Drugs of the Future 2002, 27(5): 509-523

CCC: 0377-8282/2002

Ophthalmic Drugs

N.E. Mealy, R. Castañer, L. Martín, M. del Fresno, L. Revel, M. Bayés, L.A. Sorbera, P. Cole, P.A. Leeson, J. Prous

Abstract

The second *Annual Review* for this month features updated information on ophthalmic drugs. The following table lists 35 drugs under development in this area, including some that have been published in previous issues of the journal and others that have been launched for an indication other than that discussed in the review. Information on the following products is updated here: bimatoprost, INS-365, octreotide, ruboxistaurin mesilate hydrate and travoprost.

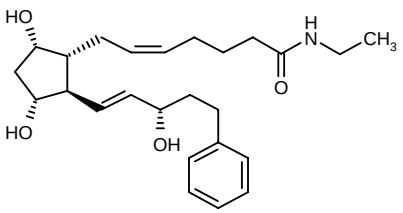
We would like to remind the readers that all of the information presented in this Review is available in electronic format in our drug discovery portal **Integrity**.

Annual Review 2002: Ophthalmic Drugs

Drug	Source	Indication	Phase
AE-941[1]	Aeterna	Age-related macular degeneration	I
AFP-168/DE-085	Asahi Glass/Santen	Glaucoma	II
AL-6598	Alcon	Glaucoma	II
AMD rhuFab V2	Genentech	Age-related macular degeneration	I/II
Anecortave Acetate	Alcon	Age-related macular degeneration	II
Apafant[1]	Santen	Antiallergic	II
Bevacizumab	Genentech	Age-related macular degeneration	I
Bimatoprost[1]	Allergan	Glaucoma	L-2000
Candesartan Cilexetil[1,2]	Takeda/AstraZeneca	Diabetic retinopathy	III
CS-088	Sankyo/Santen	Glaucoma	I
Cyclosporin A[2]	Allergan	Dry eye	III
Dacliximab[2]	Protein Design Labs	Uveitis	I/II
Epithalone	Russian Academy of Medical Sciences	Age-related macular degeneration	II
Gatifloxacin[1,2]	Kyorin/Senju	Antibacterial	I
Hyaluronidase[2]	ISTA Pharmaceuticals	Diabetic retinopathy	II
INS-365[1]	Inspire Pharmaceuticals	Retinal detachment	I/II
	Inspire Pharmaceuticals/Santen	Dry eye	III
INS-37217	Inspire Pharmaceuticals	Retinal detachment/Retinal edema	I/II
ISV-205	InSite Vision	Glaucoma	II
ISV-401	InSite Vision	Antibacterial	II
Latanoprost/Timolol Maleate	Pharmacia	Glaucoma	L-2001
Lerdelimumab	Cambridge Antibody Technology	Scarring following glaucoma surgery	II/III
Loteprednol Etabonate/Tobramycin	Bausch & Lomb	Antiinflammatory	III
Memantine Hydrochloride[1,2]	Allergan	Glaucoma	III
Motexafin Lutetium	Pharmacyclics/Alcon	Age-related macular degeneration	II
N-Acetylcarnosine	Innovative Vision Products	Anticataract	II
Octreotide[1,2]	Novartis	Diabetic retinopathy	III
Pegaptanib Sodium	EyeTech	Age-related macular degeneration	II/III
Pimagedine[1]	Alteon	Diabetic retinopathy	III
Posurdex	Oculex	Persistent macular edema	II
Rostaporfin	Miravant	Age-related macular degeneration	III
Ruboxistaurin Mesylate Hydrate[1]	Lilly	Diabetic retinopathy	III
SmartPlug	Medennium	Dry eye	L-2001
Tacrolimus[1,2]	Fujisawa	Dry eye	II
Tosufloxacin Tosylate[1,2]	Nidek	Antibacterial	III
Travoprost[1]	Alcon	Glaucoma	L-2001

Drugs in bold are covered in the review. [1]Previously published in Drugs of the Future. [2]Launched for another indication.

Bimatoprost



Bimatoprost (AGN-192024, Lumigan®) is a member of a new class of pharmacologically unique intraocular pressure (IOP)-lowering agents called prostamides, which exist naturally in ocular tissues and have significant IOP-lowering properties. As a synthetic prostamide, bimatoprost mimics the IOP-lowering activity of natural prostamides. Following the receipt of marketing authorization for bimatoprost from the European Commission and the FDA in the first quarter of this year, Allergan launched the product as a 0.03% ophthalmic solution in the U.S., Germany, the U.K. and Italy. Lumigan® is indicated for the reduction of elevated IOP in patients with chronic open-angle glaucoma or ocular hypertension, as monotherapy in patients who are insufficiently responsive to, intolerant of or contraindicated for first-line therapy, and as an adjuvant therapy to β-blockers. Bimatoprost has also been approved in 6 Latin American countries (1-3).

The pharmacology of bimatoprost has been characterized in functional and binding studies at numerous drug targets comprising a variety of receptors, ion channels and transporters, as well as in animals and humans (4). When tested in more than 100 *in vitro* drug target preparations, bimatoprost demonstrated pharmacological activity only in the prostamide-sensitive feline iris-sphincter preparation. In additional studies in dogs and monkeys, bimatoprost 0.03% potently reduced IOP 24 h after administration (5). Researchers evaluated the IOP-lowering activity of bimatoprost (0.001, 0.01, 0.03 and 0.1%) in ocular normotensive dogs and monkeys and ocular hypertensive monkeys. All concentrations reduced intraocular pressure; the 0.03% concentration was the most effective. In radioligand binding and functional studies in numerous preparations of antiglaucoma drug targets, bimatoprost was active only at prostamide-sensitive receptors (6).

Bimatoprost demonstrated efficacy in lowering IOP in ocular normotensive dogs and monkeys with ocular hypertension. Uveoscleral outflow was also significantly increased by bimatoprost in the monkeys. High ocular bioavailability was seen in monkeys, while in humans given bilateral bimatoprost 0.03% once daily for 14 days the drug was detected rapidly in blood followed by rapid decline (7).

An additive effect on IOP was seen in 8 glaucomatous monkeys administered 1 drop daily of latanoprost 0.005% or bimatoprost 0.03% for 6 days and then both treatments 5 min apart for 7 days. The maximum reduction in IOP from baseline with combination treatment was 29-30% (8).

Rabbit and human cornea were found to hydrolyze bimatoprost to the potent prostaglandin FP receptor agonist 17-phenyl-PGF2α. Bimatoprost and its hydrolysis product were both found to be agonists at the human ocular FP receptor (9). Investigators evaluated the *in vitro* metabolism of bimatoprost in excised human and bovine cornea. The results indicated that bimatoprost is a prodrug and that the hydrolysis product of the drug lowers IOP *in vivo* (10).

Researchers carried out IOP and single- and multiple-dose ocular distribution studies with bimatoprost in normal and ocular hypertensive monkeys. Intraocular pressure was significantly reduced with doses as low as 0.001% in normal and ocular hypertensive animals. Drug levels at the active site were high enough to account for long-lasting hypotensive effects. Intraocular pressure was apparently lowered by the intact molecule (11).

The pharmacokinetics of bimatoprost and its potential C-1 acid metabolite were determined in 15 healthy volunteers who received 1 drop of bimatoprost 0.03% in each eye daily for 14 days. Bimatoprost was absorbed quickly, after which blood concentrations declined rapidly. Accumulation was not seen with multiple doses. In addition, the potential C-1 acid metabolite was not detected (12).

A study of the mechanism of action of bimatoprost in healthy volunteers revealed that the agent stimulates the rate of aqueous humor flow during the day and at night (13).

A randomized, double-blind, placebo-controlled study evaluated the effects of bimatoprost on aqueous dynamics in normal subjects. Both pressure-sensitive and pressure-insensitive outflow was improved by 30%, resulting in a 20% reduction in IOP in these subjects. Aqueous humor flow during the day and night was stimulated by 13% and 14%, respectively (14, 15). This study and a number of those that follow are summarized in Table I.

Healthy volunteers (n=28) received treatment for 5 days with either latanoprost 0.005%, bimatoprost 0.03% or travoprost 0.004% in a study of conjunctival hyperemia. Evaluation by slit lamp biomicroscopy revealed that latanoprost caused less conjunctival hyperemia than bimatoprost or travoprost in these subjects (16).

A multicenter, double-blind, randomized trial compared bimatoprost 0.03%, latanoprost 0.005% and vehicle treatment in 64 patients with open-angle glaucoma or ocular hypertension. While both drugs were safe and well tolerated, bimatoprost was superior to latanoprost in controlling diurnal IOP (17).

Table I: Clinical studies of bimatoprost (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind	Bimatoprost, 0.03% eye drops od in right eye x 2 d Placebo	25	Bimatoprost enhanced both pressure-sensitive and -insensitive aqueous humor outflow without diminishing aqueous humor formation	14, 15
Healthy volunteers		Latanoprost, 0.005% eye drops x 5 d Bimatoprost, 0.03% eye drops x 5 d Travoprost, 0.004% eye drops x 5 d	28	Less conjunctival hyperemia was seen with latanoprost than with the other treatments	16
Glaucoma, ocular hypertension, open-angle glaucoma	Randomized, double-blind, multicenter	Bimatoprost, 0.03% eye drops od x 29 d (n=21) Latanoprost, 0.005% eye drops od x 29 d (n=22) Placebo (n=21)	64	Bimatoprost once daily showed a greater decrease in diurnal intraocular pressure than latanoprost in patients with ocular hypertension and glaucoma	17
Glaucoma, ocular hypertension, open-angle glaucoma	Randomized, crossover	Bimatoprost, 0.03% eye drops od x 30 d Latanoprost, 0.005% eye drops od x 30 d	15	Bimatoprost lowered intraocular pressure more than latanoprost, but a higher incidence of trace to mild conjunctival hyperemia was noted with bimatoprost	18
Glaucoma, ocular hypertension	Randomized, double-blind, multicenter	Bimatoprost, 0.03% eye drops od (n=234) Bimatoprost, 0.03% eye drops bid (n=243) Timolol, 0.5% eye drops bid (n=119)	596	Bimatoprost given once daily was significantly more effective in lowering intraocular pressure than timolol and more effective and better tolerated than twice-daily bimatoprost	20, 21
Glaucoma, ocular hypertension	Randomized, double-blind, multicenter	Bimatoprost, 0.03% eye drops od x 3 mo (n=119) Latanoprost, 0.005% eye drops od x 3 mo (n=113)	232	Both drugs were well tolerated but bimatoprost was more effective in reducing intraocular pressure, achieving low target pressures	22
Glaucoma	Retrospective	Latanoprost → Bimatoprost	40	Bimatoprost lowered intraocular pressure an additional 3 mmHg in patients in which it was substituted for latanoprost	24
Ocular hypertension	Retrospective	Bimatoprost (n=26) Latanoprost + Bimatoprost (n=13)	39	Adverse events led to discontinuation in several patients, although in others bimatoprost provided significant reductions in intraocular pressure	25
Glaucoma, ocular hypertension	Randomized, double-blind, multicenter	Bimatoprost, 0.03% eye drops od x 1 y (n=93) Bimatoprost, 0.03% eye drops bid x 1 y (n=97) Placebo x 3 mo → Bimatoprost, 0.03% eye drops od or bid x 9 mo (n=95)	285	Bimatoprost od had fewer side effects than bimatoprost bid and significantly reduced intraocular pressure	26
Glaucoma, ocular hypertension	Randomized, double-blind, multicenter	Bimatoprost, 0.03% eye drops od (n=474) Bimatoprost, 0.03% eye drops bid (n=483) Timolol, 0.5% eye drops bid (n=241)	1198	Once-daily bimatoprost was superior to timolol in lowering intraocular pressure in patients with glaucoma or ocular hypertensión, and was well tolerated	27-31

Patients (n=15) with primary open-angle glaucoma or ocular hypertension who did not respond to therapy with latanoprost 0.005% q.d. entered a randomized, crossover study of treatment with bimatoprost 0.03% which consisted of two 30-day treatment periods separated by a 30-day washout period. With bimatoprost, the mean IOP was lower than that seen at baseline and after 30 days of latanoprost treatment. Trace to mild conjunctival hyperemia was observed more often in bimatoprost-treated patients (18).

Doctors have published a case report concerning a woman with glaucoma who began treatment with bimatoprost and within 1 month experienced reactivation of herpes simplex virus keratitis which had been inactive for over 10 years. Treatment with bimatoprost and prednisolone was stopped and the patient was given aciclovir, ofloxacin and betaxolol, and prednisolone after 2 weeks. The reaction resolved after 1 month (19).

Bimatoprost 0.03% o.d. or b.i.d. or timolol 0.5% b.i.d. was administered to 596 patients with ocular hypertension or glaucoma in a multicenter, randomized, double-blind trial. After 3 months, IOP was reduced more with bimatoprost 0.03% o.d. than with timolol or twice-daily bimatoprost, with mean reductions of 35.2, 30.4 and 26.2% for bimatoprost o.d., bimatoprost b.i.d. and timolol, respectively (20). A 1-year, randomized, double-blind clinical trial compared long-term treatment of glaucoma and ocular hypertension with bimatoprost 0.03% (q.d. or

b.i.d.) and timolol 0.5% (b.i.d.) in 596 patients. Both bimatoprost doses were significantly superior to timolol in lowering IOP, with once-daily dosing being more effective than twice-daily dosing (21).

Bimatoprost 0.03% was compared to latanoprost 0.005% in a multicenter, randomized trial in 232 patients with glaucoma or ocular hypertension. Treatments were administered once daily for 3 months. Bimatoprost reduced IOP more throughout the study and enabled more patients to achieve target pressures than latanoprost. Both treatments were well tolerated, with a greater incidence of conjunctival hyperemia seen in the bimatoprost-treated group and a greater incidence of headache observed in the latanoprost-treated patients (22).

In 2 multicenter, randomized, double-blind phase III trials, 223 patients with glaucoma or ocular hypertension received either 1 drop of bimatoprost 0.03% bilaterally once daily, the same treatment twice daily or timolol 0.5% b.i.d. for 12 months. Plasma concentrations of bimatoprost were low and remained stable over the course of 1 year (23).

Researchers conducted a retrospective review of 40 patients with uncontrolled glaucoma who switched treatment from latanoprost to bimatoprost. Intraocular pressure was lowered by 3 mmHg from baseline in 13 of 40 eyes treated with bimatoprost, while the reductions in IOP were not significant in the remaining patients (24).

A retrospective analysis examined patients with ocular hypertension who received bimatoprost as either add-on therapy with latanoprost (group A, n=13) or as a replacement for latanoprost (group B, n=26). Discontinuations due to adverse events were seen in 4 and 5 patients in groups A and B, respectively. Additional reductions in IOP of 5.08 and 1.33 mmHg were seen with bimatoprost in groups A and B, respectively (25).

In a 3-month, multicenter, randomized, double-blind, placebo-controlled study, patients with ocular hypertension not controlled by β-blocker treatment received adjunctive therapy with bimatoprost 0.03% q.d., bimatoprost 0.03% b.i.d. or vehicle. A 9-month, double-blind extension followed, with those on bimatoprost continuing treatment and those on placebo switched to a bimatoprost regimen. Once-daily bimatoprost reduced baseline IOP by 31 and 33% at 3 months and 1 year, respectively, and was better tolerated than the b.i.d. regimen (26).

Researchers pooled and analyzed data from 2 multicenter, randomized, double-blind phase III trials of bimatoprost in a total of 1198 patients with glaucoma or ocular hypertension to evaluate the drug's effect on IOP. Patients in the trials received either bimatoprost 0.03% once daily, bimatoprost 0.03% b.i.d. or timolol 0.5% b.i.d. Once-daily bimatoprost was found to be safe, well tolerated and more effective in lowering IOP than timolol or twice-daily bimatoprost (27-32).

1. *Lumigan approved by European Commission, introduced in three countries.* DailyDrugNews.com (Daily Essentials) April 29, 2002.

2. *Lumigan introduced following mid-March approval by FDA.* DailyDrugNews.com (Daily Essentials) April 26, 2001.

3. *Positive opinion issued for Lumigan by CPMP.* DailyDrugNews.com (Daily Essentials) Nov 21, 2001.

4. Woodward, D.F., Krauss, A.H.P., Chen, J. et al. *The pharmacology of bimatoprost (Lumigan™).* Surv Ophthalmol 2001, 45(6, Suppl. 1): S337.

5. Krauss, A.H.-P., Chen, J., Woodward, D.F. *The pharmacology of AGN 192024 (Lumigan), a novel ocular hypotensive agent.* 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 39.

6. Woodward, D.F., Krauss, A.H.-P., Burk, R.M., Andrews, S.W., Chen, J., Brar, B., Garst, M.E., Kaplan, L.J., Wheeler, L.A. *Lumigan (AGN 192024): Studies on a pharmacologically novel ocular hypotensive agent.* 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 29.

7. Krauss, A.H.P., Andrews, S.W., Chen, J., Tang-Liu, D., Nilsson, S.F.E., Woodward, D.F. *The ocular pharmacology and bioavailability of AGN 192024 (Lumigan™), a novel ocular hypotensive agent.* Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

8. Wang, R.-F., Serle, J.B., Gagliuso, D., Mittag, T.W., Podos, S.M. *Effect of latanoprost (L) or bimatoprost (B) alone and in combination on intraocular pressure (IOP) in glaucomatous monkey eyes.* Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4070.

9. Sharif, N.A., Ke, T.L., Haggard, C.R., Kelly, C.R., Williams, G.W., Graff, G., Hellberg, M.R., Dean, T.R. *Bimatoprost hydrolysis to 17-phenyl PGF2α by human and rabbit ocular tissues and agonist activity of bimatoprost and 17-phenyl PGF2α.* Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4080.

10. Maxey, K.M., Johnson, J., LaBrecque, J. *The hydrolysis of bimatoprost in corneal tissue generates a potent prostanoid FP receptor agonist.* Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4071.

11. Woodward, D.F., Madhu, C., Burk, R.M., Andrews, S.W., Chen, J., Krauss, A.H., Brar, B., Garst, M.E., Tang-Liu, D.D.S., Wheeler, L.A. *AGN 192024 (Lumigan®): A synthetic prostamide analog that lowers primate intraocular pressure by virtue of its inherent pharmacological activity.* Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4110.

12. Tang-Liu, D.D., Cherukury, M., Acheampong, A., Cheetham, J., VanDenburgh, A., Yu, D. *Systemic pharmacokinetics of bimatoprost 0.03% solution following once daily ocular dosing in normal, healthy subjects.* Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 1085.

13. Brubaker, R.F. *Mechanism of action of bimatoprost (Lumigan™).* Surv Ophthalmol 2001, 45(6, Suppl. 1): S347.

14. Brubaker, R.F., Schoff, E.O., Nau, C.B., Carpenter, S.P., Chen, K., Vandenburgh, A.M. *Effects of AGN 192024, a new ocular hypotensive agent, on aqueous dynamics.* Am J Ophthalmol 2001, 131(1): 19.

15. Brubaker, R.F. *Mechanism of action of AGN 192024, a new ocular hypotensive agent.* 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 22.

16. Albritton, A.E., Stewart, J.A., Leech, J.N., Jackson, A.L., Stewart, W.C. *Conjunctival hyperemia with latanoprost, travoprost and bimatoprost.* Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4112.

17. DuBiner, H., Cooke, D., Dirks, M., Stewart, W.C., VanDenburgh, A.M., Felix, C. *Efficacy and safety of bimatoprost in patients with elevated intraocular pressure: A 30-day comparison with latanoprost.* Surv Ophthalmol 2001, 45(6, Suppl. 1): S353.

18. Gandolfi, S.A., Cimino, L. *Effects of 0.03% bimatoprost on patients non-responders to 0.005% latanoprost: A cross-over study.* Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 3408.

19. Kroll, D.M., Schuman, J.S. *Reactivation of herpes simplex virus keratitis after initiating bimatoprost treatment for glaucoma.* Am J Ophthalmol 2002, 133(3): 401.

20. Brandt, J.D., VanDenburgh, A.M., Chen, K., Whitcup, S.M. *Comparison of once- or twice-daily bimatoprost with twice-daily timolol in patients with elevated IOP: A 3-month clinical trial.* Ophthalmology 2001, 108(6): 1023.

21. Higginbotham, E.J. *1-Year comparison of the new prostamide AGN 192024 with timolol for the management of glaucoma and ocular hypertension.* Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

22. Gandolfi, S., Simmons, S.T., Sturm, R., Chen, K., VanDenburgh, A.M. *Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension*. Adv Ther 2001, 18(3): 110.

23. Cheetham, J.K., Tang-Liu, D., Yu, Z., VanDenburgh, A., Acheampong, A., Yu, D. *Long-term systemic exposure of Lumigan in patients with glaucoma or ocular hypertension*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4108.

24. Stamper, R.L. *Intraocular pressure lowering effect with substitution of bimatoprost for latanoprost*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4101.

25. Chen, M.-J., Lin, S., Stamper, R.L. *Efficacy and safety of bimatroprost as additive and replacement therapy in patients uncontrolled with latanoprost: Early results*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 3411.

26. Melamed, S., Bossawska, I., Laroch, C. *Effectiveness of bimatoprost (Lumigan) as adjunctive therapy with topical β-blockers in patients with glaucoma or ocular hypertension. A 3-month, multi-center, double-masked, randomized, vehicle-controlled trial with double-masked extension of bimatoprost treatment to 1 year*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 1068.

27. Goldberg, I., Cantor, L. et al. *Clinical evaluations of AGN 192024 (Lumigan™)*. 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 29.

28. Goldberg, I. *6-Month comparison of AGN 192024 qd and bid with timolol bid in patients with elevated IOP*. 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 27.

29. Cheetham, J., Higgintotham, E.J., Goldberg, I., Schuman, J.S., Gross, R.L., VanDenburgh, A.M., Whitcup, S.M. *1-Year comparison of bimatoprost with timolol in patients with glaucoma or ocular hypertension*. 4th Int Symp Ocular Pharmacol Pharm (Feb 28-March 3, Seville) 2002, 19.

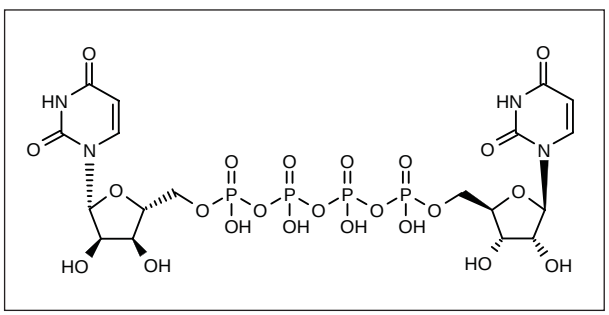
30. Sherwood, M., Brandt, J. *Six-month comparison of bimatoprost once-daily and twice-daily with timolol twice-daily in patients with elevated intraocular pressure*. Surv Ophthalmol 2001, 45(6, Suppl. 1): S361.

31. Cantor, L.B. et al. *6-Month comparison of AGN 192024 once-daily and twice-daily with timolol twice-daily in patients with elevated IOP*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst .

32. *Six-month trial results show Lumigan clinically superior to timolol in lowering IOP*. DailyDrugNews.com (Daily Essentials) March 6, 2001.

Original monograph - Drugs Fut 2001, 26(5): 433.

INS-365



Inspire's INS-365 is a small-molecule $P2Y_2$ agonist that activates receptors on the surface and inner lining of the eyelid to release water, salt, mucin and lipids. The product is believed to promote corneal healing and improve ocular surface health. It is currently in late-stage clinical development for the treatment of dry eye, also known as keratoconjunctivitis sicca, a painful, burning and irritating condition involving abnormalities and deficiencies in the tear film due to a variety of causes, for which there are currently no FDA-approved pharmacologically active treatments.

Inspire has a licensing, development and marketing agreement for INS-365 Ophthalmic with Allergan, pursuant to which Allergan holds an exclusive license to develop and commercialize INS-365 Ophthalmic worldwide, with the exception of Japan and 9 other Asian countries covered by Inspire's previous agreement with Santen. Inspire retains rights to copromote INS-365 Ophthalmic in the U.S. A multicenter phase III program for INS-365 Ophthalmic is now under way in the U.S. and Santen is currently conducting a phase I study in Japan (1, 2).

Eye drops containing INS-365 0.03-3% were administered to rats with experimental dry eye 6 times/day for 4 weeks. INS-365 improved tear secretion and restored corneal epithelial barrier function in these animals. Release of glycoprotein-containing moieties from goblet cells was also observed (3).

The ocular safety and tolerability of INS-365 (0.5, 1, 2 and 5% solution 3 times over 6 h) were demonstrated in a randomized, double-blind, placebo-controlled, intrasubject-paired comparison, dose-escalation study conducted in 5 cohorts of 10 healthy subjects. The incidence of ocular adverse events was similar in both treated and placebo groups. Adverse events possibly related to treatment with the 5% solution included painless blepharospasm and an increase in lacrimation. According to Schirmer testing, the agent had no acute effects on tear secretion as compared to placebo (4) (Table II).

In a multicenter, double-blind, parallel-group phase II trial, patients with dry eye (n=158) were randomized to INS-365 0.5, 1, 2 or 5% or placebo for 4 weeks. After 4 weeks, half of the INS-365-treated patients were randomized again to placebo for 2 weeks. Results indicated a strong and consistent trend for improvement in both signs and symptoms of dry eye, including a statistically significant improvement over placebo on an important objective efficacy endpoint –corneal staining. Although not the aim of the study, results showed significant improvement in several other important measures of efficacy, including conjunctival staining, tear breakup time and the unanesthetized Schirmer test (a test measuring tear secretion) in the INS-365 treatment groups at various time points throughout the study. In addition, the subjective endpoints of ocular itching and burning consistently

Table II: Clinical studies of INS-365 Ophthalmic (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, crossover	INS-365 ophthalmic solution, 0.5% tid x 1 d INS-365 ophthalmic solution, 1.0% tid x 1 d INS-365 ophthalmic solution, 2.0% tid x 1 d INS-365 ophthalmic solution, 5% tid x 1 d Placebo	50	INS-365 was well tolerated when administered by ocular instillation	4
Dry eye	Randomized, multicenter	INS-365 ophthalmic solution, 0.5% INS-365 ophthalmic solution, 1% INS-365 ophthalmic solution, 2% INS-365 ophthalmic solution, 5% Placebo	158	Low and high concentrations of INS-365 were superior to placebo in changes in corneal fluorescein and conjunctival lissamine green staining and in evaluations of itching and burning/painful eye	5

improved in drug-treated cohorts, with burning showing a statistically significant difference. Ocular tolerability was excellent over a 10-fold range of concentrations (0.5-5.0%). Based on these positive results, the company initiated a 64-site U.S. phase III trial of INS-365 designed to compare the efficacy and safety of 2 concentrations of INS-365 Ophthalmic to placebo in 900 patients with dry eye (2, 5) (Table II).

Enrollment has begun in Inspire's third phase III trial of INS-365 Ophthalmic for dry eye. The trial was designed based on results from the first phase III trial in which patients with dry eye (n=558) showed improvement on INS-365 Ophthalmic (1 and 2%) that did not reach statistical significance over placebo. The new placebo-controlled, double-masked trial will compare the safety and efficacy of 2% INS-365 Ophthalmic eye drops to placebo in 200 dry eye patients. The study will be conducted in a controlled adverse environment to allow for a more precise measurement of patients' signs and symptoms of dry eye and consistent measurement of responses to the treatment. The FDA has confirmed that results from the trial may be used in an NDA for INS-365 Ophthalmic in dry eye. Meanwhile, Inspire's second phase III trial with INS-365 Ophthalmic is ongoing, and the company is expected to meet with the FDA in the second quarter of 2002 to discuss detailed findings (6-10).

1. *Allergan and Inspire collaborate on development of two ophthalmic products for dry eye*. DailyDrugNews.com (Daily Essentials) July 2, 2001.

2. *Statistically significant phase II results reported for INS-365 Ophthalmic*. DailyDrugNews.com (Daily Essentials) Feb 28, 2001.

3. Fujihara, T., Murakami, T., Fujita, H., Nakamura, M., Nakata, K. *Improvement of corneal barrier function by the $P2Y_2$ agonist INS365 in a rat dry eye model*. Invest Ophthalmol Visual Sci 2001, 42(1): 96.

4. Mundasad, M.V., Novack, G.D., Allgood, V.E., Evans, R.M., Gorden, J.C., Yerxa, B.R. *Ocular safety of INS365 ophthalmic solution: A $P2Y_2$ agonist in healthy subjects*. J Ocular Pharmacol Ther 2001, 17(2): 173.

5. Foulks, G., Sall, K., Greenberg, M., Tauber, J., Donshik, P., Berdy, G., Sylvester, R., Yerxa, B., Crockett, S., Kellerman, D. *Phase 2 dose ranging efficacy trial of INS365 ophthalmic solution, a $P2Y_2$ agonist, in patients with dry eye*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

6. *Third phase III trial under way for INS-365 Ophthalmic in dry eye*. DailyDrugNews.com (Daily Essentials) April 9, 2002.

7. *Disappointing preliminary results from first phase III trial of INS-3 Ophthalmic in dry eye*. DailyDrugNews.com (Daily Essentials) Jan 17, 2002.

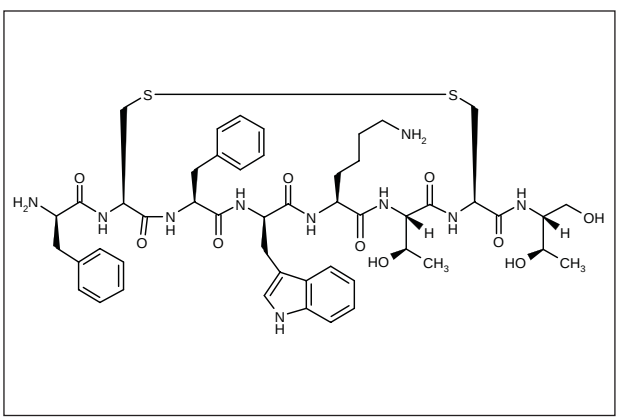
8. *Enrollment of patients completed for phase III INS-365 Ophthalmic clinical program*. DailyDrugNews.com (Daily Essentials) Sept 19, 2001.

9. *Inspire's agent for dry eye enters phase III evaluation*. DailyDrugNews.com (Daily Essentials) Jan 11, 2001.

10. *Inspire reprioritizes its pipeline*. DailyDrugNews.com (Daily Essentials) Jan 30, 2002.

Original monograph - Drugs Fut 1999, 24(7): 759.

Octreotide



Octreotide (Sandostatin®; Novartis), a long-acting somatostatin analogue presently available for the treatment of acromegaly and certain endocrine tumors, is in phase III clinical trials for the treatment of diabetic retinopathy (1).

A randomized trial was conducted to evaluate long-term treatment of patients (n=9) with advanced proliferative diabetic retinopathy with octreotide 100 µg t.i.d. Assessment after 3 years showed that the incidence of vitreous hemorrhage and the need for vitreoretinal surgery were significantly lower in these patients compared with untreated diabetic controls (2) (Table III).

Table III: Clinical studies of octreotide acetate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetes mellitus, diabetic retinopathy	Randomized, single-blind	Octreotide, 100 g sc tid x 36 mo (max.) Controls (patients with diabetes)	9	The incidence of vitreous hemorrhage and the need for vitreoretinal surgery were significantly lower in patients treated with octreotide compared with untreated diabetic controls	2

Somatostatin analogs have been claimed for the treatment of ocular disorders such as vision loss due to progressive retinal or optic nerve diseases (3).

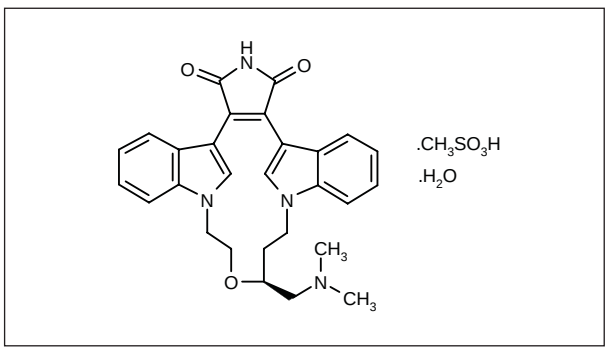
1. Reinhardt, J. *Innovation and productivity drive sustained growth*. Novartis R&D Invest Semin (Dec 6, Basel) 2000.

2. Boehm, B.O., Lang, G.K., Jehle, P.M., Feldmann, B., Lang, G.E. *Octreotide reduces vitreous hemorrhage and loss of visual acuity risk in patients with high-risk proliferative diabetic retinopathy*. Horm Metab Res 2001, 33(5): 300.

3. Fsadni, M. and Wyss, K. (Novartis AG) *Treatment of ocular disorders with somatostatin analogues*. WO 0209739.

Original monograph - Drugs Fut 1984, 9(5): 342.

Ruboxistaurin Mesilate Hydrate



The protein kinase C inhibitor ruboxistaurin mesilate hydrate (LY-333531) is in late-stage development at Lilly for the treatment of diabetic retinopathy and macular edema.

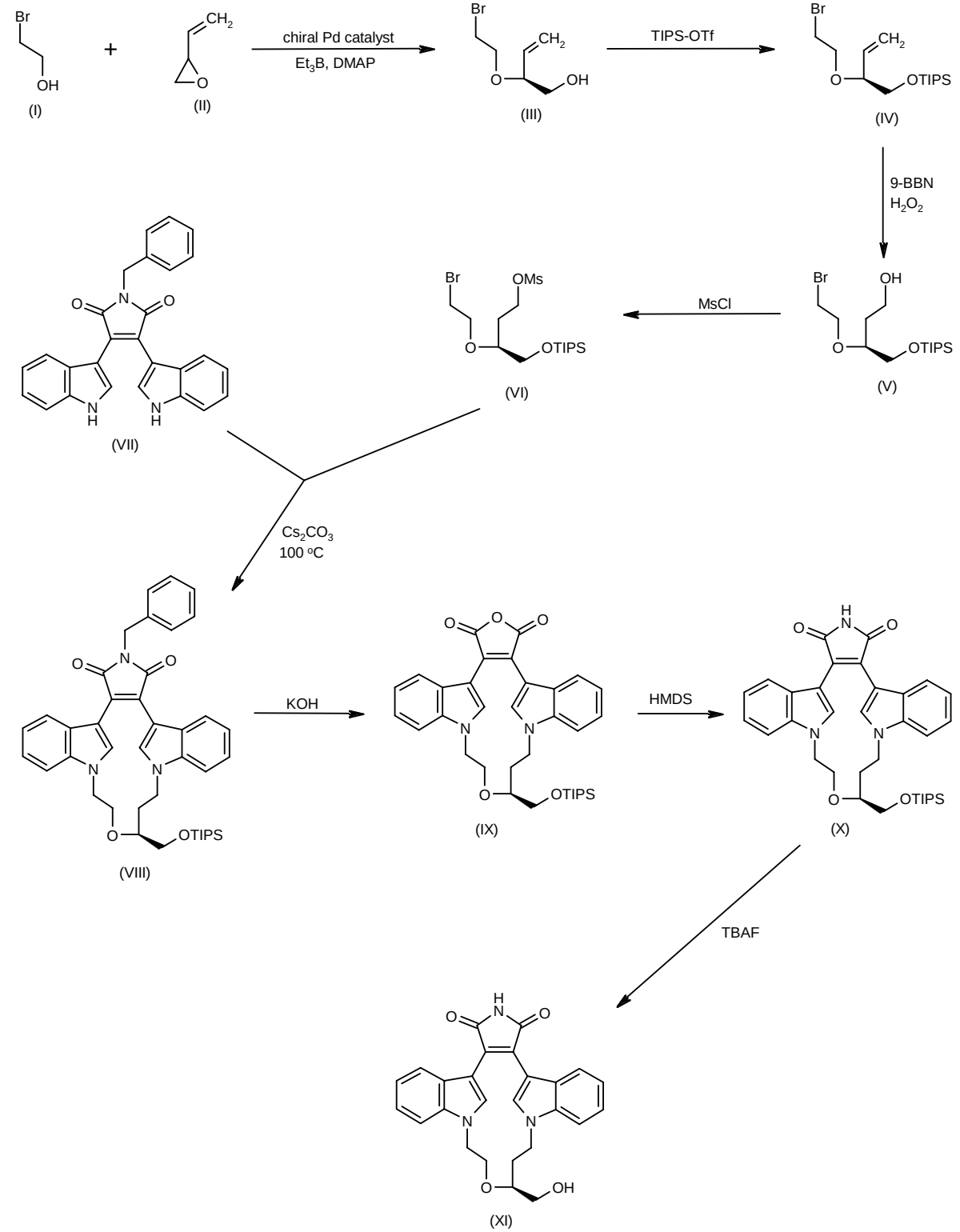
A new synthesis of (9*S*)-9-(hydroxymethyl)-6,7,10,11-tetrahydro-9*H*,18*H*-5,21:12,17-dimethenodibenzo[*e*,*k*]-pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecine-18,20-dione (XI), a key intermediate in the synthesis of LY-333531, has been reported: Enantiocontrolled condensation of 2-bromoethanol (I) with epoxide (II) by means of a chiral Pd catalyst, triethylborane and DMAP in dichloromethane gives the chiral allyl ether (III), which is protected with TIPS-OTf yielding the silyl ether (IV). Hydroboration of ether (IV) with 9-BBN followed by oxidation with H_2O_2 provides the primary alcohol (V), which is mesylated with MsCl to afford the mesylate (VI). Mesylate (VI) is cyclized with the bisindolylmaleimide (VII) by means of Cs_2CO_3 in DMF at 100 °C resulting in the macrocyclic compound (VIII). Hydrolysis of (VIII) with KOH, followed by acidic workup yields the anhydride (IX), which by treatment with HMDS in methanolic DMF provides the maleimide (X). Finally, this compound is desilylated with TBAF to afford the target intermediate (XI) (1). Scheme 1.

The effects of LY-333531 on retinal vascular permeability were recently investigated in diabetic and nondiabetic rats. The study examined the effects of 2 weeks of treatment with LY-333531 given in the chow (0.06%) as primary intervention, *i.e.*, initiated at onset of diabetes, or secondary intervention, *i.e.*, begun 2 weeks after onset of diabetes. Although no effect on retinal vascular permeability was seen in nondiabetic animals treated with LY-333531, both preventive and interventional therapy with the drug normalized the increase in retinal vascular permeability seen in diabetic animals, with 92 ± 50 and 100 ± 32% inhibition, respectively, for primary and secondary intervention. Thus, LY-333531 may have potential therapeutic utility in the treatment of diabetic macular edema and related disorders (2).

Recent preclinical studies have shed light on the molecular mechanism for retinal vascular permeability and have indicated that LY-333531 may be a promising treatment for diabetic retinopathy (3).

As diabetic retinopathy and macular edema are frequently associated with renal dysfunction, the effect of renal insufficiency on the pharmacokinetics of LY-333531 and its active metabolite LY-338522 was examined in humans. The study included 6 patients with end-stage renal disease requiring chronic hemodialysis and 6 healthy volunteers, all administered a single dose of 32 mg of LY-333531. No significant differences in the pharmacokinetics or elimination of either compound were seen between healthy volunteers and those with chronic renal insufficiency, and it was well tolerated in both groups of subjects (4).

Scheme 1: Synthesis of Intermediate (XI)



1. Trost, B.M., Tang, W. *An enantioselective strategy to macrocyclic bisinsolylmaleimides, an efficient formal synthesis of LY 333531*. Org Lett 2001, 3(21): 3409.

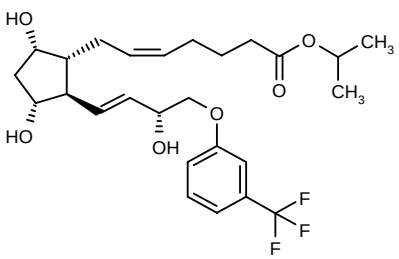
2. Clermont, A.C., Salti, H.I., Goddard, L.E., King, G.L., Aiello, L.P. *Diabetes-induced retinal vascular permeability is both prevented and reversed in vivo by oral administration of PKC-β selective inhibitor LY333531*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 3863.

3. Gardner, T.W., Antonetti, D.A., Wolpert, E.B., Harjaj, N.S. *Preclinical studies of a PKCβ inhibitor for diabetic retinopathy*. 4th Int Symp Ocular Pharmacol Pharm (Feb 28-March 3, Seville) 2002, Addendum.

4. Sathirakul, K., Voelker, J.R., Teng, L.L., Yeo, K., Chan, C. *Chronic renal insufficiency does not affect the pharmacokinetics of LY333531 or that of its active metabolite, compound LY338522*. Clin Pharmacol Ther 2002, 71(2): Abst MPI-24.

Original monograph - Drugs Fut 2000, 25(10): 1017.

Travoprost



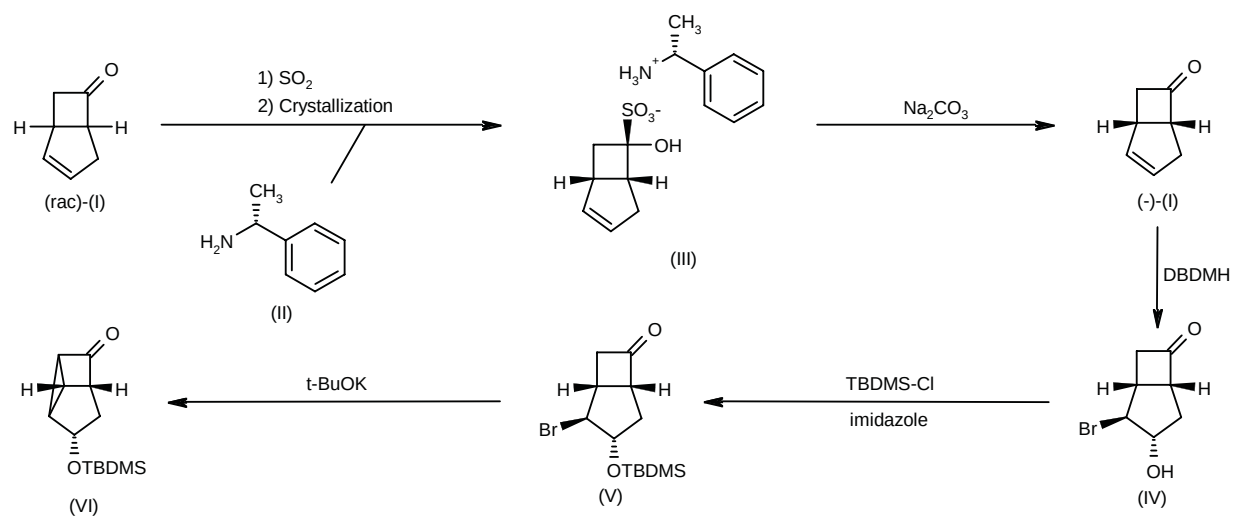
Alcon's prostaglandin PGF2α analogue travoprost (Travatan®), a selective prostanoid FP receptor agonist, has been introduced in the U.K. and the U.S. for reducing elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma who are intolerant of or insufficiently responsive to another intraocular pressure-lowering medication, as monotherapy or adjunctive therapy. The product is supplied as eye drops of 0.004%, or 40 µg/ml (1, 2).

A commercial synthesis of travoprost has been described:

a) Synthesis of the tricyclic ketone intermediate (VI): Optical resolution of racemic bicyclo[3.2.0]hept-2-en-6-one (I) by reaction with SO_2 and (+)-α-methylbenzylamine (II) yields a mixture of diastereomeric salts of the α-hydroxysulfonic acid with the chiral amine (II), which are separated by crystallization. Treatment of the purified salt (III) with aqueous Na_2CO_3 results in the pure enantiomer (–)-(I). Reaction of (–)-(I) with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in acetone/water affords the bromohydrin (IV), which is treated with TBDMS-Cl and imidazole to provide the silyl ether (V). Finally, reaction of the protected bromohydrin (V) with potassium *tert*-butoxide in toluene gives the target tricyclic ketone intermediate (VI). Scheme 2.

b) Synthesis of the alkenyl cuprate (XVII): Enzymatic acylation of the racemic acetylenic alcohol (VII) with vinyl butyrate (VIII) by means of Chirazyme L9 gives a mixture of the ester (*R*)-(IX) and the alcohol (*S*)-(X). Reaction of this mixture with Ms-Cl and TEA yields a mixture of ester (*R*)-(IX) and the mesylate (*S*)-(XI). Treatment of this mixture with butyric acid and TEA results in the acylation of mesylate (*S*)-(XI) with optical inversion, providing pure

Scheme 2: Synthesis of Intermediate (VI)



ester (*R*)-(IX). Enzymatic hydrolysis of (*R*)-(IX) with Chirazyme L2 affords the enantiomerically pure alcohol (*R*)-(XIII). Silylation of alcohol (XIII) with TBDMS-Cl and imidazole gives the silyl ether (XIV), which is iodinated with Cp_2ZrCl_2 and I_2 to yield the iodovinyl derivative (XV). Finally, the reaction of compound (XV) with the lithium cuprate (XVI) –prepared by lithiation of thiophene with BuLi followed by treatment with copper(I) cyanide– affords the alkenyl cuprate (XVII). Scheme 3.

Condensation of the alkenyl cuprate (XVII) with the tricyclic ketone (VI) in toluene provides the bicyclic ketone (XVIII), which is submitted to a Baeyer-Villiger oxidation with peracetic acid to give a mixture of the regioisomeric lactones (XIX) and (XX). The minor and unwanted regioisomer (XIX) is selectively hydrolyzed by treatment with aqueous Na_2CO_3 and separated by crystallization. Reduction of lactone (XX) with DIBAL in toluene gives lactol (XXI), which is submitted to a Wittig condensation with (4-carboxybutyl)triphenylphosphonium bromide and *t*-BuOK in THF, followed by esterification with isopropyl iodide and DBU, yielding a mixture of the monosilylated compounds (XXIII) and (XXIV) due to migration of the silyl group on the cyclopentane ring. Finally, this mixture is deprotected with HCl in isopropanol (3). Scheme 3.

In studies in various animal models, travoprost at doses up to 1 μg demonstrated ocular hypotensive efficacy equal to that of PGF2α isopropyl ester but with a better side effect profile (4).

An *in vivo* study in monkeys with 1 hypertensive and 1 normotensive eye examined the mechanism by which travoprost (0.004% at 9:00 and 17:00 for 2 days and at 9:30 on day 3) reduced IOP. Treatment of hypertensive eyes resulted in a significant reduction in IOP at 2.5 h (25.8 ± 1.2 mmHg *vs.* 33.5 ± 13.4 mmHg) and 16 h (26.3 ± 10.2 mmHg *vs.* 35.4 ± 13.2 mmHg) posttreatment. The IOP of normotensive eyes was also significantly reduced at 2.5 h (19 ± 3.7 mmHg *vs.* 22.8 ± 3.7 mmHg), but not at 16 h posttreatment. Uveoscleral flow (1.0 ± 0.4 μl/min *vs.* 0.4 ± 0.7 μl/min) was significantly increased with treatment in normotensive eyes but only tended to increase in hypertensive eyes (1.1 ± 0.9 μl/min *vs.* 0.9 μl/min). It was concluded that travoprost-induced reductions in IOP are possibly due to enhancement of uveoscleral outflow (5).

The commercial aqueous formulation of travoprost 0.004% ophthalmic solution, Travatan®, was shown to have long-term thermal and photostability. The agent was stable at 25, 40 and 55 ºC for > 18 months, at least 6 months and at least 3 months, respectively. In contrast, after exposure to 40 and 55 ºC, the concentration of latanoprost decreased within 3 months by 72 and 92%, respectively. Good stability was also observed following refrigeration (4 ºC), freezing and thawing (3 alternating cycles of –20 ºC followed by 30 ºC) and accelerated light exposure simulating 2 years of normal room lightening. In contrast, latanoprost was light- and temperature-sensitive (6).

A study comparing the packaging systems for travoprost reported that the novel syndiotactive polypropylene packaging system was optimal, reducing loss of the product to the container. The study also concluded that travoprost solution should not be transferred to γ- or ethylene oxide-sterilized low-density polypropylene containers since 20 and 8% decreases, respectively, in active concentrations of the agent were observed. No changes in active concentrations were observed when travoprost was stored in ethylene oxide-sterilized polypropylene containers (7).

The pharmacokinetics and safety of travoprost 0.004% (1 drop in each eye every morning for 7 days) were reported from 2 studies involving a total of 12 normal subjects, 18 patients with renal impairment and 18 patients with hepatic impairment. Results showed that no dose adjustments are required in individuals with renal or hepatic dysfunction. Treatment was well tolerated. There were no serious adverse events reported, no alterations in vital signs or laboratory parameters and no subjects discontinued the study. Travoprost was rapidly converted to its active free acid metabolite, AL-5848, via esterase hydrolysis. Peak AL-5848 concentrations, reached within 15-30 min of dosing, were 32, 17 and 52 pg/ml, respectively, in normal, renally impaired and hepatically impaired subjects. C_{max} values for AL-5848 did not correlate with creatinine clearance or hepatic impairment. AL-5848 detected in urine was less than 1% of the total ocular dose of travoprost (8).

Healthy volunteers (n=28) received treatment for 5 days with either latanoprost 0.005%, bimatoprost 0.03% or travoprost 0.004% in a study of conjunctival hyperemia. Evaluation by slit lamp biomicroscopy revealed that latanoprost caused less conjunctival hyperemia than bimatoprost or travoprost in these subjects (9). The results of this study and many of those that follow are summarized in Table IV.

Four phase III trials involving a total of 1,679 patients with open-angle glaucoma or ocular hypertension examined the changes in iris pigmentation following ocular treatment with travoprost (0.0015 or 0.004%) or latanoprost (0.005%). Changes in pigmentation were noted in 2.8 and 2.7% of the patients administered the respective travoprost doses as compared to 2.1% of the latanoprost-treated patients. Hazel or green (7-9%) changes in pigmentation were most frequent, while a lower incidence of brown (3%) or blue (< 1%) changes was observed. Changes in pigmentation were first detected in 72.5% of the patients at 6 months or more after the initiation of treatment (10).

An open-label study of travoprost 0.004% was undertaken in 21 patients with open-angle glaucoma. Patients were treated for 2 weeks. Intraocular pressure was significantly reduced by travoprost, with the greatest reduction observed at 8 AM (–11.2 mmHg) and the smallest reduction seen between midnight and 4 AM. At the end of treatment, IOP reductions of > 6 mmHg were seen for up to 3.5 days (11).

A multicenter, randomized, double-blind clinical study in 573 patients with open-angle glaucoma or ocular hypertension was conducted to compare treatment with travoprost 0.0015% once daily, travoprost 0.004% once

Scheme 3: Synthesis of Travoprost

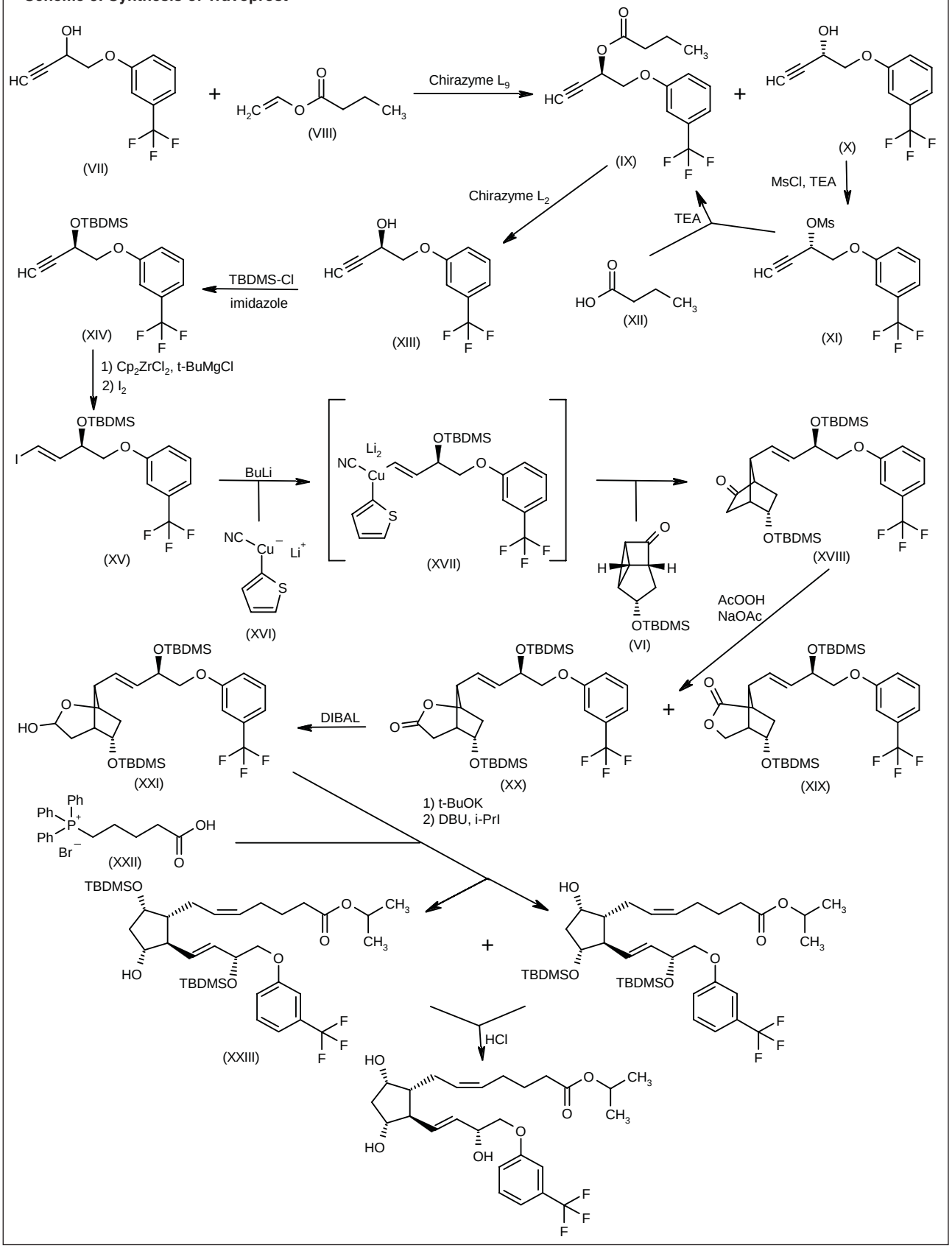


Table IV: Clinical studies of travoprost (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers		Latanoprost, 0.005% x 5 d Bimatoprost, 0.03% x 5 d Travoprost, 0.004% x 5 d	28	Less conjunctival hyperemia was seen with latanoprost than with the other treatments	9
Ocular hypertension, glaucoma	Double-blind, multicenter, pooled/meta-analysis	Travoprost, 0.0015% Travoprost, 0.004% Latanoprost, 0.005%	1679	Travoprost showed a similar rate of iris pigmentation (3%) to latanoprost (5%)	10
Open-angle glaucoma	Open	Travoprost, 0.004% x 2 wk	21	Travoprost reduced intraocular pressure with the greatest reduction @ 8 AM (–11.2 mmHg), which was maintained up to 3.5 days after the last dose	11
Ocular hypertension, open-angle glaucoma	Randomized, double-blind, multicenter	Travoprost, 0.0015% od (evening) x 9 mo Travoprost, 0.004% od (evening) x 9 mo Timolol, 0.5% bid x 9 mo	573	Both travoprost concentrations were safe and well tolerated. Travoprost 0.004% was more effective than timolol in decreasing intraocular pressure in patients with open-angle glaucoma or ocular hypertension but produced iris pigmentation	12, 13
Ocular hypertension, open-angle glaucoma	Randomized, double-blind, multicenter	Travoprost, 0.0015% od (evening) x 12 mo (n=205) Travoprost, 0.004% od (evening) x 12 mo (n=200) Latanoprost, 0.005% od (evening) x 12 mo (n=196) Timolol, 0.5% bid x 12 mo (n=200)	801	Travoprost was safe and well tolerated and more effective than timolol and similar to latanoprost in lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Latanoprost and travoprost produced iris pigmentation changes. In black patients, travoprost 0.004% was significantly better than latanoprost or timolol in reducing intraocular pressure	14-16
Ocular hypertension, open-angle glaucoma	Randomized, double-blind	Study 1: (n=138) Travoprost, 0.0001% od (morning) x 4 wk Travoprost, 0.001% od (morning) x 4 wk Travoprost, 0.002% od (morning) x 4 wk Placebo Study 2: (n=227) Travoprost, 0.001% od (morning) x 4 wk Travoprost, 0.002% od (morning) x 4 wk Travoprost, 0.004% od (morning) x 4 wk Travoprost, 0.006% od (morning) x 4 wk Placebo	365	Travoprost was safe and effective in decreasing intraocular pressure in patients with open-angle glaucoma or ocular hypertension	17
Ocular hypertension, open-angle glaucoma	Randomized, double-blind, multicenter	Travoprost, 0.0015% od (evening) x 6 mo Travoprost, 0.004% od (evening) x 6 mo Timolol, 0.5% bid x 6 mo	605	Both concentrations of travoprost were safe and well tolerated and induced greater reductions in intraocular pressure than timolol in patients with open-angle glaucoma or ocular hypertension	18
Ocular hypertension, open-angle glaucoma	Pooled/meta-analysis	Travoprost, 0.0015% od Travoprost, 0.004% od Latanoprost, 0.005% od Timolol, 0.5% bid		In blacks, significantly greater reductions in intraocular pressure were observed in patients given travoprost as compared to those given latanoprost or timolol; the effect of travoprost 0.004% on intraocular pressure was significantly greater in blacks *versus* non-blacks	22
Ocular hypertension, open-angle glaucoma	Randomized, double-blind, multicenter	Timolol, 0.5% bid x 3 wk → Travoprost, 0.0015% od (evening) + Timolol, 0.5% bid x 6 mo Timolol, 0.5% bid x 3 wk → Travoprost, 0.004% od (evening) + Timolol, 0.5% bid x 6 mo Timolol, 0.5% bid x 3 wk → Vehicle + Timolol, 0.5% bid x 6 mo	426	Travoprost was safe and well tolerated. The addition of travoprost to therapy with timolol led to significant supplementary reductions in intraocular pressure in patients with open-angle glaucoma or ocular hypertension	19, 20

daily or timolol 0.5% b.i.d. Patients received placebo in both eyes in the morning and travoprost in the evening, or timolol both in the morning and in the evening, for up to 9 months. Travoprost was safe and well tolerated and the 0.004% concentration was associated with significantly greater reductions in mean IOP compared to timolol. Significant reductions in IOP were obtained on both concentrations of travoprost, with mean decreases of 7.1-8.3 mmHg on the lower concentration and of 8.0-8.9 mmHg on the higher concentration, versus 6.3-7.9 mmHg on timolol. Little or no hyperemia was seen, and changes in iris pigmentation were observed on travoprost (4-5% of patients) but not timolol (12, 13).

The safety and efficacy of travoprost (0.0015 or 0.004% once daily), latanoprost (0.005% once daily) and timolol (0.5% b.i.d.) were compared in 801 patients with open-angle glaucoma or ocular hypertension over 12 months. The IOP-lowering effects of travoprost appeared to increase over the day, with a mean IOP reduction at the higher concentration 0.8 mmHg greater than that for latanoprost at 4:00 PM. Travoprost 0.004% also appeared to be superior to timolol, with a mean IOP of 17.7-19.1 mmHg on the former versus 19.4-20.3 mmHg on the latter. Little hyperemia was observed and changes in iris pigmentation were detected in 3.1% of the travoprost patients and 5.2% of the latanoprost patients. Overall, the investigators concluded that travoprost 0.004% is at least equivalent to latanoprost 0.005% and superior to timolol 0.5% in reducing IOP in patients with ocular hypertension or open-angle glaucoma. The higher concentration of travoprost was significantly superior to latanoprost and timolol in reducing IOP in black patients (14-16).

The results from several clinical studies provide support for the use of travoprost as primary therapy. Two randomized, placebo-controlled, parallel trials in patients with ocular hypertension or open-angle glaucoma examined the safety and efficacy of different concentrations of the drug given in the morning or the evening. A study in 138 patients compared doses of 0.0001, 0.001 and 0.002% to vehicle, both given at 8:00 AM, and another trial compared travoprost at 0.001, 0.002, 0.004 or 0.006% and vehicle, both given at 8:00 PM. All concentrations of travoprost were well tolerated with minimal ocular hyperemia. Similar reductions in IOP were obtained with morning or evening dosing. The concentration of 0.004% was the most effective, producing IOP reductions of 6.8-8.2 mmHg (17).

Patients (n=605) with open-angle glaucoma or ocular hypertension were randomized to travoprost 0.0015 or 0.004% once daily or timolol 0.5% b.i.d. in a multicenter, double-blind study lasting 6 months. Greater reductions in IOP were obtained on both doses of travoprost compared to timolol, and more patients receiving travoprost had clinically relevant responses (80.3-87.3% *vs.* 64.8%) (18).

Two concentrations of travoprost were evaluated as adjunctive therapy in patients with open-angle glaucoma or ocular hypertension who were taking timolol 0.5% b.i.d. During the 6-month, multicenter, randomized, double-blind study, patients received travoprost 0.0015 or 0.004% once daily or vehicle in addition to timolol. The addition of travoprost led to increased reductions in IOP and the combination of timolol and travoprost 0.004% was the most effective regimen (19, 20).

In a study including 79 patients with open-angle glaucoma or ocular hypertension, subjects received travoprost 0.0015% once daily for 4 weeks, after which they were randomized to travoprost 0.0015% plus brimonidine b.i.d., travoprost 0.0015% b.i.d. or placebo for another 6 weeks. The combination of travoprost and brimonidine was superior to travoprost alone in reducing IOP. Once-daily dosing with travoprost was found to be just as effective as twice-daily dosing in lowering IOP (21).

Researchers analyzed data pooled from studies in patients with open-angle glaucoma and ocular hypertension to compare treatment with travoprost 0.0015 and 0.004%, timolol 0.5% and latanoprost 0.005% in blacks and non-blacks. In black patients, significantly greater intraocular pressure-lowering efficacy was seen with travoprost than with the other treatments. Travoprost 0.004% was also more effective in blacks than in non-blacks (22).

Combinations of antiinflammatory agents and prostaglandin F agonists have been claimed for the treatment of glaucoma and ocular hypertension (23).

1. *Travatan introduced in the U.K.* DailyDrugNews.com (Daily Essentials) Jan 21, 2002.

2. *Travatan launch quickly follows first approval in U.S.* DailyDrugNews.com (Daily Essentials) April 4, 2001.

3. Boulton, L.T., Brick, D., Fox, M.E. et al. *Synthesis of the potent antiglaucoma agent, travoprost*. Org Process Res Dev 2002, 6(2): 138.

4. Hellberg, M.R., Sallee, V.L., McLaughlin, M.A., Sharif, N.A., Desantis, L., Dean, T.R., Zinke, P.W. *Preclinical efficacy of travoprost, a potent and selective FP prostaglandin receptor agonist*. J Ocular Pharmacol Ther 2001, 17(5): 421.

5. Toris, C.B., Zhan, G.-L., Camras, C.B., McLaughlin, M.A. *Travoprost increases uveoscleral outflow in monkeys*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 1970.

6. Weiner, A.L., Kabra, B., Sternitzke, K. et al. *Travatan® is stable to extremes of temperature and light exposure*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 2307.

7. Hellberg, M.R., Airy, S., Chiou, J.S., Clifford, J., Gan, O., Jani, R., Kabra, B., McCune, B., Nguyen, H., Weiner, A. *Unique polypropylene packaging system for Travatan® minimizes loss to the container*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 2318.

8. Robin, A.L., Faulkner, R., Curtis, M., Patil, S., McCarty, G., Clifford, W., Dahlin, D.C. *Safety and pharmacokinetics of travoprost a potent prostaglandin F (FP) receptor agonist, in patients with renal and hepatic impairment*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4106.

9. Albritton, A.E., Stewart, J.A., Leech, J.N., Jackson, A.L., Stewart, W.C. *Conjunctival hyperemia with latanoprost, travoprost and bimatoprost*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 4112.

10. Schenker, H.I., Williams, L., Goode, S.M., Gross, R.D., Mathis, J.A., Mallick, S., Dickerson, J.E., Andrew, R., Silver, L., Landry, T. *Iris pigmentation changes following treatment with travoprost or latanoprost in patients with open-angle glaucoma or ocular hypertension*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 3431.

11. Dubiner, H.B. *Travatan administration results in effective diurnal reduction in intraocular pressure over 36 hours and lower pressures up to 3.5 days without further dosing*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 1066.

12. Goldberg, I., Cunha-Vaz, J., Jakobsen, J.-E. et al. *Comparison of topical travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension*. J Glaucoma 2001, 10(5): 414.

13. Orgul, S. *The safety and IOP lowering-efficacy of a new topical ocular prostaglandin analogue, travoprost (0.0015% and 0.004%), compared to timolol 0.5% in a nine-month multicenter study*. 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 26.

14. Netland, P.A., Landry, T., Sullivan, E.K. et al. *Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension*. Am J Ophthalmol 2001, 132(4): 472.

15. Netland, P.A. *Comparison of the safety and efficacy of travoprost, latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension*. 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 26.

16. Netland, P.A., Landry, T., Silver, L.H., Sullivan, E.K., Andrew, R., Weiner, A.L., Bergamini, M.V.W., Robertson, S.M., Mallick, S., Davis, A.A. *IOP-lowering efficacy and safety of travoprost compared to latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

17. Dean, T., Garadi, R., Landry, T., Silver, L., Turner, F.D. *Dose response studies with Travatan™ a new prostaglandin analog in patients with ocular hypertension or open-angle glaucoma*. 3rd Int Glaucoma Symp (March 21-25, Prague) 2001, 26.

18. Whitson, J.T., Ratliff, M., Fellman, R.L., Sullivan, E.K., Turner, F.D., Silver, L.H., Weiner, A.L. *Travoprost, a new prostaglandin analogue, is superior to timolol in lowering IOP in patients with open-angle glaucoma or ocular hypertension*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

19. Orengo-Nania, S., Landry, T., Von Tress, M. et al. *Evaluation of travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%*. Am J Ophthalmol 2001, 132(6): 860.

20. Orengo-Nania, S.D., Landry, T., Von Tress, M., Silver, L.H., Dickerson, J., Weiner, A.L., Davis, A.A. *Travoprost significantly decreased IOP in patients with open-angle glaucoma or ocular hypertension when used adjunctively with timolol*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

21. Kothe, A.C., Ripp, K.M., Sharma, V., Von Tress, M.S., DeSantis, L., Bergamini, M.V.W., Robertson, S.M. *IOP-lowering efficacy and safety of travoprost BID vs. concomitantly dosed travoprost and brimonidine BID vs. placebo BID in patients with open-angle glaucoma or ocular hypertension*. Invest Ophthalmol Visual Sci 2000, 41(4): Abst 1483.

22. Robertson, S.M., Sullivan, E.K., Silver, L.H., Turner, F.D., Bergamini, M.V.W., Krueger, S., Weiner, A.L., Davis, A.A. *Differences between black and non-black patients with open-angle glaucoma or ocular hypertension in IOP-lowering response to travoprost*. Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

23. Hellberg, M.R. and Nixon, J.C. (Alcon Laboratories, Inc.) *Use of non-steroidal anti-inflammatory agents in combination with cpds. that have FP prostaglandin agonist activity to treat glaucoma and ocular hypertension*. US 6342524.

Original monograph - Drugs Fut 2000, 25(1): 41.