# Glaucoma Update 2020

Dr. James Thimons, Founding Partner, Medical Director

Ophthalmic Consultants of Connecticut Chairman, National Glaucoma Society

# New Concepts in Glaucoma Diagnosis and Treatment

- OCT vs VF
- CH in Glaucoma Suspects
- SLT as Primary Therapy
- Repeat SLT
- OCTA in Glaucoma

# Ganglion Cell Anatomy



# "Wiper" Defect



# **Ganglion Cell Anatomy**

- Analysis of VF in RGC loss in Glaucoma
  - 24-2 protocol has 6 degrees separation allowing for thinning the RGC to be missed to due point placement
    - Drazdo t al: Vision Research 2007
  - 10-2 testing substantially improves correlation with RGC analysis
    - Hood and Raza; Vis Science 2011
  - Stamper(1984) identified the relationship between NTG and macular damage with typically near fixation visual field loss.
  - Heijl & Lundqvist 1984
    - 45 patients followed from normal to abnormal VF's using test points at 5,10,15 & 20 degrees from fixation
    - Largest number at 15 degrees but a surprising number at 5 degrees confirming Hood's work showing that early damage occurs in the macula as well as more traditional arcuate zones

## "Green Disease"





# Myopia = "Red Disease"



# Optical Coherence Tomography as a Biomarker for Diagnosis, Progression, and Prognosis of Neurodegenerative Diseases Satue, etal AJO 2016

- Recent research using the latest SD OCT imaging technology has demonstrated that an early damage of the anterior visual pathway occurs in MS, PD, and AD and that the ganglion cell layer is the ultimate biomarker for disease diagnosis, severity, and progression.
- Thus, OCT technology should be used as a common and very useful clinical complement in the diagnosis and control of neurodegenerative disorders.
- 85 Citations



# <u>American Journal of Ophthalmology</u> <u>December 2017</u>

Baseline Fourier-Domain Optical Coherence Tomography Structural Risk Factors for Visual Field Progression in the Advanced Imaging for Glaucoma Study

## David Huang, MD etal

# AIG/ 2017

- A total of 277 eyes of 188 participants were followed up for 3.7 ± 2.1 years.
- VF progression was observed in 83 eyes (30%).
- Several baseline NFL and GCC parameters, but not disc parameters, were found to be significant predictors of progression on univariate Cox regression analysis.
- The most accurate single predictors were the GCC focal loss volume (FLV), followed closely by NFL-FLV. An abnormal GCC-FLV at baseline increased risk of progression by a hazard ratio of 3.1

# New Perspectives on Disease Management

- SD-OCT is superior in identifying progression in glaucoma suspects, pre-perimetric glaucoma, mild glaucoma and early moderate disease compared with SAP are superior in identifying progression, after an initial VF to set baseline.
- Average time to identification of statistically significant progression is 2-3 years with SD-OCT and up 6 years with SAP
- Intra-test variability is up to 10x less with OCT( 3%) than VF( 20%)

# New Perspectives on Disease Management

- RNFL "Floor" limits usefulness in late moderate to advanced glaucoma (50-60 microns)
- GCC progression analysis can continue to be useful in late moderate to advanced glaucoma due to density of fibers in the macula and the later involvement of central vision in the disease



VOLUME 393, ISSUE 10180, P1505-1516, APRIL 13, 2019

- Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial
- Gus Gazzard, FRCOphth
- Evgenia Konstantakopoulou, PhD
- Prof David Garway-Heath, MD
- Anurag Garg, FRCOphth
- <u>Victoria Vickerstaff, MSc</u>
- Rachael Hunter, MSc
- et al.

# The LIGHT Study



# LIGHT Study

- Standardization of laser delivery was achieved by protocol-defined settings and clinical endpoints.<sup>14</sup>
- Selective laser trabeculoplasty was delivered to 360° of the trabecular meshwork. 100 non-overlapping shots (25 per quadrant) were used, with the laser energy varied from 0·3 to 1·4 mJ by the clinician, using an appropriate laser gonioscopy lens.
- One re-treatment with selective laser trabeculoplasty was allowed, provided there had been a reduction in intraocular pressure after the initial treatment; the next escalation was medical therapy.
- Significant complications of selective laser trabeculoplasty (eg, a spike in intraocular pressure) precluded repetition of selective laser trabeculoplasty.

# LIGHT Study

- Drug classes for first, second, or third line treatment were defined by NICE<sup>15</sup>and European Glaucoma Society<sup>19</sup>guidance
- First line was prostaglandin analogues, second line was β blockers, third or fourth line was topical carbonic anhydrase inhibitors or α agonists. Fixed combination drops were allowed.
- Systemic carbonic anhydrase inhibitors were only permitted while awaiting surgery. Maximum tolerated medical therapy was defined by the treating clinician as the most intensive combination of drops an individual could reasonably, reliably, and safely use and thus varied between patients.
- A need for treatment escalation beyond maximum tolerated medical therapy triggered an offer of surgery.

# The Light study

- Methods
- In this observer-masked, randomized controlled trial treatmentnaive patients with open angle glaucoma or ocular hypertension and no ocular comorbidities were recruited between 2012 and 2014 at six UK hospitals.
- They were randomly allocated (web-based randomization) to initial selective laser trabeculoplasty or to eye drops.
- An objective target intraocular pressure was set according to glaucoma severity.
- The primary outcome was health-related quality of life (HRQoL) at 3 years (assessed by EQ-5D). Secondary outcomes were cost and cost-effectiveness, disease-specific HRQoL, clinical effectiveness, and safety.
- Analysis was by intention to treat. This study is registered at <u>controlled-trials.com</u> (ISRCTN32038223).

# The Light study

- Findings
- Of 718 patients enrolled, 356 were randomised to the selective laser trabeculoplasty and 362 to the eye drops group. 652 (91%) returned the primary outcome questionnaire at 36 months.
- Average EQ-5D score was 0.89 (SD 0.18) in the selective laser trabeculoplasty group versus 0.90 (SD 0.16) in the eye drops group, with no significant difference (difference 0.01, 95% CI -0.01 to 0.03; p=0.23).
- At 36 months, 74·2% (95% CI 69·3–78·6) of patients in the selective laser trabeculoplasty group required no drops to maintain intraocular pressure at target.
- Eyes of patients in the selective laser trabeculoplasty group were within target intracoluar pressure at more visits (93.0%) than in the eye drops group (91.3%), with glaucoma surgery to lower intraocular pressure required in none versus 11 patients.
- Over 36 months, from an ophthalmology cost perspective, there was a 97% probability of selective laser trabeculoplasty as first treatment being more cost-effective than eye drops first at a willingness to pay of £20 000 per quality-adjusted life-year gained.



Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naive Open-Angle Glaucoma and Ocular Hypertension during the LiGHT Trial

AnuragGargFRCOphth; VictoriaVickerstaffMSc. NeilNathwaniBSc. DavidGa rway-

<u>HeathMD</u>, EvgeniaKonstantakopoulouPhD, GarethAmblerPhD, CateyBunce DSc., RichardWormaldFRCOphth, KeithBartonFRCS, GusGazzardMD, Laser

# **Repeat SLT**

- Participants
- Treatment-naive OAG or OHT requiring repeat 360-degree SLT within 18 months. Retreatment was triggered by predefined IOP and disease-progression criteria (using objective individualized target IOPs).
- Methods
- After SLT at baseline, patients were followed for a minimum of 18 months after second (repeat) SLT. A mixed-model analysis was performed with the
  eye as the unit of analysis, with crossed random effects to adjust for correlation between fellow eyes and repeated measures within eyes. Kaplan
  Meier curves plot the duration of effect.
- Main Outcome Measures
- Initial (early) IOP lowering at 2 months and duration of effect after initial and repeat SLT.
- Results
- A total of 115 eyes of 90 patients received repeat SLT during the first 18 months of the trial. Pretreatment IOP before initial SLT was significantly higher than before retreatment IOP of repeat SLT (mean difference, 3.4 mmHg; 95% confidence interval [CI], 2.6–4.3 mmHg; P < 0.001). Absolute IOP reduction at 2 months was greater after initial SLT compared with repeat SLT (mean difference, 1.0 mmHg; 95% CI, 0.2–1.8 mmHg; P = 0.02). Adjusted absolute IOP reduction at 2 months (adjusting for IOP before initial or repeat laser) was greater after repeat SLT (adjusted mean difference, -1.1 mmHg, 95% CI, -1.7 to -0.5 mmHg; P = 0.001). A total of 34 eyes were early failures (retreatment 2 months after initial SLT) versus 81 later failures (retreatment >2 months after initial SLT). No significant difference in early absolute IOP reduction at 2 months after repeat SLT was noted between early and later failures (mean difference, 0.3 mmHg; 95% CI, -1.1 to 1.8 mmHg; P = 0.655). Repeat SLT maintained drop-free IOP control in 67% of 115 eyes at 18 months, with no clinically relevant adverse events.
- Conclusions
- These exploratory analyses demonstrate that repeat SLT can maintain IOP at or below target IOP in medication-naive OAG and OHT eyes requiring
  retreatment with at least an equivalent duration of effect to initial laser.

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## OPHTHALMOLOGY VOLUME 127, ISSUE 4

Measuring Glaucomatous Focal Perfusion Loss in the Peripapillary Retina Using OCT Angiography David Huang, MD et al

## Participants

A total of 47 patients with primary open-angle glaucoma (POAG) and 36 normal participants were analyzed.

## Methods

One eye of each subject was scanned using an AngioVue (Optovue, Fremont, CA) 4.5-mm OCTA scan centered on the disc.

En face nerve fiber layer (NFL) plexus angiogram was generated. With the use of custom software, a capillary density map was obtained by computing the fraction of area occupied by flow pixels after low-pass filtering by local averaging 21×21 pixels.

The low-perfusion map is defined by local capillary density below 0.5 percentile over a contiguous area above 98.5 percentile of the normal reference population. The LPA parameter is the cumulative area, and the FPL is the percent capillary density loss (relative to normal mean) integrated over the LPA.

Measuring Glaucomatous Focal Perfusion Loss in the Peripapillary Retina Using OCT Angiography David Huang, MD et al

- Main Outcome Measures
- Peripapillary retinal LPA and FPL.
- Results
- Among patients with POAG, 3 had preperimetric glaucoma and 44 had perimetric glaucoma, with visual field (VF) mean deviation (MD) of -5.14±4.25 decibels (dB). The LPA was 3.40±2.29 mm<sup>2</sup> in those with POAG and 0.11±0.18 mm<sup>2</sup> in normal subjects (*P* < 0.001). The FPL was 21.8%±17.0% in those with POAG and 0.3%±0.7% in normal subjects (*P* < 0.001).</li>
- The diagnostic accuracy as measured by the area under the receiver operating curve was 0.965 for both LPA and FPL, with a sensitivity of 93.7% at 95% specificity. The repeatability as measured by intraclass correlation coefficient was 0.977 for LPA and 0.958 for FPL.
- The FPL had excellent correlation with VF MD (Spearman's rho = -0.843), which was significantly (P = 0.008) better than the correlation between NFL thickness and VF MD (rho = 0.760). The hemispheric difference correlation between FPL and VF (Spearman's rho = 0.770) was significantly (P < 0.001) higher than the hemispheric difference correlation between LPA and VF (rho = 0.595).

Measuring Glaucomatous Focal Perfusion Loss in the Peripapillary Retina Using OCT Angiography David Huang, MD et al

## Conclusions

• The low-perfusion map and LPA and FPL parameters are able to assess the location and severity of focal glaucoma damage with good agreement with VF.

# OCTA the New View (Normal Eye)



Images and data courtesy of Robert Weinreb, MD and Linda Zangwill, PhD, UC San Diego

# OCTA Moderate Glaucoma



Images and data courtesy of Robert Weinreb, MD and Linda Zangwill, PhD, UC San Diego

# Advanced Glaucoma



Images and data courtesy of Robert Weinreb, MD and Linda Zangwill, PhD, UC San Diego

# New Technologies in Glaucoma Diagnosis and Management

A Comparison of Perimetric Results from a Tablet Perimeter and Humphrey Field Analyzer in Glaucoma Patients

- Y. Kong, M. He, J Crowston, A Vingrys
- <u>Transl Vis Sci Technol</u>. 2016 Nov; 5(6):2
- University of Melbourne College of Optometry

## Melbourne Rapid Fields Automated threshold perimeter



Australian Government Department of Health Therapeutic Goods Administration

Australian Register of Therapeutic Goods Certificate

#### hasued to

#### Glance Optical Pty Ltd

for approval to supply

Glance Optical Pty Ltd - Visual field plotter

ARTG Identifier	282166
ARTG Start date	7/11/2016
Product Category	Medical Device Included Class 1
GMDN	14380
GMDN Term	Visual field plotter



- MRF registered as Medical Device with TGA (Australia) and MedSafe (NZ)
- Complies with MBS 10940, 10941 11221, 11224 definition

# MRF



### SPACE SAVING **DESIGN**

## Perimetry made simple

Introducing Melbourne Rapid Fields (MRF) Powered by M&S

MRF is a simple solution, meticulously designed to perform visual field testing and developed by a name you can trust.

## 借 Ease of Use

- Intuitive, unique design and patient experience
   Simple user interface, auto-populate existing patient data
- Easy interpretation with straight-forward, accurate reports
- Portability and flexibility allow for reliable daily testing in the office or off-site

#### Functions & Features

- Seamless 30-2, 24-2 and 10-2 Full Threshold and Screening tests.
- Comparison to normative data by decade
   Quicker and accurate test times
- Advanced test\retest allows for reduced
- test time on subsequent fields

  Near Visual Acuity testing

#### 🐲 Peer Reviewed & Published

American Journal of Ophthalmology, Mar. 2018
Clinical & Experimental Ophthalmology, Sept. 2017

Co-developed by M&S Technologies, Inc., University of Melbourne and Glance Optical Pty. Ltd

mstech-eyes.com

#### Toll Free: 1-877-225-6101

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The First Choice in Vision Testing Systems



# MRF





## M&S | Melbourne Rapid Fields (MRF) Introducing MRF with reliable online testing



Studies show MRF delivers reliable detection and assessment of peripheral retinal sensitivity loss as well as a means for accurate patient monitoring.

#### **Optimize your practice**

- Convenient at-home testing
- Keep clinics safe
- Patient results are securely transmitted
- Testing under 3 minutes per eye
- Precisely calibrated with immediate, accurate results
- Easily monitors and records patient's progress
- Short test time improves patient experience
- Including 24-2 and 10-2 testing
- Scientific evidence with validated studies\*
- \* A Comparison of Perimetric Results from a Tablet Perimeter and Humphrey Field Analyzer in Glaucoma Patients Translational Vision Science & Technology, 2016

mstech-eyes.com

Toll Free: 1-877-225-6101

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Learn how remote MRF testing can compliment your office.







## Threshold strategy — Bayes prediction + neighborhood logic



Epsilon = ideal sweat factor = # trials need to yield min variance in threshold. This presumes NO lapse response from patient.

From Fig 6. King-Smith et al. Vis Res 1994; 34 (7); 885-912.











But an early False response makes it hard to recover using normal methods: requires > 20 trials. Solution - **Neighbourhood logic** 

From Fig 2. Phipps et al. Clin Exp Optom 2001 ; 84: 5: 264-269


# formats

#### **HFaA**



#### MRF







#### Results: outputs in familiar formats. Advanced defect HFA MRF





#### Equivalent diagnostic ability between MRF and HFA

Independent study from Macquarie University, NSW

N=60 OAG: 43 manifest HFA defects, 17 GS: 20 controls

Diagnoses based on Optic Disc

Schultz et al Clin Exper Ophthalmol 2017.





100-Specificity %

# Transformative approach to visual field testing

- Glaucoma patients know their vision can get worse
- Patients feel terrible when their results are unreliable
- Patients have anxiety not from their perceived failure to be a good testtaker
- Current tests such as the Humphrey and Octopus are difficult to take
  - Eye movements, false-alarm trials, loss of concentration
  - Test results reflect "1/3 the retina, 1/3 the patient, and 1/3 the perimetrist"
- Goal is to transform the patient's role from *test subject* to *team member*

## Patients want to help. But they hate VF tests.

• Glen, Baker, David Crabb (BMJ 2014):

**Open Access** 

Research

BMJ Open: first published as 10.1136/bmjopen-2013-003996 on 10 January

# **BMJ Open** A qualitative investigation into patients' views on visual field testing for glaucoma monitoring

Fiona C Glen, Helen Baker, David P Crabb

**To cite:** Glen FC, Baker H, Crabb DP. A qualitative investigation into patients' views on visual field testing for glaucoma monitoring. *BMJ Open* 2014;**4**:e003996. doi:10.1136/bmjopen-2013-003996

 Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/ bmjopen-2013-003996).

#### ABSTRACT

**Objectives:** To investigate the views and experiences of patients regarding their glaucoma follow-up, particularly towards the type and frequency of visual field (VF) testing.

**Design:** A qualitative investigation using focus groups. The group discussion used broad open questions around the topics in a prompt guide relating to experiences of glaucoma follow-up, and in particular, VF monitoring. All the groups were taped, transcribed and coded using manual and computer-aided methods. **Setting:** Three National Health Service (NHS) hospitals in England; two focus groups took place at each heapital.

#### Strengths and limitations of this study

- This is the first qualitative study to examine patients' views of visual field monitoring using focus groups.
- Focus groups took place at three selected hospitals in the South of England; it is assumed that the views expressed represent the experiences of patients in a wider population.
- Not all patients approached by their ophthalmologist took part, but reasons for nonparticipation were not monitored. Patients who chose to volunteer may be more articulate, motivated and opinionated than the general patient

**Results:** These patients did not enjoy the VF test but they recognised the importance of regular monitoring for preserving their vision. These patients would agree to more frequent VF testing on their clinician's recommendation. A number of themes recurred throughout the focus groups representing perceived barriers to follow-up care. The testing environment, waiting times, efficiency of appointment booking and travel to the clinic were all perceived to influence the general clinical experience and the quality of assessment data. Patients were also concerned about aspects of patient–doctor communication, and often received little to no feedback about their results.

# The VVP Uses Off-the-Shelf VR HMDs The test requires only a headset. Head movements record responses to stimuli

ORMAC

# Olleyes

- Visual Field:
  - All common protocols e.g. 24-2, 10-2, 30-2, etc).
  - Testing time is about 3 minutes for threshold and 1.5 minutes for screening.
- Visual Acuity (near and far acuity).
- Color Vision.
- Pediatrics Visual Field.

# Olleyes

- The VisuALL is a VR visual field perimeter designed for standardized and mobile assessment of the visual field.
  VisuALL automatically analyzes the retOLLEYES
  VIRTUAL VISUAL FIELD PRODUCTS
- The VisuALL is a VR visual field perimeter designed for standardized and mobile assessment of the visual field. VisuALL automatically analyzes the retinal sensitivity in patients with Glaucoma and other visual disorders. VisuALL enables the examination of multiple patients at a time increasing office productivity.

**ORIGINAL STUDY** 

#### Preliminary Report on a Novel Virtual Reality Perimeter Compared With Standard Automated Perimetry

Reza Razeghinejad, MD,\* Alberto Gonzalez-Garcia,† Jonathan S. Myers, MD,\* and L.J Katz, MD\*

Precise The VisuALL head-mounted perimetry in normal subjects and glaucoma patients had a moderate to strong correlation with the Humphrey Field Analyzer (HFA).

Purpose: Visual field testing has a vital role in diagnosing and managing glaucoma. The current clinical practice relies on large, table-based testing units. This study investigated the performance of a novel virtual reality head-mounted visual perimetry device (VisuALL), in normal and glaucoma patients.

Methods: This prospective observational study was conducted on 50 cycs of 25 healthy subjects (normal group) and 52 cycs of 26 patients with a controlled mild or moderate stage of glaucoma (glaucoma group). All participants had visual field testing with VisaALL and the HFA (24-2, Swedish Interactive Threshold Algorithm). The mean sensitivity of the whole visual field and each quadrant were compared between both machines and the receiver operating characteristic was used to compare the diagnostic abilities and the Bland-Alman plot to evaluate the agreement of the 2 perimeters.

**Results:** The global mean sensitivity of the VisuALL and the HFA correlated significantly in both normal (r=0.5, P=0.001) and glaucoma (r=0.8, P<0.001) groups. The mean sensitivity of all quadrants also correlated significantly in both groups. The VisuALL mean sensitivity had a greater (0.98) receiver operating characteristic curve than HFA (0.93) mean sensitivity (P=0.06) in discriminating normal versus glaucoma.

Conclusion: There was an excellent correlation between the VisuALL and the Standard Automated Perimetry in normal and glaucoma patients and VisuALL showing high diagnostic performance.

Key Words: glaucoma, visual field, perimetry, virtual reality, headmounted device

(J Glaucoma 2020;00:000-000)

neurological diseases and for detecting the disease progression.<sup>1</sup>

The SAP requires maintenance of constant fixation for several minutes and conscious decision making in identification of near the threshold level stimuli.<sup>2,3</sup> In addition, it has a number of disadvantages including being stressful for debilitated, claustrophobic, ill, or elderly patients to keep their heads still in the perimeter bowl during the test. Patients with musculoskeletal problems and admitted patients in the hospital that are not able to position their head in the proper position for visual field testing may have unreliable, artifact laden results or be unable to take the test.

Several devices have been developed since the advent of the HFA and the Octopus perimeters, in an effort to improve the detection of visual field defects and make the test easier for patients.4-6 Examples include the use of laptops and iPads.7-9 These modalities bring portability, but lack of fixation monitoring methods and hardware standardization have been the limiting factors in their widespread use. In addition, specificity and sensitivity studies have been mixed.7,3,10,11 The majority of these devices are composed of a head-mounted device (HMD) controlled by a laptop or a tablet.8.12 The size and cost of current tabletop perimeters limit their use in screening efforts as well as clinical care in remote and raral settings. HMD perimeters may allow inoffice, remote, and home visual field testing owing to their lower cost and portability and could promote a change in the screening protocol.

The aim of this study was to characterize a novel perimeter that includes an HMD with eye-tracking capabilities, to evaluate the age influence on the resultant retinal sensitivity, and to compare its results with the HFA.



Visu**ALL VRP** 



**Perimetry Adults Perimetry Ped Visual Acuity Color Vision** More...



### Perimetry Kids

### Gamified

Binocular

Patch-Free

Validated



# Visual Acuity (immersive)



## Visu**ALL VRP**



#### **Color Vision**



## Visu**ALL VRP**

### Annie VisuALL Virtual Assistant



CORNEAL HYSTERESIS: The Newest Disruptive Technology In Glaucoma

- 2002: Clinical research with ORA commences
- 2005: The 1<sup>st</sup> generation ORA was made commercially available
- 2012: Generation II ORA was launched
- 3<sup>rd</sup> Generation "ORA G3" introduced September 2015 Measures:
  - Corneal Hysteresis (CH)
  - Goldmann-correlated IOP (IOP<sub>g</sub>)
  - Corneal compensated IOP (IOP<sub>CC</sub>)



# Corneal Hysteresis as a Biomarker of Glaucoma: Current Insights



# Corneal Hysteresis as a Biomarker of Glaucoma: Current Insights

PROBABILITY OF GLAUCOMA DEVELOPMENT



#### IOPcc Key Benefit #2 IOPcc is superior for glaucoma risk assessment

IOPcc is clinically superior to GAT, other NCTs, and iCare because it is more associated with Glaucoma risk, status of glaucoma, and glaucoma progression

"the results of this study suggest that IOPcc may represent a superior test for the evaluation of glaucoma"



• Average IOPcc was **5 mmHg higher** than GAT in NTG eyes

Goldmann applanation tonometry compared with corneal-compensated intraocular pressure in the evaluation of primary open-angle Glaucoma Joshua R Ehrlich, Nathan M Radcliffe, and Mitsugu Shimmyo

# Falck Medical Multi-Function DEVICE



### Intraocular Pressure

- ✓ Optical Applanation Measurement
- ✓ Compensates for Corneal Biomechanics
- ✓ Multiple Serial IOP Measurements N Value
- $\checkmark$  Systolic and Diastolic IOP
- ✓ Average IOP Displayed
- $\checkmark$  IOP Variation with Cardiac Cycle OPA
- ✓ Precision Displayed



#### OPHTHALMODYNAMOMETRY

- ✓ Mean Central Artery Pressure (MCRAP) measurement.
- ✓ Data Captured During Multiple Cardiac Cycles.
- ✓ Mean Arterial BP Displayed.
- ✓ MCRAP IOP = True Ocular Perfusion Pressure (OPP).
- ✓ Reduced OPP is a risk factor for glaucoma progression.
- ✓ Abnormal OPH Increased Risk of Stroke



### TONOGRAPHY

- ✓ Optical Aqueous Humor Outflow Measurement.
- ✓ Aqueous Outflow Decreased in Glaucoma.
- ✓ Decreased Outflow = Increased TM Resistance.
- ✓ Decreased Outflow = Increased IOP Fluctuation.
- ✓ Document Therapeutic Efficacy of Outflow Interventions.
- ✓ Document Need for Additional Intervention.
- ✓ Glaucoma risk assessment.



#### Clinical comparison of the FAT1 and THE GAT

Protocol: FDA PMA single site blinded randomized clinical study. IOP, pachymetry and keratometry recorded. Two-hundred nine eyes enrolled.

Results:

- 1. No relationship between corneal thickness, curvature and FAT1 readings ( p=0.06, 0.04).
- 2. Linear regression relationship between FAT1 and GAT IOP readings, r squared value 0.925.
- 3. Bland Altmann Analysis, mean paired difference of diastolic IOP, FAT1 GAT 0.7 mmHg.
- 4. Bias testing; Distribution and Randomness Test, T-Test and Wilcoxon Rank Sum Test. No bias found for measurement sequence, operator, intra—visit or inter-visit measurements.

Conclusion;

- 1. FAT1 readings not effected by corneal thickness or curvature.
- 2. No significant difference between FAT1 and GAT1 diastolic IOP readings.
- 3. FAT1 measurement results are independent of operator, visit sequence or testing sequence.

## Falck Multi Medical Device

FAT1<sup>™</sup> User Reference Sheet\* **Tonometry (Intraocular Pressure):** 1. FAT1 IOP = Diastolic + Systolic IOP 2. To estimate a Goldmann IOP, subtract one-half the FAT1 OPA from FAT1 IOP. Tonography (Aqueous Outflow): 1. Outflow < 0.18 red flag\*. 2. IOP / Outflow > 100 red flag\*. Ophthalmodynamometry (Perfusion / Blood Flow): 1. MCRAP < 0.6 X MAP red flag\*. 2. OPP = MCRAP - IOP. 3. OPP < 45 red flag\*.

 User must interpret results along with clinical presentation, contributing risk factors and additional testing to arrive at the correct diagnosis.
For additional information go to falckmedical.com.

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# The Case of the Asymmetric ONH

- 63 y/o white male presented for consultation for glaucoma evaluation
- VA: 20/20 OU
- Peak IOP: 26/23
- Ta: 21/19 mmHg
- Tonography: 0.18 OD / 0.24 OS
- Pach: 560/558
- CH: 8.9/9.1









# The Case of the Asymmetric ONH

- Tx: Vyzulta 1 gtt qhs OU
- Follow up: 3 weeks
- IOP post Tx:
  - OD 17
  - OS 15
  - Tonography: OD 0.25 / OS 0.29
- Next step?




















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# Equinox: The New Horizon in Glaucoma Therapy

- Dr. John Berdahl
- Non Pharmacologic/ Non Surgical Glaucoma Therapy

# Visual Impairment and Intracranial Pressure - VIIP

Optic Disc Edema, Globe Flattening, Choroidal Folds, and Hyperopic Shifts Observed in Astronauts after Long-duration Space Flight

Thomas H. Mader, MD,<sup>1</sup> C. Robert Gibson, OD,<sup>2</sup> Anastas F. Pass, OD, JD,<sup>3</sup> Larry A. Kramer, MD,<sup>4</sup> Andrew G. Lee, MD,<sup>5</sup> Jennifer Fogarty, PhD,<sup>6</sup> William J. Tarver, MD,<sup>6</sup> Joseph P. Dervay, MD,<sup>6</sup> Douglas R. Hamilton, MD, PhD,<sup>7</sup> Ashot Sargsyan, MD,<sup>7</sup> John L. Phillips, PhD,<sup>8</sup> Duc Tran, DO,<sup>2</sup> William Lipsky, MD,<sup>2</sup> Jung Choi, OD,<sup>2</sup> Claudia Stern, MD, PhD,<sup>9</sup> Raffi Kuyumjian, MD,<sup>10</sup> James D. Polk, DO<sup>6</sup>



Normal – IOP slightly greater than ICP

Glaucoma-IOP greater than ICP

Papilledema– IOP lower than ICP

#### Normal

Normal IOP Normal CSFp



### Glaucoma

High IOP Mild Low CSFp



## Zero Gravity

Normal IOP High CSFp



## ICP changes with Age





Advanced imageprocessing algorithm locates exact treatment area

2

Camera-guided system enables precise **non-contact procedure** 

**100 laser beams** are directed to the trabecular meshwork

3

Delivery in **1.2 seconds** 

4

**IN VIEW:** The investigational non-invasive, non-contact procedure is performed with automated laser technology that delivers **100** spots to the trabecular meshwork through the limbus in just **1.2** seconds. (Images courtesy of BELKIN Laser Ltd.)

#### **WATCH THE PROCEDURE** Go to OphthalmologyTimes.com/1Second

# •BELKIN DSLT

ARVO Annual Meeting Abstract | April 2014 Direct Trans-Scleral Selective Laser Trabeculoplasty (SLT) Without a Gonioscopy Lens Michael Belkin; Noa Geffen; Shay Ofir; Audrey Kaplan Messas; Yaniv Barkana; Avner Belkin; Ehud Assia; Direct Trans-Scleral Selective Laser Trabeculoplasty

# Belkin DSLT

- An investigational IOP-lowering modality, direct selective laser trabeculoplasty (DSLT) (BELKIN Laser), is being developed for its potential as a first-line treatment for ocular hypertension (OHT) open-angle glaucoma (OAG) and possibly for angle-closure glaucoma (ACG) that overcomes the limitations of current initial therapeutic options.
- The non-invasive, non-contact procedure is performed with automated laser technology that delivers 100 spots to the trabecular meshwork through the limbus in just 1.2 seconds.
- A proof-of-concept study provided evidence for the efficacy and safety of the transscleral approach to laser beam delivery using a conventional SLT instrument, and studies are under way outside of the United States using the external automatic glaucoma laser device itself

# Belkin DSLT

- **Results**: In the trial group (N=16), IOP decrease from an average of 20.21 mmHg before treatment to 15.50 at 6 months.
- The corresponding numbers for the control group (n=16), were 21.14 mmHg and 15.00. There was no statistical difference between the two groups in IOP reduction.
- Complications rate was significantly higher in the control group (p<0.0001, OR 6.881, 95% CI 1.676/28.248).
- Anterior chamber inflammation and superficial punctate keratitis rates were significantly higher in the control group and compared to the study group (p=0.006).

## **BELKIN DSLT**

https://youtu.be/Im1x8JZ22yl

#### **CATS: Correcting Applanation Tonometry Surface**



Inventor Sean McCafferty MD



After years of work, the device became FDA cleared in October 2018.

CATS is simply a replacement prism for any Goldmann applanation or Perkins tonometer. The CATS Tonometer Prism<sup>™</sup> utilizes a concave contact surface to minimize mechanical bending resistance of the cornea. The device also features a tapered edge, which helps to reduce the influence of tear-film adhesion.





#### **CATS: Correcting Applanation Tonometry Surface**



Flattens the Cornea Amplifying Intra-Corneal Stress and IOP errors

**CATS™** Tonometer Prism – the New Shape of IOP

**Traditional GAT Prism – No change in 65 Years** 





#### **CATS: Compare CATS to GAT in Normal Eyes**

#### **Purpose:**

1. Compare CATS to GAT in 243 Normal Eyes with Central Corneal Thickness between 400 – 650 Microns

2. Evaluate the impact of corneal properties on GAT and CATS



A significant reduction in CATS prism's sensitivity to CCT and CH was demonstrated compared with the traditional GAT prism

#### **CATS Intercameral Pressure Validation**

#### Methods:

- Intracameral IOP measured on 58 eyes undergoing cataract surgery
- IOP manometrically modulated to 10, 20, and 40 mmHg
- Difference between the CATS and GAT IOP measurements from true intracameral pressure correlated to the error parameters





The CATS prism is significantly more accurate compared to the GAT prism compared to true intracameral pressure, and is unaffected by CCT.

# Glaucoma Therapy for the 21<sup>st</sup> Century



#### INTRODUCING RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02%

- RHOPRESSA<sup>®</sup> is a new class of drug and has a white cap
- RHOPRESSA<sup>®</sup> is available in 1-month supply (2.5 mL)
- After opening, the product may be kept at room temperature for up to 6 weeks

Ô	
Pharmaceulicals. Inc.	
rhopresso® (netarsudil ophthalmic solution) 0.02%	
For topical application in the eye	
Sterile Rx only	
2.5 mL	Intersudi optivinik

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#### RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% IS A ONCE-DAILY THERAPY DESIGNED TO INHIBIT ROCK

# RHOPRESSA<sup>®</sup> PRODRUG<sup>1</sup> **ACTIVE METABOLITE<sup>1</sup> Corneal esterases Cleavage site**

- RHOPRESSA<sup>®</sup> was specifically designed to target the TM at the cellular level<sup>1,2</sup>
- RHOPRESSA<sup>®</sup> prodrug is converted by corneal esterases into an active metabolite that has 5 × higher potency for ROCK inhibition<sup>1</sup>
- RHOPRESSA<sup>®</sup> inhibits the creation of stress fibers in the TM tissues to relax the meshwork and improve trabecular outflow<sup>1,2</sup>

# Rhopressa

Inhibitor of Rho Kinase (ROCK) and Norepinephrine Transporter (NET)

Potentially lower IOP by three mechanisms

- 1.Increasing TM outflow
- 2.Reducing episcleral venous pressure
- 3.Reducing aqueous production (via NET inhibition

#### **ROCK INHIBITION RELAXES THE TM STRUCTURE**



CONTROL

Magnification of both images are identical

#### **+ ROCK INHIBITOR**



#### **Expansion of TM structure**

Morphology of the TM in perfused human donor eyes was examined using light microscopy. Images were taken by using a 20× objective along the inner wall of the SC.

ROCK, Rho kinase; SC, Schlemm's canal; TM, trabecular meshwork.

1. Ren et al. Invest Ophthalmol Vis Sci. 2016;57:6197.
#### IN A ROBUST CLINICAL TRIAL PROGRAM, OVER 800 PATIENTS WERE TREATED WITH RHOPRESSA<sup>®</sup> (NETARSUDIL OPHTHALMIC SOLUTION) 0.02%

- RHOPRESSA<sup>®</sup> 0.02% QD (PM) was compared with timolol 0.5% BID in ROCKET 1, ROCKET 2, and ROCKET 4<sup>1,2</sup>
- Primary efficacy endpoint for all trials was mean IOP at week 2, week 6, and month 3<sup>1,2</sup>

	n	PRIMARY EFFICACY ANALYSIS	SAFETY ANALYSIS	EFFICACY POPULATION
<b>ROCKET 1</b> <sup>1</sup> (NCT02207491)	n=202 (RHOPRESSA®) n=209 (timolol)	3 months	3 months	<27 mmHg ( <i>post hoc</i> analysis, <25 mmHg)
<b>ROCKET 2</b> <sup>1</sup> (NCT02207621)	n=251 (RHOPRESSA®) n=251 (timolol)	3 months	12 months	<25 mmHg
<b>ROCKET 4</b> <sup>2</sup> (NCT02558374)	n=351 (RHOPRESSA®) n=357 (timolol)	3 months	6 months	<25 mmHg

BID, twice daily; IOP, intraocular pressure; QD, once daily.

1. Serle et al. Am J Ophthalmol. 2018;186;116. 2. Khouri et al. Association for Research in Vision and Ophthalmology oral presentation 2017 [E-abstract 2461].

#### RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% MAINTAINED EFFICACY THROUGH 1 YEAR IN THE ROCKET 2 TRIAL



• IOP was collected at 8 AM only at months 6, 9, and 12 as a safety measure

For important safety information refer to the RHOPRESSA<sup>®</sup> Prescribing Information at the end of this presentation or at <u>www.RHOPRESSA.com</u>. IOP, intraocular pressure; QD, once daily; SEM, standard error of the mean.

1. Serle et al. Abstract accepted at Association for Research in Vision and Ophthalmology 2018 annual meeting. 2. Serle et al. Am J Ophthalmol. 2018;186;116-127. 3. Data on file, Aerie Pharmaceuticals Inc. VISIONaerie science

#### RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% OCULAR ADVERSE EVENT PROFILE

PREFERRED TERM (with Incidence ≥5% [pooled safety population <sup>a</sup> ])	RHOPRESSA® 0.02% QD (N=805) n (%)	TIMOLOL 0.5% BID (N=816) n (%)
Eye Disorders		
Conjunctival hyperemia	428 (53.2)	85 (10.4)
Cornea verticillata (corneal deposits)	162 (20.1)	2 (0.2)
Conjunctival hemorrhage	137 (17.0)	15 (1.8)
Vision blurred	60 (7.5)	12 (1.5)
Lacrimation increased	53 (6.6)	5 (0.6)
Erythema of eyelid	52 (6.5)	4 (0.5)
Visual acuity reduced	44 (5.5)	13 (1.6)
General Disorders and Administration Site Conditions		
Instillation site pain	158 (19.6)	175 (21.4)
Instillation site erythema	74 (9.2)	13 (1.6)
Investigations		
Vital dye staining cornea present	65 (8.1)	57 (7.0)

1. Data on file, Aerie Pharmaceuticals, Inc.

<sup>a</sup>Includes

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## **Corneal Verticillata**

- Corneal Verticillata
  - Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies.
  - The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing.
  - This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

# IN THE POOLED ROCKET STUDIES, CORNEA VERTICILLATA WAS MILD AND DID NOT AFFECT VISION

- Whorl-like pattern of phospholipid deposits caused by several cationic amphiphilic drugs<sup>1</sup>
- The corneal verticillata were first noted at 4 weeks of daily dosing in RHOPRESSA<sup>®</sup> (netarsudil ophthalmic solution) 0.02% -treated patients <sup>2</sup>
- Were asymptomatic and did not result in an apparent change in visual function<sup>2</sup>
- Resolved in majority upon discontinuation of RHOPRESSA<sup>®2</sup>

#### **RHOPRESSA®-treated patient**<sup>3</sup>



Amiodarone-treated patient<sup>1</sup>



QD, once daily.

1. Raizman et al. *Surv Ophthalmol.* 2017;62:286. 2. RHOPRESSA<sup>®</sup> (netarsudil ophthalmic solution) 0.02% Prescribing Information. 3. Courtesy of ROCKET investigator.

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### IN THE POOLED ROCKET STUDIES, MILD CONJUNCTIVAL HEMORRHAGE WAS SELF-RESOLVING AND RARELY RESULTED IN DISCONTINUATION

- Typically small microhemorrhages localized to the limbal area which may be related to vasodilatory effect of the molecule<sup>1</sup>
- Onset was variable, and duration was typically 1-3 weeks<sup>1</sup>
- Conjunctival hemorrhage was mild in 90% of cases and selfresolving with continued dosing<sup>2</sup>
- Resulted in discontinuation in 1% of patients treated with RHOPRESSA<sup>®</sup> (netarsudil ophthalmic solution) 0.02% QD<sup>2</sup>



Mild conjunctival hemorrhage<sup>2</sup>







## Rhopressa 0.02%: Two Sides to Every Story

For patients with baseline IOP < 25 mmHg, the IOP reductions with RHOPRESSA 0.02% dosed once daily were similar to those with timolol 0.5% dosed twice daily (see Table 1).

Patients with baseline IOP equal to or above 25 mmHg RHOPRESSA 0.02% resulted in smaller mean IOP reductions at the morning time points than timolol 0.5% for study visits on Days 43 and 90 T

The difference in mean IOP reduction between the two treatment groups was as high as 3 mmHg, favoring timolol.

## Rocklatan<sup>®</sup> and Rhopressa<sup>®</sup> Usage



NC 10727-477-25 Thoursels of the Interessed working Solution 2025 Bris 2.5 ml Bart

- Rocklatan<sup>®</sup> (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is a new combination drug product and has a white cap
- Rocklatan<sup>®</sup> is available in a 1-month supply (2.5 mL)
- Protect from light. Must remain refrigerated

- Rhopressa<sup>®</sup> (netarsudil ophthalmic solution) 0.02% is a new class of drug and has a white cap
- Rhopressa<sup>®</sup> is available in a 1-month supply (2.5 mL)
- Refrigerate until opened. After opening, the product may be kept at room temperature for up to 6 weeks

## Rocklatan

- The FDA approval of Rocklatan<sup>™</sup> is based on data from two Phase 3 registration trials, MERCURY 1 and MERCURY 2.
- In these studies, Rocklatan<sup>™</sup> achieved its primary 90-day efficacy endpoint as well as positive 12-month safety and efficacy results, demonstrating statistically superior IOP reduction over latanoprost and netarsudil at every measured time point.
- More than 60% of patients taking Rocklatan<sup>™</sup> in the two MERCURY studies achieved an IOP reduction of 30% or more, a frequency that was nearly twice that achieved by participants taking latanoprost alone.
- Rocklatan<sup>™</sup> also helped more patients get to low target pressures. Nearly twice as many patients taking Rocklatan<sup>™</sup> reached 16 mmHg or lower and nearly three times as many reached 14 mmHg or lower compared to latanoprost.

# Rocklatan<sup>®</sup> Achieved the Primary Endpoint of Superiority vs Both Individual Components Over 3 Months<sup>1</sup>

- Rocklatan<sup>®</sup> (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% was compared to its individual components Rhopressa<sup>®</sup> QD and latanoprost QD to establish statistical superiority in MERCURY-1 and MERCURY-2<sup>2,3</sup>
- Primary efficacy endpoint for both trials was mean IOP at 8 AM, 10 AM, and 4 PM at Week 2, Week 6, and Month 3, respectively. Primary safety endpoint was ocular and systemic AEs over the treatment period<sup>2,3</sup>

	n	PRIMARY EFFICACY ANALYSIS	SAFETY ANALYSIS	PRIMARY EFFICACY POPULATION
MERCURY-1 <sup>2</sup>	n=238 (Rocklatan <sup>®</sup> QD) n=244 (Rhopressa <sup>®</sup> QD) n=236 (latanoprost QD)	3 months	12 months	>20 mmHg @ 08:00 AM, >17 mmHg @ 10:00 AM and 16:00 PM, and <36 mmHg any time prior to randomization
MERCURY-2 <sup>3</sup>	n=245 (Rocklatan <sup>®</sup> QD) n=255 (Rhopressa <sup>®</sup> QD) n=250 (latanoprost QD)	3 months	3 months	>20 mmHg @ 08:00 AM, >17 mmHg @10:00 AM and 16:00 PM, and <36 mmHg any time prior to randomization

AE, adverse event; FDC, fixed-dose combination; QD = once a day.

1. Asrani S et al. 13th Biennial Meeting of the European Glaucoma Society. Poster #2210. 2. Brubaker et al. Annual Meeting of the American Glaucoma Society 2018. Poster #074. 3. Walters et al. Annual Meeting of the American Glaucoma Society 2018, Poster #073.

# Over 60% of Rocklatan<sup>®</sup> Patients Achieved ≥30% Mean IOP Reduction at 3 Months<sup>1</sup>

Pooled MERCURY Studies: Proportion of Patients Achieving Prespecified Percentage of Mean Diurnal IOP Reduction at Month 3 (ITT Population)



\**P*<0.0001 vs Rhopressa\* and latanoprost. ITT, intent-to-treat 1.Data on file, Aerie Pharmaceuticals, Inc.

# Vyzulta (Latanoprostene Bunod)

## Nitric Oxide and Glaucoma

- Patients with primary open-angle glaucoma (POAG) have lower levels of NO synthase activity in the trabecular meshwork (TM), Schlemm's canal, and ciliary muscle<sup>1</sup>
- NO donors lower IOP in normal and POAG eyes
- A major site of action for NO donors is the TM
  - NO relaxes the TM and ciliary muscle
  - NO donors increase outflow facility in anterior segments, mediated by a decrease in TM cell volume
  - Endothelial NO synthase (eNOS) overexpression increases conventional outflow and lowers IOP in a mouse eye model

## Latanoprostene Bunod: NO-Donating Latanoprost

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



## How Does Nitric Oxide, as Released by VYZULTA, Contribute to Reduction in IOP?



#### LBN Relaxed Human Trabecular Meshwork Cells Through Activity increased *Nitro* Models mean cGMP in primary HTMCs<sup>4</sup>



*In vitro* studies showed that LBN increased HTMC cGMP signaling and relaxation of trabecular meshwork

#### The clinical significance of in vitro data is unknown.

ET-1=Endothelin-1; HTMCs=human trabecular meshwork cells; LBN=latanoprostene bunod.

Cavet ME, et al. Invest Ophthalmol Vis Sci. 2015;56:4108-16.

#### Notable reduction of F-actin filaments with LBN vs latanoprost



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# Efficacy Results: Primary Endpoint Voyager Study

At highest doses, lowered IOP 1-1.5 mmHg more than latanoprost Most common AE: pain upon instillation



**REDUCTION IN MEAN DIURNAL IOP ON VISIT 6 (DAY 28)** 

1. Weinreb RN et al. Br J Ophthalmol. 2015;99(6):738-45

## Statistically Superior Efficacy vs Xalatan 0.005%<sup>1,2</sup>

### VYZULTA delivered significantly greater mean IOP reduction from baseline vs Xalatan 0.005% at Day 28<sup>1</sup>



#### Baseline Mean Diurnal IOP<sup>1</sup>

- VYZULTA 0.024%: 26.01 mmHg
- Xalatan 0.005%: 26.15 mmHg

1. Weinreb RN, Ong T, Scassellati SB, Vittitow JL, Singh K, Kaufman PL. Br J Ophthalmol. June 2015;99(6):738-745. 2. Data on File. Bausch & Lomb Incorporated.

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## Statistically Superior Efficacy vs Xalatan 0.005%<sup>1,2</sup>

### VYZULTA delivered significantly greater mean IOP reduction vs Xalatan 0.005%



of VYZULTA patients achieved ≥2 mmHg IOP reduction vs Xalatan 0.005% mean diurnal IOP reduction<sup>2†</sup>

†Post-hoc analysis; Xalatan 0.005% mean diurnal IOP reduction of 7.8 mmHg.

Percentage of VYZULTA patients that achieved even greater IOP reductions than the Xalatan 0.005% mean diurnal IOP reduction<sup>2</sup>:

- 30% achieved <u>></u>3 mmHg
- 19% achieved <u>></u> 4 mmHg
- 12% achieved <u>></u> 5 mmHg

1. Weinreb RN, Ong T, Scassellati SB, Vittitow JL, Singh K, Kaufman PL. Br J Ophthalmol. June 2015;99(6):738-745. 2. Data on File. Bausch & Lomb Incorporated.

Only 6 out of 811 Patients Discontinued VYZULTA Due to Ocular Adverse Events in APOLLO and LUNAR<sup>1</sup>

## Less than 1% of patients treated with VYZULTA discontinued due to ocular adverse reactions in the APOLLO and LUNAR clinical studies<sup>1</sup>

• These included ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis, and foreign body sensation

Adverse Reactions	VYZULTA (n=811)	TIMOLOL 0.5% (n=271)
Conjunctival Hyperemia	5.9%	1.1%
Eye Irritation	4.6%	2.6%
Eye Pain	3.6%	2.2%
Ocular Hyperemia	2.0%	0.7%
Instillation Site Pain	2.0%	1.8%

#### Most Common Ocular Adverse Reactions in ≥2% of Study Eyes\*<sup>1,2</sup>

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

1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2. Weinreb RN, Liebmann JM, Martin KR, et al. Glaucoma. January 2018;27(1):7-15.

#### **JUPITER: Sustained IOP-lowering Efficacy through One Year**

○ IOP was reduced by ≥22% with LBN at each post-treatment visit vs. baseline (P<0.001 for all).



1. Kawase K, et al. Adv Ther 2016;33:1612-27

# The Next Generation of Medical Management in Glaucoma

Sustained Release Systems

## Mati Therapeutics

- The Evolute has an L-shaped design and is inserted into the nasolacrimal duct. The device is cosmetically invisible, but can be easily seen with eversion of the lower lid.
- The glaucoma product has a core of latanoprost-polymer matrix that is surrounded by silicone, and it delivers the medication into the tear film at a constant rate.
- In a phase II clinical trial, the latanoprost punctal plug was found to be comfortable. It was associated with a 20% lowering from baseline IOP over a 3-month period, and in two separate clinical trials.
- Retention rate of 92% and 96%, respectively.

## Mati Therapeutics



## Evolute<sup>®</sup> Punctal Plug Delivery System

## **Successful By Design**

- 1. Easy to place and remove
- 2. Cosmetically invisible easy to identify
- 3. Tolerable
- 4. Consistent, sustained efficacy
- 5. Use in multiple disease states







## Excellent Plug Retention Rates Over 12 Weeks

#### U.S. Phase II Multi-center Trials – Lower Puncta

Study	Week 4	Week 8	Week 12
Glau 12 (n = 92)	98%	97%	96%
Glau 13 (n = 87)	98%	96%	92%

## Evolute<sup>®</sup> Tearing & Comfort Scores



## L-PPDS – Target Dosing

- Commercial latanoprost Xalatan :
  - Concentration : 0.005% latanoprost
  - Dosing : Once a day
- Assumptions :
  - Drop volume =  $25\mu$ L to  $35\mu$ L
  - Delivery efficiency = 10%
- Estimated concentration the surface of the eye receives from a drop:
  - 15µg to 25µg per day of active therapeutic
- Amount of latanoprost delivered per day by Evolute<sup>®</sup> Punctal Plug
  - 0.5µg to 0.7µg per day of active therapeutic without any preservatives

## Animal IOP Model (Mean Time Points) - Travoprost

Animal model confirms greater efficacy of T-Evolute<sup>®</sup>



## Ocular Therapeutix



## **Ocular Therapeutix**

- Phase II study randomly assigned 73 patients into two groups to receive either the travoprost plug with twice daily artificial tears or timolol 0.5% twice daily with placement of a drug-free punctal plug.
- At 90 days, there was a 4.5 to 5.7 mm Hg reduction from baseline IOP in patients who had the travoprost punctal plug, which was clinically meaningful.
- However, the control group had an average IOP lowering of 6.4 to 7.6 mm Hg.
- The safety profile was good—no hyperemia was seen. The retention rate at 60, 75, and 90 days was 91%, 88%, and 48%, respectively.

# Latanoprost-Eluting Contact Lenses in Glaucomatous Monkeys.

## Ciolino, J, Kohane, DS etal Ophthalmology 2016

### • **RESULTS**:

- Latanoprost ophthalmic solution resulted in IOP reduction of 5.4±1.0 mmHg on day 3 and peak IOP reduction of 6.6±1.3 mmHg on day 5.
- The CLLO reduced IOP by 6.3±1.0, 6.7±0.3, and 6.7±0.3 mmHg on days 3, 5, and 8, respectively.
- The CLHI lowered IOP by 10.5±1.4, 11.1±4.0, and 10.0±2.5 mmHg on days 3, 5, and 8, respectively.
- For the CLLO and CLHI, the IOP was statistically significantly reduced compared with the untreated baseline at most time points measured.
- The CLHI demonstrated greater IOP reduction than latanoprost ophthalmic solution on day 3 (P = 0.001) and day 5 (P = 0.015), and at several time points on day 8 (P < 0.05).</li>
- Coating Polylactic co-glycolic acid (PLGA) is coated with films containing Polyhydroxymethacrylate by UV polymerization

## Glaukos iDose

- The iDose is a titanium implant that is comparable in size to Glaukos' proprietary devices for microinvasive glaucoma surgery
- The 150-patient, multicenter, randomized, double-blind phase 2 trial evaluated two models of the iDose delivery system with different travoprost elution rates in comparison to a topical timolol maleate ophthalmic solution, 0.5%.
- The unit is filled with a formulation of travoprost specific to the device and capped with a membrane designed for continuous controlled drug elution into the anterior chamber.
### Glaukos iDose



### MIGS Glaucoma Video Grand Rounds

# iStent<sup>®</sup> Surgical Procedure

- iStent<sup>®</sup> rails are seated against scleral wall of Schlemm's canal
- iStent<sup>®</sup> Snorkel sits parallel to the iris plane



## **Distribution of Aqueous Veins**

(Among 409 Aqueous Veins)



De Vries 1947

# Microbypass Stent











### Ivantis /Hydrus Microstent

- The FDA's approval was based on the 24-month results from the <u>HORIZON trial</u>, the largest MIGS study to date.
- The study included 556 mild to moderate glaucoma patients randomly assigned to undergo cataract surgery with or without the microstent.
- More than 77% of patients with the implant exhibited a significant decline in unmedicated IOP, compared with 58% of the control group.
- On average, the device reduced IOP by 7.5 mmHg, approximately 2.3 mmHg more than the cataract surgery-only group.

### Hydrus Microstent



### Hydrus Microstent



### Hydrus





Intention-to-Treat analysis

Intention to Treat Analysis

Per Protocol Analysis

1. Samuelson TW, Chang DF, Marquis R, et al. A Schlemm canal microstent for intraocular pressure reduction in primary open-angle glaucoma and cataract: The HORIZON Study. Ophthalmology 2019;126:29-37. 2. US Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED): CyPass® System (Model 241-S). US Food and Drug Administration website https://www.accessdata.fda.gov/cdrh docs/pdf15/P150037B.pdf. Published July 29, 2016..

3. US Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED): iStent inject Trabecular Micro-Bypass System. US Food and Drug Administration website. https://www.accessdata.fda.gov/cdrh docs/pdf17/P170043b.pdf. Published June 21, 2018.

### XEN



#### XEN Glaucoma Implant<sup>™</sup> Mechanism of Action

#### Ab Interno Sub-Conjunctival Drainage

- •Surgical "Gold Standard" IOP reduction in minimally invasively procedure
- •Clinically proven outflow pathway
- •Bypasses all potential outflow obstructions
- Conjunctiva sparing: alternative surgical options remain
  Single implant delivers desired effectiveness

Gelatin Material is Tissue Conforming



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Summed patients: primary, combined and refractory

Mean IOP Over Time and Mean % Change in IOP



1.0

1.0

0.9

1.3

1.5

0.3

-----Mean % Change in IOP Mean IOP

\*Mean preoperative IOP is best medicated. Patients were not washed out prior to surgery.

0.8

0.5

POAG Only

0.0

2.8

meds

0.3



### Ab Interno Viscocanalostomy (Visco 360)



### Ab interno Viscocanalostomy



### Ab Interno Trabeculotomy (Trab 360)



NOECKER- Glaucoma Surgery

### Trab 360



### How MicoPulse<sup>®</sup> Works

MicroPulse technology finely controls thermal elevation by "chopping" a continuous-wave (CW) beam into an envelope of repetitive short pulses.

Continous-Wave (CW) Mode

**CW Pulse** 

Duration

.

Power -



Time →



### Micropulse treatment



# 6½ Year Results Show Long-Term Efficacy & Durability



Chew P, Aquino M. Long Term Efficacy of MicroPulse Diode Transscleral Cyclophotocoagulation in the Treatment of Refractory Glaucoma. EGS abstract, Prague, Czech Republic, June 19-22, 2016.