

OUT WITH THE OLD AND IN WITH THE NEW: ANT SEG

Marc R. Bloomenstein OD, FAAO
Schwartz Laser Eye Center

2

FINANCIAL DISCLOSURES FOR MARC R BLOOMENSTEIN, OD, FAAO

- Allergan-Speaker/Consultant
- Avellino-Consultant
- Azura-Consultant
- Bausch & Lomb-Speaker/Consultant
- Bruder-Consultant
- Dome-Speaker/Consultant
- Eyevance-Consultant
- Harrow-Speaker
- Iveric-Consultant
- LENZ-Consultant
- Ocuphire-Consultant
- OcuSOFT-Consultant
- Olleyes-Consultant
- Oyster Point-Speaker/Consultant
- Novartis-Speaker/Consultant
- Reichert-Consultant
- Sydnexus-Consultant
- Sight Science-Speaker/Consultant
- Visus-Consultant
- STAAR Surgical-Speaker/Consultant
- Sun-Speaker/Consultant
- Tarsus-Speaker/Consultant
- Thea-Consultant
- Topcon-Consultant

All financial relationships have been mitigated.

3

THE STATE OF THE INDUSTRY

- **Novartis**- crickets...BYEEEE
- **Kala**-only investigational med
 - Sold Eyesuvis/Inveltys to Alcon
- **Thea**
 - Buys Akorn
 - Buys AcellFx
- **Bausch +Lomb**
 - Buys Acufous
 - Xiidra
 - Blink Tears
- **Alcon**
 - Buys Kala's meds..
 - Buys Aerie
- **Viartis**
 - Buys Oyster Point and
 - Buys Fomy Life Sciences
 - Licenses Ocuphire's pipeline-Nyxo
 - Ocuphire sold to Opus Genetics
- **Coopervision**
 - Buys SynergEyes
- **Santen**-"who dis, new phone?"

5

MERRIAM-WEBSTER WORD OF THE YEAR 2022

GASLIGHTING

A driver of disorientation and mistrust, *gaslighting* is: "the act or practice of grossly misleading someone especially for one's own advantage." 2022 saw a 1740% increase in lookups for *gaslighting*, with high interest throughout the year

6

dry adjective

Save Word

\ 'drɪ \

drier also dryer \ 'drɪ(-ə)r \; driest also dryest \ 'drɪ-əst \

Definition of dry (Entry 1 of 3)

- a : free or relatively free from a liquid and especially water
// Mix the dry ingredients first.
// as dry as a bone
 - b : not being in or under water
// happy to be on dry land
 - c meteorology : lacking precipitation or humidity
// a dry climate



7

K.I.S.S



L.L.P.P

8

SCREEN TIME, ARTIFICIAL TEARS AND BLBCG CLIP ON!

9

There Is No Substitute for Natural Tear Film

Growth factors, such as nerve growth factor (NGF) and epidermal growth factor (EGF), found in natural human tears, are critical regulators for corneal wound healing.

A healthy tear film lubricates and protects the eyes from injury and infection, washes away foreign particles, and contributes refractive power for clear vision.

TFOS DEWS II tear film report

Natural tears contain a complex mixture of lipids, proteins, mucins, and electrolytes^{1,2}

- Over 1,500 proteins
- 5+ lipid classes
- 20+ mucins
- Contains growth factors and has anti-inflammatory and antimicrobial properties

1. Denstler K, Sheardown H, Jones L. Growth factors in the tear film: role in tissue morphogenesis, wound healing, and ocular pathology. Clin Exp. 2007;15:128-139.
2. Wilson ADP, Angstrom P, Gannan GA, et al. TFOS DEWS II tear film report. Clin Exp. 2017;15:134-165.

10

Meibomian Gland - ANATOMY

- Large sebaceous glands
- No direct contact to hair follicles
- Located in the tarsal plates
- Upper and lower eye lids

Modified and colored from Kriegl H. Human microscopic anatomy. Springer Medizin Verlag 1991; (reproduced from Kriegl N & Kriegl E. Ophthalmologie 2009; 108:872-883)

11

Meibomian Gland - ANATOMY

- **Length**
 - Follows the tarsus
- **Number**
 - More in upper lid (30-40)
 - Less in lower lid (20-30)
- **Volume**
 - Higher in upper lid (26μl vs. 13μl)
- Relative functional contribution (upper vs. lower) to the tear film lipid layer is unknown

Modified from Schulte Atlas der Anatomie des Menschen, Urban & Schwarzenberg Verlag 1982; (reproduced from Kriegl N & Kriegl E. Ophthalmologie 2009; 108:872-883)

12

Meibomian Gland – PATHOLOGY

- Obstructive MGD leads to a progressive ductal DILATATION and acinar ATROPHY

Fern Kriegl E & Kriegl N. Meibom-Glanden Teil IV. Funktionelle Interaktionen in der Pathogenese der Dysfunktion (MGD). Ophthalmologie 2009; 108:880-887

13

Prevalence

“MGD is currently thought to be the **leading cause of dry eye.**”

Caroline Blackie
Donald Korb

Blackie, Caroline A., and Donald R. Korb. "MGD: getting to the root cause of dry eye: Review of Optometry 149.6 (2012): 30-37.
Nelson JD, Shimazaki J, Benitez-del-Castillo JM, et al. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1930-7.

14

Prevalence

“Overall, **86%** of these qualified DED patients demonstrated signs of MGD.”
Michael Lemp

Lemp, Michael A., et al. "Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study." *Cornea* 31.5 (2012): 472-478.

15

OBSTRUCTION AND INFLAMMATION

Like Peanut butter and Jelly
Like Travis and Taylor

16

LID EVALUATION

17

MORNING SYMPTOMS: ILS

18

MORNING SYMPTOMS: THINK ILS (NOCTURNAL EXPOSURE)

- And leads to desiccative stress, MGD, blepharitis, exposure keratitis etc.
- It is NOT lagophthalmos
- ILS - is an overnight inadequate lid seal
- Overnight eye seals
- Hypoallergenic
- Oxygen permeable
- Adequate mild adhesive
- Sensitive and regular

19

OBSTRUCTION TREATMENT

20

CYCLOSPORINE

- CEQUA (Sun)
 - HEAD TO HEAD DATA
 - Cross over study-2023
- VEYVYE (Harrow)
 - Cyclosporine 0.1%
 - perfluorobutylpentane vehicle
 - No Ph
 - No water
 - Low molecular weight
 - Fast spreading
 - High O2 content



29

THE NEXT LINE OF TREATMENTS....

- Amniotic Membranes
- Autologous Serum
- Plasma Tears
 - Mahnia Madan, OD
 - Vancouver, BC
- Regenereyes
- Dextenza
- Cenegermin bkbj 0.002%



30

NEW DRUGS

Anterior Segment

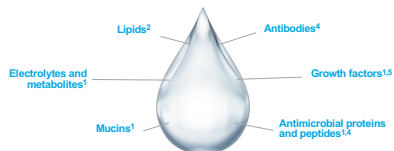
31

TYRVAYA VARENICLINE SOLUTION).03MG NASAL SPRAY

32

BASAL TEAR FILM CONTAINS A COMPLEX MIX OF MORE THAN 2000 MOLECULES^{1,2}

There is no substitute for a patient's own natural tear film³



An imbalance of some of these tear film components leads to loss of tear film homeostasis and may result in dry eye disease.²

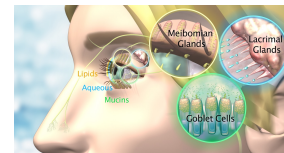
1. Wilson ME, et al. Clin Exp Allergy. 2017;47(12):1402-1412. 2. Lippman ME, et al. J Allergy Clin Immunol. 2014;133(2):289-298. 3. Vignoli de la Torre M, et al. Polymers (Basel). 2018;10(4):425. 4. MacDermott AM. Exp Eye Res. 2013;117:124-131. 5. Rhee SK, et al. Clin Exp Allergy. 2007;37(5):228-239.

33

Parasympathetic Nervous System Controls Tear Film Homeostasis

The trigeminal nerve is **accessible within the nasal cavity**, and is activated by OC-01 (varenicline) by stimulating **cholinergic receptors**.

The trigeminal nerve provides the pathway for **parasympathetic stimulation** of the lacrimal functional unit (LFU) to activate **complete natural tear film**.




34% of basal tear production is due to inhaling air through the nose¹

1. Gupta A, Hege T, and Pfeiffer G. Neuroendocrine regulation of aqueous tear production. Clin Exp Allergy. 2017;47(12):1402-1412.

34

TYRVAYA™: A DIFFERENT PATH TO TREATING DRY EYE DISEASE

- While the exact mechanism of action is unknown, Tyrvaya is believed to:
 - Activate the trigeminal-parasympathetic pathway via the nose¹
 - Increase basal tear film production¹
- The trigeminal-parasympathetic pathway:
 - Plays a role in tear film homeostasis^{2,3}
 - Promotes basal tear production when inhaling air through the nose⁴

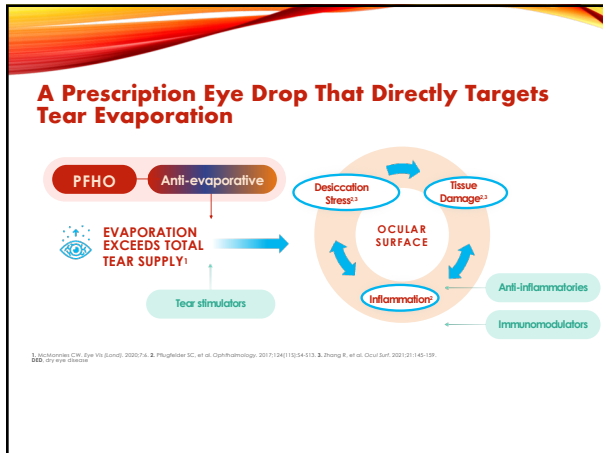


1. Tyrvaya. Prescribing Information. GlaxoSmithKline; 2021. 5. Deschamps C, et al. Ocul Surf. 2019;17(2):26-37. 2. Goldschmidt M, et al. Acta Ophthalmol. 2012;90(1):10-18. 3. Goldschmidt M, et al. Cornea. 2012;31(10):1447-1454. 4. Tyrvaya. Prescribing Information. GlaxoSmithKline; 2021.

35

PFHO

36



37

PFHO DEMONSTRATED RAPID AND SUSTAINED RELIEF

IN 2 LARGE CLINICAL TRIALS WHERE 100% OF PARTICIPANTS HAD CLINICAL SIGNS OF MGD


Improvement in the Signs and Symptoms of DED at Day 57 (primary endpoint) and Day 15 (secondary endpoint)	Excellent Tolerability
<ul style="list-style-type: none"> Total corneal fluorescein staining Eye dryness score (visual analog scale) 	<ul style="list-style-type: none"> No serious ocular AEs Low discontinuation rate due to AEs Low rate of burning or stinging on instillation Only 1 ocular AE with an incidence ≥2% (blurred vision, 2.1%)

1. Toubian J, et al. Ophthalmology. 2023;130(1):114-124. 2. Sheppard D, et al. Am J Ophthalmol. 2023;232:245-274. 3. Data on file. Research & Labs Incorporated. AE, adverse event; DED, dry eye disease; MGD, meibomian gland dysfunction.

38


DEMODEX

that other Thug!



39

DEMODEX



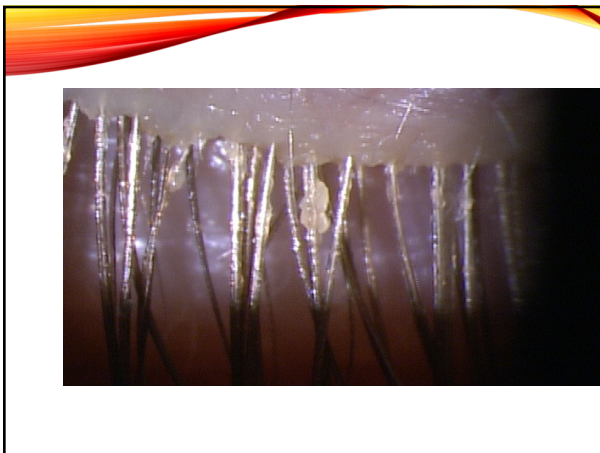
HANDBOOK OF MEDICAL ENTOMOLOGY

Dr. WM. A. RILEY, Professor of Insect Morphology and Parasitology, Cornell University

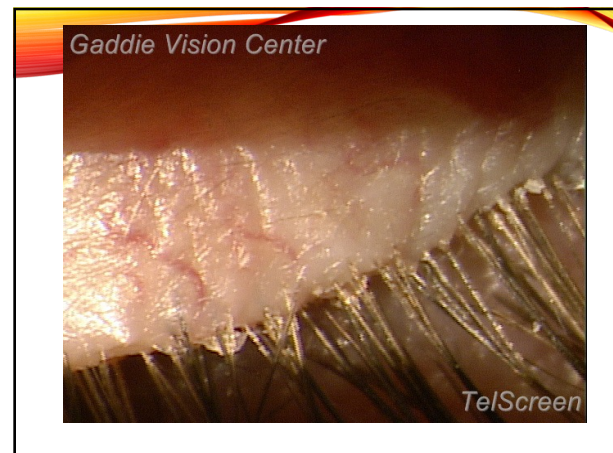
Dr. O. A. JOHANNSEN, Professor of Biology, Cornell University

1915

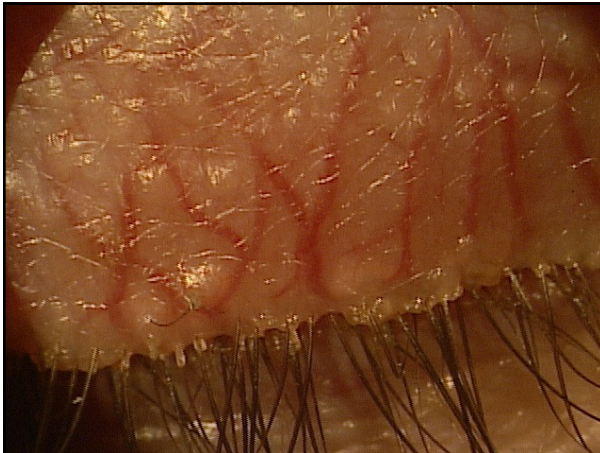
40



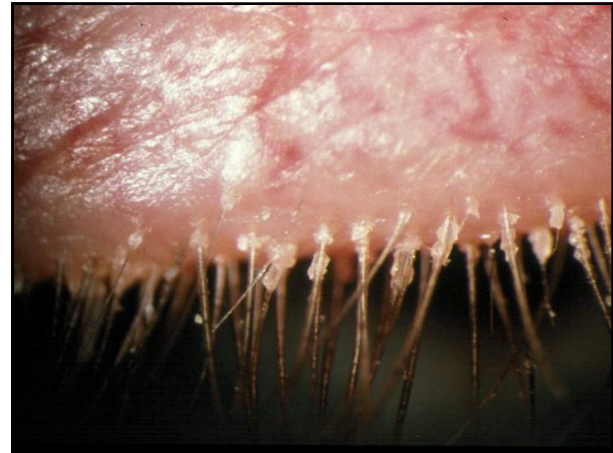
41



42



43



44



45

ROSACEA AND DEMODEX?

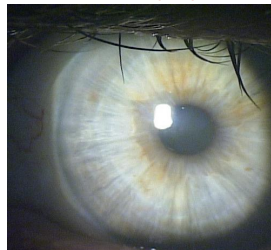
- Rosacea and demodex
 - Meta-analysis of 48 studies
 - 10 different countries
 - 28,527 subjects
 - Rosacea patients 7-8x chance have Demodex

Zhao YE, Wu LP, Peng Y, Cheng H.
Retrospective analysis of the association between Demodex infestation and rosacea. Arch Dermatol 2010;146:896Y902.

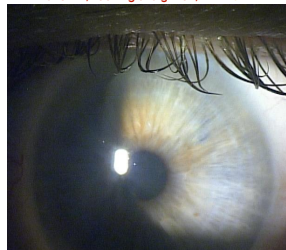
46

Collarettes Can Be Easily Missed on the Upper Lid!

Patient 1, Looking straight on



Patient 1, Looking straight on, with lid up

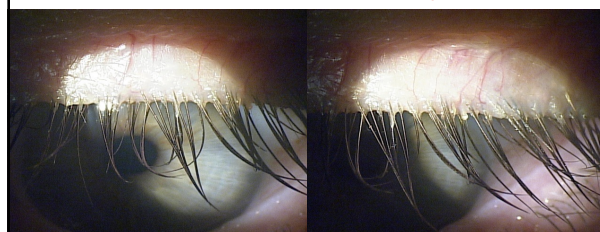


c/o E. Yeu, MD, 1.0 mag

50

Collarettes Can Be Easily Seen on the Upper Lid when Patient Looks DOWN

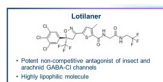
Patient : Diffuse collarettes, misdirected and missing lashes



c/o E. Yeu, MD, 1.0 mag

51

TP-03 IS A NOVEL THERAPEUTIC DESIGNED TO ERADICATE DEMODEX MITES AND TREAT DEMODEX BLEPHARITIS



Product Form	Multi-dose eye drop solution bottle, preserved
Targeted Use	Treatment of Demodex blepharitis
MOA	Paralysis and death of Demodex mites
Diagnosis	Collarettes identified in standard eye examination
Dosing	BID* for 6 weeks
Efficacy Goal	1 st collarette cure, 2 nd mite eradication, 2 nd redness + collarette cure
Safety Goal	Well-tolerated safety profile

TP-03 Product profile based on Saturn-1 Trial Design

52

EXTENSIVE CLINICAL TRIAL PROGRAM FOR TP-03

Study	# of Subjects	Effectiveness Endpoints	Study Highlights	Status
PoC: Mercury	80 mites	Ex-vivo mite death count	Ex-vivo mite testing	Completed ✓
P2a: Mars	15 - Single arm	Collarette grade Mite density	28-day BID dosing	Completed ✓
P2a: Jupiter	60 - 1:1	1 st - Collarette grade 2 nd - Mite density	28-day BID dosing; RCT	Completed ✓
P2a: Io	18	1 st - Collarette cure 2 nd - Mite eradication	Crossover of Jupiter control arm subjects; 42-day BID dosing	Completed ✓
P2b: Europa	54 - 1:1	1 st - Collarette cure 2 nd - Mite eradication 2 nd - Redness composite	42-day BID dosing; RCT	Completed ✓
P2b/3: Saturn-1	421 - 1:1	1 st - Collarette cure 2 nd - Mite eradication 2 nd - Redness composite	Pivotal registration study 42-day BID dosing; RCT	Completed
P3: Saturn-2	418 - 1:1 <small>Some formulation of TP-03 at 1:1 expected in the Saturn-2 study</small>	1 st - Collarette cure 2 nd - Mite eradication 2 nd - Redness composite	Pivotal registration study 42-day BID dosing; RCT	Completed

Two Pivotal Trials

53

LOTEPRADNOL ETAOBANTE
OPHTHALMIC SUSPENSION) 0.25%

INDICATED FOR THE SHORT TERM (UP TO 2 WEEKS) TREATMENT THE SIGNS AND SYMPTOMS OF DRY EYE DISEASE

Alcon Pharmaceuticals

62

THE GROWING PREVALENCE AND DEMOGRAPHICS OF DRY EYE DISEASE (DED)

Nearly **38** million US adults have symptoms consistent with dry eye disease²⁻⁴

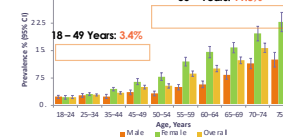
~**17.2** million diagnosed DED patients in the US⁴

Aging is one of most common risk factors. Other common risk factors include female gender and post-menopausal estrogen therapy⁵

The burden of DED is predicted to escalate in the future, likely because of an aging population and an increasing dependence on multiscreen technologies^{1,5,6}

From 2005-2012 prevalence has increased by⁵

0.5% among 18 to 39-year old population
1.44% among 40 to 49-year old population
4.23% among 50-year old and older population



References: 1. Sigurdson F, Agha R, Bhatia VY, et al. Ocul Surf. 2017;15:336-345. 2. Ruben AJ, et al. Am J Ophthalmol. 2014;157:799-804. 3. Rouds L, et al. J. 2010. Current Med. 2011. 4. Dainoff R, et al. J. 2011. 5. Dainoff R, et al. J. 2011. 6. Dainoff R, et al. J. 2011.

63

EPISODIC FLARE IS A COMMON FEATURE OF CHRONIC INFLAMMATORY DISEASES SUCH AS DRY EYE

Many chronic inflammatory and autoimmune diseases have episodic exacerbations of signs and symptoms versus consistent continuous disease, often called "flares"¹

- Asthma
- Uveitis
- Sjögren's syndrome
- Rheumatoid arthritis
- Lupus erythematosus

Dry eye is a chronic immune disease with periods of dysregulation causing homeostatic imbalance, leading to ocular surface stress²

- Contains its own local lymphoid tissues
- Has a diverse microbiome whose composition may be regulated
- by the antimicrobial and immunomodulatory factors in tears
- Ocular surface inflammation plays a key role in all types of dry eye

References: 1. Rasmussen BE et al. *Clin Immunol*. 2017;164:329-333. doi:10.1016/j.clim.2016.11.005. 2. Patel M et al. *Ocul Immunol Inflamm*. 2014;14(1):33-47. doi:10.1080/09273743.2014.944441

64

MOST PATIENTS WITH DED SUFFER EPISODIC EXACERBATIONS, DRY EYE FLARES

Example of a Typical Journey for a Patient With Dry Eye

- Episodic increases in symptoms and signs, or **Dry Eye Flares**, are rapid-onset, inflammation-driven responses to a variety of triggers that typically cannot be adequately managed with a patient's ongoing maintenance therapy, such as artificial tears and chronic therapies¹⁻⁴
- Triggers may include seasonal allergies, A/C use, digital screen time, air travel, contact lens wear, smoking, diet medications, and cataract and refractive surgery⁵⁻⁷

References: 1. Rasmussen BE et al. *Ocul Immunol Inflamm*. 2017;16(1):40-51. 2. Rasmussen BE et al. *Ocul Immunol Inflamm*. 2018;16(1):40-51. 3. Rasmussen BE et al. *The Scientific World Journal*. 2013;2013:1-5. 4. Rasmussen BE et al. *Clin Immunol*. 2017;164:329-333. 5. Wabner PE et al. *Clin Exp Allergy*. 2010;40(1):67-72. 6. Wabner PE et al. *Clin Exp Allergy*. 2010;40(1):67-72. 7. Toubi M et al. *Investig Ophthalmol Vis Sci*. 2013;54(13):3073-3079.

65

NEARLY 80% OF PATIENTS WITH DRY EYE SUFFER DRY EYE FLARES

~80% OF PATIENTS WITH DRY EYE SUFFER FLARES^{1,3*}

45% OF PATIENTS WITH DRY EYE REPORT HAVING PRIMARILY FLARES INSTEAD OF CONTINUOUS SYMPTOMS^{1*}

*Data based on:
Study of Dry Eye Symptoms Conducted by Multi-Sponsor Surveys, Inc. (referred to as "Study")
2016 Study Period: 1/1/2016-12/31/2016
2016 Study Period: 1/1/2016-12/31/2016

References: 1. Rasmussen BE et al. Presented at: AAO 2019, October 12-16, 2019, San Francisco, CA. 2. Rasmussen BE et al. Presented at: AAO 2019, October 22-27, 2019, Orlando, FL. 3. Study of Dry Eye Symptoms. Conducted by Multi-Sponsor Surveys, Inc.

66

THE DRY EYE DISEASE TREATMENT LANDSCAPE: A PROSPECTIVE NEED FOR A PARADIGM SHIFT IN MANAGEMENT

Hackneyed Mindset

Dry Eye is a Chronic, Progressive Disease that Needs Chronic Rx Tx; for Mild Patients Artificial Tears are Good Enough

Nevegiu Mindset

Majority of Dry Eye Patients Suffer Dry Eye Flares vs. Chronic Continuous Symptoms and Need a Short-Term Rx Treatment

~17.2M U.S. patients diagnosed with Dry Eye disease and **75%** of Dry Eye patients have **never tried prescription therapy**¹

80% of patients discontinue their chronic Rx medication by 4 months²

~80% of patients with Dry Eye suffer from Dry Eye Flares^{3,4}

References: 1. 2019 Dry Eye Products Market Report. Market Scope. 2. Dry Eye Surveys 2020 Multi-Sponsor Survey. 3. Rasmussen BE et al. Presented at: AAO 2019, October 12-16, 2019, San Francisco, CA. 4. Rasmussen BE et al. Presented at: AAO 2019, October 22-27, 2019, Orlando, FL. 5. Wabner PE et al. *Clin Exp Allergy*. 2010;40(1):67-72.

67

POWERED BY AMPLIFY® TECHNOLOGY

Mucus Is a Barrier for Topical Ophthalmic Drug Delivery¹

Human corneal mucus. Scale bar represents 500nm.

Mucus on the tear film surface of human corneal epithelium.

Mucus on the tear film forms a barrier to particulate matter (e.g., allergens, pathogens, etc.) by trapping them and facilitating their removal from the ocular surface through blinking.

Drug particles in traditional suspensions are also trapped with mucus and are rapidly removed.

AMPLIFY® Utilizes Mucus-Penetrating Particles (MPP) With 2 Proprietary Attributes¹⁻³

1. Selectively sized nanoparticles to allow for penetration into mucus pores. (Drug particles less than 300nm to penetrate into the mucus pores)^{1,4}

2. Mucus-penetrating surface coating to prevent adherence to mucus

References: 1. Pappas A. *J Ocul Pharmacol Ther*. 2020; 34(2):344-375. 2. Schepel A. *Optophthalmol Ther*. 2014;3(1-2):43-72. 3. Data on file. Kala Pharmaceuticals, Wellesley, MA. 4. Ensign LM, Schneider C, Lee JS, et al. *Adv Mat*. 2015;27(35):5887-5894.

68

TEPRTUMUMAB TRBW

Horizon

69

Temprotumumab trbw is the first and only FDA-approved Thyroid Eye Disease (TED) treatment

80% of Graves' patients have ocular involvement

15% develop severe visual impairment

70

THYROID EYE DISEASE VS GRAVES' DISEASE

	THYROID EYE DISEASE	GRAVES' DISEASE
Area of body affected	Front and back of the eyes	Thyroid (a gland at the base of your neck in front of your windpipe)
What's going on inside the body	Muscle and fat tissue behind the eye become inflamed (red and swollen)	The thyroid becomes overactive, also known as hyperthyroidism
Common symptoms	<ul style="list-style-type: none"> *Dry, gritty eyes *Sensitivity to light *Eyelid redness and swelling *Itchy eyes *Eye pain, including pain around and behind the eye *Watery, tearful eyes *Bulging eyes *Other vision changes 	<ul style="list-style-type: none"> *Fast heartbeat *Irritability *Anxiety *Tiredness *Too much sweating, sensitivity to temperature

71

TED

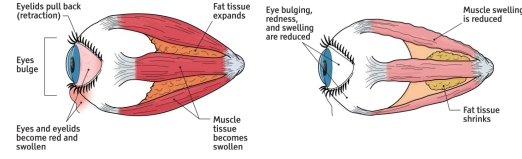
- Clinical Symptoms of TED
 - Dry eye
 - Foreign body sensation
 - Epiphora
 - Photophobia
 - Blurry vision
- Classic symptoms
 - Eyelid retraction (Dalrymple sign)
 - Eyelid lag (von Graefe's sign)



72

TEMPROTUMUMAB TRBW

- During the progressing (or "active") phase of TED, a special switch called a receptor gets turned on
- Once on, the receptor makes the muscle and fat tissue become swollen, causing symptoms like eye bulging, double vision, pain, and redness
- TEPEZZA is the only medicine that blocks this receptor to treat TED at its source
- By blocking the receptor, TEPEZZA reduces muscle and fat tissue swelling and improves TED symptoms



73

TEMPROTUMUMAB TRBW

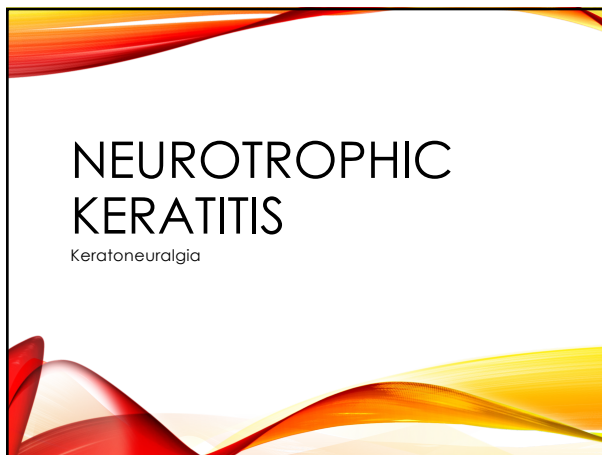
- Given as 1 (10mg/kg) infusion and then (20mg/kg) every 3 weeks, for a total of 8 infusions.
- TEPEZZA treatment should last about 5 months.
- Administered in an infusion chair. The first 2 infusions of TEPEZZA will take about 90 minutes each to complete. The next 6 infusions may be as short as 60 minutes.

74

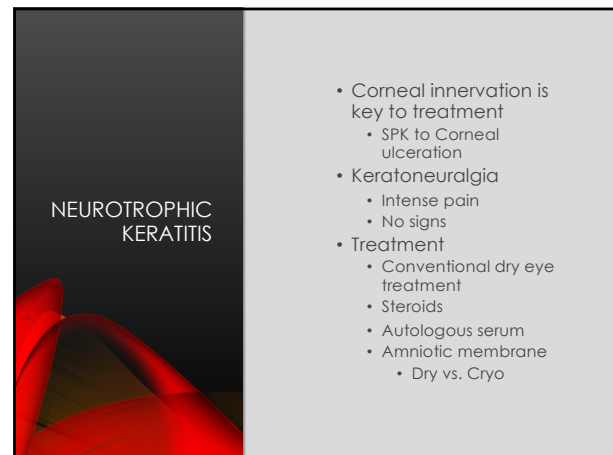
"LERHNER AND ROWE" TEPEZZA HEARING LOSS LAWSUITS

- In particular, one 2021 study conducted at Stanford University showed that 46% of the patients studied developed some level of hearing loss following Tepezza infusion, and the hearing loss failed to improve after stopping Tepezza use in at least 15% of those patients.
- The first Tepezza hearing loss lawsuit was filed in August 2022. The complaint alleges that despite these well-documented risks of Tepezza, its manufacturers failed to change the warning label to reflect these severe risks.
 - Injuries or Side Effects
 - Permanent hearing loss
 - Partial hearing loss
 - Tinnitus (ringing in the ears)
 - Sensorineural hearing loss

75



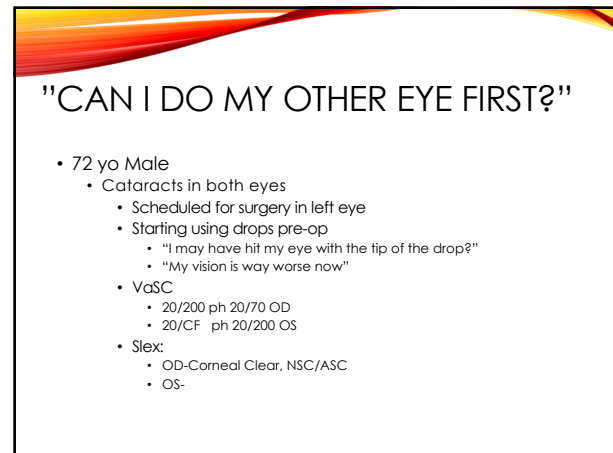
76



77



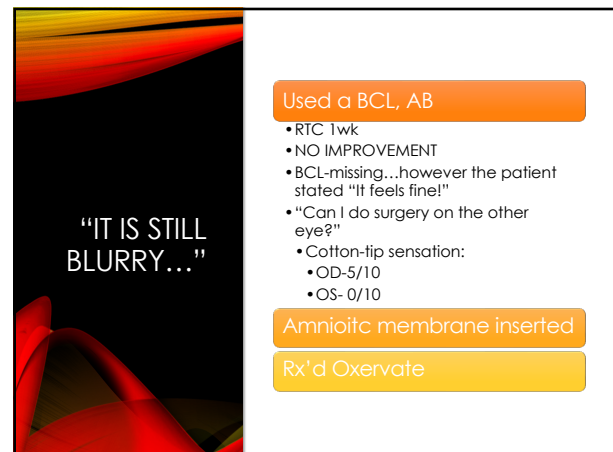
78



79



80



81

ENDOGENOUS NGF MAINTAINS CORNEAL INTEGRITY BY THREE MECHANISMS

Endogenous Nerve growth factor acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e., p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.¹

SHOWN IN PRECLINICAL MODELS²

- CORNEAL INNERVATION**
NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves.^{2,3}
- TEAR SECRETION**
NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion.^{4,5}
- CELL PROLIFERATION AND DIFFERENTIATION**
NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells.¹

1. Monteggia L, Maffei G, Giallari C, Nelli M, Scaramella G. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. J Cell Physiol. 2012 Apr;196(4):1212-24. 2. Maffei G, Monteggia L, Maffei G, et al. Nerve growth factor in the cornea: a review. J Cell Physiol. 2012 Apr;196(4):1212-24. 3. Maffei G, Monteggia L, Maffei G, et al. Nerve growth factor in the cornea: a review. J Cell Physiol. 2012 Apr;196(4):1212-24. 4. Maffei G, Monteggia L, Maffei G, et al. Nerve growth factor in the cornea: a review. J Cell Physiol. 2012 Apr;196(4):1212-24. 5. Maffei G, Monteggia L, Maffei G, et al. Nerve growth factor in the cornea: a review. J Cell Physiol. 2012 Apr;196(4):1212-24.

82

Active ingredient structurally identical to human nerve growth factor produced in ocular tissues

- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons¹
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s¹
- Cenegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein²

1. Gundersen A, Rasmussen P, Bævre S, et al. Topical treatment with nerve growth factor for corneal neurotrophic keratitis. N Engl J Med. 1998;339(17):1245-51. 2. Vastak R, New Drug, Trade Name, Cerebrolin Neurotrophic Keratitis. JAMA. 2000;283(1):1245-51.

83

cenegermin-bkbj ophthalmic solution 0.002% Weekly Device Kit

- is supplied in a weekly carton containing 7 multiple-dose vials*
- A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

- 7 vial adapters
- 42 pipettes
- 42 sterile disinfectant wipes
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra wipes are included as spares

*Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration

84

cenegermin-bkbj ophthalmic solution 0.002% Dosing and Administration

Instill 1 drop of (cenegermin-bkbj) ophthalmic solution 0.002% in the affected eye(s)

2 Every 2 hours

6 Apply 6 times daily

8 Continue for 8 weeks

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) (30 package insert), Boston, MA: Dompé U.S. Inc.; 2018.

85

Study Conclusions

After 8 weeks of treatment, 6 times daily

50 clinical trial sites in Europe and the U.S.

Study NGF0212 (REPARO) (N=52 per group)

European patients with NK in one eye
NCT01756456

72.0% completely healed

Vehicle response rate: 33.3%

Study NGF0214 (N=24 per group)

U.S. patients with NK in one or both eyes
NCT02227147

65.2% completely healed

Vehicle response rate: 16.7%

80% Of patients who healed after one 8-week course of treatment... Remained healed for one year*

*Based on REPARO study with longer follow-up

Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 14% of patients. Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

1. Borek L, Lortieva A, Borek P, et al. Phase 3 Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125(12):3301-3310. 2. Borek L, Lortieva A, Borek P, et al. Phase 3 Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125(12):3301-3310. 3. Borek L, Lortieva A, Borek P, et al. Phase 3 Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125(12):3301-3310.

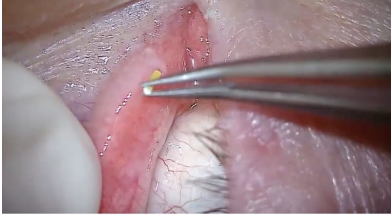
86

(DEXAMETHASONE OPHTHALMIC INSERT) 0.4MG

- NEW indication:**
 - itching associated with allergic conjunctivitis
- Is the first, FDA-approved, physician-administered intracanalicular insert capable of delivering a preservative-free drug for the treatment of ocular itching associated with allergic conjunctivitis with a single administration for up to 30 days
- Dextenza originally received FDA approval in November 2018
 - The treatment of ocular pain following ophthalmic surgery
- Dextenza originally received FDA expansion approval June 2019
 - The treatment of ocular inflammation following ophthalmic surgery.

87

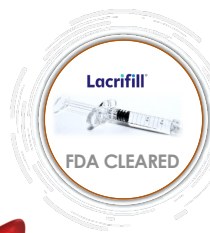
DEXENZA (DEXAMETHASONE OPTHALMIC INSERT) 0.4MG



88

CANALICULAR GEL

89



INTRODUCING LACRIFILL® CANALICULAR GEL

Dry eye treatment,
reinvented.

- 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)



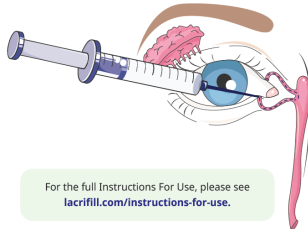
90

91

SIMPLE & EFFICIENT FOR YOUR PRACTICE

Instructions for Use

- 1 LACRIFILL 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 LACRIFILL 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.



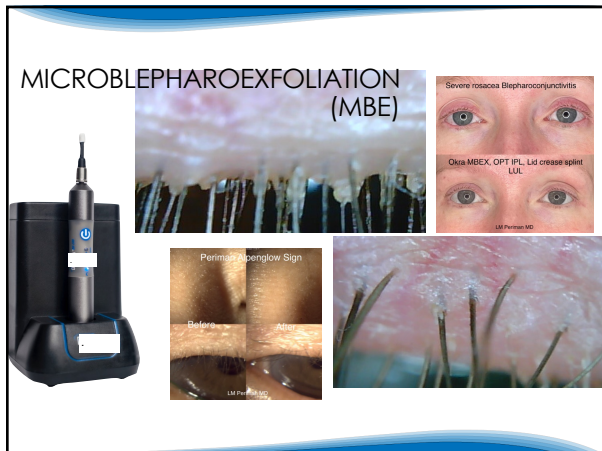
For the full Instructions For Use, please see
lacrifill.com/instructions-for-use.

92

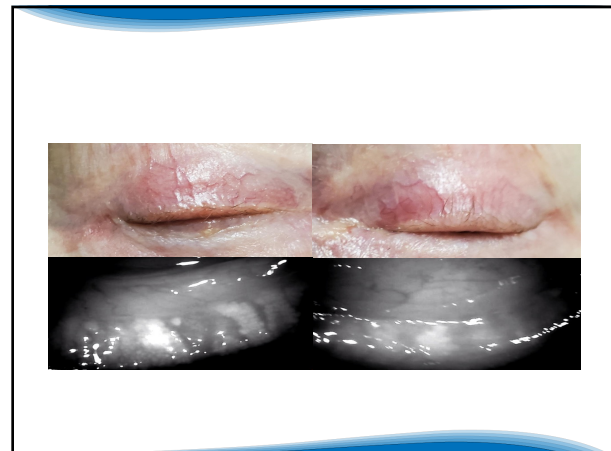
EVEN MORE, NEWER STUFF

Anterior Segment

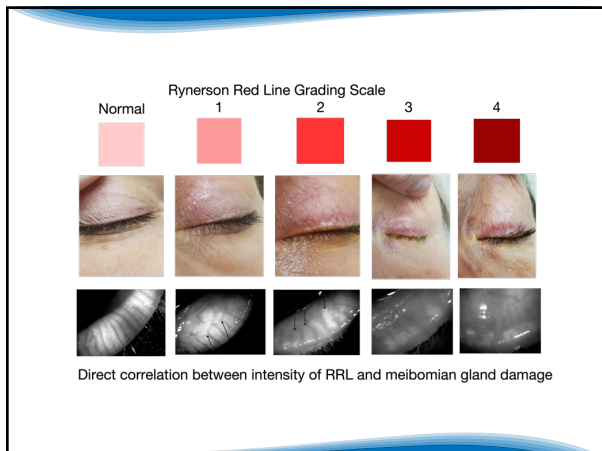
93



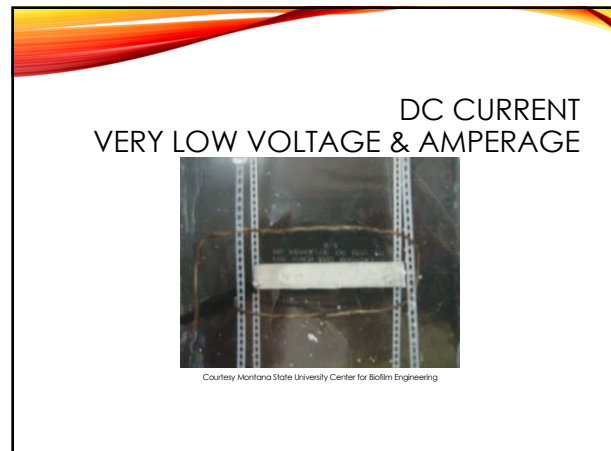
94



96



97



98



99



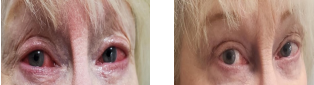
100

Study Results

PATIENT #0719

- 156 patients treated
- All 312 eyes received the protocol
- Duration of study 10 months
- TBUT increased by an average 6 seconds per eye
- SPEED Score dropped from 17 to 6
- Zero complications or adverse effects

MARCH 1, 2023, RED EYES DECEMBER 12, 2023




101

SDP-4: SILK PROTEIN DERIVED

Differentiated Biologic Product with Unique Properties:

- Highly soluble protein in aqueous formulation
- Broad acting anti-inflammatory activity
- Prolonged wetting without increased viscosity
- Absence of toxicity & immunogenicity
- Transparent, preservative free & single unit dose format
- Highly stable at room temperature

Silkworm Cocoon → **Drug**



102

SILK PROTEIN IS "INSECT CONCRETE"

Creates external structure for most arthropods

- Evolved over 400M years
- Produced by hundreds of thousands of species

Commercial silk produced by one species

- Domesticated by humans ~10,000 years ago
- >600,000 tons produced annually



103

FIBROIN IS HYDROLYZED INTO SILK-DERIVED PROTEIN (SDP)

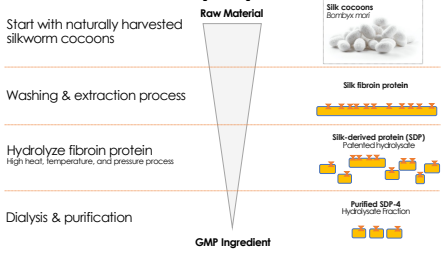
Start with naturally harvested silkworm cocoons

Washing & extraction process

Hydrolyze fibroin protein
High heat, temperature, and pressure process

Dialysis & purification

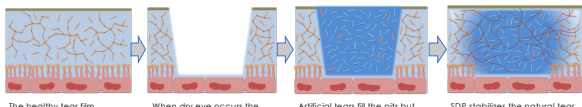
Raw Material → **Silk cocoons Bombyx mori** → **Silk fibroin protein** → **Silk-derived protein (SDP) Indirect hydrolysis** → **Purified SDP-4 Hydrolysis fraction** → **GMP Ingredient**



104

SDP-4 Enhances Tear Coating & Stability

Healthy Tear Film **Dry Eye "Pitting"** **Artificial Tear** **Plus SDP**



The healthy tear film maintains a protective and lubricating coating over the ocular surface.

When dry eye occurs the tear film is compromised leaving dried areas on the waxy ocular surface.

Artificial tears fill the pits but do not provide an interface between the natural tear film components.

SDP stabilizes the natural tear film and creates long lasting, anti-inflammatory protection on the ocular surface.


105

SDP Enhances Formulation Wetting & Coating

Effective wetting & coating agent

Increases surface coating adhesion

Saline **Saline + 1% SDP** **Saline** **+ 1% SDP**

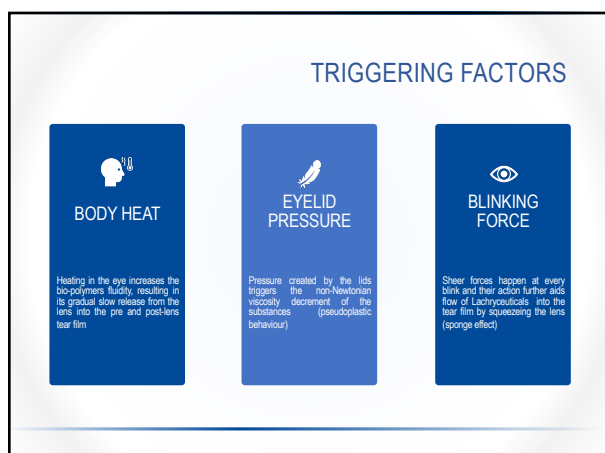


Paraffin Wax Surface

90° to base axis

Wax Surface

106



113

TEAR FILM SUBSTITUTES

- Hyaluronic Acid - HA
- Biological polymer
- Excellent water binding
- Non-Newtonian rheologic behaviour
- Bio-adhesive properties
- Reduced Rose Bengal staining
- Increased TBUT

Tamarind Seed Polysaccharide - TSP

- Chemical structure similar to MUC1 mucins
- Non-Newtonian rheologic behaviour
- Mucoadhesivity better than hyaluronic acid
- Promotes epithelium regrowth




114




115

CONTROLLED RELEASE OF SUBSTANCES




NEW LENS

Safranine tagged HA is evenly distributed in the entire lens during the manufacturing process



IN USE

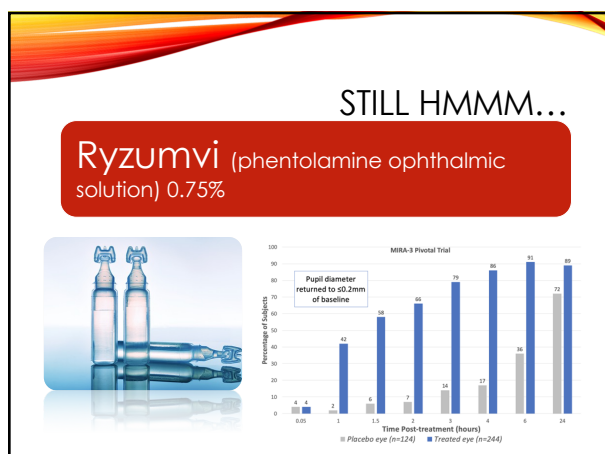
The delivery front is visible in the anterior curve of the lens



USED LENS

After use (16h) the available quantity of substances is almost completely released

116



117

MORE COOL STUFF FOR ANTERIOR SEG ...COMING SOON

118

FDA INVESTIGATIVE DRUGS

119

THE MOST COMMON COMPLICATION

Meibomian Gland Dysfunction

120

HYPERKERATINIZATION IN MG

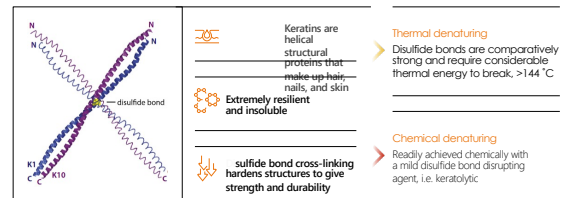
- Hyperkeratinization directly or indirectly leads to physical alterations of both the gland ductal epithelium and secreted meibum resulting in:¹⁻⁵
 - Decreased meibum
 - Gland atrophy
 - Tear film instability
 - Gland atrophy
 - Cystic dilation
 - Ductal plugging
- Hyperkeratinization is a primary cause of obstructive MGD and leads to degenerative gland dilatation and atrophy¹

¹Knapik E, et al. Invest Ophthalmol Vis Sci. 2011; Mar 30;52(6):1158-76. ²Touko GK, et al. Ocul Surf. 2002; Jul;1(2):107-26. ³Goulgeall V, et al. Am J Ophthalmol. 1982;94:350-367. ⁴Born AJ, et al. Ocul Surf. 2004;2:149-165. ⁵Knapik E, Acta Ophthalmol. 2009;87:2232

121

AZR-MD-001

- Targeting Aberrant Keratin



¹Burick, et al. Journal of Investigative Dermatology 2011, Volume 121, 140-150a. ²Shetty et al. Macromol. Biosci. 2009, 9, 805-812

122

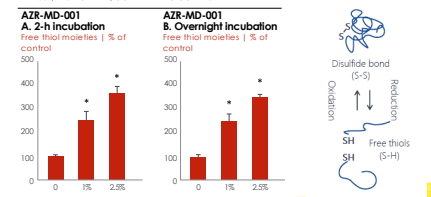
AZR-MD-001 (SELENIUM SULFIDE) MOA

- Keratostatic
 - Slows down rate of keratinocyte and keratin production
- Keratolytic
 - Softens keratin plug
 - Breaks down disulphide bonds
- Lipogenesis
 - Stimulates lipid production

123

Keratolytic Effect AZR-MD-001 has keratin softening effect

IN A STUDY EVALUATING THE KERATOLYTIC EFFECT OF AZR-MD-001 IN A HUMAN EX VIVO SKIN MODEL, A STATISTICALLY SIGNIFICANT 2.5- AND 3.5-FOLD INCREASE IN FREE THIOLS, INDICATIVE OF A PROFOUND KERATOLYTIC EFFECT, WAS SEEN AT 1% AND 2.5% AZR-MD-001, RESPECTIVELY, COMPARED TO CONTROL. KERATOLYTIC EFFECT OF AZR-MD-001 IN A HUMAN EX VIVO SKIN MODEL, A STATISTICALLY SIGNIFICANT 2.5- AND 3.5-FOLD INCREASE IN FREE THIOLS, INDICATIVE OF A PROFOUND KERATOLYTIC EFFECT, WAS SEEN AT 1% AND 2.5% AZR-MD-001, RESPECTIVELY, COMPARED TO CONTROL.



124

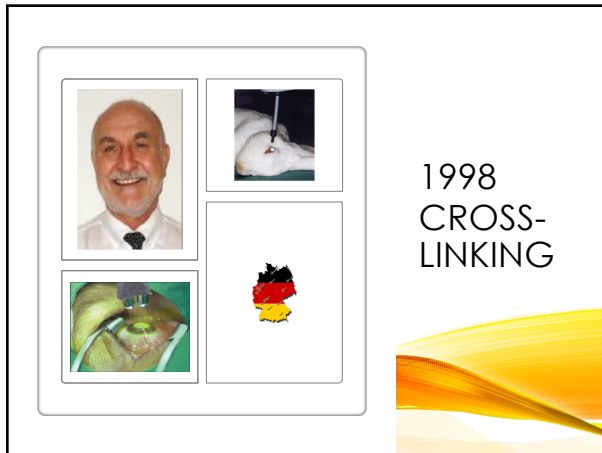
ANTERIOR SEGMENT

Corneal Dystrophy
Diagnosis

125

CXL

126



1998
CROSS-
LINKING

127

Drop it like it's hot

PRESBYOPIA

128

PRESBYOPIA NO ESCAPING..

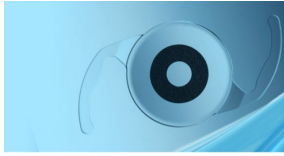
- Projected 2 Billion people world wide
- Starts in 4-5th decade
- Different theories of causation
 - Ciliary contraction is weakened
 - Lens builds disulfide bonds and keratinizes
- Treatment
 - Glasses
 - Contact lenses
 - Monovision
 - Multi-focal

129

NEW REFRACTIVE CATARACT LENS...

130

SMALL APERTURE IOL



- B+L
 - Monocular
 - Hydrophobic acrylic
 - UV blocking
 - Polyvinylidene fluoride
 - Carbon nano-particles
 - 3.23 mm total diameter
 - 1.36 mm aperture

135

RX SIGHT LIGHT ADJUSTABLE LENS

136

POST-OP IS THE NEW PRE-OP!

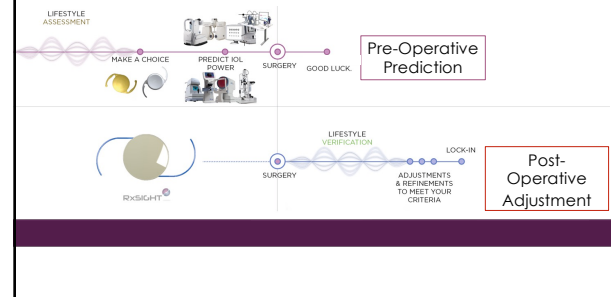
The RxLAL is the world's first adjustable intraocular lens that allows office-based optimization of vision after lens implantation and healing

- Delivers world's best clinical outcomes for cataract patients
- Overcomes limitations of both pre-operative and intra-operative prediction processes
- Premium channel driver
- Private pay

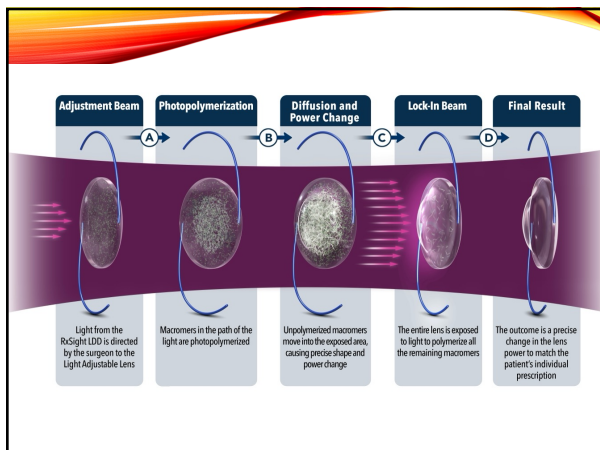


137

A BETTER WAY TO DELIVER PREMIUM CATARACT SURGERY

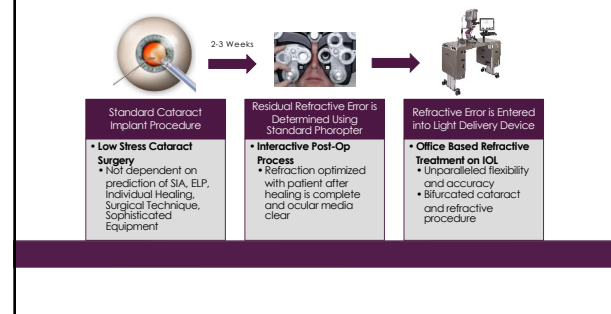


138

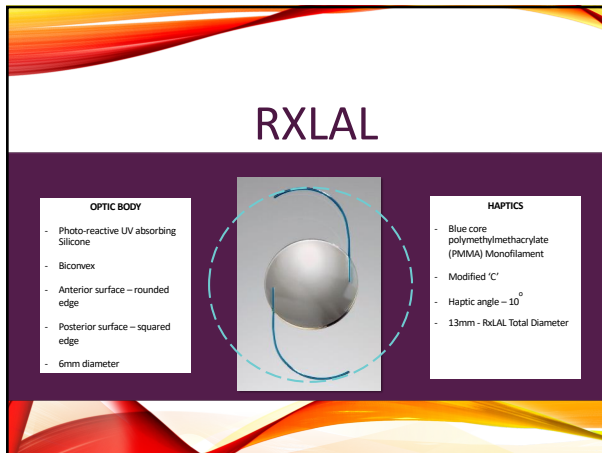


139

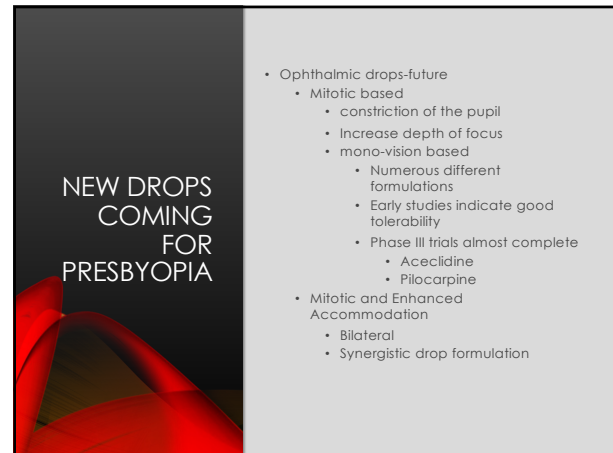
How It Works



140



141



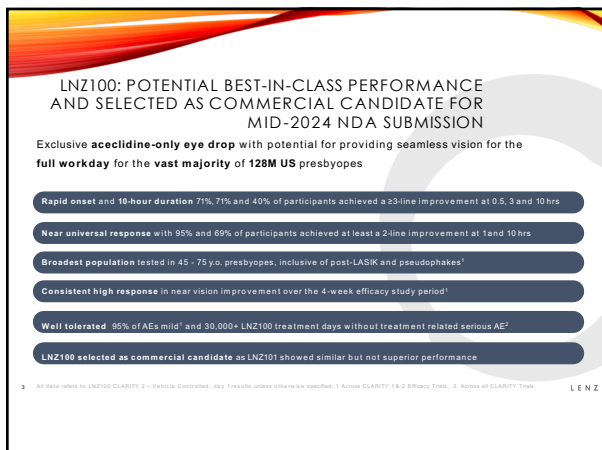
142



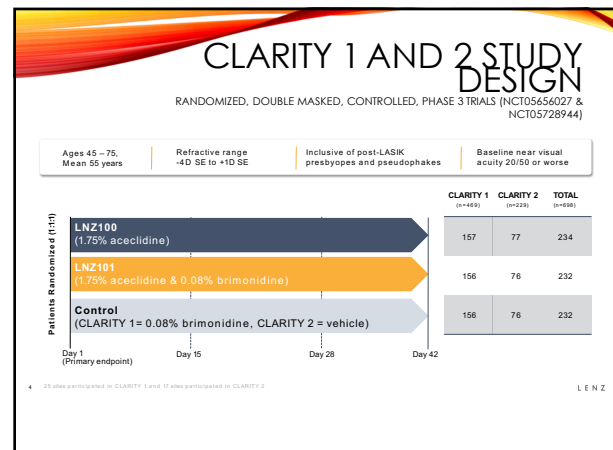
143



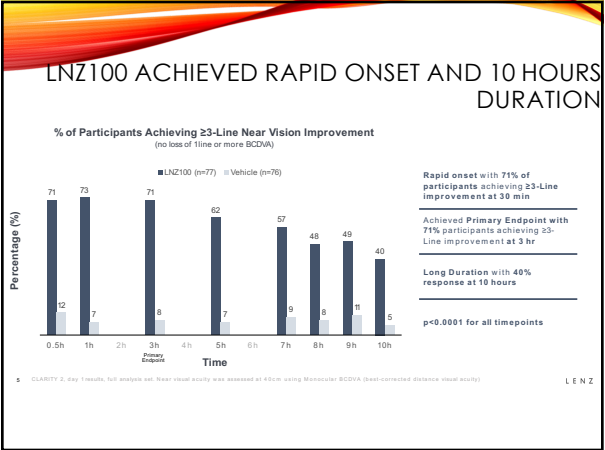
144



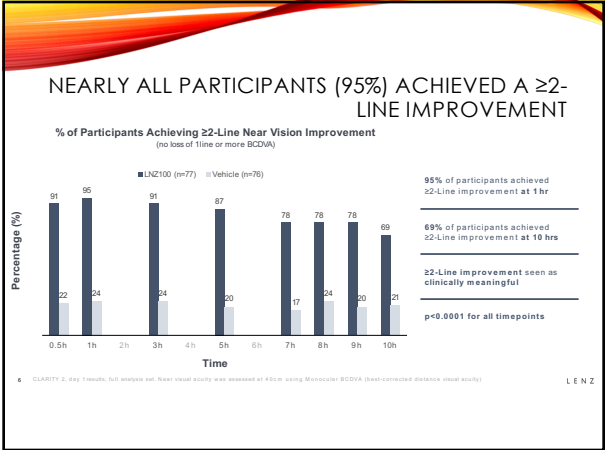
145



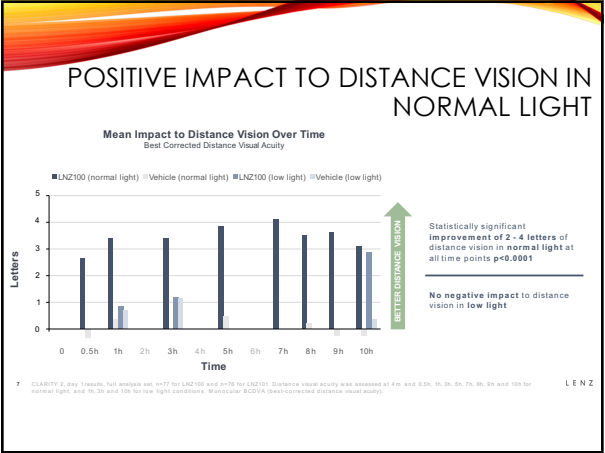
146



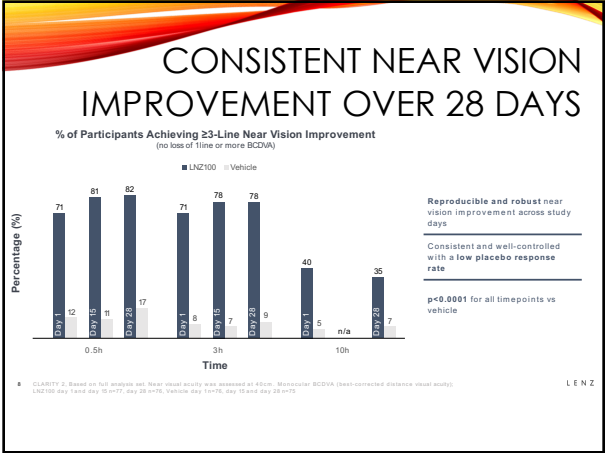
147



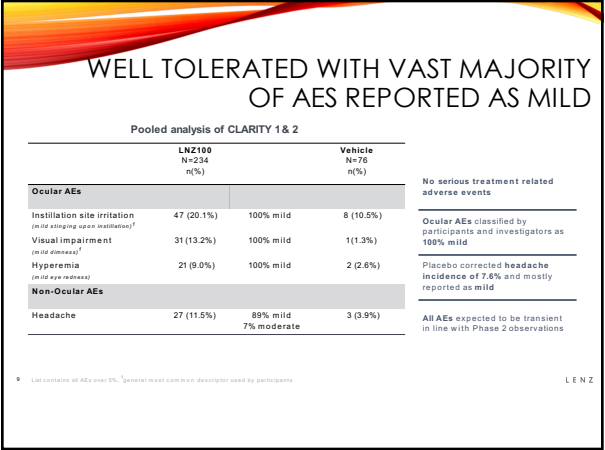
148



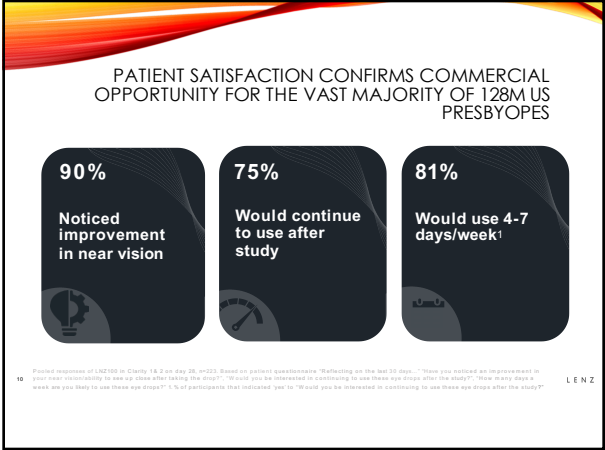
149



150

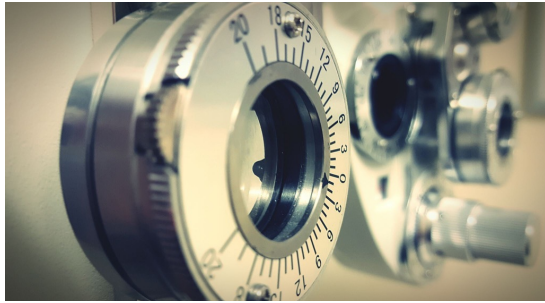


151



152

REFRACTIVE SURGERY



153

RELEX SMILE

APPROVED 2016

154

REFRACTIVE LENTICULAR EXTRACTION (RELEX) SMALL-INCISION LENTICULE EXTRACTION (SMILE)

Carl Zeiss Meditec

Small lenticule

2mm-4mm corneal incisions

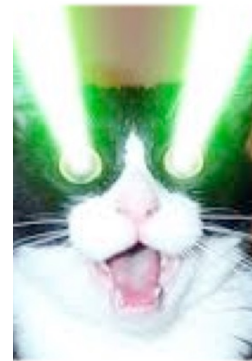
Manually removal of the lenticule

- Myopia up to -11 D
- Astigmatism up to about -5 D

155

ADVANTAGES OF RELEX SMILE

- No stromal hydration
- No laser fluence projection
- No reflection losses
- No environmental controls
- Integrity of cornea
- Less nerve damage
- ONLY VARIABLE IS THE ACCURACY OF THE LASER

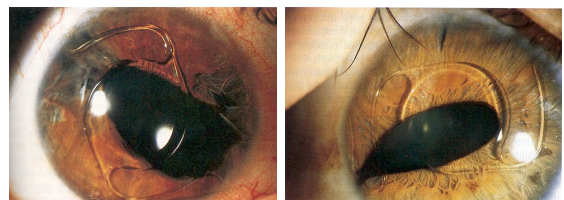


156

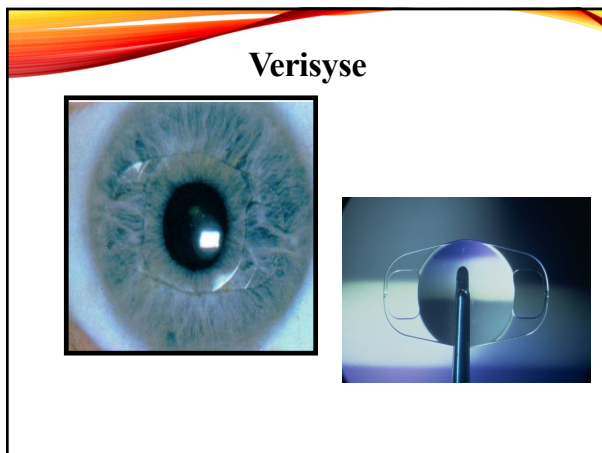
PHAKIC IOL'S

157

NUVITA™



158



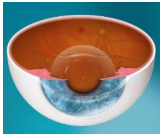
159



160

THE ADVANTAGES OF PHAKIC VISIAN ICL INCLUDE:

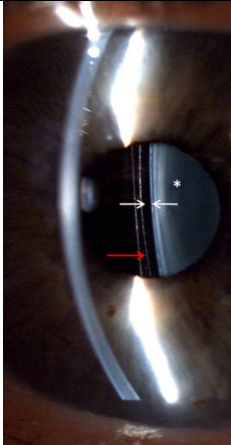
- Sharp, clear vision¹
- Excellent night vision²
- Does not cause dry eye syndrome³
- Quick procedure and recovery
- No removal of corneal tissue
- Removable by the surgeon
- Protection from UV rays



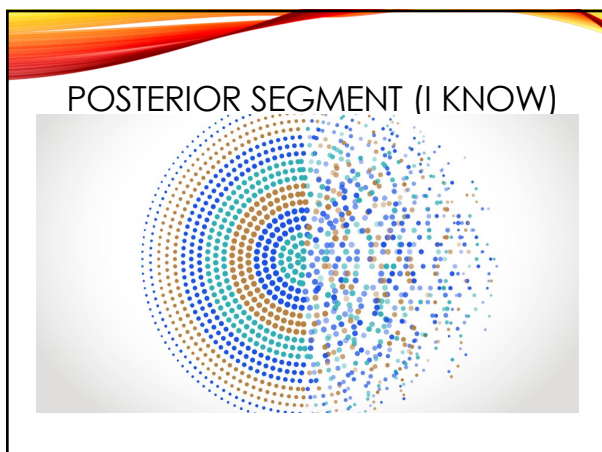
1. Igarashi A, Kompa K, Shiozu K, Komatsu M. Visual Performance after implantable Collamer lens implantation and wavefront-guided laser in the keratoconus for high myopia. Am J Ophthalmol. 2009.
2. Maitre-Puig E, Lopez-Algorta A, Lopez-de la Rosa A, et al. Effect of the EVO+ Vision Phakic Implantable Collamer Lens on Visual Performance and Quality of Vision and Life. Am J Ophthalmol. 2017;226:117-125.
3. Cornett S, Ruiz S, Fawcett A. Matched population comparison of visual outcome and patient satisfaction between 3 modalities for the correction of low to moderate myopic astigmatism. Clin Ophthalmol. 2017 Jul 3;11:1225-1243.

163

- Designed for the correction of moderate to high nearsightedness.
- Vision ICL and Vision TICL surgery is intended to safely and effectively correct nearsightedness
 - From -3.0 D to -15.0 D, the reduction in nearsightedness up to -20.0 D
 - Astigmatism from 1.0 D to 4.0 D.



167



168

Geographic Atrophy Is an Advanced Form of Age-Related Macular Degeneration

<ul style="list-style-type: none"> • Globally, AMD is among the leading causes of blindness in adults aged ≥50 years¹ • GA is a progressive, advanced form of dry AMD characterized by loss of the RPE, photoreceptors, and choriocapillaris leading to significant, irreversible loss of visual function² 	<p>GA affects more than 5 million people worldwide³</p> <p>4x After age 50, prevalence of GA approximately quadruples every 10 years⁴</p>	<p>~973,000 people in the United States have GA in ≥1 eye⁴</p> <p>GA accounts for 20% of all legal blindness attributed to AMD^{5,7}</p>
---	--	---

AMD, age-related macular degeneration; GA, geographic atrophy; RPE, retinal pigment epithelium.
1. GBD 2019 Blindness and Vision Impairment Collaborators. Vision Loss Expert Group of the Global Burden of Disease Study. Lancet Glob Health. 2021;9(2):e144-e160.
2. Fleckenstein et al. Ophthalmology. 2018;125(3):389-390. 3. Wang et al. Lancet Glob Health. 2014;2(2):e116-e118. 4. Friedman et al. Arch Ophthalmol. 2004;122(4):564-572.
5. Ruitink et al. Ophthalmology. 2012;119(7):1480-1489. 6. Barakat et al. Ophthalmol. 2011;118(7):1481-1489. 7. Fawcett et al. Arch Ophthalmol. 1994;112(10):1560-1562.

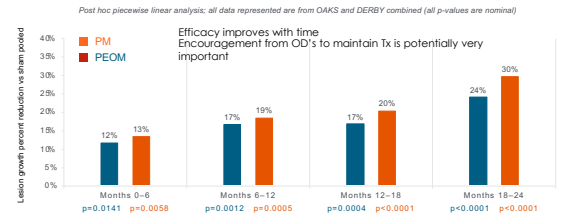
169

PEGCETACOPLAN FORM APELLIS PHARMACEUTICAL DERBY AND OAKS

- Complement C3 inhibitor
- 19-22% and 16-18% decrease in lesion growth if given monthly vs EOM over 24 mos
- Treatment affect seems to "compound" as the slowing is more dramatic at 18-24 mos than before...up to 36% reduction in growth
- VA may not be affected at 2 yrs but functional vision IS
- 11.9 vs 6.7 vs 3.1% new exudation in monthly vs EOM vs sham

170

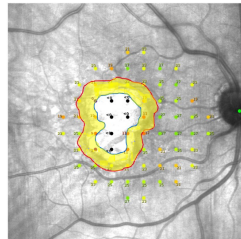
OAKS AND DERBY COMBINED REDUCTIONS IN GA LESION GROWTH BY 6-MONTH PERIOD



171

MICROPERIMETRY: POST HOC ANALYSIS OF THE PERILESIONAL AREA

- Hypothesis: linear expansion of GA lesions of ~100-150 microns/year^a means that pegcetacoplan preservation of retinal tissue may primarily be reflected in preserved photoreceptor function in retina near GA lesion borders at baseline
- Perilesional area (area within 250 microns of each side of GA lesion border) was created on FAF for each patient
- Microperimetry endpoints were assessed within this region
- See decrease in further growth and scotomatous points



^aYoon L, et al. Ophthalmol Retina 2020;4:889-910. ^bSee spots on grid. FAF=fundus autofluorescence; GA=geographic atrophy.

172

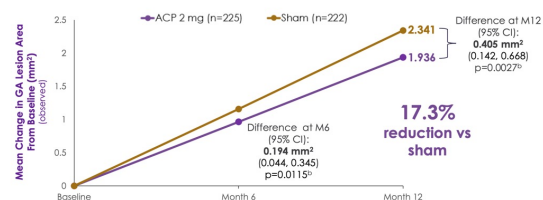
ZIMURA® (AVACINCAPTAD PEGOL) FROM IGAYERIC BIO GATHER 1 & 2

- Complement c5 inhibitor
- Phase iii
- Decrease slope of GA growth by 17.7% over 12 months of monthly injections
- 32% decrease in GA growth amongst US subjects (started with 13% smaller lesions)
 - Better results with earlier intervention
- Increase of exudation from 4.1 to 6.7%

173

GATHER 2

Mean change from baseline analysis utilizing observed data^a was consistent with primary analysis

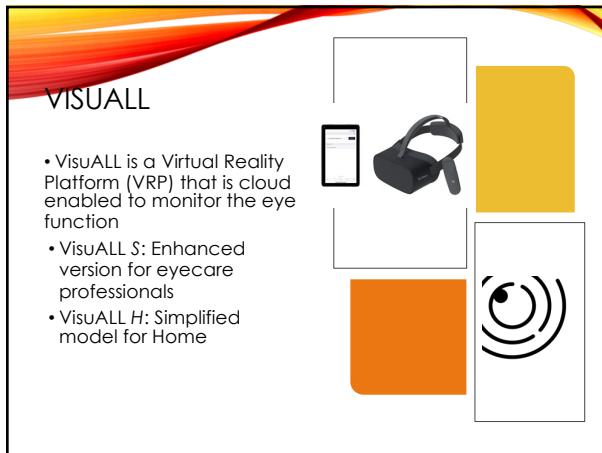


174

AR VISUAL FIELD

- VisuAll-Olleyes
 - VR visual field
 - Cloud based and totally portable
 - Visual acuity
 - Color vision capable
 - Integratable

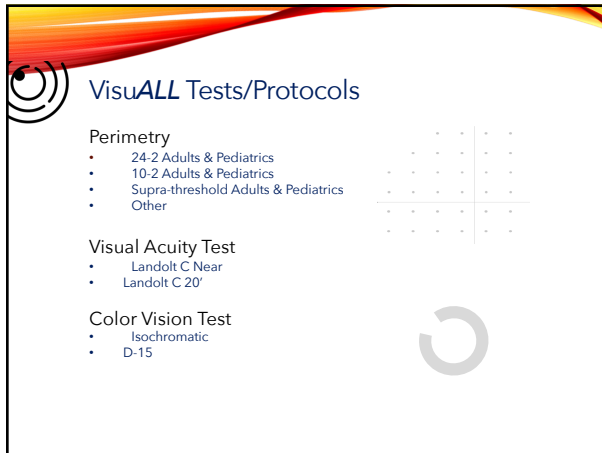
175



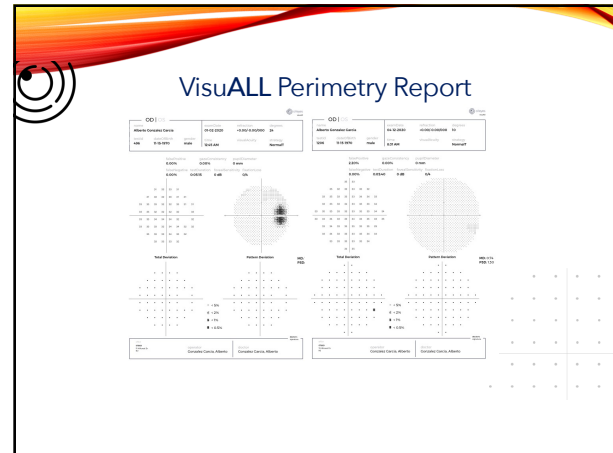
176



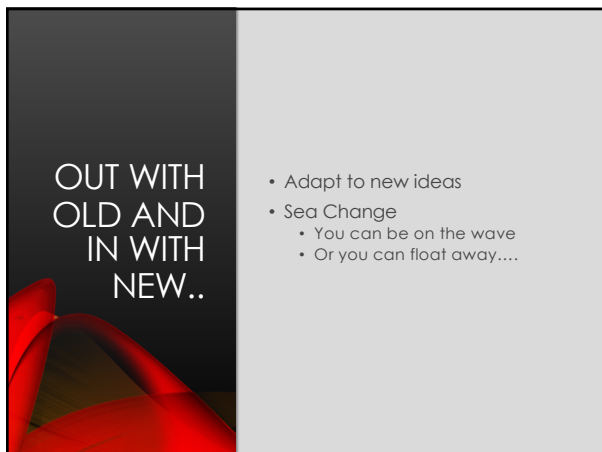
177



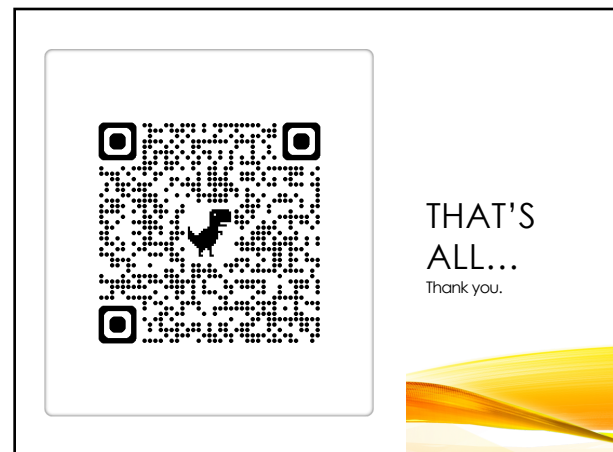
178



179



180



181