Update on Glaucoma Therapy and Delivery

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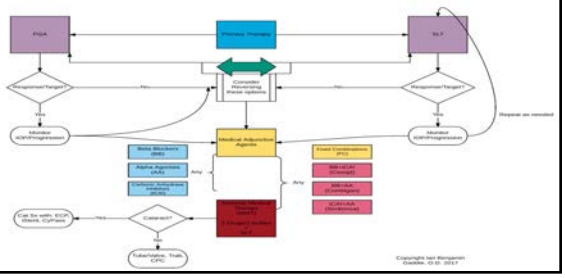
Disclosures

- Allergan-C
- Bausch and Lomb-C
- Tarsus-C,SH

- C=Consultant; SH=Shareholder; R=Research funding;

2

Today's Treatment Algorithms



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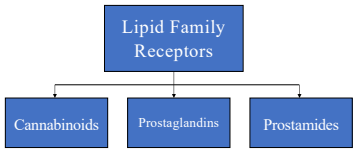
Lipid Family Receptors



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Prostaglandin analogues-Branded

- Xalatan (latanoprost 0.005%) – Prostaglandin Analogue
- Travatan-Z (travaprost 0.004%) – Prostaglandin Analogue
- Lumigan (bimatoprost 0.03%) – Prostamide (ocular hypotensive lipid)
- Zioptan PF (tafluprost 0.015%)- Prostaglandin
- IYUZEH Non preserved, Thea

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Latanoprost

- Acts as a selective F2α agonist (FP receptor agonist)
- FP receptors have been identified in ciliary muscle, ciliary epithelium and sclera
- Enhances outflow through the uveoscleral pathway by
  - upregulating matrix metalloproteinase expression
  - remodeling of the ciliary muscle's extracellular matrix resulting in increased extracellular remodeling, increased permeability, decreased outflow resistance

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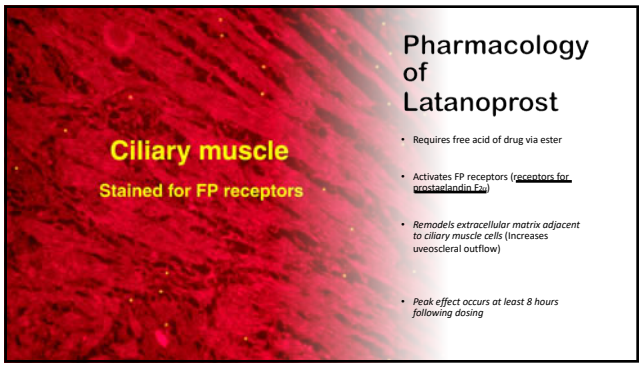
Ciliary muscle
Stained for FP receptors
Pharmacology of Latanoprost
• Requires free acid of drug via ester
• Activates FP receptors (receptors for prostaglandin F2α)
• Remodels extracellular matrix adjacent to ciliary muscle cells (Increases uveoscleral outflow)
• Peak effect occurs at least 8 hours following dosing

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latanoprost ophthalmic solution

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SANDOZ

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NDC 49884-044-53
5 mL
Travoprost Ophthalmic Solution USP, 0.004%
Rx only

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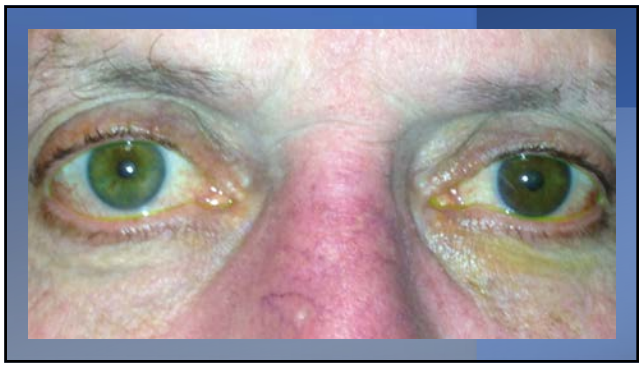

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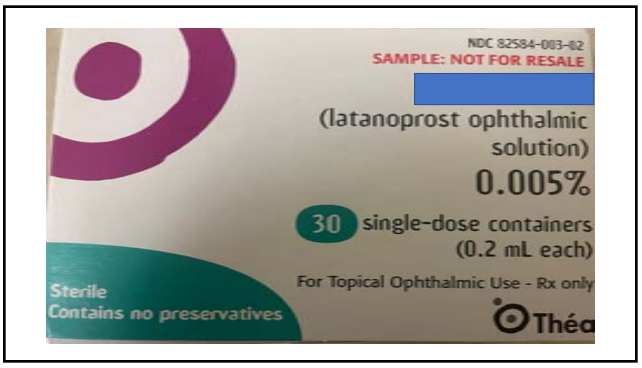
NDC 82584-003-02
SAMPLE: NOT FOR RESALE
(latanoprost ophthalmic solution)
0.005%
30 single-dose containers
(0.2 mL each)
For Topical Ophthalmic Use - Rx only
Sterile
Contains no preservatives
Théa

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Latanoprostene Bunod 0.024%(LBN)

- First nitric oxide donating compound investigated for topical ophthalmic use
- Novel nitric oxide donating prostaglandin F2α receptor agonist
- Received FDA approval in 2017
- The data has demonstrated significant IOP lowering and a favorable safety profile
- Dual mechanism of action

Hoy SM. Latanoprostene Bunod Ophthalmic Solution 0.024%: A Review in Open-Angle Glaucoma and Ocular Hypertension (published correction appears in Drugs. 2018;78(8):857). *Drugs*. 2018;78(7):773-780. Fingeret M, Gaddie IB, Bloomenstein M. Latanoprostene bunod ophthalmic solution 0.024%: a new treatment option for open-angle glaucoma and ocular hypertension. Clin Exp Optom. 2019;102(6):541-550.

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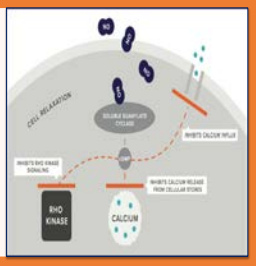
Nitric Oxide (NO)

Gas that can freely diffuse across plasma membranes

Signals via second messenger cGMP with inhibition of 3 key contractile signals (calcium influx, intracellular calcium stores and Rhokinase activity)

Relaxes vascular smooth muscle cells → Vasodilation

Exerts relaxing effect on highly contractile TM cells causing cytoskeleton relaxation and enhanced outflow via TM/Schlemm canal



Wareham LK, Buys ES, Sappington RM. The nitric oxide-guanylate cyclase pathway and glaucoma. *Nitric Oxide*. 2018;77:75-87.

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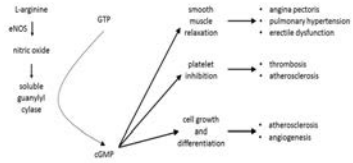
NO plays key roles in both health and disease throughout the body, including the eye



Adapted from Murad F. NEJM 2006;355:2003-11.

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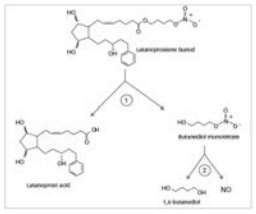
LBN

LBN is hydrolyzed by endogenous corneal esterases to

- Latanoprost acid: the active compound of latanoprost
- Butanediol mononitrate: a NO donating moiety



Hoy SM. Latanoprostene Bunod Ophthalmic Solution 0.024%: A Review in Open-Angle Glaucoma and Ocular Hypertension (published correction appears in Drugs. 2018;78(8):857). *Drugs*. 2018;78(7):773-780. Fingeret M, Gaddie IB, Bloomenstein M. Latanoprostene Bunod ophthalmic solution 0.024%: a new treatment option for open-angle glaucoma and ocular hypertension. Clin Exp Optom. 2019;102(6):541-550.

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Greater IOP reductions than Xalatan[1]

JOYAGER study design: Phase 2, randomized, investigator-masked, parallel-group, dose-ranging study vs Xalatan in patients with open-angle glaucoma or ocular hypertension (N=413) to determine the optimal drug concentration of VYZULTA in reducing IOP.[3]

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Most Common Ocular Adverse Reactions in APOLLO and LUNAR*[1,2]

Adverse Reactions	LBN (n=811)	TIMOLOL 0.05% (n=271)
Conjunctival Hyperemia	5.9%	1.1%
Eye Irritation	4.6%	2.6%
Eye Pain	3.6%	2.2%
Ocular Hyperemia	2.0%	0.7%
Instillation Site Pain	2.0%	1.8%

*Pooled data from all tested time points in the APOLLO and LUNAR studies: ocular adverse reactions occurring in ≥2% of study eyes

Less than 1% discontinuation due to ocular adverse reactions[1]

- Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions
- These included ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis, and foreign body sensation

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Rho Kinase Inhibitors

Netarsudil ophthalmic solution 0.02%

Rho kinase drug discovery program initiated in 2006

Goal to identify an effective and well-tolerated ROCK inhibitor with a durable IOP lowering effect.

Most effective compounds were ROCK/NET inhibitors (norepinephrine transporter)

In addition to trabecular outflow, animal and donor eye studies showed a decrease in aqueous humor production and episcleral venous pressure

The decrease in EVP is felt to be related to NET inhibition.

Moshirfar M, Parker L, Birdsong OC, et al. Use of Rho kinase Inhibitors in Ophthalmology: A Review of the Literature. *Med Hypothesis Discov Innov Ophthalmol.* 2018;7(3):101-111.

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Netarsudil

Netarsudil is a ROCK/NET inhibitor

In the trabecular meshwork ROCK activation leads to:
Actomyosin contraction
Extracellular matrix production
Increase in cell stiffness

Inhibitors of ROCK in cultured TM and Schlemm canal cells
Reduce cell contraction
Decrease expression of fibrosis-related proteins
Reduce cell stiffness

Tanna AP, Johnson M. Rho Kinase Inhibitors as a Novel Treatment for Glaucoma and Ocular Hypertension Ophthalmology 2018;125:1741-1756

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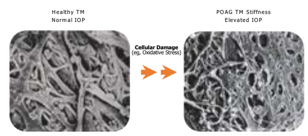
Disease at the TM is Responsible for Elevated IOP in Glaucoma[1,2]



Scanning electron microscopy (2000x) was used to examine human TM under physiological conditions and in patients with POAG. 2 POAG, primary open-angle glaucoma; TM, trabecular meshwork.

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1. He et al. *Invest Ophthalmol Vis Sci.* 2008;49:1447.
2. Saccà et al. *J Cell Physiol.* 2015;230:510.

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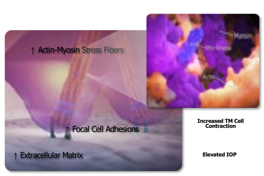
Rho-kinase Increases TM Contraction and Elevates IOP



1. Rao et al. *Exp Eye Res.* 2017;158:23.

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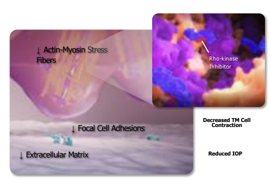
Rho-kinase Inhibitors Relax TM Cells and Reduce Fibrosis[1,2]



1. Rao et al. *Exp Eye Res.* 2017;158:23.

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Preferred Term (with Incidence ≥5% (Pooled Safety Population)	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Eye Disorders		
Conjunctival Hyperemia	456 (54.4)	87 (10.4)
Cornea Verticillata (corneal deposits/corneal opacity)	175 (20.9)	2 (0.2)
Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
Vision Blurred	62 (7.4)	12 (1.4)
Lacrimation Increased	60 (7.2)	5 (0.6)
Erythema of Eyelid	57 (6.8)	6 (0.7)
Visual Acuity Reduced	44 (5.2)	13 (1.5)

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- Cornea verticillata (lipid micro-deposits in the corneal epithelial layer)
- Rocklatan (netarsudil .02% + latanoprost .005% FDC)™: ~5%
- Rhopressa (netarsudil .02%)™: ~4%
  - ~5-9% reported in Rocket 1 and Rocket 2
- Asymptomatic
- Only visible via biomicroscopy evaluation
- Benign corneal deposits (phospholipidosis) are a familiar outcome with other drugs such as amiodarone

Cornea Verticillata

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- Cornea verticillata observed (20.9%)
  - Resolved in 95.6% of patients after treatment ended (OBS01); 2 patients still being followed
  - Not associated with changes in visual function
- Cornea verticillata well-studied in patients on amiodarone therapy[1,2]
  - Approved 1984 USA, observed for decades
  - Present in >98% of patients taking standard oral dosages of amiodarone
  - Rarely interferes with vision

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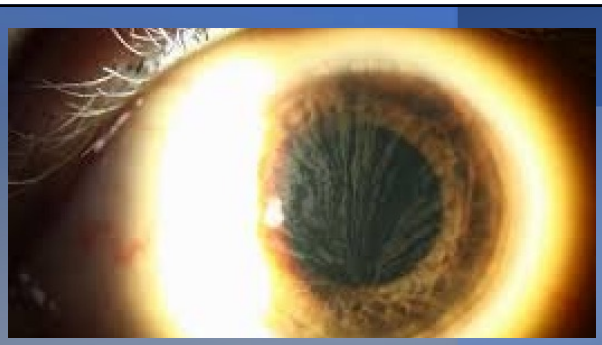

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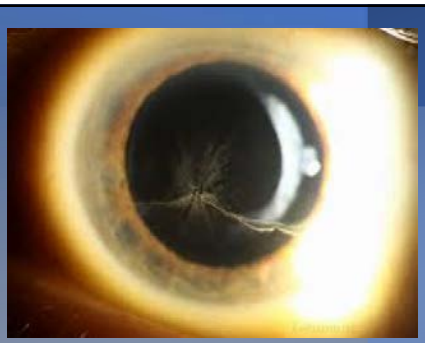

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Table 2. Safety summary

	Netarsudil/ Latanoprost FDC (n=238)	Netarsudil 0.02% (n=243)	Latanoprost 0.005% (n=237)
Eye disorders, n (%)			
Conjunctival hyperemia	150 (63.0)	125 (51.4)	52 (21.9)
Conjunctival hemorrhage	31 (13.0)	44 (18.1)	3 (1.3)
Cornea verticillata	42 (17.6)	33 (13.6)	0 (0)
Eye pruritus	27 (11.3)	22 (9.1)	3 (1.3)
Punctate keratitis	12 (5.0)	18 (7.4)	10 (4.2)
Lacrimation increased	17 (7.1)	20 (8.2)	1 (0.4)
Visual acuity reduced	13 (5.5)	13 (5.3)	6 (2.5)
Vision blurred	11 (4.6)	15 (6.2)	3 (1.3)
Blepharitis	14 (5.9)	8 (3.3)	5 (2.1)
Administration site conditions, n (%)			
Instillation site pain	55 (23.1)	60 (24.7)	18 (7.6)

Adverse events occurring in ≥5% of patients in any treatment arm are presented.
Patients with known contraindications or hypersensitivity to latanoprost were ineligible for participation in this study.
FDC: fixed-dose combination.

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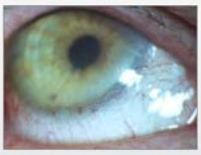
Netarsudil Side Effects: Conjunctival Hemorrhage

- Conjunctival hemorrhage (17.2%)
  - Small
  - Transient
  - Visualized by examiner with slit lamp magnification
- Do not appear to be associated with or cause ocular pathology



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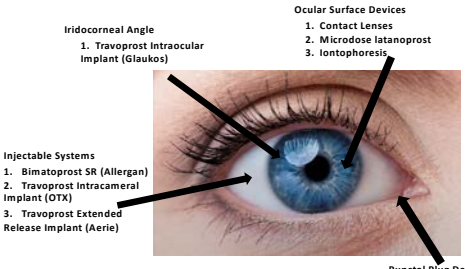

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Bimatoprost SR (Durysta)

- Allergan
- Sustained release bio erodible implant that lasts 4-6 months with similar efficacy to eyedrops
- Small dissolvable pellet is injected into the anterior chamber
  - Sits in/near the angle that resorbs over time
- Can be performed in the office
- Insert can be visualized in the inferior angle
- Ensures patient compliance
- Phase III trial underway comparing SR to timolol
- Will there ever be a need for removal?
- Could it cause cataracts?

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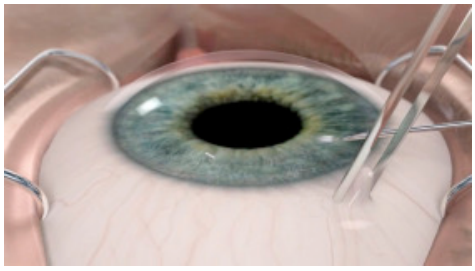

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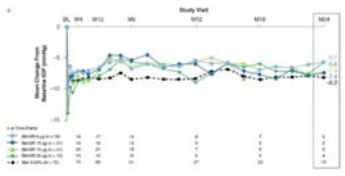
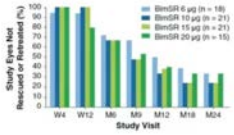
BIM SR (Durysta) Phase I/II Apollo Trial: Efficacy



Data censored after rescue or retreatment

Similar to topical bimatoprost 0.03% through 16 weeks
Second administration efficacy similar to first administration



Rescue or retreatment not required at
6 months – 68%
12 months – 40%
24 months – 28%

Craven ER, Walters T, Christie WC, et al. Drugs. 2020;80(2):167-179.

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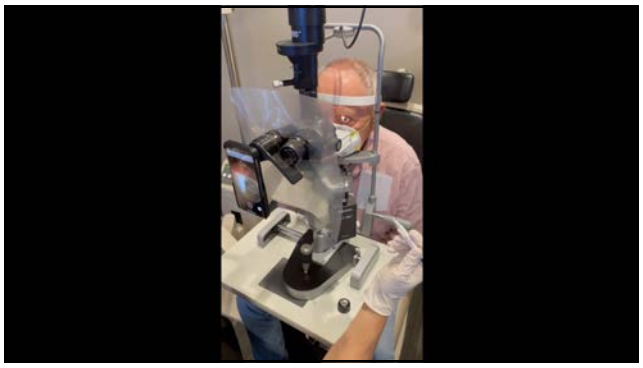

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24 Month Phase I/II/II Clinical Trial

bimatoprost pellet VS topical bimatoprost 0.03%

(6, 10, 15, or 20 micrograms)

24 months – IOP reduction
7.5, 7.3, 7.3, 8.9 mm Hg

24 months – Mean IOP reduction of 8.2 mm Hg

No Rescue or Retreatment
68% - 6 mos.
40% - 12 mos.
28% - 24 mos.

Craven ER, Walters T, Christie WC, Day DG, et al. 24-Month Phase I/II Clinical Trial of Bimatoprost Sustained-Release Implant (Bimatoprost SR) in Glaucoma Patients. Drugs. 2020 Feb;80(2): 167-179.

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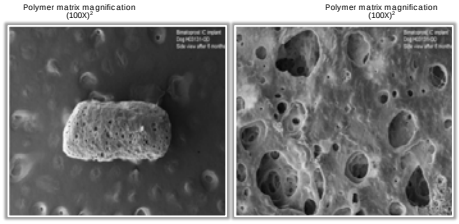
Polymer matrix-based implants biodegrade into lactic acid and glycolic acid.[1]

Polymer matrix magnification (100X)[2]



Polymer matrix magnification (100X)[2]

1. DURYSTA™ Prescribing Information; 2. Medeiros et al, *Ophthalmology*. 2020

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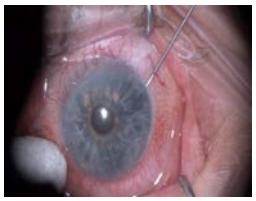
Stabilize the eye as the needle is advanced through the cornea.

Enter the anterior chamber with the needle bevel visible through clear cornea. Enter parallel to the iris plane, adjacent to the limbus through clear cornea in the superotemporal quadrant.

Insert the needle approximately 2 bevel lengths, ensuring the bevel is completely within the anterior chamber; avoid positioning the needle bevel directly over the pupil.

Ensure the needle is not bent before depressing the actuator button.

Release the implant by depressing the back half of the actuator button firmly until an audible and/or palpable click is noted.



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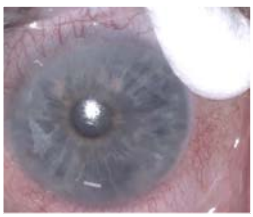
-Following the release of the implant, remove the needle via the same track in which it was inserted and tamponade the opening. The implant should not be left in the corneal injection track.

-Check the injection site for leaks; make sure that it is self-sealing and the anterior chamber is formed.

-After injection, **do not** recap the needle. Dispose of the used applicator in a sharps disposal container and in accordance with local requirements.

-Instruct the patient to remain upright for at least 1 hour after the procedure so the implant can settle.

-Some degree of eye redness and discomfort is expected following administration. However, it is recommended to instruct patients that if the eye becomes progressively red, sensitive to light, painful, or develops a change in vision, they should immediately contact the physician.



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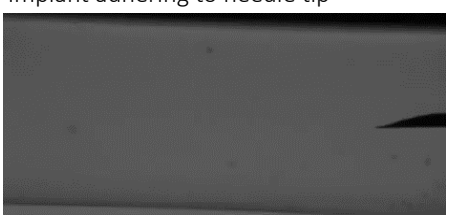
Troubleshooting Injection Issues:

Implant adhering to needle tip



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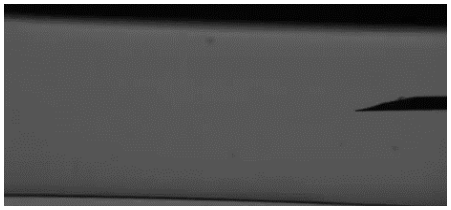
Troubleshooting Injection Issues:

Implant Floating in Anterior Chamber



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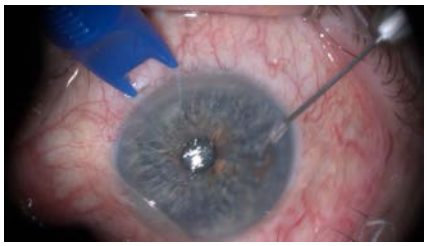
Troubleshooting Injection Issues:

Implant Gets Stuck in Corneal Injection Track



44

82.4%
1.7 meds to 0.3 meds

75%
1.6 meds to 0.4 meds

35%
1.7 meds to 1.1 meds

OSD and MIGS

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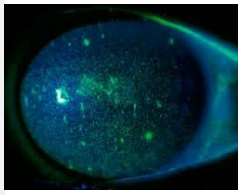
Prospective Interventional Cohort Study of Ocular Surface Disease Changes in Eyes After Trabecular Micro-Bypass Stent(s) Implantation (iStent or iStent *inject*) with Phacoemulsification

Justin A. Schweitzer,[2a] Whitney H. Hauser,[2] Mitch Ibach,[1] Brandon Baartman,[1] Subba R. Gollamudi,[2] Andrew W. Crothers,[2] John E. Linn,[2] and John P. Berdahl[1]

Study Design

- Prospective multi-surgeon study at 2 U.S. sites
- Trabecular meshwork bypass stent implantation with phaco in 50 eyes with OAG and cataract
- Follow-up through 3 months postop
- Measures:
  - IOP and # topical meds (glaucoma drops, artificial tears, ocular surface meds)
  - Ocular Surface Disease Index (**OSDI**)
  - Corneal/conjunctival staining (**Oxford** Scale)
  - Fluorescein tear break-up time (**FTBUT**)
  - Conjunctival hyperemia (**Efron** Scale)



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Gel Stent Strategy in Glaucoma

Gel Stent Versus Trabeculectomy: The Randomized, Multicenter, Gold-Standard Pathway Study (GPS) of Effectiveness and Safety at 12 Months

ARSHAM SHEYBANI, VANESSA VERA, DAVINDER S. GROVER, STEVEN D. VOLD, FRANK COTTER, SAHAR BEDROOD, GAGAN SAWHNEY, SCOTT D. PIETTE, SUSAN SIMONYI, XUEMIN GU, MINI BALARAM, AND MARK J. GALLARDO

• PURPOSE: To compare effectiveness and safety of the gel stent to trabeculectomy in open-angle glaucoma (OAG).
• DESIGN: Prospective, randomized, multicenter, noninferiority study.

IOP change-related Δ (2.8 mm Hg) favored trabeculectomy ($P=.024$). The gel stent resulted in fewer eyes requiring in-office postoperative interventions ($P=.024$ after excluding laser suture lysis), faster visual recovery ($P\leq.048$), and greater 6-month improvements in vi-

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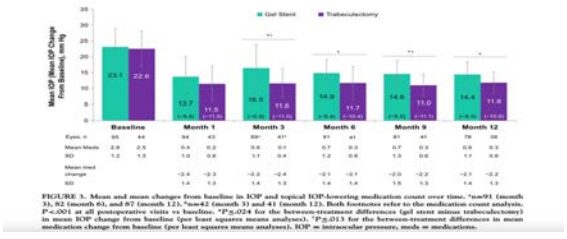
1 Year Mean IOP Data Gel Stent vs. Trab



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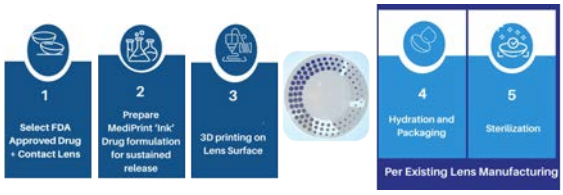
Mediprint Platform 3D Drug Printing on Contact Lens

Proprietary digital printing technology provides platform to make contact lens drug delivery a reality



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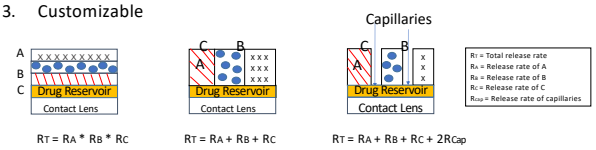
Modulating Drug Release Rate with Digital Printing

1. Modulating Drug Release Rate with 'drug reservoir layer' and 'barrier layers' (A, B, C)
2. Release of more than one API, including comfort enhancer rewetting agent
3. Customizable



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Phase 2b Group 1 Results

Summary of study design

Investigational Product:	:	**Test:** • LL-BMT1 26 µg/lens • LL-BMT1 32 µg/lens • LL-BMT1 40 µg/lens **Reference:** • Timolol 0.5% (b.i.d.) Topical eye drop • bimatoprost ophthalmic solution 0.01% (q.d.) Topical eye drop.
Group 1	**:**	**LL-BMT1 26 µg/lens vs Timolol 0.5% (b.i.d.) Topical eye drop (randomized allocation)**
Group 2	:	LL-BMT1 32 µg/lens vs bimatoprost ophthalmic solution 0.01% (q.d.) Topical eye drop (randomized allocation)
Group 3	:	LL-BMT1 40 µg/lens (Single arm)

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Glaucoma: Phase 2b Reference Comparison

	Test (MediPrint® 26 µg contact lens, x1/week)	Reference (Timolol 0.5% topical eye drops, x2/day)
Clinically meaningful reduction in IOP comparable	Yes	Yes
Number of instillations in 3 weeks (both eyes)	6	84
Preservative-free	Yes	No
	N=11	N=14

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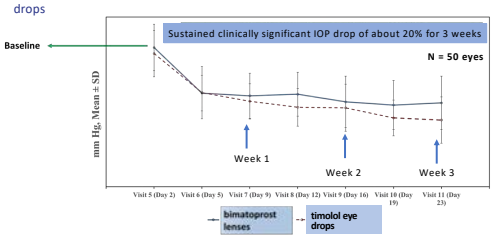
Efficacy Analysis

Ongoing Phase 2b dose ranging trial (group 1) of bimatoprost lens for Glaucoma has established clinically meaningful IOP reduction comparable to positive control IOP-lowering drops



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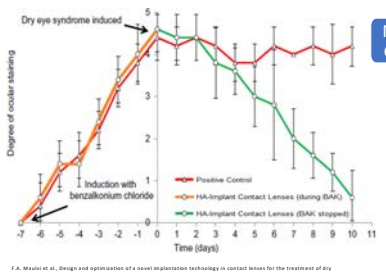
Rabbit HA Dry Eye Model



Model: Rabbits with Induced Dry Eye

Test: HA lens; Control: no treatment

F.A. Maulvi et al., Design and optimization of a novel implantation technology in contact lenses for the treatment of dry eye syndrome: In vitro and in vivo evaluation, Acta Biomater. (2017), http://dx.doi.org/10.1016/j.actbio.2017.01.063

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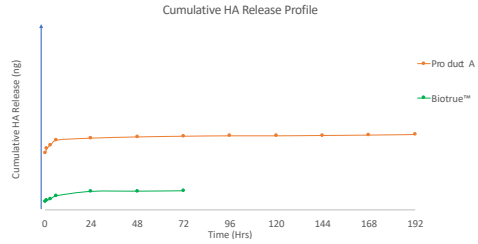
HA In-Vitro Release Profile



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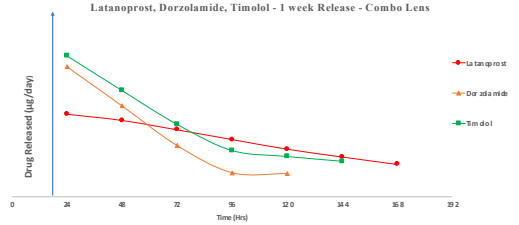
3 Molecules printed on one lens + HA



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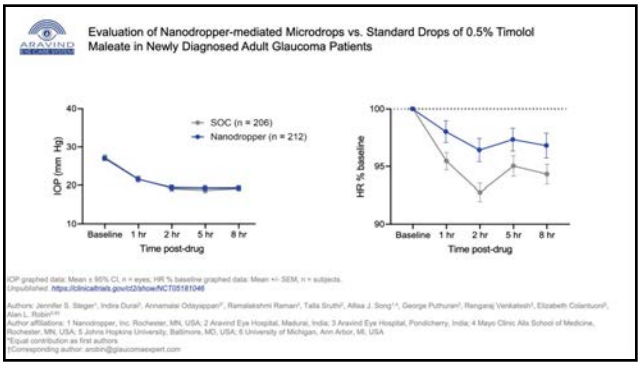

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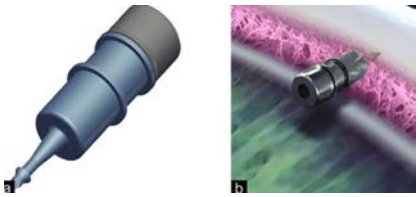

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iDose Travoprost Sustained-release Implant

- Glaukos
- 1.8mm x .5 mm biocompatible titanium implant that releases travoprost inside the anterior chamber
  - Eluting medication inside the eye bypasses corneal surface permeability issues
  - Consistent 24-hour IOP reduction without PGA side effects associated with topical use on ocular surface
  - 3 parts – scleral anchor that passes through TM and sits in scleral wall, body of device which serves as drug reservoir and elution membrane
  - Performed in sterile in-office surgical suite or ambulatory surgical suite
  - Implantation like iStent with 2.2 mm incision, fill anterior chamber with viscoelastic, and implant device

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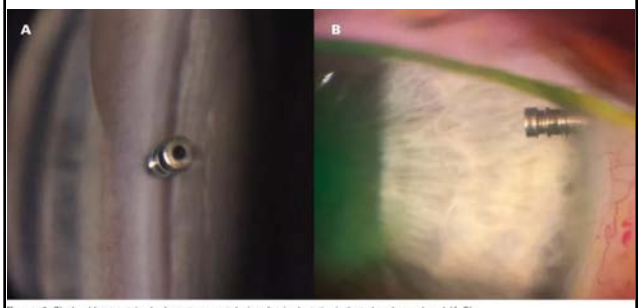

Figure 1. Glaukos Idose sustained-release travoprost device after implantation in the trabecular meshwork (A, B).

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iDose Travoprost Sustained-release Implant

- Phase 2 trials
  - Fast-elution, slow-elution or sham surgery followed with timolol 0.5 bid
  - At 3 months, IOP reduction 33% in fast elution, 32% in slow elution and 30% reduction in timolol group
  - Rate of reduction continued through 12 and then 36 months with rate of reduction like timolol but fewer medications needed
  - No serious adverse advents at 12 months
  - Phase 3 trials to be completed in 2022 with FDA submission expected in 2022
  - Hopeful for 2023 release

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iDose Travoprost Sustained-release Implant

- How to incorporate iDose in clinical practice
  - Key benefits is length of time for release of medication
  - Downside is insertion procedure requires opening the eye
- When will it be used?
  - Time of cataract and MIGS procedure?
  - At time of stand-alone MIGS procedure?
  - Will one be comfortable inserting as a free-standing device?
- Will it be approved for reimplantation once medication is gone?
- Can be left in place since biocompatible?
- What will the reimbursement be?

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Drug Delivery

The SpyGlass Platform combines the heritage and performance of a single-piece IOL and the ability to secure innovative, drug-eluting pads to the haptics of the IOL prior to loading and implantation

Beyond bimatoprost, the SpyGlass drug-eluting pads are uniquely designed to deliver additional drugs to address multiple ophthalmic indications

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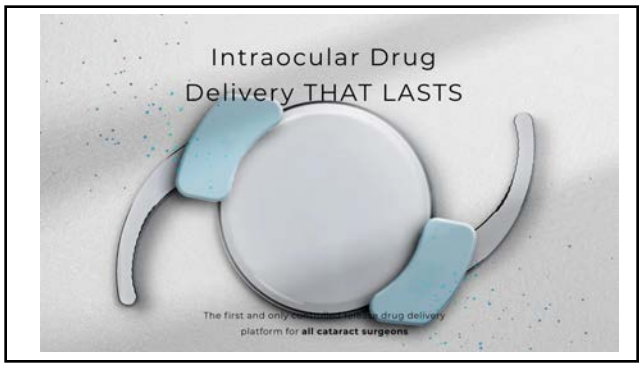
Intraocular Drug
Delivery THAT LASTS
platform for all cataract surgeons

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Single-piece
hydrophobic
acrylic IOL
Drug-eluting
pads

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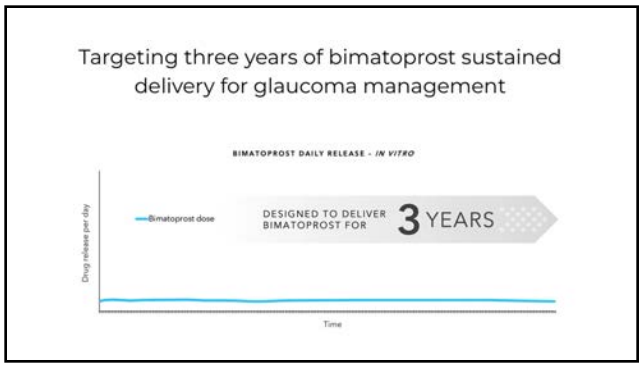
Targeting three years of bimatoprost sustained
delivery for glaucoma management
BIMATOPROST DAILY RELEASE - IN VITRO
Drug release per day
Bimatoprost dose
DESIGNED TO DELIVER
BIMATOPROST FOR
3 YEARS
Time

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