Understanding the Art and Science of Glaucoma 2018

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Goals

- Underlying mechanisms for GLC
  - Historical and new understandings for the development of glaucomatous optic atrophy
- Structure-Function
- Update Non-surgical treatments
  - Medications
  - Generics vs branded
- Update Surgical Treatments
  - MIGS
  - Cataracts

3376 Patients Observed in NEI-Sponsored Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Dx</th>
<th>Randomization</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMGT1 255 patients</td>
<td>OAG</td>
<td>Tx (ALT + betaxolol) vs observation</td>
<td>4 to 9 years</td>
<td></td>
</tr>
<tr>
<td>OHTS1 1528 patients</td>
<td>OHT</td>
<td>Medical Tx vs observation</td>
<td>5 years</td>
<td></td>
</tr>
<tr>
<td>CIGTS1 607 patients</td>
<td>OAG</td>
<td>Medical Tx vs surgery</td>
<td>5 years</td>
<td></td>
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<tr>
<td>AGIS1 738 eyes</td>
<td>OAG</td>
<td>ALT vs surgery</td>
<td>8 years</td>
<td></td>
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<tr>
<td>CNTGS1 140 eyes</td>
<td>NTG</td>
<td>Medical Tx and/or surgery vs observation</td>
<td>7 years</td>
<td></td>
</tr>
</tbody>
</table>

Note: Standard end points and regimens varied for each individual study.

Lowering IOP Halts or Delays Disease Progression: OHTS, EMGT, CNTGS

<table>
<thead>
<tr>
<th>Study</th>
<th>IOP</th>
<th>Progression (Tx/No Tx)</th>
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</thead>
<tbody>
<tr>
<td>EMGT* 25% reduction</td>
<td>45%/62% (6 years)</td>
<td></td>
</tr>
<tr>
<td>OHTS1 20% reduction</td>
<td>4.4%/9.5% (5 years)</td>
<td></td>
</tr>
<tr>
<td>CNTGS* 30% reduction</td>
<td>12%/35% (7 years)</td>
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</tbody>
</table>

*EMGT showed 10% reduction in risk with every 1 mm Hg of IOP lowering.

What We Know From the Past

- RCT looked at way to reduce the risk of progression of GLC
  - OHTS
  - Lower IOP by 20% reduces the risk of progressing to GLC by 50%
  - EMGT
  - 1 mm Hg IOP reduction reduces the risk of progression by 10%
  - Canadian GLC Study
  - For every 1 mm Hg increase in IOP, there is a 19% risk of progression
  - CNTGS
  - When IOP is reduced by 30% in NTG pts only 12% progress
  - AGIS
  - IOPs consistently <18 mm Hg demonstrated virtually no VF progression
It’s Not Complicated…or is it?

It is well known that IOP reduction is beneficial in open-angle glaucoma (OAG) regardless of the baseline IOP.

1. WHY does lowering the IOP help reduce progression?
2. WHY do some patients progress despite a low target IOP?

What in the Normal Physiology of the ONH is Affected that Causes Glaucomatous Optic Atrophy?

Axonal Transport

- Interruption of blood flow to the axons (injury, ischemia, hypoxia) will reduce axonal transport.
- Axonal death may develop in days/weeks or months/years from compromised blood flow.

Loss of axons ultimately leads to “excavation” and “cupping” of the optic nerve head.

How does interruption of axonal transport cause cupping in glc?

- 2 primary theories on the origin of glaucomatos cupping
  - Mechanical Theory
  - Vascular Theory

Normal ONH Anatomy

- The axons of the retinal ganglion cell (RGC) exit the eye through the lamina cribrosa.
- RGC axons become mylenated post-laminar region.
- With normal axonal transport, RGC are functioning and quiet.
• Increased IOP puts "stress" on RGC causing a reaction to the stress.
• Elevated IOP leads to the production of a variety of substances which damage the RGC axon at the lamina cribrosa.
• Damage to the RGC axon is followed by cell death through apoptosis.
• Loss of the axons followed by RGC loss results in thinning of the RNFL.
• The lamina cribrosa initially becomes thicker and bows posteriorly.

Summary of Mechanical Theory
• Misalignment of the lamina cribrosa or movement and displacement of ganglion cell axon bundles.
• Backward bowing of the LC causes cupping
• This "kinking" results in blockage of axonal transport.
• Ultimately axonal death occurs and more cupping.
• Well accepted at high IOP's GLC.

Lamina Deformation
• The mechanical theory shows that the lamina cribrosa deformation contributes to the loss of axonal transport which damages the ganglion cells in the ONH.
• A biomechanical paradigm suggests that posterior deformation of the LC depends not only on the IOP, but also on the geometry and material properties (i.e., thickness, compliance, or rigidity) of the ONH and the peripapillary scleral tissue.

Burgoyne CF. A biomechanical paradigm for axonal insult within the optic nerve head in aging and glaucoma. Exp Eye Res 2011;93:120 –32.
Principle distribution of forces, pressures and the translaminar pressure gradient within the optic nerve head

Early GLC is “laminar” in origin

Trans-lamina cribrosa pressure difference correlated with neuroretinal rim area in glaucoma

- IOP - CSF pressure = trans-lamina pressure difference

Results:
- Pt with OHTN had higher trans-lamina pressure difference; no VF loss
- Pts with GLC had lower trans-lamina pressure difference
  - Both high IOP and normal tension GLC

**CSF pressure may play role in pathogenesis of Glaucomatous optic neuropathy**
Is CFS important?

- Trans-lamina cribrosa pressure difference was the main pressure parameter associated with the amount of glaucomatous optic nerve damage.
- This shows the importance the counter pressure the CSF exerts against the IOP across the lamina cribrosa of the optic nerve and contribute to the pathogenesis of glaucomatous optic neuropathy.
- Through the CSF pressure, glaucoma is not only an ocular disorder but a cerebral disease.


Can the lamina cribrosa deformation be reversed?

Mechanical Theory...

- Our knowledge of the underlying mechanism for the development of glaucomatous optic neuropathy continues to develop

What about the vascular theory developments?

Review of ONH Blood Flow
Review of ONH Blood Flow

Historical: Vascular Theory
- Ischemia (decreased blood flow) lowers axonal transport rate.
  - Reduced/Initiated by mechanical constriction (2nd to high IOP) and/or reduced blood flow (perfusion pressure).
- Ultimately axonal death occurs.
- Explains glaucoma in patients with low or normal IOP’s (e.g. NTG)

Ocular Perfusion Pressure and Glaucoma

The “Other” Story of Pressure in the Eye

Ocular Perfusion Pressure and Glaucoma
- SPP = SBP – IOP
- DPP = DBP – IOP
  - (perhaps best to use to clinically measure PP)
- MPP = 2/3 mean arterial pressure – IOP
  - Arterial Pressure = DBP + 1/3(SBP – DBP)

Clinical Example
- 56 yo AA/M
- Current IOP is 25 mmHg OU
- Current BP is 110/70
- OPP is what?
  - 70-25= 45

Low OPP
- May be due to:
  - High IOP
  - Low BP
  - Physiological
  - Over treatment of systemic HTN
  - Nocturnal Hypotension

How can we increase OPP?
- Increase DBP
- Decrease IOP

If lower IOP to 15, what is OPP if IOP remains 110/70?
- 70-15=55
Summary

- IOP Fluctuation
- Increased Nocturnal IOP
- Low Nocturnal Blood Pressure
- Low Diastolic Perfusion Pressure

Summary of Mechanisms Involved in Glaucoma

- Glaucomatous optic neuropathy can occur in the presence or absence of detectable increased IOP.
- There is no unifying theory, but a large body of conflicting evidence.
- Neither Mechanical or Vascular theories resolve all the questions.
- POAG is induced by several factors alone or in combination.

- MULTIFACTORIAL

POAG Risk Factors 9-year Barbados Eye Study (BES)


Mechanism of Glaucoma has gotten complicated:
Summary of Mechanisms Involved in Glaucoma

- Regional differences in the size of fenestrations in the LC account for distinct, focal damage patterns.
- The optic nerve head microcirculation is also very important in the pathogenesis of glaucoma.
- The collagenous LC is a conduit for the microvasculature.

Summary of Mechanisms Involved in Glaucoma

- In association with high IOP, the microvasculature can be mechanically affected by distortion of the LC, causing decreased blood flow.
- Poor auto regulation in certain individuals may also result in poor blood flow.

Back to the Questions...

It is well known that IOP reduction is beneficial in open-angle glaucoma (OAG) regardless of the baseline IOP

1. WHY does lowering the IOP help reduce progression?
2. WHY do some patients progress despite a low target IOP?

WHY does lowering the IOP help reduce progression?

- Lowering the IOP reverses, to some degree, the translaminar pressure gradient which allows laminar deformation to be reversed... to some degree
- Lowering IOP reduces some of the “stress” that limits blood flow through the microcirculation of the lamina

WHY do some patients progress despite a low target IOP?

- Some reversal of the laminar deformation can occur if treated early, BUT it is likely that the LC does not completely reverse.
- Axonal transport of nutrients continues to be affected by damaged RGC.
- Non-IOP related insults occur
  - Connective tissue changes
  - Thickening due to age
  - Ischemia
  - Immune-mediated
  - CSF
  - Translaminar pressure gradient differences
Outline

• Structure-Function then and now
• Why some patients with glaucoma have structure changes and no functional change
• Why some glaucoma patients have functional loss, but no apparent structural loss
• Why is there so much variability from one patient to the next

Glaucoma

• Chronic, progressive and potentially blinding optic neuropathy characterized by distinctive morphological ('structural') changes of the optic nerve head and RNFL associated with visual field changes ('functional').
• Both structural and functional changes result from loss of the retinal ganglion cells (RCG's) and their axons.

Historical Thinking:
Structural Damage Precedes Functional Change

• NFL injury can be observed up to 6 years before VF defects
  – Mean number of axons in normal ONH ~800,000–1,200,000
  – 25-40% of ONH fibers can be lost from an eye that retains normal visual field


Risk Factors

• IOP
• C-D ratio
• CCT
• Age, Other

VF=visual field; CCT=central corneal thickness; C-D = cup-disc.

View of Structural Damage and the Progression to Functional Vision Loss

• Nerve fibers arching over and under the macula = the arcuate bundles (A)
• Fibers traveling from the disc directly to the macula make up the papillo-macular bundle (B).
• Nerve fibers do not cross over the horizontal raphe (C).
How much loss before **detection**?

- **Structural:**
  - Recognition of RGC loss by disc or nerve fiber layer examinations would ideally be possible with a loss of 5% of RGC, but under average circumstances, it requires a loss of 15-40% of RGC.

- **Functional:**
  - Loss occurs with variable RGC loss, depending on method and retinal eccentricity, with a greater loss required centrally. Visual field damage by probability values on the Humphrey requires a 25-35% loss in a local area.

- H. Quigley

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**Structure-Function**

**Structural Changes**
- Progressive loss of RGC
- Enlargement of optic cup
- Loss of RNFL
- Loss of neuroretinal rim tissue
- Color changes to ONH (late disease)

**Functional Changes**
- Visual Field defects
- Abnormal VEP
- Abnormal electrotoretinography waveforms
- Loss of chromatic discrimination

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**Images:**
- Illustration of the structure-function map for the right eye used for sequential estimation of retinal ganglion-cell survival.
- Six corresponding regions of neuroretinal rim area (A), parapapillary retinal nerve fiber layer (B), and visual field (C), used to measure the structure-function relationship (based on structure-function map introduced by Gardner-Hensley et al.)

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**References:**
Clinical Reality Truths
1. Patients with the same degree of neuroretinal rim loss can have different and variable amounts of VF loss.
2. Some patients have evidence of glaucomatous optic neuropathy without a detectable VF abnormality.
3. Some patients have classic glaucomatous VF defects without detectable structural abnormalities.

Why is there variability of functional loss of vision in patients with same degree of rim loss?
- There are different types and sizes of RGC
- The function of these variable RGC will cause variable functional loss.
- Different types of RGC respond to different stimuli

Example of Patient with Function > Structure

Why Structural Change and No Functional Change?
AIGS Consensus Paper on Structure-Function:
- Evidence suggest that RGC’s with larger cell bodies and larger axons die FIRST in glaucoma
  - Smaller axons and cell bodies die first in ischemic optic neuropathies (AION).
- The RGC may "shrink" and change in morphology before dying
  - RGC become “dysfunctional” in early glaucoma before they die.
- There is a “functional reserve” period where ONH gets worse before the VF.
Why Structural Change and No Functional Change?

• There is “functional latency” where structural change occurs early in the disease without functional vision loss.
• In early glaucoma, more glaucoma induced structural damage relative to the amount of glaucoma-induced functional damage.
• In moderate-late glaucoma, functional loss is greater than structural loss.

Why Do Some Glaucoma Patients have Functional Loss Prior to Structural Loss?

• RGC become “dysfunctional” in early glaucoma before they die.
  – Dysfunction causes reduced VF sensitivity that does not correlate with RNFL loss of ganglion cell complex loss.
• Quigley:
  – The translation of anatomical selectivity into psychophysical testing depends upon the sensitivity with which the loss of RGCs of particular types can be detected by functional testing.

Treatments on the Horizon

Review of Aqueous Outflow

- The aqueous humor leaves the eye at the anterior chamber angle through trabecular meshwork, the Schlemm’s canal, intraocular channels, and episcleral and conjunctival veins.
- This pathway is referred to as the conventional or trabecular outflow.
- In the unconventional or uveoscleral outflow, aqueous humor exits through the root of the ciliary muscle bundles, then through the suprachoroidal - scleral tissues.
- Trabecular outflow accounts for 70% to 95% of the aqueous outflow.
- And remaining 5% to 30% by uveoscleral outflow.

Aqueous Outflow
Latanoprostene bunod ophthalmic solution 0.024% (VYZULTA™)

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

LBN

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

A Randomized, controlled comparison of latanoprostene bunod and latanoprost 0.005%: Voyager Study
• The pivotal Phase 3
  – two separate randomized, multicenter, double-
    masked, parallel-group clinical studies
  • APOLO and LUNAR
    – designed to compare the efficacy and safety of
      VYZULTA™ administered once daily (QD) against
      timolol maleate 0.5% administered twice daily (BID) in
      lowering IOP in patients with open-angle glaucoma or
      ocular hypertension.
• The primary endpoint of both studies (n=840)
  – reduction in mean IOP measured at specified time
    points during three months of treatment.
• The collection of patient safety data for a total of up
  to 12 months is still ongoing.

Rhopressa® (netarsudil ophthalmic solution) 0.02%
• FDA approved for the Lowering of Elevated Intraocular Pressure
  in Patients with Open-Angle Glaucoma or Ocular Hypertension
• Aerie Pharmaceuticals
• Once-daily
• Inhibits Rho Kinase (ROCK)
• Inhibits norepinephrine transporter (NET)
• Novel biochemical targets for lowering IOP

Mechanisms of Action for Rhopressa
• Rhopressa™ (netarsudil ophthalmic solution) 0.02% reduces
  IOP via three separate MOAs:
  1. Through ROCK inhibition, it increases fluid outflow through the
     trabecular meshwork which accounts for approximately 80% of
     fluid drainage from the eye
  2. Reduces episcleral venous pressure: the pressure of the blood
     in the episcleral veins of the eye where eye fluid drains into the
     bloodstream
  3. Through norepinephrine transporter inhibition, it reduces the
     production of aqueous.

Rho Kinase Inhibitors
• These selective agents work by relaxing the trabecular
  meshwork through inhibition of the actin cytoskeleton contractile
  tone of smooth muscle.
• This results in increased aqueous outflow directly through the
  trabecular meshwork, achieving lower intraocular pressures in a
  range similar to prostaglandins.
• There are also animal studies indicating that ROCK inhibitors
  may improve blood flow to the optic nerve, increase ganglion
  cell survival, and reduce bleb scarring in glaucoma surgery
Phase 3 Registration Trials for Rhopressa

Rocket 1 Study
- Compared 182 Rhopressa™ qd patients to 188 timolol bid patients
- Baseline IOP 20-27mmHg
- Results showed loss of efficacy at week 6 and on day 90 in ~20% of Rhopressa arm
- Hyperemia in 35% of patients
  - 80% reported it as “mild”

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

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

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

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

- **Table 2**
  - Number of patients with treatment-emergent adverse events by treatment group.
  - Systemic events and patients from safety population: most frequent UTI in AR group.
  - Adverse event rate:
    - AR-13324: 13.5%
    - Latanoprost: 16.7%
    - Combined: 16.6%
    - Bimatoprost: 16.7%
    - Combined: 16.7%
  - Most frequent events:
    - AR-13324: infection and infestations
    - Bimatoprost: infections and infestations
  - Table adapted from the clinical trial report.

**Roclutan™**

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

**Bimatoprost SR**

- **Allergan Pharmaceuticals**
- **Sustained release implant**
- **Biodegradable, preservative-free implant preloaded into a single use applicator**
- **Bimatoprost SR is placed in the anterior chamber**
- **The drug is slowly released for about 3 to 4 months and the implant slowly dissolves in about 12 to 15 months.**
- **As of April, 2014, a total of 87 patients had received a single administration and of those, 12 had received a repeat administration of Bimatoprost SR on the 190204-041D study.**

**Bimatoprost SR**

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

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

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

**MATRx-1 (trabodenoson)**

- **MATRx-1** is a Phase 3 randomized, double-masked, placebo-controlled trial of trabodenoson in approximately 300 patients diagnosed with primary open-angle glaucoma (POAG) or ocular hypertension (OHT).
- **Goal:**
  - Assess the efficacy, safety and tolerability of trabodenoson over three months of treatment.
  - The primary endpoint will be the reduction of intraocular pressure (IOP) as compared to the placebo treatment arm. In addition, the trial will incorporate a triplet 0.5% arm to validate the sensitivity of the patient population.
  - Intraocular pressure (IOP) will be measured at four time points during the day: 8AM, 10AM, 12PM, and 4PM on days 1, 2, 4, 8, and 14. Three doses of trabodenoson will be administered: 1000 mcg once daily, 1500 mcg twice daily, and 2000 mcg once daily.
  - These doses were selected to assess efficacy in intraocular pressure lowering, while maintaining the tolerability and safety profile observed in Phase 2 trials.
- **The trial will enroll patients with IOP greater than or equal to 24 mm Hg and less than or equal to 34 mm Hg.**

**Micro/Minimally-Invasive Glaucoma Surgery (MIGS)**

**Outline**

- Review of Aqueous Outflow
- What are MIGS?
  - Review of MIGS approved by FDA
  - Istent (Tabecular Meshwork Outflow)
  - CyPass (Uveoscleral Outflow)
  - XEN (Subconjunctival Space)
- Cataract Surgery
Outline

- Review of Aqueous Outflow
- What are MIGS?
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  - CyPass (Uveoscleral Outflow)
  - XEN (Subconjunctival Space)
- Cataract Surgery

Phacoemulsification Cataract Surgery and Primary Open Angle Glaucoma (POAG)

- Increases the postoperative aqueous outflow facility of the TM
- Cultured trabecular meshwork cells have been found to release interleukins and tumor necrosis factors, which may lead to increased synthesis of MMPs in the TM

Effect of Cataract Surgery on IOP Reduction

According to the AAO Preferred Practice Patterns, cataract surgery with IOL implantation alone results in a modest reduction in IOP of less than 2mm Hg on average.1

- Chart review of 588 normotensive and OHT subjects2
  - 53% had a mean reduction of 1.6 to 2.5 mm Hg

Baseline IOP (mm Hg)

<table>
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<tr>
<th>IOP (mm Hg)</th>
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<tr>
<td>20-22</td>
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<tr>
<td>18-19</td>
<td>86</td>
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<tr>
<td>15-17</td>
<td>223</td>
</tr>
<tr>
<td>9-14</td>
<td>198</td>
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Will Cataract Extraction Lower IOP?

- Varied results from numerous studies.
- The mean decrease in IOP from preoperatively to the final recording was 17%
  - Eyes with higher pre-operative IOP showed a greater IOP reduction post-operatively.

How can the IOP lowering effects of cataract surgery be further enhanced?

- About 20% of patients undergoing cataract surgery have a concurrent diagnosis of glaucoma
  - in the U.S., this leads to over 700,000 patients per year who could benefit from this therapy.
- Microinvasive glaucoma surgeries (MIGS)
  - Ab Interno
  - Ab Exteno
Surgical Advances

FDA-Approved MIGS
- Canaloplasty
  - Ab externo
- Trabectome
- iStent®
- CyPass Stent®
- Xen Gel Stent®

MIGS in FDA Trials
- Hydrus Stent

Glaucoma Surgical Procedures: Ab externo vs. ab interno

Ab externo
- Major incisional/sutures required
- Drainage "assist"
- Artificial outflow pathway → bleb
- Potential early and late serious complications

Ab interno
- Micro incision
- Enhanced drainage via natural, physiologic outflow pathway
- Highly safe – similar profile to cataract surgery

iStent® Indication for Use (US Label)

The iStent Trabecular Micro-Bypass Stent is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication

iStent® Specifications

iStent is the smallest medical device known to be implanted in the human body and weighs just 60 µg

- iStent dimensions are customized for a natural fit within the 270 µm canal space
- Made of surgical-grade nonferromagnetic titanium
- Heparin-coated to promote self-priming

Mechanism of Action: Anatomic Placement & Rationale

iStent® is an ab interno trabecular micro-bypass stent for the treatment of glaucoma:
- Placed in inferonasal locations with high presence of collector channel congregations
- Designed to improve continuous, physiological outflow in the lower nasal quadrants
Pre-operative Considerations

- iStent Candidate
  - Mild to moderate open angle glaucoma (no more severe than a mean deviation of -12dB)
  - Visually significant cataract is present on examination
  - Patient desires to reduce dependence on glaucoma medications

Any patient with cataracts being treated for mild to moderate open angle glaucoma with medications may be a potential candidate for an iStent.

Clinical Data

iStent® Pivotal US IDE Trial

Prospective, randomized, multi-centered study of POAG patients who underwent iStent + cataract surgery vs. cataract surgery (CE) alone
- 290 subjects at 29 sites
  - 240 randomized subjects with cataract and mild-to-moderate OAG (1:1 randomization)
  - 50 additional non-randomized subjects for safety
- Patient population
  - Mild-to-moderate POAG (also PXE and PDS)
  - IOP ≤ 24 mm Hg on 1-3 medications
  - Post-medication washout IOP 22 – 36 mm Hg
- Efficacy endpoints
  - Primary: IOP ≤ 21 mm Hg without medications at month 12
  - Secondary: IOP reduction ≥ 20% without medications at month 12
- Follow-up through 2 years postoperative


US IDE Trial – Primary Endpoint

Percent of Patients with IOP ≤ 21 mm Hg Without Medication Use

- At 12 months, 72% of iStent® subjects with IOP ≤ 21 mm Hg without medication vs. 50% with cataract surgery alone (P<0.001)

US IDE Trial – Secondary Endpoint

Percent of Patients with ≥20% IOP Reduction in IOP Without Medication Use

- At 12 months, 66% of iStent® subjects with ≥ 20% IOP reduction without medication vs. 48% with cataract surgery alone (P=0.003)

Summary

A single iStent® implanted during cataract surgery is designed to:
- Reduce IOP while potentially reducing or eliminating medication use
- Spare the conjunctiva
- Decrease risk of large IOP fluctuations associated with nonadherence to medication
- Avoid serious complications associated with end-stage filtration and shunt surgeries
- Minimize risks of iatrogenic hypotony and bleb formation
- Safely preserve potential for future treatment options

iStent® - The “first” MIGS device
Indications for CyPass

- The CyPass® Micro-Stent is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG).

CyPass (Alcon)

- 6.35mm x 0.3mm fenestrated stent
- Targets the suprachoroidal space via supraciliary location
- Designed to improve uveoscleral outflow by creating a controlled cyclodialysis.

COMPASS: The COMPASS clinical trial is a randomized, controlled, multicenter study comparing the safety and efficacy of CyPass Micro-Stent with cataract surgery vs. cataract surgery alone, as part of the US regulatory approval process.

COMPASS COMPASS

- At the Screening Visit
  - mean (or median) medicated IOP $\leq 25.0$ mmHg or an unmedicated IOP $\geq 21.0$ mmHg and $\leq 33.0$ mmHg.
- At the Baseline Visit
  - Unmedicated mean diurnal IOP $\geq 21.0$ mmHg and $\leq 33.0$ mmHg
**COMPASS Results:**

<table>
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<th>Effects</th>
<th>XEN45 Gel Stent (Allergan)</th>
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<tbody>
<tr>
<td>First ab interno subconjunctival approach for lowering IOP.</td>
<td></td>
</tr>
<tr>
<td>It involves a soft, flexible, permanent gelatin implant, about the diameter of a human hair.</td>
<td></td>
</tr>
<tr>
<td>The implant procedure can be done alone, or as part of cataract surgery.</td>
<td></td>
</tr>
<tr>
<td>The implant is placed through a small, self-sealing corneal incision using an inserter.</td>
<td></td>
</tr>
<tr>
<td>It's implanted into the subconjunctival space opposite the incision.</td>
<td></td>
</tr>
<tr>
<td>The gelatin material is non-inflammatory, exerts minimal stress on surrounding tissue and doesn't migrate once placed.</td>
<td></td>
</tr>
<tr>
<td>The surgery doesn't disrupt the conjunctiva, so it leaves all other options open for future use if needed, and it can be repeated.</td>
<td></td>
</tr>
</tbody>
</table>

**XEN Indications**

- For the management of refractory glaucomas, including cases where previous surgical treatment has failed, cases of primary open angle glaucoma, and pseudoxfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy.

---

**Table 1: Preoperative Baseline and Preoperative Results**

<table>
<thead>
<tr>
<th>Effect</th>
<th>XEN45 Gel Stent (Allergan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Effectiveness</td>
<td></td>
</tr>
<tr>
<td>XEN45 Control</td>
<td>15.0%</td>
</tr>
<tr>
<td>XEN45 Gel Stent</td>
<td>14.4%</td>
</tr>
<tr>
<td>Secondary Effectiveness</td>
<td></td>
</tr>
<tr>
<td>XEN45 Control</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

Additional detail regarding the reasons patients did not achieve the primary endpoint (IOP non-responders is shown in Table 2).
ACRS 2016

The Xen Procedure: 1-Year Results of an Ab Interno Gelatin Stent Along with Cataract Surgery for the Treatment of Glaucoma (APEX Study)

Richard A. Lewis, MD1; Herbert A. Reilbamer, MD, PhD2

METHODS

- **Design:** Phase IV, prospective, non-randomized, 24-month, ongoing study
  - Subanalysis of combined gelatin stent placement and cataract removal
- **Sites:** 22 sites in Europe, Venezuela
  - ClinicalTrials.gov registration number: NCT03000693
- **Population:** Moderate POAG with cataract
  - Treatment: Gelatin stent + phacoemulsification
  - Both eyes could be treated (≤33 days apart)
  - Use of an antimetabolite/antibiotic agent prior to implantation was allowed at the discretion of the investigator
- **1-year interim analysis of the following endpoints:**
  - Mean IOP
  - Reduction in medications
  - Mean IOP change from baseline
  - Advance events (AEs)
SUMMARY AND CONCLUSIONS

At 12 months

- Mean IOP reduction from baseline reached 32.5% (p=0.001)
- 96.4% of eyes needed fewer hypotensive medications
  - 54.2% did not need any
- 79.9% of eyes achieved a 20% IOP reduction from preoperative IOP
  - 47.0% achieved 20% reduction and no longer require hypotensive medications
- The gelatin stent had an acceptable safety profile

- The clinically proven, ab interno subconjunctival pathway combined with the gelatin stent has a favorable safety profile and provides an effective approach to controlling IOP and reducing medications in patients with POAG who also need cataract surgery

One-Year Results of an Ab Interno Gelatin Stent as a Standalone Procedure for the Treatment of Moderate Primary Open-Angle Glaucoma (APEX study)

Rohit Varma, MD, MPH; Herbert A. Reitsamer, MD, PhD

XEN Gel Stent without Cataract Removal

Mean IOP and Mean IOP Change from Baseline in Study Eyes

- Statistically significant reduction in mean IOP from the medicated, preoperative baseline at all post-implantation visits (p<0.001)
- At 12 months, mean IOP reduction (SD) was 5.0 (4.1) mm Hg

Summary

<table>
<thead>
<tr>
<th>Procedure</th>
<th>IOP Reduction from Baseline</th>
<th>Medication Needed</th>
<th>Additional Results</th>
<th>Clinical Indication</th>
<th>Outflow Mechanism</th>
<th>Additional Outflow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabeculectomy</td>
<td>35%</td>
<td>20% or less methylcellulose</td>
<td>30-40% with IOP ≤ 21 mm Hg</td>
<td>Trabecular</td>
<td>Trabecular Meshwork Outflow</td>
<td></td>
</tr>
<tr>
<td>Skilt</td>
<td>64% get ≤ 21% IOP</td>
<td>72% get IOP ≤ 16 mm Hg</td>
<td>Mild-tense</td>
<td>Trabecular</td>
<td>Trabecular Meshwork Outflow</td>
<td></td>
</tr>
<tr>
<td>CyPass</td>
<td>72% get ≤ 21% IOP</td>
<td>87% get IOP ≤ 14 mm Hg</td>
<td>Minimal-tense</td>
<td>Trabecular</td>
<td>Trabecular Meshwork Outflow</td>
<td></td>
</tr>
<tr>
<td>XEN Gel (w/CyPass)</td>
<td>32%</td>
<td>84% on less than half of medications</td>
<td>85% IOP ≤ 15%</td>
<td>Trabecular</td>
<td>Sub-conjunctival Drainage</td>
<td></td>
</tr>
<tr>
<td>XEN Gel (only)</td>
<td>18.8%</td>
<td>99% on less than half of medications</td>
<td>IOP ≤ 21%</td>
<td>Trabecular</td>
<td>Sub-conjunctival Drainage</td>
<td></td>
</tr>
</tbody>
</table>

*Trabecular Shuntless Outflow  **Uveoscleral Outflow

Stand-Alone

SUMMARY AND CONCLUSIONS

At 12 months

- Mean IOP reduction of 32.6% from baseline
- 89.9% of eyes needed fewer hypotensive medications
  - 56.9% did not need any
- 86.4% of eyes achieved a 20% IOP reduction from preoperative IOP
  - 56.6% achieved 20% reduction and no longer require hypotensive medications
- No major stent-related AEs were reported

- The gelatin stent is an excellent minimally invasive, standardized alternative to grid standard subconjunctival drainage for patients with moderate POAG