Glaucoma 2019; What is Hot and What is Not

Kevin Lavery, MD
March 20, 2019

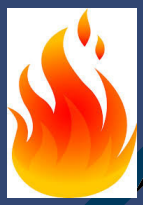
Glaucoma Can Be Devastating

- Glaucoma is the second leading cause of blindness worldwide
- In the US, there are an estimated 3.7M cases of OAG, growing to more than 4M cases by 2020, with a significant number of patients going blind every year[1]

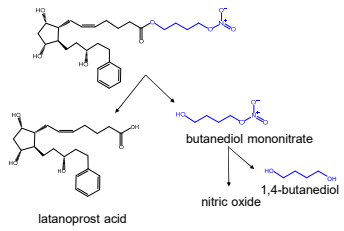
1. 2017 Market Scope Glaucoma Report, data on file.

Vyzulta™ (latanoprostene bunod ophthalmic solution), 0.024%

?



Latanoprostene Bunod is Metabolized to Latanoprost Acid and Nitric Oxide



- Vyzulta™ (latanoprostene bunod ophthalmic solution), 0.24% is a prostaglandin analog indicated for the reduction of IOP in patients with OAG or OHT.
- The active, latanoprostene bunod (LBN), is a single chemical entity that releases latanoprost acid and nitric oxide on topical ocular administration

1. Krauss AH, et al. *Exp Eye Res.* 2011;93:250-5. 2. Kawase K, et al. *Adv Ther.* 2016 Sep;33(9):1624-37.

LBN Possesses Two Independent Mechanisms for Lowering IOP

Latanoprost acid	Nitric oxide
FP receptor	Soluble guanylyl cyclase
Matrix metalloproteinases	cGMP/PKG
Extracellular matrix remodeling	Trabecular meshwork (TM) cell relaxation
Uveoscleral outflow	TM/Schlemm's canal outflow

Reduced IOP

Abbreviations: cGMP=cyclic guanosine monophosphate; FP=prostaglandin F; IOP=intraocular pressure; PKG=protein kinase G.

1. Lindsey JD, et al. *Invest Ophthalmol Vis Sci.* 1997;38:2214-23.
2. Schachtschabel U, et al. *Curr Opin Ophthalmol.* 2000;11(2):112-5.
3. Cavet ME, et al. *Invest Ophthalmol Vis Sci.* 2015;56:4108-16.

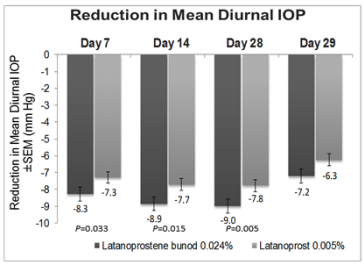
APOLLO and LUNAR: Adverse Events

Clinical Studies

- The most common ocular adverse reactions observed in patients treated with Vyzulta™ (n=811, across both studies) were
  - conjunctival hyperemia (6%)
  - eye irritation (4%)
  - eye pain (3%)
  - instillation site pain (2%)
- Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

VYZULTA™ [prescribing information]. Bridgewater, NJ: Bausch + Lomb, 2018.

VOYAGER: Latanoprostene bunod 0.024% Led to Greater IOP Reductions at All Study Visits

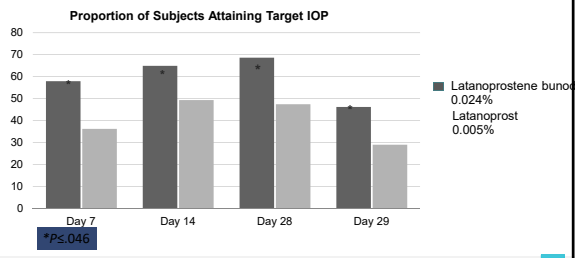


- 1.23 mm Hg greater IOP lowering with LBN 0.024% vs. latanoprost 0.005%
- Significantly greater reduction in IOP compared to latanoprost 0.005% at all on-treatment visits
- Reductions from baseline maintained through Day 29, or 36-44 hours after the last study dose

1. Weinreb RN, et al. *Br J Ophthalmol* 2015;99:738–45.

VOYAGER: Latanoprostene bunod 0.024% Led to Greater Proportions of Subject Reaching Target IOP at All Visits

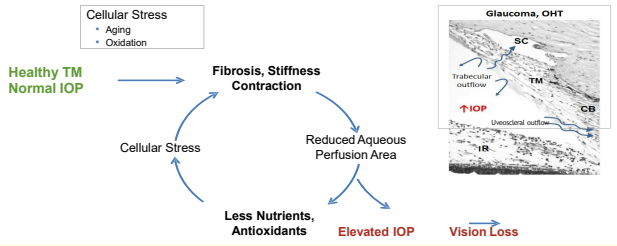
- 69% of LBN subjects vs 48% of latanoprost subjects attained target IOP at Day 28



1. Weinreb RN, et al. *Br J Ophthalmol* 2015;99:738–45.

Ropressa

Degeneration of TM Outflow Pathway Causes Elevated IOP and Vision Loss in Glaucoma



Commonly Used Medications Do Not Target the Diseased TM

Wang SK, Chang RT. Clin Ophthalmol. 2014;8:883-890 Yuan He, et al. Invest Ophthalmol Vis Sci. 2008;49:1447-58

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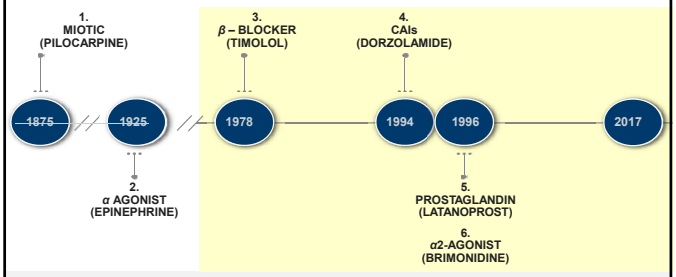
Current Glaucoma Market: 21 Years Without a New Drug Class

Timeline of currently approved glaucoma drops



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All IOP-lowering Medications Cause Multiple Ocular and Systemic Side Effects

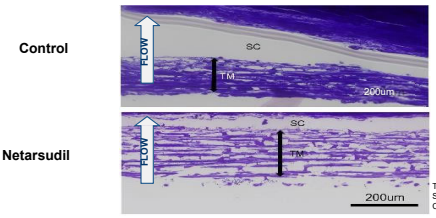
Drug	Ocular Side Effects	Systemic Side Effects
1. Prostaglandins	Hyperemia, increased iris pigmentation, eyelash growth, foreign body sensation, loss of orbital fat tissue, periocular hyperpigmentation, eye ache	Minimal
2. Beta adrenergic antagonists	Dry eyes, hyperemia	Decreased exercise tolerance, decreased pulse, bronchospasm, fatigue, depression, impotence
3. Selective alpha$_2$ adrenergic agonists	Hyperemia, allergic conjunctivitis/dermatitis, follicular conjunctivitis	Dry mouth and nose, hypotension, headache, fatigue, somnolence
4. Topical carbonic anhydrase inhibitors	Hyperemia, burning, blurred vision, allergic conjunctivitis/ dermatitis	Bitter taste, sulfa-related side effects
5. Nonselective α and β adrenergic agonists	Ocular allergy, irritation, hyperemia, tachyphylaxis	Tachycardia, arrhythmia, headache, hypertension
6. Miotics	Decreased vision, dermatitis, small pupil, increased myopia, cataract, retinal tears, eye pain	Brow ache, headache, increased salivation, abdominal cramps

The Glaucoma Medication Wish List

1. Targeted therapy for the diseased trabecular outflow
   - Restore conventional outflow pathways
   - New adjunctive use with existing glaucoma medications
2. Effective IOP lowering
   - Longer term stable efficacy at all baseline IOPs
3. Safety and Tolerability
   - No drug-related systemic side effects
   - Tolerable and reversible ocular side effects
4. Convenience
   - Once a day dosing to enhance compliance and quality of life

Affordability?

Netarsudil* Causes Expansion of TM Tissue, Opening Spaces for Increased Outflow



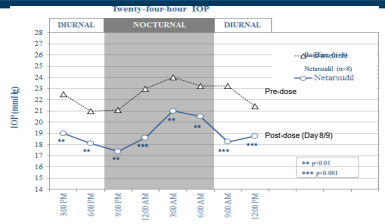
TM: Trabecular Meshwork SC: Schlemm's Canal
Control = buffered saline solution

Increasing Trabecular Outflow, Reducing Fibrosis Could Stop Degeneration of Outflow Tissues in Glaucoma

*Active ingredient of Rhopressa®

Source: Ren R et al. Invest Ophthalmol Vis Sci. 2016; 57(14):6197-6209.

Rhopressa® 24-hour IOP Pilot Study Demonstrates Effective Nocturnal Efficacy

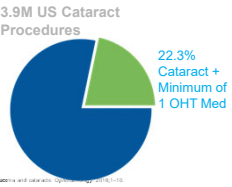


- Netarsudil (active ingredient of Rhopressa®) equally effective during nocturnal and diurnal periods
- Current glaucoma medications either have no efficacy at night (beta blockers, alpha agonists) or reduced efficacy at night (PGAs, CAIs)[1-4]

Micro-Invasive Glaucoma Surgery (MIGS)

Addressing the burden of glaucoma

- Approximately 20% of the annual cataract surgeries in the United States are in patients with comorbid glaucoma[2]
- Cataract surgery alone has been shown to lower IOP[3,4]
- Implanted at the time of cataract surgery MIGS lower IOP
- better than cataract surgery alone



1. Tham Y, Hore B, Li X, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040. *Ophthalmology*. 2014;121:2081–2090.
2. Tseng VL, Yu F, Lum F, Coleman AL. Risk of fractures following cataract surgery in Medicare beneficiaries. *JAMA*. 2012;308:493–501.
3. Vold S, Ahmed I, Craven E, et al. Two-year COMPASS trial results: Supraciliary microstenting with phacoemulsification in patients with open-angle glaucoma and cataract. *Ophthalmology*. 2016;123:748–757.
4. Vizzeri G, Weinreb RN. Cataract surgery and glaucoma. *Curr Opin Ophthalmol* 2010;21:20–4.
5. CyPass® Micro-Stent Instructions for Use.

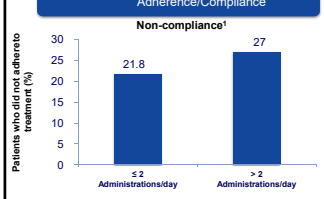
Standard Treatment Options for Glaucoma

- Standard Treatment Options
  - Glaucoma Medications
  - Laser Trabeculoplasty
  - Surgery
    - Trabeculectomy / Shunt
- Challenges
  - Long-term exposure to glaucoma medication can cause corneal surface damage
  - Non-compliance to medication
    - More than 90% of patients are non-adherent, and nearly 50% stop taking their medications before 6 months[1]
  - Less durability in laser treatments
  - Risks associated with surgery
  - Cost burden to patients & system

1. Nordstrom BL. Persistence and adherence with topical glaucoma therapy. *Am J Ophthalmol* 2005;140:598-596.

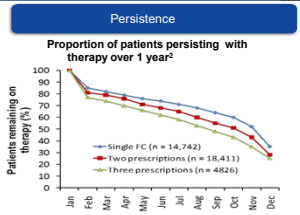
Adherence and Persistence with Medical Therapy for Glaucoma

Adherence/Compliance



In a 12-month retrospective study of 2440 patients older than age 65, more than 23.3% of the patients were nonadherent to therapy. Patients prescribed medications requiring > 2 administrations per day were significantly more likely to be nonadherent.

Persistence



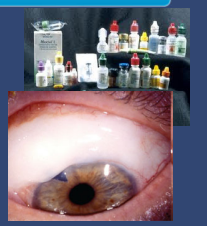
Over 12 months, patient (n = 37,979) persistence with medication significantly decreased as the number of concurrent medications increased (35.3%, 27.2% and 23.9% for one, two and three prescriptions, respectively)[2]

1. Gurwitz JH, et al. *Am J Public Health* 1993; 83:711—716.; 2. Higginbotham E, et al. *Curr Med Res Opin* 2009;25:2543–7.

Glaucoma Patients & Ocular Surface Disease (OSD)

Glaucoma Patients:

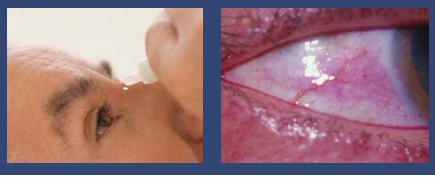
- Elderly (decreased tear secretion)
- On medications for life
- Frequently on multiple topical ophthalmic medications[1]
- Abnormal tear film breakup time is associated with increasing number of eye drops and drops with and without BAK[2]
- May undergo filtering surgery (impact on healing)



1. McKinnon SJ, Goldberg LD, Peeples P, Walt JG, Bramley TJ. Current management of glaucoma and the need for complete therapy. *Am J Manag Care.* 2008;14(suppl 1):S30-S27.
2. Rienti N, Supramaniam G, Siamoutin A, et al. Ocular Surface Disease in Glaucoma: Effect of Polypharmacy and Preservatives. *Optom and Vision Sciences.* 2015;92(9):e222-e226.

Glaucoma Medications & Ocular Surface Disease (OSD)

Nearly 60% of Medically Treated Glaucoma Patients Report OSD Symptoms[1]

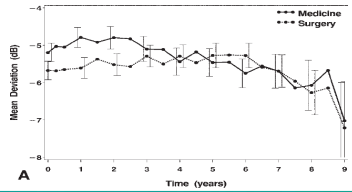


Reduction in topical glaucoma medications, which typically contain the preservative benzalkonium chloride (BAK), can help maintain the quality of tear film and potentially improve refractive outcomes.[2]

1. Leung E, Medeiros F, Weinreb R. Prevalence of Ocular Surface Disease in Glaucoma Patients. *J of Glaucoma.* 2008;17(5):350-355.
2. Thygeson J. Glaucoma Therapy: Preservative-Free For All? *Clin Ophthal.* 2018;12:707-717.

Visual Field Progression Despite Medical Therapy

- Both randomized and real-world clinical trials have demonstrated that in patients with primary open-angle glaucoma, visual field progression can occur despite being on long- term, controlled drop therapy[1,2]



In the landmark Collaborative Initial Glaucoma Treatment Study (CIGTS), medically-treated patients had an average baseline MD of -5.2 dB (standard error, 0.2 dB), which worsened to -5.5 dB at 5 years and to -6.1 dB at 8 years.[1]

* Enrollees in the study were randomized to receive initial treatment with topical medications (n = 307) or trabeculectomy (n = 300). If initial treatment failed to control IOP or if progression in VF loss was noted, argon laser trabeculoplasty was administered.

1. Musch DC, et al. *Ophthalmology* 2009;116:200–207.; 2. Aptel F, et al. *Acta Ophthalmol* 2015; 93: e615–e620.

Allergan

Large R&D Investment across the industry

Alcon A Novartis Division
- *CyPass*® Micro-Stent

IVANTIS
- Hydrus*

GLAUKOS
- iStent* (Gen 1)
- iStent* Inject (Gen 2)
- iStent* Supra (Gen 3)

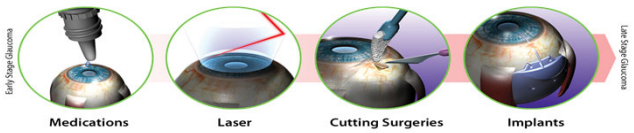
SIGHT SCIENCES
- TRAB360*
- VISCO360*

Allergan
- XEN45*

NWM New World Medical, Inc.
- Kahook* Dual Blade

*Trademarks are property of their respective owners.

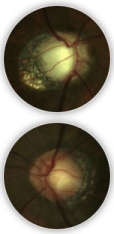
Treatment Spectrum



MIGS

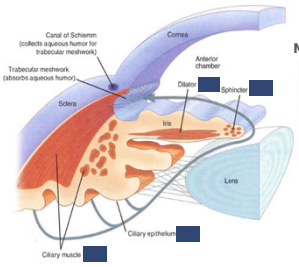
Minimally Invasive Glaucoma Surgery (MIGS) Goal

- Intervene earlier in the disease and lower IOP to potentially reduce morbidity of progression through a procedure that is:
  - *Ab interno*
  - Minimally traumatic, tissue sparing
  - Safe and effective
  - Rapid recovery
- Reduce the need for more aggressive surgical options while preserving that option
- Reduce medication burden



Slide Courtesy of Ike Ahmed, MD

Areas of Aqueous Outflow



MIGS devices can be used to restore outflow through:

Outflow Pathway	Disease State
Trabecular Meshwork	Mild-to-Moderate
Suprachoroidal Space	Progressive
Subconjunctival Space	Refractory

Benefit-to-risk ratio is the ultimate criterion in determining MIGS treatment algorithm

MIGS: Mild-to-Moderate Disease Intervention

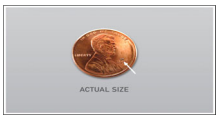
Trabecular Bypass First

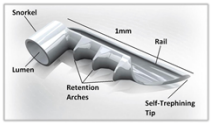
- Designed to restore and maintain natural physiological outflow
- Overall safety profile consistent with cataract surgery alone
- Maintaining the natural pathway avoids atrophy of Schlemm's canal[1]
- Foundational therapy → preferred safety-to-benefit option for mild-to-moderate intervention

1. Rosenquist R, Epstein D, Melamed S, Johnson M, Grant WM. Outflow resistance of enucleated human eyes at two different perfusion pressures and different extents of trabeculotomy. Curr Eye Res. 1989;8(12):1233–40.

First-Ever Micro-Invasive Glaucoma Surgery Device

iStent® TRABECULAR MICRO-BYPASS



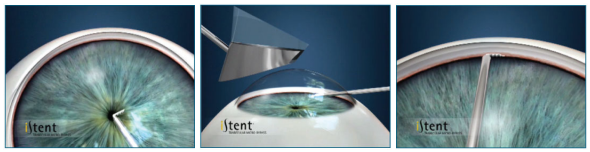


- FDA approved in 2012; implanted in conjunction with cataract surgery
- Smallest device known to be implanted in the human body (1.0 mm x 0.33 mm)
- Heparin-coated stent, pre-loaded in inserter
- Ergonomic rail design protects and accesses underlying collector channels in Schlemm's canal; retention arches help ensure secure placement
- Prolonged reduction in IOP, combined with excellent safety profile
- Overcomes many of the drawbacks of conventional treatment options
- Initial indication in combination with cataract surgery creates revenue to drive pipeline and platform development

16 | Investor Day | September 14, 2017 | © 2017 Glaukos Corporation GLAUKOS

iStent® Surgical Procedure

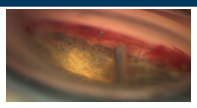
- **The iStent® is inserted *ab interno* through the clear-cornea phaco incision and can be performed under topical anesthesia**

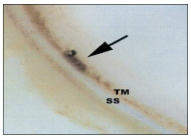


- **The physiological preservation of the trabecular meshwork ensures a natural episcleral back pressure of 8 to 11 mm Hg, ensuring minimal to no risk for hypotony.[1]**

1. Rosenquist R, Epstein D, Melamed S, Johnson M, Grant WM. Outflow resistance of enucleated human eyes at two different perfusion pressures and different extents of trabeculotomy. Curr Eye Res. 1989;8(12):1233–40.

Customized for Optimal Fit and Retention within Schlemm's Canal





- **iStent® dimensions are customized for a natural fit within the 270 µm Schlemm's canal space**
  - Three retention arches ensure secure placement
  - Rail design protects and accesses the underlying collector channels

iStent® bypasses the primary source of resistance to outflow

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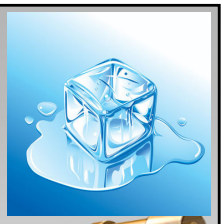
NOT CyPass® MICRO-STENT

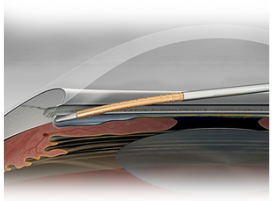


MIGS: Leading the Way in Breakthrough Innovation

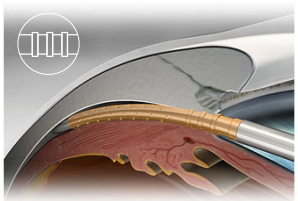
US-CYP-16-E-4391 Alcon

CyPass® Micro-Stent: Intuitive Implantation Approach

The *CyPass*® Micro-Stent is minimally invasive, spares the conjuctiva, and avoids the formation of a filtering bleb.

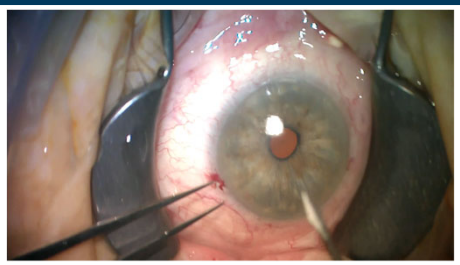


The procedure is ab-interno, using the primary clear corneal incision made at the time of cataract surgery.



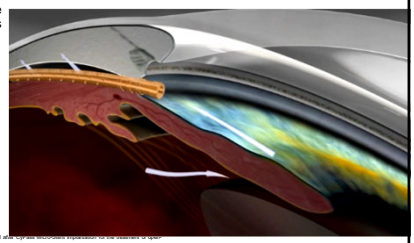
Proximal rings, clearly visible under a gonioscopy lens, provide guidance for proper insertion and depth.

Cypass Insertion



CyPass® Micro-Stent: Enhanced Aqueous Outflow

- The supraciliary space has a negative pressure gradient that drives aqueous outflow and reduction of intraocular pressure[1]
- The uveoscleral pathway bypasses Schlemm's canal and collector channels, which may be atrophic in glaucoma patients[2]
- The *CyPass*® Micro-Stent utilizes the same outflow pathway as first line prostaglandin analogues[3]

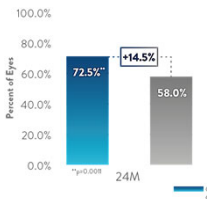


1. Saheb H, Ianchulev T, Ahmed I. Optical coherence tomography of the suprachoroid after *CyPass* Micro-Stent implantation for the treatment of open-angle glaucoma. *Br J Ophthalmol*. 2012;96:19–23.
2. Fellman. Episcleral venous fluid wave correlates with the type and extent of canal-based surgery. AGS 2014 abstract.
3. Weinreb RN, Toris CB, Gabelt BT, et al. Effects of prostaglandins on the aqueous humor outflow pathways. *Surv Ophthalmol*. 2002;47(Suppl 1):S53–S64.

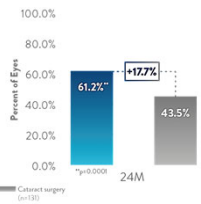
Two-Year COMPASS Trial Results: Supraciliary Microstenting with Phacoemulsification in Patients with Open-Angle Glaucoma and Cataracts

Two-Year COMPASS Trial Results: *CyPass*® Micro-Stent Achieved Primary & Secondary Endpoints

72.5% of eyes achieved a ≥20% reduction in unmedicated diurnal IOP at two years*



61.2% of eyes maintained an unmedicated diurnal IOP range between 6 and 18 mmHg at 24 months



*Prospective, randomized, multicenter clinical trial in patients (n=505) with open-angle glaucoma undergoing cataract surgery randomized to microstent (n=374) or phacoemulsification (n=131). Primary outcome measure was unmedicated diurnal IOP reduction at 24 months versus cataract surgery alone at baseline. Secondary outcomes measures included mean change in 24 month DIOP from baseline and 24 month unmedicated mean IOP (between 6 mmHg to 18 mmHg) versus cataract surgery alone. Medication use at 24 months was also analyzed. The primary and secondary effectiveness analyses were performed using intent to treat (ITT) population.

Safety Findings Support Intended Use

- Safety based on 2-year follow-up with 95% of randomized patients completing study
- Comparable BCVA to cataract surgery
- Ocular SAEs had no long-term impairment
- Overall rate of ocular AEs balanced
- Significant ocular AEs infrequent
- *CyPass*® Micro-Stent – specific AEs managed with good outcomes
- ECL as expected after cataract surgery

Early Success

- First in the state to perform the procedure.
- Allowed select patients to purchase the device and inserted free of charge.
- As a stand alone procedure especially for some sick eyes and complicated patients it offered a unique solution
- Then we started rolling it out with our cataract patients with pre-existing glaucoma.
- Learned quickly that this was not an iStent substitute

Where did we go wrong?

- Significant complications including
- Myopic shift
- Chronic hypotony
- Delayed supra choroidal hemorrhage
- Intermittent postoperative IOP spikes
- Company was very responsive and concerned, but "You are the only one seeing these complications"
- Due to the increased endothelial cell loss found in the 5 year Compass Trial the product was voluntarily withdrawn from the market.

What now?

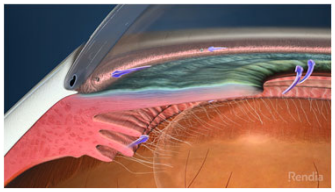
- We sent out a letter to all of our patients explaining that CyPass was withdrawn from the market and why.
- We have brought in every patient for a free exam to check the positioning of the CyPass and to answer any questions.
- We are looking for CyPass alternatives for our patients

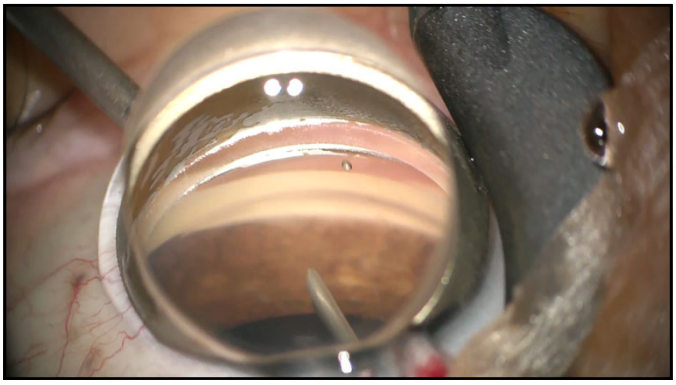
The iStent *inject* Trabecular Micro-bypass

For patients with cataracts and glaucoma

Restore the Pathway for Natural Outflow

iStent *inject* creates two patent bypass pathways through the trabecular meshwork, resulting in multi-directional flow through Schlemm's canal





Outflow Comparison

Aqueous angiography study conducted by Alex Huang, MD

iStent *inject* Advantages

- Creates two patent bypasses through the trabecular meshwork to restore natural outflow
- Significantly and effectively reduces IOP[1-2]
- Optimizes aqueous outflow through the natural physiologic pathway
- Can reduce or eliminate the need for glaucoma medications (at discretion of eye care professional)
- Excellent overall safety profile similar to cataract surgery alone[1]

1. iStent inject® Trabecular Micro-Bypass System: Directions for Use, Part # 45-0176.
2. Hengerer FH. Personal Experience with Second-Generation Trabecular Micro-Bypass Stents in Combination with Cataract Surgery in Patients with Glaucoma: 3-Year Follow-up. ASCRS 2018 Presentation.

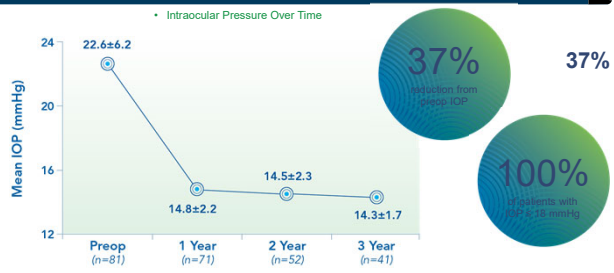
Who is an iStent *inject* Candidate?

- Patients undergoing cataract surgery with mild-to-moderate primary open-angle glaucoma
- Cataract surgery patients who could benefit from better control of their IOP, which may allow for their medications to be reduced
- Patients wanting to decrease risk of IOP fluctuations associated with medication compliance or who are non-adherent to prescribed regimens
- Patients looking to avoid the risks of more invasive procedures
- Patients challenged in paying for medications or who cannot tolerate medications or have experienced negative side effects of glaucoma medications

HENGERER (3 YEAR)

Long-term IOP Reduction at 3 Years[1]

- Intraocular Pressure Over Time

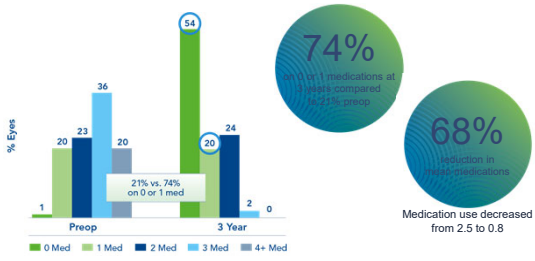


1. Hengerer FH. Personal Experience with Second-Generation Trabecular Micro-Bypass Stents in Combination with Cataract Surgery in Patients with Glaucoma: 3-Year Follow-up. ASCRS 2018 Presentation.

HENGERER (3 YEAR)

Sustained Medication Reduction[1]

- Medication Use Over Time



74%
reduction in medications at 3 years compared to preop

68%
reduction in mean medications

Medication use decreased from 2.5 to 0.8

1. Hengerer FH. Personal Experience with Second-Generation Trabecular Micro-Bypass Stents in Combination with Cataract Surgery in Patients with Glaucoma: 3-Year Follow-up. ASCRS 2018 Presentation

1 YEAR DATA (CLEMENT)

Real-World Results with 1 Year Follow Up

- Retrospective case study pooling data from four surgeons in Australia[1]
- n=172 eyes analyzed at 1 year
- Evaluation of iStent *inject* in combination with cataract surgery
- Continuing follow-up planned on all eyes
- High safety profile observed

66%
medication-free vs. 58% preop

65%
reduction in mean number of meds

Medication use decreased from 1.7 to 0.6

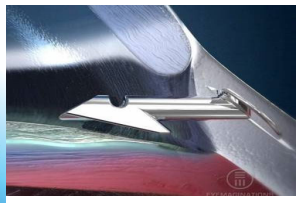
1. Clement C. Outcomes with 2nd generation trabecular micro-bypass stents in patients with glaucoma: multi-center, multi-surgeon experience. APGC 2018 Presentation.

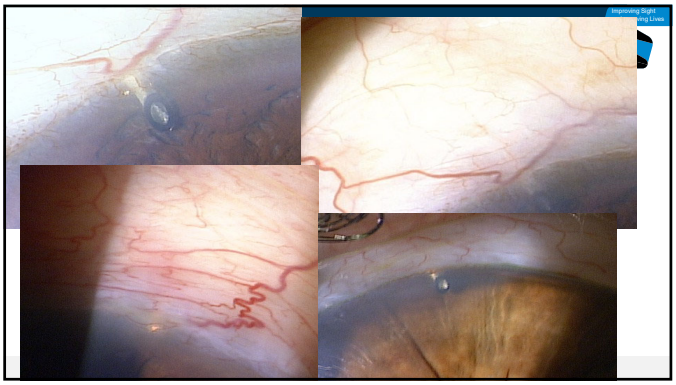
Express the Benefits of iStent *inject* to Your Patients

- You play an important role in the patient's decision about the iStent *inject*– they trust you and want your guidance.

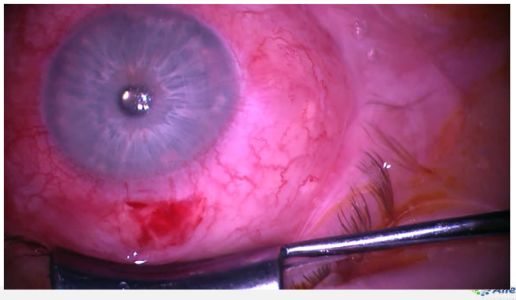
- iStent *inject* is implanted at the same time as cataract surgery with an excellent overall safety profile
- Proven in patients all around the world
- Proven to reduce IOP and may reduce glaucoma medication usage

Ex-PRESS





Traditional Glaucoma Filtering Surgery

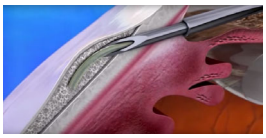


Xen® 45 Gel Stent: Clinical Overview

MIGS: Refractory Disease: Subconjunctival Space

Subconjunctival Bypass

- Labeled for refractory glaucoma:
- Where previous surgical treatment has failed or for patients unresponsive to maximum tolerated medical therapy[1]
- Requires use of an antimetabolite and creates a bleb, requiring ongoing bleb observation and management[1]
- Alternative to a trabeculectomy or tube shunt procedure for refractory patients



1. Directions for Use. MODEL # 5513-001. XEN® GLAUCOMA TREATMENT SYSTEM https://allergan-web-cdn-prod.azureedge.net/actavis/actavis/media/allergan-pi/-/documents/labeling/xen/dfu_xen_glaucoma_treatment_system_us_feb2017.pdf

Overview

- The Xen 45 Gel Stent is composed of gelatin derived from porcine dermis, formed into a cylindrical tube, and then cross-linked with glutaraldehyde[1]
- The microstent is 6 mm long, with an interior diameter of approximately 45 microns and an outer diameter of approximately 150 microns in its dry state[1]
- Prior to implantation, the stent is hard but bendable. Once it is placed, the stent hydrates and swells to create a soft, flexible, non-migrating, drainage channel that is tissue conforming[2]
- The hydration process takes about 2 minutes, during which the outer diameter swells to about 220 microns and the length remains the same at 6 mm[2,3]
- The stent is preloaded in an injector (27 G)[1]

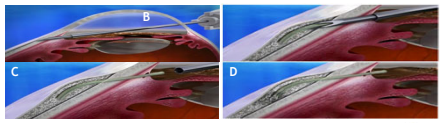


1. Xen 45 Directions for Use (DFU). Irvine, CA: Allergan, Inc.; Feb 2017.
2. Lewis et al. *J Cataract Refract Surg* 2014;40:1301–6
3. Xen45. Schematic. 2016.

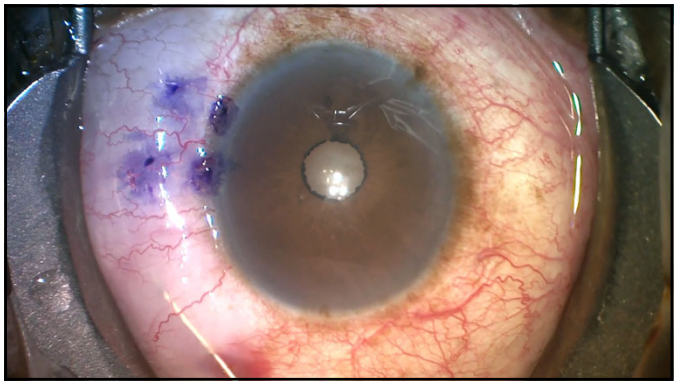
Mechanism of Action

- The Xen 45 Gel Stent is placed in the eye through an ab interno approach[1]:
  - Placed through a small incision in the cornea
  - Eliminates damage to conjunctiva, allowing for future filtration surgery
  - Can be done as a standalone procedure
- Creates a permanent channel through the sclera allowing flow of aqueous humor from the anterior chamber into the subconjunctival space[1,2]
- IOP reduction via:[1]
  - Low and diffuse outflow into intact tissue anatomy

Main Steps of the Xen 45 Gel Stent Procedure[2]:

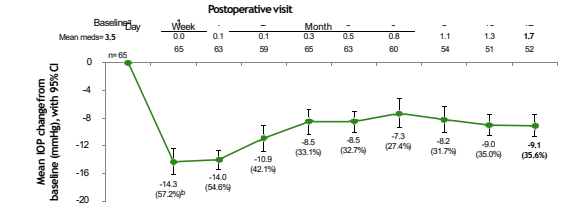


1. Vera V, Horvath C. In: Samples, Ahmed (eds) Surgical Innovations in Glaucoma. Springer Science and Business Media, New York, 2014.; 2. Xen® 45 Directions for Use (DFU). Irvine, CA: Allergan, Inc.; Feb 2017.



Primary Effectiveness Analyses: IOP Reduction

- 76.3% of patients achieved ≥ 20% IOP reduction from baseline at 12 months on the same or fewer medications (n = 65)



This graph shows a subgroup analysis that excluded patients with missing data (n = 4) as well as nonresponders who required secondary surgical intervention (n = 9)
[a]Mean diurnal IOP
[b]Shown in parentheses: mean percentage changes from baseline
CI = confidence interval

1. Grover DS, et al. *Am J Ophthalmol* 2017;183:25–36.

Additional Effectiveness Analyses: IOP and Glaucoma Medications Based on Observed Data

Visit IOP and Medications	Mean (SD) (n = 52)
Baseline	
Medicated IOP	25.1 (3.7)
# Glaucoma Medications	3.5 (1.0)
Month 12	
IOP	15.9 (5.2)
# Glaucoma Medications	1.7 (1.5)

This table shows a subgroup analysis that excluded patients with missing data (n = 4) as well as nonresponders who required secondary surgical intervention (n = 9); Observed data

1. Grover DS, et al. *Am J Ophthalmol* 2017;183:25–36.

Bleb Needling Procedures at ≤ 12 Months

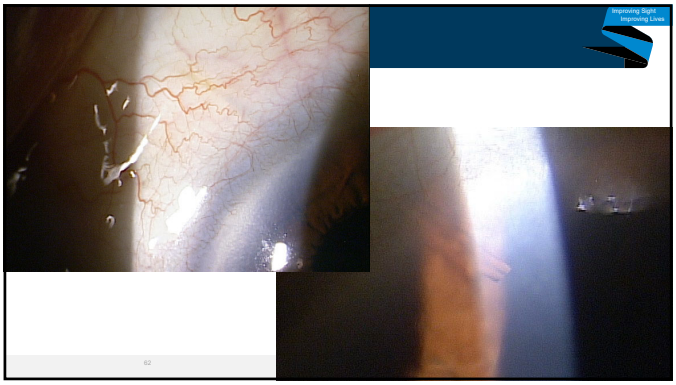
Bleb Needling Procedure at ≤ 12 Months	N = 65 n (%)
Bleb Needling Performed	
Yes	21 (32.3%)
No	44 (67.7%)
Reason for Bleb Needling	
Flat bleb with absence of microcysts	11 (16.9%)
Bleb filtration area is fibrotic or blocked	12 (18.5%)
Subject has a high risk of bleb failure based on assessment by the investigator	10 (15.4%)
Number of Needling Procedures Performed per Subject	
1	14 (21.5%)
2	6 (9.2%)
3	1 (1.5%)
# of Subjects who had Needling Procedure with MMC	
No	14 (21.5%)
Yes	7 (10.8%)

1. Xen 45 Directions for Use (DFU). Irvine, CA: Allergan, Inc.; Feb 2017.

Overview of Literature: Xen 45 as a Standalone Procedure

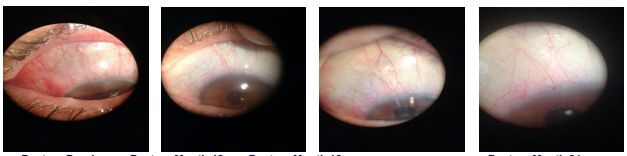
	Xen 45 Gel Stent (Implant Only)	
	Tan et al[1] RETROSPECTIVE N = 39 eyes	Schlenker et al[2] RETROSPECTIVE N = 185 Xen eyes
Pre-op IOP (medicated)	24.9 ± 7.8 mm Hg	Median 24.0
Post-op IOP (12M medicated)	14.5 ± 3.4 mm Hg	Median 13.0
IOP reduction from baseline at 12M (%)	41.8%	45.8%
Pre-op # of Meds	3	3.0
Post-op # Meds (12M)	0.7	0
Change from baseline # Meds	-2.3	-3
Needling Rate	51.3%	43.2%

1. Tan SZ, et al. *Eye (Lond).* 2018;32(2):324-332.; 2. Schlenker MB, et al. *Ophthalmology* 2017;124:1579-1588.



Appearance/Morphology of the Xen 45 Bleb (cont'd)

Images below provide an example of bleb post Xen implantation on postoperative days 1, month 12, 18 and 24:



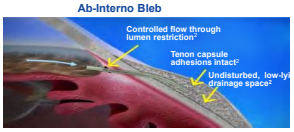
Post-op Day 1 | Post-op Month 12 | Post-op Month 18 | Post-op Month 24

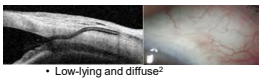
*Photos property/courtesy of Francisco Millan MD and Vanessa Vera MD

Appearance/Morphology of the Xen 45 Bleb

Xen is the first procedure that creates a low-lying, ab-interno bleb in refractory glaucoma[1,2]

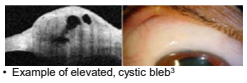
Ab-Interno Bleb





- Low-lying and diffuse[2]

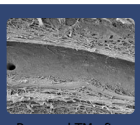
Ab-Externo Bleb



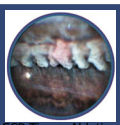
- Example of elevated, cystic bleb[3]

1. Xen 45 Directions for Use (DFU). Irvine, CA: Allergan, Inc.; November 2016.; 2. Dapena CL, Ros RC. *Revista Española de Glaucoma e Hipertensión Ocular.* 2015;5(3):350-357.; 3. Errico D, et al. *Clin Ophthalmol.* 2011;5:1679-1686.

Where Do Tissue Ablative Procedures Fit in the Algorithm?



Removed TM after Trabectome



ECP Tissue Ablation

Kahook Dual Blade

Permanent tissue destruction can preclude future canal-based procedures (such as trabecular stenting or drug-eluting stents).

Very limited data available on newer devices. Long-term results not yet published.

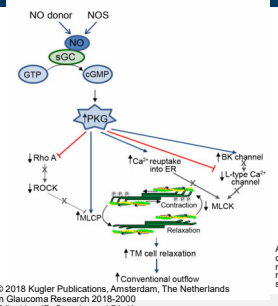
Thank You

Improving Sight – Improving Lives

"Placing Patients First by Making Excellence in Eye Care a Tradition"

SPECIALTY EYE INSTITUTE

Nitric Oxide Activates the Soluble Guanylate Cyclase-Cyclic Guanosine Monophosphate Signaling Pathway



In Glaucoma Research 2018-2000
Edited by: JR. Samples and PA. Knepper

- NO activates the sGC-cGMP cascade in trabecular meshwork (TM) cells resulting in activation of PKG which, in turn,
  - inhibits Rho GTPases, the proteins that directly activate the Rho kinase pathway
  - inhibits intracellular calcium release and extracellular calcium influx
- Culminates in TM cell relaxation and increased aqueous humor outflow

Abbreviations: BK channel, large conductance Ca2+-activated K+ channel; Ca2+, calcium; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; MLCP, myosin light chain phosphatase; MLCK, myosin light chain kinase; NO, nitric oxide; NOS, nitric oxide synthase; PKG, protein kinase G; ROCK, rho-associated protein kinase; sGC, soluble guanylatel cyclase; TM, trabecular meshwork.

Cavet ME, et al. *J Ocul Pharmacol Ther.* 2018;34(1-2):52-60

Demonstrated safety as compared to cataract surgery alone

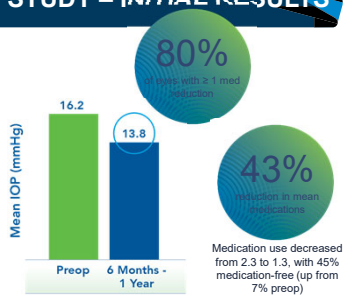
Adverse Event, %	CyPass® Micro-Stent + Phaco (n=224)	Phaco only (n=131)
Blepharitis	1.9%	0.0%
Corneal abrasion	1.9%	1.5%
Corneal edema	3.5%	1.5%
Conjunctivitis	1.1%	2.3%
Cyclodialysis cleft	1.9%	0.0%
Hyphema, intraoperative	2.7%	0.0%
Hypotony IOP <6 mmHg	2.9%	0.0%
IOL complication	1.1%	0.0%
IOP elevation, ≥10 mmHg above baseline	4.3%	2.3%
Iritis	8.6%	3.8%
Loss of BCVA; ≥10 letters read	8.8%	15.3%
Maculopathy/retinopathy (cystoid, diabetic, other)	3.2%	3.1%
Microstent obstruction	2.1%	N/A
Subconjunctival hemorrhage	2.1%	0.8%
Surgical reintervention	5.1%	5.3%
[illegible]	5.6%	3.1%
Visual field loss progression	6.7%	9.9%

- Intraoperative adverse events
  - 5% of *CyPass*® Micro-Stent patients
- Incidence of postoperative adverse events
  - 39% of *CyPass*® Micro-Stent patients
  - 36% of Control patients
- Postoperative AEs were generally manageable and transient and did not negatively affect functional outcomes such as visual acuity

Safety Population, events occurring at rate of 1.0% or greater

HARASYMOWYCZ (6 MONTH - 1 YEAR)
LARGE RETROSPECTIVE STUDY – INITIAL RESULTS[1]

- Retrospective case review with iStent *inject* from a single clinic in Montreal[1]
- n=179 eyes of 105 patients
- Evaluation of IOP and medication reduction following implantation of iStent *inject* with concomitant cataract surgery in glaucoma patients
- 6 months - 1 year outcomes presented with continued data collection



Medication use decreased from 2.3 to 1.3, with 45% medication-free (up from 7% preop)

1. Harasymowycz P. Single surgeon evaluation of second-generation trabecular micro-bypass stents in patients with mild to severe glaucoma. ASCRS 2018 Presentation.