

# Changing Paradigms in the Management of Glaucoma

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# Disclosures

- Aeon
- Alcon
- Allergan
- AqueSys
- Calhoun Vision
- Carl Zeiss Meditec
- ForSight Labs
- Glaukos
- InnFocus
- IRIDEX
- Ivantis
- NeoMedix
- Ocular Therapeutix
- Ocunetics
- SOLX
- Transcend Medical
- TrueVision Systems
- WaveTec Vision

# Case 1. Clinical History

- 72 y.o. man presents for regular yearly examination complaining of ocular redness, ocular FB sensation and difficulty reading fine print
- Past Ocular History: POAG OU
- Past Medical History: Coronary artery disease
- Family History: Multiple family members with POAG
- Medications: Timolol 0.5% OU QAM; Latanoprost OU QHS

# Clinical Examination

- Best-corrected Visual Acuity: 20/30 OU, but does glare to 20/50 OU
- Manifest Refraction: -1.50 sphere OU
- Visual fields: Early arcuate defects OU
- Corneal Pachymetry: 540  $\mu\text{m}$  OD; 546  $\mu\text{m}$  OS
- Goldmann Tonometry: 23 mm Hg OU
- OHS: 0.7 OU with disc heme inferiorly OD



# How do you recommend that we manage this patient?

- 1) Alter glaucoma medication regimen
- 2) Laser trabeculoplasty
- 3) Filtration surgery alone
- 4) Combined cataract and filtration surgery
- 5) Combined cataract and iStent surgery

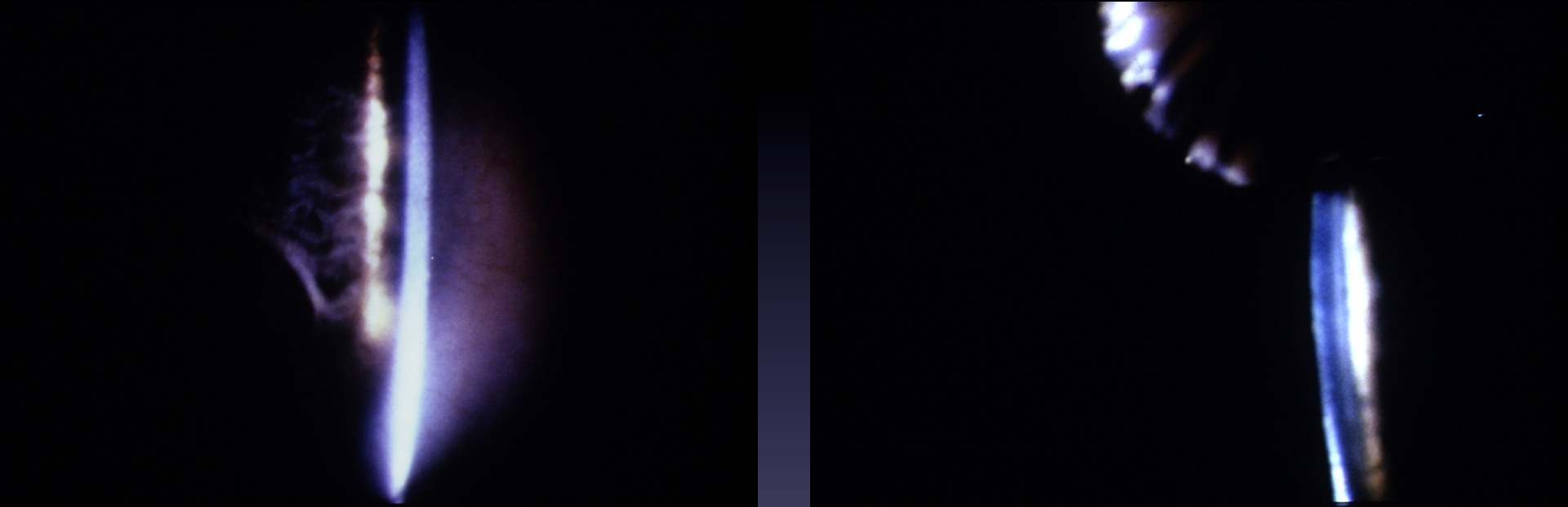
# Case 2. Clinical History

- 64 y.o. woman presents for regular yearly examination complaining of glare difficulty while driving at night
- Past Ocular History: unremarkable
- Past Medical History: systemic hypertension
- Family History: Maternal grandmother with chronic angle closure glaucoma

# Clinical Examination

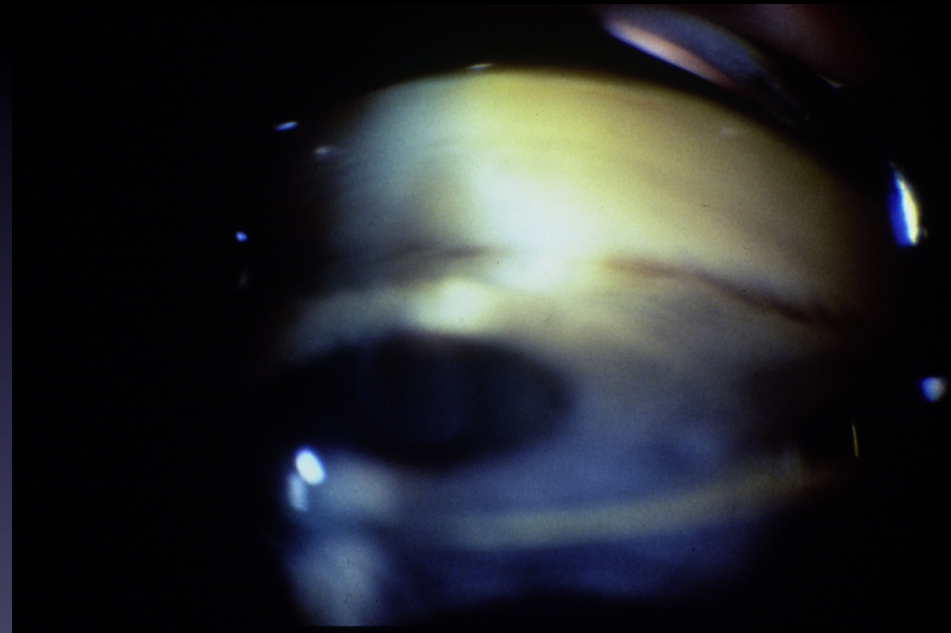
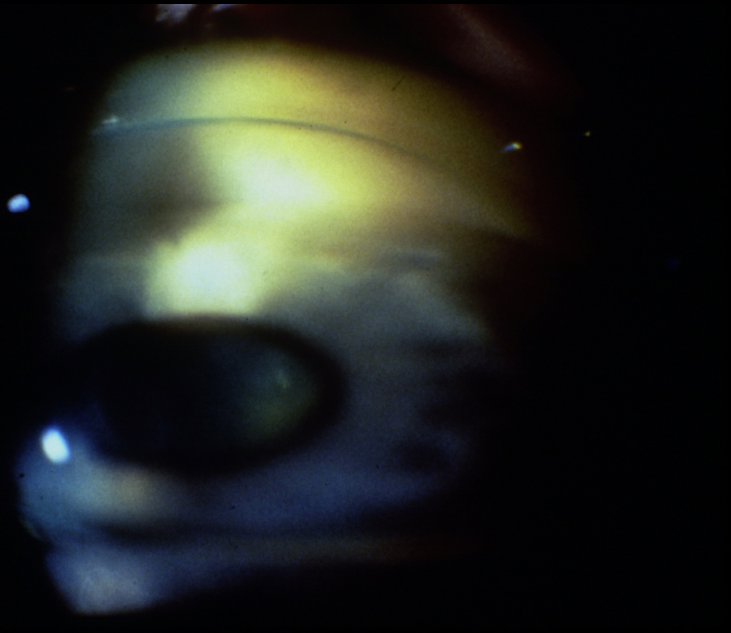
- Best-corrected Visual Acuity: 20/25 OU, but does glare to 20/50 OU
- Manifest Refraction: +2.50 sphere OU
- Visual fields: full OU
- Corneal Pachymetry: 520  $\mu\text{m}$  OD; 525  $\mu\text{m}$  OS
- Goldmann Tonometry: 22 mm Hg OU

# Slit Lamp Examination



- 1-2 Nuclear Sclerosis OU
- Healthy ONHs OU (0.2 CDR OU)

# Indentation Gonioscopy



# How do you recommend that we manage this patient?

- 1) Close observation
- 2) Laser peripheral iridotomy
- 3) Laser peripheral iridoplasty
- 4) Cataract surgery alone
- 5) Cataract surgery combined with iStent

# What Has Changed?

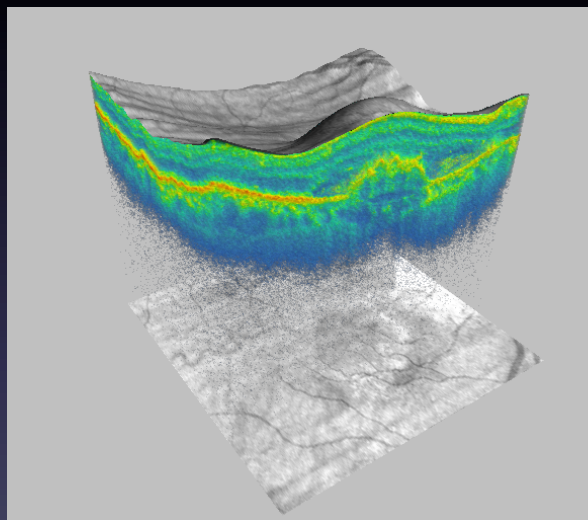
**Improved Glaucoma Diagnostic Technology**

**Advances in Medical Therapy**

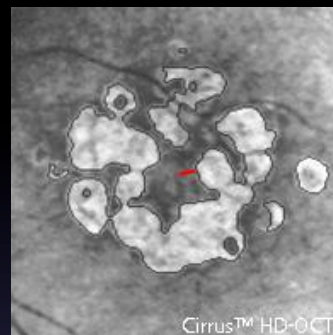
**Advances in Laser Technology**

**Advances in Incisional Surgery**

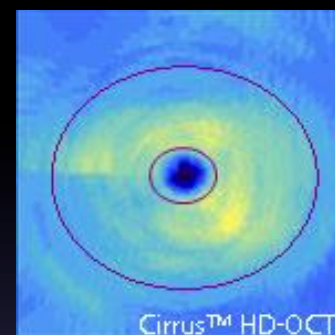
# Advances in OCT



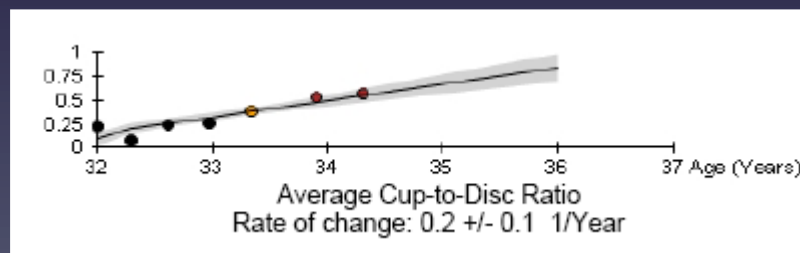
Existing Cirrus Cube data



Advanced RPE Analysis



Ganglion Cell Analysis



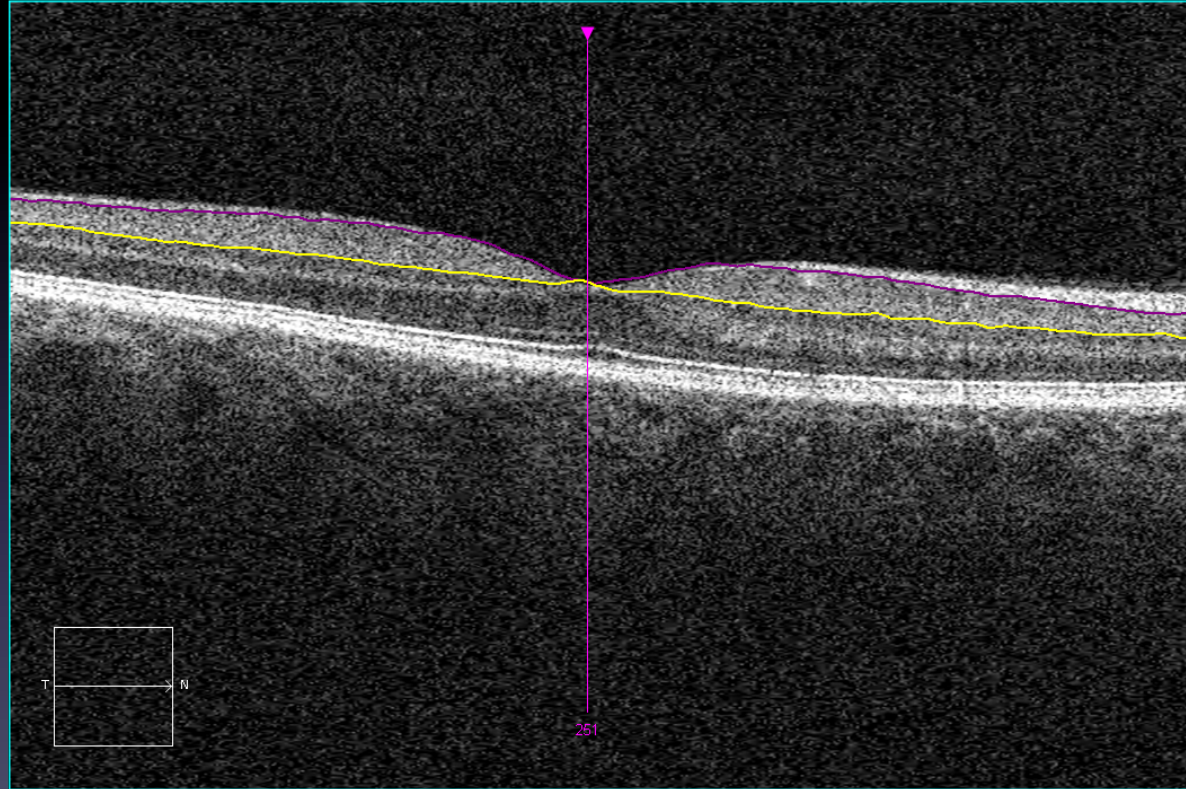
GPA™ with Optic Nerve Head



# Ganglion Cell Analysis

- Measures thickness for the sum of the ganglion cell layer and inner plexiform layer (GCL + IPL layers) using data from the Macular 200 x 200
- or 512 x 128 cube scan patterns.

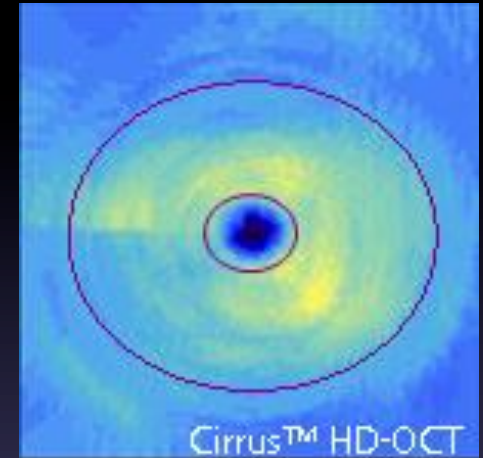
RNFL distribution in the macula depends on individual anatomy, while the GCL+IPL appears regular and elliptical for most normals. Thus, deviations from normal are more easily appreciated in the thickness map by the practitioner, and arcuate defects seen in the deviation map may be less likely to be due to anatomical variations.



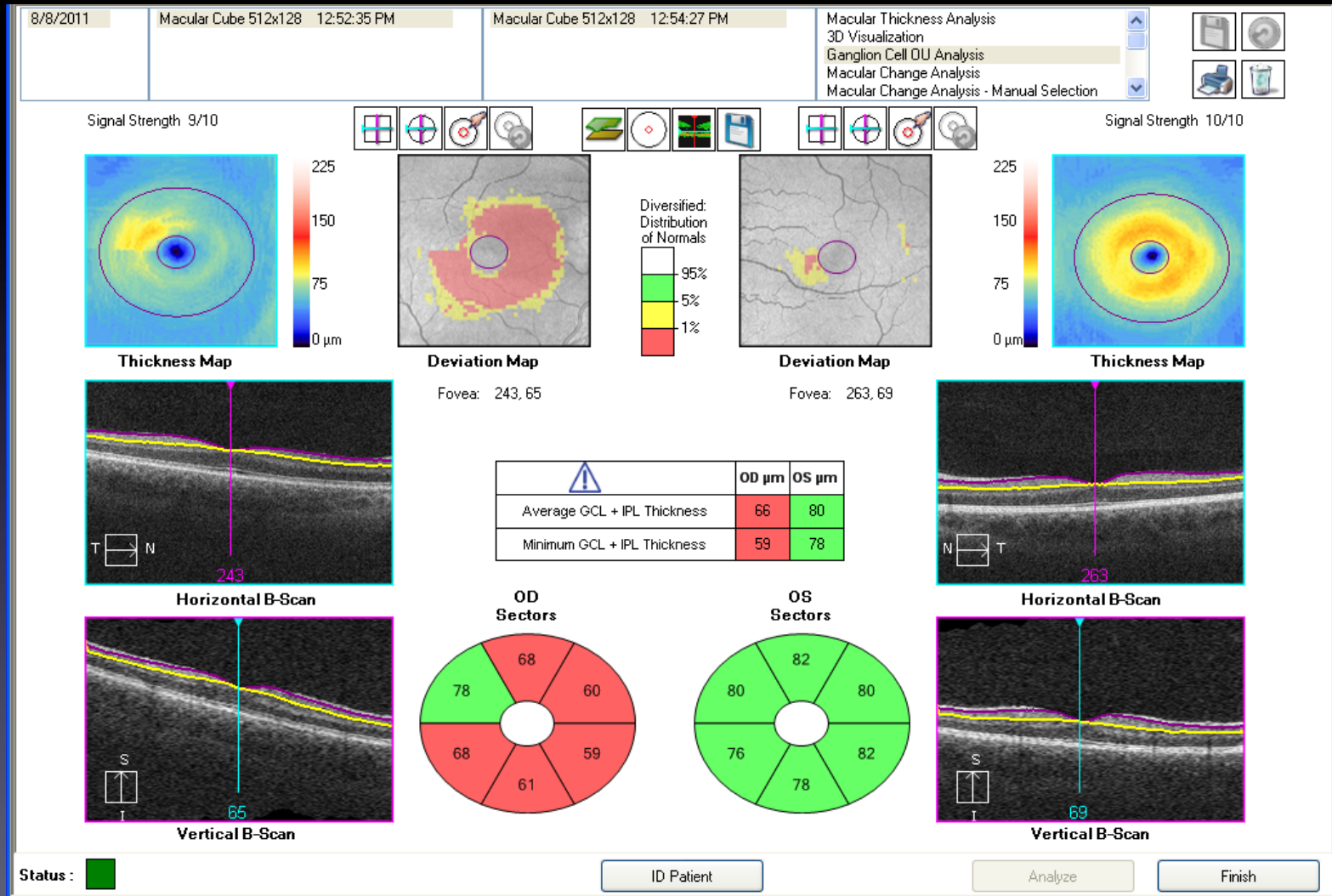
# Ganglion Cell Analysis

The analysis contains:

- Data for both eyes (OU)
- Thickness Map - shows thickness measurements of the GCL + IPL in the 6mm by 6mm cube and contains an elliptical annulus centered about the fovea.
- Deviation Maps - shows a comparison of GCL + IPL thickness to normative data.
- Thickness table - shows average and minimum thickness within the elliptical annulus.
- Sector maps - divides the elliptical annulus of the Thickness Map into 6 regions: 3 equally sized sectors in the superior region and 3 equally sized sectors in the inferior region. Values are compared to normative data.
- Horizontal and Vertical B-scans.



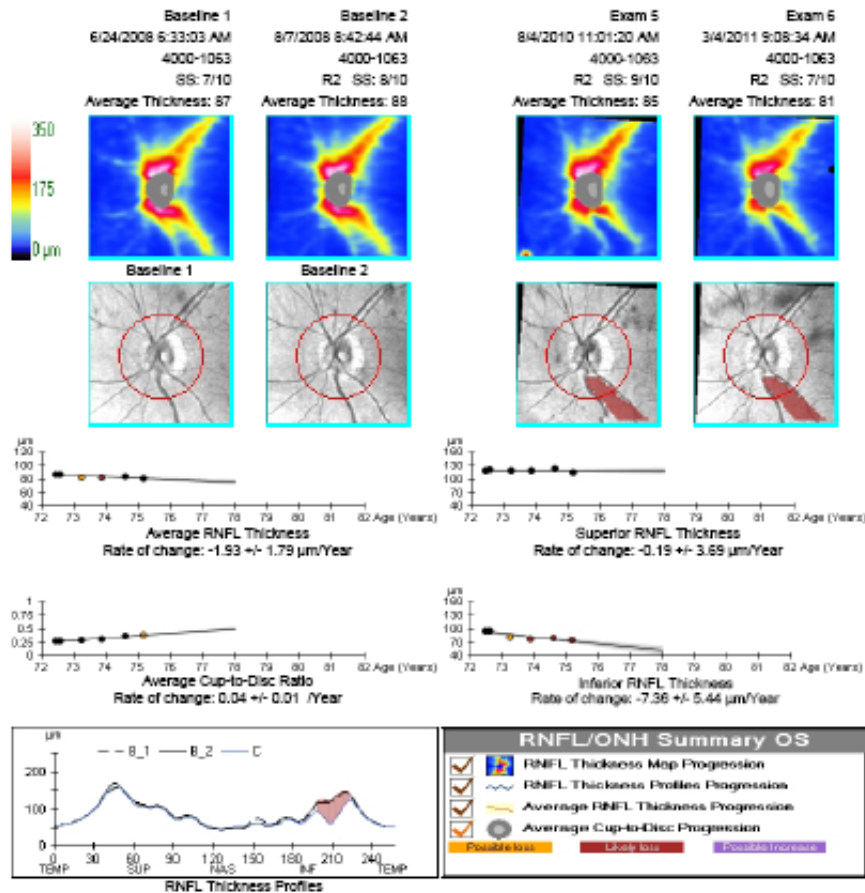
# Ganglion Cell Analysis



# Guided Progression Analysis

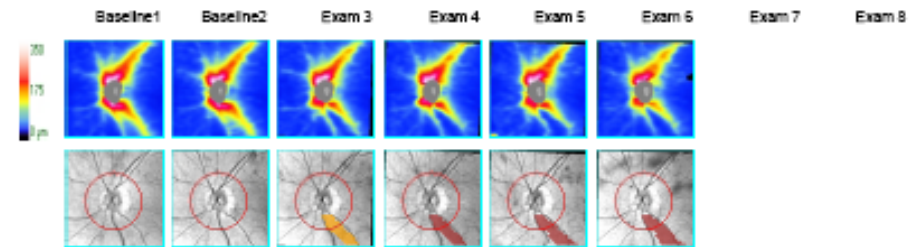
## Guided Progression Analysis: (GPA™)

OD ☐ OS ☒



## Guided Progression Analysis: (GPA™)

OD ☐ OS ☒



RNFL and ONH Summary Parameters

	Exam	Date/Time	Serial Number	Registration Method	SS	Avg RNFL Thickness ( $\mu\text{m}$ )	Inf Quadrant RNFL ( $\mu\text{m}$ )	Sup Quadrant RNFL ( $\mu\text{m}$ )	Rim Area ( $\text{mm}^2$ )	Average Cup-to-Disc Ratio	Vertical Cup-to-Disc Ratio	Cup Volume ( $\text{mm}^3$ )
Baseline1:	1	6/24/2008 6:33:53 AM	4000-1063		6/10	87	97	123	1.32	0.30	0.33	0.028
Baseline2:	2	8/7/2008 8:42:44 AM	4000-1063	R2	8/10	87	97	120	1.28	0.28	0.29	0.025
	3	4/2/2009 3:44:24 PM	4000-1063	R2	7/10	83	82	118	1.25	0.34	0.39	0.040
	4	11/18/2009 2:27:57 PM	4000-1063	R2	7/10	83	79	119	1.23	0.31	0.33	0.030
	5	8/4/2010 11:01:20 AM	4000-1063	R2	9/10	84	81	125	1.24	0.37	0.42	0.036
Current:	6	3/4/2011 9:08:34 AM	4000-1063	R2	7/10	81	76	116	1.20	0.39	0.44	0.053

### Registration Methods

R2 - Registration based on translation and rotation of OCT fundus  
R1 - Registration based only on translation of disc center

**Likely Loss**

Possible Loss

Possible Increase

Compared to baseline, statistically significant loss of tissue detected. For Average RNFL, Superior RNFL, Inferior RNFL, Rim Area the values have decreased. For Cup-to-Disc Ratios and Cup Volume values have increased.

Compared to baseline, statistically significant increase detected. For Average RNFL, Superior RNFL, Inferior RNFL, Rim Area values have increased. For Cup-to-Disc Ratios and Cup Volume values have decreased.

# Landscape of Medical Therapy

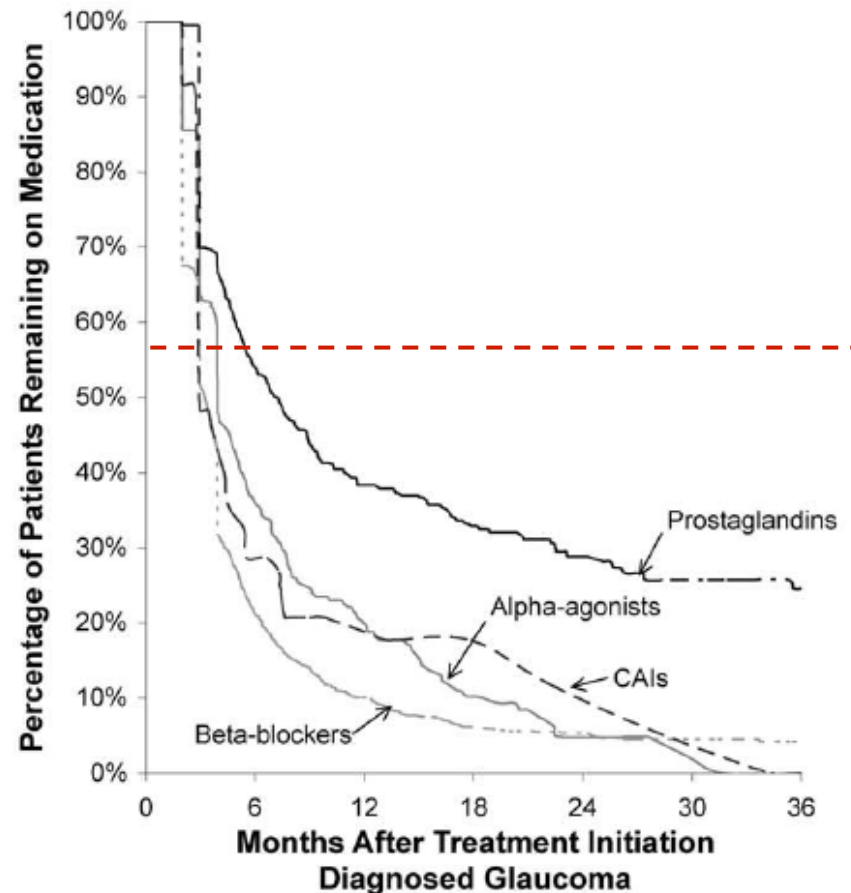
Poor patient compliance leads to diminished efficacy/disease progression

Difficulty in administration

Need for high drug concentrations

Preservatives can cause side effects

Persistence and Adherence With Topical Glaucoma Therapy<sup>(1)</sup>





# Advances in Medical Therapy

- Combination Medications
- Preservative Free Drug Alternatives
- Novel Drugs on Horizon
- Novel Drug Delivery Systems

# Combination Medications

- Timolol-dorzolamide  
(Cosopt)
- Timolol-brimonidine  
(Combigan)
- Brinzolamide-brimonidine  
(Simbrinza)



# Preservative Free Alternatives

- Ocudose Timolol
- Tafluprost (Zioptan)
- Timolol-dorzolamide (Cosopt PF)
- Compounded formulations



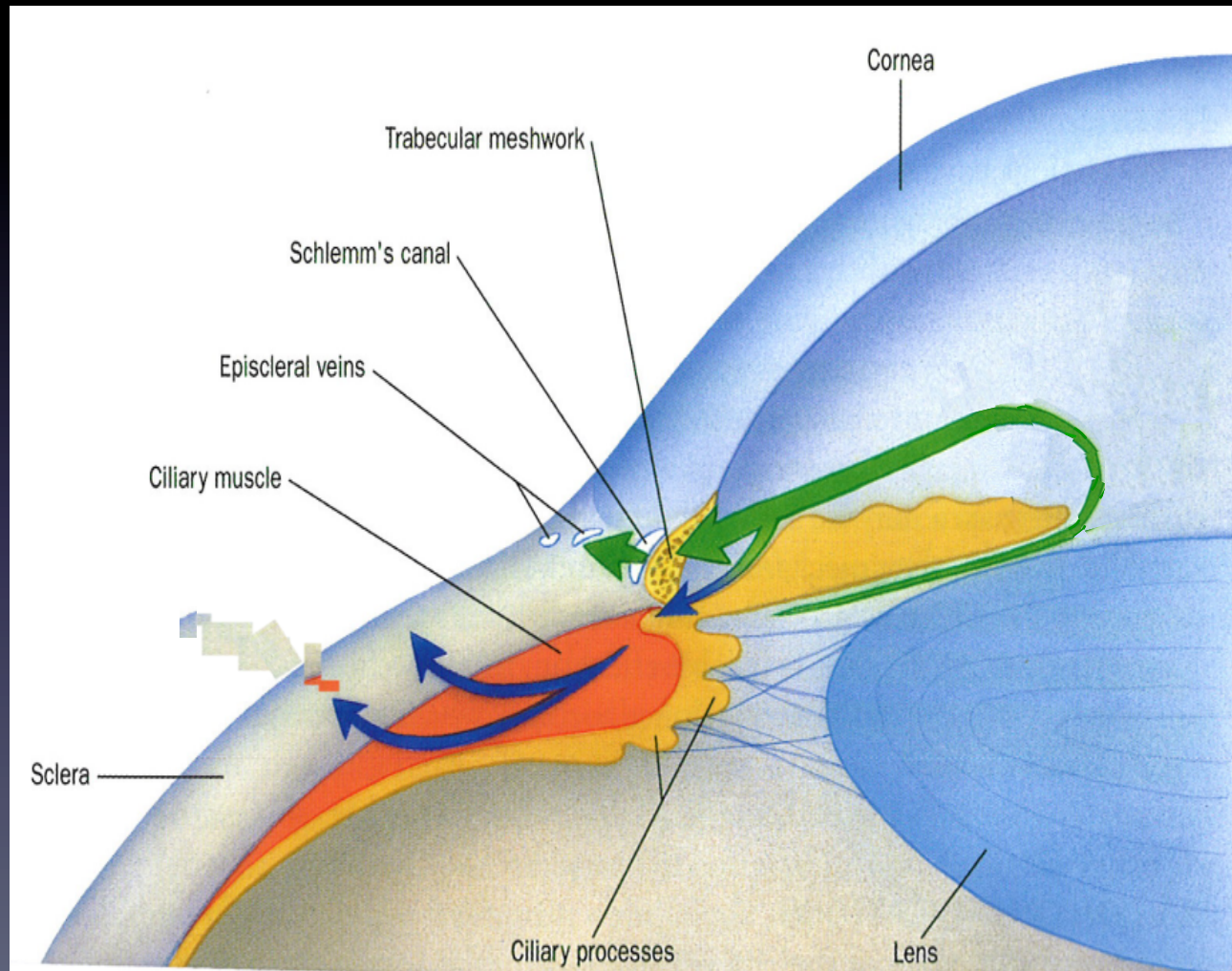
# Drugs Under Investigation

- Nitric oxide-donating prostaglandins
- Rho-kinase (ROCK) inhibitors

# Aqueous Humor Dynamics

## IOP – A complex homeostasis

- Aqueous formation in ciliary body – passive diffusion, ultrafiltration and active secretion
- Conventional Outflow – Trabecular Meshwork → Schlemm's Canal → Episcleral Venous System
- Non-Conventional Outflow – Uveoscleral

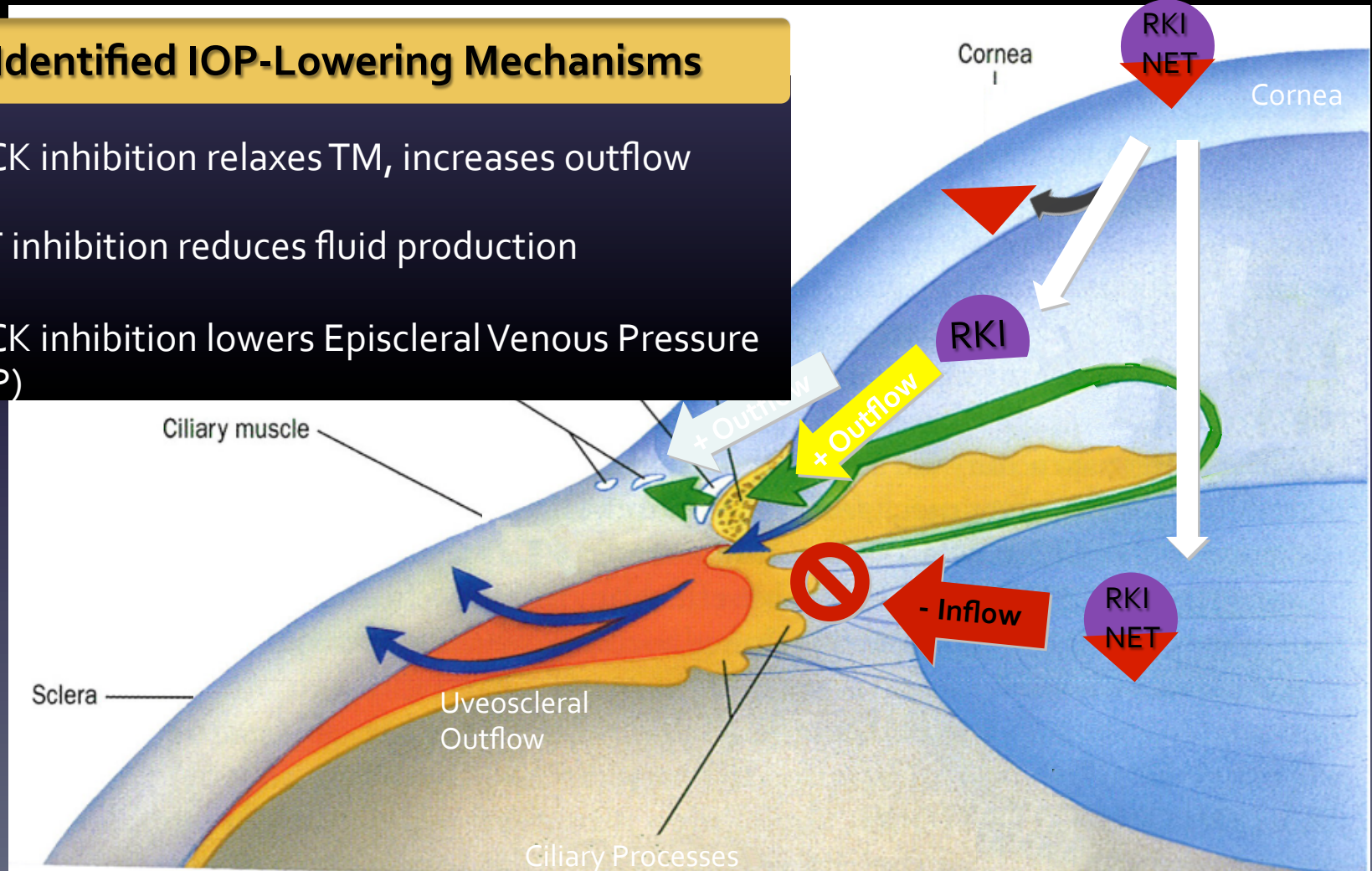


# AR-13324 (ROCK-NET Inhibitor)

## Triple-Action

### 3 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM, increases outflow
- NET inhibition reduces fluid production
- ROCK inhibition lowers Episcleral Venous Pressure (EVP)

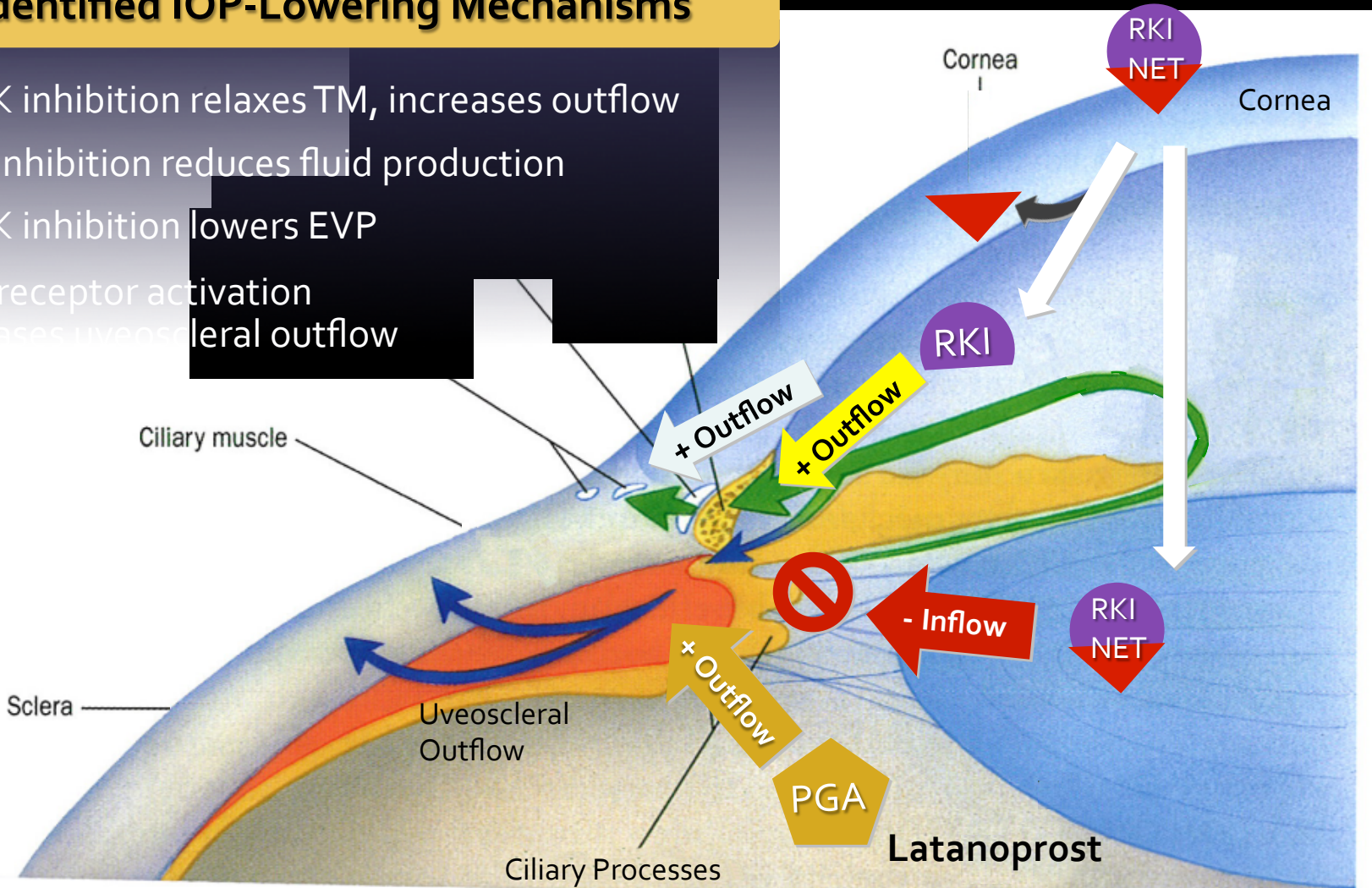




# Quadruple-Action PG<sub>324</sub> (ROCK-NET Inhibitor/latanoprost)

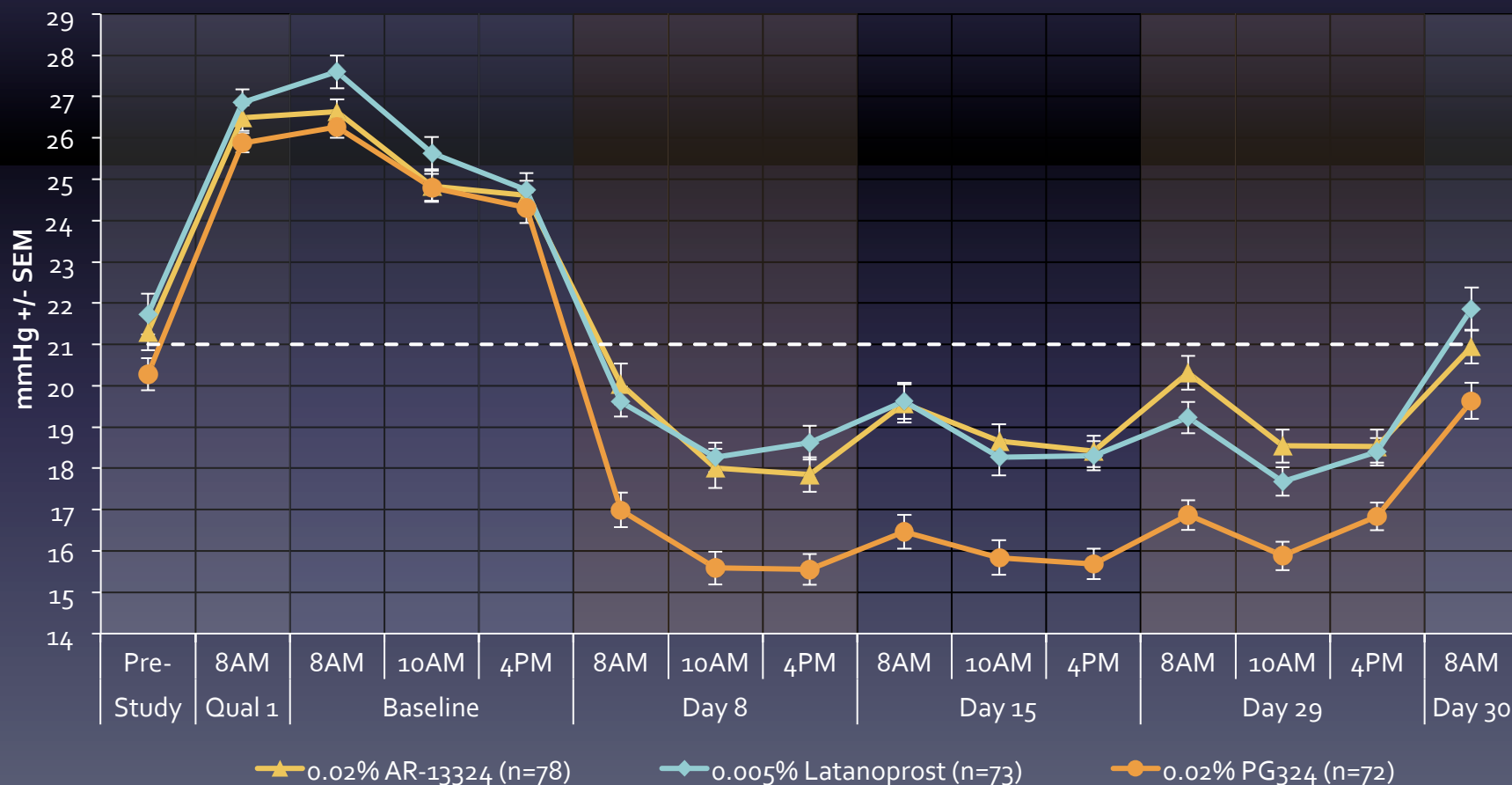
## 4 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM, increases outflow
- NET inhibition reduces fluid production
- ROCK inhibition lowers EVP
- PGA receptor activation increases uveoscleral outflow



# 0.02% PG324 Achieved Statistical Superiority Over Individual Components at All Time Points ( $p < 0.001$ )

## Mean IOP at Each Time Point Primary Efficacy Measure



# PG<sub>324</sub> (ROCK-NET Inhibitor/ latanoprost)

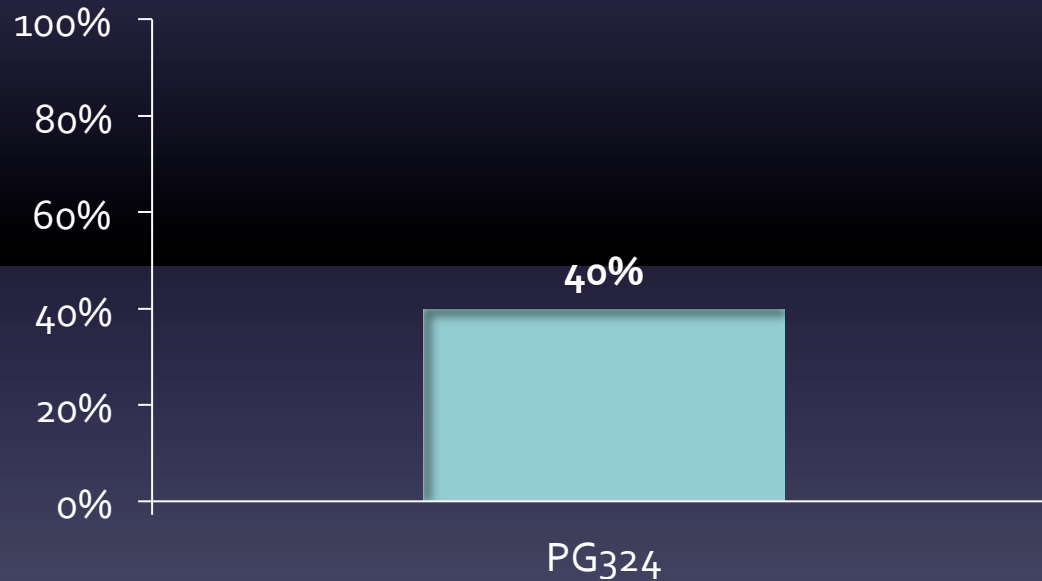
	0.02% PG <sub>324</sub> (n = 72)	0.005% latanoprost (n = 73)		0.02% AR-13324 (n = 78)	
	Mean	Mean	Difference*	Mean	Difference*
Day 8					
8 AM	17.0	19.6	-2.6	20.0	-3.1
10 AM	15.6	18.3	-2.7	18.0	-2.4
4 PM	15.6	18.6	-3.1	17.9	-2.3
Day 15					
8 AM	16.5	19.6	-3.2	19.6	-3.1
10 AM	15.8	18.3	-2.4	18.7	-2.8
4 PM	15.7	18.3	-2.6	18.4	-2.7
Day 29					
8 AM	16.9	19.2	-2.4	20.3	-3.4
10 AM	15.9	17.7	-1.8	18.6	-2.7
4 PM	16.8	18.4	-1.6	18.5	-1.7

- 0.02% PG<sub>324</sub> superior to latanoprost by 1.6–3.2 mmHg (p<0.001)
- 0.02% PG<sub>324</sub> superior to AR-13324 by 1.7–3.4 mmHg (p<0.001)

\* Difference between 0.02% PG<sub>324</sub> and latanoprost or AR-13324

# Most Common AE in PG324 Phase 2b was Conjunctival

**Asymptomatic, Transient, Self Limited**



**80% of Hyperemia was graded Mild by Biomicroscopy**

# Summary

## **AR-13324 Novel ROCK-NET Inhibitor**

- Targets diseased tissue – Trabecular Meshwork
- Lowers EVP
- Reduces AH production
- + latanoprost (PG<sub>324</sub>) ↑ uveoscleral outflow

## **Positive Phase 2 Study Results**

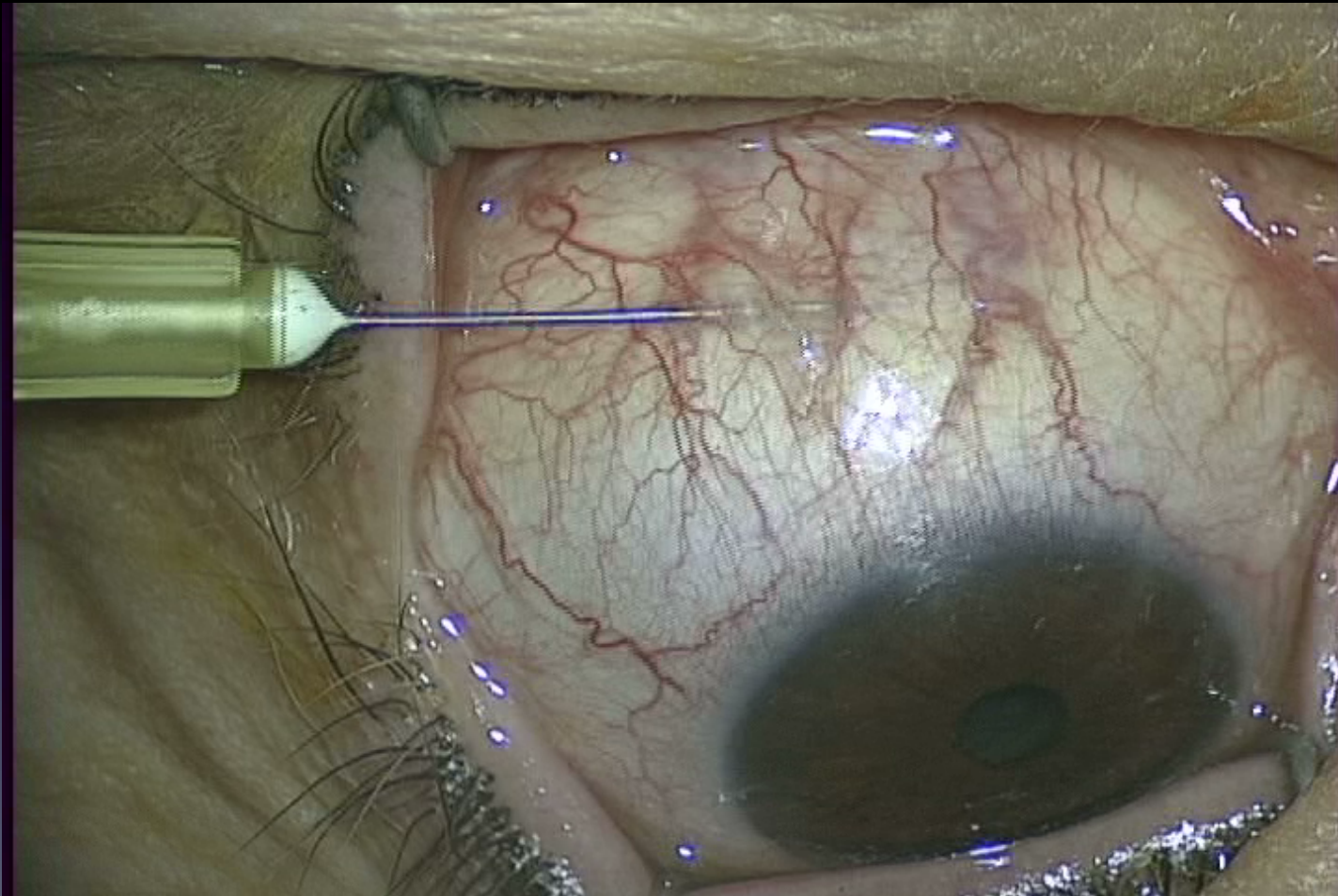
- AR-13324 0.02% QD
  - ♦ Consistent IOP reduction independent of baseline pressure
- PG<sub>324</sub> 0.02% QD
  - ♦ Significantly better IOP lowering than latanoprost or AR-13324 0.02%
- Hyperemia rates similar to prostaglandin analogs



# Advances in Drug Delivery

- Injectable
- Contact lenses
- Punctal plug delivery
- Other implantable systems

# Anecortave Acetate Injection

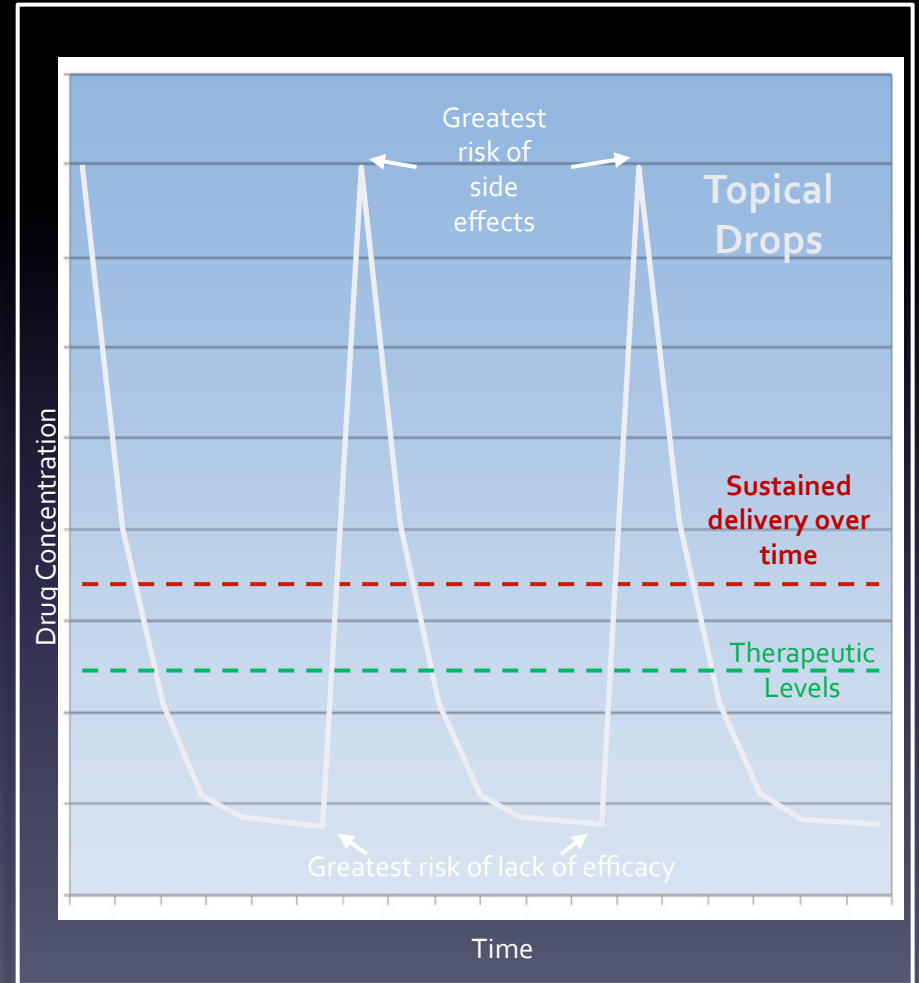




# Drug Eluting Punctum Plugs

## Expected Punctum Plug Benefits:

- Sustained delivery over time
- Improves compliance
- Vastly reduces dosing frequency
- Reduces patient burden
- May improve safety/efficacy



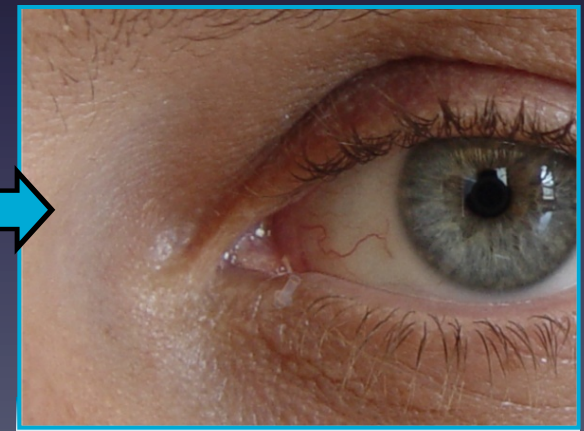
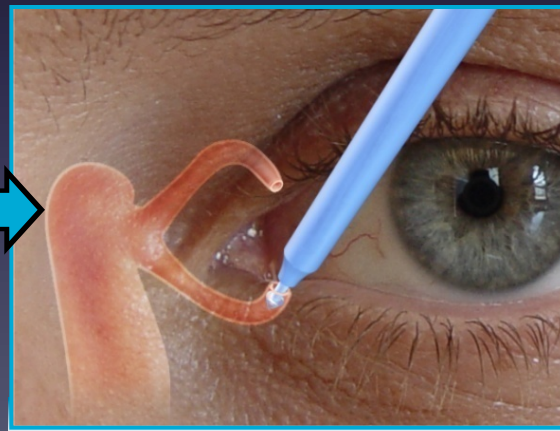
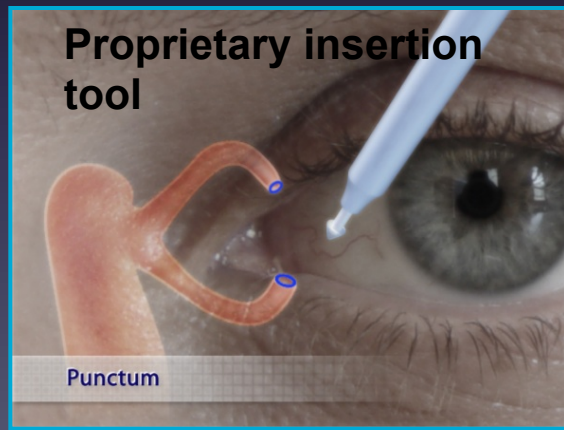
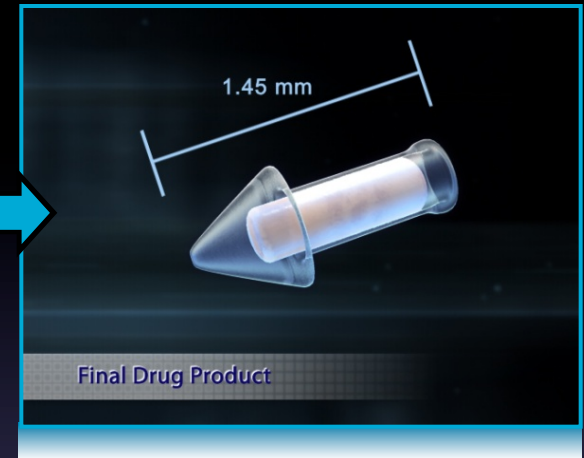
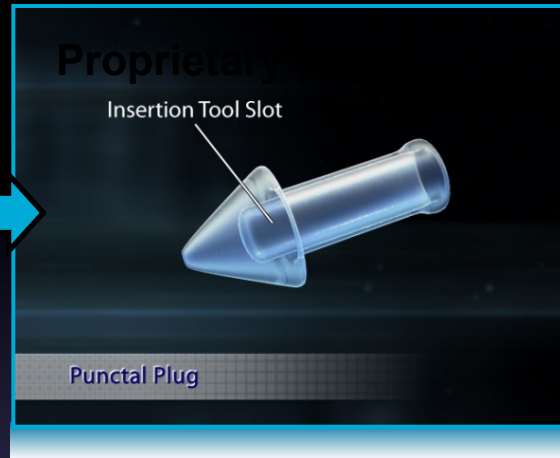
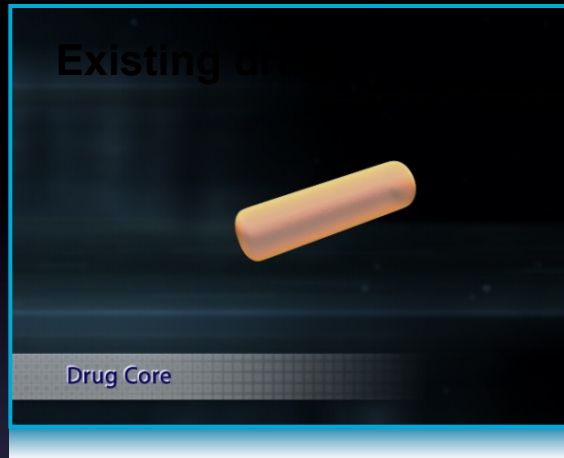
# Eluting Plugs Under Investigation



	Biodegradable Plugs	Classic Plugs
Drug capacity	Higher capacity	Lower capacity <sup>(1)</sup>
Drug release	Adjustable, consistent release rate	High initial release rate which decreases over time
Plug design	Drug encapsulated in pliable hydrogel; incorporates fluorescent label for patient visualization	Drug core within hard plastic shell
Patient experience	Soft plug sits beneath punctal opening	Foreign body sensation due to protrusion of plastic cap
Absorption	Bioresorbable material	Non-absorbable material

1. Clinical trial required use of two plugs per eye to achieve clinically meaningful results, which caused epiphora.

# Non-Absorbable Eluting Punctal Plug





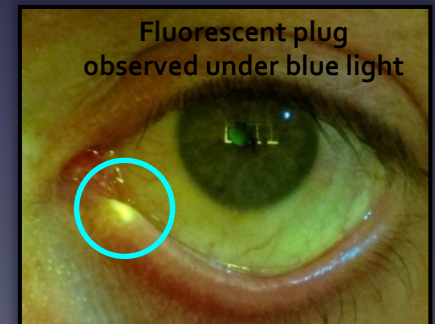
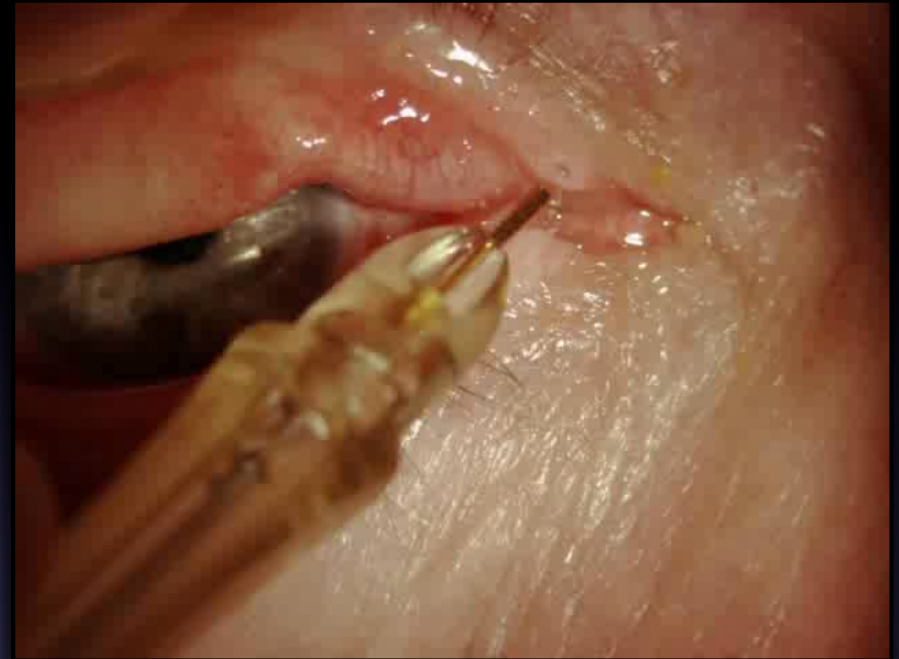
# Biodegradable Eluting Plug

## Product Design

- Disease-specific, tailored drug release and plug persistence

## Procedure <sup>(1)</sup>

- Easy to insert, familiar procedure to physicians <sup>(2)</sup>
- Upon insertion, shrinks in length and expands in width
- Non-invasive
- Absorbable – no need for removal



1. Drug-eluting punctum plugs are investigational new drugs and not commercially available in the United States or other geographies  
2. Based on clinical trials conducted and on physician experiences with commercially available punctum plugs for the treatment of dry eye

## Replenish Intraocular Pump

Stores 3 to 9 months volume of drug molecule or biologic

Biocompatible materials

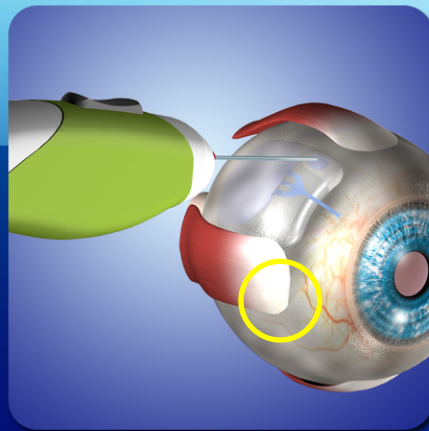
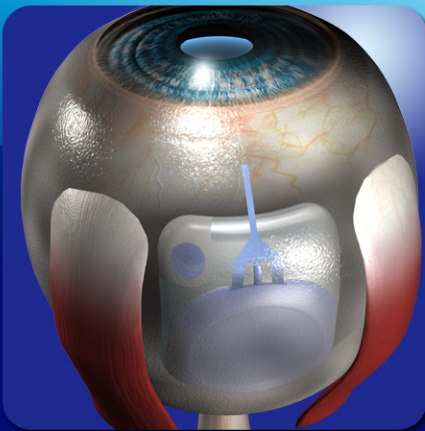
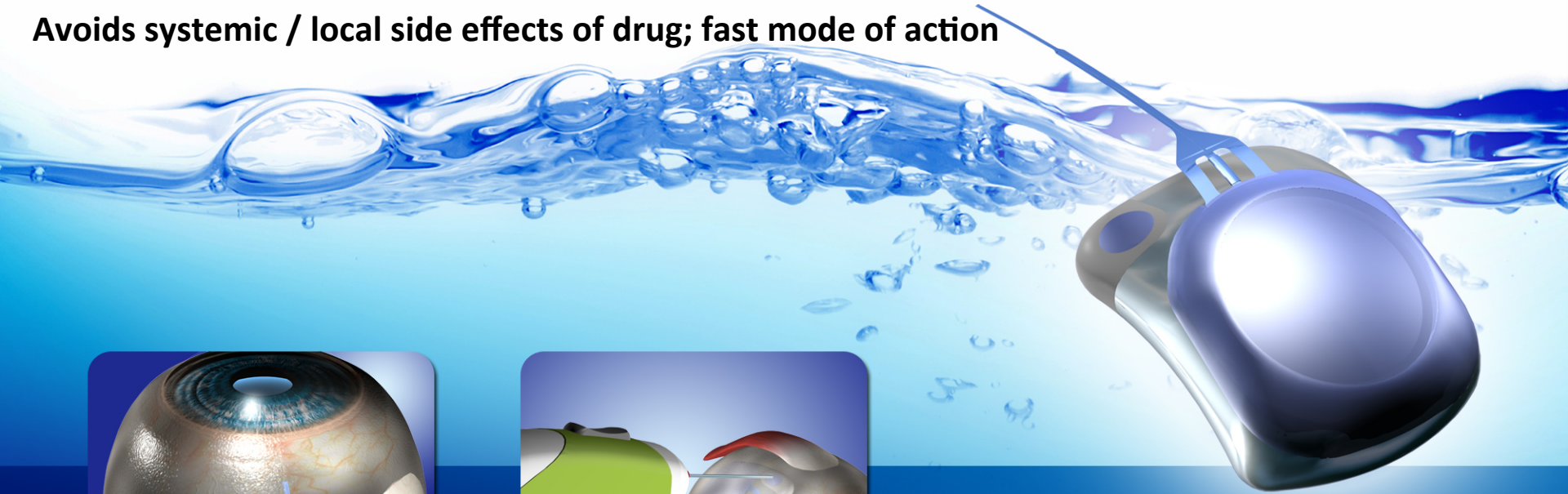
Minimally Invasive Implant uses established surgical procedures for glaucoma setons

Metered dose with +/- 5% accuracy

Anterior chamber or intravitreal drug delivery

Multiple year (5-10) lifetime of implant

Avoids systemic / local side effects of drug; fast mode of action



**Implant**



# Advances in Laser Technology

	ALT	SLT	MLT
Wavelength	488/514 nm, 532 nm	532 nm	532 nm, 577 nm, 810 nm
Mechanism	Shrinkage of TM with adjacent stretching	Selective destruction of pigmented TM cells without thermal or collateral damage	Thermally effects - not destroys - pigmented TM cells without thermal or collateral damage
Repeatable	No	Yes	Yes
Treatment Endpoint	Blanching (mild) to bubbles (intense)	Yes	None
Post op inflammation	Yes	Yes	None
Spot Size	50 $\mu\text{m}$	400 $\mu\text{m}$	300 $\mu\text{m}$
Complications	PAS, IOP spikes	IOP spikes	Minimal

# Why Laser Trabeculoplasty First?

- Medical Compliance
  - Forgetfulness
  - Side effects
  - Cost of topical medications
- Efficacy of Procedure
- Quality of Life

# Glaucoma Laser Trial (GLT)

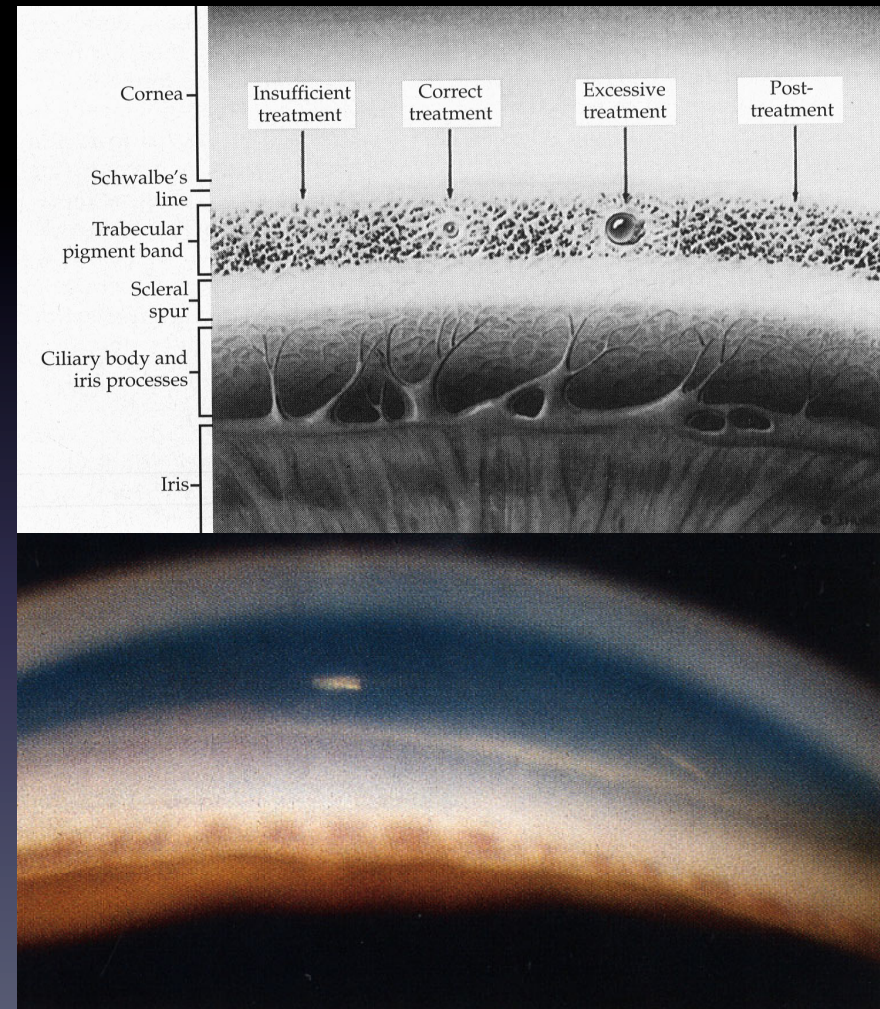
- Proposed ALT as initial glaucoma therapy
- 44% patients controlled IOP without meds at 2 years
- 70% patients controlled by ALT alone or with timolol at 2 years
- Results controversial

# Pathophysiology of Trabeculoplasty

- Mechanical Theory
  - Opening of aqueous channels by TM tissue shrinkage (not supported by histologic studies)
- Cellular or Biologic Theory
  - Migration of macrophages may clear debris in TM
  - Trabecular cell division enhanced
  - Expression of IL-1 and TNF- $\alpha$  may increase expression of stromelysin in juxtacanalicular TM
  - Upregulation of TM matrix metalloproteinases

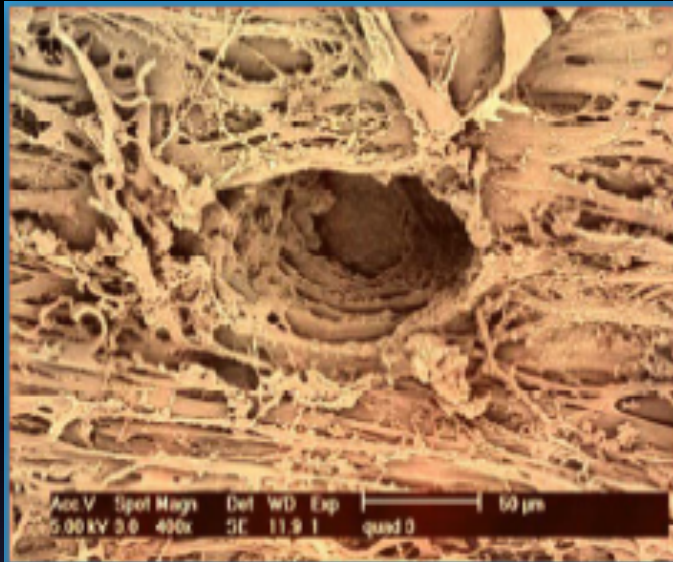
# ALT Technique

- 50  $\mu\text{m}$  spot, 0.1 sec/burst, 400-1000 mW
- 180 or 360° treatment
- 20-25 laser spots per quadrant
- Laser burns equally spaced at anterior half of TM



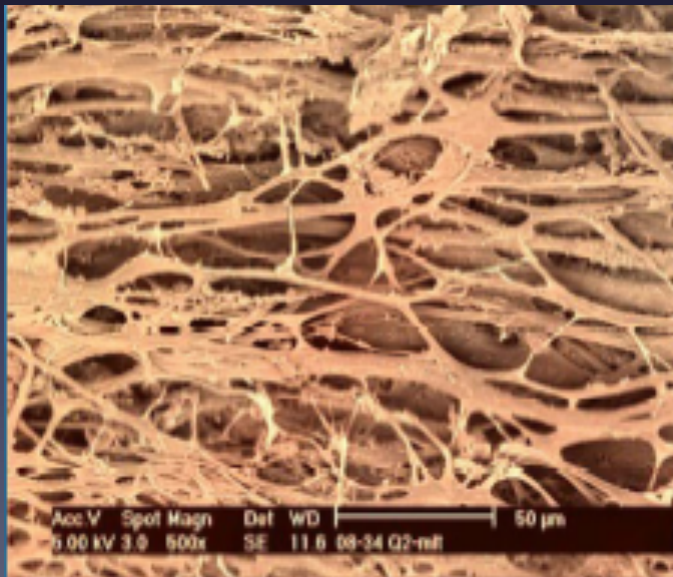
# ALT Results

- No uniform definition for success
- 90% have IOP lowering at 1 yr; 50% at 5 yrs;  
20-30% at 10 yrs
- Optimal IOP lowering effect occurs by 4 to 6 weeks
- Multiple factors affect success



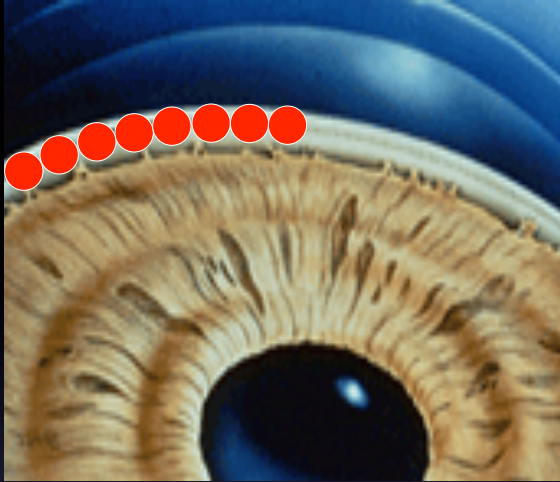
## ALT: CW Pulse

Laser exposures can create high thermal rise resulting in photocoagulation

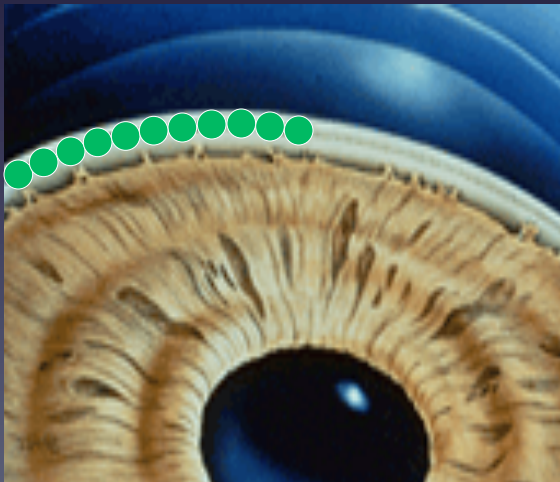


MLT: Meshwork architecture remains intact without the signs of coagulation as seen with ALT





SLT: available space for more content if needed



MLT: available space for more content if needed

# SLT Technique

- Fixed spot size (400 microns)
- Fixed time (3 nanoseconds)
- Treat TM (large spot size covers angle)
- Applications confluent, not overlapping
- Adjust power to a slight blanch of TM or just at bubble formation (0.8-1.2 mJ)
- Treat 180-360 degrees



# MLT Technique

- 300  $\mu\text{m}$  spot (smaller spot than SLT accesses narrow angles)
- 300 ms
- 1000 mW
- 15% duty cycle
- 360° confluent treatment
- No visual signs of treatment during or post treatment
- ? provides comparable IOP-lowering effects as ALT and SLT with less energy and inflammation

# Retrospective MLT Study

- 13 of the 33 patients responded to MLT utilizing a power of 700 mW with a decrease in IOP at 4+ months
- The average decrease in IOP in these responders was 23.2% at 4+months
- An additional 2 patients resulted in the same IOP at 4+ months after a decrease by 1 class of anti-ocular hypertensive medications

# MLT Early Observations

- No postop IOP spikes observed
- No postop anti-inflammatory medication required
- No perioperative glaucoma medication required
- Likely need to treat with 1000 mW power in most patients

# Laser Options for Angle Closure

**Laser Iridotomy**

**Laser Iridoplasty**

**Endocycloplasty**

# Laser Iridotomy

- Indications
- Contraindications
- Technique





# Indications for LPI

- Acute angle-closure glaucoma
- Chronic angle-closure glaucoma
- Aphakic or pseudophakic pupillary block
- Malignant glaucoma
- Occludable narrow angles
- Nanophthalmos
- Pigment dispersion syndrome (?)

# Contraindications for LPI

- Corneal opacification
- Flat anterior chamber
- $\geq 180$  degrees of PAS
- Angle closure cause by primary synechial closure (uveitis, NVG, ICE)

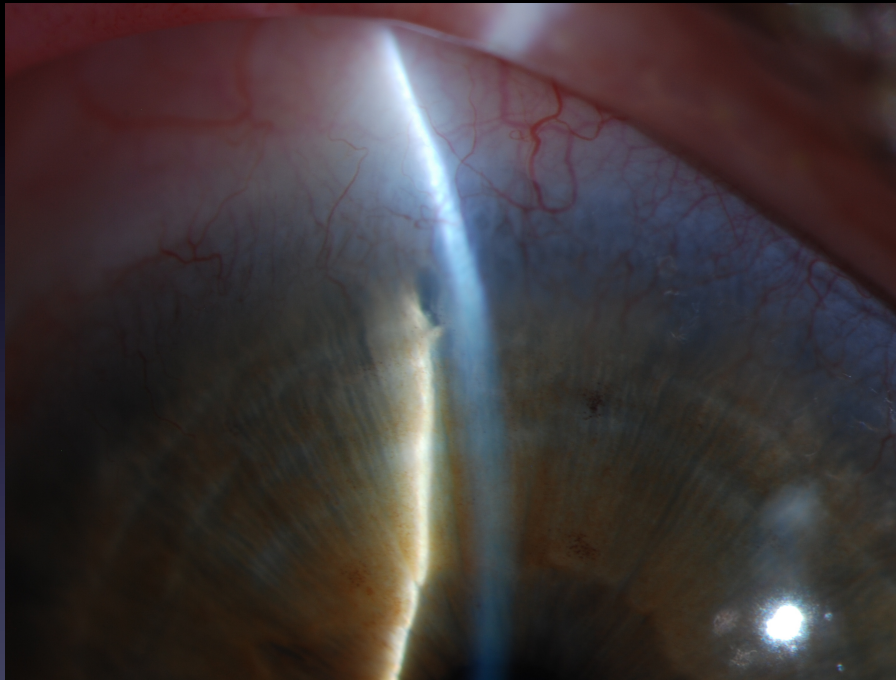
# Iridotomy Technique

- YAG laser generally preferred
- Contact lens required
  - Abraham lens (+66 D planoconvex)
  - Wise lens (+103 D button)
- Use 2% pilocarpine preoperatively
- Use apraclonidine or brimonidine perioperatively
- Use topical steroid postoperatively

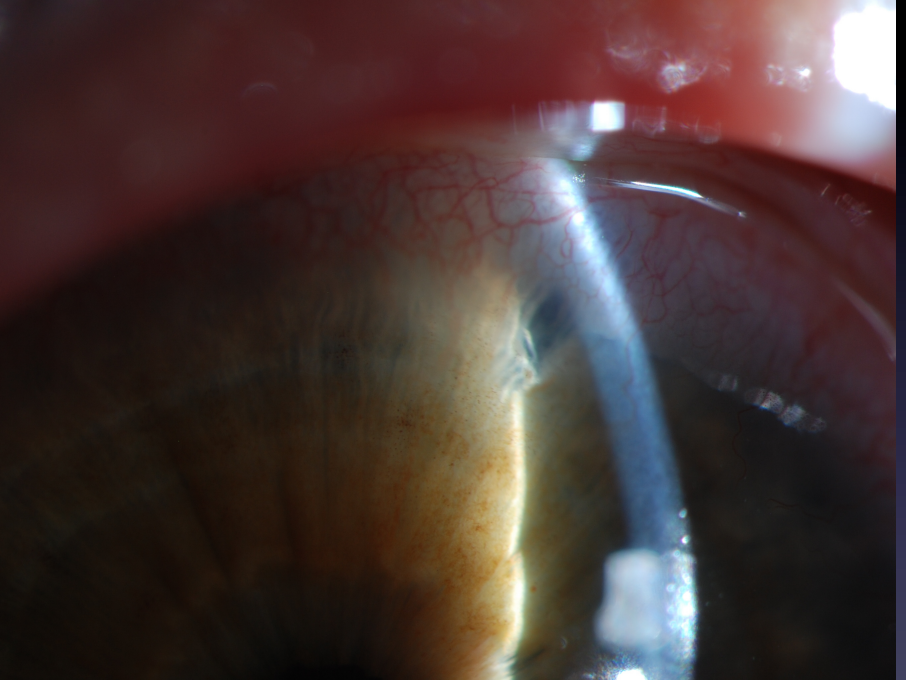
# Iridotomy Location

- Classically placed between 11:00 & 1:00
- Temporal/nasal locations reasonable alternative
- Choose site beyond lens equator
- Perform LPI in base of iris crypt
- Traditionally 150-200  $\mu\text{m}$  size

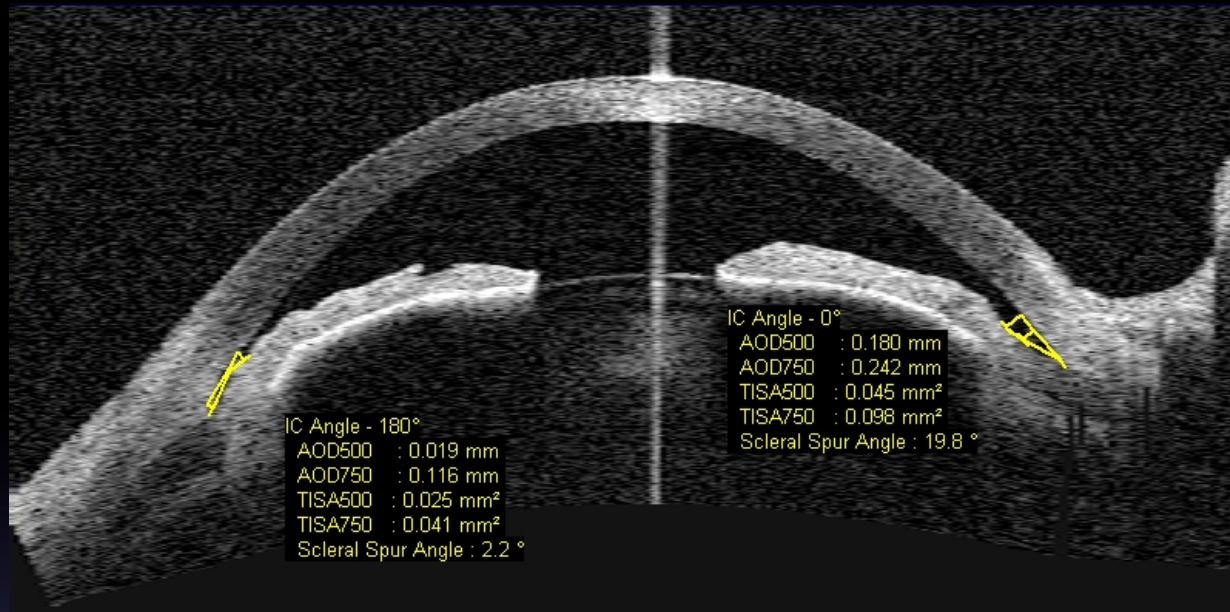
# Nanophthalmos Case



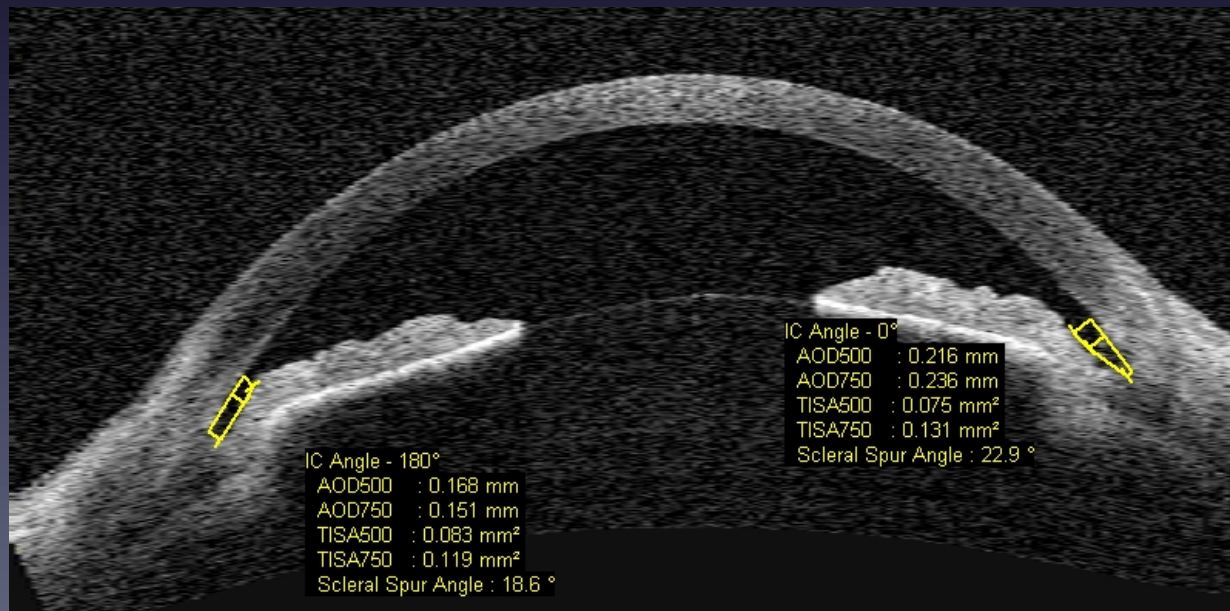
Right Eye



Left Eye



PRE



POST

# Laser Iridotomy Outcomes

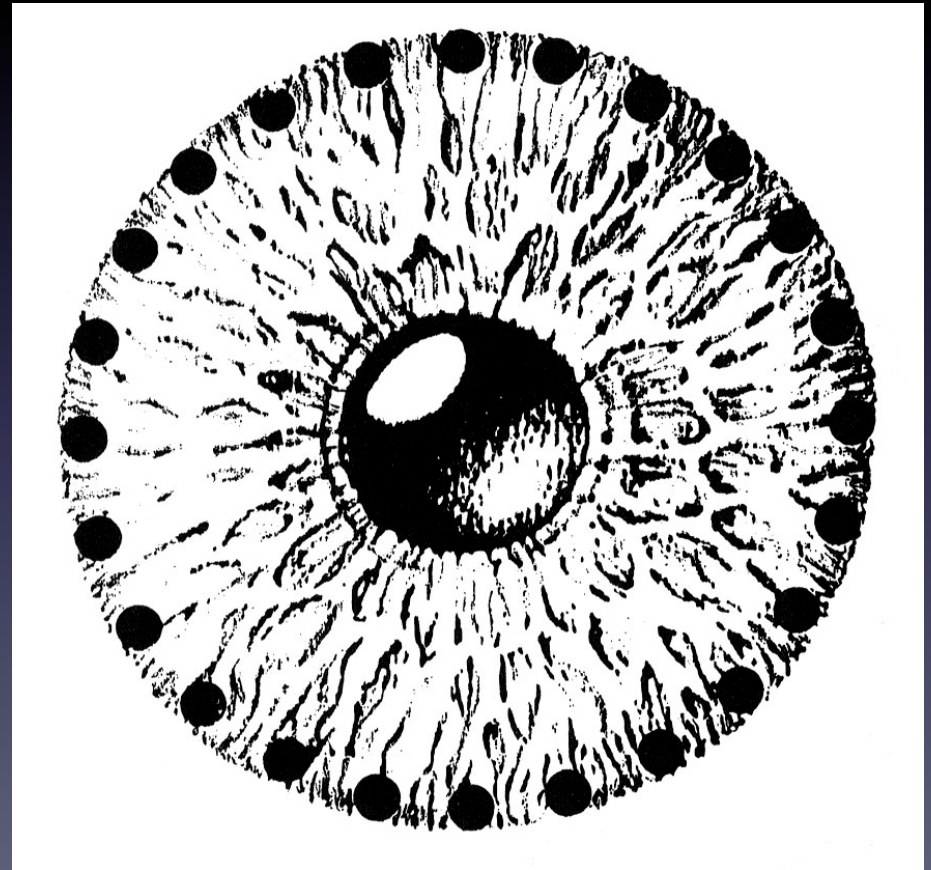
- Success\* after LPI
  - PACS → 100%
  - PAC → 97%
  - PACG → 53%
  - Follow up = 1-3 yrs

\*Success=no further surgery and no vision loss



# Laser Peripheral Iridoplasty

- Indications
- Contraindications
- Technique



# Iridoplasty Indications

- Recalcitrant acute angle-closure glaucoma
- Plateau iris syndrome
- Angle closure related to lens size or position
- Adjunct to laser trabeculoplasty
- Nanophthalmos

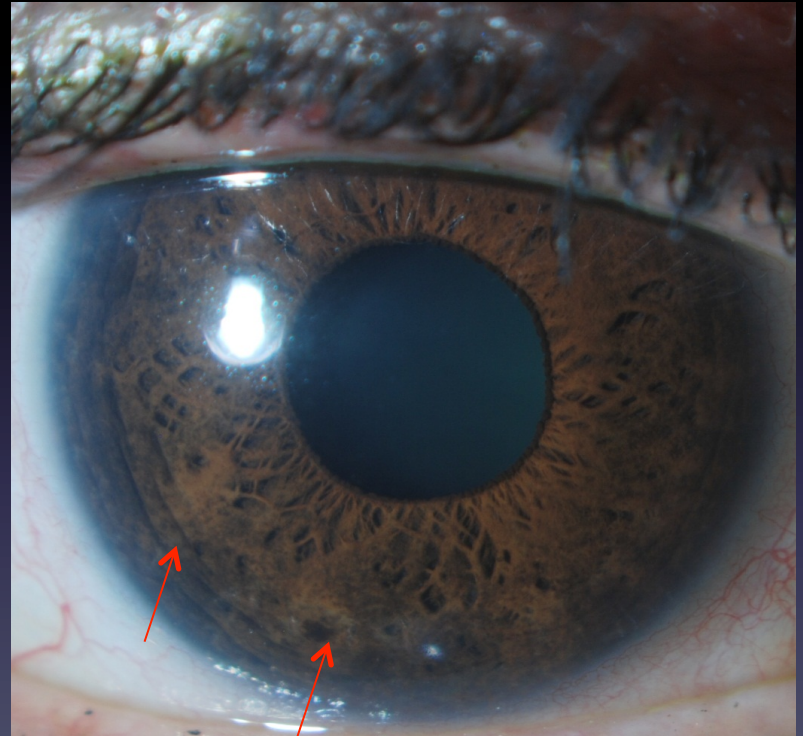
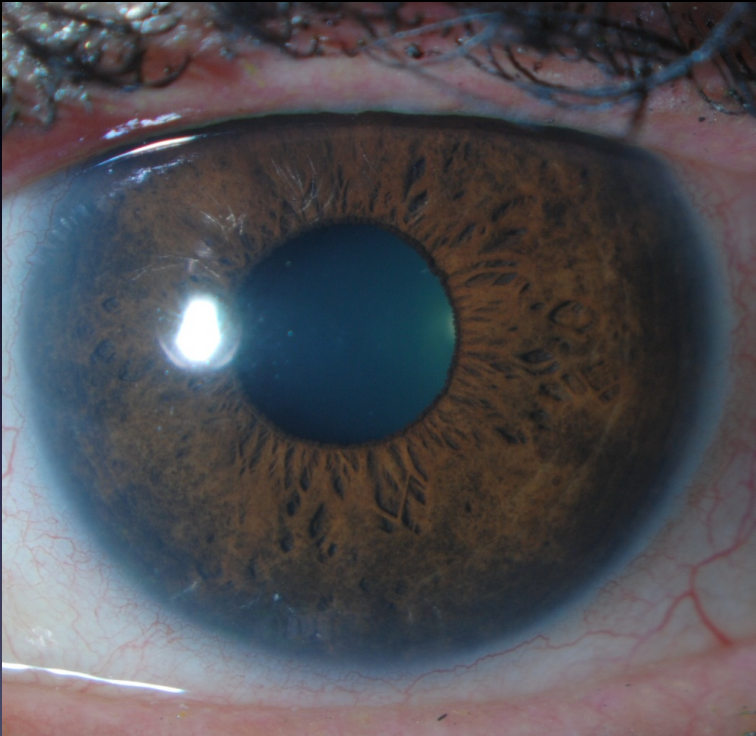
# Iridoplasty Contraindications

- Advanced corneal edema or opacification
- Flat anterior chamber
- Synechial angle closure

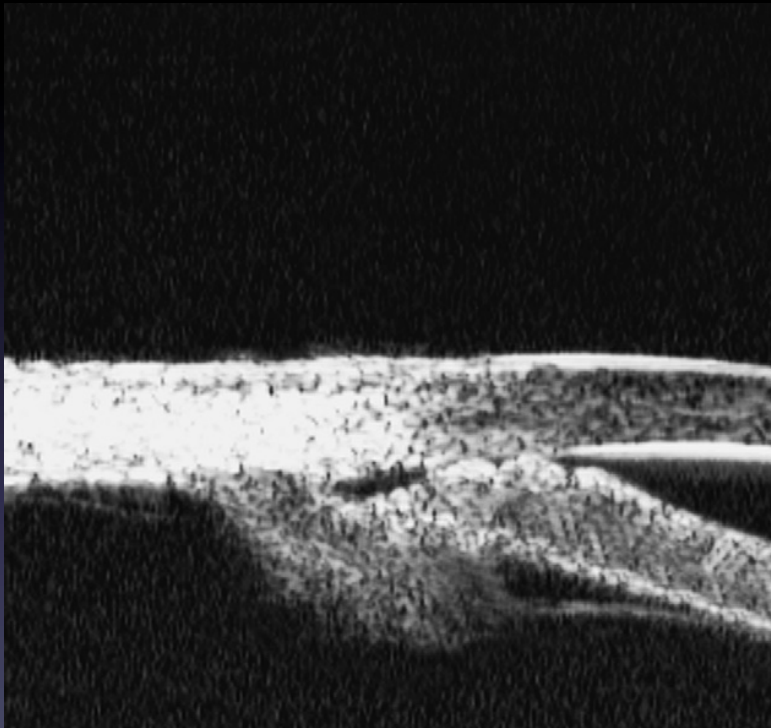
# Argon Laser Iridoplasty Technique

- Pretreat with pilocarpine
- 500  $\mu$  spot, 0.5 sec/burst, 200-400 mW
- Place 20 to 24 spots over 360 degrees as peripherally as possible
- Leave 2 spot diameters between each spot
- Avoid large visible radial vessels
- Use topical steroids postoperatively

# Laser Iridoplasty



# Laser Iridoplasty



Before ALPI



After ALPI

Effective in opening the angle in many cases

# Laser Iridoplasty

- Should you perform this in all cases of narrow/closed angle after LPI?
  - We don't know
- Risks
  - More PAS, IOP spike
  - Is it effective?
    - Angle opening?
    - Preventing glaucoma?



# Laser Peripheral Iridotomy With and Without Iridoplasty for Primary Angle-Closure Glaucoma: 1-Year Results of a Randomized Pilot Study

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XIA SUN, YUAN BO LIANG, NING LI WANG, SU JIE FAN, LAN PING SUN, SI ZHEN LI, AND WEN RU LIU

- Am J Ophthalmol 2010;150:68-73.
- Beijing Tongren Eye Center

# Results

- LPI: 77 eyes (61 at 1 yr)
- LPI + Iridoplasty: 81 eyes (65 at 1 yr)
- IOP

	Pre-op	At 1 yr
– LPI	26.2	19.6
– LPI + Iridoplasty	29.0	21.3

# Results

- IOP
  - No significant difference in IOP reduction between groups
- Corneal Endo Cell counts
  - No difference pre- and post-laser
- Complications
  - No significant difference between groups

# Results

- PAS

– LPI	4.5 clock hours	3 clock hours
– LPI + Iridoplasty	5 clock hours	2 clock hours

- Iridotomy → Iridoplasty

- 3 clock hours → 2 clock hours
    - PREVENTION OF 1 CLOCK HOUR OF PAS

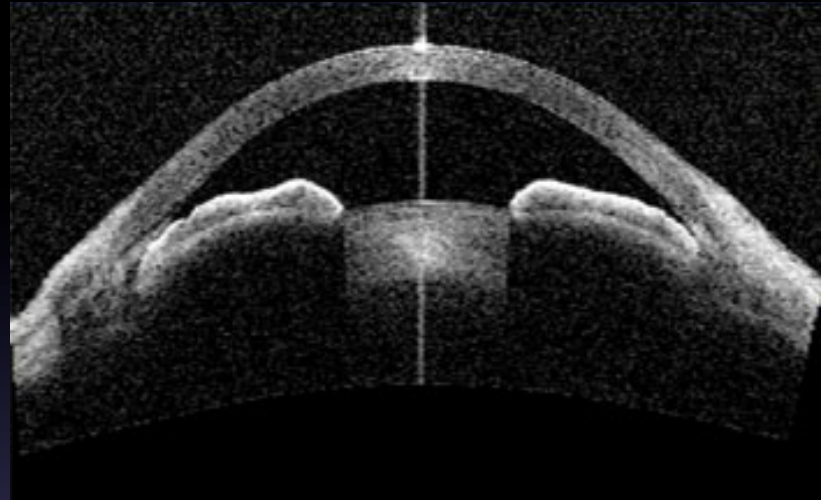
# Endocycloplasty

- Endolaser of the ciliary processes—cause shrinkage and posterior rotation
  - Goal—allow iris to retract, thus opening angle
  - Procedure—laser posterior part of ciliary processes
  - Generally combined with cataract extraction

# Endocycloplasty

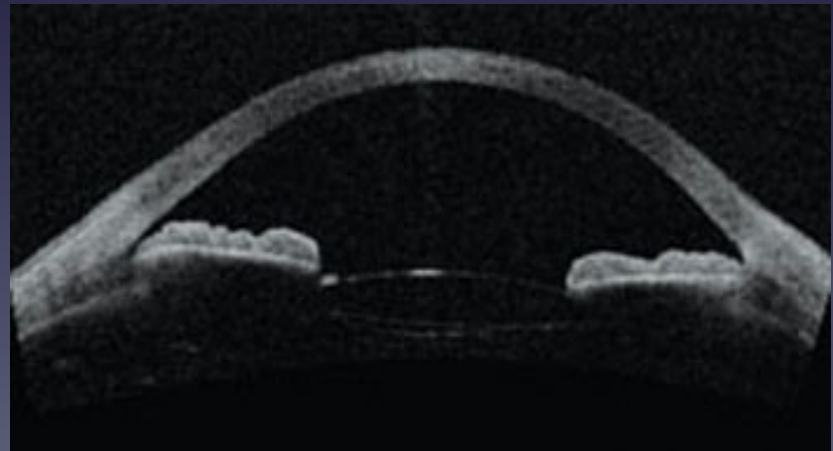


Pre-op



Posterior treatment

Post ECPL+Phaco



# Angle Closure Summary

- Laser iridotomy first line
  - Unless  $\geq 180$  degrees of PAS
- Laser iridoplasty in select patients
  - Data lacking
- Endocycloplasty may be helpful in plateau iris
  - But phaco alone may be sufficient



# Case Studies Revisited

- Case 1. Consider cataract surgery combined with MIGS procedure as next step
- Case 2. Consider cataract surgery alone as next step. ECP can be nice alternative to filtration surgery, especially in patients with plateau iris syndrome

# Conclusions

- Diagnostic technology continues to improve and may allow for better early glaucoma detection and assessment of glaucoma progression
- Novel drug delivery systems potentially will improve patient issues related to medical compliance
- Laser surgery provides an excellent alternative to medical and incisional surgical options in select patients
- MIGS procedures may be performed with good facility and may expand the role of surgery in the management of glaucoma
- Comprehensive cataract surgeon can now expand practice into surgical glaucoma

# Thank You

