Innovations in Clinical Practice
COPE#94461-GO

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1

Financial Disclosures: Walt Whitley, OD, MBA, FAAO

- Abbvie: Advisory Board, Consultant, Speaker
- Alcon: Advisory Board, Consultant, Speaker
- Azura Pharmaceuticals: Consultant
- Bausch and Lomb: Advisory Board, Speaker
- Bruder: Advisory Board
- Dompe: Consultant, Speaker
- Eyenovia: Consultant
- Iveric: Consultant
- Lumenis: Consultant
- Mediprint Pharma: Consultant
- Ocuphire: Consultant
- Ocular Therapeutix: Consultant
- Regener-Eyes: Consultant
- Science Based Health: Advisory Board
- Sight Sciences: Consultant
- Sun Pharmaceuticals: Advisory Board
- Tarsus Pharmaceuticals: Advisory Board
- Thea Pharmaceuticals: Consultant
- Viatris: Advisory Board, Consultant, Speaker
- Zeiss Meditec: Consultant

All financial relationships have been mitigated.

2

The Big Picture

- Eye Care Remains Strong
- The Population Grows Older
- Innovation Continues Relentlessly
- Consolidation Threatens Institutions
- OD/MD Collaboration Continues to Grow
- Artificial Intelligence Changes Everything

"To be on the cutting edge of optometry, you need to be on the cutting edge of science and technology."

3

- The optometric workforce is projected to experience growth of 1.4% each year
- A continued shift toward a female OD majority
- A more limited additional capacity for the profession to expand than previously suggested, a recent national survey suggests.[1]

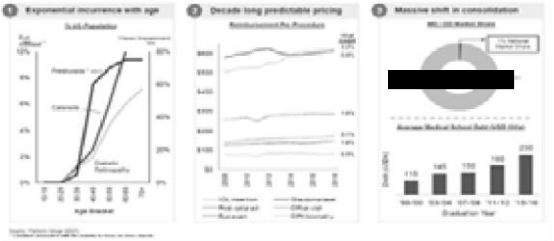
1. Heath, David A. et al. 2017 National Optometry Workforce Survey, Optometry and Vision Science: May 2021 - Volume 98 - Issue 5 - p 500-511

4

- No significant differences between men and women for:
  - Hours works (38.9 vs 37.5)
  - Professional growth satisfaction 65% for both
  - Productivity (patient visits per hour, 2.0 vs. 1.9)
- Data indicate a likely range of additional patient capacity of 2.29 to 2.57 patients per week
- Employed vs. self employed up from 29% in 2012 to 44% employed

5

Medical Vision: Generational Megatrends Drive Growth, Stability, Consolidation



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The Future of Eyecare

- **Artificial Intelligence**
  - Transactional AI – Amazon
  - Behavioral AI – Cogito
- **Machine Learning**
  - Image/speech recognition
  - Online purchases
- **Deep Learning**
  - Think Siri and Alexa
  - Driverless cars

https://www.mathworkscom/discovery/deep-learning.html

7

8

Digital Health in Modern Optometry

Incorporating digital health care models can help propel optometrists into the realm of **artificial intelligence** and leverage the latest innovations in **remote monitoring**.

Artificial Intelligence

AI diagnostic that autonomously diagnoses diabetic retinopathy

CURRENT TECHNOLOGY ONLY OFFERS ONE OR THE OTHER

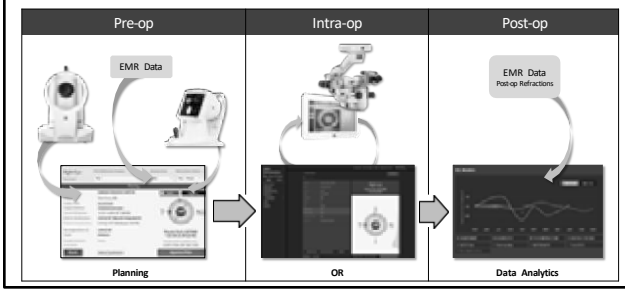
OR

Remote Monitoring

Tonometer designed for home-based IOP monitoring

9

Cataract Suite



10

Algorithm Optimization

Optical Biometer

K | ACD | AL | ??

Self-Calibrating Biometer

- Automated and objective data
- Millions of eyes
- Integrated Lens Calculations (AI)
- Can be tailored to individual surgeons
- Evolves in perpetuity

More Data

IOL Calculation (Deep Learning)

Wavefront Analyzer/ Autorefractor

Lens Selection

Post-op Outcome

Intellectual Property of Advanced Euclidean Solutions. Patent Pending.

11

AI and Dry Eye

12

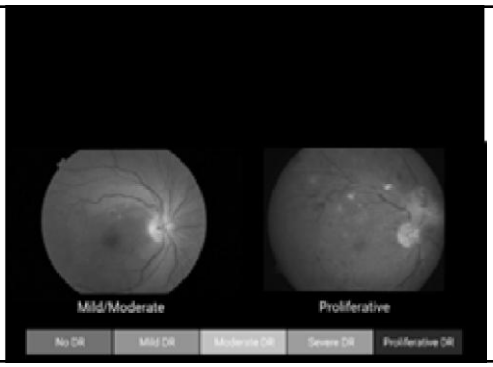
Current Diabetes DIAGNOSTIC SCREENING

FULLY AUTONOMOUS AND NOT DECISION SUPPORT

EYE

AI CPT Code 92229 $50 / Exam
NCQA HEDIS (QM 117)
Value Based Care: Incentive Payments Up to $1,700 / Patient

13



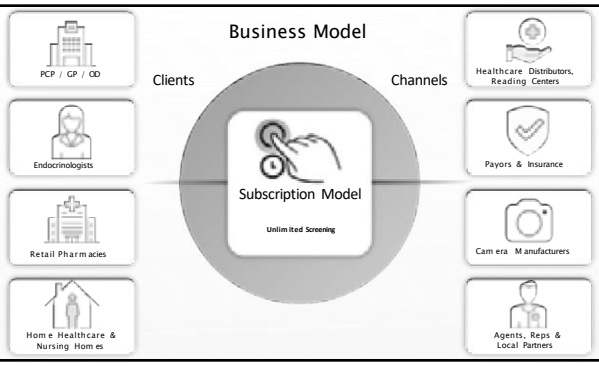
14

Phase III Clinical Study Results

Diagnostic Screening accuracy for Diabetic Retinopathy

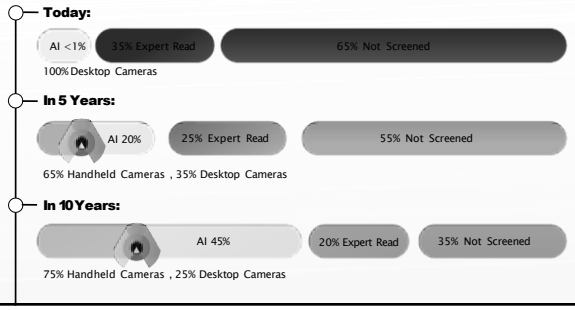
	Desktop Camera	Handheld Camera
EFFICACY		
Sensitivity	93.0%	91.9%
Specificity	91.4%	93.6%
USABILITY	1 image per eye Imageability >99%	1 image per eye Imageability >99%

15



16

Forefront of automizing the screening development process



17

Evaluation of an AI system for the automated detection of glaucoma from stereoscopic optic disc photographs: the European Optic Disc Assessment Study

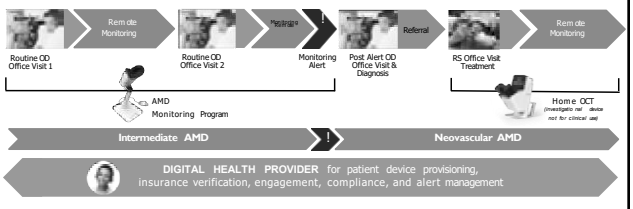
- Objectives - To evaluate the performance of a deep learning based Artificial Intelligence (AI) software for detection of glaucoma from stereoscopic optic disc photographs, and to compare this performance to the performance of a large cohort of ophthalmologists and optometrists.
- Results
  - Pegasus was able to detect glaucomatous optic neuropathy with an accuracy of 83.4% (95% CI: 77.5–89.2)
  - This is comparable to an average ophthalmologist / optometrist accuracy of 80.5% / 80% respectively (95% CI: 67.2–93.8) / (95% CI: 67–88) on the same images.
  - There was no statistically significant difference between the performance of the deep learning system and ophthalmologists or optometrists.

Rogers, TW, Jaccard, N., Carbonara, F. et al. Eye 2019. DOI:10.1038/s41433-019-0951-903

18

Digital health care services for AMD patients

Dedicated remote monitoring programs with advanced, AI-based technologies support Optometrist diagnosis of acute nAMD conversion and monitoring of chronic therapy by Retina Specialists between office visits



19

Home OCT for monitoring chronic therapy of neovascular AMD between office visits

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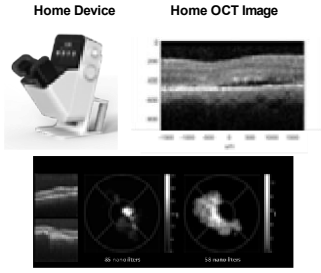
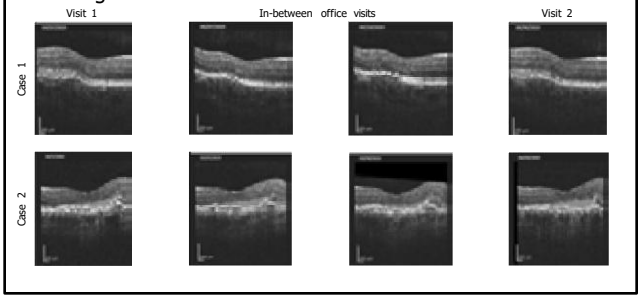


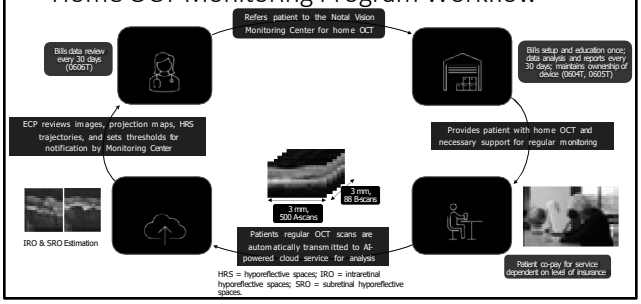
20

Background: Status of Retina In-Between Office Visits



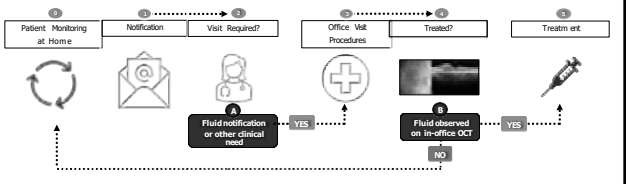
21

Home OCT Monitoring Program Workflow



22

Physician Notification and Patient Management Workflow



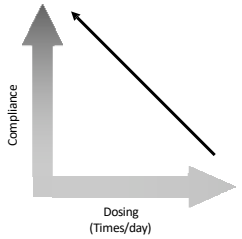
23

Innovations in Glaucoma

24

Patient Compliance and Dosing

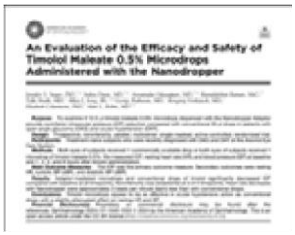
- Literature review of 76 studies show
  - Compliance increases with decreased dosage regimen and complexity[1]
  - 79% compliance with QD regimen vs 51% for QID regimens (p=0.001)[1]
  - Simpler, less-frequent dosing results in better compliance in a variety of therapeutic classes[1]

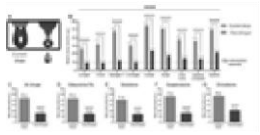


1. Claxton et al. *Clinical Therapeutics.* 2001; 23:1296-1310.

25

Delivering Treatment


An Evaluation of the Efficacy and Safety of Timolol Maleate 0.5% Microdrops Administered with the Nanodropper



Steger, Jennifer S. et al. An Evaluation of the Efficacy and Safety of Timolol Maleate 0.5% Microdrops Administered with the Nanodropper. Ophthalmology, Volume 131, Issue 9, 1045 - 1055

26

Latanoprost PF 0.005% (Iyuzeh)

	Phase 3 (US) Trial (n=325)		Phase 3 (Europe) Trial (n=353)	
	PF-Latanoprost	Xalatan	PF-Latanoprost	Xalatan
Mean baseline IOP ± SD(mmHg)	18.8 ± 2.9	19.2 ± 3.1	24.1 ± 1.8	24.0 ± 1.7
Mean IOP reduction from baseline (mmHg) (range)	2.7 (2.2 - 3.0)	3.4 (2.9 - 3.8)	8.6 (8.3 - 8.8)	8.9 (8.8 - 9.0)

27

27

Omidenepag Isopropyl (OMDI) (Omlonti)

- Selective, non-prostaglandin, prostanoid EP2 receptor agonist
- MOA: Increase outflow via both conventional and uveoscleral
- Phase 3 AYAME Study - OMDI 0.002% vs latanoprost 0.005%
  - N = 190
  - QD dosing x 4 week
  - Baseline – 24mmHg
  - OMDI = 25.1% reduction (17.81 mm Hg)
  - AE: Conjunctival hyperemia = 24.5%

28

SINGLE	**LAT** (Latanoprost 0.005%)**	7.5mL
	DOR (Dorzolamide 2%)	10mL
COMBINATION	**BRIM-DOR*** (Brimonidine 0.15% and Dorzolamide 2%)	10mL
	TIM-LAT* (Timolol 0.5% and Latanoprost 0.005%)**	5mL
	TIM-DOR-LAT* (Timolol 0.5%, Dorzolamide 2%, and Latanoprost 0.005%)**	5mL
	TIM-BRIM-DOR* (Timolol 0.5%, Brimonidine 0.15%, and Dorzolamide 2%)	10mL (2 x 5mL bottles per shipment)
	TIM-BRIM-DOR-LAT* (Timolol 0.5%, Brimonidine 0.15%, Dorzolamide 2%, and Latanoprost 0.005%)**	5mL
TRIPLE/QUAD KIT	**TIM-BRIM-DOR*** (Timolol 0.5%, Brimonidine 0.15%, and Dorzolamide 2%)	5mL
	TIM-BRIM-DOR-LAT* (Timolol 0.5%, Brimonidine 0.15%, Dorzolamide 2%, and Latanoprost 0.005%)**	5mL

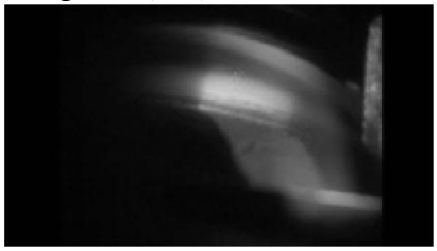
29

…Other Drop Options

- PDP-716 (0.35% brimonidine tartrate)
  - QD dosing, preservative free, seeking FDA approval
- NCX 470 (NO-donating bimatoprost)
  - Phase 3 trial = superior to latanoprost 0.005%
- CKLP1 (ATP-sensitive potassium channel opener)
  - Lowers EVP 1:1 with IOP reduction
- QLS-111 (ATP-sensitive potassium channel opener)
  - Lowers EVP

30

SLT Video Courtesy of
Nathan Lighthizer, OD, FAAO



31

Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial.

Primary Outcome - Quality of Life at 3 years
Secondary Outcome – Cost, cost-effectiveness, clinical effectiveness, and safety

Conclusions:
- No significant difference in QOL
- 97% probability of SLT as 1st treatment being more cost-effective
- SLT at target IOP 93% of visits vs 91.3% at target for meds
- 78.2% of SLT Drop Free @ 3 Years

32

LiGHT trial: 6-year results of primary selective laser trabeculoplasty versus eye drops for the treatment of glaucoma and ocular hypertension

Gus Gazzard, Evgenia Konstantakopoulou, David Garway-Heath, Mariam Adeleke, Victoria Vickerstaff, Gareth Ambler, Rachael Hunter, Catey Bunce, Neil Nathwani, Keith Barton, on behalf of the LiGHT Trial Study Group

Primary Outcome - Quality of Life at 6 years
Secondary Outcome – clinical effectiveness and safety

Conclusions:
- No significant difference in QOL
- 26.8% VS 19.6% progressed drops vs SLT
- Trab required in 32 eyes in drops arm compared to 13 eyes in the SLT arm
- 69.8% of SLT Drop Free @ 6 Years

33

Low-Energy SLT Repeated Annually: Rationale for the COAST Trial

Tony Realini, MD, MPH, Gus Gazzard, MD, Mark Latina, MD, Michael Kass, MD

Newly diagnosed POAG treated with:
1. ALT 360 x 1
2. Standard SLT 360 as needed
3. Low-energy SLT 360 repeated annually

10-year Results
Medication Free Rates
1. ALT – 22.6%
2. Standard SLT -25.0%
3. Low-energy SLT – 58.3%

10-year Results
Median Times to Treatment
1. ALT – 2.8 years
2. Standard SLT -3.2 years
3. Low-energy SLT – 6.2 years

34

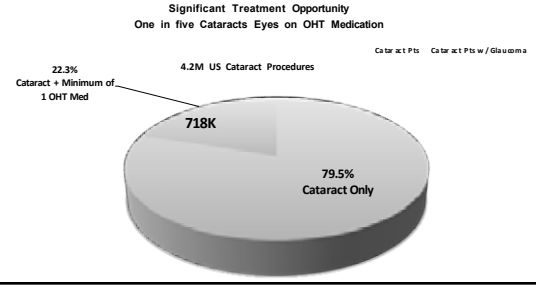
Automated Direct SLT (BELKIN Laser Ltd.)

Automated Direct Selective Laser Trabeculoplasty: First Prospective Clinical Trial

Belkin, M. **GLAUrious, a multicentre, randomised, controlled study of direct selective laser trabeculoplasty in open angle glaucoma.** Investigative Ophthalmology & Visual Science June 2023, Vol.64, 5393. doi:

35

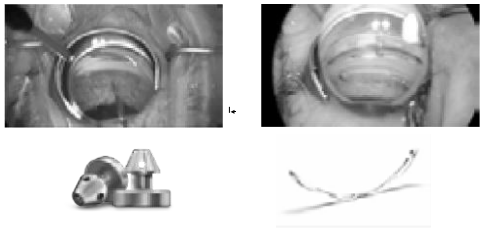
Concomitant Cataract & Glaucoma Patients - US



36

Trabecular Microbypass Stent (iStent Inject W)

Schlemm Canal Microstent (Hydrus)



37

HORIZON Trial – 4 Year Update

	Stent + Cataract (n=369)	Cataract Only (n=187)
Baseline IOP (mm Hg) after washout	25.5 (+/- 3.0)	25.4 (+/-2.9)
48 months medication free	65%	41%
48 months mean IOP (mm Hg) unmedicated	16.7 (+/-3.1)	17.2 (+/-3.2)
48 months mean IOP (mm Hg)	16.9 (+/-3.3)	17.3 (+/-3.4)
1 preoperative med	52.6%	54%
2 to 4 preoperative med	47.4%	46%

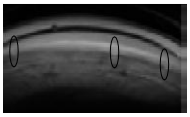
5 Year Update – 66% patient's remain medication-free and 61% reduction in risk to need further surgery

38

Trabecular Microbypass Stent x 3 (iStent infinite)

Three-stent, standalone procedure

Three wide-flange stents preloaded in injector system, to facilitate placement across ~6 clock hrs. of Schlemm's canal



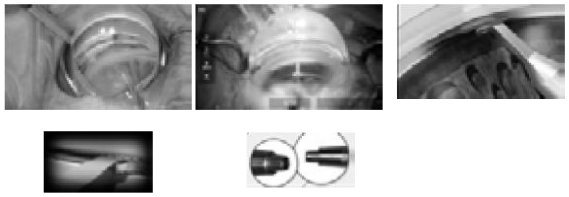
- 73.4% met the responder endpoint of 20% MDIOP reduction
- 53.0% achieved >30% MDIOP reduction

39

Excisional Goniotomy (Kahook Dual Blade)

Goniotomy (iAccess)

Goniotomy (SION)



40

41

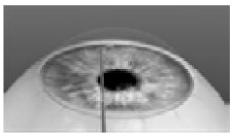
Interim Analysis of STREAMLINE® Surgical System Clinical Outcomes in Eyes with Glaucoma

- Single-arm, prospective, single-arm, first-in-human case series (n=20)
- Baseline medicated IOP 16.3 mmHg
- Unmedicated baseline IOP after washout: 23.5 mmHg
- At month 6, mean IOP reduction of ≥20% from baseline was achieved in 89.5% of eyes (17/19).
- 57.9% (11/19) of eyes decreased dependence on IOP-lowering medications by at least one medication
- 42.1% (8/19) were medication free
- Mean medication use was reduced from 2.0 (0.8) at screening to 1.1 (1.1) at 6 months (p<0.001).

Lazcano-Gomez G, Garg SJ, Yeu E, Kahook MY. Interim Analysis of STREAMLINE® Surgical System Clinical Outcomes in Eyes with Glaucoma. Clin Ophthalmol. 2022 Apr 27;16:1313-1320.

42

Ab-interno Trabeculotomy + Canaloplasty
(OMNI)



IOP reductions of ~30-40%
Medication reductions of ~45-75%.

43

Xen 45 Gel Stent
US Pivotal Clinical Trial

Subconjunctival Stent
(Xen)

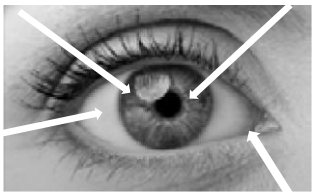
	Baseline	12 month
Medicated IOP	25.1 (3.7)	15.9 (5.2)
Glaucoma Meds	3.5 (1.0)	1.7 (1.5)

Hypotony 16 (24.6%)
Bleb Needling 21 (32.3%)

44

Iridocorneal Angle
1. **Travoprost Intraocular Implant (Glaukos)**

Ocular Surface Devices
1. **Contact Lenses**
2. **Microdose latanoprost (EyeNovia)**
3. **Iontophoresis**



Injectable Systems
1. **Bimatoprost SR (Abbvie)**
2. **Travoprost Intracameral Implant (OTX)**
3. **Travoprost Extended Release Implant (Aerie)**

Punctal Plug Devices
1. **Latanoprost and Travoprost punctal plug delivery system (Mati)**

45

Patients Attitudes Towards Drug Delivery

- Triple Combination Eye Drop – 85%
- Microdose Eye Spray – 54%
- Drug-eluting Contact Lens – 31%
- Drug-eluting Periocular Ring Insert – 43%
- Injectable Subconjunctival Drug Insert- 32%
- Injectable Anterior Chamber Implant – 30%

N=199

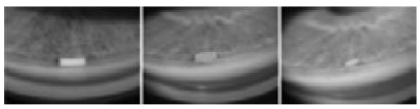
Wang BB., Lin MM., Nguyen, T., et al. Patient attitudes towards novel glaucoma drug delivery approaches. Digit J Ophthalmol. 2018; 24(3): 16-23

46

Bimatoprost SR (Allergan)

(10-microgram bimatoprost sustained-release implant)

- Biodegradable bimatoprost sustained-release implant
- FDA-approved and indicated to reduce IOP in patients with open angle glaucoma or OHT
- Single intracameral administration
- Phase I/II/III Studies



47

48

24 Month Phase I/II Clinical Trial

bimatoprost pellet
(6, 10, 15, or 20 micrograms)

topical bimatoprost 0.03%

24 months – IOP reduction
7.5, 7.3, 7.3, 8.9 mm Hg

24 months – IOP reduction
of 8.2 mm Hg

No Rescue or Retreatment
68% - 6 mos.
40% - 12 mos.
28% - 24 mos.

Craven ER, Walters T, Christie WC, Day DG, et al. 24-Month Phase I/II Clinical Trial of Bimatoprost Sustained-Release Implant (Bimatoprost SR) in Glaucoma Patients. Drugs. 2020 Feb;80(2): 167-179.

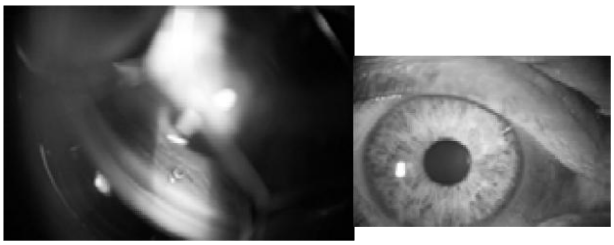
49

Travoprost intraocular implant

36 Month Update

1. 70% and 68% of subjects in fast and slow-release were well-controlled on fewer or same medications as baseline.
2. Average IOP reductions were 8.3 mmHg and 8.5mmHg in the fast and slow-release arms.

50



51

Drug-Eluting Contact Lens

Attractive option secondary to large residence time in the eye and upward of 50% bioavailability in comparison with eye drop formulations.

Li, CC, Chauhan, A. Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 2006; 45: 3718–3734.
Peng, C-C, Kim, J, Chauhan, A. Extended delivery of hydrophilic drugs from silicone-hydrogel contact lenses containing Vitamin E diffusion barriers. Biomaterials 2010; 31: 4032–4047.

52

CL Drug Delivery

- Silicon hydrogel CL addressed hypoxia-related complications
- Rapid release kinetics
  - May differ based on CL material / drug combos
  - Rate of drug release is not constant over time
- March 2022 – FDA Approval of etafilcon A drug-eluting contact lens with ketotifen

Li CC, Chauhan A (2006) Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 45: 3718-3734.

53

CL Drug Delivery – What does the future hold?

- Molecular imprinting - Creates specific drug recognition sites within the polymer through the use of molecular templates
- Vitamin E coatings - Form diffusion barriers within the lens, which forces the target drug to take long complex paths to diffuse from the lens
- Nanoparticles - Encapsulated with the target drug can be loaded and released from the CL, and the extended release is controlled by the degradation of the nanoparticles
- Concerns - Frequent lens application?? Non-CL wearers?? Cost??

Li CC, Chauhan A (2006) Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 45: 3718-3734.

54

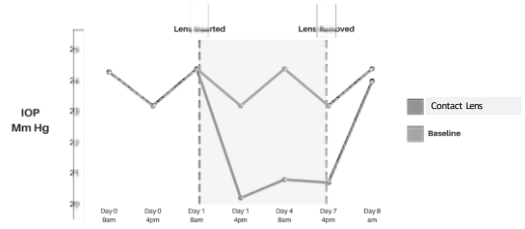
Drug-Eluting Contact Lens

- MediPrint Ophthalmics
  - LLT-BMT1 – drug eluting contact lens - bimatoprost
- Phase I – SIGHT-1
  - 5 Subjects wore the lens for 7 days continuously
  - Demonstrated 100% tolerability and no adverse events
  - IOP efficacy was noted
- SIGHT-2 – Phase 2b dose-ranging clinical study is underway

55

Glaucoma: SIGHT-1 Human Clinical Results

Intraocular Pressure (IOP) reduction at each timepoint over 7 days of continuous wear



56

Punctal Plug Delivery System

Latanoprost and Travoprost designs

U.S. Phase II Multi-center Trials (Lower Puncta)
Glau 12 (n=92) – 96% retention rate
Glau 13 (n=87) – 92% retention rate

Phase II Clinical Study
L-Evolute - 5.5 mmHg IOP lowering over 12 weeks study

57

Travoprost Intracameral Implant

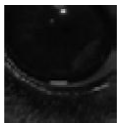
(Ocular Therapeutix)

Bioresorbable sustained-release implant injected into the AC

Goal: Steady release of travoprost with target duration from 4 to 6 months

Preclinical Models (beagle dogs)
Steady state release through 4 months

IOP lowering of 25-30% through 4 months



58

Travoprost Intracameral Implant

(Ocular Therapeutix)

Phase 1, prospective, multi-center, open label

Cohort 1 n=5 (15 micrograms)
Day 28 -9.1 mm Hg (n=5)
Mo. 4 -7.6 mm Hg (n=4)
Mo. 6 –7.5 mm Hg (n=3)

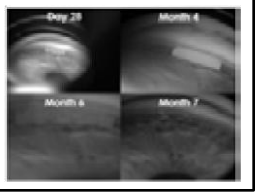
*Mo. 21 - -9.3 (n=1)

Cohort 2 n=4 (26 micrograms)
Day 28 -6.0 mm Hg (n=4)
Mo. 4 -6.8 mm Hg (n=4)
Mo. 6 –6.1 mm Hg (n=3)

*Mo. 9 - -5.9 (n=2)

Cohort 3 n=4 (15 micrograms Fast Degrading)
Day 28 -11.5 mm Hg (n=3)
Mo. 4 -13.8 mm Hg (n=2)

*Mo. 6 -12.5 (n=1)



59

IOL-Haptic-Based Drug Delivery

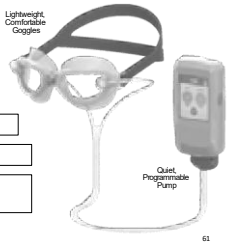
- Drug-eluting pads attached to haptics
- Goal is 3 years of drug delivery
- Feasibility Study – 23 patients
  - 45% mean IOP reduction
  - 100% of patients were 18 mmHG or below
  - All were off topical medications
  - No significant adverse events
  - Visual outcomes similar to other IOLs

60

AN ELEGANT SOLUTION

FYSX O-PAP
(Ocular Pressure Adjusting Pump)

- Only nonsurgical, non-pharma way to lower IOP
- Lowers IOP in every eye, every time
- Lowers IOP safely
- Can be used in combination with existing therapies
- Titrates IOP to target pressure level
- Lowers IOP during the vulnerable period at Night
- Ability to monitor usage, encourage compliance, and obtain data



61

61

THE SOLUTION IS BASED ON PHYSICS

The atmosphere pressurizes the entire body

By lowering the pressure only over the eye, we lower the IOP relative to the rest of the body

It's just physics, and physics works every time

We can dial in the IOP to the specific target

62

62

2 Multi-Center Randomized Controlled Trials

Apollo – Open-Angle Glaucoma

- N = 128 eyes of 64 Subjects
- Contralateral Eye Served as Control
- IOP Inclusion - 13-32 mmHg
- **POAG, NTG, OHT, and Glaucoma Suspects**
- 89.7% had IOP Reduction of >20%
- 100% of eyes had IOP Reduction
- **IOP decreased from 19.4 to 12.9 mmHG (34%)**
- IOP Decreased in addition to existing therapy
- IOP Decrease regardless of Baseline IOP
- No SAEs
- ~20% of eyes had temporary lid edema

Artemis – Normal Tension Glaucoma

- N = 182 eyes of 91 Subjects
- Contralateral Eye Served as Control
- IOP Inclusion - ≤ 21 mmHg
- **NTG Only – IOP Measure Overnight in Sleep Lab**
- 98.2% had IOP Reduction of >20% at night
- 100% of eyes had IOP Reduction
- **IOP decreased from 20.2 to 12.2 mmHG (39%)**
- IOP Decreased in addition to existing therapy
- IOP Decrease regardless of Baseline IOP
- No SAEs
- ~17% of eyes had temporary lid edema

63

63

Home IOP Monitoring

- A device is intended as an adjunct for monitoring IOP of adult patients (self-use). The tonometer is designed for use at home or on the go.

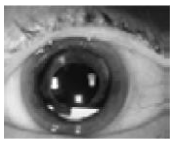
64

64

Continuous IOP Sensors

Implandata Eyemate

- Sulcus based IOP sensor
- 8 pressure-sensitive capacitors
- Diameter: 11.2 mm
- Thickness: 0.5 mm

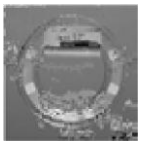


66

66

ARGOS-02 Trial: 1-year Results

- 22 Patients
- Major Design Changes:
  - 0.9 to 0.5mm thickness with 0.1mm rounded tapering
  - 4 haptics to prevent ciliary sulcus rotation
- IOP Concordance:
  - D30:
    - Eyemate: 22.2 ± 9.2 mmHg
    - GAT: 19.5 ± 6.8 mmHg
  - D360:
    - Eyemate: 15.7 ± 3.8 mmHg
    - GAT: 14.1 ± 2.2 mmHg



American Journal of Ophthalmology DOI: (10.1016/j.ajo.2010.03.011)

67

Smart soft contact lens (BVS Sight)

- 24-hour IOP monitoring
  - Lens power
  - Wettable
  - O2 Transmissibility
  - Overnight wearability

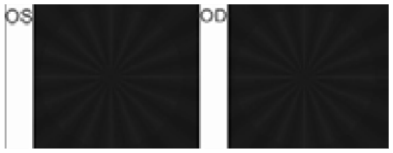
68

Sensors on the horizon…

- AcuMEMS (Menlo Park, CA)
  - iSense System: implantable sensor
- Glaukos (San Clemente, CA)
  - DOSE Medical IOP Sensor
- Implandata Ophthalmic Products GmbH
  - Suprachoroidal IOP sensor
- Injectsense Inc (Emeryville, CA)
  - Configurable on-demand sensor
- LaunchPoint Technologies (Goleta, CA)
  - Sensor attached to IOL or injected into vitreous
- Solx (Waltham, MA)
  - wireless intraocular sensor

69

Multifocal Pupillographic Objective Perimetry (mfPOP),



- 100% objective
- Improve scheduling
- Simultaneous bilateral exam
- Easy to use & sanitize

Video Courtesy of Konan Medical

70

The Future of Visual Field Testing?

Validation of a Wearable Virtual Reality Perimeter for Glaucoma Staging, The NOVA Trial: Novel Virtual Reality Field Assessment | TVST | ARVO Journals

71

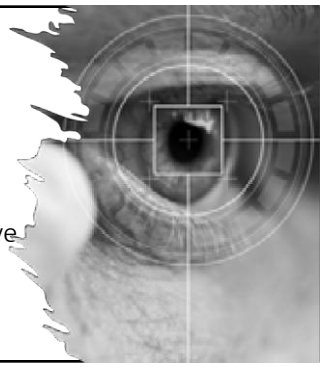
Augmented / Virtual Reality

- Patient education
- Visual Field
- Visual Acuity
- Color Vision (D-15) 92283
- Pediatrics Visual Field
- Contrast Sensitivity
- Low Contrast Visual Acuity
- Dark Adaptation 92284
- Many more tests in the works….

Imaged from https://www.apple.com/apple-vision-pro/

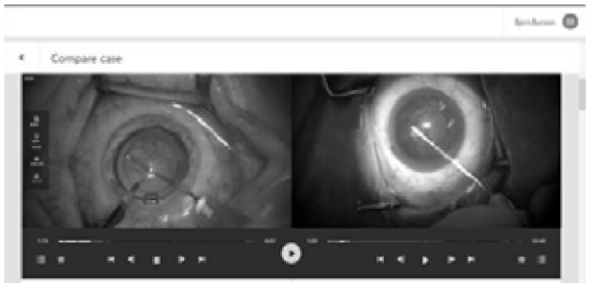
72

Innovations in Refractive + Cataract Surgery



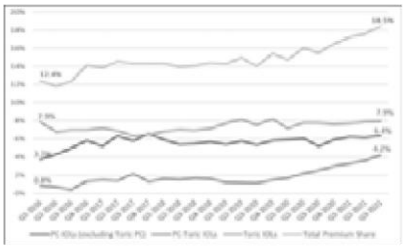
73

AI Based Segmentation – Case Comparison



74

Advanced Technology IOLs Driving Innovation and Market Penetration

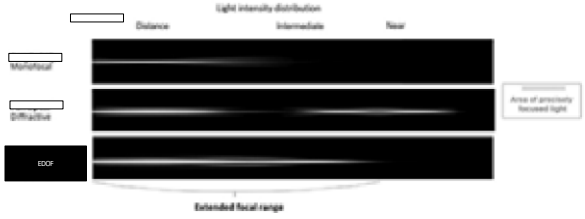


49.1%

Increase in ATIOL penetration from Q1 2016 to Q3 2021[1]

75

Optics



76

AN OPPORTUNITY TO EXPAND WITH PATIENT SELECTION

Extended Depth of Focus (EDOF)

Possibly Candidate To Select:

- For a patient who might have been thinking about distance only, but who would benefit from extended vision
- Unsuited to a diffractive lens or a lens that splits light

Have a healthy cornea (if moderate to severe ocular surface disease [e.g., dry eye], is diagnosed, treat and resolve prior to cataract surgery

Have astigmatism levels within the available toric range

Multifocal/Trifocal

Possibly Candidate To Select:

- Have not undergone refractive surgery
- No glaucoma or retinal pathology
- Desire to be glasses-free as much as possible

77

Presbyopic Correcting IOLs (PCIOL)

EDOF

Tecnis Symphony

Alcon Vivity

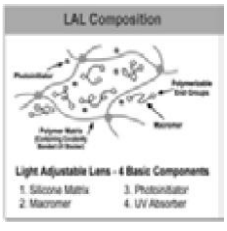
Trifocal

Alcon Panoptix

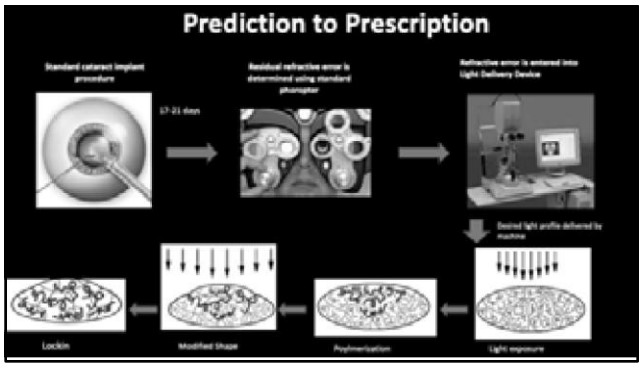
Tecnis Odyssey

78

Light Adjustable Lens-What's Special?



79



80

FDA Clinical Results

- 91.8% within 0.50 D of target manifest refraction spherical equivalent
- Results showed that 100% of study eyes had a best corrected visual acuity of 20/40 or better at the 6 month po visit.

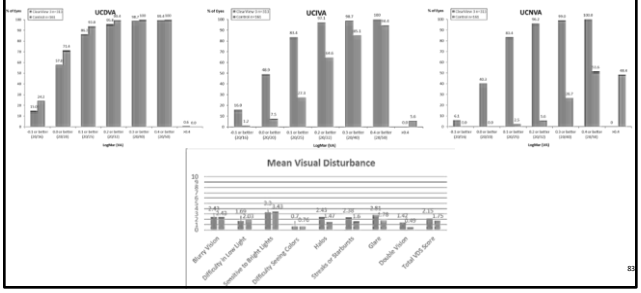
81

Multifocal – Clearview 3

- Asymmetric segmented multifocal IOL
- Available in 0.25 Diopter power increments.
- 3.0 diopter sector-shaped add
- Zero Aberration lens
- Bi-aspheric

82

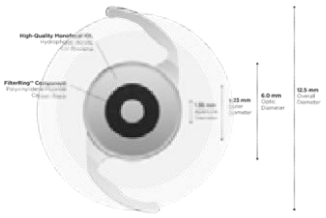
Multifocal – Clearview 3



83

Apthera™ Small Aperture IOL:

Non-Diffractive, Wavefront-Filtering, Extended Depth of Focus Design



84

The Toric IOL Challenge

- 52.6% of patients present with ≥ 0.75 D of cylinder prior to cataract surgery[1]
- Global toric IOL adoption remains below 5%[2]
- Toric IOLs challenges
  - Inability to correct astigmatism exactly due to limited power options
  - Surgical planning complexity and added expense
  - Surgical misalignment and post-implantation rotation reduces effectiveness
  - Surgically induced astigmatism can reduce effectiveness of the correction and axis shifts can induce misalignment
  - Low levels of corneal astigmatism (<0.75 D) are left uncorrected by today's available toric IOL powers

[1]Warren Hill, IMD Keratometry Databases, n=6,000
[2]Market Scope 2016 IOL Report

85

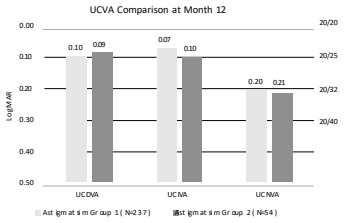
Study Overview

- To assess the efficacy a non-toric small aperture IOL in eyes that have preop corneal astigmatism of up to 1.5 D.
- **Study Design:** Prospective, multi-center, clinical FDA study.
  - Cataract Patients (N=343) received the IC-8 IOL in one eye and a monofocal or monofocal toric IOL in the fellow eye. Patients were then assigned into two groups based on preop corneal astigmatism in their Apthera IOL Eye:
    - **Group 1:** less than 1.0 D of astigmatism, N= 273
    - **Group 2:** 1.0 to 1.5 D of astigmatism, N= 70
- Mean monocular uncorrected visual acuities for Distance (UCDVA), intermediate(UCIVA) and near (UCNVA) were reported for the Apthera IOL eye in logMAR ± standard deviation at 12 months post-op

86

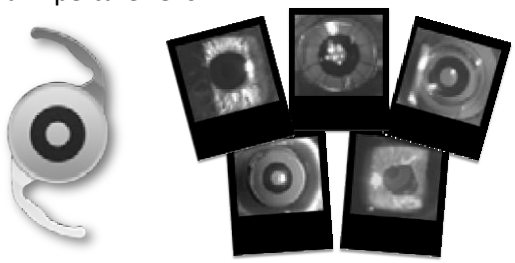
Small Aperture Optics with Corneal Astigmatism

- At 12 Months, no statistically significant differences were noted between groups at any given distance (p > 0.05)
- Mean MRSE by Astigmatism Group:
  - Group 1: -0.338 D ± 0.48
  - Group 2: -0.224 D ± 0.45



87

Small Aperture Lens



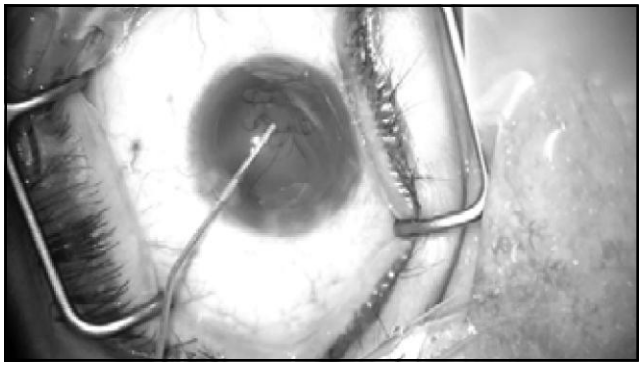
Approval letter December 2021 from FDA

88

What's Next in IOL Technology?

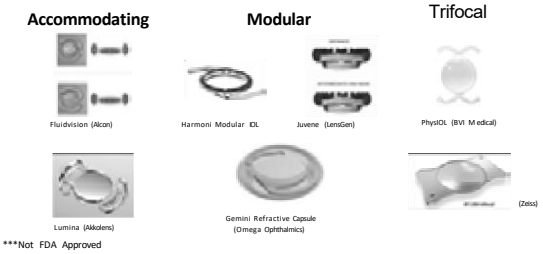
- Modular IOL Systems
- Accommodating
- Multifocal / trifocal
- Extended Depth of Focus

89



90

Pipeline IOL Technology

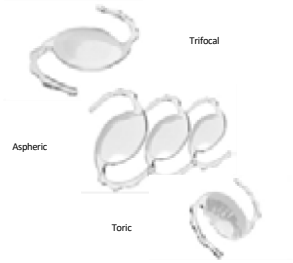


***Not FDA Approved

91

Supplementary IOLs

- Designed for sulcus implantation
- Reduces risk for complications
  - Interlenticular opacification
  - Pigment dispersion
  - Iris chafing



***Not FDA Approved

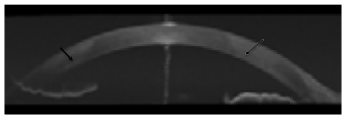
92

92

Presbyopia

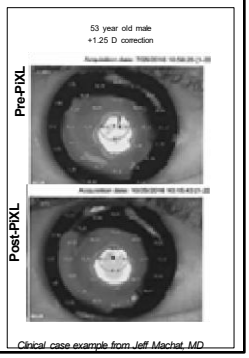
Spatially targeted, epithelium-on, accelerated cross-linking

More than 200 eyes treated internationally to date



- Midperipheral cross-linking, no UVA applied to central cornea
- Image above: High resolution OCT image showing mid peripheral corneal stromal demarcation line after epi-ON PiXL with oxygen

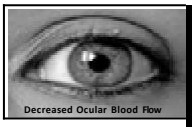
Investigational. Not FDA approved.



Clinical case example from Jeff Machat, MD

93

Ocular Rigidity Correlation Age-Related Eye Diseases



Ocular Rigidity & Age-related Eye Diseases:

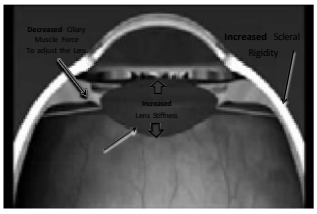
- **Age Related Loss of Visual Accommodation → Presbyopia**
- **Age Related Increase in IOP→ Glaucoma**
- **Age Related lens stiffening→ Cataract**
- **Age Related decrease → AMD & other Pathos**

Age Related Cataract

94

94

Ocular Rigidity: Leads to Loss of Visual Accommodation



Detorakis ET, Pallikaris, IG. Ocular rigidity: bio-mechanical role, in vivo measurements and clinical significance. *Clin Experiment Ophthalmol* 2012 May 18.

95

95

Solution: Laser Scleral Microporation "Uncrosslinking" Scleral Microfibrils to Rejuvenate BioDynamics

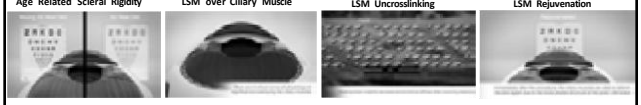
Problem

- ⇧ Ocular/ Scleral rigidity
- ⇩ Efficiency Ciliary Muscle Forces
- ⇩ Lens shape changes during accommodation
- ⇧ Positive Spherical Aberration (SA)/undesirable monochromatic aberrations

LSM Solution

- ⇩ Scleral biomechanical Stiffness
- ⇧ Ciliary Muscle forces on the Lens
- ⇧ Lens shape changes during accommodation
- ⇩Positive Spherical Aberration SA /undesirable monochromatic aberrations

Age Related Scleral Rigidity | **LSM over Ciliary Muscle** | **LSM Uncrosslinking** | **LSM Rejuvenation**



96

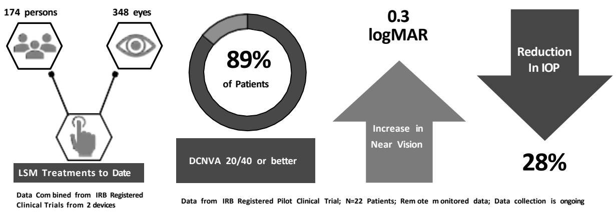
96

Laser Scleral Microporation: LSM Procedure

Courtesy Dr. Mitch Jackson

97

Clinical Data Summary



Growing Evidence on LSM Ocular Rejuvenation

Internal information from Ace Vision Group: AnnMarie Hipsley, DPT, PhD, Robert T. Ang, MD, Mitch Jackson, MD

98

Pharmacologic Treatments for Presbyopia Are Coming, With Miotic Drops Occupying the Majority of Development

Topical Drops in Development	Active Ingredient(s)	Mechanism of Action
Brimochol™ (Visus Therapeutics)	Carbachol + brimonidine tartrate	Carbachol: Miotic Brimonidine tartrate: Prevents pupil dilation, inhibits contraction of ciliary muscle, increases bioavailability of carbachol[1,2], prevents redness[3]
CSF-1 (Orasis)	Pilocarpine	Miotic
PRX-100/Liquid Vision (Presbyopia Therapies)	Aceclidine	Miotic
AGN 190584 (Allergan)	Pilocarpine	Miotic
MicroLine (Eyenovia)	Pilocarpine	Miotic
AcuStream™ (Kedalion)	Pilocarpine	Miotic
Nyxol® and Pilocarpine Combination Kit (Ocuphire)	Phentolamine mesylate and pilocarpine	Miotic (both pilocarpine and phentolamine mesylate products) Vasodilates small muscles (phentolamine mesylate product)[6]
True Vision Treatment® Contact lenses and Eye Drops Kit (Yolia Health)	Hyaluronidase and collagenase	Alters cornea [7]
UNR844 (Novartis)	Lipoic acid choline ester	Lens-softening agent
VP1-001 (Viewpoint Therapeutics)	Stabilizing alpha-crystallin molecule	Target's protein misfolding to restore native, functional shape[8]

- Miotic drops increase depth of field by inducing a pinhole effect
  - Low risk, highly effective and easily reversible compared to surgical alternatives
  - Miotic drops aren't without side effects - headache, brow ache, IOP fluctuations, myopic shift and hyperemia[4,5]
  - Single-agent cholinergic miotics likely to have more of an issue with these side effects than combination drops
- Lens softening topical agents intend to increase ability to accommodate with usage over time

1. Suzuki et al. Ocular and Systemic Pharmacokinetics of Brimonidine and Timolol After Topical Administration in Rabbits: Comparison Between Fixed-Combination and Single Drugs. *Ophthalmol Ther* (2020) 9:115–125; 2. Allergan patent application (Pub. No.: US 2018 / 0078500 A1). 3. LUMIFY Product Insert www.fda.gov accessed 9/24/2020. 4. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas (Eighth Edition), 2009. 5. Korczyn et al. Effect of Pilocarpine on Intraocular Pressure in Normal Humans. *Ophthalmic Res.* 14:182-187 (1982). 6. Pepose. Phentolamine Mesylate Ophthalmic Solution Provides Long Lasting Pupil Modulation And Improves Visual Acuity, ARVO 2020 Abstract: #3364450.7 .Yolia Health. 8. Viewpoint Therapeutics .February 2021

99

CSF-1 (Orasis)

- Demonstrated efficacy 20 minutes after administration and can last up to 8 hours, as measured on day 15,
- Preservative-free formulation of pilocarpine, an established eye care therapeutic, designed to achieve an optimal balance between efficacy, safety, and comfort.

PRX-100/Liquid Vision (Presbyopia Therapies)

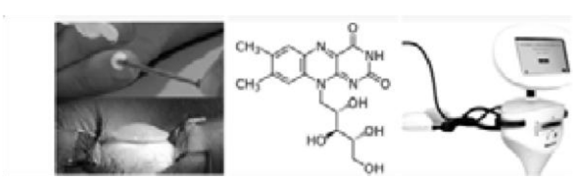
- Primary endpoint was met with 71% of participants dosed with LNZ100 achieving three-lines or greater improvement at 3 hours
- Rapid onset and long duration shown with
- 71% of participants achieving three-lines or greater improvement at 30 minutes and 40% at 10 hours

100

Innovations in Cornea and Anterior Segment

101

Epi-On Crosslinking



102

Breaking News

- Epioxa Phase 3 clinical trial successfully achieved its primary efficacy outcome by demonstrating a Kmax treatment effect of –1.0 diopter (D) (p <0.0001) at the Month 12 study endpoint.
- The treatment was generally well-tolerated, with 91.5% of enrolled treatment patients completing the 12-month trial, compared to 90.9% of enrolled control patients. No patients randomized to Epioxa treatment discontinued early due to an adverse event and there were no ocular serious adverse events reported.
- The majority of adverse events reported were mild and transient in nature.

103

Epstein, Randy J. MD; Belin, Michael W. MD; Gravemann, Deborah RN, CCRP; Littner, Roxanne MS; Rubinfeld, Roy S. MD. EpiSmart Crosslinking for Keratoconus: A Phase 2 Study. Cornea 42(7):p 858-866, July 2023.

- The overall mean change in CDVA was −0.06 and −0.07 logMAR at 6 and 12 months post-op, respectively ($P < 0.001$ for improvement in each of 3 groups), with the average visual acuity improving from 20/41 at baseline to 20/35 Snellen at 12 months post-op.
- Overall, UCVA was significantly improved by about 1 line of vision at 6 and 12 months post-op ($P < 0.001$ for improvement at both time points and for each group), with the average uncorrected visual acuity improving from 20/150 at baseline to 20/120 Snellen at 12 months post-op.
- Change in Kmax post-op by treatment group (mean ± 95% CI). The topographic flattening was 0.25–0.5 diopter and statistically significant for 2 groups at 6 months and all 3 groups at 12 months.

104

Novel Graft Failure Tx Options

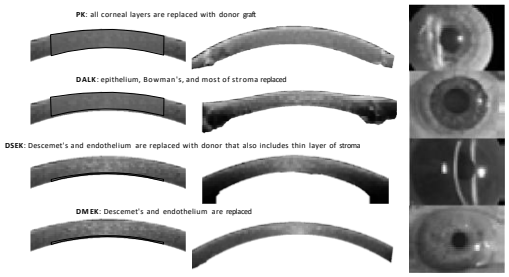
- Keratoprosthesis – "KPro"
- Restores vision by marrying mechanical central lens optic with a peripheral donor cornea
- KPro has three components which are assembled into a single unit
- A PMMA front plate with an optical stem extends through a 3 mm hole in a donor cornea and overlaps it centrally
- Titanium back plate snaps onto the optical stem and abuts the posterior side of the cornea
- K-Pro sutured into place much like a PKP
- Central optic provides for vision even if the cornea becomes cloudy or opaque.

105

KPro

106

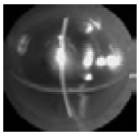
EK : Alphabet Soup Review



107

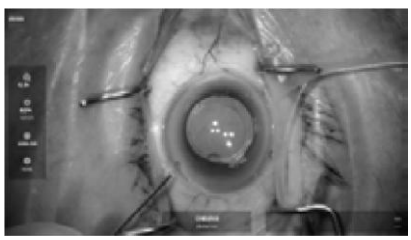
Keratoplasty Risks

- Rejection → Failure
  - Chronic corticosteroids
- Donor tissue related infections
  - Possible endophthalmitis or loss of eye (rare!)
- Gas and suture-related issues



108

Descemet's Stripping Only



109

Descemet's Stripping Only

- Indications
  - Presence of central guttae
  - Clear peripheral cornea with an endothelial cell count > 1000 cells/mm^2 on confocal or specular microscopy
  - Phakic or pseudophakic
- Contraindications
  - Advanced corneal stroma edema (haze, bullae, DM folds)
  - Peripheral endothelial cell count < 1000 cells/mm^2
  - Presence of secondary corneal pathology
  - History of herpes simplex virus or cytomegalovirus keratitis

https://eyewiki.aao.org/Descemetorhexis_Without_Endothelial_Keratoplasty#cite_note-17

110

Borkar DS, Veldman P, Colby KA. Treatment of Fuchs Endothelial Dystrophy by Descemet Stripping Without Endothelial Keratoplasty. Cornea. 2016 Oct;35(10):1267-73

- n=13
- Four eyes demonstrated resolution of K edema with visible central endo cell mosaic (410-864 cells/mm) by one month with VA 20/25-20/40
- Four eyes similar response by 3 mo
- Two eyes at 6 mos
- Final vision ranged from 20/15-20/20 in 10 eyes except for 2 with retinal pathology

111

1. Davies E, Jurkunas U, Pineda R 2nd. Predictive Factors for Corneal Clearance After Descemetorhexis Without Endothelial Keratoplasty. Cornea. 2018 Feb;37(2):137-140. doi: 10.1097/ICO.0000000000001427. PMID: 29053562.
2. Huang M-J, Kane S, Dhaliwal DK. Descemetorhexis Without Endothelial Keratoplasty Versus DMEK for Treatment of Fuchs Endothelial Corneal Dystrophy. Cornea. 2018 Dec;37(12):1479-1480. doi: 10.1097/ICO.0000000000001742. PMID: 30222716.

112

DSO Complications

- Descemetorhexis decentration
- Descemet membrane detachment
- Posterior stromal opacities
- Irregular corneal astigmatism
- Persistent corneal edema

113

DMEK vs. Descemet Stripping Only (DSO)

	DMEK	DSO
Indications	Guttata any diameter	Central < 4.5 – 5.0 mm
Surgery	DSO + graft placement (30 - 45 minutes)	DSO (10 - 15 minutes)
Postop	Supine positioning 48 hours	No positioning
Visual recovery	1-3 weeks	6-8 weeks
Drops	Chronic corticosteroid for rejection prophylaxis	Corticosteroid 1-2 months Extra Rho kinase inhibitor
Success	90-95%	80-85%

114

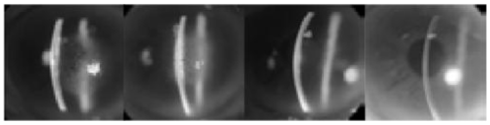
Rho Kinase Inhibitors

- Ripasudil 0.4% op sol
  - QID x 2 months
- Netarsudil 0.02% op sol
  - BID x 2 months

www.mimaki-family-japan.com/

115

POW #1 POW #3 POM #1.5 POM #2.5



1010 µm 963 µm 635 µm 565 µm

20/60 20/50 20/25 20/20

116

Trefoil Therapeutics

- 2 investigational products based on TTHX1114, its engineered FGF1, to treat a spectrum of corneal diseases.
- Intracameral injection
- Stimulates stimulates corneal endothelial cell protection, proliferation and migration

117

Allergic Conjunctivitis

- IgE is elevated in seasonal, perennial, atopic, vernal, and giant papillary conjunctivitis
- IgE is produced locally in the conjunctiva by the local plasma cells which bind to mast cells and basophils to release histamine[1]
- Diagnosis of allergic conjunctivitis in patients who have no systemic atopic disease is difficult because most of the time serum IgE concentrations are low[2-3]
- For allergic conjunctivitis, while local concentrations of IgE may be high, systemic concentrations may be low except in vernal allergic conjunctivitis (indicating both a systemic and a local response)[2-3]
- Eosinophils in conjunctival scrapings are elevated in only 45% of patients[4]
- Lipid disruption due to ocular allergy probably affects evaporation and may alter tear flow[5]

1] Yuasa T, Hiyama F, Nishi M, Hori T and Mimura Y: Local and circulating immunoglobulins in vernal conjunctivitis (VKC). 1Jml] Johansson munoglobulin-containing cells in the conjunctiva. Ringan 1977; 31:483-7. 2] McClellan BH, Whitney CR, Newman LP and Allansmith MR: Immunoglobulins in tears. Am J Ophthalmol 1973; 76:89-101. 3] Allansmith MR: Giant papillary conjunctivitis. Journal American Optometric Association (Supplement) 1990; 61(6):S44-S46. 4]Abelson MB, Udell IJ and Weston JH: Conjunctival eosinophils in compound 48/80

118

Lacrimal Fluid

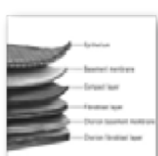
- A degeneration of the lacrimal gland can result in a diminished tear flow and changes in the protein composition of the lacrimal fluid[1,2]
- The major proteins of normal tear fluid are lysozyme, lactoferrin and tear-specific prealbumin[3,4]
- The results of immunofluorescence, tissue culture and the simultaneous disappearance of these proteins from the tear fluid of KCS patients indicate a common origin, i.e., the lacrimal gland[3,4]
- In comparison with the Schirmer test, the rose Bengal test and the tear film break-up-time, the lactoferrin test is reported to be the most reliable, single marker in the diagnosis of KCS[5]

1) Duke-Elder S: Ocular adnexa. Part II Lacrimal, orbital and para-orbital diseases. System of Ophthalmology. Vol. 13, p 626. C. V. Mosby Co., St. Louis (1974). 2) Janssen PT and van Bijsterveld OP: Comparison of electrophoretic techniques for the analysis of human tear fluid proteins. Clin Chim Acta 114:207-218 (1981). 3) Gillette TE, Allansmith MR, Greiner JV and Janusz M: Histologic and immunohistologic comparison of main and accessory lacrimal tissue. Am J Ophthalmol 89:724-730 (1980). 4) Janssen PT and van Bijsterveld OP: Origin and biosynthesis of human tear fluid proteins. Invest Ophthalmol Vis Sci 24:623-630 (1983).5). Goren MB and Goren SB: Diagnostic tests in patients with symptoms of keratoconjunctivitis sicca. Am J Ophthalmol 106:570-574 (1988).

119

What is Human Amniotic Membrane?

- Studies show AM enhances the wound healing process:
  - It reduces pain
  - It reduces inflammation
  - It reduces scar formation
  - Contains essential growth factors for cell growth and diversification
  - Antimicrobial properties



120

Cryopreserved Membrane w/BCL

Hydrated CAM

Ringless

Room Temperature Storage

Size (0): 12 mm

121


American Journal of Surgery and Clinical Case Reports

Micronized Amniotic Membrane for Dry Eye Disease: A Case Series

122

Corneal Esthesiometer

	Non Contact	Cochet-Bonnet	Cotton Wisp
Portable	✓	✓	✓
Noncontact	✓		
Stimulus	Ambient Air Pulses	Mechanical Force	Mechanical Force
Standardized and validated levels of stimulus	✓	Is dependent on multiple parameters	
Reproducible	✓	No. Depends on the user.	

123

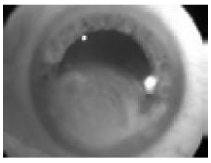
Corneal Esthesiometer

- Portable and Hand-held
- Non-Invasive system
- Five levels of stimulation
- Electronic position system
- Designed to be used in 2 modes: placed on a slit lamp and hand-held

124

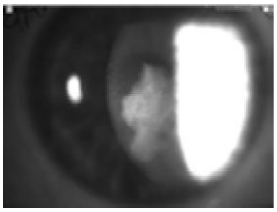
Topical Losartan

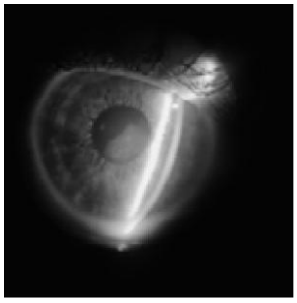
- Losartan is an angiotensin II receptor blocker (ARB) that impedes transforming growth factor (TGF) beta signaling by inhibiting activation of signal transduction molecule extracellular signal-regulated kinase (ERK)
- TGF beta roles include: scarring fibrosis associated with corneal trauma, chemical burns, infections, surgical complications, and persistent epithelial defects, as well as conjunctival fibrotic diseases, such as ocular cicatricial pemphigoid and Stevens-Johnson syndrome.



Steven E. Wilson, MD. Director of Corneal Research at Cleveland Clinic Cole Eye Institute

125





Photos Courtesy of Noa Rohson, OD MBA FAAO

126

Personalized Tear Retention

- A liquid hydrogel is deployed from a sterile, single-use applicator. The gel adapts to the shape of the tear duct then transitions to a flexible solid
  - 3-minute bilateral procedure
  - No sizing required
  - Bespoke geometry eliminates foreign body sensation
  - No falling out

127

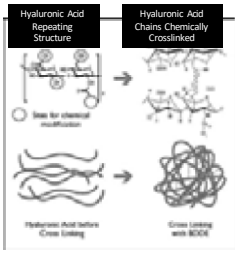
Smart Gel Transitions from Liquid to Flexible Solid

- Biocompatible
- Non-degradable
- Removes with saline rinse
- Pending recommended replacement schedule (e.g., 6 months, 1 year)

128

Punctal Occlusion

- Cross-linked hyaluronic acid gel that allows patient's eyes to be bathed in their own natural tears
- Customized for each individual patient
- Provides a full fill of the canalicular system
- Lasts for 6 months
- In-office procedure reimbursed through existing CPT code (68761)

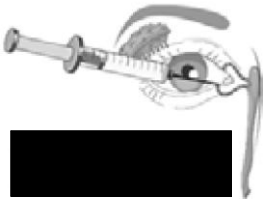


129

Simple & Efficient for your Practice

Instructions for Use

1. [redacted] comes in a pre-filled injector with enough gel to treat the lower and upper canaliculi.
2. The cannula tip is placed in the punctum and the [redacted] gel is inserted.
3. The gel flows through the punctum into the lacrimal sac.
4. If you see the gel extruding from the upper punctum, you know that both the upper and lower puncta have been blocked.



[redacted]

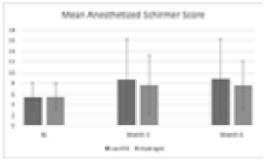
130

US FDA Clinical Trial Summary

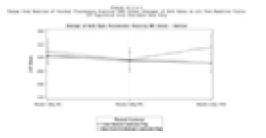
- n = 157
- Subjects with anesthetized Schirmer score ≤ 10 mm, Ocular Surface Disease Index (OSDI) score ≥ 23, presence of corneal staining and patent bilateral lacrimal drainage systems were randomized in a 2:1 ratio to LACRIFILL (n = 103) or a hydrogel plug (n = 54).
- Primary endpoint at 3 months; gel removed by irrigation at 6 months
- 510(k) Clearance December 2022

131

Greater Increase in Schirmer with CXL Filler



Trend Towards Better Maintenance of the Corneal Surface (Stable vs. Increased Staining at Month 6)



132

Sahara RCT Background

The aim of this study was to compare the effectiveness of branded Restasis twice-daily versus TearCare technology (2 procedures, baseline and month 5) at 6 months after initiation of treatment on improvement of signs and symptoms of DED.

- Restasis (cyclosporine .05%, CsA) Rx has been broadly utilized in the treatment of dry eye for the past 15 years, without regard for etiology
- Compliance and adherence challenges with all pharmaceutical and at home treatments hinder their overall effectiveness
- TearCare is an office-based ECP administered therapeutic thermal eyelid technology for the treatment of evaporative DED due to MGD
- Providers, Payors and Patients are interested to understand effectiveness of targeted interventional treatments compared to legacy pharmaceutical agents

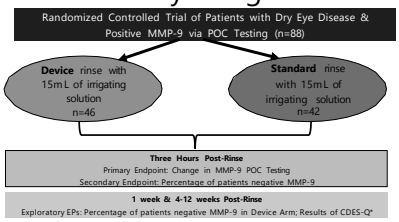
133

Conclusions

- TearCare treatment is superior to branded Restasis in improving TBUT and multiple measures of meibomian gland function
  - Both treatments produce significant improvements in patient reported symptoms
- TearCare administration and therapeutic effect in SAHARA RCT is consistent with "real-world"
  - Compliance to branded Restasis in SAHARA RCT was atypical of "real-world" patient behavior (on average 5.7 bottles over 6 months)
- Results of SAHARA RCT may warrant earlier intervention with TearCare
  - Equal patient access to TearCare may be justified

134

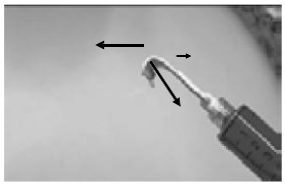
Study Design



135

Irrigating Eyelid Retractor

Fixed to a syringe, the retractor has 5 ports which aim fluid at the palpebral conjunctiva, bulbar conjunctiva and conjunctival fornix.



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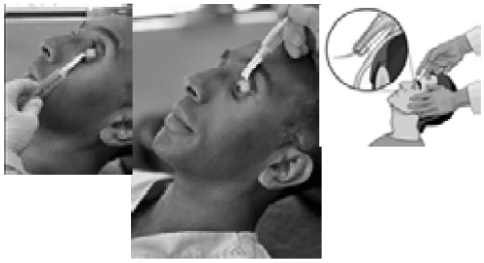
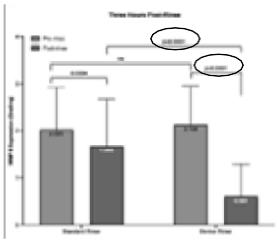


137

Results—Primary Endpoint



Paired t-test: decreased MMP-9 expression in both standard and device groups with greater attenuation in the device rinse group.

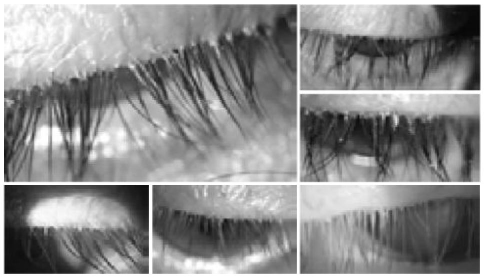
Two-way ANOVA: decreased MMP-9 expression in device group compared to standard ($p<0.0001$).

138

Tixel (MGD Procedure)

- FDA-cleared treatment
- Uses precisely-controlled heat to restore/improve eyelid gland function powered by Thermo-Mechanical Action®, this treatment consists of short pulses (6 milliseconds) of high heat applied via gentle pressure from the proprietary, self-disinfecting, Titanium-coated tip
- 2 min procedure for both eyes

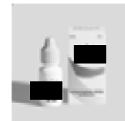
139



140

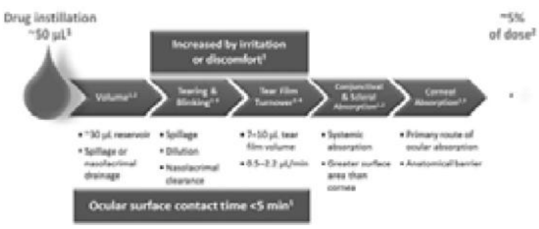
Lotilaner ophthalmic solution 0.25%
TP-03

- Indications and Usage: indicated for the treatment of Demodex blepharitis
- Dosed BID (approximately 12 hours apart) for 6 weeks
- No contraindications
- Side Effects
  - The most common ocular adverse reaction observed in controlled clinical studies with XDEMVY was instillation site stinging and burning (reported in 10% of patients)
  - Chalazion/hordeolum and punctate keratitis in 2% of patients



141

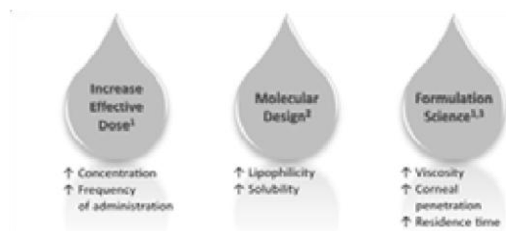
Topical Drug Delivery Considerations



1. Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Deliv. 2006;3(2):275-287. 2. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. AAPS J. 2010;12(3):348-360. 3. Coffey MJ, Decory HH, Lane SS. Development of a non-settling gel of 0.5% loteprednol etabonate for anti-inflammatory use as an ophthalmic drop. Manuscript in preparation. 4. McGhee CN. An overview of topical ophthalmic drugs and the therapeutics of ocular infection. http://www.fmhs.auckland.ac.nz/som/ophthalmology/teaching/_docs/optometry-355-05-pharmacokinetics.pdf. Accessed October 25, 2012. 5. Kaur IP, Kanwar M. Ocular preparations: the formulation approach. Drug Dev Ind Pharm. 2002;28(5):473-493.

142

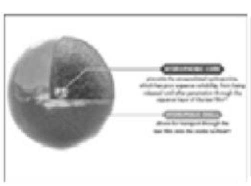
Strategies to Improve Topical Ocular Drug Delivery



1. Ghate D, Edelhauser HF. Expert Opin Drug Deliv. 2006;3(2):275-287. 2. Shirasaki Y. J Pharm Sci. 2008;97(7):2462-2496 3. Kaur IP, Kanwar M. Drug Dev Ind Pharm. 2002;28(5):473-493. 4. Barar J, et al. Expert Opin Drug Deliv. 2008;5(5):567-581

143

Nanomicelles Matter



144

Nanoparticles Matter

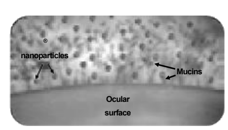
The eye's natural mucins can trap and eliminate suspension eye drops

This reduces overall penetration to the target ocular tissue

Nanoparticles of active drug with a proprietary coating to support penetration of the mucus barrier

~300 nm nanoparticle with mucopenetrating surface coating

Particles <500 nm are designed to penetrate mucus pores[2,3]



145

Water-free Cyclosporine 0.1% unfolds the full potential of cyclosporine to efficiently treat dry eye disease – fast and comfortable for the patient

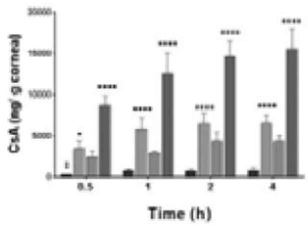
- a **fast-acting** anti-inflammatory and immunomodulatory product
- a clear 0.1% cyclosporine dissolved in a **semifluorinated alkane** solution for treatment of signs and symptoms of dry eye disease
- free of oils, surfactants, or preservatives with superior spreading properties
- no pH, no osmolarity

Perfluorobutyl-pentane (SFA) vehicle	
Spreading and API penetration	**>4x** more penetrating than water-based treatments[2]
Surface residence time	**up to 60x** longer than water-based Treatments[1,2]
Comfort	**99.8%** of patients experienced no or mild instillation site pain[3,4]

Note: * development name of the water-free ophthalmic ciclosporin solution, 0.1 % in perfluorobutylpentane
[1]ARVO 2018, Poster Krösser S, et al.; [2] Agarwal P, et al. Int J Pharm. 2018 Mar; [3]Sheppard JD, et al. Cornea. 2021 Oct; [4]Akpek EK, et al. JAMA Ophthalmol. 2023 Apr

146

In-vitro Corneal Permeability of Cyclosporine in Porcine Eyes

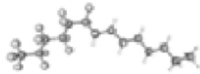


Semifluorinated alkanes for topical delivery of Cyclosporine A, P. Agarwal1, D. Scherer2, B. Günther2, I. D. Rupenthal1 1Buchanan Ocular Therapeutics Unit, Department of Ophthalmology, New Zealand National Eye Centre, The University of Auckland, Auckland, New Zealand; 2 Novaliq GmbH, Heidelberg, Germany

147

Perfluorohexyloctane (PFHO)

- Perfluorohexyloctane
  - ✓ Water free, preservative free
  - ✓ Long lasting lubricant
  - ✓ Potent inhibitor of evaporation



	Water-based Technologies	PFHO
Drop Size	~ 40–50µL	11 µL
Drug Residual Time	Brief 3–5 min	Long ~ 240 min
Spreading	High surface tension hinders spreading	Fast spreading Film forming properties
Other features	Usually preserved	Preservative free Blink reflex not activated No vision blurring

1. Krösser S, et al. *Invest Ophthalmol Vis Sci.* 2018;59:2656. 2. Broniatowski M, et al. *J Phys Chem B* 2004;108:13403-13411. 3. Liu X, et al. *Bull Chem Soc Jpn.* 2018;91(5):846-857. 4. Gaines G Jr. *Langmuir* 1991;7(12):3054-3056. 5. Meinert H, et al. *Eur J Ophthalmol.* 2000;10(3):189-197. 6. Borchmann et al. *Invest Ophthalmol Vis Sci.* 2022;63:1525 – A0250. 148

148

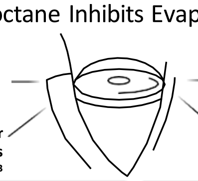
Perfluorohexyloctane Inhibits Evaporation

Mimics key functions of natural meibum[1,2]

Promotes healing on the ocular surface[4-6]

Remains in tears for up to 6 hours (PK rabbit study)[2,3]

May reduce friction[5,7]



Perfluorohexyloctane FORMS MONOLAYER at air-tear interface -can be expected to reduce evaporation.

Exact mechanism of action in DED is not known

An in vitro study showed MIEBO was 4x more effective at inhibiting evaporation compared to meibum lipids.[1]

The clinical significance of this data has not been established.

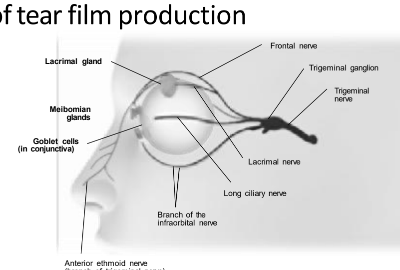
Slide Courtesy of Selina McGee, OD

149

The pathways of tear film production

Overview of Pathways Involved in Tear Film Production

1. ***Afferent* nerve impulses** from the nose (*light blue*) travel via the trigeminal nerve to the CNS[1,2]
2. ***Efferent* nerve impulses** leave the CNS via parasympathetic nerve fibers[1,2]
3. The **trigeminal parasympathetic pathway** plays a role in tear film homeostasis and innervates the lacrimal functional unit[2,3]:
   - Lacrimal glands: aqueous and mucous components
   - Meibomian glands: lipid components
   - Goblet cells: mucin components



- CNS, central nervous system.
- 1. Efron N, et al. *Invest Ophthalmol Vis Sci.* 2013;54(11):TFOS98-TFOS122. 2. Dieckmann G, et al. *Ocul Surf.* 2019;17(1):20-27. 3. Clayton JA. *N Engl J Med.* 2018;378(23):2212-2223.

150

Nasal Activation of the Trigeminal Nerve

- Research into nicotinic acetylcholine receptors (nAChR) has demonstrated they are expressed on trigeminal nerve endings and contribute detection of irritants and chemicals[1,2]
- Direct neurostimulation of nAChR-expressing fibers has been shown to increase tear production[3,4]

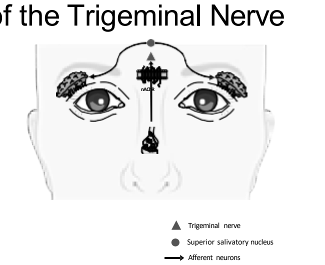
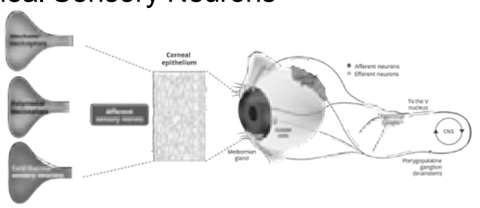


Image adapted from Servier Medical Art. Licensed under CC BY 4.0. 1. Alimohammadi H, et al. *Chem Senses.* 2000;25:61-66. 2. Arendt-Nielsen L, et al. *Nicotine Tob Res.* 2022;24:1849-1860. 3. Wirta D, et al. *Cornea.* 2022;41:1207-1216. 4. Wirta D, et al. *Ophthalmology.* 2022;129:379-387.

151

Corneal Sensory Neurons



Cold thermoreceptors monitor for changes to the tear film and regulate basal tear production[1-3]

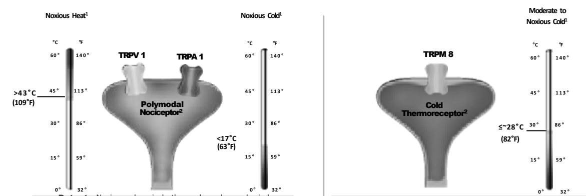
Polymodal nociceptors detect and warn of irritating and harmful stimuli and produce reflex tears[4-8]

HT, high-threshold; LT, low-threshold; Vc/C1; subnucleus caudalis/cervical vertebra; Vi/Vc, subnucleus interpolaris/caudalis

1. Yang S, et al. *Front Med (Lausanne)*. 2022;3:9:9830853. 2. Belmonte C, Gallar J. *Invest Ophthalmol Vis Sci*. 2011;52:3888-3892. 3. Belmonte C, et al. Ocul Surf. 2017;15:404-437. 4. Craig JP, et al. *Ocul Surf*. 2017;15(4):802-812. 5. Acosta CM, et al. *Invest Ophthalmol Vis Sci*. 2004;45:2333-23365. 6. Abusharha AA, et al. *Ther Adv Ophthalmol*. 2018;10:1-6. 7. Parra A, et al. *Nat Med*. 2010;16(12):1396-1399. 8. Hirata H and Meng ID. *Invest Ophthalmol Vis Sci*. 2010;51(8):3969-3976.

152

Reflex vs Basal Tears



Detect: Noxious chemical, thermal, and mechanical stimuli; low pH[3,4]

Response: Irritation and pain, reflex tearing5-7

Stimuli: Evaporative cooling, increasing osmolarity[5,2,8]

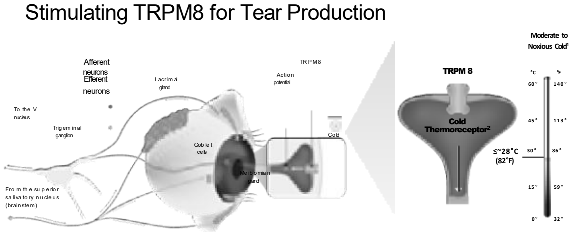
Response: Cool/cold sensation, basal tear production[4,9]

TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanilloid 1.

1. Bharate S, Bharate S. *ACS Chem Neurosci*. 2012;3:248-267. 2. Belmonte C, et al. *The Ocular Surface*. 2017;15(3):404-437. 3. Yang TJ, et al. *Ann Transl Med*. 2022;10:839. 4. Yang S, et al. *Front Med (Lausanne)*. 2022;9:830853. 5. Craig JP, et al. *Ocul Surf*. 2017;15(4):802-812. 6. Parra A, et al. *Nat Med*. 2010;16(12):1396-1399. 7. Acosta CM, et al. *Invest Ophthalmol Vis Sci*. 2004;45:2333-23365. 8. Belmonte C, Gallar J. *Invest Ophthalmol Vis Sci*. 2011;52:3888-3892. 9. Yang JM, et al. *BMC Ophthalmol*. 2017;17(1):101.

153

Stimulating TRPM8 for Tear Production



TRPM8 receptors activate trigeminal neural signaling and LFU activity, resulting in the coordinated innervation of the lacrimal gland, goblet cells, and meibomian glands to regulate basal tearing[3-5]

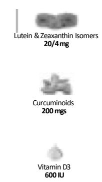
LFU, lacrimal functional unit; TRPM8, transient receptor potential melastatin 8.

1. Bharate SS, Bharate SB. *ACS Chem Neurosci*. 2012;3:248-267. 2. Belmonte C, et al. *The Ocular Surface*. 2017;15(3):404-437. 3. Dartt DA. *Prog Retin Eye Res*. 2009;28(3):155-177. 4. Ogino MH, Tadi P. Neuroanatomy, trigeminal reflexes. Updated June 5, 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK551641/. Accessed July 25th, 2024. 5. Pflugfelder SC, et al. *Exp Eye Res*. 2020;197:108115.

154

Latest Proprietary Blend of Antioxidant Ingredients for Dry Eye

Integrative Actives



Lutein & Zeaxanthin Isomers **20/4 mg**

Lutein & Zeaxanthin have demonstrated antioxidant and anti-inflammatory effects, protecting against photo-oxidative damage[1,2]

Curcuminoids **200 mgs**

In vitro, curcumin can reduce pro-inflammatory cytokines in corneal epithelial cells[3,4]

Vitamin D3 **600 IU**

Vitamin D3 supplementation has been shown to improve efficacy of artificial tears and reduce symptom severity in patients with and without vitamin D3-deficiency[5-7]

Delivered in a single soft-gel, consumed daily after food

• **1.** Cristaldi M, et al. *Appl Sci* (2022) 12(3):1268. **2.** Bian Q, et al. *Free Radic Biol Med* (2012) 53 (6):1298-307. **3.** Castro-Castaneda CR, et al. *Nutrients* (2022) 14(23):5014. **4.** Davis BM, et al. *Sci Rep* (2018) 8(1):11066. **5.** Gorimanipalli B, et al. *Indian J Ophthalmol* (2023) 71(4):1127-34. **6.** Hwang JS, et al. *Cornea* (2019) 38(3):304-10. **7.** Najjaran M, et al. *Clin Exp Optom* (2023) 106(3):257 62.

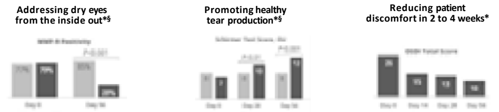
155

Evaluated in two randomized, double-masked, placebo controlled clinical studies

Addressing dry eyes from the inside out*§

Promoting healthy tear production*§

Reducing patient discomfort in 2 to 4 weeks*



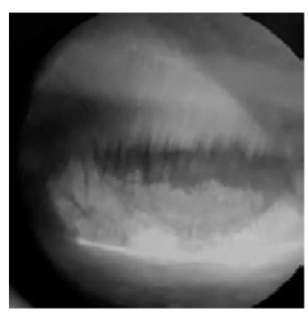
In the US study (NCT05481450), Blink NutriTears significantly improved tear volume and OSDI total score vs placebo, from baseline to end of study (Day 56; P<0.001 for both). There were also significant improvements in TBUT, SPEED, ocular staining scores (P<0.0001 for each outcome), tear osmolarity (P<0.0005), and presence of MMP-9 (P<0.0017). N=116, randomized 1:1 NutriTears and placebo

***These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

§ Based on a clinical study

Gioia N. et al. *Front Ophthalmol*. 2024. Radkar P, et al. *Ophthalmol Ther*. 2021;10(3):581-599. | **MMP-9**, matrix metalloproteinase 9; **OSDI**, ocular surface disease index; **OU**, left eye; **SPEED**, Standard Patient Evaluation of Eye Dryness questionnaire; **TBUT**, tear break up time.

156



Video Courtesy of Jake Lang, OD

157

What About the Retina?

158

Treatment for Dry AMD

- The mechanism of photobiomodulation (PBM) at the cellular level has been ascribed to the activation of mitochondrial respiratory chain components resulting in stabilization of metabolic function and initiation of a signaling cascade, which promotes cellular proliferation and cytoprotection.

**Not approved in the US

159

- The LIGHTSITE III, a prospective, double-masked, randomized, multi-center clinical trial
- The objective was to treat dry AMD subjects with PBM every four months for a duration of 24 months.
- Primary endpoints:
  - Best corrected visual acuity (BCVA) was evaluated at 13 months, and if statistically significant, ($p < 0.025$) the complete 13-month efficacy and safety endpoints would be unmasked.
  - The study will continue to treat and follow subjects for safety for a total 24 months.
- N = 100 pts 2:1 PBM to sham
- The results demonstrated statistically significant improvement in the primary endpoint in BCVA at 13 months in the PBM treatment group over the sham-treatment group ($p < 0.003$). In addition, a sustained, mean increase in ETDRS letter score of 5.5 letters from baseline was seen at the 13-month timepoint in the PBM-treated subjects BCVA ($p < 0.0001$).

160

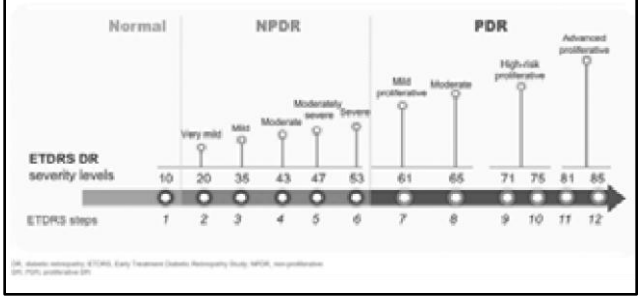
APX3330
Potential Treatment for DR and DME

- First-in-class, twice-daily oral tablet drug candidate
- Specifically targets Apurinic/Apyrimidinic Endonuclease 1/Redox Effector Factor-1 (APE1/Ref-1) protein, referred to as Ref-1.
- APX3330 has a dual mechanism of action in validated pathways, decreasing both abnormal angiogenesis and inflammation by blocking pathways downstream of Ref-1.
- APX3330 specifically blocks Ref-1's redox signaling function leading to simultaneous decreases in the activity of several important proangiogenic and proinflammatory transcription factors relevant to the pathophysiology of retinal and choroidal vascular diseases: HIF-1a to reduce VEGF signaling and NF-kB to modulate VEGF, TNF-α and other inflammatory cytokines.

**Not approved in the US

161

Diabetic retinopathy severity scale



162

FDA-Approved Ophthalmic Digital Drug Delivery Platform

1. Wirta DL, Walters TR, Flynn WJ, Rathi S, Ianchulev T. Mydrexis with micro-array print touch-free tropicamide-phenylephrine fixed combination MIST: pooled randomized Phase III trials. Ther Deliv. 2021 Mar;12(3):201-214.
2. Optecare is Eyenovia's suite of digital compliance and adherence capabilities

163

163

Tropicamide and Phenylephrine HCL ophthalmic spray 1%/2.5

- Speed and simplicity with each spray
- The only FDA approved fixed-dose combination of the leading pupil dilating drugs
- Reliable time to peak efficacy and dilation resolution
- In clinical studies 97% of patients reported zero side effects[1]

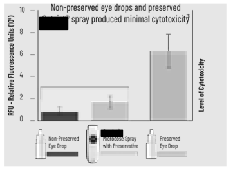
164

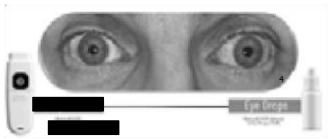
Delivers 80% Less Drug Volume Than Eye Droppers

Sufficient for efficacy while improving benefits from reducing excessive exposure to both drugs and preservatives [1,2]

Minimizes Excessive Drug Exposure to Ocular Tissues[3]

Improves Local Tolerability and Decreases Systemic Exposure[4]





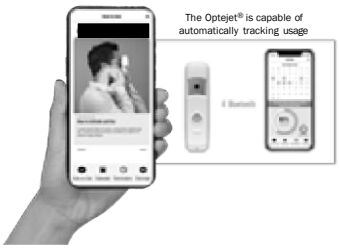
When tolerability is poor, patients are very likely to discontinue their medication or put pressure on the ECP to change their treatment[4]

1 Wirta D. et al, Presentation at 2019 ASCRS meeting | 2 Ianchulev T. et al, Therapeutic Delivery 2018 | 3 Hamrah, P. et al. Cytotoxicity Evaluation for BAK-preserved Latanoprost Delivered By Drop vs. Microdose Array Print Technology. ARVO 2023 poster. New Orleans, LA| 4 The impact of precision spray dosing of netarsudil 0.02% can be seen when compared to a single drop of the same drug.

165

165

Digital Technology



The Optejet® is capable of automatically tracking usage

OPTECARE:
Multiple Benefits for All Stakeholders

PATIENT
- Reminders to take medicine
- Ability to track compliance progress
- Opportunity for brand-specific encouragement
- May be monetized through app subscription service

PHYSICIAN
- Ability for quicker action with more accurate data
- Opportunity for billing: CPT Code (98980) for monthly check of compliance data

PAYER
- Cost savings: Less likely to have patient on second medication if compliance is the issue
- Better outcomes: Compliance with drug therapy shown to slow disease progression[1]

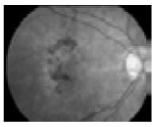
1 Shu YH et al. Topical Medication Adherence and Visual Field Progression in Open-angle Glaucoma. J Glaucoma 2021

166

166

Retina In-Office Diagnostics

OCT



OCT-A

OCT-A = optical coherence tomography angiograph.
Images courtesy of Walter O. Whitley, OD, MBA, FAAO.

167

167

Multisite Study Confirmed Automated Dark Adaptometer Is Highly Sensitive, Specific, & Accurate

High sensitivity
- Correctly identified 90.6% of confirmed AMD cases

High specificity
- Correctly identified 90.5% of confirmed normal cases

High accuracy
- 90.6% overall accuracy

JOHNS HOPKINS UNIVERSITY

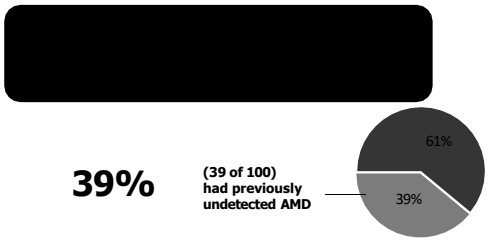
PENNSTATE HERSHEY College of Medicine

Jackson GR, et al. *Invest Ophthalmol Vis Sci.* 2014;55(3):1427-1431.

168

168

Undetected AMD Is a Significant Problem



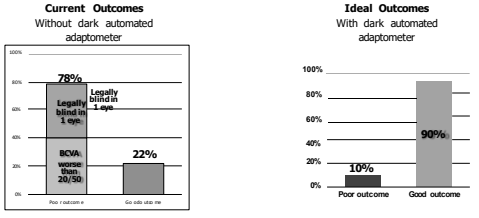
39%

(39 of 100) had previously undetected AMD

Data courtesy of Jeffry Gerson, OD, Grin Eye Care.

169

Primary Eye Care Has a Major Opportunity to Maintain the VA of Patients With AMD



BCVA = best-corrected visual acuity.
Cervantes-Castañeda RA, et al. *Eye (Lond).* 2008;22(6):777-781; Olsen TW, et al. *Ophthalmology.* 2004;111(2):250-255.

170

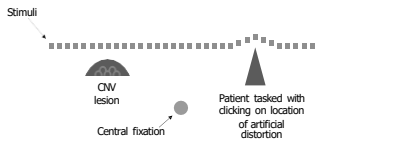
Current and Future of At-Home Testing/Monitoring

Bellsmith KN, et al. *JAMA Ophthalmol.* 2022;140(5):465-471; BrightFocus Foundation. Updated February 8, 2024. Accessed September 9, 2024. https://www.brightfocus.org/macular/news/amsler-grid-eye-test; Other images courtesy of Walter O. Whitley, OD.

171

Preferential Hyperacuity Perimetry Delivers Accurate, Highly Sensitive, Specific Disease Detection

- human ability to perceive small differences in the relative spatial localization of two objects in space.

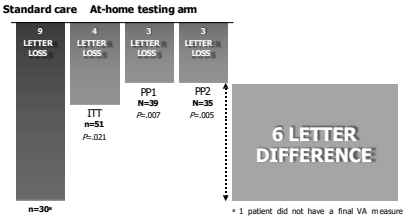


When the distortion caused by CNV is larger than the artificial distortion, the patient will preferentially pick this spot of pathological distortion.

CNV = choroidal neovascularization.

172

Patients Who Used At-Home Testing for nAMD Lost Fewer Letters

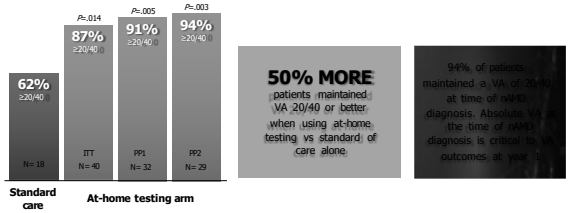


a 1 patient did not have a final VA measure at nAMD diagnosis from the total 31 patients who converted

ITT = intention-to-treat; PP1 = initial per-protocol population; PP2 = second per-protocol population.
AREDS2-HOME Study Research Group; Chew EY, et al. *Ophthalmology.* 2014;121(2):535-544.

173

More Patients Who Used At-Home Testing for nAMD Maintained VA ≥20/40

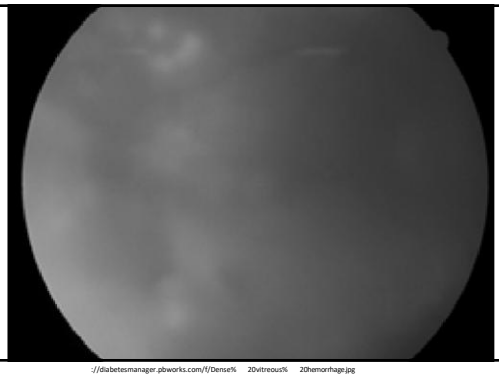


50% MORE patients maintained VA 20/40 or better when using at-home testing vs standard of care alone

94% of patients maintained a VA of 20/40 at time of nAMD diagnosis. Absolute VA at the time of nAMD diagnosis is critical to VA outcomes at year 1

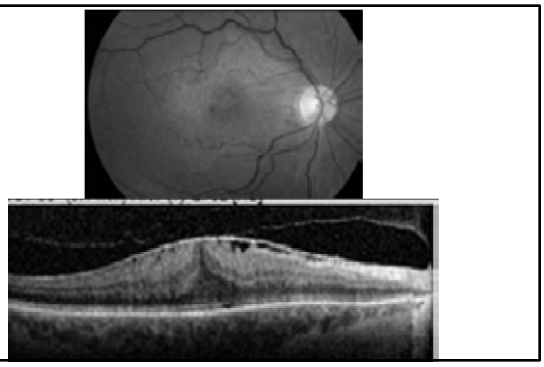
AREDS2-HOME Study Research Group; Chew EY, et al. *Ophthalmology.* 2014;121(2):535-544.

174



://diabetesmanager.pbworks.com/f/Dense% 2Dvitreous% 20hemorrhage.jpg

176



177

Treatment for PDR: Vitrectomy

- Indicated after weeks to months of blood not clearing from vitreous heme
- Best results if done within 6 months of heme (DRVS)
- Usually done at 6 weeks
- Alleviate retinal traction, ERM
- When PRP is not enough
- Cataracts!

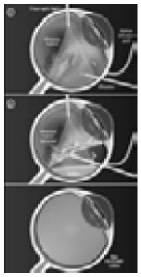


Photo accessed from http://www.eyecentersofsetexas.com/college_location/treatments.php?pl=78

178

Vitrectomy

- Inability to visualize breaks due to opacities
- In RRD, inability to close breaks
- First line treatment for pseudophakes
- Remove vitreous and replace with air, gas, or oil
- Can be performed with other procedures
- Good for single, large tears
- Unresolving Vitreous Heme
- Induce cataract
- Rarely requires sutures

179

Tamponade Agents

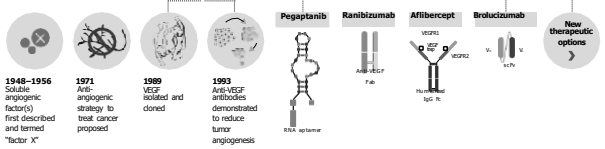
- Air
  - Lasts 3 to 5 days
- Sulfur hexafluoride (SF6)
  - Doubles its volume
  - Last 10-14 days
- Perfluoropropane (C3F8)
  - Quadruples its volume
  - Lasts approximately 60 days

180

Anti-VEGF Therapies Have Redefined the Care of Patients With Retinal Diseases

Historical timeline of VEGF discovery[1]

The evolution of anti-VEGF therapies for retinal disease management[2–6]



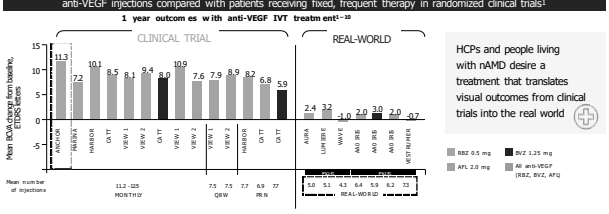
Fab = fragment antigen binding; Fc = fragment crystallizable; IgG = immunoglobulin G; scFv = single-chain fragment variable; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; VH = heavy chain variable domain; VL = light chain variable domain.

1. Apte RS, et al. *Cell.* 2019;176(6):1248-1264; 2. Sharma A, et al. *Eye (Lond).* 2020;34(4):611-613; 3. Adamis AP, et al. *Eye (Lond).* 2020;34(11):1966-1972; 4. Ranibizumab. Package insert. Genentech; 2006; 5. Aflibercept. Package insert. Regeneron; 2011; 6. Brolucizumab. Package insert. Novartis; 2019.

181

Yet, Visual Acuity Is Not Translated From Clinical Trials to the Real World

Patients with nAMD experience worse visual outcomes in the real world because they receive fewer anti-VEGF injections compared with patients receiving fixed, frequent therapy in randomized clinical trials[1]



AFL = aflibercept; BCVA = best-corrected visual acuity; BVZ = bevacizumab; ETDRS = Early Treatment Diabetic Retinopathy Study; HCP = health care professional; IVT = intravitreal; nAMD = neovascular age-related macular degeneration; PRN = as needed; Q8W = every 8 weeks; RBZ = ranibizumab; VEGF = vascular endothelial growth factor.

1. Ciulla TA, et al. *Ophthalmol Retina.* 2020;4(1):19-30; 2. Brown DM, et al. *N Engl J Med.* 2006;355(14):1432-1444; 3. Busbee DM, et al. *Ophthalmology.* 2013;120(5):1046-1056; 4. Heier JS, et al. *Ophthalmology.* 2012;119(12):2537-2548; 5. Martin DF, et al. *N Engl J Med.* 2011;364(20):1897-1908; 6. Rosenfeld PJ, et al. *N Engl J Med.* 2006;355(14):1419-1431; 7. Holz FG, et al. *Br J Ophthalmol.* 2015;99(2):220-226; 8. Cohen SY, et al. *Retina.* 2013;33(3):474-481; 9. Finger RP, et al. *Acta Ophthalmol.* 2013;91(6):540-546; 10. Rao P, et al. *Ophthalmology.* 2016;123(4):832-839; 11. Ciulla TA, et al. *Ophthalmol Retina.* 2019;3(2):162-172.

182

Visual Acuity Decreases Due to Fewer IVT Injections and Patients Lost to Follow-up

Current anti-VEGF injections place significant burden on patients and caregivers[1,2]

Most common reasons for patients discontinuing IVT injections[1,2]:

1. 52% — Distance from home to the hospital
2. 35% — Dissatisfied with injection benefit
3. 24% — Burden of follow-up visits

Other factors include[2]:

- Patient anxiety (reported in 56% of patients):
  - 39% fear going blind from injections
  - 37% have concerns around effectiveness
- Patients not being able to stick to the treatment plan

1. Boulanger-Scemama E, et al. *J Fr Ophtalmol.* 2015;38(7):620-627; 2. Senra H, et al. *Am J Ophthalmol.*

183

Current Standard of Care for nAMD Involves Frequent Injections

Drug	Hallmark Trial	Dose	Key Finding(s)	Safety
Bevacizumab	CATT	1.25 mg Q4W	• Mean BCVA Δ +7.8 letters over 24 months • BCVA and CRT comparable to ranibizumab Q4W	• Higher systemic adverse events with bevacizumab
Ranibizumab	ANCHOR/MARINA	0.5 mg monthly	• Mean BCVA Δ +6.6 to +10 letters over 24 months	• 1.3% - 2.1% endophthalmitis • 6.2% - 10% ocular inflammation ≥1+
Aflibercept	VIEW1/VIEW2	2 mg Q4W or 2 mg Q8W	• Aflibercept noninferior to ranibizumab q4w • Mean BCVA Δ +8.4 to +9.3 letters over 52 weeks • Comparable fluid resolution between groups	• Endophthalmitis in 1% in each group in VIEW1, 0% in VIEW2
Brolucizumab	HAWK/HARRIER	6 mg Q8W or 6 mg Q12W	• Noninferior to aflibercept • Mean BCVA Δ +6.1 to +6.6 letters over 48 weeks • Superior fluid resolution compared to aflibercept	• Endophthalmitis 1% • Inflammation 4% • Rare post-marketing reports of vasculitis

CRT = central retinal thickness; Q4W = every 4 weeks; Q12W = every 12 weeks.

184

Novel & Pipeline Therapeutic Agents & Treatment Delivery Systems for AMD/DME in Early- or Late-stage Development to Offer Extended Duration of Action via Various Mechanisms or Delivery

- Faricimab
- Aflibercept 8 mg
- KSI-301
- OPT-302
- OCS-01
- THR-149
- UBX1325
- Port delivery system (PDS)
- Gene therapy

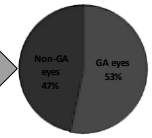
AMD = age-related macular degeneration; DME = diabetic macular edema.

185

GA is underdiagnosed

Out of 201 eyes, 75 eyes were **coded as early or intermediate AMD***

BUT, when checked using the Hoover categorization



53% of these eyes **had GA**

Patient coding may not provide adequate information about GA prevalence, which may be due to:

- Inadequate attention paid to coding GA (untreatable at the time)
- **Good visual acuity may lead to an underdiagnosis of GA**

*In a recent, retrospective study of patients (n=201 eyes) with AMD referred to a single low vision rehabilitation center, from October 2018 to June 1 2022. GA was diagnosed for the study using microperimetery with infrared imaging (dense scotoma) and often OCT imaging (complete GA).

Reference: Suness JS. The Underreporting of Age-related Geographic Atrophy of the Macula. Ophthalmol Retina. 2023 Apr;7(4):347-348.

186

Multimodal imaging of an eye with GA[1]

A: Color fundus photography

B: Fundus autofluorescence

C-D: Fluorescein angiography (over course of exam)

E-F: Optical coherence tomography

G: Near-infrared reflectance

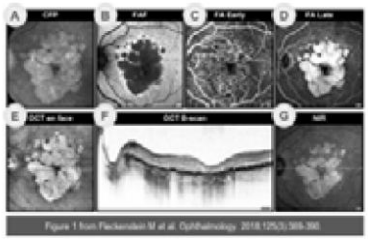


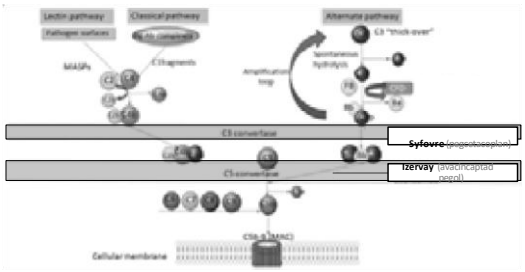
Figure 1 from Fleckenstein M et al. Ophthalmology. 2018;125(3):369-390.

187

Geographic Atrophy (GA) Treatment

- Prior to 2023, AREDS2 supplementation was the only recourse for DARMD.
- Complement factor H is an important gene in the pathogenesis of ARMD.
- Complement over-activation may result in excessive phagocytosis, inflammation, and cell lysis… resulting in retinal cell damage.

188



189

Geographic Atrophy (GA) Treatment

Syfovre (pegcetacoplan)

- FDA: Feb 2023
- MOA: C3 inhibitor
- OAKS & DERBY (n = 1,252) [7]
- 16-22% reduction in progression
- Rare cases of retinal vasculitis
- GALE – long-term extension study

190

Geographic Atrophy (GA) Treatment

Izervay (avacincaptad pegol)

- FDA: Aug 2023
- MOA: C5 inhibitor
- GATHER1/2 (n = 734) [8]
- 14-27% reduction in progression
- No definitive vision effect**

191

Geographic Atrophy (GA) Treatment

- Goal of current GA therapy is EARLY intervention.
- Although Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol) cannot completely halt the progression of GA, they have both been shown to statistically slow the progression of lesion expansion.
- Not all patients are ideal candidates for these drugs, so it's imperative to refer to a retinal surgeon in a timely fashion to establish clinical baseline.

192

Conclusions

- Numerous innovations in eye care
- Consider the impact on your patients and your practice
- Utilize evidence based medicine
- Practice at the highest level of our profession

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193