

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-275**

**MEDICAL REVIEW**

**Medical Officer's Review of NDA 21-275**

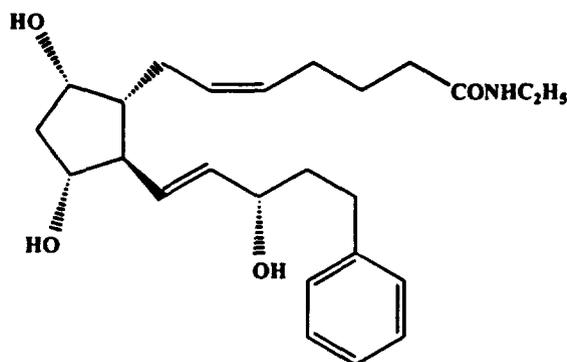
NDA 21-275  
Medical Officer's Review #3

Submission: 3/14/01  
Review Completed: 3/14/01

**Proposed Tradename:** Lumigan 0.03%

**Generic Name:** bimatoprost ophthalmic solution

**Chemical Name:**



Bimatoprost  $C_{25}H_{37}NO_4$

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

**Sponsor:** Allergan  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, California 92623-9534

**Pharmacologic Category:** synthetic analogue of prostaglandin  $F_{2\alpha}$  (PG  $F_{2\alpha}$ )

**Proposed Indication:** Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension

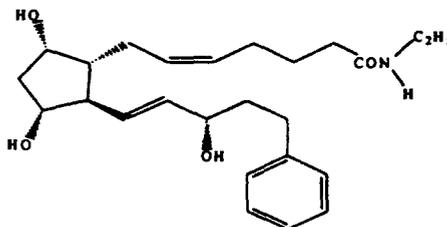
**Dosage Form and Route of Administration:** Ophthalmic solution for topical ocular administration

**Submitted:** Revised labeling based on previous review, discussion with the applicant, discussion between ODEV and the Division, and a clean-corrected package insert transmitted by the applicant on 3/14/01 at 2:44 PM.

**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<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>. 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.

Each mL contains: Active: bimatoprost 0.3 mg; Preservative: Benzalkonium chloride 0.05 mg; 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<sub>max</sub> and AUC<sub>0-24hr</sub> 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.

## 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 who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

## 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. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.**

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of LUMIGAN™.

LUMIGAN™ may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

### PRECAUTIONS

#### *General:*

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 Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see Warnings). Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris are expected to be affected by 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.

LUMIGAN™ should not be administered while wearing contact lenses.

LUMIGAN™ has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

*Information for Patients:*

Patients should be informed that LUMIGAN™ has been reported to cause increased growth and darkening of eyelashes and darkening of the skin around the eye in some patients. These changes may be permanent.

Some patients may slowly develop darkening of the iris, which may be permanent.

When only one eye is treated, patients should be informed of the potential for a cosmetic difference between the eyes in eyelash length, darkness or thickness, and/or color changes of the eyelid skin or iris.

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.

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

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:*

Carcinogenicity studies were not performed with bimatoprost.

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<sup>2</sup> 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 with turquoise polystyrene caps in the following sizes: 2.5 mL fill in 8 mL container – NDC 0023-9187-03, 5mL fill in 8 mL container - NDC 0023-9187-05, or 7.5 mL fill in 8 mL container - NDC 0023-9187-07.

#### **Rx only**

**Storage:** LUMIGAN™ should be stored in the original container at 15° to 25°C (59° to 77°F).

® and ™ Marks owned by Allergan, Inc. This product is covered under US Pat. No. 5,688,819. Additional patents pending.

Revised March 2001

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**Reviewer's Conclusions:**

*NDA 21-275, Lumigan (bimatoprost ophthalmic solution) 0.03%, is recommended for approval for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.*

William M. Boyd, M.D.  
Medical Officer

NDA 21-275  
HFD-550/Div Files  
HFD-550/MO/Boyd  
HFD-550/Dep Director/Chambers  
HFD-880/Biopharm/Tandon  
HFD-550/Chem/Khorshidi  
HFD-550/PharmTox/Chen, Z  
HFD- 800/Micro/Langille  
HFD-550/PM/Puglisi  
HFD-340/Carreras

**APPEARS THIS WAY  
ON ORIGINAL**

Medical Officer's Review of NDA 21-275

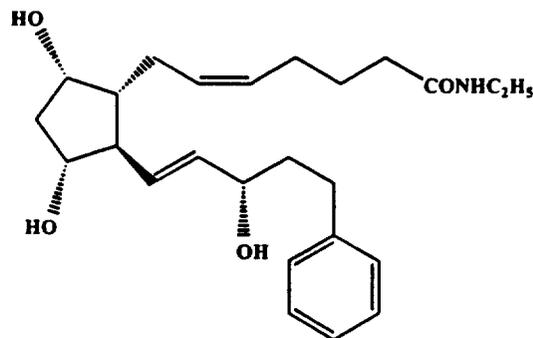
NDA 21-275  
Medical Officer's Review #2

Submission: 3/2/01  
Review Completed: 3/2/01

**Proposed Tradename:** Lumigan 0.03%

**Generic Name:** bimatoprost ophthalmic solution

**Chemical Name:**



Bimatoprost C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>

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

**Sponsor:** Allergan  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, California 92623-9534

**Pharmacologic Category:** synthetic analogue of prostaglandin F<sub>2α</sub> (PG F<sub>2α</sub>)

**Proposed Indication:** Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension

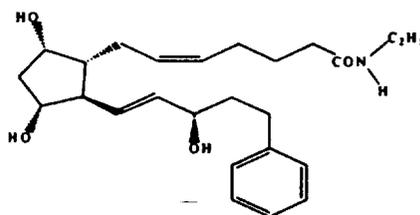
**Dosage Form and Route of Administration:** Ophthalmic solution for topical ocular administration

**Submitted:** Revised labeling based on previous review, discussion with the applicant, and a clean-corrected package insert transmitted by the applicant on 3/2/01 at 2:31 PM.

**LUMIGAN™** (bimatoprost ophthalmic solution) 0.03%

### DESCRIPTION

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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.

Each mL contains: Active: bimatoprost 0.3 mg; Preservative: Benzalkonium chloride 0.05 mg; 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<sub>max</sub> and AUC<sub>0-24hr</sub> 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.

**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 who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurement over time) to another intraocular pressure lowering medication.

**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. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.**

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

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### PRECAUTIONS

*General:*

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 Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see Warnings). Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris are expected to be affected by treatment.

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

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LUMIGAN™ should not be administered while wearing contact lenses.

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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.

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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:*

Carcinogenicity studies were not performed with bimatoprost.

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.

[REDACTED] at least 41 times the intended human exposure based on blood AUC levels.

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 [ ] mg/kg/day did not produce any toxicity. This dose expressed as mg/[ ] 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 with turquoise polystyrene caps in the following sizes: 2.5 mL fill in 8 mL container – NDC 0023-9187-03, 5mL fill in 8 mL container - NDC 0023-9187-05, or 7.5 mL fill in 8 mL container - NDC 0023-9187-07.

**Rx only**

**Storage:** LUMIGAN™ should be stored in the original container at 15° to 25°C (59° to 77°F).

® and ™ Marks owned by Allergan, Inc. This product is covered under US Pat. No. 5,688,819. Additional patents pending.

Revised February 2001

©Allergan, Inc., Irvine, CA 92612

**Reviewer's Conclusions:**

*NDA 21-275, Lumigan (bimatoprost ophthalmic solution) 0.03%, is recommended for approval for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.*

William M. Boyd, M.D.  
Medical Officer

NDA 21-275  
HFD-550/Div Files  
HFD-550/MO/Boyd  
HFD-550/Dep Director/Chambers  
HFD-880/Biopharm/Tandon  
HFD-550/Chem/Khorshidi  
HFD-550/PharmTox/Chen, Z  
HFD- 800/Micro/Langille  
HFD-550/PM/Puglisi  
HFD-340/Carreras

**APPEARS THIS WAY  
ON ORIGINAL**

**Medical Officer's Review of NDA 21-275  
120-Day Safety Update**

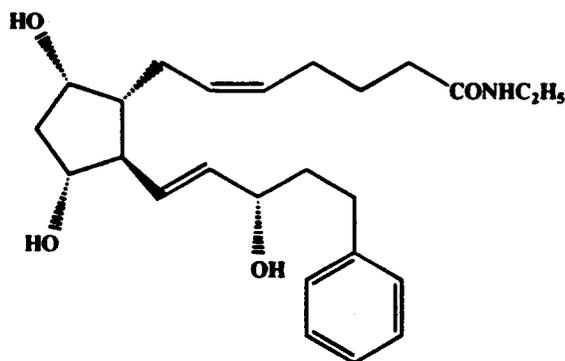
NDA 21-275  
Medical Officer's Review

Submission: 1/23/01  
Review Completed: 2/9/01

**Proposed Tradename:** Lumigan 0.03%

**Generic Name:** bimatoprost ophthalmic solution

**Chemical Name:**



**Bimatoprost C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>**

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

**Sponsor:** Allergan  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, California 92623-9534

**Pharmacologic Category:** synthetic analogue of prostaglandin F<sub>2α</sub> (PG F<sub>2α</sub>)

**Proposed Indication:** Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension

**Dosage Form and Route of Administration:** Ophthalmic solution for topical ocular administration

**Submitted:** 120-Day Safety Information for Phase 3 Studies 192024-008 and 192024-009 (Pooled 12-month Safety Data) and a Revised Package Insert (January 2001)

The incidence rates for all adverse events and serious adverse events were greater than what was previously reported in the 3-month data due to the longer duration of study treatment. Adverse events were primarily ocular and were mild in severity.

The most common adverse events were conjunctival hyperemia and growth of eyelashes. Conjunctival hyperemia was reported in 46% (216/474) of patients in the AGN 192024 QD group, 56% (272/483) of patients in the AGN 192024 BID group, and 15% (35/241) of patients in the timolol group ( $P < 0.001$ ). Growth of eyelashes was reported in 43% (202/474) of patients in the AGN 192024 QD group, 54% (259/483) of patients in the AGN 192024 BID group, and 5% (12/241) of the patients in the timolol group ( $P < 0.001$ ).

Other ocular adverse events reported for  $\geq 5\%$  of patients treated with AGN 192024 QD were eye pruritus, eye dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, and blepharal pigmentation.

Iris pigmentation was reported in 2% (7/474) of patients in the AGN 192024 QD group, 2% (9/483) of patients in the AGN 192024 BID group, and no patients in the timolol group.

Iritis was reported in 0.4% (2/474) of patients in the AGN 192024 QD group, 1% (5/483) of patients in the AGN 192024 BID group, and no patients in the timolol group. Uveitis was reported in 0.2% (1/474) of patients in the AGN 192024 QD group, 0.2% (1/483) of patients in the AGN 192024 BID group, and no patients in the timolol group. There were no reports of cystoid macular edema during the Phase 3 studies.

Two deaths were reported during the 12-month treatment period. The first involved a subject who died due to myocardial infarction (2964-Z03; AGN 192024 QD) and the second involved a subject who died of a cardiac arrest (2450-B-01; timolol). In both cases, the subjects had significant medical histories of heart disease.

#### **Reviewer's Comments:**

*Information contained in this safety update is comparable to previous safety information reviewed for the original NDA. When the overall frequency and incidence of adverse events are examined, there has been no new safety information learned about the drug that would reasonably affect the statement of contraindications, warnings, and precautions in the draft labeling. Adverse reaction rates have been updated in the draft labeling to reflect the 12-month data.*

## Labeling Review of Applicant's Draft Labeling Revised 1/19/01

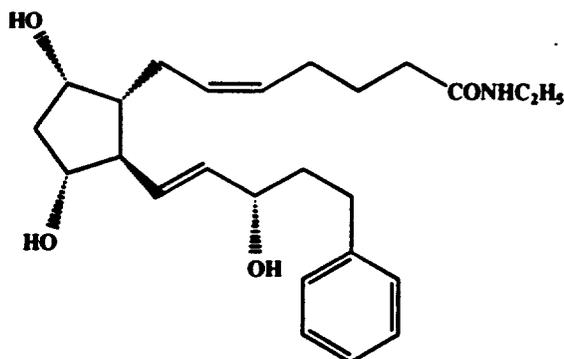
### Reviewer's Comments:

*Recommended additions are shown by underlining: recommended deletions are shown by strikethrough lines.*

**LUMIGAN™** (bimatoprost ophthalmic solution) 0.03%

### DESCRIPTION

**LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% is a synthetic prostamide analog with [redacted] 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 [redacted] molecular weight of is 415.58. Its molecular formula is C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>. 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.

Each mL contains: Active: bimatoprost 0.3 mg; Preservative: Benzalkonium chloride 0.05 mg; 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 [redacted] prostamide, a [redacted] synthetic analog of prostaglandin [redacted] with [redacted] ocular hypotensive activity. It selectively mimics the effects of a [redacted] naturally occurring substance, prostamide [redacted]

[REDACTED] 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:**

[REDACTED] After one drop of [REDACTED] 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  $AUC_{0-24hr}$  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. [REDACTED]

[REDACTED] 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. [REDACTED]

#### **Metabolism**

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

#### **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 [REDACTED] 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:**

[REDACTED] in clinical studies of patients with open angle glaucoma or ocular hypertension [REDACTED] with a mean baseline IOP of 26 mm Hg. [REDACTED] the IOP-lowering effect of LUMIGAN™ (bimatoprost ophthalmic

solution) 0.03% once daily (in the evening) was 87-98 mm Hg.

### INDICATIONS AND USAGE

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with 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. ( ) increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.**

**LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.**

**Eyelid skin darkening has also been reported in association with the use of LUMIGAN™.**

**LUMIGAN™ may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.**

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

## PRECAUTIONS

### *General:*

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 Information for Patients).

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.

LUMIGAN™ should not be administered while wearing contact lenses.

LUMIGAN™ [redacted] has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

### *Information for Patients:*

Patients should be informed that LUMIGAN™ has been reported to cause increased growth and darkening of eyelashes and darkening of the skin around the eye in some patients. These changes may be permanent.

Some patients may slowly develop darkening of the iris, which may be permanent.

When only one eye is treated, patients should be informed of the potential for a cosmetic difference between the eyes in eyelash length, darkness or thickness, and/or color changes of the eyelid skin or iris.

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.

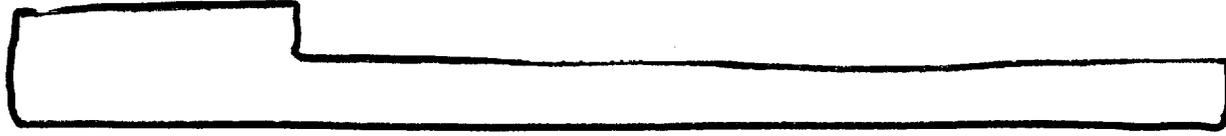
Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

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.

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

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:**  
**Carcinogenicity studies were not performed with bimatoprost.**

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 [redacted] [redacted] was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the intended human exposure [redacted] [redacted] based on blood AUC levels.

Maternal toxicity, evidenced by reduced gestation length, late resorptions, fetal death, postnatal mortality and reduced pup body weights [redacted] were observed when female rats received oral doses which achieved at least 41 times the intended human exposure based on blood AUC levels. [redacted]

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**

[redacted] In clinical trials, the most frequent event associated with the use of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% [redacted]

Ocular adverse events occurring in approximately [redacted] 3 to 10% of patients. [redacted] included [redacted] blepharitis, cataract, [redacted] In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately [redacted]

### 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 [ ] mg/kg/day did not produce any toxicity. This dose expressed as mg [ ] 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.

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 with turquoise polystyrene caps in the following sizes [ ] mL fill in 8 mL container – NDC 0023-9187-03, 5 mL fill in 8 mL container – NDC 0023-9187-05, or 7.5 mL fill in 8 mL container - NDC 0023-9187-07.

**Rx only**

**Storage:** LUMIGAN™ should be stored in the original container at 15° to 25°C (59° to 77°F). [ ]

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Revised January 2001

©Allergan, Inc., Irvine, CA 92612

**Reviewer's Conclusions:**

*Original conclusions are not altered regarding the safety of bimatoprost ophthalmic solution 0.03% for the indication of lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.*

**William M. Boyd, M.D.  
Medical Officer**

NDA 21-275  
HFD-550/Div Files  
HFD-550/MO/Boyd  
HFD-550/Dep Director/Chambers  
HFD-880/Biopharm/Tandon  
HFD-550/Chem/Tso  
HFD-550/PharmTox/Chen, Z  
HFD- 800/Micro/Langille  
HFD-550/PM/Puglisi  
HFD-340/Carreras

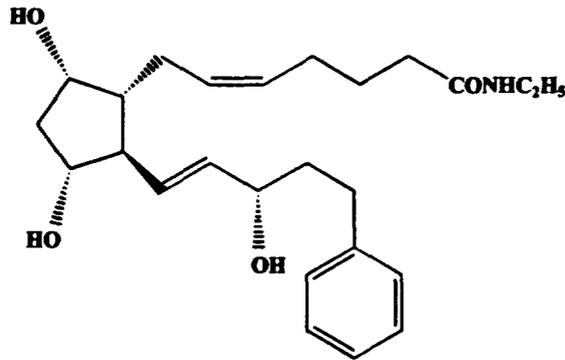
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ON ORIGINAL**

Medical Officer's Review of NDA 21-275  
Original

NDA 21-275  
Medical Officer's Review

Submission: 9/18/00  
Review Completed: 1/05/01

**Proposed Tradename:** Lumigan 0.03%  
**Generic Name:** bimatoprost ophthalmic solution  
**Chemical Name:**



Bimatoprost C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>

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

**Sponsor:** Allergan  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, California 92623-9534

**Pharmacologic Category:** synthetic analogue of prostaglandin F<sub>2α</sub> (PG F<sub>2α</sub>)

**Proposed Indication:** Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension

**Dosage Form and Route of Administration:** Ophthalmic solution for topical ocular administration

**NDA Drug Classification:** 1-P

**Related INDS:**

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**3 Material Reviewed**

NDA 21-275 Volumes 1.1, 1.51-139, 1.228-236

**4 Chemistry/Manufacturing Controls – See Chemistry Review.**

**Table 1 – Quantitative Composition of Bimatoprost Ophthalmic Solution 0.03%**

Ingredient	Concentration (% w/v)	Concentration (mg/mL)	Amount Required (g) for Commercial-Scale Batch	
Bimatoprost (AGN 192024)		0.3		
Benzalkonium Chloride		0.05		
Sodium Chloride				
Sodium Phosphate				
Citric Acid				
Hydrochloric Acid				
Sodium Hydroxide				
Purified Water				

1   page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

**Reviewer's Comments:**

*Individual unspecified impurities should be no more than 0.1%.*

**5 Animal Pharmacology Toxicology**

No specific issues. See Pharmacology Review.

**6 Clinical Background**

Glaucoma is a leading cause of irreversible blindness in the world and represents a family of diseases commonly characterized by progressive optic neuropathy with associated visual field deficits. Elevated IOP is one of the primary risk factors for glaucoma.

The main goal of glaucoma management is to reduce elevated IOP, and thus the associated risk for optic nerve damage and subsequent visual field loss. IOP may be reduced pharmacologically by decreasing the amount of aqueous humor produced by the ciliary body, and/or by increasing its outflow through the trabecular meshwork and/or the uveoscleral pathway. Currently available IOP-lowering medications by class include beta-adrenergic receptor antagonists, selective alpha<sub>2</sub>-adrenergic agonists, carbonic anhydrase inhibitors, cholinergics, sympathomimetics, and prostaglandin analogues.

Bimatoprost, a synthetic analog of prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>), is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Throughout the submitted new drug application, the applicant refers to bimatoprost as AGN 192924 and also as HTL (ocular hypotensive lipid).

The rationale for the proposed treatment concentration (bimatoprost ophthalmic solution 0.03%) is based on the results of the phase 2 dose-response studies, in which the applicant considered bimatoprost 0.03% to provide greater lowering of IOP than bimatoprost 0.003%, 0.01%, or 0.1%.

The rationale for the proposed treatment regimen (bimatoprost ophthalmic solution 0.03% administered once daily in the evening) is based on the results of the phase 3 studies, in which the applicant considered the overall efficacy of bimatoprost QD dosing to be better than that seen with bimatoprost BID dosing.

**6.1 Relevant Human Experience**

The clinical development program for bimatoprost (AGN 192024) ophthalmic solution 0.03% provided a safety database of 1604 patients or normal subjects. Specifically, 1219 patients or normal subjects were exposed to some concentration or regimen of bimatoprost, and 385 patients or normal subjects received active control or vehicle only.

**6.2 Foreign Experience**

To date, there are no marketing applications pending for bimatoprost (AGN 192024) ophthalmic solution, and it has not been marketed or withdrawn from the market in any country.

**6.4 Human Pharmacology, Pharmacokinetics, & Pharmacodynamics – See Pharmacology Review.****7 Investigator's Financial Disclosure Information**

Submitted in Volume 1.1.

**Reviewer's Comments:**

*The original NDA submission identifies only a single investigator, Mark Abelson, M.D., with a financial interest in the drug product that is the subject of this NDA.*

*If this Investigator is excluded, there is no change in the results of the single clinical study 192024-009 in which the Investigator participated.*

**7.5 Description of Clinical Data Sources**

Included in this medical officer's review are six clinical trials conducted in the United States under [redacted] or in Canada, Australia, New Zealand (see Table 3, next page).

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 3 – Clinical Data Sources**

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	Sex/Race	No. Patients Enrolled/ Completed
<b>Phase III Studies</b>							
Efficacy/ Safety 192024-008 Review Study #1	multicenter, double-masked, randomized, parallel-group, active control (31 centers)	3 months (with treatment extended to 1 year)	subjects with glaucoma or ocular hypertension	AGN 192024 0.03%  AGN 192024 0.03%  timolol 0.05%	Vehicle AM AGN 192024 PM  AGN 192024 AM AGN192024 PM  timolol AM timolol PM	<b>sex</b> M: 46% (279/602) F: 54% (323/602) <b>race</b> C: 77% (462/602) B: 17% (102/602) A: <1% ( 3/602) H: 6% ( 34/602) O: <1% ( 1/602)	602 enrolled 536 completed 3 months
Efficacy/ Safety 192024-009 Review Study #2	multicenter, double-masked, randomized, parallel-group, active control (30 centers)	3 months (with treatment extended to 1 year)	subjects with glaucoma or ocular hypertension	AGN 192024 0.03%  AGN 192024 0.03%  timolol 0.05%	Vehicle AM AGN 192024 PM  AGN 192024 AM AGN192024 PM  timolol AM timolol PM	<b>sex</b> M: 44% (262/596) F: 56% (334/596) <b>race</b> C: 75% (445/596) B: 19% (112/596) A: 4% ( 22/596) H: 2% ( 15/596) O: <1% ( 2/596)	596 enrolled 552 completed 3 months
<b>Phase II Studies</b>							
Dose-Response 192024-001 Review Study #3	single-center, double-masked, randomized, parallel-group, active and inactive control	5 ½ days	subjects with open- angle glaucoma or ocular hypertension	AGN 192024 0.01%  AGN 192024 0.03%  AGN 192024 0.1%  timolol 0.05%  vehicle	AM and PM  "  "  "	<b>sex</b> M: 33% (20/60) F: 67% (40/60) <b>race</b> C: 82% (49/60) B: 10% ( 6/60) A: 0% ( 0/60) H: 8% ( 5/60) O: 0% ( 0/60)	60 enrolled 60 completed

**Table 3 – Clinical Data Sources Continued**

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	Sex/Race	No. Patients Enrolled/ Completed
<b>Phase II Studies</b>							
Dose-Response 192024-002 Review Study #4	single-center, investigator- masked, randomized, parallel-group, active and inactive control	28 days	subjects with open- angle glaucoma or ocular hypertension	AGN 192024 0.003%  AGN 192024 0.01%  AGN 192024 0.03%  timolol 0.05%  vehicle	21 days QD (PM) 7 days BID  21 days QD (PM) 7 days BID  21 days QD (PM) 7 days BID  28 days BID  28 days BID	<b>sex</b> M: 46% (46/100) F: 54% (54/100)  <b>race</b> C: 77% (77/100) B: 6% ( 6/100) A: 0% ( 0/100) H: 16% (16/100) O: 1% ( 1/100)	100 enrolled 100 completed
Dose-Response 192024-003 Review Study #5	single-center, double-masked, randomized, parallel-group, vehicle control	1 month	subjects with open- angle glaucoma or ocular hypertension	AGN 192024 0.03%  vehicle	QD (AM)  "	<b>sex</b> M: 31% (10/32) F: 69% (22/32)  <b>race</b> C: 53% (17/32) B: 47% (15/32)	32 enrolled 28 completed
Dose-Response 192024-004 Review Study #6	multicenter, investigator- masked, randomized, parallel-group, active and inactive control (4 centers)	1 month	subjects with open- angle glaucoma or ocular hypertension	AGN 192024 0.03%  AGN 192024 0.06%  latanoprost 0.005%  vehicle	QD (PM)  "  "  "	<b>sex</b> M: 39% (41/106) F: 61% (65/106)  <b>race</b> C: 76% (81/106) B: 20% (21/106) A: 0% ( 0/106) H: 4% ( 4/106) O: 0% ( 0/106)	106 enrolled 100 completed

NDA 21-275 Lumigan (bimatoprost ophthalmic solution) 0.03%

**8 Clinical Studies****8.1.1 Study #1 Protocol 192024-008**

**Title:** A Multicenter, Double-Masked, Unevenly Randomized, Parallel, Active-Controlled Three Month Study (With Treatment Extended to One Year) of the Safety and Efficacy of Once-Daily or Twice-Daily Administered AGN 192024 0.03% Ophthalmic Solution Compared with Twice-Daily Administered Timolol 0.5% Ophthalmic Solution in Subjects with Glaucoma or Ocular Hypertension

**Test Drug Schedule:** Patients were instructed to instill one drop of study medication into each eye in the morning between 7 and 9 AM, and one drop of study medication into each eye in the evening between 7 and 9 PM for 3 months (with a planned treatment extension to one year).

Bottles with yellow labels were used at morning dosing; bottles with blue labels were used at evening dosing.

<b>Investigator Number</b>	<b>Investigator</b>	<b>Number Randomized</b>
2999	Allen Beck, M.D. Atlanta, Georgia 30322 USA	17
2117	Louis B. Cantor, M.D. Indianapolis, Indiana 46202 USA	14
2855	George A. Cioffi, M.D. Portland, Oregon 97210 USA	3
1176	John Cohen, M.D. Cincinnati, Ohio 45242 USA	18
2232	David Cooke, M.D. St. Joseph, Michigan 49085 USA	35
2003	Andrew Crighton, M.D. Calgary, Alberta T2V 1P9 Canada	19
2951	Denise Dudley, M.D. Anchorage, Alaska 99508 USA	10
2975	Richard Evans, M.D. San Antonio, Texas 78240 USA	12

<b>Investigator Number</b>	<b>Investigator</b>	<b>Number Randomized</b>
2964	<b>Stephen Greenberg, M.D.</b> Holbrook, New York 11741 USA	10
1642	<b>Ronald Gross, M.D.</b> Houston, Texas 77030 USA	27
2959	<b>Neeru Gupta, M.D., Ph.D.</b> Toronto, Ontario M5B 1W8 Canada	18
2965	<b>Leonard Gurevich, M.D.</b> West Seneca, New York 14224 USA	17
1585	<b>Oscar Kasner, M.D.</b> Montreal, Quebec H3T 1E2 USA	8
2963	<b>Donald Kellum, M.D.</b> Boulder, Colorado 80304 USA	17
2966	<b>Melvin Koby, M.D.</b> Louisville, Kentucky 40207 USA	18
2969	<b>John Kwedar, M.D.</b> Springfield, Illinois 62702 USA	11
2821	<b>David McGarey, M.D.</b> Flagstaff, Arizona 86001 USA	17
0689	<b>Frederick Mikelberg, M.D.</b> Vancouver, British Columbia V5Z 3N9 Canada	3
2942	<b>Robert Noecker, M.D.</b> Tucson, Arizona 85711 USA	24
2896	<b>Leon Remis, M.D.</b> Marblehead, Maine 01945 USA	7
0226	<b>Robert Ritch, M.D.</b> New York, New York 10003 USA	10
2037	<b>Michael Rotberg, M.D.</b> Charlotte, North Carolina 28204 USA	23
2429	<b>Howard Schenker, M.D.</b> Rochester, New York 14618 USA	26
2110	<b>Joel Schuman, M.D.</b> Boston, Massachusetts 02111 USA	8
1995	<b>Elizabeth Sharpe, M.D.</b> Mount Pleasant, South Carolina 29464 USA	43

<b>Investigator Number</b>	<b>Investigator</b>	<b>Number Randomized</b>
2118	<b>Mark Sherwood, M.D.</b> Gainesville, Florida 32610 USA	25
2952	<b>Joseph Sokol, M.D.</b> Waterbury, Connecticut 06708 USA	28
0202	<b>Alfred Solish, M.D.</b> Pasadena, California 91105 USA	19
1783	<b>William Stewart, M.D.</b> Charleston, South Carolina 29412 USA	16
2953	<b>Julia Whiteside-Michel, M.D.</b> Little Rock, Arkansas 72205 USA	15
2961	<b>Barbara Wirostko, M.D.</b> Huntington Station, New York 11746 USA	18

#### **Reviewer's Comments:**

*It is preferred to have at least 10 patients per arm per center.*

#### **8.1.1 Study Design**

This study was designed as a multicenter, randomized, double-masked, active-controlled, parallel-group study with 8 scheduled visits over a 1-year period. Three-month data were the subject of this report. A total of 602 patients were enrolled to achieve the desired sample size of at least 500 completed patients. Patients with ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma were eligible to enter the study.

Patients must have required bilateral administration of treatment, and have had IOP readings of  $\geq 22$  mm Hg and  $\leq 34$  mm Hg in each eye. Qualified patients were randomized at baseline (day 0) in a 2:2:1 fashion to AGN 192024 0.03% QD, AGN 192024 0.03% BID, or timolol 0.5% BID. IOP and other parameters were evaluated Prestudy, at Day 0, Weeks 2 and 6, and Months 3, 6, 9, and 12.

Efficacy criteria were specifically defined. The criteria for effectiveness of AGN 192024 0.03% in this study were a mean decrease in IOP from baseline that was at least 3 mm Hg, and that was no more than 1.5 mm Hg less than the mean decrease achieved with timolol 0.5%. The criterion to show that QD dosing of AGN 192024 0.03% was as effective as, or better than, BID dosing was a mean decrease in IOP from baseline with QD dosing that was no more than 1.5 mm Hg less than the mean decrease achieved with BID dosing.

Diurnal IOP measurements were performed at Hour 0 (ideally between 7:30 AM and 8:30 AM but 7:00 AM to 9:00 AM was acceptable), and at 2 and 8 hours after Hour 0 on Day 0 (Baseline), Weeks 2 and 6, and Months 3, 6, and 12. At the Prestudy visit and Month 9, IOP was measured at Hour 0 only. At selected centers, an additional IOP measurement was taken 12 hours after the morning IOP examination (for a subset of 39, 39, and 20 patients in the AGN 192024 QD, AGN 192924 BID, and timolol groups, respectively).

**Reviewer's Comments:**

*To establish equivalence between IOP-lowering products (whether comparing drug product to an active control or comparing two different regimens of the same drug), a 95% confidence interval should be obtained with the majority of data points showing less than 1 mm Hg difference and all data points showing less than 1.5 mm Hg difference.*

*Hour 12 IOP measurements are inadequately powered to establish equivalence due to small sample size.*

At each investigational site, patients were randomized to one of the 3 treatment groups based on an uneven allocation of AGN 192024 0.03% QD, AGN 192024 0.03% BID, or timolol 0.5% BID in a 2:2:1 ratio, with a block size of 5.

Patients who did not require a washout of glaucoma medications were to have a waiting period of at least 2 days after the Prestudy visit to ensure that all potential effects from pupil dilating agents were gone. Patients on IOP-lowering agents were to begin washout of those medications following the Prestudy visit.

**Table 192024-008-01 – Washout Schedule**

Medication Class	Examples	Minimum Washout Period
Parasympathomimetics	carbachol, pilocarpine, [REDACTED]	4 days
Carbonic anhydrase inhibitors (systemic or topical)	acetazolamide, brinzolamide, dorzolamide hydrochloride	4 days
Sympathomimetics	[REDACTED] epinephrine	2 weeks
Topical alpha-agonists	apraclonidine hydrochloride, brimonidine tartrate	2 weeks
Topical beta-blockers	timolol maleate, metipranolol, levobunolol hydrochloride, betaxolol hydrochloride, carteolol hydrochloride	4 weeks
Topical prostaglandins	latanoprost	4 weeks
Combination therapy	dorzolamide hydrochloride-timolol maleate	4 weeks

## Study Medications

To ensure similarity in the timing of doses across the 3 treatment groups, patients were asked to instill study medication in the morning between 7 and 9 AM and in the evening between 7 and 9 PM. For patients in the AGN 192024 QD group, the morning dose was masked vehicle. Each patient's dose and regimen were to remain the same throughout the duration of the study.

In the AGN 192024 QD group, one drop (~28  $\mu$ L) of AGN 192024-vehicle preserved sterile ophthalmic solution was instilled into each eye in the morning, and one drop (~28  $\mu$ L) of AGN 192024 0.03% preserved sterile ophthalmic solution was instilled into each eye in the evening. In the AGN 192024 BID group, one drop (~28  $\mu$ L) of AGN 192024 0.03% preserved sterile ophthalmic solution was instilled into each eye in the morning and in the evening. In the timolol group, one drop (~28  $\mu$ L) of timolol 0.5% sterile ophthalmic solution was instilled into each eye in the morning and in the evening.

- AGN 192024 0.03% preserved ophthalmic solution (Allergan formulation number 9106X, lot 11379, 11443, 11536, 11635) contained 0.3 mg/mL AGN 192024, sodium phosphate [REDACTED], sodium chloride, citric acid [REDACTED], hydrochloric acid, sodium hydroxide, benzalkonium chloride 0.005%, and purified water.



- Generic timolol maleate 0.5% ophthalmic solution (Allergan, Inc, Puerto Rico; Allergan formulation number 8770X, lot 11419, 11420, 11422, 11519, 11528, 11550, 11612) contained timolol 0.5%, benzalkonium chloride 0.01%, water for injection, monobasic and dibasic sodium phosphate, and sodium hydroxide to adjust pH.

Bottles with yellow labels were used at morning dosing; bottles with blue labels were used at evening dosing. Patients were instructed not to instill their dose on the morning of a scheduled visit. On those days, personnel at the study center instilled the study medication following the Hour 0 exam.

## Study Population – Inclusion and Exclusion Criteria

### Inclusion Criteria

The following were requirements for entry into the study:

- Male or female, 21 years of age or older.
- Patients' IOP was likely to be controlled on monotherapy.
- Patient had ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma and required bilateral administration of treatment.
- Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score equivalent to a Snellen score of 20/100 or better in each eye.

- Informed consent had been obtained.
- Ability to follow study instructions and likely to complete all required visits.
- Ability to fast (i.e., not have ingested any foods or liquids, other than water) for 8 to 10 hours prior to blood sample collection on the morning of a scheduled visit.
- Day 0, hour 0 IOP  $\geq 22$  mm Hg and  $\leq 34$  mm Hg in each eye.
- Day 0 negative urine pregnancy test result for females of childbearing potential. A female was considered of childbearing potential unless she was postmenopausal, without a uterus and/or both ovaries, or had a bilateral tubal ligation.
- Two reliable visual fields collected prior to dosing.
- Patient had been appropriately washed out of his/her antiglaucoma medication.

### **Exclusion Criteria**

The following were criteria for exclusion from participating in this study:

- Uncontrolled systemic disease (e.g., hypertension, diabetes).
- Females who were pregnant, nursing, or planning a pregnancy, or females of childbearing potential who were not using a reliable means of contraception.
- Previous use of AGN 192024 or another Allergan ocular hypotensive lipid.
- Known allergy or hypersensitivity to the study medications or their components.
- Anticipated alteration of existing chronic therapy with agents that could have a substantial effect on IOP (including, but not necessarily limited to, systemic adrenergic agents including beta-adrenergic blocking agents, e.g.,  metoprolol, nadolol, timolol, and atenolol), substantial interaction with study medications, or interaction with study outcomes.
- Clinically relevant low or high heart rate or blood pressure for age or contraindications to beta-blocker therapy, such as chronic obstructive pulmonary disease, bronchial asthma, heart block more severe than first degree, uncontrolled congestive heart failure.
- Corneal abnormalities that would have precluded accurate IOP readings with an applanation tonometer.
- Any other active ocular disease other than glaucoma or ocular hypertension (eg, uveitis, ocular infections, or severe dry eye). However, patients with chronic mild blepharitis, cataract, age-related macular degeneration, or a background diabetic retinopathy could have been enrolled at the discretion of the investigator.
- Required chronic use of ocular medications during the study other than the study medications. Intermittent use of artificial tear products or topical decongestant antihistamine was allowed. Use of these within 24 hours of a scheduled visit was prohibited.
- Functionally significant visual field loss or evidence of progressive visual field loss within the last year.
- Refractive surgery, laser trabeculoplasty, other intraocular surgery (e.g., uncomplicated cataract surgery), or other laser surgery within the past 3 months or filtering surgery within the past 6 months.
- Patients with corneal grafts.
- Contraindications to pupil dilation.

- Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to day 0.
- For centers performing endothelial cell counts, history of refractive surgery.
- Patient had a condition or was in a situation that, in investigator's opinion, might have put the patient at significant risk, might have confounded the study results, or might have interfered significantly with the patient's participation in the study.
- Day 0 significant ocular irritation.

#### **Reviewer's Comments:**

*The applicant specified a number of types of glaucoma (chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma) in the Inclusion Criteria to evaluate the use of bimatoprost (AGN 192024) in the treatment of various forms of the disease.*

*The demographic statistics for all randomized patients only list the entry diagnoses of glaucoma, ocular hypertension, or mixed diagnosis. The diagnosis of glaucoma is not broken down by type. See Table 192024-008-05, page 21.*

#### **Safety Measures**

##### Adverse Events

Throughout the course of the study, all adverse events were monitored at each follow-up visit.

##### Blood and Urine Collection (Fasting Samples)

Urine and blood (fasting samples) were to be drawn at the Prestudy visit, and Months 3, 6 and 12 for urinalysis, and hematology and serum chemistry analysis, respectively.

##### Visual Acuity

The best-corrected visual acuity (VA) was measured for each eye using a standard ETDRS chart Prestudy and at each follow-up visit.

##### Biomicroscopy

Slit lamp biomicroscopy (without pupil dilation) was performed Prestudy and at each follow-up visit.

##### Ophthalmoscopy and Cup/Disc Ratio

Ophthalmoscopy (with pupil dilation) and cup/disc ratios were evaluated at the Prestudy visit, and after the last IOP measurement at Months 3, 6 and 12.

### Laser Flare Meter

At selected centers, [redacted] laser flare meter readings were to be performed prior to any fluorescein instillation or pupil dilation, and prior to instillation of the morning medication on Day 0 and Months 3, 6, and 12.

### Endothelial Cell Density

At selected centers, endothelial cell density was evaluated on Day 0 and Months 3, 6, and 12 by viewing the corneal endothelium using a non-contact specular microscope.

### Visual Field Examination

Visual field examinations were to be performed using a [redacted] 24-2 full threshold automated perimetry test. Testing for Months 3, 6, and 12 could be performed up to 2 weeks before or after the scheduled visit.

### Heart Rate and Blood Pressure

Heart rate was measured Prestudy and at each follow-up visit with the patient in a resting state (seated) for at least 5 minutes. Systolic and diastolic blood pressure were measured at the Prestudy visit and each follow-up by a sphygmomanometer with the patient in a resting state (seated) for at least 5 minutes, and recorded in mm Hg.

### Iris Color

Each patient's eye was photographed under standardized conditions with a [redacted] camera prior to fluorescein instillation on day 0 and each follow-up visit. The investigator was to compare Day 0 and subsequent photographs to determine whether there had been any changes in iris pigmentation.

### Pregnancy

Urine pregnancy tests were performed for females of childbearing potential at day 0, Months 3 and 6, and upon exiting the study.

### Examination of Subgroups

No analyses of efficacy data were performed for subgroups of patients defined by age, sex, race, or iris color. Such analyses were planned on the pooled data from this study (192024-008) and a second phase 3 study (192024-009) which had an identical protocol.

**Table 192024-008-02 – Schedule of Assessments for Protocol 192024-008**

-----At Selected Centers<sup>f</sup>-----

Visit	Time <sup>a</sup>	Pulse/ Blood Pressure/ AEs	Iris Color <sup>b</sup>	Diurnal IOP	Biomicro scopy/ VA	Hemat/ Chem/ Urinal	Preg- nancy Test	Ophthal- moscopy <sup>c</sup>	Visual Field <sup>d</sup>	Patient Satis- faction Q'aire	Clinical Success/ Resource Utilizat <sup>e</sup>	Corneal Pachy- metry	8 PM IOP	Laser Flare Meter	Endo- thelial Cell Count	PK Sample Blood Draw
prestudy	T <sub>0</sub>	X		T <sub>0</sub>	X	X		X	X	X						
Washout period of 2 to 28 days (for ocular dilating agents and/or IOP lowering meds)																
day 0	T <sub>0</sub>	X	X	T <sub>0</sub> T <sub>0</sub> +2h T <sub>0</sub> +8h	X		X		X			X	T <sub>0</sub> + 12h	X	X	5 min post- dose
First dose instilled the evening of day 0 between 7 and 9 PM. At centers performing the 8 PM (T <sub>0</sub> + 12h) IOP exam, dose instilled after the exam.																
week 2 <sup>h</sup>	T <sub>0</sub>	X	X	T <sub>0</sub> T <sub>0</sub> +2h T <sub>0</sub> +8h	X								T <sub>0</sub> + 12h			
week 6 <sup>h</sup>	T <sub>0</sub>	X	X	T <sub>0</sub> T <sub>0</sub> +2h T <sub>0</sub> +8h	X								T <sub>0</sub> + 12h			
month 3 <sup>h</sup>	T <sub>0</sub>	X	X	T <sub>0</sub> T <sub>0</sub> +2h T <sub>0</sub> +8h	X	X	X	X <sup>h</sup>	X	X	X		T <sub>0</sub> + 12h	X	X	5 min post- dose
month 6 <sup>h</sup>	T <sub>0</sub>	X	X	T <sub>0</sub> T <sub>0</sub> +2h T <sub>0</sub> +8h	X	X	X	X <sup>h</sup>	X	X	X		T <sub>0</sub> + 12h	X	X	5 min post- dose
month 9 <sup>h</sup>	T <sub>0</sub>	X	X	T <sub>0</sub>	X								T <sub>0</sub> + 12h			
month 12 <sup>h</sup> (or Exit)	T <sub>0</sub>	X	X	T <sub>0</sub> T <sub>0</sub> +2h T <sub>0</sub> +8h	X	X	X	X <sup>h</sup>	X	X	X		T <sub>0</sub> + 12h	X	X	5 min post- dose

hemat = hematology, chem = chemistry, urinal = urinalysis, q'aire = questionnaire, utilizat = utilization, PK = pharmacokinetic, h = hour(s), min = minute(s)

**Table 192024-008-02 – Schedule of Assessments for Protocol 192024-008 Continued**

- a. Time of hour 0 examination ( $T_0$ ) ideally was to occur between 7:30 AM and 8:30 AM, however 7:00 AM to 9:00 AM was acceptable. All patients should have their visits at the same time of day during the study. Subsequent examinations were at  $T_0 + 2$  hours ( $T_0+2h$ ) and  $T_0 + 8$  hours ( $T_0+8h$ ).
- b. Centers were provided with [redacted] cameras and film for use during the study.
- c. Including cup/disc ratio.
- d. Visual field examinations (starting with baseline) were to be performed using a [redacted] 24-2 full threshold automated perimetry test. Preferred equipment was a [redacted] machine.
- e. Clinical Success Evaluation was performed at months 3, 6 and 12 (or exit). Resource Utilization will be recorded at month 12 for completed patients, or at the visit a discontinued patient exits the study. Resource Utilization for all discontinued patients returning to the investigator's office for routine ophthalmic care will be followed for 12 months from study entry.
- f. At selected centers, 1 or more of these additional procedures was performed: (1) laser flare meter readings, (2) endothelial cell counts, (3) additional blood drawn for PK analysis, (4) corneal pachymetry, or (5)  $T_0 + 12$  hours ( $T_0+12h$ ) IOP examinations.
- g. The morning doses of study medication at weeks 2 and 6 and months 3, 6, and 9 were administered after the  $T_0$  examination. At month 12, the last dose will be administered after the  $T_0$  examination, except at centers collecting PK blood samples where the last dose will be administered after the  $T_0+12h$  IOP examination.
- h. Ophthalmoscopy was performed after the last IOP measurement (i.e., following the  $T_0+8h$  IOP examination for all centers except those performing  $T_0+12h$  IOP, where ophthalmoscopy was performed after the  $T_0+12h$  IOP exam).

### Subject Disposition and Demographics

There were 602 patients enrolled in the study: 240 patients randomized to AGN 192024 QD, 240 patients randomized to AGN 192024 BID, and 122 patients randomized to timolol. In the intent-to-treat analysis, 96% (578/602) of patients completed 2 weeks of treatment, 94% (566/602) of patients completed 6 weeks of treatment, and 89% (536/602) of patients completed 3 months of treatment.

The most frequent reason for discontinuation of the study prior to Month 3 was adverse events (9%, 52/602). Six patients (1%, 6/602) discontinued prior to Month 3 due to lack of efficacy: 0 patients in the AGN 192024 QD group, 5 patients in the AGN 192024 BID group, and 1 patient in the timolol group.

**Table 192024-008-03 – Discontinued Patients and Reason**

Treatment/Duration	Investigator	Patient	Reason
AGN 192024 QD 78 days	1642	H22	Adverse event – dizziness, conj hyperemia, eye dryness, photophobia
AGN 192024 QD 14 days	1783	B02	Adverse event – uveitis
AGN 192024 QD 62 days	1783	B14	Adverse event – allergic conjunctivitis
AGN 192024 QD 43 days	1783	B15	Adverse event – asthma
AGN 192024 QD 102 days	1995	K51	Adverse event – conjunctival hyperemia

Table 192024-008-03 – Discontinued Patients and Reason Continued

Treatment/Duration	Investigator	Patient	Reason
AGN 192024 QD 45 days	2003	H64	Adverse event – facial paralysis
AGN 192024 QD Approx. 70 days	2037	F23	Adverse event – conj hyperemia, eye irritation
AGN 192024 QD 95 days	2117	V14	Adverse event – conj hyperemia, eye dryness, eye pruritus
AGN 192024 QD 15 days	2429	A03	Adverse event – iritis
AGN 192024 QD 8 days	2429	A04	Adverse event – eyelid edema, conj hyperemia, eye pruritus
AGN 192024 QD 3 days	2429	A12	Adverse event – conj hyperemia
AGN 192024 QD 83 days	2429	A27	Adverse event – myocardial infarction
AGN 192024 QD 42 days	2855	U01	Adverse event – asthenia, conj hyperemia
AGN 192024 QD 78 days	2959	J60	Adverse event – conj hyperemia
AGN 192024 QD 84 days	2961	D52	Adverse event – eye irritation, eye pruritus
AGN 192024 QD 9 days	2963	A57	Adverse event – conj hyperemia, eye pain
AGN 192024 QD 47 days	2964	Z09	Adverse event – conj hyperemia, asthenopia, eye irritation
AGN 192024 QD 9 days	2965	D17	Adverse event – dyspnea, epiphora, conj hyperemia
AGN 192024 QD 48 days	2966	X05	Adverse event – eye pruritus
AGN 192024 BID 101 days	0202	E61	Adverse event – periorbital edema
AGN 192024 BID 29 days	0226	M01	Adverse event - tingling
AGN 192024 BID 41 days	0689	J03	Adverse event – allergic conjunctivitis
AGN 192024 BID 45 days	1176	R14	Lack of efficacy
AGN 192024 BID 136 days	1176	R17	Personal reasons – other medical problems, other doctor appointments
AGN 192024 BID 45 days	1995	E01	Adverse event – breast carcinoma
AGN 192024 BID 85 days	1995	E27	Adverse event – optic nerve head hemorrhage
AGN 192024 BID 90 days	1995	E30	Lack of efficacy – discontinued at Month 3 visit
AGN 192024 BID Approx. 14 days	1995	K52	Lost to follow-up
AGN 192024 BID 28 days	1995	K54	Lack of efficacy
AGN 192024 BID 50 days	2003	H60	Adverse event – conj hyperemia, conj edema, eye pain

Table 192024-008-03 – Discontinued Patients and Reason Continued

Treatment/Duration	Investigator	Patient	Reason
AGN 192024 BID 50 days	2037	F21	Lost to follow-up – missed wk6 and m3
AGN 192024 BID 7 days	2232	C10	Adverse event - keratitis
AGN 192024 BID 3 days	2232	C19	Adverse event – conj hyperemia
AGN 192024 BID 43 days	2232	C22	Adverse event – blepharal pigmentation, eye pruritus
AGN 192024 BID 9 days	2232	C27	Adverse event – conj hyperemia
AGN 192024 BID 43 days	2429	A01	Adverse event – foreign body sensation, eye irritation
AGN 192024 BID 2 days	2429	A15	Adverse event – iritis
AGN 192024 BID 50 days	2429	A16	Adverse event - keratitis
AGN 192024 BID 6 days	2429	A20	Adverse event – asthenia, rhinitis
AGN 192024 BID 2 days	2429	A31	Adverse event – increased cough, conj hyperemia
AGN 192024 BID 92 days	2821	C67	Adverse event – blepharal pigmentation, eye irritation, visual acuity worsened
AGN 192024 BID 113 days	2896	Y03	Lack of efficacy – IOP not controlled
AGN 192024 BID 1 days	2942	L20	Personal reasons
AGN 192024 BID 11 days	2942	L24	Adverse event – uveitis
AGN 192024 BID 13 days	2942	L25	Adverse event – visual disturbance
AGN 192024 BID 14 days	2951	F52	Adverse event – conj hyperemia, eye pain, iritis, photophobia
AGN 192024 BID 79 days	2952	G18	Adverse event – diarrhea, arthritis, growth of eyelashes, eye discharge, eye pruritus
AGN 192024 BID 15 days	2953	P15	Adverse events – conj hyperemia, eye pruritus
AGN 192024 BID 5 days	2953	P18	Adverse event – conj hyperemia, eye dryness
AGN 192024 BID 90 days	2961	D59	Adverse event – blepharal pigmentation
AGN 192024 BID 12 days	2961	D70	Adverse event eye pain, photophobia
AGN 192024 BID 48 days	2963	A51	Adverse event – eyelid edema, eyelid erythema, burning sensation in eye, eye pruritus
AGN 192024 BID 27 days	2963	A60	Lack of efficacy
AGN 192024 BID 3 days	2965	D03	Adverse event – conj hyperemia

**Table 192024-008-03 – Discontinued Patients and Reason Continued**

Treatment/Duration	Investigator	Patient	Reason
AGN 192024 BID 106 days	2965	D12	Adverse event – blepharal pigmentation, growth of eyelashes, conj hyperemia
AGN 192024 BID 15 days	2966	X06	Improper entry
AGN 192024 BID 2 days	2969	B60	Adverse event – traumatic bone fracture
AGN 192024 BID 100 days	2999	S16	Adverse event – blepharal pigmentation, eyelid pruritus
TIM BID 40 days	0226	M12	Other – did not want to participate in diurnals
TIM BID 104 days	1783	B09	Adverse events - dyspnea
TIM BID ? days	1995	E11	Personal reasons – could not come in for exit visit
TIM BID ? days	2232	C30	Personal reasons – noncompliant and wished to exit
TIM BID 23 days	2821	C66	Adverse events – eye irritation, foreign body sensation
TIM BID 90 days	2953	P16	Lack of efficacy
TIM BID 93 days	2959	J65	Adverse event – respiratory disorder

Of the 602 patients enrolled in the study, 589 were included in the per-protocol analysis of the primary efficacy objective. All patients (602) were included in the ITT analysis and in the presentation of safety results.

**Table 192024-008-04 – Number of Patients Included in the ITT, PP, and Safety Populations**

Population	AGN 192024 QD	AGN 192024 BID	Timolol	All
ITT	240	240	122	602
Per-protocol	235	237	117	589
Safety	240	240	122	602

There were no statistically significant differences in demographic subgroup membership between the treatment groups for age, sex, race, iris color, or ophthalmic diagnosis. The demographic statistics for all randomized patients are shown on the next page in **Table 192024-008-05**.

**Table 192024-008-05 – Demographic Statistics for  
All Randomized Patients**

$N_{AGN\ QD} = 240$ ,  $N_{AGN\ BID} = 240$ ,  $N_{TIM} = 122$

Treatment	Mean	Std	Age N	Min	Max
AGN 192024 QD	60	12	240	22	83
AGN 192024 BID	61	12	240	33	90
Timolol	60	12	122	33	83

	Treatment Group					
	AGN 192024 QD		AGN 192024 BID		Timolol	
	N	%	N	%	N	%
<b>Sex</b>						
Male	108	45	117	49	54	44
Female	132	55	123	51	68	56
<b>Age Class</b>						
< 45 yrs	27	11	33	14	13	11
45 - 65 yrs	115	48	100	42	65	53
> 65 yrs	98	41	107	45	44	36
<b>Race</b>						
Caucasian	186	78	191	80	85	70
Black	39	16	37	15	26	21
Asian	0	0	1	< 1	2	2
Hispanic	15	6	10	4	9	7
Other	0	0	1	< 1	0	0
Black	39	16	37	15	26	21
Non-Black	201	84	203	85	96	79
<b>Iris Color</b>						
Light	137	57	131	55	56	46
Dark	103	43	109	45	66	54
<b>Ophthalmic Diagnosis</b>						
Glaucoma	123	51	122	51	55	45
Ocular Hypertension	111	46	108	45	65	53
Mixed	6	3	10	4	2	2

**Table 192024-008-06 – Mean IOP Values at Each Timepoint at Baseline (ITT-LOCF)**

Timepoint	AGN 192024 QD	AGN 192024 BID	TIM
Hour 0	25.85	26.10	25.82
Hour 2	24.64	24.80	24.01
Hour 8	23.87	23.92	23.16
Hour 12 (selected sites)	21.41	22.60	22.63

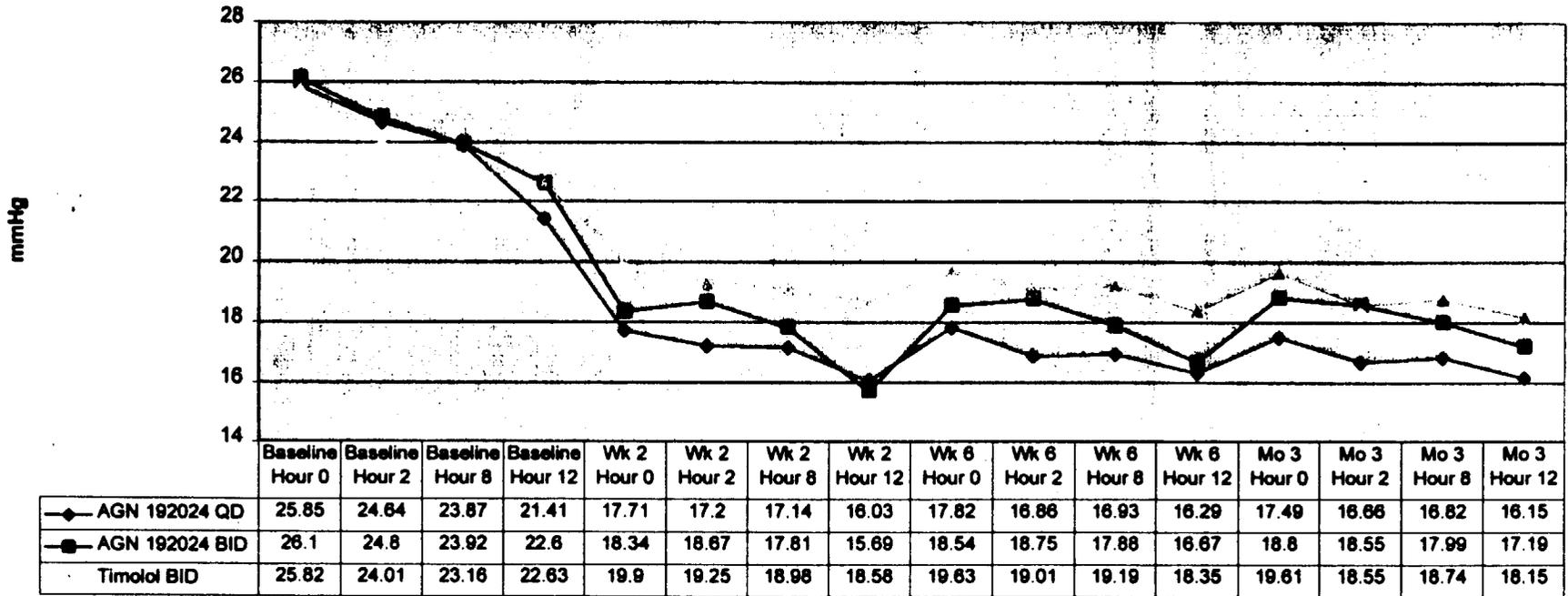
**Reviewer's Comments:**

*There are no statistically significant differences in Baseline IOP between the treatment groups at any timepoint.*

**8.1.1 Efficacy – Protocol 192024-008 Intent-to-Treat Population (LOCF)**

**Primary Efficacy Variable**

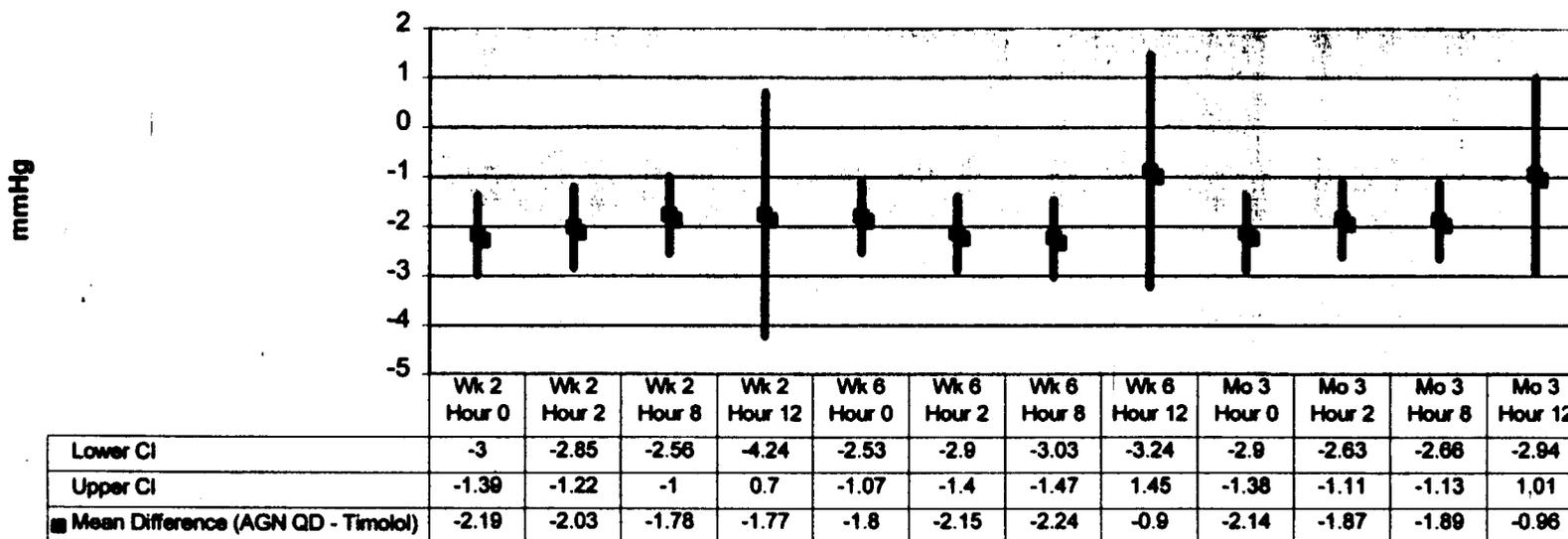
**Mean IOP per Visit and Time**



**Reviewer's Comments:**

*Mean IOPs per visit and time are lower for AGN 192024 0.03% QD than for timolol 0.5% BID at all measured timepoints beginning at Week 2. Hour 12 IOP measurements are inadequately powered to establish equivalence due to small sample size.*

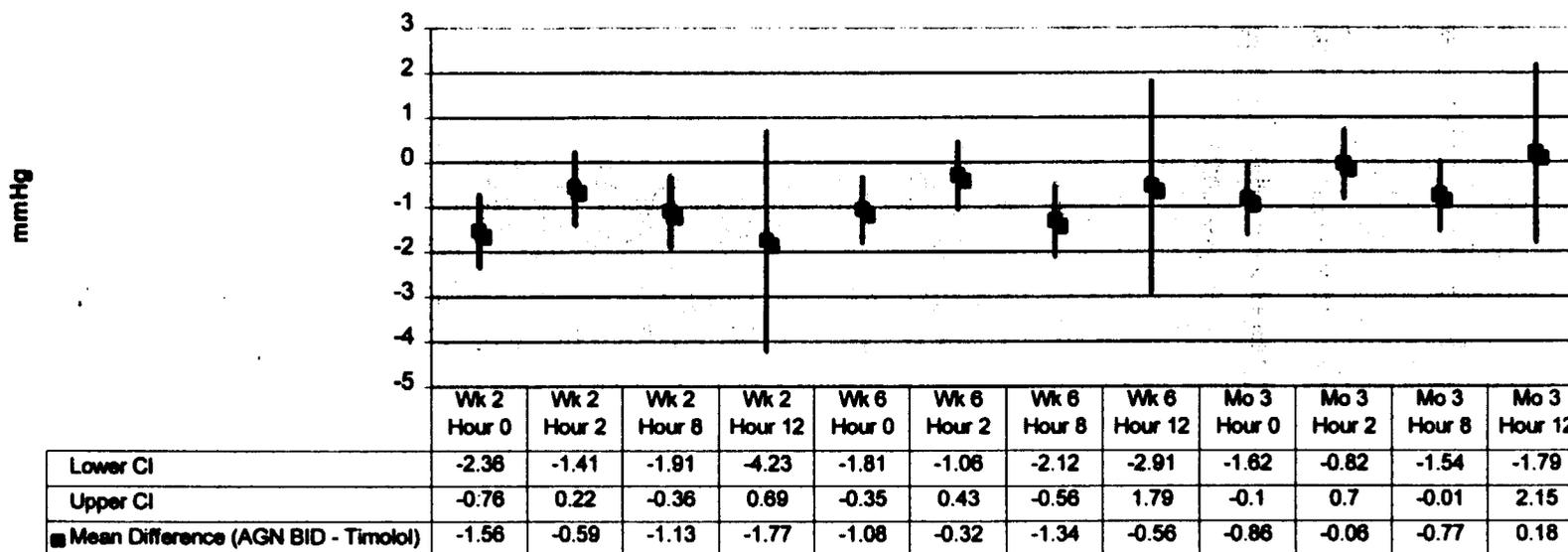
**Mean Difference (AGN 192024 QD - Timolol) in Mean Values at Each Timepoint with 95% Confidence Intervals**



**Reviewer's Comments:**

*When Hour 12 measurements are excluded, the mean difference in mean values (AGN 192024 0.03% QD minus timolol 0.5% BID) is statistically significant at each remaining timepoint (i.e. confidence intervals do not cross 0).*

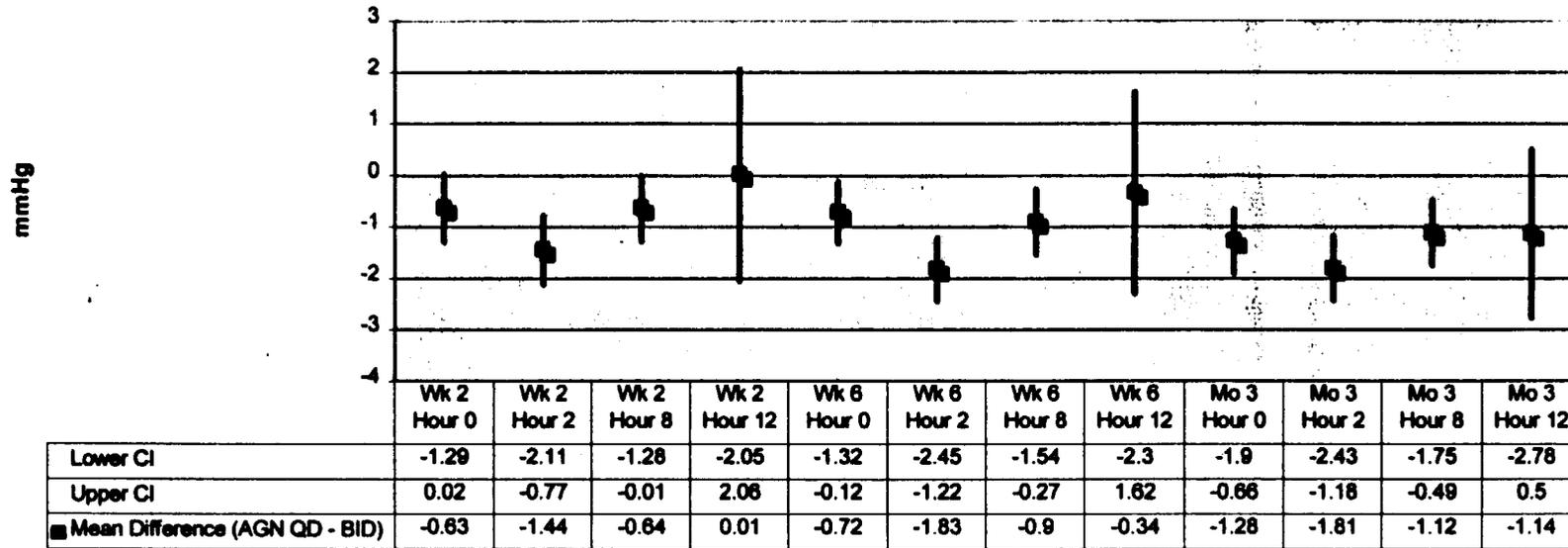
**Mean Difference (AGN 192024 BID - Timolol) in Mean Values at Each Timepoint with 95% Confidence Intervals**



**Reviewer's Comments:**

*When Hour 12 measurements are excluded, the mean difference in mean values (AGN 192024 0.03% BID minus timolol 0.5% BID) is statistically significant at six out of nine remaining timepoints (i.e. confidence intervals do not cross 0).*

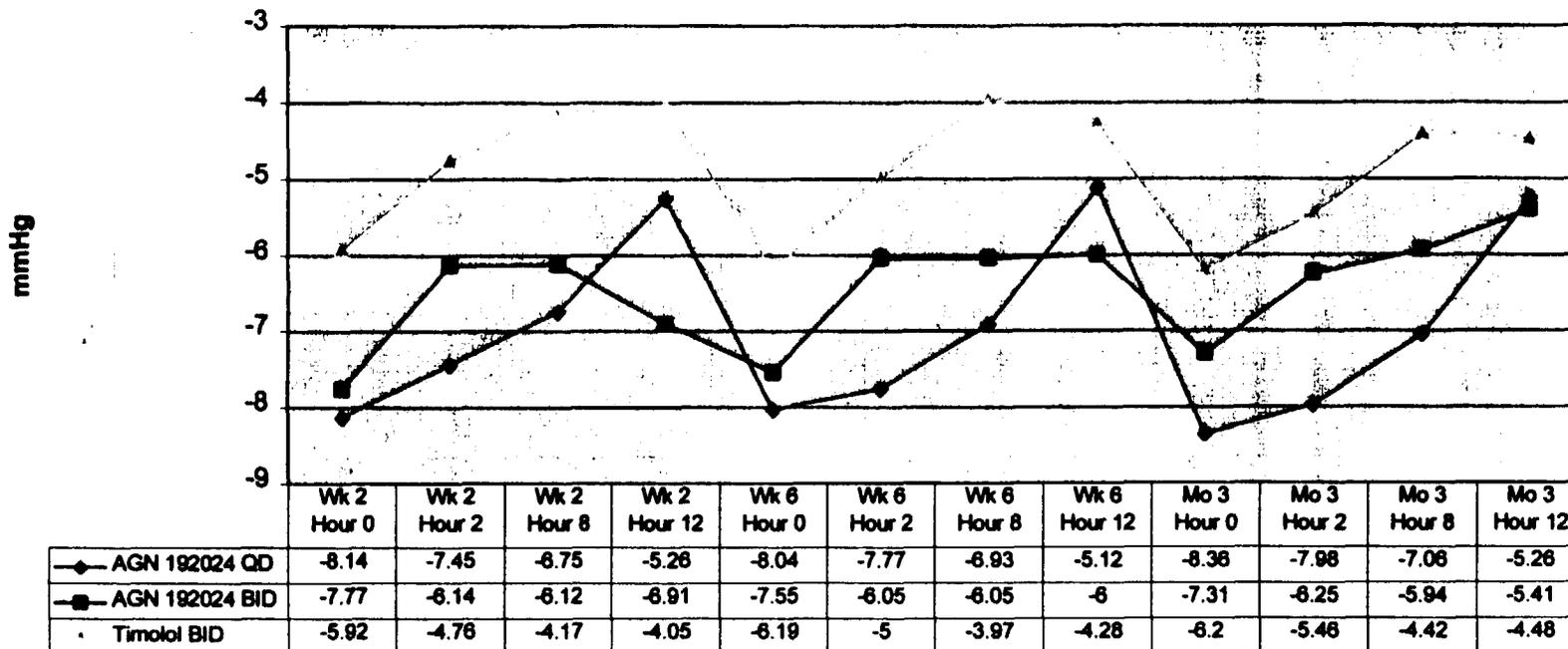
**Mean Difference (AGN 192024 QD - AGN 192024 BID) in Mean Values at Each Timepoint with 95% Confidence Intervals**



**Reviewer's Comments:**

*When Hour 12 measurements are excluded, the mean difference in mean values (AGN 192024 0.03% QD minus AGN 192024 0.03% BID) is statistically significant at eight out of nine remaining timepoints (i.e. confidence intervals do not cross 0).*

### Mean IOP Change From Baseline at Each Timepoint



#### Reviewer's Comments:

*When Hour 12 measurements are excluded, AGN 192024 0.3% QD lowers IOP between 7 and 8 mmHg from baseline. AGN 192024 0.03% BID lowers IOP between 6 and 8 mmHg from baseline. Timolol 0.5% BID lowers IOP between 4 and 6 mmHg from baseline.*

### 8.1.1 Safety

#### Adverse Events

Serious adverse events were reported for 2.5% (6/240) of patients treated with AGN 192024 QD, 3.8% (9/240) of patients treated with AGN 192024 BID, and 4.1% (5/122) of patients treated with timolol 0.5% BID.

**Table 192024-008-07 – Serious Adverse Events**

Treatment	Investigator	Patient	AE Code	Patient Disposition at Month 3
AGN 192024 0.03% OD	1995	E14	Hernia Gastrointestinal Disorder	Completed
	1995	K51	Angina Pectoris	Discontinued
	2232	C31	Carotid Occlusion	Completed
	2232	C38	Hypertension	Completed
	2429	A27	Myocardial Infarction	Discontinued (Death)
	2999	S08	Urinary Tract Infection	Completed
AGN 192024 0.03% BID	1642	H03	Depression	Completed
	1783	B07	Syncope	Completed
	1995	E01	Breast Carcinoma	Discontinue
	1995	E02	Colitis	Completed
	2037	F14	Kidney Calculus	Completed
	2118	W03	Intestinal Obstruction	Completed
	2118	W12	Angina Pectoris Coronary Artery Disorder	Completed
	2966	X10	Bronchitis Flu Syndrome	Completed
	2969	B60	Traumatic Bone Fracture	Discontinue
	Timolol 0.05% BID	1176	R11	Asthenia Bradycardia Chest Pain
1783		B11	Breast Carcinoma	Completed
1995		E36	Jaundice Hyperglycemia	Completed
2232		C02	Urogenital Dysplasia	Completed
2959		J65	Respiratory Disorder	Discontinue

Patient 2429-A27 was receiving AGN 192024 QD for 84 days when he suffered a myocardial infarction that resulted in his death. The patient had a history of diabetes, hypertension, and daily tobacco use.

The most common adverse event was conjunctival hyperemia, which was reported for 33.3% (80/240) of patients treated with AGN 192024 QD, 41.3% (99/240) of patients treated with AGN 192024 BID, and 7.4% (9/122) of patients treated with timolol.

Other ocular adverse events reported for at least 5 patients ( $\geq 2\%$ ) treated with either AGN 192024 QD or BID were growth of eyelashes, eye pruritus, eye dryness, burning

sensation in eye, foreign body sensation, visual disturbance, irritation eye, eye pain, allergic conjunctivitis, blepharal pigmentation, photophobia, asthenopia, corneal erosion, stinging sensation eye, eye discharge, eyelash discoloration, conjunctival edema, and eyelid pruritus.

The most common non-ocular adverse events reported for at least 5 patients ( $\geq 2\%$ ) treated with either AGN 192024 QD or BID were infection, headache, flu-syndrome, hypertension, abnormal liver function tests, hypercholesterolemia, and sinusitis.

**Table 192024-008-08 – Number (%) of Patients with Adverse Events Reported by at Least 5 Patients ( $\geq 2\%$ ) in Either AGN 192024 Group**

<b>BODY SYSTEM Preferred Term</b>	<b>AGN 192024 QD (N = 240)</b>	<b>AGN 192024 BID (N = 240)</b>	<b>timolol (N = 122)</b>	<b>Among-group P-value<sup>a</sup></b>
<b>BODY AS A WHOLE</b>				
infection	13 ( 5.4%)	6 ( 2.5%)	0 ( 0.0%)	0.009 <sup>b</sup>
headache	10 ( 4.2%)	7 ( 2.9%)	4 ( 3.3%)	0.777 <sup>b</sup>
flu syndrome	2 ( 0.8%)	6 ( 2.5%)	2 ( 1.6%)	0.384 <sup>b</sup>
<b>CARDIOVASCULAR</b>				
hypertension	5 ( 2.1%)	5 ( 2.1%)	1 ( 0.8)	0.790 <sup>b</sup>
<b>DIGESTIVE</b>				
liver function tests abnormal	5 ( 2.1%)	1 ( 0.4%)	0 ( 0.0%)	0.148 <sup>b</sup>
<b>METABOLIC</b>				
hypercholesteremia	1 ( 0.4%)	6 ( 2.5%)	1 ( 0.8%)	0.162 <sup>b</sup>
<b>RESPIRATORY</b>				
sinusitis	6 ( 2.5%)	3 ( 1.3%)	3 ( 2.5%)	0.601 <sup>b</sup>

<sup>a</sup> Among-group p-value based on Pearson's chi-square test unless indicated otherwise.

<sup>b</sup> Among-group p-value based on Fisher's exact test.

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ON ORIGINAL**

**Table 192024-008-08 – Number (%) of Patients with Adverse Events Reported by at Least 5 Patients (≥ 2%) in Either AGN 192024 Group Continued**

BODY SYSTEM Preferred Term	AGN 192024 QD (N = 240)	AGN 192024 BID (N = 240)	timolol (N = 122)	Among-group P-value <sup>a</sup>
<b>SPECIAL SENSES (OCULAR)</b>				
conjunctival hyperemia	80 (33.3%)	99 (41.3%)	9 ( 7.4%)	< 0.001
growth of eyelashes	43 (17.9%)	74 (30.8%)	2 ( 1.6%)	< 0.001
eye pruritus	33 (13.8%)	44 (18.3%)	5 ( 4.1%)	< 0.001
eye dryness	17 ( 7.1%)	22 ( 9.2%)	3 ( 2.5%)	0.060
burning sensation in eye	16 ( 6.7%)	17 ( 7.1%)	11 ( 9.0%)	0.709
foreign body sensation	12 ( 5.0%)	17 ( 7.1%)	3 ( 2.5%)	0.172
visual disturbance	9 ( 3.8%)	11 ( 4.6%)	4 ( 3.3%)	0.893 <sup>b</sup>
irritation eye	8 ( 3.3%)	8 ( 3.3%)	3 ( 2.5%)	0.911 <sup>b</sup>
allergic conjunctivitis	6 ( 2.5%)	1 ( 0.4%)	0 ( 0.0%)	0.080 <sup>b</sup>
eye pain	6 ( 2.5%)	20 ( 8.3%)	2 ( 1.6%)	0.002
blepharal pigmentation	5 ( 2.1%)	14 ( 5.8%)	0 ( 0.0%)	0.004 <sup>b</sup>
asthenopia	4 ( 1.7%)	9 ( 3.8%)	0 ( 0.0%)	0.056 <sup>b</sup>
corneal erosion	4 ( 1.7%)	5 ( 2.1%)	2 ( 1.6%)	> 0.999 <sup>b</sup>
photophobia	4 ( 1.7%)	15 ( 6.3%)	0 ( 0.0%)	0.001 <sup>b</sup>
eye discharge	3 ( 1.3%)	6 ( 2.5%)	0 ( 0.0%)	0.206 <sup>b</sup>
eyelash discoloration	3 ( 1.3%)	6 ( 2.5%)	0 ( 0.0%)	0.206 <sup>b</sup>
stinging sensation eye	3 ( 1.3%)	6 ( 2.5%)	1 ( 0.8%)	0.538 <sup>b</sup>
conjunctival edema	2 ( 0.8%)	5 ( 2.1%)	2 ( 1.6%)	0.562 <sup>b</sup>
eyelid pruritus	1 ( 0.4%)	9 ( 3.8%)	0 ( 0.0%)	0.006 <sup>b</sup>

<sup>a</sup> Among-group p-value based on Pearson's chi-square test unless indicated otherwise.

<sup>b</sup> Among-group p-value based on Fisher's exact test.

### Iris Color Assessment

240 subjects treated with AGN 192024 0.03% QD, 240 subjects treated with AGN 192024 0.03% BID, and 122 subjects treated with timolol 0.5% BID were assessed for potential iris color changes. Iris photographs were performed at Baseline (Day 0), Weeks 2 and 6, and Month 3 (and planned for Months 6, 9 and 12).

Investigators were instructed to note any ocular changes from Baseline (e.g. iris color, lashes, etc.) on the Adverse Event Form.

One patient receiving AGN 192024 QD (2964-Z10) was noted to have iris color change OU from blue to green-brown (COSTART preferred term iris disorder) at the Month 3 exam. The patient continued in the study.

**Table 192024-008-09 – Summary of Specific Ocular Adverse Events by Severity and Percent of Patients**

Adverse Event	Severity	AGN 192024 0.3% QD (N = 240)	AGN 192024 0.3% BID (N = 240)	Timolol 0.5% BID (N = 122)
Growth of eyelashes	Overall	43 (17.9%)	74 (30.8%)	2 (1.6%)
	Mild	36 (15.0%)	54 (22.5%)	2 (1.6%)
	Moderate	3 (1.3%)	14 (5.8%)	0 (0.0%)
	Severe	0 (0.0%)	3 (1.3%)	0 (0.0%)
	N/A*	4 (1.7%)	3 (1.3%)	0 (0.0%)
Eyelash discoloration	Overall	3 (1.3%)	6 (2.5%)	0 (0.0%)
	Mild	2 (0.8%)	5 (2.1%)	0 (0.0%)
	Moderate	1 (0.4%)	0 (0.0%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
	N/A*	0 (0.0%)	1 (0.4%)	0 (0.0%)
Blepharal pigmentation	Overall	5 (2.1%)	14 (5.8%)	0 (0.0%)
	Mild	4 (1.7%)	8 (3.3%)	0 (0.0%)
	Moderate	1 (0.4%)	5 (2.1%)	0 (0.0%)
	Severe	0 (0.0%)	1 (0.4%)	0 (0.0%)
	N/A*	0 (0.0%)	0 (0.0%)	0 (0.0%)

\* N/A: not applicable for severity

#### Reviewer's Comments:

*Changes in eyelash growth are consistent with an ocularly administered prostaglandin-type effect.*

#### Laboratory Parameters

At baseline, there were no statistically significant differences among the 3 treatment groups for any hematology, chemistry, or urinalysis parameter.

Within-group changes from baseline to month 3 were statistically significant as follows: in the AGN 192024 QD group for hemoglobin, red blood cell count (RBC), mean corpuscular volume (MCV), eosinophils, albumin, aspartate aminotransferase (AST), urea nitrogen, creatinine, uric acid, calcium, chloride, and hydrogen ion concentration (pH); in the AGN 192024 BID group for hematocrit, MCV, monocytes, urea nitrogen, creatinine, uric acid, calcium, and cholesterol; and in the timolol group for MCV, albumin, creatinine, calcium, and inorganic phosphorus. These changes were generally small and were not clinically relevant.

**Reviewer's Comments:**

*Agree. There does not appear to be a clinically significant difference between treatment groups in any of the hematology, chemistry, or urinalysis parameters evaluated.*

**Visual Acuity**

**Table 192024-008-10 – Visual Acuity Tabulated by Changes in Line Number Comparing Patient's Final Evaluation to Baseline<sup>a</sup>**

Line Changes	HTL QD (N=240)	HTL BID (N=240)	TIM (N=122)
N	240	239	119
>= -2	22 ( 9.2%)	8 ( 3.3%)	12 ( 10.1%)
> -2 to <= -1	66 ( 27.5%)	74 ( 31.0%)	23 ( 19.3%)
> -1 to < 0	26 ( 10.8%)	29 ( 12.1%)	14 ( 11.8%)
0	91 ( 37.9%)	106 ( 44.4%)	56 ( 47.1%)
> 0 to < +1	15 ( 6.3%)	8 ( 3.3%)	5 ( 4.2%)
>= +1 to < +2	15 ( 6.3%)	9 ( 3.8%)	6 ( 5.0%)
>= +2	5 ( 2.1%)	5 ( 2.1%)	3 ( 2.5%)

[a] The final evaluation at or prior to month 3. Tabulation was based on the eye with worse change comparing to the fellow eye.

**Cup/Disc Ratio**

**Table 192024-008-11 – Cup/Disc Ratio Change from Baseline<sup>a</sup>**

Change from Baseline	HTL QD (N=240)	HTL BID (N=240)	TIM (N=122)
N	230	225	116
<= -0.2	2 ( 0.9%)	1 ( 0.4%)	2 ( 1.7%)
>= +0.2	4 ( 1.7%)	2 ( 0.9%)	3 ( 2.6%)

[a] The final evaluation at or prior to month 3. Tabulation was based on the eye with worse change compared to the fellow eye.

**Reviewer's Comments:**

*There are no clinically significant differences in visual acuity or cup/disc ratio between treatment groups.*

### **Biomicroscopy**

An increase from the baseline severity of conjunctival erythema was reported for 37.9% (91/240) of patients in the AGN 192024 QD group, 45.8% (110/240) of patients in the AGN 192024 BID group, and 5.7% (7/122) of patients in the timolol group ( $p < 0.001$ ).

Eyelash growth was reported for 10.4% (25/240) of patients in the AGN 192024 QD group, 19.6% (47/240) of patients in the AGN 192024 BID group, and 1.6% (2/122) of patients in the timolol group ( $p < 0.001$ ).

Pairwise comparisons of either AGN 192024 QD or BID versus timolol were statistically significant ( $p \leq 0.004$ ) for each of these findings.

Growth of eyelashes was reported more frequently as an adverse event than noted on the biomicroscopy evaluations.

### **Reviewer's Comments:**

*Agree. Growth of eyelashes was reported more frequently as an adverse event than noted on biomicroscopy evaluations.*

*Note, however, the percentage of each treatment group reporting growth of eyelashes in Table 192024-008-09, page 30.*

### **Laser Flare Meter Reading**

Laser flare meter data were collected for a subset of 123 patients at selected centers. The laser flare meter readings at baseline ranged from 0.15 to 52.25 p/msec, and were similar across the 3 treatment groups.

### **Endothelial Cell Counts**

Endothelial cell counts were collected for a subset of 126 patients at selected centers. The cell counts at baseline ranged from 1000 to 3150 cells, and were similar across the 3 treatment groups. There were no statistically significant within-group changes from baseline to month 3 in any treatment group.

### **Visual Fields**

Patients' final visual fields mean deviation at or prior to month 3 was compared to baseline, based on the eye with the worst change. The changes from baseline in the visual fields mean deviation ranged from -30.5 to +4.1 dB, and were similar across the 3 treatment groups ( $p = 0.607$ ).

**Reviewer's Comments:**

*There are no clinically significant differences in laser flare meter data, endothelial cell counts, or visual fields between treatment groups.*

**Heart Rate/Blood Pressure**

Heart rate at baseline ranged from 48 to 112 bpm, and was similar across the 3 treatment groups. The mean changes from baseline were generally small with AGN 192024, ranging from -1.76 to +0.99 bpm, and not clinically relevant.

Systolic blood pressure at baseline ranged from 95 to 240 mm Hg, and was similar across the 3 treatment groups. The mean changes from baseline were generally small, ranging from -4.79 to +0.11 mm Hg, and not clinically relevant.

Diastolic blood pressure at baseline ranged from 50 to 130 mm Hg, and was similar across the 3 treatment groups. The mean changes from baseline were generally small, ranging from -1.78 to +1.15 mm Hg, and not clinically relevant.

**Reviewer's Comments:**

*Agree. Mean changes from baseline in heart rate and blood pressure were not clinically significant with either AGN 192024 0.03% QD or BID.*

**8.1.1 Reviewer's Summary of Efficacy and Safety**

*AGN 192024 0.03% administered QPM did not demonstrate equivalence to AGN 192024 0.03% administered BID in the ability to lower intraocular pressure.*

*When Hour 12 measurements are excluded, AGN 192024 0.3% QD lowers IOP between 7 and 8 mmHg from baseline. AGN 192024 0.03% BID lowers IOP between 6 and 8 mmHg from baseline. Timolol 0.5% BID lowers IOP between 4 and 6 mmHg from baseline.*

*The IOP lowering ability of AGN 192024 0.03% (either QD or BID) is not superior to timolol 0.5% BID by a clinically significant amount.*

*Both AGN 192024 0.03% QD and BID regimens are associated with conjunctival hyperemia, at 33% and 41% respectively.*

*Changes in iris color may signal the ability of AGN 192024 to increase the number of melanosomes (pigment granules) in melanocytes. Changes in eyelash growth are consistent with an ocularly administered prostaglandin-type effect.*

**8 Clinical Studies****8.1.2 Study #2 Protocol 192024-009**

Title: Identical to Protocol 192024-008

Study Design: Identical to Protocol 192024-008

Test Drug Schedule: Identical to Protocol 192024-008

<b>Investigator Number</b>	<b>Investigator</b>	<b>Number Randomized</b>
1584	<b>Mark Abelson, M.D.</b> North Andover, Massachusetts 01845 USA	29
0359	<b>George Baerveldt, M.D.</b> Indianapolis, Indiana 46202 USA	2
2671	<b>Steven Best, M.D.</b> Auckland 10005 New Zealand	10
3225	<b>James Branch, M.D.</b> Winston-Salem , North Carolina 27103 USA	28
2846	<b>James Brandt, M.D.</b> Sacramento, California 95817 USA	16
3219	<b>John Brennan, M.D.</b> Sherman, Texas 75092 USA	16
2008	<b>Anne Brooks, M.D.</b> East Melbourne, Victoria 3002 Australia	3
3209	<b>Salim Butrus, M.D.</b> Washington, DC 20003 USA	5
2957	<b>Leonard Cacioppo, M.D.</b> Brooksville, Florida 34610 USA	13
2991	<b>Guy D'Mellow, M.D.</b> Brisbane, Queensland 4000 Australia	2
2450	<b>Harvey DuBiner, M.D.</b> Morrow, Georgia 30260 USA	41
0169	<b>Efraim Duzman, M.D.</b> Irvine, California 92604 USA	27
0207	<b>Robert Foerster, M.D.</b> Colorado Springs, Colorado 80907 USA	10

<b>Investigator Number</b>	<b>Investigator</b>	<b>Number Randomized</b>
2954	<b>Jonathan Frantz, M.D.</b> Fort Myers, Florida 33907 USA	1
2860	<b>Walter Fried, M.D.</b> Gurnee, Illinois 60031 USA	17
2958	<b>David Geiser, M.D.</b> Wheaton, Illinois 60187 USA	19
2005	<b>Ivan Goldberg, M.D.</b> Sydney, New South Wales 2000 Australia	21
2869	<b>Eve Higginbotham, M.D.</b> Baltimore, Maryland 21201 USA	10
0526	<b>Richard Lewis, M.D.</b> Sacramento, California 95819 USA	32
2992	<b>Andrew Logan, M.D.</b> Wellington 6001 New Zealand	7
2993	<b>Richard McGovern, M.D.</b> Adelaide, South Australia 5000 Australia	9
1485	<b>Thomas Mundorf, M.D.</b> Charlotte, North Carolina 28204 USA	19
2956	<b>George Nardin, M.D.</b> Kailua, Hawaii 96734 USA	35
2955	<b>Jonathan Nussdorf, M.D.</b> Louisville, Kentucky 40202 USA	25
2666	<b>Julian Rait, M.D.</b> East Melbourne, Victoria 3002 Australia	19
1724	<b>Robert Shields, M.D.</b> Denver, Colorado 80210 USA	12
1634	<b>Thomas Walters, M.D.</b> Austin, Texas 78705 USA	46
3185	<b>Jeffrey Whitsett, M.D.</b> Houston, Texas 77055 USA	21
0296	<b>Jacob Wilensky, M.D.</b> Chicago, Illinois 78705 USA	10
2710	<b>Robert Williams, M.D.</b> Louisville, Kentucky 40217 USA	47

**Reviewer's Comments:**

*It is preferred to have at least 10 patients per arm per center.*

**8.1.2 Study Design** Identical to Protocol 192024-008

**Subject Disposition and Demographics**

There were 596 patients enrolled in the study: 234 patients randomized to AGN 192024 QD, 243 patients randomized to AGN 192024 BID, and 119 patients randomized to timolol. In the intent-to-treat analysis, 97% (575/596) of patients completed 2 weeks of treatment, 95% (563/596) of patients completed 6 weeks of treatment, and 93% (552/596) of patients completed 3 months of treatment.

The most frequent reason for discontinuation of the study prior to Month 3 was adverse events (5%, 27/596). Four patients (1%, 4/596) discontinued prior to Month 3 due to lack of efficacy: 2 patients in the AGN 192024 QD group, 1 patient in the AGN 192024 BID group, and 1 patient in the timolol group.

**Table 192024-009-01 – Discontinued Patients and Reason**

Treatment/Duration	Investigator	Patient	Reason
AGN 192024 QD 6 days	0169	A13	Personal reasons
AGN 192024 QD 2 days	0169	A14	Personal reasons
AGN 192024 QD 2 days	1485	E16	Adverse event – “off balance feeling”
AGN 192024 QD 14 days	1584	J06	Adverse event – arthralgia
AGN 192024 QD 11 days	1634	K01	Personal reasons
AGN 192024 QD 51 days	1724	V07	Lack of efficacy
AGN 192024 QD 12 days	2005	W03	Adverse event – conj hyperemia, eye pruritus, eye pain, foreign body sensation
AGN 192024 QD 42 days	2005	W18	Adverse event – arteritis, glossitis
AGN 192024 QD 16 days	2008	S03	Lack of efficacy – pressure control suboptimal
AGN 192024 QD 43 days	2008	S05	Adverse event – conj hyperemia, conj edema
AGN 192024 QD 39 days	2671	U02	Improper entry – BP uncontrolled
AGN 192024 QD Approx. 14 days	2860	G17	Personal reasons – can't get off work for visits
AGN 192024 QD 57 days	2958	H17	Adverse event – eyelid erythema
AGN 192024 QD 92 days	3185	J70	Personal reasons