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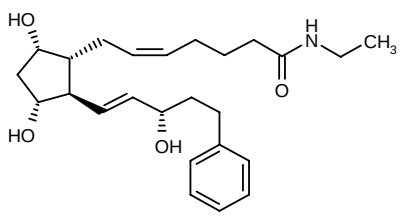
# Bimatoprost

*Antiglaucoma*

AGN-192024
Lumigan®

(5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-*N*-ethyl-5-heptenamide
17-Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ ethylamide
(5*Z*,9α,11α,13*E*,15*S*)-9,11,15-Trihydroxy-17-phenyl-18,19,20-trinorprosta-5,13-dienoic acid ethylamide




$C_{25}H_{37}NO_4$ Mol wt: 415.5703

CAS: 155206-00-1

EN: 251988

## Synthesis

The esterification of 17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ (I) with methyl iodide and DBU in acetone gives the corresponding methyl ester (II), which is finally treated with ethylamine in methanol at 80-5 °C (1, 2). Scheme 1.

## Introduction

Glaucoma encompasses a group of eye diseases that are usually associated with elevated intraocular pressure (IOP). It is characterized by cellular changes in the optic nerve and retina which leads to loss of retinal ganglion cells and visual field. It is estimated that 67 million people suffer from glaucoma worldwide, with 4 million afflicted in the U.S. alone (3). The major forms of glaucoma include open-angle (primary or chronic glaucoma) and angle-closure (closed-angle). Open-angle glaucoma is the most common form of the disorder affecting approximately 3 million Americans and is the leading cause of preventable blindness worldwide. In open-angle glaucoma, the angle of the anterior chamber of the eye is open to aqueous humor outflow which is then drained too slowly through the trabecular network. This results in an increase in IOP. In contrast, angle-closure glaucoma occurs when part of the iris obstructs the angle of the anterior chamber thus blocking aqueous humor from passing to the trabecular meshwork and causing an increase in IOP. Other types of glaucoma include low-tension or normal-tension glaucoma in which individuals with normal IOP present nerve damage and decreases in peripheral vision, congenital glaucoma in which children are born with a defect in the angle of the eye which interferes with normal drainage of aqueous humor, secondary glaucoma which can result following cataract surgery, eye injuries, uveitis or with ocular tumors and neovascular glaucoma which can develop in individuals with diabetes (3).

The increase in IOP is only one of the factors associated with glaucoma that causes optic nerve damage. However, it is one of the few factors that can be clinically managed and therefore is the target for treatment of the disorder. Antiglaucoma agents act by improving the flow of intraocular fluid and/or by reducing the amount of aqueous humor produced by the eye; laser or conventional surgery may be employed if medication alone does not reduce IOP. The classes of antiglaucoma agents currently available are mitotics which constrict the ciliary muscle thus opening the drainage channels in the trabecular meshwork to increase drainage, β-blocker and carbonic anhydrase inhibitors which reduce aqueous humor production and $\alpha_2$-adrenoceptor agonists which decrease both aqueous humor production and increase uveoscleral outflow. An additional class of antiglaucoma agents includes the prostaglandin analogs which are shown in Table I. These agents increase the uveoscleral outflow of the aqueous humor. Topical administration of prostaglandins (PGs) was observed to lower IOP in animal models as early as 25 years ago. $PGF_{2\alpha}$ and its isopropyl ester have been shown to possess potent ocular antihypertensive activity in both animals and humans. However, they are associated with conjunctival

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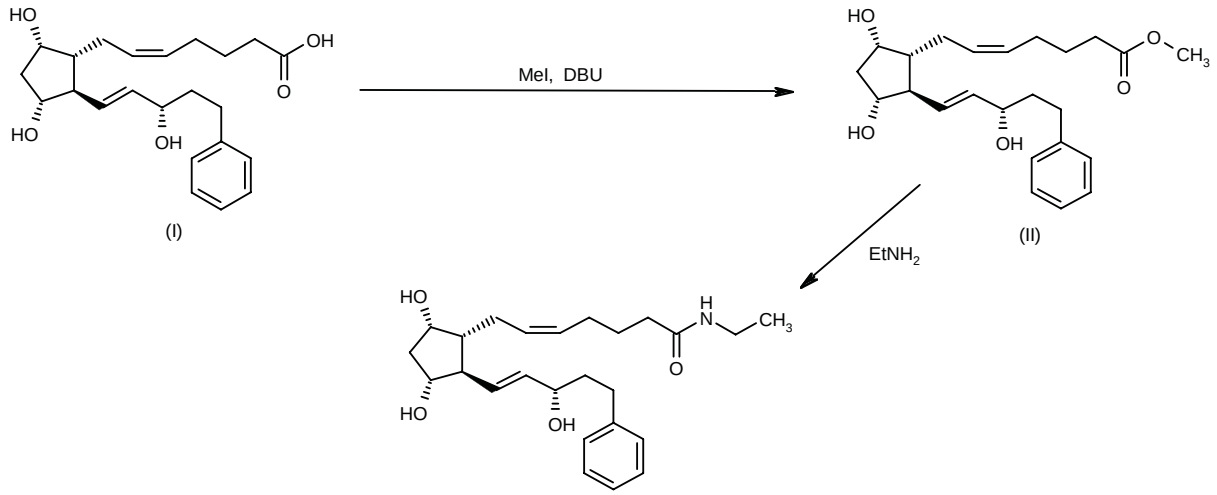
**Scheme 1: Synthesis of Bimatoprost**




hyperemia, irritation and headache (3). Thus, the search for PG analogs as a treatment to decrease IOP continues. AGN-192024 (bimatoprost, Lumigan™) is one such synthetic $PGF_{2\alpha}$ analog discovered through research efforts. AGN-192024 is thought to lower IOP by increasing outflow of aqueous humor through both the trabecular meshwork and the uveoscleral routes. It has shown both preclinical and clinical efficacy and was chosen for further development.

## Pharmacological Actions

Studies characterizing the pharmacological activity of AGN-192024 showed that the agent was devoid of many of the biological activities of typical $PGF_{2\alpha}$ and its analogs. The agent did not stimulate pregnant or nonpregnant human uterus, was not mitogenic and was markedly less potent than $PGF_{2\alpha}$ in inducing endothelium-dependent vasorelaxation. Moreover, the agent did not interact with any known prostanoid receptors. AGN-192024 was, however, more potent than $PGF_{2\alpha}$ in stimulating cat lung parenchymal tissue (4).

Further *in vitro* characterization of AGN-192024 in radioligand and functional studies revealed that the agent did not display activity for several recombinant or natural plasma membrane associated and intracellular receptors, ion channels and transporters. The $IC_{50}$ or $EC_{50}$ values obtained for the agent against adenosine ($A_{1-3}$), adrenergic ($\alpha_1$, $\alpha_2$, $\beta_1$ and $\beta_2$), cannabinoid ($CB_1$ and $CB_2$), dopamine ($D_{1-5}$), muscarinic ($M_{1-5}$), serotonin ($5HT_1$-$5HT_7$) and prostanoid (DP, $EP_{1-4}$, FP, IP and TP) receptors were greater than 10,000 nM. However, the agent exhibited potent activity in a feline iris sphincter smooth muscle preparation ($EC_{50}$ = 34 nM). Results indicated that the agent did not interact with prostaglandin receptors (5).

The ocular efficacy of AGN-192024 was also demonstrated *in vivo* in a study conducted in ocular normotensive beagle dogs and cynomolgus monkeys and monkeys with laser-induced ocular hypertension. Treatment with a single dose (0.03% ophthalmic solution, 1 drop) decreased IOP by 37 and 35% in dogs and monkeys, respectively. Effects were sustained for 24 h postdosing. A significant 42% increase in uveoscleral outflow (0.964 to 1.372 µl/min) was observed in monkeys with no effects observed on total outflow and aqueous humor flow. Although systemic exposure to AGN-192024 was low, high ocular bioavailability was observed with permeability coefficients of 14.5 ± 5.3 and 3.24 ± 0.58 cm/s obtained for the sclera and cornea, respectively (6).

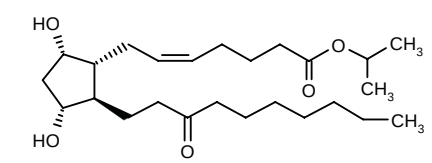
## Pharmacokinetics

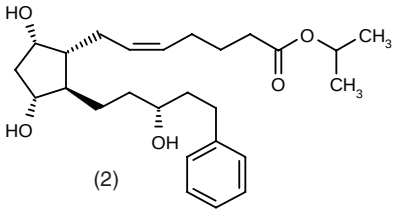
The pharmacokinetics of AGN-192024 (0.03% ophthalmic solution, 1 drop once daily bilaterally for 2 weeks) were examined in a study involving 14 healthy subjects. Maximum blood concentrations of the agent were observed 10 min postdosing. Levels then decreased to below the limits of detection (0.025 ng/ml) within 1.5 h postdosing. Steady state was achieved within the first week of dosing since the mean $C_{max}$ (0.08 ng/ml) and $AUC_{0\text{-}24h}$ (0.09 ng·h/ml) values were similar on days 7 and 14. No significant drug accumulation was observed (6, 7). The steady-state volume of distribution was 0.67 l/kg and the majority of the agent was found unchanged in plasma with about 12% remaining unbound. Following ocular dosing and arrival to systemic circulation, AGN-192024 underwent oxidation, *N*-deethylation and glucuronidation forming several metabolites (7).

Elimination of the agent was examined in a study conducted in 6 healthy subjects administered radiolabeled

*Table I: Prostaglandin compounds for the treatment of glaucoma.*

| Drug name | Company | Mechanism of Action | Status |
|---|---|---|---|
| 1. Unoprostone isopropyl ester (*Rescula*) | Ueno | Prostaglandin $F_{2\alpha}$ analog | Launched 1994 |
| 2. Latanoprost (*Xalatan*) | Pharmacia | Prostaglandin $F_{2\alpha}$ analog | Launched 1996 |
| 3. Travoprost (*Travatan*) | Alcon | Prostaglandin $F_{2\alpha}$ analog | Launched 2001 |
| 4. Latanoprost/timolol maleate (*Xalcom*) | Pharmacia | Prostaglandin analog/β-blocker combination | Approved 2000 |
| 5. Bimatoprost (*Lumigan*) | Allergan | Prostaglandin $F_{2\alpha}$ analog | Launched 2001 |
| 6. AGN-190910 | Allergan | Prostaglandin $F_{2\alpha}$ analog | Preclinical |
| 7. AGN-191129 | Allergan | Prostaglandin $F_{2\alpha}$ analog | Preclinical |
| 8. AL-8810 | Alcon | Prostaglandin $F_{2\alpha}$ analog | Preclinical |
| 9. OSA-8302 | Santen/Ono | Prostaglandin $F_{2\beta}$ analog | Preclinical |


(1)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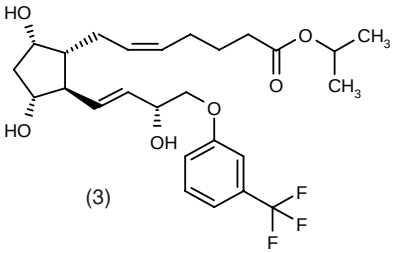
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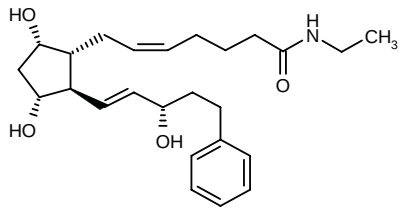
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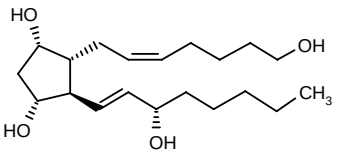
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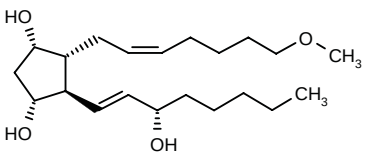
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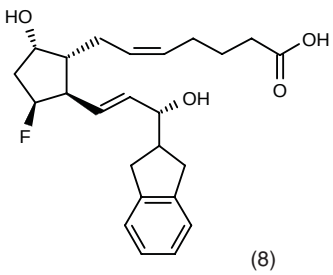
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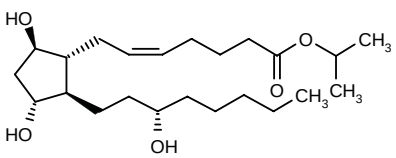
(9)

AGN-192024 (3.12 µg/kg i.v.). The $C_{max}$ of the unchanged compound was 12.2 ng/ml which rapidly decreased with an elimination $t_{1/2}$ value of 45 min. Total blood clearance was 1.5 l/h/kg and up to 67 and 25% of the dose was excreted in urine and feces, respectively (7).

## Clinical Studies

A randomized, double-blind, placebo-controlled, paired-comparison trial in 25 normal healthy volunteers (21-48 years; IOP = 12-21 mmHg) examined the mechanism of action of AGN-192024 (0.03% ophthalmic solution). IOP pressure, aqueous humor flow and tonographic resistance were measured during the day and while subjects slept. IOP decreased significantly by 20% on day 3 in eyes treated with the agent as compared to placebo and significant 13 and 14% increases in aqueous humor flow were observed in treated patients during the day and night, respectively. In addition, tonographic resistance to outflow was significantly reduced by 26% and apparent resistance to outflow (*i.e.*, IOP: aqueous flow ratio) was significantly decreased by 31%. It was concluded that AGN-192024 enhanced pressure-insensitive outflow by 50% and tonographic facility of outflow by 35%. Aqueous humor formation was not altered by treatment (8) (Box 1).

The short-term safety and efficacy of AGN-192024 (0.01, 0.03 and 0.1% b.i.d. for 5.5 days) was evaluated and compared to timolol (0.5% b.i.d. for 5.5 days) in a randomized, double-blind, parallel-group study involving 60 patients with open-angle glaucoma or ocular hypertension. The percent mean change from baseline in IOP

*Box 1: Effects of bimatoprost on aqueous dynamics in healthy volunteers (8) [Prous Science CSline database].*

| | |
|---|---|
| Design | Randomized, placebo-controlled, double-blind clinical study |
| Population | Healthy volunteers (n = 25) |
| Treatments | Bimatoprost 0.03% instilled o.d. in right eye x 2 d<br>Placebo |
| Results | Intraocular pressure (mmHg), change @ d 3: B (–4.1) > P (–1.5) [$p$ <0.001]<br>Aqueous humor flow (ml/min) @ d 3: B (2.79) > P (2.47) [$p$ = 0.007]<br>Tonographic resistance (mmHg.min/ml) @ d 3: P (4.43) > B (3.27) [$p$ <0.001]<br>Apparent resistance (mmHg.min/ml) @ d 3: P (5.36) > B (3.68) [$p$ <0.001] |
| Conclusions | Bimatoprost enhanced both pressure-sensitive and pressure-insensitive aqueous humor outflow without diminishing aqueous humor formation |

*Box 2: Safety and efficacy of bimatoprost versus timolol in ocular hypertension (9) [Prous Science CSline database].*

| | |
|---|---|
| Design | Randomized, placebo-controlled, comparative, double-blind, dose-finding clinical study |
| Population | Patients with open-angle glaucoma or ocular hypertension (n = 60) |
| Treatments | Bimatoprost 0.01% instilled b.i.d. x 6.5 d<br>Bimatoprost 0.03% instilled b.i.d. x 6.5 d<br>Bimatoprost 0.1% instilled b.i.d. x 6.5 d<br>Timolol 0.5% instilled b.i.d. x 6.5 d<br>Placebo |
| Results | Intraocular pressure at 8 AM, % change @ d 3: B0.03 (–35) ≥ B0.1 (–30) ≥ B0.01(–22) ≥ T (–17) > P (–0.3);<br>@ d 7: B0.03 (–28) ≥ B0.1 (–19) ≥ B0.01 (–15) ≥ T (–13) > P (1)<br>Ocular hyperemia was more frequent in the B0.1 than in the T ($p$ = 0.036) and P ($p$ = 0.009) groups |
| Conclusions | Bimatoprost was highly effective for lowering intraocular pressure |

*Box 3: Efficacy and safety of bimatoprost versus latanoprost in ocular hypertension (10) [Prous Science CSline database].*

| | |
|---|---|
| Design | Randomized, placebo-controlled, comparative, single-blind, multicenter clinical study |
| Population | Patients with primary open-angle glaucoma or ocular hypertension (n = 64) |
| Treatments | Bimatoprost, 0.03% instilled o.d. x 29 d<br>Latanoprost 0.005%, instilled b.i.d. x 29 d<br>Placebo |
| Results | Minimum intraocular pressure at 8 AM, % change: B* (–25) > L* (–20) [*$p$ <0.001 *vs.* baseline]<br>Maximum intraocular pressure at 8 AM, % change: B* (–34) > L* (–31) [*$p$ <0.001 *vs.* baseline] |
| Conclusions | Bimatoprost 0.03% given during 1 month was at least as effective as latanoprost for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension and provided better diurnal control |

measured at 8 AM prior to daily instillation with 0.01, 0.03 and 0.1% AGN-192024, respectively, were 26, 34 and 30% on day 2; 23, 32 and 29% on day 5; 22, 35 and 28% on day 6; and 15, 28 and 19% on day 7. Timolol decreased IOP from baseline by 18, 16, 14 and 13% on days 2, 5, 6 and 7, respectively. All treatments were well tolerated with no discontinuations observed due to adverse events. A significantly higher incidence of hyperemia was observed in the group receiving 0.1% AGN-192024 as compared to timolol and placebo (9) (Box 2).

A multicenter, investigator-blinded, placebo-controlled, randomized, 30-day trial conducted in 64 subjects with primary open-angle glaucoma or ocular hypertension compared the efficacy and safety of AGN-192024 (0.3% once daily in the PM for 29 days) with latanoprost (0.005% once daily in the PM for 29 days). Both treatments were well tolerated with no difference observed between groups in the incidence of adverse effects. No serious adverse events were seen and development of conjunctival hyperemia was comparable in the two treatment groups. Both AGN-192024 and latanoprost significantly lowered IOP from baseline. AGN-192024 (25-34%; 5.9-8.9 mmHg) tended to lower IOP more than latanoprost (20-31%; 4.4-7.9 mmHg) at all time points examined although statistical significance was not reached. AGN-192024 also appeared to afford better diurnal control as compared to latanoprost (10) (Box 3).

*Box 4: Efficacy of bimatoprost versus timolol and latanoprost in ocular hypertension (11) [Prous Science CSline database].*

| | |
|---|---|
| Design | Randomized, comparative, double-blind, multicenter, dose-finding clinical study |
| Population | Patients with open-angle glaucoma and/or ocular hypertension (n = 206) |
| Treatments | Bimatoprost 0.001%, 1 drop instilled in each eye o.d. x 4 wks<br>Bimatoprost 0.001%, 1 drop instilled in each eye o.d. x 3 wks → b.i.d. x 1 wk<br>Bimatoprost 0.003%, 1 drop instilled in each eye o.d. x 4 wks<br>Bimatoprost 0.003%, 1 drop instilled in each eye o.d. x 3 wks → b.i.d. x 1 wk<br>Bimatoprost 0.03%, 1 drop instilled in each eye o.d. x 4 wks<br>Bimatoprost 0.03%, 1 drop instilled in each eye o.d. x 3 wks → b.i.d. x 1 wk<br>Timolol 0.5%, 1 drop instilled in each eye b.i..d. x 4 wks<br>Latanoprost 0.005%, 1 drop instilled in each eye o.d. x 4 wks |
| Results | Intraocular pressure change during study: B > T ($p$ <0.021); B similar to L; diurnal: Bod > T; B ~ L |
| Conclusions | Once-daily bimatoprost 0.03% provided superior intraocular pressure control than timolol and proved to be at least as effective as latanoprost in patients with glaucoma or ocular hypertension |

*Box 5: Bimatoprost versus timolol in ocular hypertension (12) [Prous Science CSline database].*

| | |
|---|---|
| Design | Randomized, comparative, double-blind clinical study |
| Population | Patients with glaucoma or ocular hypertension (n = 596) |
| Treatments | Bimatoprost 0.03%, 1 drop instilled in each eye o.d. x 3 mo<br>Bimatoprost 0.03%, 1 drop instilled in each eye b.i.d. x 3 mo<br>Timolol 0.5%, 1 drop instilled in each eye o.d. x 3 mo |
| Results | Intraocular pressure (mmHg), change @ 3 mo: Bod* (–9.16) ≥ Bbid (–7.78) ≥ T (–6.74) [*$p$ <0.001 *vs.* T] |
| Conclusions | Once-daily bimatoprost 0.03% provided superior intraocular pressure control than timolol in patients with ocular hypertension or glaucoma |

The short-term efficacy of AGN-192024 was also demonstrated in two other 30-day, randomized, parallel-group trials in subjects with ocular hypertension and/or open-angle glaucoma. The first trial involving 100 subjects compared the efficacy of AGN-192024 (0.003, 0.01 or 0.03%, 1 drop once daily in the PM bilaterally for 3 weeks followed by b.i.d. for 1 week) with timolol (0.5% b.i.d. for 4 weeks), while the second trial conducted in 106 subjects compared the efficacy of AGN-192024 (once daily in the PM for 30 days) with latanoprost (0.005% once daily in the PM for 30 days). IOP was measured at 8 AM and at 12, 4, 8, and 10 PM. Treatment with AGN-192024 was found to dose-dependently and significantly decrease IOP at all time points. The 0.03% solution of AGN-192024 was significantly better than timolol at all time points except one and was equally effective as latanoprost. All treatments were well tolerated. A significantly higher incidence of conjunctival hyperemia was observed in the AGN-192024 group as compared to the timolol group and a significant increase in laser flare measurements was seen in the timolol-treated group. AGN-192024 had no significant effects on other ocular safety parameters, heart rate, blood pressure or blood chemistry (11) (Box 4).

Long-term treatment with AGN-192024 was shown to be superior to timolol (0.5% b.i.d.) in 3-month, 6-month and 1-year trials involving patients with glaucoma and/or ocular hypertension. The 3-month trial was a randomized, double-blind trial conducted in 596 patients and showed that AGN-192024 (0.3% once daily or b.i.d.)-treated patients displayed mean changes in IOP from baseline of –9.16 and –7.78 mmHg for once- and twice-daily dosing, respectively, as compared to –6.74 mmHg seen with timolol; once-daily treatment with AGN-192024 was significantly superior to timolol. Treatment was well tolerated with mild conjunctival hyperemia the most common adverse event (12) (Box 5).

Results from two ongoing 6-month, multicenter, randomized, double-blind trials conducted in a total of 1198 patients showed the significant superiority of once-daily AGN-192024 (0.03% at 8 PM) as compared to AGN-192024 b.i.d. or timolol (0.5% b.i.d.) in reducing IOP. AGN-192024 administered b.i.d. was also significantly better than timolol at most time points but not superior to once-daily dosing with AGN-192024. Once-daily AGN-192024 dosing resulted in effects that were sustained for 6 months. Mean IOP decreases from baseline with once- and twice-daily AGN-192024 were 33% (–8.1 mmHg) and 26% (–6.3 mmHg), respectively, as compared to 23% (–5.6 mmHg) seen in the timolol group. In

*Box 6: Bimatoprost once- and twice-daily versus timolol twice-daily in ocular hypertension (13) [Prous Science CSline database].*

| | |
|---|---|
| Design | Randomized, comparative, double-blind, multicenter clinical study |
| Population | Patients with glaucoma or ocular hypertension (n = 1198) |
| Treatments | Bimatoprost 0.003%, instilled o.d. x 6 mo (n = 474)<br>Bimatoprost 0.003%, instilled b.i.d. x 6 mo (n = 483)<br>Timolol 0.5%, instilled b.i.d. x 6 mo (n = 241) |
| Adverse Events | B: Increased iris pigmentation 11/957 (1.1%) |
| Results | Intraocular pressure @ 10 AM, % change @ mo 6: Bod* (-33) ≥ Bbid (–26) >/= T (–23) [*$p < 0.05$ *vs.* T]<br>Intraocular pressure < 17 mmHg rate (%) @ mo 6: Bod (63.9) > T (37.3) [$p < 0.001$] |
| Conclusions | Once-daily bimatoprost 0.03% was superior to timolol in lowering intraocular pressure in patients with glaucoma or ocular hypertension and was well tolerated |

*Box 7: Bimatoprost versus timolol in ocular hypertension (14) [Prous Science CSline database].*

| | |
|---|---|
| Design | Randomized, comparative, double-blind, multicenter clinical study |
| Population | Patients with glaucoma or ocular hypertension (n = 596) |
| Treatments | Bimatoprost 0.03%, instilled o.d. x 1 y (n = 234)<br>Bimatoprost 0.03%, instilled b.i.d. x 1 y (n = 243)<br>Timolol 0.5%, instilled b.i.d. x 1 y (n = 119) |
| Adverse Events | Bod: Increased iris pigmentation 4/234 (1.7%) |
| Results | Intraocular pressure @ 10 AM, % change @ 1 y: Bod* (–32.1) ≥ Bbid (–24.8) ≥ T (-22.9) [*$p < 0.001$ *vs.* T] |
| Conclusions | Once-daily bimatoprost 0.03% was superior to timolol for the long-term lowering of intraocular pressure in patients with glaucoma or ocular hypertension |

addition, a significantly higher percentage of patients treated with once-daily AGN-192024 reached low target pressure as compared to the timolol group (IOP > 17 mmHg: 63.9 *vs.* 37.3% at 6 months). Treatments were well tolerated with trace to mild conjunctival hyperemia the most common adverse event. Few discontinuations due to adverse events occurred. Only 1.1% of the patients treated with AGN-192024 reported changes in iris pigmentation and treatment had no effect on slit lamp examinations, ophthalmoscopy, visual acuity, visual fields or systemic safety parameters (13) (Box 6).

Similar superior efficacy was shown for once-daily (at 8 AM) AGN-192024 (0.03%) over twice-daily dosing (at 8 AM and 8 PM) and timolol (0.5% b.i.d.) in a 1-year, multicenter, randomized, double-blind, parallel-group trial conducted in 596 patients with glaucoma or ocular hypertension. IOP was evaluated at 8 and 10 AM and 4 PM at baseline, weeks 2 and 6 and months 3, 6, 9 and 12. Mean IOP reductions with once-daily AGN-192024 were sustained for 12 months and were significantly greater at all time points as compared to twice-daily AGN-192024 dosing and timolol; twice-daily dosing was significantly better than timolol but inferior to once-daily AGN-192024. Mean IOP reductions from baseline at 12 months were 32.1 (–7.94 mmHg), 24.8% (–6.04 mmHg) and 22.9% (–5.53 mmHg) for once- and twice-daily AGN-192024 and timolol, respectively. Once-daily AGN-192024 dosing afforded excellent diurnal control and more patients receiving this dosing regimen achieved low target pressures as compared to timolol. Conjunctival hyperemia was the most common adverse event which was mild and led to few discontinuations. An increase in iris pigmentation was only reported in 1.7% patients treated with once-daily AGN-192024. Treatment had no effects on systemic safety parameters (14) (Box 7).

Overall, the most frequent adverse events seen in patients (about 15-45%) treated with AGN-192024 were (in descending order of incidence) conjunctival hyperemia, growth of eyelashes and ocular pruritus. Only 3% of the patients discontinued due to conjunctival hyperemia. Other adverse events seen in 3-10% of the patients treated with the agent included (in descending order of incidence) 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. Those infrequent adverse events seen in ~1-3% or less of the patients treated with the agent were eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema and iritis (7).

The FDA has approved bimatoprost (Lumigan™) 0.03% ophthalmic solution for reduction in IOP in patients with open-angle glaucoma or ocular hypertension, and the agent is undergoing regulatory review in Europe (15, 16).

## Manufacturer

Allergan, Inc. (US).

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