Roadmap to Medical Management of Glaucoma

Michael Chaglasian, OD
Associate Professor
Illinois College of Optometry
Chief of Staff
Illinois Eye Institute

Danica Marrelli, OD
Clinical Professor
Assistant Dean of Clinical Education
University of Houston College of Optometry
University Eye Institute

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Disclosures: M. Chaglasian, OD

- Consultant:
  - Allergan, Alcon, Carl Zeiss Meditec, Topcon
- Advisory Boards:
  - Allergan, B+L, Carl Zeiss, Santen
- Research Grants:
  - Avellino, Equinox, Optos,

2

Disclosures: D. Marrelli, OD

- Allergan
- Bausch & Lomb
- Carl Zeiss Meditec
- Ivantis
- Santen

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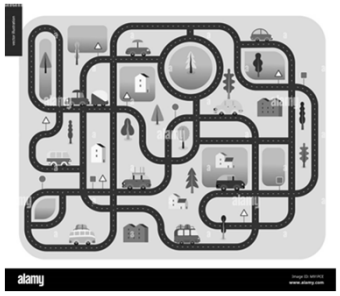
Where are you on the Glaucoma Road Map?



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How are we treating glaucoma patients in 2022 and beyond?

Changing paradigm:

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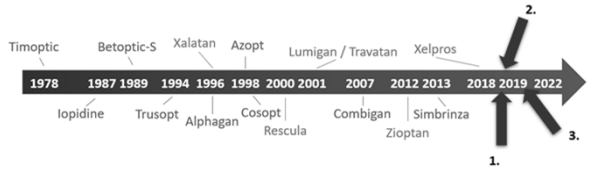
Medications to Treat Glaucoma:



1. Vyzulta
2. Rhopressa
3. Rocklatan

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Deciding when to treat a patient and selecting a medication:

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Deciding When to Treat: Not always black and white

- The decision to initiate treatment in glaucoma suspects is challenging because it requires the **clinician to synthesize multiple risk factors** for progression and predicting which patients will **most likely** develop glaucoma.
- Because clinicians may tend to underestimate risk, clinical tools including the OHTS Risk Calculator, have been developed to help clinicians integrate the numerous risk factors for glaucoma and stratify a glaucoma suspect into low, intermediate, or high risk.

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Deciding When to Treat: Not always black and white

- Some glaucoma suspects may lie further along the continuum towards glaucoma than others and, in addition to these tools, nerve OCT imaging is useful in aiding the decision to treat when there are no overt clinical signs (ophthalmoscopic evidence of disc damage, confirmed visual field loss etc.).
- All of this objective information can help customize a discussion with patients in terms of the advantages of therapy versus observation, but they must be weighed against the costs of treatment in terms of a patient's quality of life.

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Note:

- A "decision to treat" is essentially a life-long decision
- Sometimes up to 50 years of treatment and follow up
- That's a long time to be treated for something that isn't there
- We don't need, nor want to, make this quickly
- Glaucoma is a SLOW MOVING disease, there is rarely a rush
- Slow down and collect good quality data, confirm it's repeatibilty if/when necessary

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Easy Decision

- In patients presenting with **obvious, characteristic** signs of glaucoma damage (RNFL, optic nerve) and vision loss (VF testing), the decision to start glaucoma treatment is relatively straightforward.
  - The benefit of initiating treatment, in terms of preventing further loss of vision and maintaining quality of life (QoL), generally greatly outweighs the negatives of treatment.
- The problem is that MANY patients fall into a *"gray zone"* where the disease damage is **NOT** definitively identifiable, even with multiple repeat testing.

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Less Clear Decision

- Choosing to begin therapy in a glaucoma suspect, on the other hand, is a more difficult decision to make on a patient's behalf.
- Even among glaucoma specialists, there can be significant uncertainty regarding the appropriateness of treatment initiation in glaucoma suspects.
  - As an example, within a 10- to 15-year span, one untreated glaucoma suspect may notice changes in visual function and progress to overt glaucoma, while the next suspect may remain stable.
- So, who do you treat??

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More considerations

- The optometrist must constantly balance the risk for possible long-term irreversible visual disability against life expectancy, treatment side effects, financial impact, and negative effects on QoL (quality of life).
- Ultimately, the goal of therapy is not to lower IOP but to preserve functional vision as well as QoL.
- Thus our treatment, medical, laser or surgical must be delivered in conjunction with the severity and progression of the disease
  - This varies widely between patients.

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Steps in Making the Decision to Treat

First Steps:

1. Review of ALL Diagnostic Data
   - What does it point to?
2. Identification of Positive Risk Factors
   - How do these contribute?
3. Assessment of critical data points
   - What things stand out?

Steps after Deciding to Treat:

1. Set Target Pressure
2. Choose Medication
3. General Strategies -follow up

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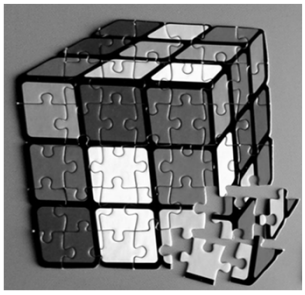
Glaucoma diagnosis can be a very complex puzzle:



- Requirements
  - Organized, step-by-step approach
  - Sort and organize the data
  - Identify good data
  - Ignore bad/unreliable data
  - Confirm data when necessary
  - Sort and organize again
  - No need to rush your decision
  - Individualize to your patient
- Begin therapy (later) or monitor

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Treatment Initiation In The Glaucoma Suspect—When To Treat

- Glaucoma suspects can be categorized into two groups:
  1. subjects with significant risk factors for the future development of glaucoma (e.g., increased IOP)
     - **These patients are addressed by OHTS data and who to treat**
  2. subjects with very early glaucomatous damage that cannot definitely be distinguished from normal (e.g., suspicious appearance of optic disk, OCT RNFL or VF) and IOP that is 21 mmHg or lower

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Initiating Treatment-Diagnosis Decision Making Points

- Ocular and Medical History Risk Factors
- IOP
  - Anterior Chamber Angle (gonio)
- Optic Nerve and Nerve Fiber Layer
  - Clinical exam and OCT
- Pachymetry, Corneal Hysteresis
- Visual Fields

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"Target Pressure"

- The concept of "Target: IOP" is, that of an IOP that prevent further progression of glaucomatous visual field (VF) loss, without compromising a patient's quality of life.
  - Quality of life would be significantly and permanently affected by progression of VF loss and stabilization of the VF is therefore the major goal.
- A "target pressure" may be identified by taking into account the severity of ONH damage, visual field loss, initial IOP and time over which the damage took place.

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"Target Pressure"

- There is no exact method for determining this target pressure, it is an individual, clinical decision which may be modified based on future follow up of the patient.
- There is no, single IOP level that is "safe" for **all** patients
  - Patients have varying target pressures due to their individual risk factors and stage of disease
    - Many can be stable at IOP range of 18-24 mmHg
    - Others continue to progress at IOP of 10 mmHg or under

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Target IOP Based on Disease Stage*

- Established based upon ONH and visual field status (stage) + pre-treatment IOP
- More advanced disease requires lower target IOP:
- Mild/Early: 25-30% Reduction *New*
- Moderate: 30-35% Reduction
- Severe/Advanced: 40% + Reduction

*AGS Staging System

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Target IOP Using IOP Targets (not % decrease)

- Mild / Early*: 18-22+ mmHg
- Moderate: 15-18 mmHg
- Severe: 10-15 mmHg

*AGS Staging System

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Target IOP: IMPORTANT

- Even for an individual patient, TP is NOT a single number
  - TP is understood to **range** +/- 2 mmHg from identified TP
- TP is dynamic over time and must be re-evaluated and updated based upon new clinical data.

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Glaucoma Meds Update/Review:

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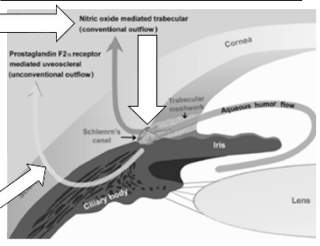
Timeline of Glaucoma Topical Treatment Options

YEAR	DRUG CLASS
1877	Cholinergic agonists
1897	Crystalline alkaloids
1904	Osmotic agents
1948	Adrenergic antagonists
1954	Carbonic anhydrase inhibitors
1955	Adrenergic agonists
1978	β-adrenergic inhibitors
1987	α-adrenergic agonists
1995	Carbonic anhydrase inhibitors
1995	Adrenergic agonist prodrug
1996	Prostaglandin analogs
2017	Rho kinase inhibitors

Last New MOA

- New Target: Trabecular Meshwork
- Latanoprostene bunod (LBN)



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Timeline of Glaucoma Topical Treatment Options

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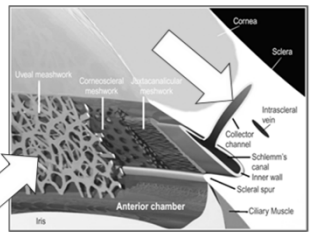
1995	Carbonic anhydrase inhibitors
1995	Adrenergic agonist prodrug
1996	Prostaglandin analogs
2017	**Rho kinase inhibitors**

- **New Target: Trabecular Meshwork**
  - Leading to: Schlemm's Canal, Collector channels and then to Episcleral Venous System



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Currently Available Medications by Category
(single agent)

- **Beta Blockers**
  - Decrease aqueous production
  - Do NOT work during nocturnal time
  - Virtually all generic
    - 0.25%/0.5% timolol, levobunolol
    - 0.25%/0.5% betaxolol (beta1 selective)
- **Carbonic Anhydrase Inhibitors**
  - Decrease aqueous production
  - 2% dorzolamide (generic)
  - brinzolamide
- **Alpha Agonists**
  - Decreased production/Inc outflow
  - 0.15%/0.2% brimonidine (generic)
  - Brimondine P (0.1%)
- **Prostaglandin Analogs**
  - Increase uveoscleral
  - Latanoprost, travoprost, bitamatopost
    - All generically available
  - Bitmatoprost 0.1%,Z

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Currently Available Medications
(fixed dose combination)

- Dorzolamide/timolol (generic)
  - "Cosopt"
- Brimonidine/timolol (generic/brand)
  - "Combigan"
- Brinzolamide/brimonidine (brand only)
  - "Simbrinza"

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Recent Therapies for OHTN/Glaucoma

- Latanoprostene bunod (LBN)
- Netarusdil
- Netarusdil + latanoprost

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(latanoprostene bunod)

- Latanoprostene bunod is a dual mechanism, dual pathway molecule, consisting of latanoprost acid, linked to an ***Nitric Oxide-donating moiety***, which enhances trabecular meshwork/Schlemm's canal (conventional) outflow by inducing cytoskeletal relaxation.
- **Latanoprost plus nitric oxide (NO)**

Kaufman, P. EXPERT OPINION ON PHARMACOTHERAPY, 2017

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Latanoprostene Bunod:
Nitric Oxide–Donating Prostaglandin

- NO plays key roles in both health and disease throughout the body, including the eye
  - Relaxes smooth muscle, thus promoting vasodilation
- Disease states in which NO is a therapeutic target
  - Cardiovascular disease
  - Pulmonary hypertension
  - Many others

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Nitric Oxide (NO)

- First identified in 1770
  - Considered toxic
- 1970s
  - NO identified as an important component in the MOA of nitrates in producing vasodilation
- 1980s
  - recognized to have important regulatory roles in many biologic systems
- 1992: "Molecule of the Year"

Pasquale L. et al. The Role of Nitric Oxide in Glaucoma. CME Monograph

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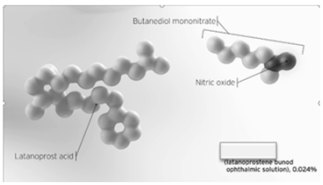
Latanoprostene Bunod (LBN): MOA



- Latanoprostene
  - latanoprost
  - Increases uveoscleral outflow
- Bunod donates Nitric Oxide (NO)
  - Exerts its effect in **trabecular smooth muscle**
  - **Resulting in trabecular *relaxation* and increased conventional outflow**

Nitric Oxide may have other therapeutic roles in the eye and optic nerve

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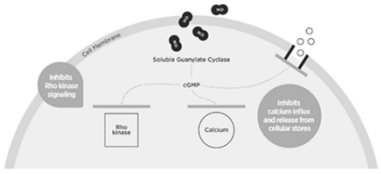
Nitric Oxide Released by LBN Inhibits Rho Kinase and Calcium Signaling

Nitric oxide inhibits Rho kinase and calcium signaling—key causes of trabecular meshwork contraction—by activating the soluble guanylate cyclase–cGMP cascade



Activation of soluble guanylate cyclase–cGMP cascade produces relaxation of the trabecular meshwork and increased permeability

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Latanoprostene Bunod vs Timolol: Phase III: Apollo and Lunar

- Study design
  - Randomized (multicenter, double-masked, parallel-group studies)
- 2 treatment groups
  - ***LBN, 0.024%, qhs for 3 months***
  - Timolol, 0.5%, bid for 3 months

	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]

Weinreb RN, et al. Ophthalmology. 2016;123(5):965-973; Medeiros FA, et al. Am J Ophthalmol. 2016;168:250-259

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APOLLO and Lunar: Efficacy and Safety

- IOP reductions
  - **7.5 to 9.1 mm Hg for LBN (n = 264)**
  - 6.5 to 7.5 mm Hg for timolol (n = 123)
- Adverse events
  - Similar rates between groups
  - Most common:
    - Conjunctival hyperemia
    - Eye Irritations

Weinreb RN, et al. Ophthalmology. 2016;123(5):965-973; Medeiros FA, et al. Am J Ophthalmol. 2016;168:250-259

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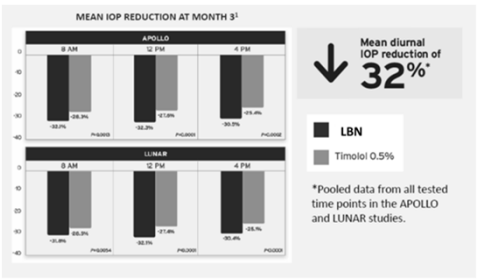
LBN Non-Inferior to Timolol



Weinreb RN, et al. Ophthalmology. 2016;123(5):965-973; Medeiros FA, et al. Am J Ophthalmol. 2016;168:250-259

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Adverse Reactions in APOLLO and LUNAR

Low rate of discontinuation due to ocular AR [1,2]

MOST COMMON OCULAR ADVERSE REACTIONS IN THE APOLLO AND LUNAR STUDIES

Adverse Reactions (%)	APOLLO[1] VYZULTA	APOLLO[1] TIMOLOL 0.5 %	LUNAR[2] VYZULTA	LUNAR[2] TIMOLOL 0.5 %
Eye Irritation	3.9	2.2	7.2	4.4
Conjunctival Hyperemia	2.8	1.5	9.0	0.7
Eye Pain	1.4	2.2	5.8	3.7
Instillation Site Pain	1.1	1.5	1.4	–

- Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions[1,2]
  - These included ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis, and foreign body sensation

1. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J *Ophthalmology*. 2016;123(5):965-973. 2. Medeiros FA, Martin KR, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN. *Am J Ophthalmol*. 2016;168:250-259.

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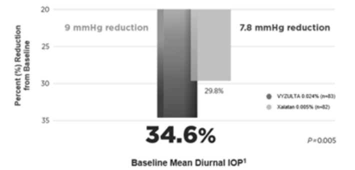
VOYAGER: Phase 2 Study of LBN vs Latanoprost



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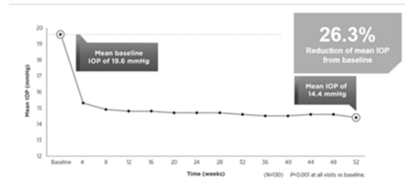
JUPITER Study: Long-term safety in Japanese pop.

NTG in US Populations:
- 30%+
  - Bever Dam Eye Study



CONCLUSIONS:
- Safe and well tolerated
- Effective for 52 weeks
  - 5.2 mmHg lower; from a low baseline of 19.6

Adv Ther 2016 DOI 10.1007/s12325-016-0385-7

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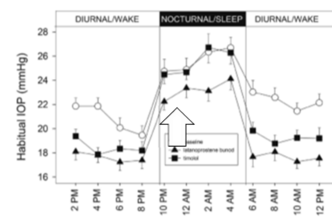
LBN provides nocturnal IOP lowering



- Nocturnal IOP with latanoprostene bunod treatment was 2.5 mmHg lower than baseline

Liu J et al Am J Ophthalmol 2016;

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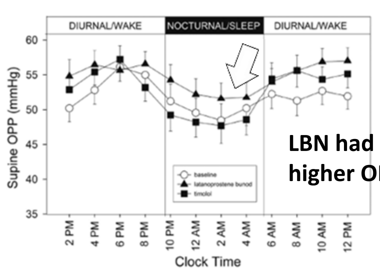
24 Hour Supine Ocular Perfusion Pressure

- LOW OPP has been identified as a risk factor for OAG
  - OPP = S/D/M BP minus IOP
  - Under 50 suggests increased risk



LBN had higher OPP

Caprioli J, Coleman AL. Am J Ophthalmol 2010;149(5):704–712; Quaranta L, Surv Ophthalmol 2013;58(1):26–41; 27. Costa VP, Acta Ophthalmol 2014;92(4):e252–e266.

Liu J et al Am J Ophthalmol 2016;

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LBN 0.024% once daily for OHT/OAG

- Two mechanisms:
  - Latanoprost with with Nitric Oxide to add improving Trabecular Meshwork outflow
- FDA Clinical Trials
  - 7.5-9.1 mmHg lowering of IOP
- Other Trials:
  - Effective in patients with IOP in normal range
  - May be more effective than latanoprost (-1.23 mmHg)
- Minimal new Side Effects
  - Same as other PGAs

FDA approval in November 2017

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Potential Roles of LBN:

- **First Line Therapy**
  - Alternate/Replacement for latanoprost/PGA
  - Good for all? Better for those with more advanced disease? Better for those with lower IOP?
- **Switch/Adjunctive Therapy**
  - When small additional IOP is needed, advantage of maintaining single bottle therapy
  - PGA w/ adjunctive med and not @ target
    - Switch to LBN w/ adjunctive
- No data on adjunctive therapy role

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Rho Kinase (ROCK) Inhibitor: netarsudil

netarsudil 0.02%
- **Once daily (evening)**

FDA approval in December 2017

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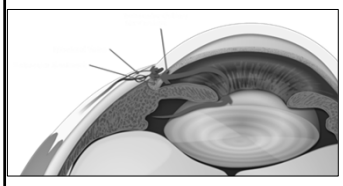
Netarsudil Has a Targeted IOP-Lowering Effect on Trabecular Outflow[1]



- Netarsudil - MOA:
  1. ROCK causes alteration of cellular components of the trabecular meshwork and Schlemm's canal; rho kinase inhibitors ***decrease resistance in the trabecular meshwork outflow pathway*** and promote reduction of IOP.
  2. ROCK inhibition lowers Episcleral Venous Pressure
  3. NET inhibition lowers AH production

ROCK, rho kinase.
1. Kazemi et al. *J Ocul Pharmacol Ther*. 2018;34:380.
2. 2. Weinreb et al. *Nat Rev Dis Primers*. 2016;2:16067. 3. Goel et al. *Open Ophthalmol J*. 2010;4:52.

Lin, et al Discovery and Preclinical Development of Netarsudil, a Novel Ocular Hypotensive Agent for the Treatment of Glaucoma. J Ocul Pharmacol Ther. 2017

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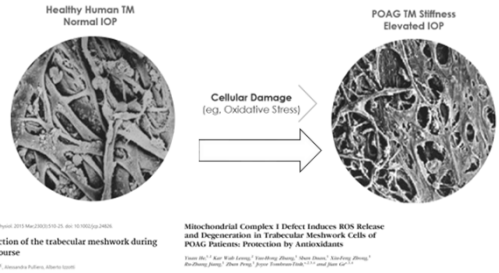
Disease at the TM is responsible for elevated IOP in glaucoma



The dysfunction of the trabecular meshwork during glaucoma course

Mitochondrial Complex I Defect Induces ROS Release and Degeneration in Trabecular Meshwork Cells of POAG Patients: Protection by Antioxidants

- Scanning electron microscopy (2000x) was used to examine human TM under physiological conditions and in patients with POAG.[2]
- **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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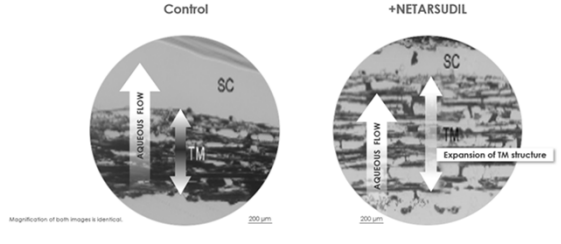
Netarsudil has a targeted IOP-lowering effect on the trabecular outflow



Morphology of the TM in perfused human donor eyes was examined using light microscopy. Images were taken using a 20× objective along the inner wall of the SC. SC, Schlemm's canal.
Ren et al. Invest Ophthalmol Vis Sci. 2016;57:6197.

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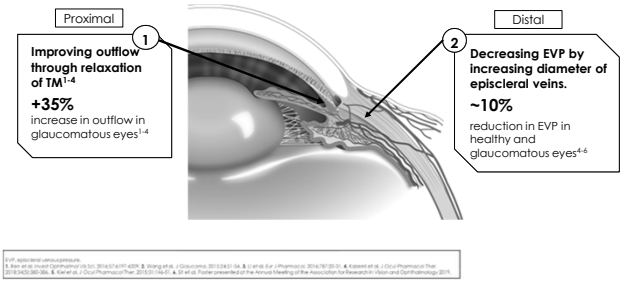
Netarsudil increases trabecular outflow through the entire conventional outflow pathway in glaucomatous eyes



EVP, episcleral venous pressure.

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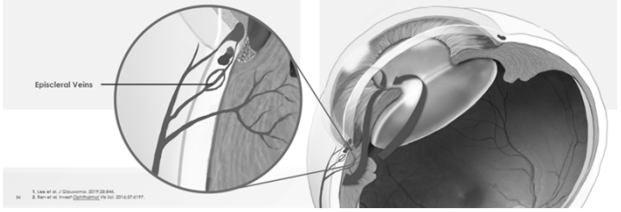
Normal EVP ranges between 7–11 mmHg, playing a significant role in IOP regulation

EVP, the pressure of the blood in the episcleral veins, accounts for half of IOP in healthy, normotensive subjects[1]

Episcleral Veins

Netarsudil has been demonstrated to induce the dilation of episcleral veins[2]



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Netarsudil Clinical Trials: ROCKET 1-2, 4

Two Phase 3 Clinical Trials Comparing the Safety and Efficacy of Netarsudil to Timolol in Patients With Elevated Intraocular Pressure: Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2)

Once-Daily Netarsudil Versus Twice-Daily Timolol in Patients With Elevated Intraocular Pressure: The Randomized Phase 3 ROCKET-4 Study

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Netarsudil: Clinical Trial Data (Rocket 1,2,4)

- **Netarsudil QD**
  - met the criteria for non-inferiority to timolol BID for the primary efficacy analysis
    - for baseline IOP 20-30mmHg
- **Mean IOP Reduction ~ 4.8 mmHg**
- **Consistent across all IOP levels**

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Netarsudil: 3-Month Safety Profile

- The most common ocular AE observed in controlled clinical studies with netarsudil **was conjunctival hyperemia**, which was reported in 53% of patients.
- Other ocular adverse reactions (~20%) in these clinical studies included cornea verticillata, instillation site pain, and conjunctival hemorrhage

Adverse Events (≥5% in any group)	Rhopressa™ QD N = 351	Timolol BID N = 357
Eye Disorders		
Conjunctival Hyperemia	168 (47.9%)	33 (9.2%)
Cornea Verticillata	86 (24.5%)	0 (0.0%)
Conjunctival Hemorrhage	56 (16.0%)	11 (3.1%)
Lacrimation Increased	26 (7.4%)	5 (1.4%)
Erythema of Eyelid	26 (7.4%)	2 (0.4%)
Vision Blurred	22 (6.3%)	4 (1.1%)
Administration Site Conditions		
Instillation Site Pain	83 (23.6%)	92 (25.8%)
Instillation Site Erythema	36 (10.3%)	4 (1.1%)

The corneal verticillata seen in netarsuil-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients.
Most corneal verticillata resolved upon discontinuation of treatment.

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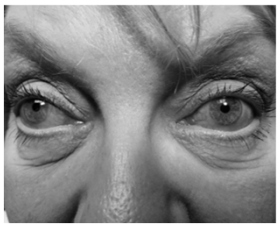
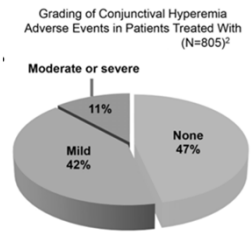
When Present, ~89% of Netarsudil Hyperemia Graded as Mild-None





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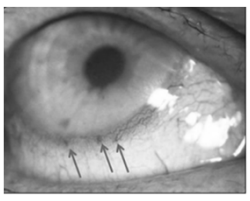
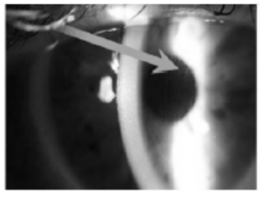
Netarsudil: Adverse Events from Phase III

Limbal Conjunctival Hemorrhage



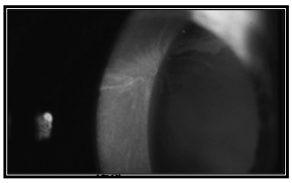
Corneal Verticillata



54

Corneal Verticillata
Pooled Data From Rocket 1,2 & 4

- Brownish, grayish subepithelial corneal deposits seen in the central cornea in a "whorl" pattern
- Occurred in approximately 21% of patients in the Rocket trials
- Similar in appearance to that associated with amiodarone, though milder and less distinct.
- Usually asymptomatic
- Most resolved with discontinuation of the drug



Patient on netarsudil

1. Serle et al. Aqueous humor dynamics: a review. *Am J Ophthalmol J.* 2018; 186,116
2. Khouri et al. ARVO Presentation 2017 (e Abstract 2461)

55

Phase 4 Multicenter Open Label Study (MOST)

M.O.S.T.: 12-week, prospective, multi-center, non-comparative, open-label study of 260 subjects diagnosed with OAG or OHT

-assess the efficacy of the concomitant use of netasurdil with other standard therapies (PGA)

Primary Endpoint:
- Percent change from treated baseline in mean IOP at Week 12

Secondary Endpoint:
- Change from treated baseline in mean IOP at Week 12
- Mean IOP at Week 12

The most common adverse event (AE) reported when netarsudil was used adjunctively was conjunctival hyperemia (19.9%), resulting in a discontinuation rate of 4.3%. Other common AEs were blurred vision (6.2%), conjunctival hemorrhage (5.0%), and instillation site pain (5.0%)[1]

Data on file, Aerie Pharmaceuticals, Inc.

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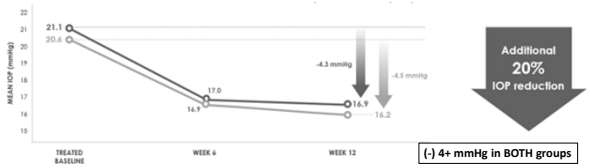
Phase 4 Multicenter Open Label Study (MOST)

Adjunct Therapy Treatment Group*
Netarsudil + PGA (n=55); Netarsudil + ≥2 meds (n=64)



(-) 4+ mmHg in BOTH groups

*Modified intent-to-treat population.
PGA, prostaglandin analog.
Data on file, Aerie Pharmaceuticals, Inc.

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Netarsudil and Latanoprost 0.02%/0.0005%
Fixed Dose Combination (FDC)

Aerie Pharmaceuticals Announces U.S. FDA Approval of Rocklatan™ (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% for the Reduction of Intraocular Pressure in Patients with Open-Angle Glaucoma or Ocular Hypertension

– First and Only Once-Daily, Fixed-Dose Combination of a Prostaglandin Analog and a Rho Kinase (ROCK) Inhibitor –

– Rocklatan™ Demonstrated Statistical Superiority over Widely-Prescribed First-Line Agent Latanoprost –

DURHAM, NC, March 12, 2019-- Aerie Pharmaceuticals, Inc. (NASDAQ:AERI) (Aerie or the Company), an ophthalmic pharmaceutical company focused on the discovery, development and

- **Netarsudil/Latanoprost**
- **Once daily dosing**

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Phase 3 Clinical Trials: netarsudil/latanoprost FDC

- Compared with latanoprost, netarsudil/latanoprost FDC **lowered IOP by an additional 1.3–2.5 mmHg**
- **Absolute reductions from baseline in mean IOP ranged from**
  - **7.2–9.2 mm Hg netarsudil/latanoprost FDC**
  - 5.1–6.1 mm Hg for netarsudil
  - 5.3–7.1 mm Hg latanoprost, respectively


Netarsudil/Latanoprost Fixed-Dose Combination for Elevated Intraocular Pressure: Three-Month Data from a Randomized Phase 3 Trial

Asrani S, Robin AL, Serle JB, Lewis RA, Usner DW, Kopczynski CC, Heah T; MERCURY-1 Study Group. Am J Ophthalmol. 2019 Nov;207:248-257. doi: 10.1016/j.ajo.2019.06.016. Epub 2019 Jun 21. PMID: 31229466.

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Adverse Events: netarsudil/latanoprost FDC

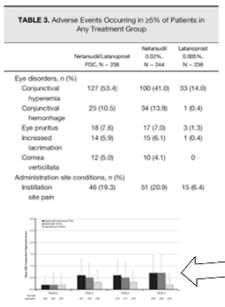
TABLE 3. Adverse Events Occurring in ≥5% of Patients in Any Treatment Group

	Netarsudil/Latanoprost FDC, N = 238	Netarsudil 0.02%, N = 244	Latanoprost 0.005%, N = 256
Eye disorders, n (%)			
Conjunctival hyperemia	127 (53.4)	100 (41.0)	33 (14.0)
Conjunctival hemorrhage	25 (10.5)	34 (13.9)	1 (0.4)
Eye pruritus	18 (7.6)	17 (7.0)	3 (1.3)
Increased lacrimation	14 (5.9)	15 (6.1)	1 (0.4)
Cornea verticillata	12 (5.0)	10 (4.1)	0
Administration site conditions, n (%)			
Instillation site pain	46 (19.3)	51 (20.9)	15 (6.4)

- Based on AE reporting, conjunctival hyperemia was graded as mild in most affected patients (netarsudil/latanoprost FDC), 85.8%.
- In most affected patients who completed 3 months, conjunctival hyperemia occurred intermittently 63.0%
- Conjunctival hyperemia led to treatment discontinuation in 7.1%.
- On biomicroscopy, mean conjunctival hyperemia score across all study visits was <1 and remained relatively unchanged from week 2 to month 3 in all treatment groups.

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Mercury Results - netarsudil/latanoprost FDC Role

- statistically superior to latanoprost and netarsudil at all time points
- IOP-lowering 1-3 mmHg greater than PGA monotherapy through Month 12

Potential Role:

- Initial therapy
- Switch Therapy

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Netarsuil's Role in Glaucoma

Advantages

- Efficacy vs. other adjunctive therapies
- QD PM dose
- Lack of serious and systemic drug-related AE's

- Potential drug of choice as *adjunctive therapy to PGAs* when additional IOP lowering is desired

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Maximum Topical Therapy

- Additionally, recent data on the concomitant use of netarsudil with other IOP-lowering agents showed that netarsudil reduced IOP by a mean of 17.0% (standard deviation, 16.8%) at 12 weeks when added to two to five other topical agents.
  - Full trial results have not yet been published.
- Unfortunately, to date, there are no published data on the concomitant use of latanoprostene bunod with other topical medications .

GLAUCOMA TODAY | JANUARY/FEBRUARY 2021

A multicenter, open-label study of Rhopressa (netarsudil ophthalmic solution) 0.02% for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension in a real-world setting. ClinicalTrials.gov identifier: NCT03808688.

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Coming Soon

PFUDA Date = November 2022

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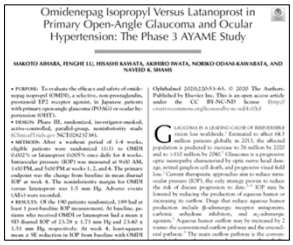
New Med Expected in 2022: New MOA!



Omidenepag Isopropyl Versus Latanoprost in Primary Open-Angle Glaucoma and Ocular Hypertension: The Phase 3 AYAME Study

MAKOTO AIHARA, FENGHI LU, HISASHI KAWATA, AKIHIRO IWATA, NORIKO ODANI-KAWABATA, AND NAVEED K. SHAMS

- PURPOSE: To evaluate the efficacy and safety of omidenepag isopropyl (OMDI), a selective, non-prostaglandin, prostanoid EP2 receptor agonist, in Japanese patients with open-angle glaucoma (POAG) or ocular hypertension (OHT).
- DESIGN: Phase III, randomized, investigator-masked, active-controlled, parallel-group, noninferiority study (UMIN000012749).
- METHODS: After a washout period of 1–4 weeks, eligible patients were randomized (1:1) to OMDI 0.002% or latanoprost 0.005% once daily for 4 weeks. Intraocular pressure (IOP) was measured at 9:00 AM, 1:00 PM, and 5:00 PM at weeks 1, 2, and 4. The primary endpoint was the change from baseline in mean diurnal IOP at week 4. The noninferiority margin for OMDI versus latanoprost was 1.5 mm Hg. Adverse events (AEs) were recorded.
- RESULTS: Of the 190 patients randomized, 189 had at least 1 post-baseline IOP measurement. At baseline, patients who received OMDI or latanoprost had a mean ± SD diurnal IOP of 23.28 ± 1.73 mm Hg and 23.40 ± 1.53 mm Hg, respectively. At week 4, least-squares mean ± SE reduction in IOP from baseline with OMDI

Ophthalmol 2020;220:53–63. © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

GLAUCOMA IS A LEADING CAUSE OF IRREVERSIBLE vision loss worldwide.[1] Estimated to affect 68.5 million patients globally in 2013, the affected population is predicted to increase to 76 million by 2020 and to >111 million by 2040.[2] Glaucoma is a progressive optic neuropathy characterized by optic nerve head damage, retinal ganglion cell death, and progressive visual field loss.[3] Current therapeutic approaches aim to reduce intraocular pressure (IOP), the only strategy proven to reduce the risk of disease progression to date.[4–6] IOP may be lowered by reducing the production of aqueous humor or increasing its outflow. Drugs that reduce aqueous humor production include β-adrenergic receptor antagonists, carbonic anhydrase inhibitors, and α2-adrenergic agonists.[7] Aqueous humor outflow may be increased by 2 routes: the conventional outflow pathway and the uveoscleral outflow pathway.[8] The main outflow pathway is the conven-

Am J Ophthalmol 2020;220:53–63

- ▶ **OMDI**
  - ▶ **Omidenepag isopropyl 0.002%**

- The active metabolite, omidenepag, has a different, novel mechanism of action compared to other currently available medications.
- It is a selective agonist for the prostanoid receptor, EP2, in contrast to the prostaglandin analogs (PGAs), a commonly prescribed class of medications that acts on a FP receptor.
- Omidenepag isopropyl increases the pathway of aqueous humor drainage through the conventional (or trabecular) and uveoscleral outflow pathways, while PGAs are thought to increase the uveoscleral outflow pathway only.
- Comparable to latanoprost, reduced ocular side effects

65

OMDI (omdenepag isopropyl)

- The active metabolite, omidenepag, has a different, novel mechanism of action compared to other currently available medications.
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- Comparable to latanoprost, *potentially reduced ocular side effects*

Am J Ophthalmol 2020;220:53–63

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OMDI (omdenepag isopropyl)

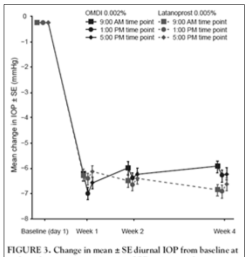

FIGURE 3. Change in mean ± SE diurnal IOP from baseline at each study assessment time point. IOP = intraocular pressure; OMDI = omidenepag isopropyl.

Phase 3 Clinical Trial

- N=190
- The most frequently reported treatment-related ocular AEs (OMDI vs latanoprost) were:
  - conjunctival hyperemia
    - (23/94 patients [24.5%] vs 10/96 patients [10.4%]),
  - corneal thickening
    - (11/94 patients [11.7%] vs 1/96 patients [1.0%]), and
  - punctate keratitis
    - (0/94 patients vs 5/96 patients [5.2%]).

Am J Ophthalmol 2020;220:53–63

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Reduced PGA Long Term Side Effects? 12m Study


Japanese Journal of Ophthalmology (2021) 65:810–819
https://doi.org/10.1007/s10384-021-00868-y

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

CLINICAL INVESTIGATION

Twelve-month efficacy and safety of omidenepag isopropyl, a selective EP2 agonist, in open-angle glaucoma and ocular hypertension: the RENGE study

Makoto Aihara[1] · Fenghe Lu[2] · Hisashi Kawata[3] · Akihiro Iwata[3] · Noriko Odani-Kawabata[2,3]

Received: 26 February 2021 / Accepted: 28 June 2021 / Published online: 8 September 2021
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Abstract

Purpose To assess the long-term safety and efficacy of omidenepag isopropyl (OMDI) 0.002% (a first-in-class, selective, non-prostaglandin, prostanoid EP2 receptor agonist), alone or administered concomitantly with timolol 0.5%, in patients with open-angle glaucoma (OAG, including normal-tension and exfoliation glaucoma) or ocular hypertension (OHT).
Study design Open-label, multicenter, Phase 3 study (NCT02822729).
Methods Patients aged ≥ 20 years, with OAG or OHT, and a baseline diurnal intraocular pressure (IOP) ≥ 16– < 22 mmHg (Group 1) or ≥ 22– ≤ 34 mmHg (Groups 2 and 3) were enrolled. All patients (N = 125) received OMDI 0.002% once daily. Group 3 also received timolol 0.5% twice daily. IOP was measured at baseline and at Weeks 2, 4, 8, 12, 26, 40, and 52.
Results Significant reductions in mean diurnal IOP from baseline occurred at every visit (P < 0.0001). Mean ± SE diurnal IOP reduction at Week 52 was −3.7 ± 0.3 mmHg (Group 1), −5.6 ± 0.5 mmHg (Group 2), and −8.4 ± 0.6 mmHg (Group 3). Most adverse events (AEs) were mild, and no serious treatment-related AEs were reported. Conjunctival hyperemia (incidence: monotherapy [Groups 1 and 2], 18.8%; concomitant [Group 3], 45.0%) and macular edema (ME)/cystoid macular edema (CME) (incidence: monotherapy, 11.8%; concomitant, 15.0%) occurred most frequently. All treatment-related ME/CME cases occurred in pseudophakic eyes and responded to standard-of-care treatment and study drug discontinuation.
Conclusions In this study, OMDI 0.002%, alone or administered concomitantly with timolol 0.5%, resulted in sustained IOP reduction over 52 weeks in patients with OAG or OHT. Concomitant treatment resulted in increased efficacy and increased incidence of conjunctival hyperemia.

Appearance-altering AEs, such as increased pigmentation of the iris or eyelid, abnormal eyelash growth, or DUES, frequently observed with FP agonists [7, 45], were not observed with OMDI treatment over the 52-week treatment period. Two non-clinical studies found that, in contrast with FP agonists, OMDI did not lead to abnormal eyelash growth or adipocyte differentiation [46, 47]. As this study was conducted in a Japanese patient population with a brown iris color, further studies in populations with a light iris color are required to further verify the lack of pigmentation changes with OMDI. Post-marketing studies in Japan found that treatment with OMDI 0.002% did not result in DUES and, in some cases, led to an improvement in DUES after switching from FP agonists [48, 49].

It should be noted that the interpretation of the results from this study may be limited by the open-label design and lack of an active comparator.

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Drug Delivery Option(s)

Not all medical options have to be topical drops:

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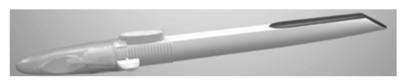
Bitmatoprost SR

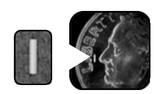
Applicator

- Sterile applicator designed for single use[1]
- Preloaded with 1 implant[1]
- 28-gauge needle[2]



Implant

- Solid polymer matrix containing 10 mcg of bimatoprost[1]
- Slowly biodegrades in the eye[1]
- Tiny, biodegradable, intracameral implant, ≈ 1 mm in length[1,2]
- Preservative-free[2]
- should not be re-administered to an eye that received a prior implant



Medeiros et al. Ophthalmology. 2020

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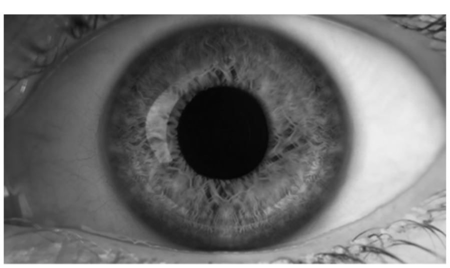
Targeted Delivery to Diseased Tissues (video)

1



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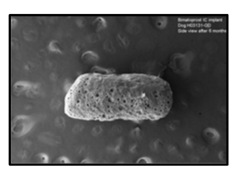
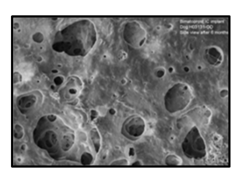
24/7 Drug Release for Several Months

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





Images of implants from in vivo studies

2. Medeiros et al. Ophthalmology. 2020

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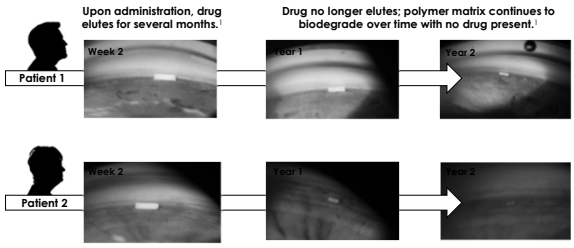
Implant Biodegradation: Patient Variability Over Time

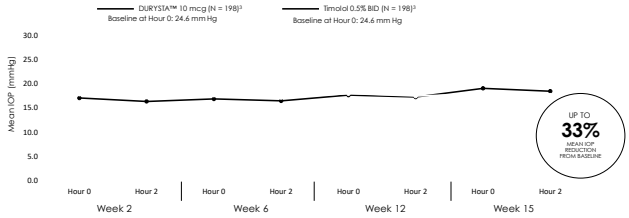


1. Data on file.

73

Consistent IOP Control Over Time: Study 1

Demonstrated a mean IOP reduction of approximately 5 to 8 mm Hg over 15 weeks in patients with a mean baseline IOP of 24.6 mm Hg[1,2]



2. Medeiros et al. *Ophthalmology*. 2020; 3. Data on file, Allergan.

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Effective for up to 2 yrs in 28%

24-Month Phase I/II Clinical Trial of Bimatoprost Sustained-Release Implant (Bimatoprost SR) in Glaucoma Patients

Key Points

A single administration of bimatoprost sustained-release implant (Bimatoprost SR) lowered intraocular pressure for up to 1 year in 40% of patients and up to 2 years in 28%, with no additional treatment.

Efficacy of re-administration with a second implant of Bimatoprost SR was similar to that with the first implant.

The safety profile of Bimatoprost SR was favorable during the 24-month study.

Drugs (2020) 80:167–179

75

Microdose latanoprost: Piezoelectric microdosing technology

Latanoprost with high precision, piezo-print microdose delivery for IOP lowering: clinical results of the PG21 study of 0.4 µg daily microdose

Clinical Ophthalmology 2018:12 2451–2457

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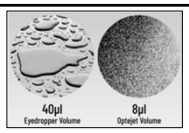
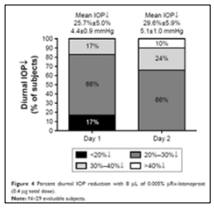
Reduced volume:

- Typical Eye Drop:
  - Excessive volume means excessive drug and preservative
- Microdosing:
  - Less drug loss and medication dilution.
  - Increased bioavailability to the eyes.
  - Reduced local drug reactions.
  - User friendliness may increase compliance with ocular dosing regimens.
  - Systemic drug absorption and related side effect risk are decreased





Clinical Ophthalmology 2018:12 2451–2457

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Ocular Surface Disease in the Presence of Glaucoma

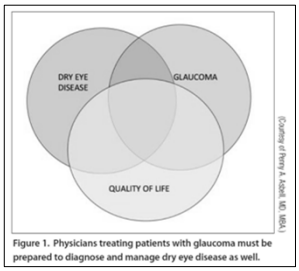

Figure 1. Physicians treating patients with glaucoma must be prepared to diagnose and manage dry eye disease as well.

(Courtesy of Penny A Asbell, MD, MBA.)

- This is our everyday clinical practice life.

SUPPLEMENT TO GLAUCOMA TODAY AND ADVANCED OCULAR CARE FEBRUARY/MARCH 2011

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OSD, Glaucoma and Quality of Life (QOL)

Ocular Surface Disease and Quality of Life in Patients With Glaucoma

SIMON E. SKALICKY, IVAN GOLDBERG, AND PETER MCCLUSKEY

Measured with: **Quality of Life-15 (GQL-15)**

- The GQL-15 is a 15-item questionnaire with which patients subjectively evaluate their own ability to perform visually demanding tasks of daily living.
- Poorer QoL scores are associated with worse functional status and increased visual morbidity from glaucoma.

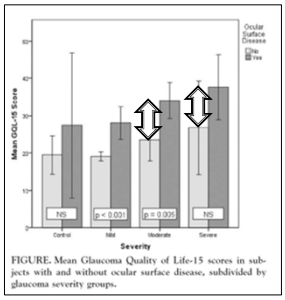

FIGURE. Mean Glaucoma Quality of Life-15 scores in subjects with and without ocular surface disease, subdivided by glaucoma severity groups.

Am J Ophthalmol 2012;153:1–9

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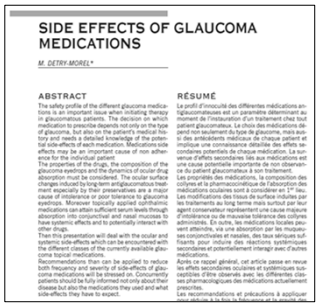
Compliance Component

- "A major cause of intolerance or poor tolerance to glaucoma medication is the ocular surface changes created by treatment."
  - Detry-Morel M. Side effects of glaucoma medications. *Bull Soc Belge Ophtalmol.* 2006;27-40.



SIDE EFFECTS OF GLAUCOMA MEDICATIONS

M. DETRY-MOREL*

ABSTRACT

RÉSUMÉ

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BAK % in current Medications

PGAs:

Latanoprost 0.005%	0.02% BAK
Bitmatoprost 0.01%	0.02% BAK
Latanoprostene bunod	0.02% BAK
Bitmatoprost 0.03%	0.005% BAK

As reported on Package Insert

All Others BAK:

- Netarsudil
  - 0.015%
- Azopt
  - 0.01%
- Timolol sol
  - 0.01%
- Cosopt
  - 0.0075%
- Simbrinza
  - 0.003%

Higher

Lower

81

Glaucoma Medications with BAK alternative or Preservative Free formulations

BAK Free

- Brimonidine with Purite
  - (Alphagan P)
- Travoprost with Sofiza preservative
  - (Travatan Z)
- Latanoprost with potassium sorbate preservative
  - (Xelpros)

Preservative Free (PF)

- Timolol PF
  - (Timoptic Ocudose)
- Dorzolamide/Timolol FDC PF
  - (Cosopt PF)
- Tafluprost PF
  - (Zioptan)

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Case Examples:

83