Treatments on the Horizon

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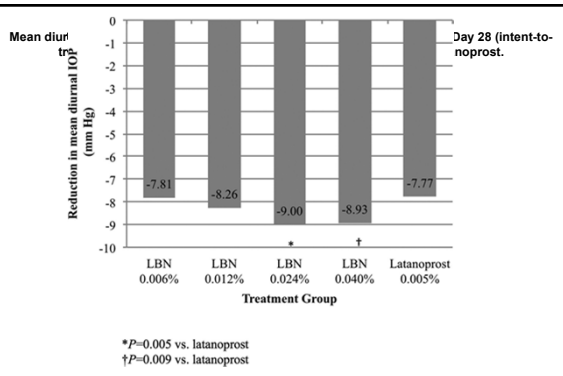
Latanoprostene bunod (Vesneo)

- Valeant (B+L)
- Nitrous oxide-donating prostaglandin F2-alpha analogue that reduces IOP
- When exposed to ubiquitous esterases in the ocular environment, is cleaved into latanoprost acid, a prostaglandin F2α receptor agonist, and butanediol mononitrate, a nitric oxide (NO)-donating moiety

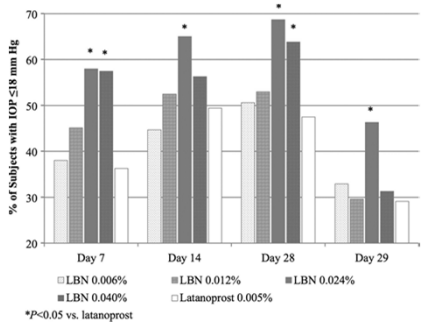
LBN

- NO donors relax the trabecular meshwork (TM) and increase aqueous humour outflow.
- They activate the large conductance calcium-activated potassium channel, or BK_{Ca} ion channel, involved in reducing TM cell volume.
- NO donors may trigger, among other things, reduction of actomyosin contractility and disassembly of the actin cytoskeleton and cell adhesion system in the cells of the conventional outflow pathway, causing cell shape changes and overall relaxation of the TM and inner wall of Schlemm's canal leading to decreased resistance to aqueous humour outflow
- Increasing the conventional outflow of aqueous through the TM results in better IOP lowering than that of latanoprost alone.



Robert N Weinreb et al. Br J Ophthalmol 2015;99:738-745

Proportion of subjects with intraocular pressure (IOP) ≤18 mm Hg at follow-up visits (intent-to-treat population). *p<0.05 versus latanoprost.



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A Randomized, controlled comparison of latanoprostene bunod and latanoprost 0.005%: Voyager Study

System/organ class preferred term	LBN 0.006% (n=82)	LBN 0.012% (n=84)	LBN 0.024% (n=83)	LBN 0.040% (n=81)	Latanoprost 0.005% (n=82)
No of subjects with ≥1 TEAE	20 (24.4)	18 (21.4)	20 (24.1)	23 (28.4)	10 (12.2)
No of subjects with ≥1 treatment-related TEAE	17 (20.7)	18 (21.4)	16 (19.3)	19 (23.5)	10 (12.2)
Eye disorders					
Ocular hyperaemia	1 (1.2)	5 (6.0)	2 (2.4)	4 (4.9)	7 (8.5)
Conjunctival hyperaemia	1 (1.2)	3 (3.6)	4 (4.8)	3 (3.7)	0
Eye irritation	1 (1.2)	2 (2.4)	3 (3.6)	5 (6.2)	0
Punctate keratitis	1 (1.2)	1 (1.2)	2 (2.4)	2 (2.5)	1 (1.2)
Dry eye	1 (1.2)	0	2 (2.4)	0	0
Abnormal sensation in eye	2 (2.4)	0	0	0	0
Eye pain	0	0	0	2 (2.5)	0
Photophobia	0	0	2 (2.4)	0	0
Administration site conditions					
Instillation site pain	12 (14.6)	14 (16.7)	10 (12)	14 (17.3)	5 (6.1)
Instillation site pruritus	0	0	0	2 (2.5)	0

- The pivotal Phase 3 program includes two separate randomized, multicenter, double-masked, parallel-group clinical studies, APOLLO and LUNAR, designed to compare the efficacy and safety of VESNEO™ administered once daily (QD) against timolol maleate 0.5% administered twice daily (BID) in lowering IOP in patients with open-angle glaucoma or ocular hypertension.
- The primary endpoint of both studies, which include a combined total of 840 patients, was the reduction in mean IOP measured at specified time points during three months of treatment.
- The collection of patient safety data for a total of up to 12 months is still ongoing.

- The primary endpoint of non-inferiority to timolol maleate 0.5% was achieved in both Phase 3 studies.
- VESNEO™ showed a reduction in mean IOP of 7.5 to 9.1 mmHg from baseline between 2 and 12 weeks of treatment in the two Phase 3 studies.
- This IOP effect was statistically superior ($p < 0.05$) to timolol in both studies.
- VESNEO™ also showed positive results on a number of secondary endpoints.
- There were no significant safety findings in either study.

Rhopressa™

- Aerie Pharmacueticals
- Once-daily
- Inhibits Rho Kinase (ROCK)
- Inhibits norepinephrine transporter (NET)
- Novel biochemical targets for lowering IOP

Mechanisms of Action for Rhopressa

- Rhopressa™ reduces IOP via three separate MOAs:
  1. Through ROCK inhibition, it increases fluid outflow through the trabecular meshwork which accounts for approximately 80% of fluid drainage from the eye
  2. Reduces episcleral venous pressure: the pressure of the blood in the episcleral veins of the eye where eye fluid drains into the bloodstream
  3. Through norepinephrine transporter inhibition, it reduces the production of aqueous.

Rho Kinase Inhibitors

- These selective agents work by relaxing the trabecular meshwork through inhibition of the actin cytoskeleton contractile tone of smooth muscle.
- This results in increased aqueous outflow directly through the trabecular meshwork, achieving lower intraocular pressures in a range similar to prostaglandins.
- There are also animal studies indicating that ROCK inhibitors may improve blood flow to the optic nerve, increase ganglion cell survival, and reduce bleb scarring in glaucoma surgery

Phase 2b Clinical Trial

- Once-daily Rhopressa™ demonstrated mean IOP reductions of 5.7 and 6.2 mmHg on days 28 and 14, respectively.
- What doe this mean clinically?
  - EMGT demonstrated a sustained 5 mmHg reduction in IOP reduces risk of disease progression by approximately 50%

Ocular Hypotensive Effect of the Rho Kinase Inhibitor AR-12286 in Patients With Glaucoma and Ocular Hypertension

ROBERT D. WILLIAMS, GARY D. NOVACK, THOMAS VAN HAARLEM, AND CASEY KOPCZYNSKI, ON BEHALF OF AR-12286 PHASE 2A STUDY GROUP

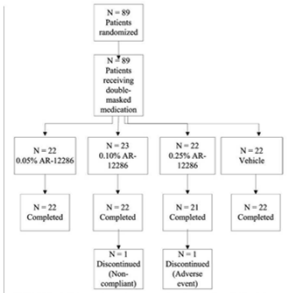


FIGURE 1. Disposition of patients in the study of Rho kinase inhibitor AR-12286 in patients with elevated intraocular pressure.

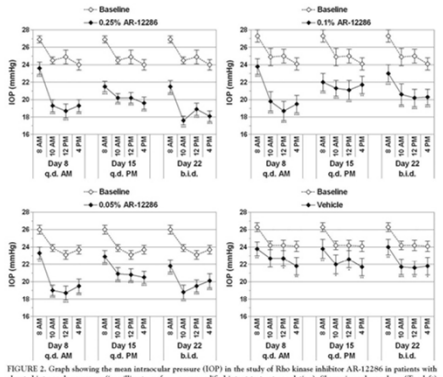


FIGURE 2. Graph showing the mean intraocular pressure (IOP) in the study of Rho kinase inhibitor AR-12286 in patients with elevated intraocular pressure (in millimeters of mercury; modified intent-to-treat population). Shown in each panel are (Top left) 0.25% AR-12286, (Top right) 0.1% AR-12286, (Bottom left) 0.05% AR-12286, and (Bottom right) vehicle, along with the respective baseline (nonmedicated) diurnal observations. b.i.d. = twice daily; q.d. = once-daily.

Phase 2 Randomized Clinical Study of a Rho Kinase Inhibitor, K-115, in Primary Open-Angle Glaucoma and Ocular Hypertension

HIDENOBU TANIHARA, TOSHIHIRO INOUE, TETSUYA YAMAMOTO, YASUAKI KUWAYAMA, HARUKI ABE, AND MAKOTO ARAIE, FOR THE K-115 CLINICAL STUDY GROUP

• PURPOSE: To identify the optimal dose of a novel Rho kinase inhibitor, K-115, by assessing dose dependency of the intraocular pressure (IOP)-lowering effects and the safety in patients with primary open-angle glaucoma or ocular hypertension.
• DESIGNS: Multicenter, prospective, randomized, placebo-controlled, double-masked, parallel group comparison clinical study.
• METHODS: After appropriate washout periods, 210 patients with primary open-angle glaucoma or ocular hypertension were subdivided into 4 groups and were treated with K-115 in concentrations of 0.1%, 0.2%, and 0.4% or placebo twice daily for 8 weeks. The dose response of IOP reduction and the incidence of adverse events by K-115 or placebo were investigated.
• RESULTS: The mean baseline IOP was between 23.0 and 23.4 mm Hg. The mean IOP reductions of the last visit from baseline were −2.2 mm Hg, −3.4 mm
• CONCLUSIONS: On the basis of this dose-response study, K-115 0.4% has been selected to be the optimal dose and has the potential to be a promising new agent for glaucoma to control 24-hour IOP by twice-daily dosing. (Am J Ophthalmol 2013;156:731–736.

GLAUCOMA IS A PROGRESSIVE OPTIC NEUROPATHY that is characterized by a specific pattern in visual field defects and structural changes in the optic nerve head.[1,2] To date, numerous drugs to reduce intraocular pressure (IOP) have been developed and used to treat glaucoma in clinical practice. In addition to currently used antiglaucoma medications, some candidate drugs are under development.[3] Rho kinase inhibitors are one of those candidate drug classes to reduce IOP in glaucomatous patients. Accumulating experimental evidence suggests

Am J Ophthalmol. 2013 Oct;156(4):731-736.

Phase 3 Registration Trials for Rhopressa

Rocket 1 Study

- Compared 182 Rhopressa™ qd patients to 188 timolol bid patients
- Baseline IOP 20-27mmHg
- Results showed loss of efficacy at week 6 and on day 90 in ~20% of Rhopressa arm
- Hyperemia in 35% of patients
  - 80% reported it as “mild”

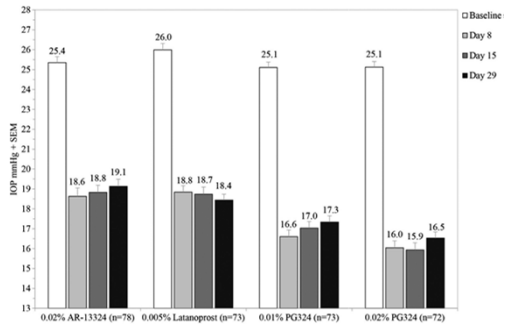
Rocket 2 Study

- Baseline IOP 20-25mmHg
  - Why?
- In Rocket 1, this range of IOP had better IOP lowering success that those above 25.
- Results of Rocket 2 not yet available

Roclatan™

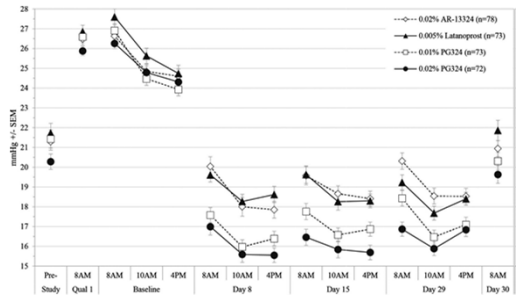
- Aerie Pharmaceuticals
- Single-drop, fixed combination with “quadruple-action”
  - Rhopressa
    - Triple MOA
      - Increased outflow through TM
      - Decreased episcleral venous pressure
      - Decreased aqueous production
  - Latanoprost
    - Primary MOA
      - Increase uveoscleral outflow

Mean±SEM. diurnal intraocular pressure (mm Hg, modified Intent to Treat analysis population).



Richard A Lewis et al. Br J Ophthalmol doi:10.1136/bjophthalmol-2015-306778

Mean±SEM.



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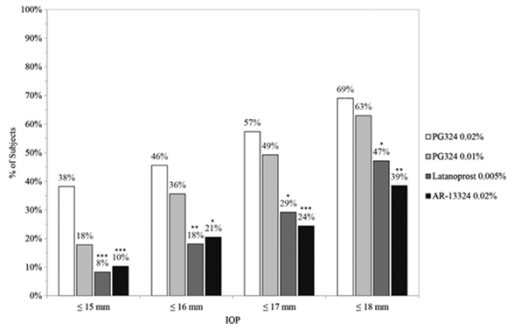
Proportion of patients with mean diurnal intraocular pressure reduced to ≤15, 16, 17 or 18 mm Hg at day 29.



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Fixed-dose combination of AR-13324 and latanoprost: a double-masked, 28-day, randomised, controlled study in patients with open-angle glaucoma or ocular hypertension

Table 2

Number and percentage of patients with treatment-emergent adverse events by treatment group, system organ class and preferred term (safety population): most frequent (≥5% in any group)

System organ class (SOC) Preferred term (PT)	PG324 0.01% (N=73) n (%)	PG324 0.02% (N=73) n (%)	Latanoprost 0.005% (N=73) n (%)	AR-13324 0.02% (N=78) n (%)	All patients (N=297) n (%)	p Value†
Any treatment-emergent adverse events	47 (64.4)	55 (75.3)	24 (32.9)	60 (76.9)	186 (62.6)	<0.0001***
Eye disorders	35 (47.9)	43 (58.9)	19 (26.0)	45 (57.7)	142 (47.8)	0.0001***
Conjunctival hyperaemia	30 (41.1)	29 (39.7)	10 (13.7)	31 (39.7)	100 (33.7)	0.0003***
Conjunctival haemorrhage	1 (1.4)	5 (6.8)	0	5 (6.4)	11 (3.7)	0.0368*
Lacrimation increased	1 (1.4)	4 (5.5)	1 (1.4)	5 (6.4)	11 (3.7)	0.2576
Eye pruritus	2 (2.7)	4 (5.5)	2 (2.7)	2 (2.6)	10 (3.4)	0.8293
General disorders and administration site conditions	18 (24.7)	22 (30.1)	3 (4.1)	20 (25.6)	63 (21.2)	<0.0001***
Instillation site erythema	12 (16.4)	14 (19.2)	1 (1.4)	17 (21.8)	44 (14.8)	0.0003***
Instillation site pain	5 (6.8)	8 (11.0)	2 (2.7)	4 (5.1)	19 (6.4)	0.2410
Infections and infestations	4 (5.5)	2 (2.7)	4 (5.5)	4 (5.1)	14 (4.7)	0.8857
Investigations	3 (4.1)	2 (2.7)	2 (2.7)	3 (3.8)	10 (3.4)	>0.9999

Roclatan™

- Phase 2b Clinical Trial
  - 297 patients
  - Mean baseline=25.1mmHg
  - Lowered mean IOP by 34% to mean 16.5mmHg
  - Roclatan mean IOP reduction was ~2mmHg greater than the IOP reduction with latanoprost alone.
- Phase 3 trial (Mercury 1) expected to begin end 2015.

Bimatoprost SR

- Allergan Pharmaceuticals
- Sustained release implant
- biodegradable, preservative-free implant preloaded into a single use applicator
- Bimatoprost SR is placed in the anterior chamber
- the drug is slowly released for about 3 to 4 months and the implant slowly dissolves in about 12 to 15 months.
- As of April, 2014, a total of 87 patients had received a single administration and of those, 12 had received a repeat administration of Bimatoprost SR on the 192024-041D study.

Bimatoprost SR

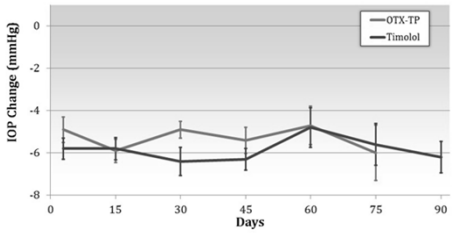
- Phase 2
  - Patients received implant in one eye and the fellow eye continued topical administration of bimatoprost 0.01% daily.
  - Results: no difference in efficacy
- Phase 3 trial currently underway
- Clinical Advantage: Do not need to rely on patients to self administer

Sustained-release travoprost (OTX-TP)

- Ocular Therapuetics
- Intracanalicular depot composed of polyethylene glycol hydrogel and drug containing micro-particles
  - Sustain release travoprost punctal plug
- Phase 2 clinical trials underway

OTX-TP Phase 2a Study Results

OTX-TP Comparison to Timolol and Placebo Plug
Mean 8:00 AM Reduction from Baseline



Trabodenoson

- Inoteck
- a potent and highly selective adenosine mimetic acting only at the A1 receptor subtype
- In Phase 2 trials, treatment with trabodenoson was shown to significantly reduce IOP in glaucoma and OHT patients and was well-tolerated.
- After 28 days of trabodenoson monotherapy, the IOP-lowering efficacy achieved was in the range of the market leading prostaglandins (e.g., latanoprost).

- Stimulation of the A1 adenosine receptor in the trabecular meshwork causes a meaningful improvement in metabolic activity there which helps to clear the pathway for the aqueous humor to flow out of the eye (lowering IOP).
- This metabolic activity takes the form of an increase or upregulation of proteases - such as Protease A or MMP-2 - that digest and remove accumulated proteins which can block the healthy flow of aqueous humor out of an eye with glaucoma.
- This metabolic activity is a naturally occurring process that is enhanced by treatment with trabodenoson.
- We believe this process does not radically change the way that the trabecular meshwork controls eye pressure, but rather restores the natural process of pressure control in this region, which is different from other glaucoma therapies, which decrease aqueous humor production

MATRx-1 (trabodenoson)

- MAT**Rx**-1 is a Phase 3 randomized, double-masked, placebo-controlled trial of trabodenoson in approximately 335 patients diagnosed with primary open-angle glaucoma (POAG) or ocular hypertension (OHT).
- Goal:
  - Assess the efficacy, safety and tolerability of trabodenoson over three months of treatment.
  - The primary endpoint will be the reduction of intraocular pressure (IOP) as compared to the placebo treatment arm. In addition, the study will contain a timolol 0.5% arm to validate the sensitivity of the patient population.
  - Intraocular pressure (IOP) will be measured at four timepoints during the day, 8AM, 10AM, 12PM, and 4PM on days 14, 28, 42, and 84. Three doses of trabodenoson will be administered: 1000 mcg once daily, 1500 mcg twice daily, and 2000 mcg once daily.
    - These doses were selected to assess efficacy in intraocular pressure lowering, while maintaining the tolerability and safety profile observed in Phase 2 trials.
- The trial will enroll patients with IOP greater than or equal to 24 mm Hg and less than or equal to 34 mm Hg,

Product Name	Company	Type of Drug	MOA	Status
Latanoprost bunod (Vesneo)	Valeant (B+L)	Nitric oxide-donating PG F2-α analog	Increases outflow through TM	NDA Submitted to FDA
Rhopressa	Aerie	Inhibit Rho kinase and norepinephrine transported	Increase TM outflow; reduce episcleral venous pressure; reduce production	Phase 3
Roclatan	Aerie	Combo Rhopressa + latanoprost	Rhopressa MOA and increased uveoscleral outflow	Phase 3
Bimatoprost SR	Allergan	Sustained release prostinoid implant	Increase uveoscleral outflow	Phase 3
Trabodenoson	Inotek	Selective adenosine mimetic acting at A1 receptor subtype	Increase TM outflow by increase uptake of Proteases	Phase 3