLQ	NC	NA	NA	NA
Lower Eyelid Margin	BLQ	NC	NA	NA	NA
Bulbar Conjunctiva	0.129	0.055	1.62	0.69	52
Periorbital Fat	BLQ	NC	NA	NA	NA
Retina (Macula)	BLQ	NC	NA	NA	NA

^a Half-life (T_{1/2}) was not calculable for any matrix in either study group

SE = standard error; NC = not calculable

PK15022-PK: Ocular pharmacokinetics of bimatoprost following 7 daily topical ophthalmic administrations or a single bimatoprost SR administration to female aphakic Beagle dogs

This study evaluated the ocular distribution of bimatoprost and its acid metabolite, bimatoprost acid, in aphakic dogs. Bimatoprost was given as either a topical ocular instillation (LUMIGAN® 0.03%) QD (once daily) for 7 days or a single intracameral injection of bimatoprost intracameral implant formulation similar in excipient content but

different in drug substance content (15 µg bimatoprost; i.e. not 10 µg proposed for approval) than that proposed for registration.

Prior to administration of bimatoprost, dogs underwent lens removal surgery in their right eye followed by a recovery period of at least 6 weeks. Dogs received either a topical drop (~35 µL) in their right aphakic eye of LUMIGAN 0.03% QD for 7 consecutive days (n=4) or the intracameral bimatoprost implant in their right aphakic eye. At designated timepoints post dose, corneal endothelium, cornea (remaining), conjunctiva (bulbar and palpebral), upper and lower eyelid margin, periorbital fat, aqueous humor, iris-ciliary body (ICB), retina (macula and periphery), vitreous humor, and remnant dose implants were collected. Concentrations of bimatoprost and bimatoprost acid were measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS) and high-performance liquid chromatography (HPLC). Key pharmacokinetic parameters in ocular tissues are summarized below.

Table 7. Pharmacokinetic parameters of bimatoprost and bimatoprost acid in ocular tissues following topical administration of Lumigan 0.03% or administration of a single bimatoprost intracameral implant

Ocular Tissue	LUMIGAN (0.03%)		Bimatoprost SR (15 µg)		
	Day 7, 2h Postdose (ng/mL or ng/g)		C _{max} (ng/mL or ng/g)		T _{max} (Day)
	Mean	SD	Mean	SE	Mean
Cornea (remaining)	BLQ	NC	593	171	27
Cornea Endothelium	BLQ	NC	3730	1340	55
Bulbar Conjunctiva	5.94	2.72	0.807	0.427	27
Palpebral Conjunctiva	9.62	2.97	BLQ	NC	NA
Upper Eyelid Margin	419	235	BLQ	NC	NA
Lower Eyelid Margin	262	142	BLQ	NC	NA
Periorbital Fat	BLQ	NC	BLQ	NC	NA
Aqueous Humor	BLQ	NC	13.9	1.5	55
Iris-Ciliary Body	BLQ	NC	864	777	27
Retina – Macula	BLQ	NC	19.5	13.3	55
Retina – Periphery	BLQ	NC	55.9	55.0	27
Vitreous Humor	BLQ	NC	BLQ	NC	NA

BLQ = below the limit of quantitation; NC = not calculable; NA = not applicable; SD = standard deviation; SE = standard error; N = 4 animals (4 eyes)

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: Bimatoprost (AGN-192024) IC DDS Implant: A 6-month single dose intracameral ocular toxicity study in monkeys

Study no.: TX09051-TX

Study report location: <\\cdsesub1\evsprod\nda211911\0001\m4\42-stud-rep\423-tox\4231-single-dose-tox\tx09051-tx\tx09051-tx.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: 7/23/2009

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: AGN-192024 (bimatoprost); Lot# 0904715; 99.7% purity

Methods

Doses: **Generation 1 formulation:**

10020X: 30 µg

10021X: 60 µg

10021X(x2): 120 µg (2x60µg implants)

Placebo implants (1 or 2 implants)

Frequency of dosing: Single administration to left eye (Day 1)

Route of administration: Intracameral implant administered via intracameral drug delivery system (IC DDS)

Dose volume: Formulation 10020X: (b) (4)

Formulation 10021X: (b) (4)

Formulation 10021X: (b) (4)

Formulation/Vehicle: (b) (4)
PEG-3350 (different ratios compared to proposed clinical formulation)

Species/Strain: Cynomolgus monkey

Number/Sex/Group: Females only:

- Interim Sacrifice (Week 18):
n=2/treatment
- Terminal Sacrifice (Week 27):
n=2/treatment

Age: 2 – 3 years

Weight: 2.1 – 2.8 kg

Deviation from study protocol: None noted.

Observations and Results

Mortality (daily)

- All animals survived until scheduled sacrifice

Clinical Signs (cageside: daily; detailed: weekly)

- Intracameral administration related findings
 - Eye rubbing
 - On Day 1 of the dosing phase, rubbing of eyes was noted in some animals. Since this abnormal observation was only noted on Day 1 and was seen in animals given 0 µg (placebo implants)/left eye, this observation was not related to bimatoprost but attributed to the dosing procedure.
 - Squinting of both eyes
 - Day 1 – Day 2
 - observed in the dosed and non-dosed eyes and was typically only noted on Day 1.
- Potential bimatoprost implant related findings
 - Squinting of left eye only (dosed eye)
 - Day 12
 - Noted sporadically for one animal given 120 µg/left eye and resolved without sequelae on Day 23. This abnormal observation was also noted on Days 131 and 132 of the dosing phase for one animal given 60 µg/left eye.
 - Pupil constriction
 - Constricted pupil of the left eye was noted in some animals throughout the study.
 - A dose-dependent trend for frequency of constricted pupil left eye was not apparent but coincided with the number of implants. Animals given two implants (0 µg/left eye or 120 µg/left eye) had a similar total number of days with this abnormal observation, which suggested it may have been related to greater physical trauma caused by two implants.
 - Drooping eyelid of the left eye
 - Starting Day 23
 - Observed initially in two animals given 120 µg/left eye.
 - Animal No. I01688 (Day 230. Day 92, this abnormal observation was noted for Animal No. I01689, and on Day 131 of the dosing phase, for two animals given 60 µg/left eye. On Day 135 or 136 of the dosing phase, two animals given placebo polymers were noted with this observation, and in general, this observation persisted throughout the study for these animals.
 - Corneal cloudiness
 - Starting Day 99
 - Sporadic corneal cloudiness was noted in the left eye of two animals given 0 µg/left eye, and starting Day 169, this observation was noted for two animals given 60 µg/left eye.

- Considered likely related to physical trauma to the corneal endothelium caused by the implants.

Table 8. Incidence of ocular clinical signs

	Sex		Females		
	$\mu\text{g}/\text{left eye}$	0	30	60	120
Observation ^a	N	4	4	4	4
Constricted Pupil - Left Eye		4(58)	3(7)	4(38)	4(66)
Drooping Eyelid - Left Eye		2(48)	0	2(29)	2(76)
Opaque - Left Eye ^b		2(69)	0	2(6)	0

a Number of animals affected (total number of the days observation was recorded).

b Due to system limitation, corneal haziness was recorded as opaque eye.

Body Weights (weekly)

- No changes in body weight attributed to the test article

Feed Consumption

- No changes in feed consumption attributed to the test article.

Ophthalmology findings / Ophthalmoscopy

- Ocular irritation scoring
 - Conjunctival redness
 - 1+ (mild) and occasionally moderate to severe (up to 3+) noted in the first 5 days in eyes given 0, 30, or 120 $\mu\text{g}/\text{left eye}$ but not in eyes given 60 $\mu\text{g}/\text{left eye}$. Mild conjunctival redness was also sporadically noted on Days 64 and 71 of the dosing phase in some eyes given placebo implants or 60 or 120 $\mu\text{g}/\text{left eye}$. No abnormalities were detected on irritation scoring after Day 71 of the dosing phase.
 - Considered likely associated with preparation of the eye for dosing and/or the intracameral injection itself.
- Slit lamp ocular irritation scoring (weekly)
 - Opacification of the inferior cornea in the region of the implant
 - Darkening (hyperpigmentation) of the left iris relative to the right
 - Week 13
 - 30 μg implant group
 - One eye noted with hyperpigmentation
 - Week 18
 - Hyperpigmentation present in all groups treated with the bimatoprost implant, but in no eyes given placebo implants.
 - No other signs of ocular irritation attributed to the test article.
- Ophthalmoscopy (slit lamp and indirect ophthalmoscopy; predose phase; on Day 3; and during Weeks 2, 5, 13, 18, and 26)

- Week 2 (Day 8)
 - The implant was physically intact in all eyes on Week 2 of the dosing phase
 - Anterior chamber cell scores
 - 0.5 to 1+ levels in all groups.
 - One eye given 30 µg/left eye exhibited two small, free-floating pigmented spheres in the anterior chamber. These spheres eventually adhered to the anterior lens capsule in this eye, where they remained throughout the study.
 - Applicant attributes spheres as likely uveal pigment liberated from the iris surface, perhaps due to the implant rubbing on the iris surface.
- Week 5 (Day 29)
 - Conjunctival hyperemia
 - One eye given 30 µg/left eye and one eye given 120 µg/left eye (two implants).
 - Aqueous flare
 - Mild (1+) aqueous flare was present in one or more animals in all groups, and moderate (2+) aqueous flare was present in one eye each given 0 or 120 µg/left eye (two implants).
 - The occurrence of 2+ aqueous flare in eyes with two placebo implants suggests this finding was more likely attributable to the physical presence and number of implants rather than to bimatoprost.
 - Miosis
 - The left pupil was noted as miotic relative to the right pupil in two eyes given 0 µg/left eye, two eyes given 60 µg/left eye, and three eyes given 120 µg/left eye.
 - In eyes given 120 µg/left eye, pupil dilated incompletely after topical application of a mydriatic.
- Week 13 (Day 85)
 - Implant condition
 - Noted as intact but swollen.
 - Conjunctival hyperemia
 - Was present in two eyes given 0 µg/left eye and two eyes given 120 µg/left eye (two implants).
 - Corneal cloudiness
 - Originated from the endothelial surface and extended for the full thickness of the cornea (2+) was typically present in all left eyes. The area involved was typically 1+ in size and principally located inferiorly over the implants, suggesting it was attributable to the presence of an implant and not AGN-192024. Areas of 2+ were found in one eye given 0 µg/left eye and one eye given 120 µg/left eye (two implants).
 - Aqueous flare

- Was present (at ~ 1+ levels) in three animals given 0 or 120 µg/left eye (two implants), suggesting this finding was more likely attributable to the physical presence and number of implants than AGN-192024. Anterior chamber cell scores were typically mild (0.5 to 1+) in all eyes on this day, although 2+ to 3+ anterior chamber cell appeared in two eyes given 0 or 120 µg/left eye (two implants). Again, the occurrence of these higher cell scores in eyes with two implants suggests they were attributable to the number and size of the implants rather than to AGN-192024.
- Miosis
 - The left pupil was noted to have a resting miosis relative to the right pupil in most eyes in all four groups. It was also noted that the pupil dilated incompletely in three eyes given 0 µg/left eye, one eye each given 30 or 60 µg/left eye, and in three eyes given 120 µg/left eye (two implants). One eye given 0 µg/left eye was noted to have 1+ iridal congestion where the implants were in contact with the iris. The implants in this eye had fibrin and blood over the surface, and this eye also had pigment and white cell on the anterior lens capsule. At the examination during Week 13 of the dosing phase, the left iris appeared darker in color (hyperpigmented) than the right in one animal given 30 µg/left eye and one animal given 120 µg/left eye (two implants).
- Week 18 (Day 121)
 - Implant condition
 - Implants typically appeared intact but swollen in all left eyes. In one animal given 120 µg/left eye, one implant was intact but the other was partially fragmented.
 - Conjunctival hyperemia
 - More frequent than that seen on Week 13 of the dosing phase and was present in three eyes given 0 µg/left eye, one eye given 60 µg/left eye, and three eyes given 120 µg/left eye (two implants).
 - Corneal cloudiness
 - Originated from the endothelial surface and extended for the full thickness of the cornea (2+) and present in all left eyes. The area involved was typically 1+ in size in eyes given 30, 60, or 120 µg/left eye (two implants) and principally located inferiorly over the implants, suggesting it was attributable to the presence of an implant and not bimatoprost. In eyes given 0 µg/left eye, the area of cornea involved was greater than that in eyes with any of the bimatoprost implants.
 - Aqueous flare
 - More frequent in eyes than at the examination during Week 2 of the dosing phase. Aqueous flare scores were 1+ in two

eyes given 0 µg/left eye, three eyes given 60 µg/left eye, and in all four eyes given 120 µg/left eye (two implants). Furthermore, moderate (2+) aqueous flare was present in two eyes given 0 µg/left eye at this examination. Anterior chamber cell scores were typically mild (0.5 to 1+) in all eyes at the examination during Week 18 of the dosing phase, although 2+ anterior chamber cell appeared in two eyes given 0 µg/left eye and one eye given 120 µg/left eye (two implants). The presence of increased anterior chamber cell scores in eyes with two placebo implants (or two bimatoprost implants) suggests the increased anterior chamber cell score was associated with the number of implants and not bimatoprost.

- Miosis
 - The left pupil was noted to have a resting miosis relative to the right pupil in all eyes in all four groups. It was also noted that the pupil dilated incompletely following the topical application of a mydriatic in all four eyes given 0 or 30 µg/left eye and in two eyes given 60 or 120 µg/left eye (two implants).
- Pigmentation
 - Implants in one eye with two placebo implants were noted to have pigment and fibrin over their surface, and pigment and white cell were noted on the anterior lens capsule in this eye as well. In two eyes given 60 or 120 µg/left eye, pigment over the surface of the implant was also noted. It was likely the pigment originated from the iris surface and was attributable to the implant rubbing on the iris. At the examination during Week 18 of the dosing phase, the left iris appeared darker in color (hyperpigmented) than the right in two eyes given 30 µg/left eye, one eyes given 60 µg/left eye, and two eyes given 120 µg/left eye (two implants).
- Week 26 (Day 171)
 - Implant condition
 - Implants were intact but swollen in all left eyes but one. As noted on Week 18 of the dosing phase, one implant appeared fragmented in one animal (120 µg/left eye).
 - Conjunctival hyperemia
 - Present in both eyes given 0 µg/left eye, one eye given 30 µg/left eye, and both eyes given 120 µg/left eye (two implants).
 - Corneal cloudiness
 - Originated from the endothelial surface and extended for the full thickness of the cornea (2+) was present in all left eyes, except for one eye given 0 µg/left eye, in which the corneal cloudiness was 3+. The area involved was 3 to 4+ in eyes

given 0 µg/left eye, 1+ in eyes given 30 µg/left eye, 1 to 2+ in eyes given 60 µg/left eye, and 1 to 2+ in eyes given 120 µg/left eye. The corneal edema was principally located inferiorly over the implants.

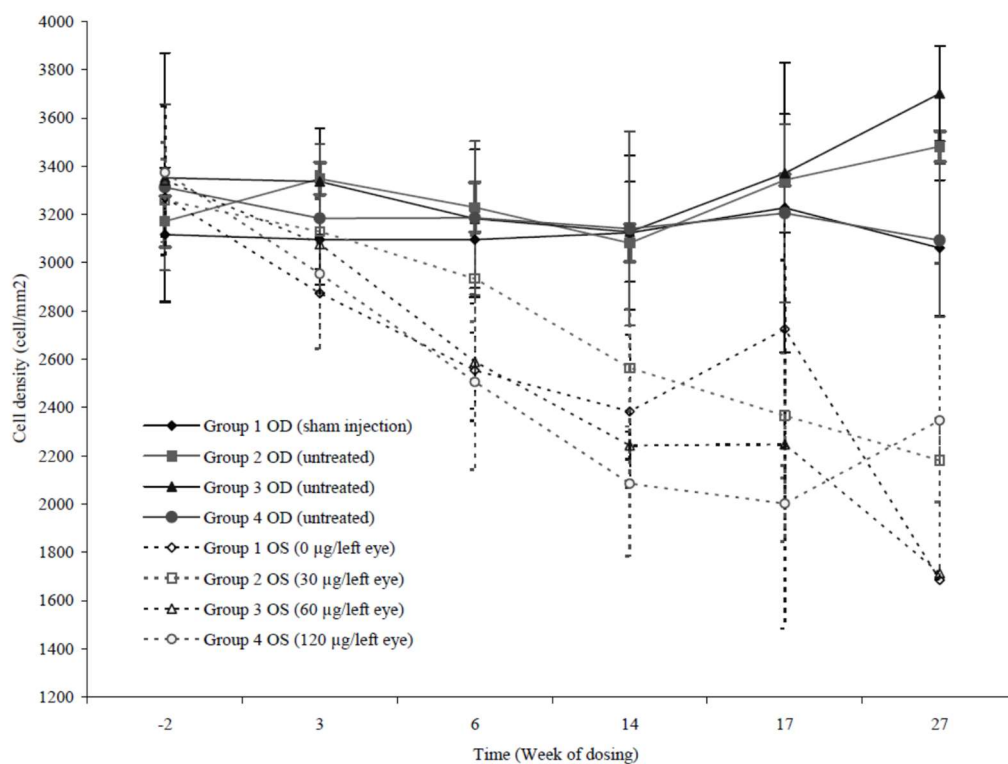
- Aqueous flare
 - (1+ levels) was present in one eye each given 0, 30, or 120 µg/left eye. Anterior chamber cell scores were mild (0.5 to 1+) and present in both eyes given 0 or 120 µg/left eye (both groups having two implants) and in one of two eyes given 30 or 60 µg/left eye (both groups having one implant). The presence of increased anterior chamber cell scores in eyes with two placebo implants (or two bimatoprost implants) suggests the increased anterior chamber cell score was associated with the number of implants and not bimatoprost.
- Miosis
 - The left pupil was noted to have a resting miosis relative to the right pupil in all eyes in all four groups. It was also noted that the pupil dilated incompletely following the topical application of a mydriatic in both eyes given 0 µg/left eye.
- Pigmentation
 - Implants were noted to have pigment on their surface in all four groups. It was likely the pigment originated from the iris surface and was attributable to the implant rubbing on the iris. At the examination during Week 26 of the dosing phase, the left iris appeared darker in color (hyperpigmented) than the right in one eye given 30 µg/left eye, one eye given 60 µg/left eye, and two eyes given 120 µg/left eye (two implants).
- Pupil diameter (Weeks 8, 13, 18, and 27)
 - Miosis; incomplete dilation upon application of topical mydriatic
- Specular microscopy (pre-dose phase and during Weeks 3, 6, 14, 17, and 27 of the dosing phase)
 - Endothelial cell toxicity
 - Steady decline in mean endothelial cell density occurred in the left eye in all groups (see Figure below), including the placebo.
 - Pre-dose mean cell area, percent hexagons, and endothelial cell density values were within typically accepted normal limits for this species.
 - Mean endothelial cell density reductions of 30 to 49% occurred in the left eye of all groups (including the group treated with placebo) at Week 27 when compared to baseline values.
 - Decline in mean endothelial cell density correlated with increase in average cell area (in general, mean increase of 60 to 111% occurred in the left eye of all groups) and decrease in percent

hexagons (in general, mean reductions of 11 to 45% occurred in the left eye of all groups).

- The presence of this finding in eyes given 0 µg (placebo)/left eye indicated it was the presence of an implant rather than the concentration of bimatoprost that was responsible for the reduction in endothelial cell counts.
- Loss of corneal endothelial cells was consistent with the finding of increased central corneal thickness in the treated eyes in animals given placebo (up to 65%), 60 µg (up to 13%) and 120 µg (up to 8%) when compared to pretest values.
- Applicant states that it is likely that an implant designed for use in a human eye with a comparatively deep anterior chamber would be crowded in the much smaller cynomolgus monkey anterior chamber and, thereby, damage the corneal endothelium.

Mean endothelial cell density throughout the dosing phase

Mean Endothelial Cell Density throughout the Dosing Phase



- Intraocular pressure
 - Week 26 of the dosing phase, IOP reduction in the left eye versus the right was 48% for eyes given 0 µg/left eye, 20% for eyes given 30 µg/left eye, 17% for eyes given 60 µg/left eye, and 52% for eyes given 120 µg/left eye.
 - The IOP of the untreated right eye remained normal throughout the study.

- Gonioscopy (predose phase and during Weeks 5, 18, and 26 of the dosing phase)
 - Iridocorneal angle
 - Weeks 18 and 26 of the dosing phase
 - Pigment on the inferior corneal endothelium and in the inferior trabecular meshwork.
 - Noted as a small amount in one or more animals given 30, 60, or 120 µg/left eye.
 - Implant integrity
 - The implants appeared intact in all eyes on Week 5, but by Week 18, the placebo implants generally were misshapen in appearance, whereas only one AGN-192024 implant (a Group 4 animal) appeared fragmented on Week 18 of the dosing phase. By Week 26 of the dosing phase, almost all implants appeared swollen. Corneal edema precluded complete gonioscopic examination in most left eyes in all groups on Week 26 of the dosing phase, but on this examination, broad-based peripheral anterior synechia were present in one animal with two placebo implants.
- Pachymetry
 - Mean central corneal thickness increased in the treated eye in animals given two placebo (up to 65%), 60 µg (up to 13%) and 120 µg (up to 8%) when compared to baseline values.

Gross Pathology (Week 18, Week 27)

- Discoloration of the cornea of the left eye
 - Three animals (two controls and one 60-µg/left eye animal) at the Week 27 necropsy had discoloration of the cornea of the left eye characterized by opacity of the cornea. This finding was likely due to the implanted device and not due to bimatoprost.

Histopathology

Adequate Battery: Eye and adnexa only:

- eye - left and right
- bulbar conjunctiva with attached optic nerve
- eyelids (upper and lower to include palpebral conjunctiva)
- lacrimal gland – left and right
- muscle -left and right
 - ocular: superior oblique, inferior oblique, rectus dorsalis, rectus lateralis, rectus medialis, and rectus ventralis
 - eyelids - right (upper and lower to include palpebral conjunctiva)
- optic nerve – left and right

Peer Review: Yes

Histological Findings

- Animals in all groups had minimal attenuation of the corneal endothelium of the left eye, characterized by decreased numbers of endothelial nuclei adjacent to one of the iris leaflets but not the other. Because the eyes were sectioned in a vertical plane and the attenuation occurred exclusively in the left eye, the affected area of endothelium was assumed to be ventral and considered a consequence of mechanical trauma due to the implant in the anterior chamber.
- The macroscopic observation of discoloration of the left cornea characterized by opacity occurred in two animals given 0 µg/left eye and one animal given 60 µg/left eye was associated microscopically with attenuation of the corneal endothelium in the ventral (inferior) aspect of the cornea in the left eye.
- In one animal given 30 µg/left eye, thickening of Descemet's membrane also occurred.
- Bimatoprost related increase in melanin of the iris stroma occurred in one animal given 120 µg/left eye.

Toxicokinetics

Summary of Mean Blood Toxicokinetic Parameters of AGN-192024 and AGN-191522

Group	Dose (µg/left eye)	C _{max} (ng/mL)	AUC _{0-t} (ng hours/mL)
		Mean	Mean
AGN-192024 ^a			
1 Bimatoprost Implant (1 mm)	30	0.280	NC
1 Bimatoprost Implant (2 mm)	60	0.244	NC
2 Bimatoprost Implants (2 mm)	120	0.0850	NC
AGN-191522 ^a			
1 Bimatoprost Implant (1 mm)	30	0.165	NC
1 Bimatoprost Implant (2 mm)	60	NC	NC
2 Bimatoprost Implants (2 mm)	120	NC	NC

NC = Not Calculable.

a N = 2 to 4/group/timepoint.

Dosing Solution Analysis

- Results indicated concentrations of Bimatoprost in the formulations were between 94.0 and 95.7% of the nominal/target concentration and therefore, considered acceptable for use on study.

6.2 Repeat-Dose Toxicity

Study title: Bimatoprost (AGN-192024) PF IC DDS: 18-month (three doses) intracameral ocular toxicity study in dogs

Study no.: TX12102-TX
 Study report location: <\\cdsesub1\evsprod\nda211911\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\tx12102-tx\tx12102-tx.pdf>
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 1-16-2013
 GLP compliance: Yes
 QA statement: Yes; signed
 Drug, lot #, and % purity: Bimatoprost (AGN-192024); Lot# 1105023; 99.4% purity

Key Study Findings

Methods

Doses: Unilateral (right eye):

- 10µg implant
- 15µg implant
- 2x10 µg implant

Frequency of dosing: Day 1, Day 120, Day 232
 Route of administration: Intracameral injection
 Dose volume:

- 10µg implant: (b) (4) mm diameter and (b) (4) mm average length
- 20µg implant: (b) (4) mm diameter and (b) (4) mm average length

Formulation/Vehicle: Generation 2 formulation (proposed clinical formulation)
 Species/Strain: Dog / Beagle
 Number/Sex/Group: Females only:

- Interim sacrifice (Week 40): 12/group
- Terminal sacrifice (Week 79): 12/group

Age: 10 – 14 months
 Weight: 5.0 – 13.4 kg
 Deviation from study protocol: None which affected integrity or interpretability of results

Observations and Results

Mortality

- All animals survived until scheduled sacrifice.

Clinical Signs

- Clinical signs attributed to the test article were limited to constricted pupil and red palpebral conjunctiva in the treated eye.

Body Weights

- No changes in body weight attributed to the test article.

Feed Consumption

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy

- Miosis prevented fundus examination in many animals.
- Ocular irritation scoring
 - Hyperemia (mild – moderate)
 - Congestion (mild – moderate)
 - In the first week, all treated eyes were reported with congestion/hyperemia. In eyes receiving sham treatment, congestion/hyperemia resolved by Week 2, whereas it persisted in animals treated with the bimatoprost implant(s). It appears that the initial cause of hyperemia was due to the dosing procedure and/or handling and persistent hyperemia was considered bimatoprost related.

Summary of Ocular Irritation Scoring - Hyperemia/Congestion

Dosing Regimen	Right Eye		Left Eye			
	One Implant	One Implant	Two Implants	Sham Injected	Not Treated	Not Treated
Dose Level ($\mu\text{g}/\text{eye}/\text{dose}$)	10	15	20	0	0	0
No. of Animals	24	24	24	24	24	24
Study Week	Total Hyperemia Scores					
Week 1 (Day 1 Predose)	0	0	0	0	0	0
Week 1 (Day 1 Postdose)	15	26	22	13	15	17
Week 1 (Day 2)	24	25	33	16	9	16
Week 1 (Day 3)	14	16	23	12	9	9
Week 1 (Day 4)	15	14	15	11	3	1
Week 1 (Day 5)	5	11	11	1	0	1
Week 1 (Day 6)	6	5	8	2	0	0
Week 1 (Day 7)	4	8	11	3	0	0
2	2	11	13	0	0	0
3	5	8	9	0	0	0
4	8	9	11	0	0	2
5	17	19	23	4	3	5
6	3	1	2	0	0	0
7	19	23	26	9	3	6
8	5	4	6	0	0	0
9	5	4	7	0	0	1
10	8	10	14	0	0	0
11	8	12	13	4	0	1
12	6	12	16	2	1	7
13	8	5	8	2	0	1
14	1	3	4	1	1	0
15	1	2	1	1	1	1
16	3	3	6	2	1	2
17	3	1	2	1	1	1
18 (Day 120 Predose)	3	2	5	2	1	3
18 (Day 120 Postdose)	46	48	49	43	46	45
18 (Day 121)	35	35	36	24	8	8
18 (Day 122)	24	30	31	13	0	2
18 (Day 123)	21	23	27	6	0	0
18 (Day 124)	12	19	19	4	0	0
18 (Day 125)	7	13	11	1	0	0
18 (Day 126)	13	14	15	4	0	0
19	9	12	19	1	0	0
20	13	17	14	2	1	1
21	11	13	11	1	0	0
22	6	10	9	1	1	0
23	11	15	14	1	0	1
24	10	16	14	1	1	1
25	18	18	21	6	4	1
26	10	13	11	3	1	2

27	18	22	18	4	3	3
28	15	21	18	1	1	3
29	12	15	14	4	2	2
30	9	13	16	1	0	2
31	5	9	10	1	0	3
32	7	7	10	2	1	4
33	3	4	7	2	2	2
34 (Day 232 Predose)	6	4	4	4	1	1
34 (Day 232 Postdose)	25	22	23	22	21	21
34 (Day 233)	28	28	25	17	10	10
34 (Day 234)	23	22	22	10	1	2
34 (Day 235)	22	19	19	7	2	8
34 (Day 236)	15	16	18	7	4	5
34 (Day 237)	21	22	21	6	2	2
34 (Day 238)	22	24	20	7	3	2
35	20	23	20	7	1	3
36	14	20	17	2	1	3
37	12	16	16	0	1	1
38	9	14	15	0	0	0
39	11	12	14	3	0	2
40	12	13	14	0	1	1
41	7	5	9	0	0	0
42	3	7	4	0	0	0
43	5	8	9	0	0	0
44	3	1	4	1	0	0
45	2	3	8	0	0	0
46	2	1	3	1	0	0
47	1	3	5	0	0	0
48	2	2	2	2	0	0
49	2	3	4	1	0	0
50	2	2	1	2	1	0
51	2	3	2	2	2	2
52	4	2	4	2	0	1
53	5	3	3	3	1	0
54	3	2	1	1	0	0
55	2	3	4	3	0	2
56	2	2	3	1	0	0
57	2	3	2	0	0	0
58	2	3	5	0	0	1
59	3	2	3	0	0	0
60	2	0	4	0	0	0
61	0	4	2	1	0	1

62	2	0	3	1	0	0
63	2	0	1	0	0	0
64	3	1	0	2	0	0
65	3	1	0	2	0	0
66	1	0	0	0	0	0
67	1	1	2	0	0	0
68	3	0	0	1	0	0
69	0	0	0	0	0	0
70	2	0	1	0	0	0
71	2	0	0	2	0	0
72	2	0	0	1	0	0
73	1	0	0	0	1	0
74	1	0	0	0	0	0
75	1	1	0	0	0	0
76	2	0	0	0	0	0
77	1	0	0	0	0	0
78	1	0	0	0	0	0
79	1	1	0	0	0	0

Total hyperemia score = Sum of hyperemia scores for the eyes in each group.

Animals were dosed on Days 1, 120, and 232.

12 animals/groups were sacrificed during Week 40 of the dosing phase.

- Changes to anterior chamber
 - At Week 18 (1 week after the second dose), and to a lesser extent Week 19 of the dosing phase, the anterior chamber of all right eyes given a bimatoprost implant appeared shallower on slit lamp biomicroscopy than left eyes. At Week 21 of the dosing phase, shallowing of the right anterior chamber relative to the left eye was no longer apparent on slit lamp biomicroscopy for any eye. A similar effect and trend occurred following the third dose administration.
- Other findings which occurred sporadically but may be related to the test article include:
 - Corneal vascularization (one to three vessels; 0.5 mm to 2 mm long); recoverable.

Gonioscopy (implant disposition)

- Implants in all three groups subjectively swelled.
- In some animals, the implant appeared broken or resting in anatomical areas such as posterior to the pectinate ligament, adherent or resting on the iris or in contact with the iridocorneal angle.
- At each successive dose administration, at least a portion of the original implants remained in nearly all eyes of each group. At the last observation (Week 78, 44 weeks after the third dose), one or more implant remnants were located in the trabecular meshwork (9/12 eyes given 10 µg implant, in 11/12 eyes given 15 µg implant and in all 12 eyes given 2x10 µg implant).

Intraocular Pressure

- Decreased intraocular pressure
 - Pharmacologic response to bimatoprost
 - Decreased IOP for approximately 8 weeks following each dose administration at which time IOP returned to near baseline levels until the next dose administration or study termination.

APPEARS
THIS WAY
ON
ORIGINAL

Predose Summary of Percent Change in Intraocular Pressure from

Group	% Change in IOP from Predose in the Left Eyes ($\pm$ SD)		
	Week 1	Week 18	Week 34
1 (Sham-injected)	-13.4 $\pm$ 14.4	-11.6 $\pm$ 13.7	-11.9 $\pm$ 11.0
2 (Untreated)	0.7 $\pm$ 16.1	-4.2 $\pm$ 12.6	-1.7 $\pm$ 9.5
3 (Untreated)	-0.9 $\pm$ 13.3	-8.2 $\pm$ 12.5	-4.7 $\pm$ 12.9

IOP = Intraocular pressure; SD = Standard deviation.

Specular Microscopy

- No changes in axial endothelial cell density (and corresponding mean cell area and percent hexagons) attributed to the test article.

Pupillometry

- Miosis (reduction of pupil diameter)
 - Doses related; up to 85.9% reduction compared to untreated left eye at high dose. Group 1: 10 μ g implant; Group 2: 15 μ g implant; Group 3: 2x10 μ g implant

Mean Delta% Change in Pupil Diameter

Week	Group 1	Group 2	Group 3
2	-46.0	-53.3	-63.8
4	-60.7	-63.2	-70.3
8	-74.0	-77.9	-85.9
12	-7.4	-16.1	-20.1
17	-9.0	-13.6	-14.2
19	-51.9	-54.7	-69.5
21	-64.5	-70.5	-77.1
25	-53.6	-66.6	-74.1
29	-19.4	-23.2	-30.8
33	-13.3	-13.4	-22.9
35	-58.6	-68.9	-80.9
38	-68.6	-73.0	-75.9
47	-9.0	-21.7	-28.8
55	-6.3	-14.1	-24.1
62	-1.8	-9.7	-15.9
70	-0.3	-5.9	-19.2
78	-1.7	-2.5	-14.2

Note: Data are presented as right eye % change - left eye % change.

Pachymetry

- No changes in corneal thickness attributed to the test article.

Optical Coherence Tomography (anterior segment)

- Results indicated that the iridocorneal angle became narrower after exposure to bimatoprost. Results are based on an estimation of the size of an implant which would fit within the iridocorneal angle during the pre-dose period compared to size at the time of each measurement.

Summary of Percent Change in Iridocorneal Angle Size:

	Maximum % Change in Iridocorneal Angle Size (Right Eye Compared with Baseline)		
	Weeks 4 to 16 (after 1st dose)	Weeks 21 to 33 (after 2nd dose)	Week 38 (after 3rd dose)
Group 1			
Subset A	-19.2	-20.9	-11.8
Subset B	-22.4	-22.5	-10.9
Subset C	-24.5	-28.4	-17.8
Subset D	-25.3	-24.7	-22.8
Group 2			
Subset A	-11.9	-13.0	-4.5
Subset B	-24.0	-24.2	-12.6
Subset C	-22.1	-25.1	-23.5
Subset D	-28.6	-27.8	-25.0
Group 3			
Subset A	-7.7	-5.9	-3.6
Subset B	-18.1	-16.8	-14.5
Subset C	-28.4	-28.6	-22.8
Subset D	-33.9	-31.5	-24.4

Subset A = Predose maximal phantom fit between < 0.443 mm.

Subset B = Predose maximal phantom fit between 0.443 mm and 0.486 mm.

Subset C = Predose maximal phantom fit between 0.493 mm and 0.529 mm.

Subset D = Predose maximal phantom fit between 0.550 mm and 0.630 mm.

Gross Pathology

- No macroscopic changes attributed to the test article.

Histopathology

Adequate Battery: Ocular tissues only

Peer Review: Yes

Histological Findings

- At the interim sacrifice, all eyes administered implants except one were reported with the following:

- Schwalbe's line cell/limbal endothelial cell hypertrophy and/or Schwalbe's line cell/limbal endothelial cell hyperplasia and subendothelial/sub-Schwalbe's line cell fibrillar matrix deposition
 - Minimal Schwalbe's line cell/limbal endothelial cell hypertrophy and minimal Schwalbe's line cell limbal endothelial cell hyperplasia consisted of enlarged nuclei with cytoplasmic swelling and piling of hypertrophic cells, respectively.
 - Minimal subendothelial fibrillar matrix in the inferior iridocorneal angle consisted of eosinophilic staining fibrillar material between Schwalbe's line cells/limbal endothelial cells and Descemet's membrane.
 - At the interim sacrifice, all three changes occurred with equal incidence in >90% of treated eyes; however, at the terminal sacrifice, the incidence of hyperplasia decreased to approximately 25% in eyes given one implant/dose and 0% in eyes given two implants/dose.
 - The location of the implant-related changes varied, depending on the number of implants and included implant-related changes in the deep angle, mid limbus and changes in the corneal-limbal border.
- Implant casts
 - One or more implant casts were observed in the inferior angle of some animals.
 - Casts were typically adhered to one or more surfaces within the deep angle: the anterior iris adjacent to the pectinate ligaments, operculum, or pectinate ligaments. A few implant casts were also observed within the inferior trabecular meshwork beyond the pectinate ligaments. The adhered implants were covered and partially infiltrated by hypertrophied and hyperplastic Schwalbe's line cells extending from the operculum or base of the pectinate ligament, pigmented cells from the anterior iris, or both.

Toxicokinetics

- Concentrations of AGN-192024 and its metabolite of AGN-191522 (bimatoprost acid) were analyzed from plasma samples collected up to Day 261 of the dosing phase. Except for five samples, concentrations in 792 analyzed samples were below the lower limit of quantitation (<0.025 ng/mL for bimatoprost and <0.050 ng/mL for bimatoprost acid). Samples for which bimatoprost or bimatoprost acid were detected showed concentrations <0.7 ng/mL.

Dosing Solution Analysis

- Potency and impurity profile remained within the release specifications.

Conclusion

- Given that findings were generally mild in severity and recoverable, the high-dose level of 20 µg Bimatoprost (as two 10 µg implants) is considered the No Observed Adverse Effect Level.

7 Genetic Toxicology

The Applicant is relying on data obtained for the approval of Lumigan (NDA 021-275). The Applicant owns these data. In the labeling for Lumigan, the following is stated:

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

8 Carcinogenicity

The Applicant is relying on data obtained for the approval of Lumigan (NDA 021-275). The Applicant owns these data. In the labeling for Lumigan, the following is stated:

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage for 104 weeks at doses up to 2 mg/kg/day and 1 mg/kg/day, respectively (192 and 291 times the estimated human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily, respectively, based on blood AUC levels).

The proposed statement by the Applicant for the labeling for Durysta® is:

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses up to 2 mg/kg/day and 1 mg/kg/day respectively for 104 weeks (approximately 3100 and 1700 times, respectively, the maximum human exposure [based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858]).

The sponsor uses *blood-to-plasma partition ratio (0.858)* to allow conversion of the human plasma concentration to a blood concentration to compare to animal blood levels, as follows:

- Supporting data calculations:
 - Human
 - $C_{max} = 2.24$ pg/mL (in plasma)
 - *Blood-to-plasma partition ratio of 0.858* = C_{max} : 2.24 pg/mL $\times$ 0.858 = 1.92 pg/mL
 - Mouse
 - NOAEL: 2 mg/kg
 - C_{max} (in blood): 5.98 ng/mL (5980 pg/mL)

- Exposure margin at NOAEL over human C_{max} :
5980 pg/mL / 1.92 pg/mL = 3115-fold (rounded to 3100).
- Rat
 - NOAEL: 1 mg/kg
 - C_{max} (in blood): 3.23 ng/mL (3230 pg/mL)
 - Exposure margin at NOAEL over human C_{max} :
3230 pg/mL / 1.92 pg/mL = 1682-fold (rounded to 1700).

Table 9. TK parameters in mice from Study ALG053: Mouse carcinogenicity

Analyte	AGN 192024 Dosage	C_{max} (ng/mL)	AUC_{0-4}
AGN 192024	0.3 mg/kg/day	2.53	0.874
	1.0 mg/kg/day	5.93	4.77
	2.0 mg/kg/day	5.98	8.10
AGN 191522	0.3 mg/kg/day	BLQ	NC
	1.0 mg/kg/day	0.569	NC*
	2.0 mg/kg/day	0.410	NC*

n 3/sex/group/timepoint

BLQ Below the lower limit of quantitation

NC Not calculable

*AUC Not calculated because concentration values were quantifiable in less than 2 timepoints

Table 10. TK parameters in rats from Study ALG 058: Rat carcinogenicity

Analyte	AGN 192024 Dosage	C _{max} (ng/mL)	AUC ₀₋₄
AGN	0.1 mg/kg/day	0.459	0.273
192024	0.3 mg/kg/day	1.43	2.32
	1.0 mg/kg/day	3.23	9.11
AGN	0.1 mg/kg/day	BLQ	NC
191522	0.3 mg/kg/day	BLQ	NC
	1.0 mg/kg/day	0.274	0.756

n 3/sex/group/timepoint

BLQ Below the lower limit of quantitation

NC Not calculable

9 Reproductive and Developmental Toxicology

The Applicant is relying on data obtained for the approval of Lumigan (NDA 021-275). The Applicant owns these data. Current Lumigan labeling is presented in the Appendices.

The sponsor uses *blood-to-plasma partition ratio (0.858)* to allow conversion of the human plasma concentration to a blood concentration to compare to animal blood levels, as follows:

With these considerations, the following text regarding the nonclinical embryofetal toxicity studies are suggested for the animal data section of the label:

In an embryofetal development rat study, oral administration of bimatoprost to pregnant rats during organogenesis produced abortion at 0.6 mg/kg/day (1770-times the human systemic exposure to bimatoprost from DURYSTA®, based on C_{max} and a blood-to plasma partition ratio of 0.858). The No Observed Adverse Effect Level (NOAEL) for abortion was 0.3 mg/kg/day (estimated at 470-times the human systemic exposure to bimatoprost from DURYSTA®, based on C_{max}). No fetal abnormalities were observed at doses up to 0.6 mg/kg/day.

In an embryofetal development mouse study, oral administration of bimatoprost to pregnant mice during organogenesis produced abortion and early delivery at 0.3 mg/kg/day (2240-times the human systemic exposure to bimatoprost from DURYSTA®, based on plasma C_{max} level; blood-to plasma partition ratio of 0.858). The NOAEL for abortion and early delivery was 0.1 mg/kg/day (400-times the human systemic exposure to bimatoprost from DURYSTA®, based on C_{max}). No fetal abnormalities were observed at doses up to 0.6 mg/kg/day (5200-times the human systemic exposure to bimatoprost from DURYSTA®, based on C_{max}).

Calculations:

- The exposure margin calculations made for Lumigan cannot be made for Durysta because human AUC values were not able to be calculated for Durysta based on low exposure. Exposure margins can be calculated based on $C_{\max}$ comparisons, using *blood-to-plasma partition ratio of 0.858*, to allow comparison of human plasma level to animal blood levels.
- Embryofetal development
 - Human
 - $C_{\max} = 2.24$ pg/mL (in plasma)
 - *Blood-to-plasma partition ratio of 0.858* = $C_{\max}$: 2.24 pg/mL $\times 0.858 = 1.92$ pg/mL
 - Mouse
 - Effect (abortion / early delivery): 0.3 mg/kg
 - $C_{\max}$ (GD15): 4.3 ng/mL (4300 pg/mL)
 - Exposure margin at LOAEL over human $C_{\max}$: 4300 pg/mL / 1.92 pg/mL = 2239 (rounded to 2240).
 -
 - NOAEL (abortion): 0.1 mg/kg
 - $C_{\max}$ (GD15): 0.744 ng/mL (774 pg/mL)
 - Exposure margin at NOAEL over human $C_{\max}$: 774 pg/mL / 1.92 pg/mL = 403 (rounded to 400).
 - NOAEL (all other abnormalities): 0.6 mg/kg
 - $C_{\max}$ (GD15): 10 ng/mL (10000 pg/mL)
 - Exposure margin at NOAEL over human $C_{\max}$: 10000 pg/mL / 1.92 pg/mL = 5208 (rounded to 5200).
 - Rat
 - Effect (abortion / early delivery): 0.6 mg/kg
 - $C_{\max}$ (GD17): 3.4 ng/mL (3400 pg/mL)
 - Exposure margin at LOAEL over human $C_{\max}$: 3400 pg/mL / 1.92 pg/mL = 1771 (rounded to 1770).
 - NOAEL: 0.3 mg/kg
 - $C_{\max}$ (GD17): 0.898 ng/mL (898 pg/mL)
 - Exposure margin at NOAEL over human $C_{\max}$: 898 pg/mL / 1.92 pg/mL = 468 (rounded to 470).

Pre- / postnatal development

Recommended labeling statement:

In a pre/postnatal development study, oral administration of bimatoprost to pregnant rats from gestation day 7 through lactation resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 470-times the human systemic exposure to bimatoprost from DURYSTA®, based plasma C_{max} and a blood-to plasma partition ratio of 0.858). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA®, based on plasma C_{max}).

Supporting data calculations:

- Human
 - C_{max} = 2.24 pg/mL (in plasma)
 - Blood-to-plasma partition ratio of 0.858 = C_{max} : 2.24 pg/mL x 0.858 = 1.92 pg/mL
- Rat
 - Reviewer's note: No TK data was available for the rat pre/postnatal developmental toxicity study. For Lumigan PLLR, the Applicant based safety margin calculations on the toxicokinetics obtained for the rat embryofetal development toxicity study (see NDA 022184; SDN407)
 - Effect (reduced gestation length and fetal body weight): 0.3 mg/kg
 - C_{max} (GD17): 0.898 ng/mL (898 pg/mL)
Exposure margin at LOAEL over human C_{max} :
898 pg/mL / 1.92 pg/mL = 468 (rounded to 470).
 - NOAEL: 0.1 mg/kg
 - C_{max} (GD7): 0.655 ng/mL (655 pg/mL)
 - Note GD17 C_{max} was BLQ, so GD7 data is used.
 - Exposure margin at NOAEL over human C_{max} : 665 pg/mL / 1.92 pg/mL = 346 (rounded to 350).

Fertility

Recommended labeling statement:

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (1770-times the maximum human exposure, based on plasma C_{max} ; blood-to plasma partition ratio of 0.858).

- Supporting data calculations:
 - Human
 - C_{max} = 2.24 pg/mL (in plasma)

- *Blood-to-plasma partition ratio of 0.858 = C_{max}: 2.24 pg/mL x 0.858 = 1.92 pg/mL*
- Rat
 - Reviewer's note: No TK data was available for the rat pre/postnatal developmental toxicity study. For Lumigan PLLR, the Applicant based safety margin calculations on the toxicokinetics obtained for the rat embryofetal development toxicity study (see NDA 022184; SDN407)
 - NOAEL: 0.6 mg/kg
 - C_{max}: 3.4 ng/mL (3400 pg/mL)
 - Exposure margin at NOAEL over human C_{max}: 3400 pg/mL / 1.92 pg/mL = 1771 (rounded to 1770).

Supporting tables of exposure data from mouse and rat embryofetal development studies:

Table 11. TK parameters in rats from Study 1801-018 "Oral (gavage) developmental toxicity study of AGN 192024, 0.2% in rats

Dose (mg/kg)	AGN 192024			AGN 191522
	C _{max} (ng/ml)	T _{max} (min)	AUC _{0-4 hr} (ng-hr/ml)	C _{max} (ng/ml)
Gestation day 7				
0.1	0.655±0.287	5		BLQ
0.3	0.919±0.094	15		BLQ
0.6	2.73±3.21	15	2.95±0.60	BLQ
Gestation day 17				
0.1	BLQ			BLQ
0.3	0.898±0.391	5		BLQ
0.6	3.40±1.31	5	3.23±0.50	BLQ

BLQ: < 0.125 ng/ml for AGN 192024 and < 0.25 ng/ml for AGN 191522

Table 12. TK parameters in mice of bimatoprost (AGN192024) and bimatoprost acid (AGN 191522) from Study TX99038 entitled "Oral (gavage) developmental toxicity study of AGN 192024 in mice

Dose (mg/kg)	AGN 192024			AGN 191522		
	C _{max} (ng/ml)	T _{max} (min)	AUC _{0-1 hr} (ng-hr/ml)	C _{max} (ng/ml)	T _{max} (hr)	AUC _{0-1 hr} (ng-hr/ml)
Gestation Day 6						
0.1	1.67±2.55	10	0.107±0.062	BLQ		
0.3	16.3±8.8	2	1.89±0.34	BLQ		
0.6	3.68±3.64	5	1.10±0.21	BLQ		
Gestation day 15						
0.1	0.774±0.886	2	0.109±0.025	BLQ		
0.3	4.30±3.40	10	1.37±0.26	BLQ		
0.6	10.0±5.2	10	3.01±0.50	BLQ		

BLQ: < 0.5 ng/ml

11 Integrated Summary and Safety Evaluation

Table 13 Summary of safety margins based on nonclinical NOAEL

Toxicity	Species	NOAEL (g/eye)	Safety Margin Based on Dose Comparison
Limbal cell changes; no toxicity was considered adverse and non-reversible	Dog	20 µg/eye; 3 dose administrations	2-fold
Corneal endothelium cellular toxicity	Monkey	No NOAEL (occurred in placebo treated animals as well)	No safety margin

12 Appendix/Attachments

APPENDIX A: Current Lumigan labeling (NDA 21-275; Sections 8, 12.1, and 13 only)

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of LUMIGAN® (bimatoprost ophthalmic solution) 0.01% administration in pregnant women. There is no increase in the risk of major birth defects or miscarriages based on bimatoprost postmarketing experience.

In embryofetal developmental studies, administration of bimatoprost to pregnant mice and rats during organogenesis, resulted in abortion and early delivery at oral doses at least 33 times (mice) or 94 times (rats) the human exposure to bimatoprost 0.03% dosed bilaterally once daily (based on blood area under the curve [AUC] levels). These adverse effects were not observed at 2.6 times (mice) and 47 times (rats) the human exposure to bimatoprost 0.03% dosed bilaterally once daily (based on blood AUC levels).

In pre/postnatal development studies, administration of bimatoprost to pregnant rats from organogenesis to the end of lactation resulted in reduced gestation length and fetal body weight, and increased fetal and pup mortality at oral doses at least 41 times the

human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily (based on blood AUC levels). No adverse effects were observed in rat offspring at exposures estimated at 14 times the human exposure to bimatoprost 0.03% dosed bilaterally once daily (based on blood AUC levels).

Because animal reproductive studies are not always predictive of human response LUMIGAN® 0.01% should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Data

Animal Data

In an embryofetal development rat study, abortion was observed in pregnant rats administered bimatoprost orally during organogenesis at 0.6 mg/kg/day (94 times the human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily, based on AUC). The No Observed Adverse Effect Level (NOAEL) for abortion was 0.3 mg/kg/day (estimated at 47 times the human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily, based on AUC). No abnormalities were observed in rat fetuses at doses up to 0.6 mg/kg/day.

In an embryofetal development mouse study, abortion and early delivery were observed in pregnant mice administered bimatoprost orally during organogenesis at doses greater than or equal to 0.3 mg/kg/day (33 times the human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily, based on AUC). The NOAEL for abortion and early delivery was 0.1 mg/kg/day (2.6 times the human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily, based on AUC). No abnormalities were observed in mouse fetuses at doses up to 0.6 mg/kg/day (72 times the human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily, based on AUC).

In a pre/postnatal development study, treatment of pregnant rats with bimatoprost orally from gestation day 7 to lactation day 20 resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at doses greater than or equal to 0.3 mg/kg/day. These effects were observed at exposures at least 41 times the human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily, based on AUC. The NOAEL for postnatal development and mating performance of the offspring was 0.1 mg/kg/day (estimated at 14 times the human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily, based on AUC).

8.2 Lactation

Risk Summary

It is not known whether topical ocular treatment with LUMIGAN® 0.01% could result in sufficient systemic absorption to produce detectable quantities in human milk. In animal studies, bimatoprost has been shown to be present in breast milk of lactating rats at an intravenous dose (i.e., 1 mg/kg) 970 times the RHOD (on a mg/rn 2 basis), however, no animal data is available at clinically relevant doses.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUMIGAN® 0.01% and any potential adverse effects on the breastfed child from LUMIGAN® 0.01%.

8.4 Pediatric Use

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

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

12.1 Mechanism of Action

Bimatoprost, a prostaglandin analog, is 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage for 104 weeks at doses up to 2 mg/kg/day and 1 mg/kg/day, respectively (192 and 291 times the estimated human systemic exposure to bimatoprost 0.03% dosed bilaterally once daily, respectively, based on blood AUC levels)

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 (at least 103 times the recommended human exposure to bimatoprost 0.03% dosed bilaterally once daily based on blood AUC levels).

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/s/

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