New Understandings in Ocular Surface Disease

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Disclosure
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- Consultant
  - Alcon, Valeant, J&J,
    RVL, TearScience,
    Kala, Santen, Sun,
    Lumenis, Nike, Smith

An example of the difficulty in separating aqueous-deficiency and evaporative DES

Increased Tear Fluid Production as a Compensatory Response to Meibomian Gland Loss

A Multicenter Cross-sectional Study

Reiko Arita, MD, PhD,[1,2,3,4,] Naoyuki Morishige, MD, PhD,[1,5,*] Shizuka Koh, MD, PhD,[1,6] Rika Shirakawa, MD,[1,3] Motoko Kawashima, MD, PhD,[1,4] Tohru Sakimoto, MD, PhD,[1,7] Takashi Suzuki, MD, PhD,[1,8] Kazuo Tsubota, MD, PhD[4]*

Conclusions: An increase in tear fluid production likely compensates for loss of meibomian glands in individuals with MGD. *Ophthalmology 2015;122:925-933*

Clinical diagnosis of DES is difficult

- Diagnosis of DED requires both patients symptoms and "objective" signs [1]
- Often, symptoms and signs are poorly correlated [1]
- A substantial percentage of pts with signs do not have symptoms [1]
- Lack of gold standard [2]
- No clear dichotomous separation between affected and healthy eyes [2]
- Most diagnostic tests are still poorly standardized [3]
- Many pts have both an aqueous-deficient AND an evaporative component [4]
- Measurements are influenced by external conditions [5] & and inter-rater variability [6]

1 Bron et al, 2014: Rethinking dry eye disease: a perspective on clinical implications, *Ocul Surf* (2 Suppl)
2 Savini et al, 2008: The challenge of dry eye diagnosis, *Clin Ophthalmol* 2(1):31-55
3 Foulks, 2003: Challenges and pitfalls in clinical trials of treatments for dry eye. *Ocul Surf* 1:20–30
4 Lemp et al, 2012: Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study, *Cornea 31(5) :472-8*
5 *Yokoi & Komuro, 2004:* Non-invasive methods of assessing the tear film. *Experiment Eye Res*. 2004;78:399–407
6 Bandlitz, 2008: Inter-rater reliability, sensivity and specificity of tear meniscus height evaluation. *Optom Vis Sci* 01/2008; 85:E-Abstract 85321

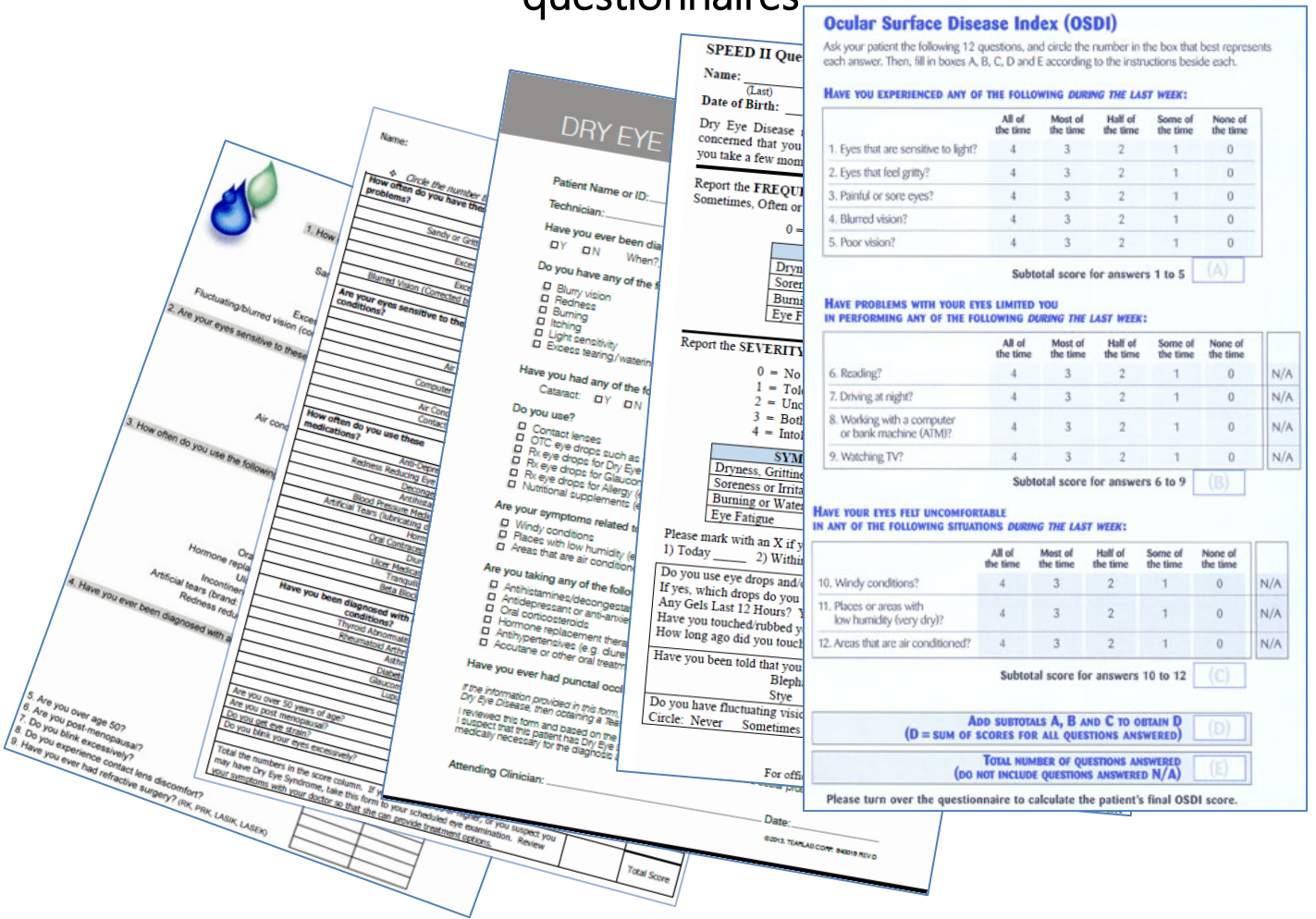
WHAT IS YOUR GO TO DIAGNOSTIC TEST AND WHY??

Clinical Sensitivity/Specificity Data

Test	Cutoff	Sensitivity (n=224)	Specificity (n=75)
Osmolarity	> 311 mOsms/L	72.8%	92.0%
TBUT	< 10 seconds	84.4%	45.3%
Schirmers	< 18 mm	79.5%	50.7%
Corneal Stain	> Grade 1	54.0%	89.3%
Conjunctival Stain	> Grade 2	60.3%	90.7%
Meibomian Grade	> Grade 5	61.2%	78.7%

Lemp M et al. Tear osmolarity in the diagnosis and management of dry eye disease. *Am J Ophthalmol.* 2011;151:792-798.

Symptoms of DES are subjective and assessed with questionnaires



Ocular Surface Disease Index (OSDI)

Ask your patient the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D and E according to the instructions beside each.

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

ADD SUBTOTALS A, B AND C TO OBTAIN D
(D = SUM OF SCORES FOR ALL QUESTIONS ANSWERED) (D)

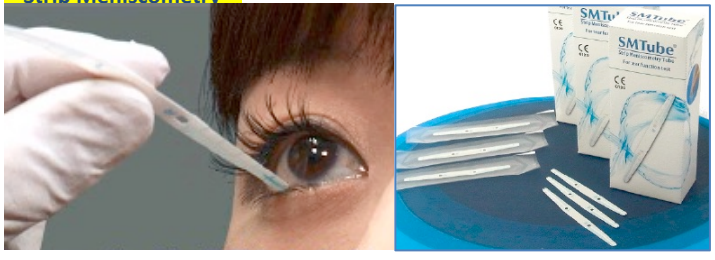
TOTAL NUMBER OF QUESTIONS ANSWERED
(DO NOT INCLUDE QUESTIONS ANSWERED N/A) (E)

Please turn over the questionnaire to calculate the patient's final OSDI score.

Signs that support aqueous deficiency dry eye (ADDE)

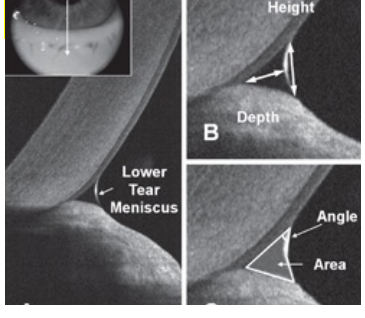
Schirmer's test

Strip Meniscometry

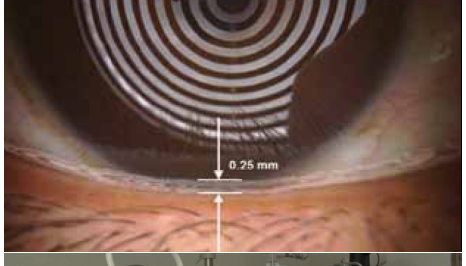


Osmolarity

Tear meniscus height

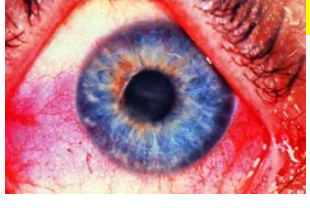


Tear meniscus height (Keratograph)



Corneal Fluorescein Staining

Conjunctiva Staining (Rose



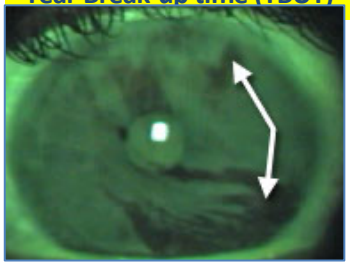
Signs that support evaporative dry eye (Mostly MGD)

Slit exam

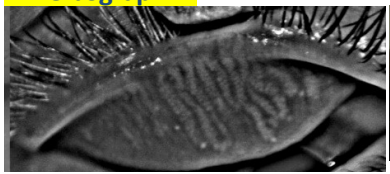
Meibum

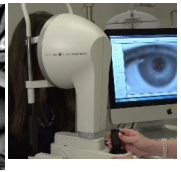
Osmolarity

Tear Break-up time (TBUT)



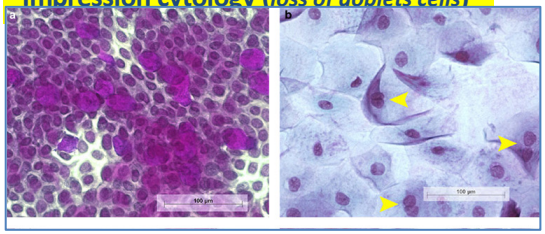
Meibograph



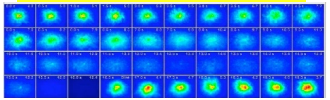


Lipid Layer Thickness

Impression cytology (*loss of goblets cells*)

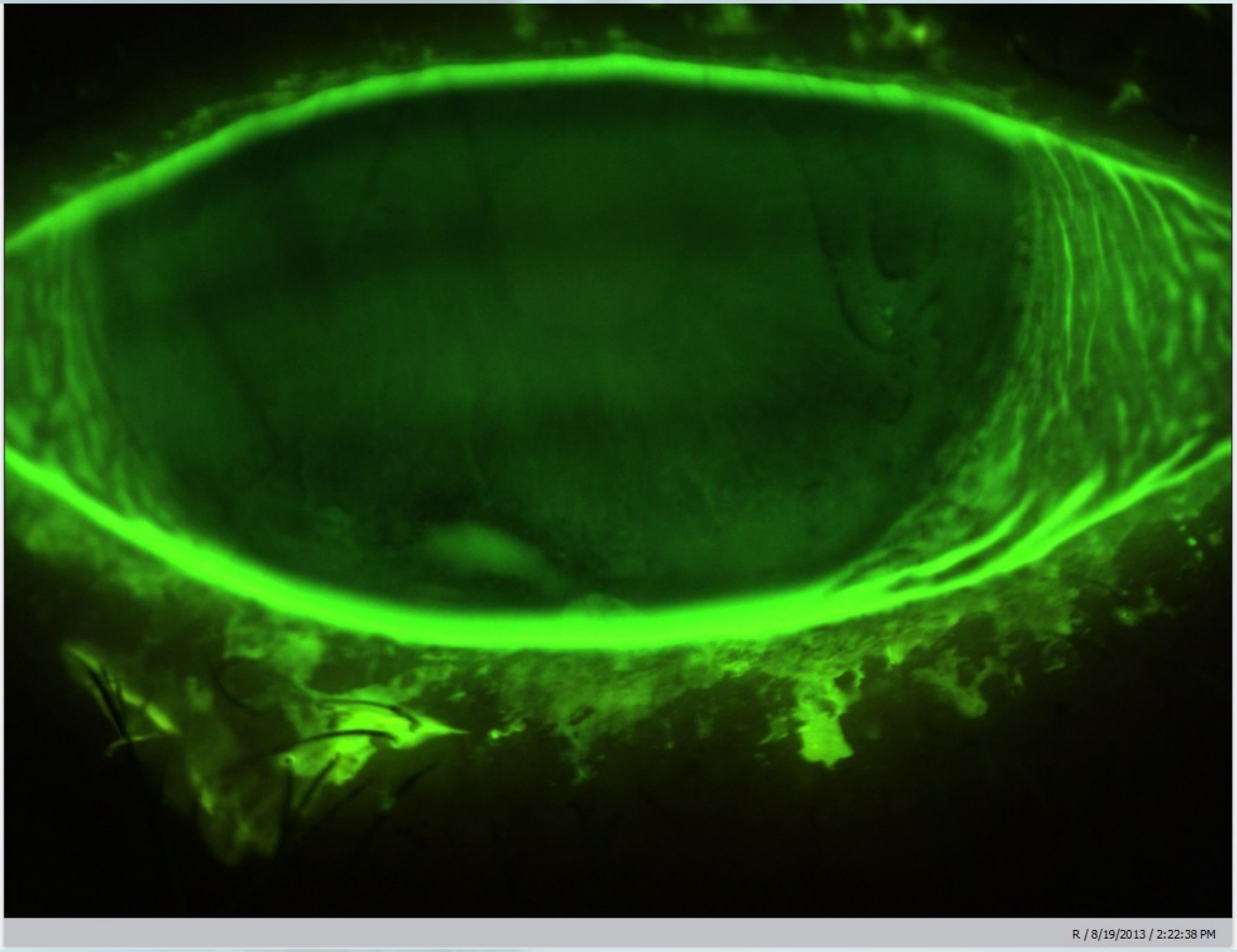


Optical scatter index



Inflammatory Markers (*MMP-9*)

Corneal Fluorescein Staining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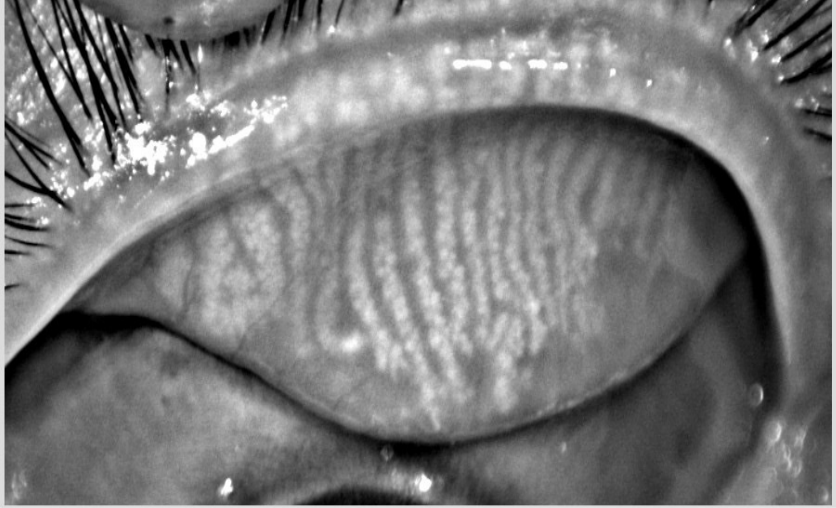
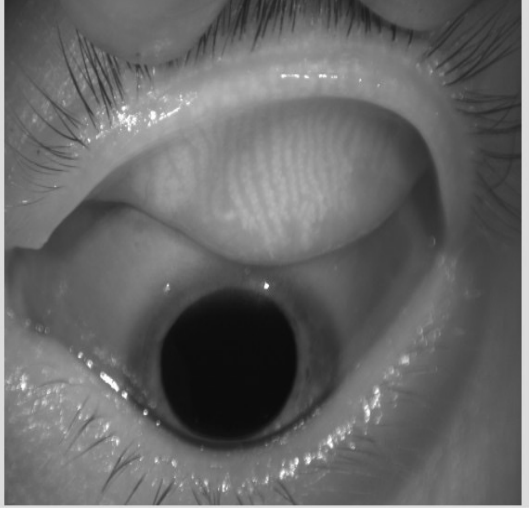
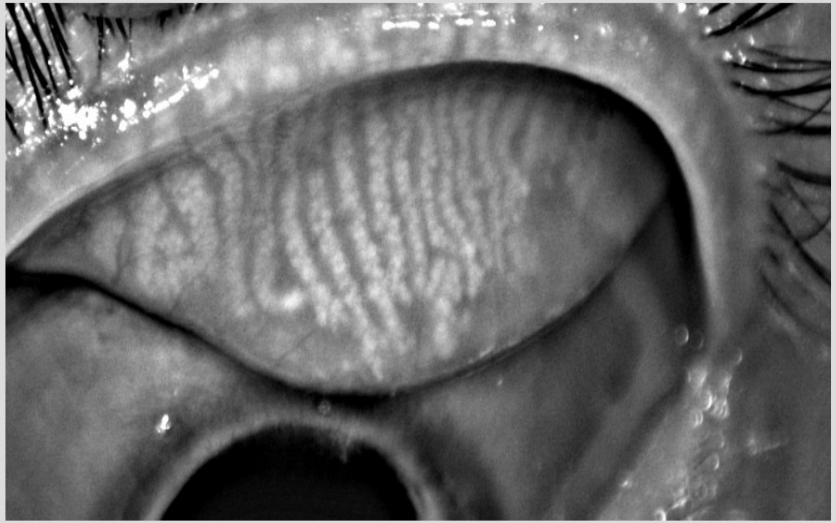
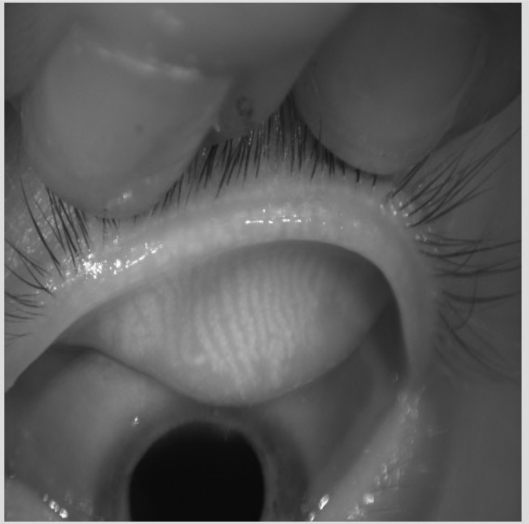
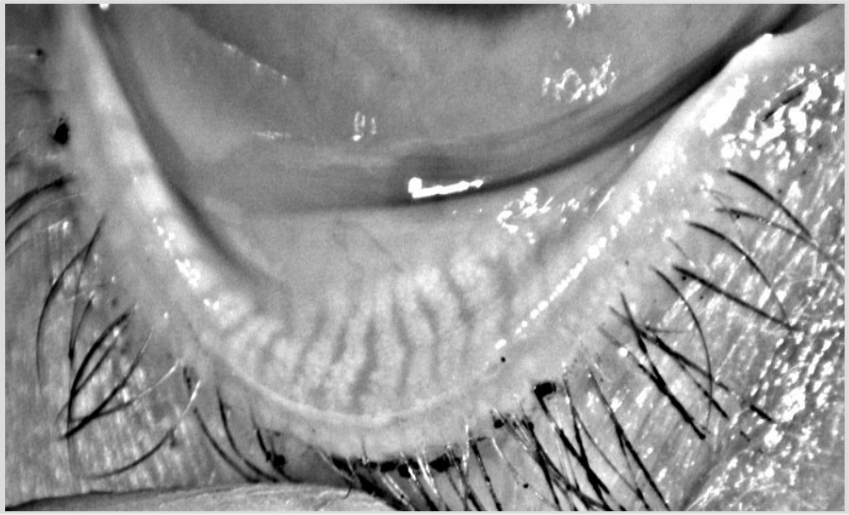
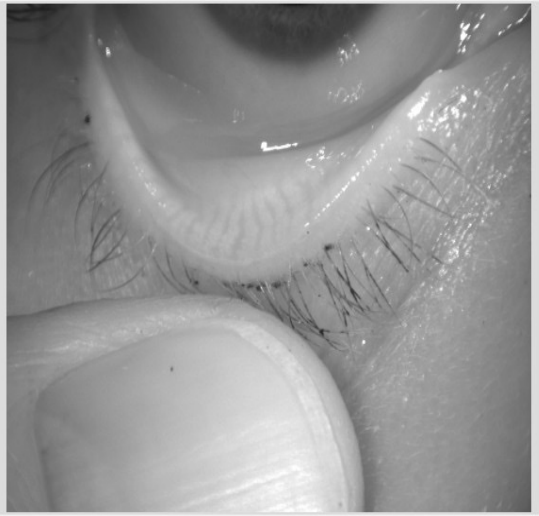
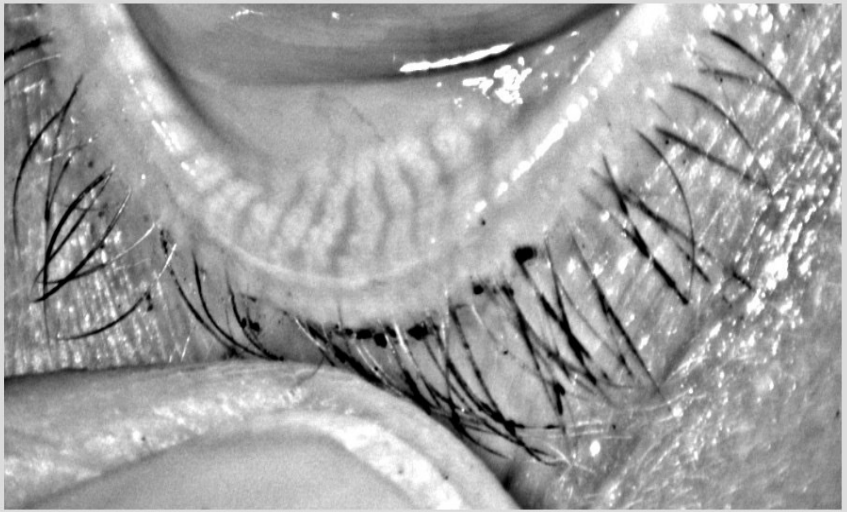
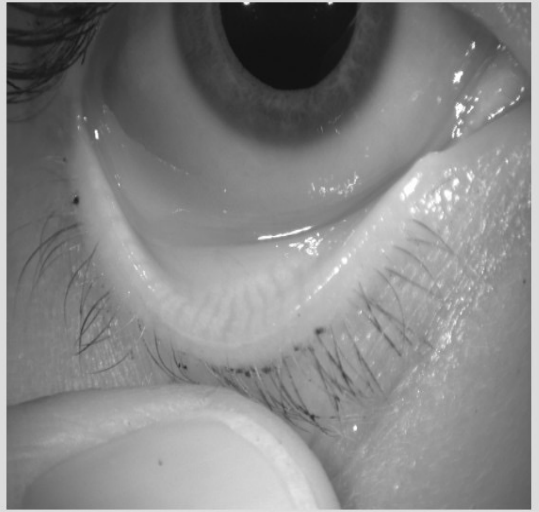
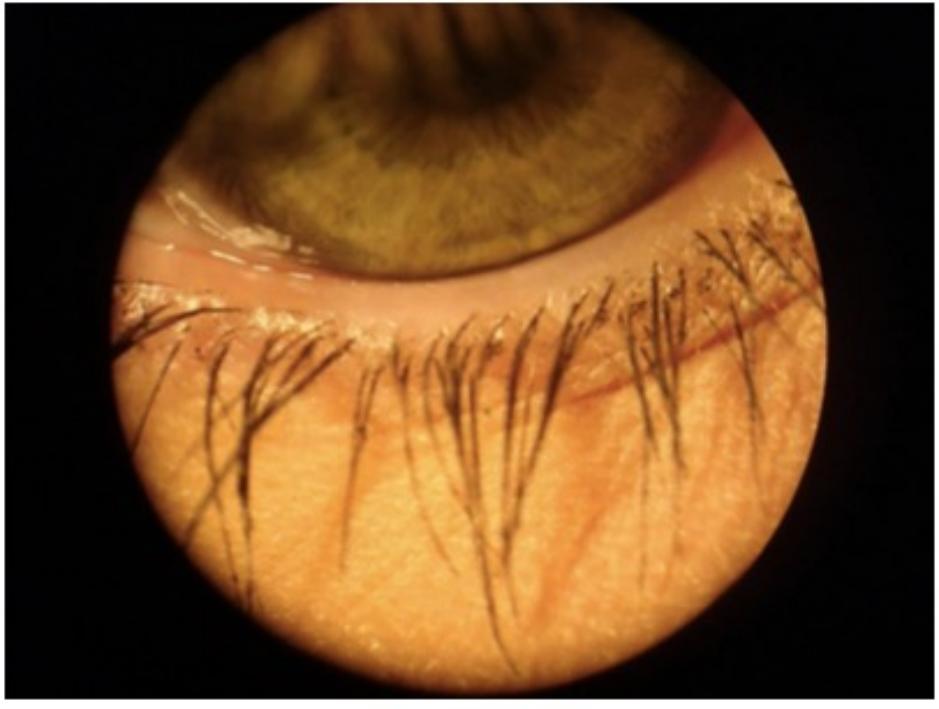





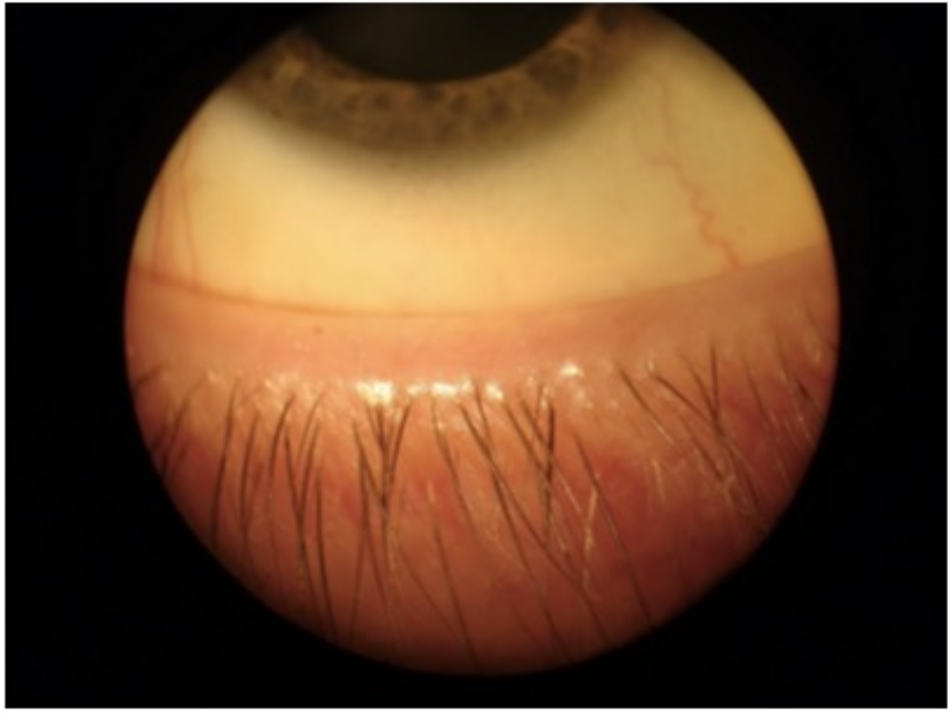
Eyelid Vascularity

Scale by Derek Cunningham, O.D.

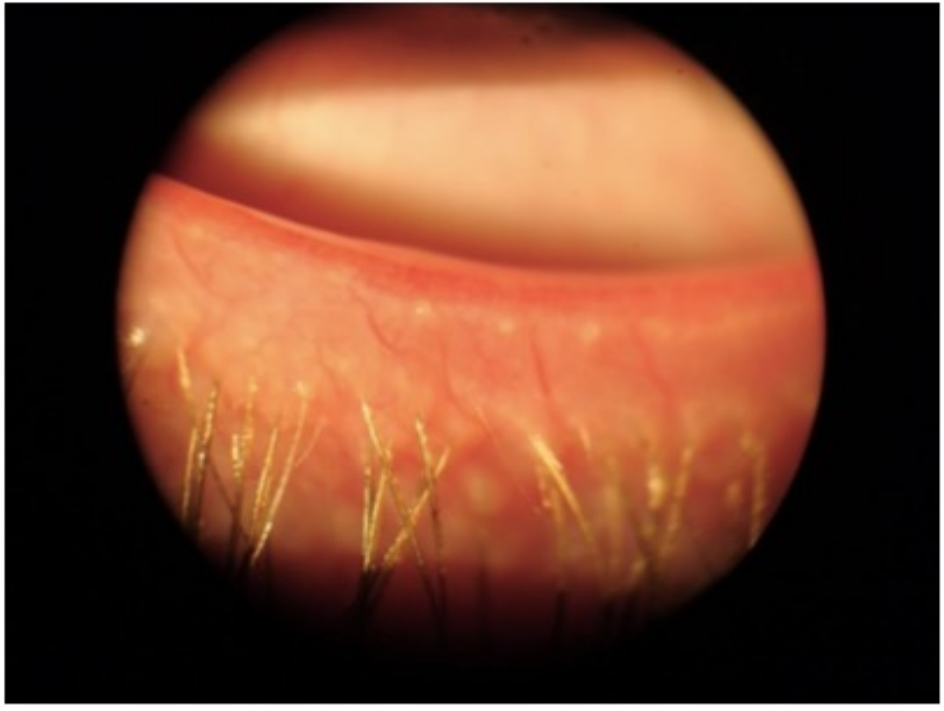
Normal – No visible vasculature on eyelid margin



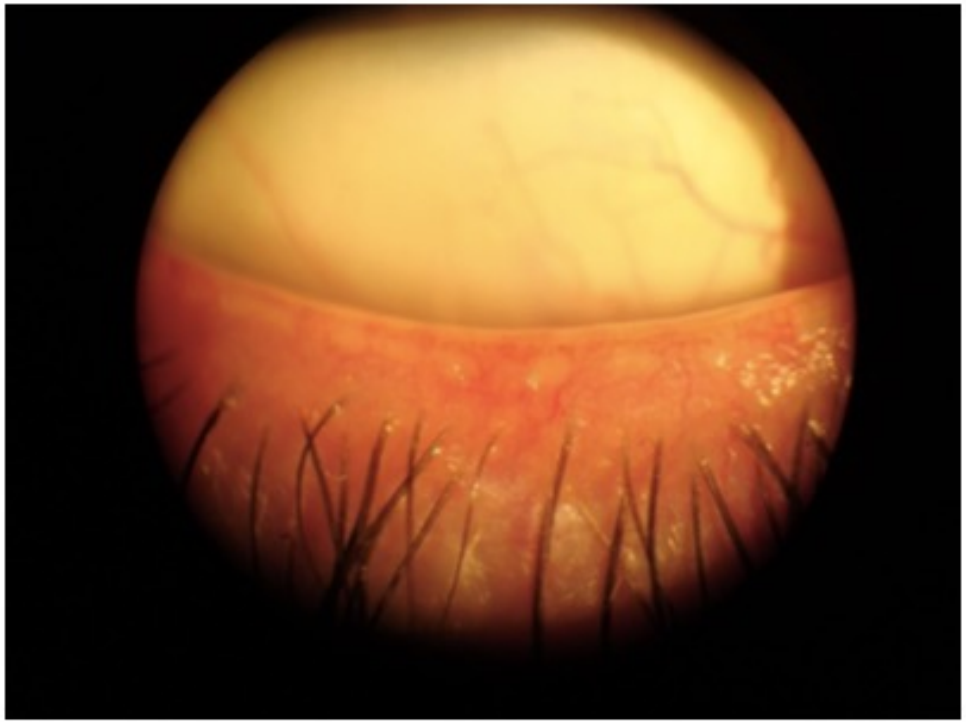
Mild – minimally visible vasculature on eyelid margin, can have occasional large blood vessel near surface



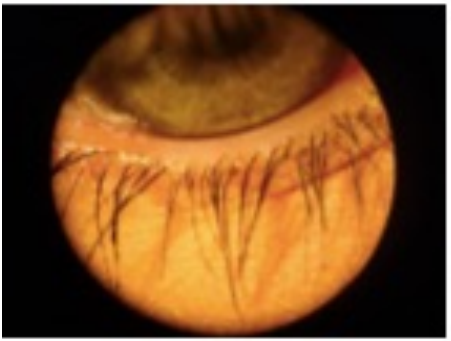
Moderate – Clear visible vasculature near skin surface including smaller blood vessels



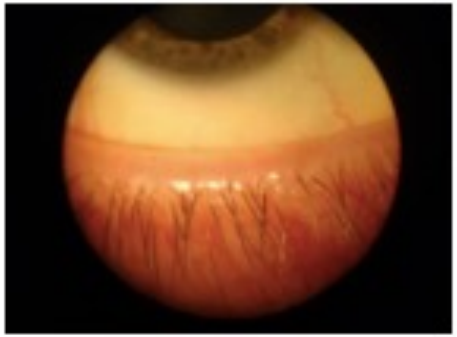
Severe – numerous blood vessels of multiple sizes with associated telangiectasia or hemorrhages.



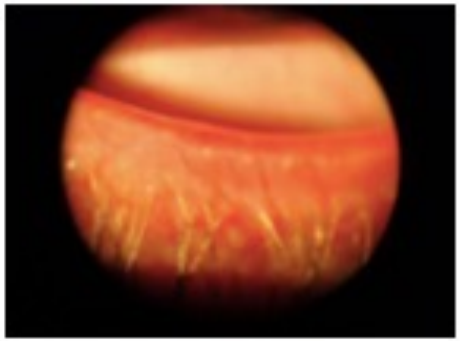
Normal



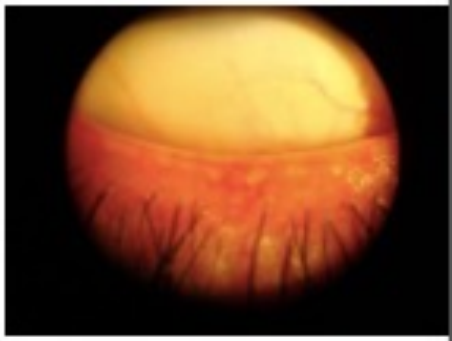
Mild

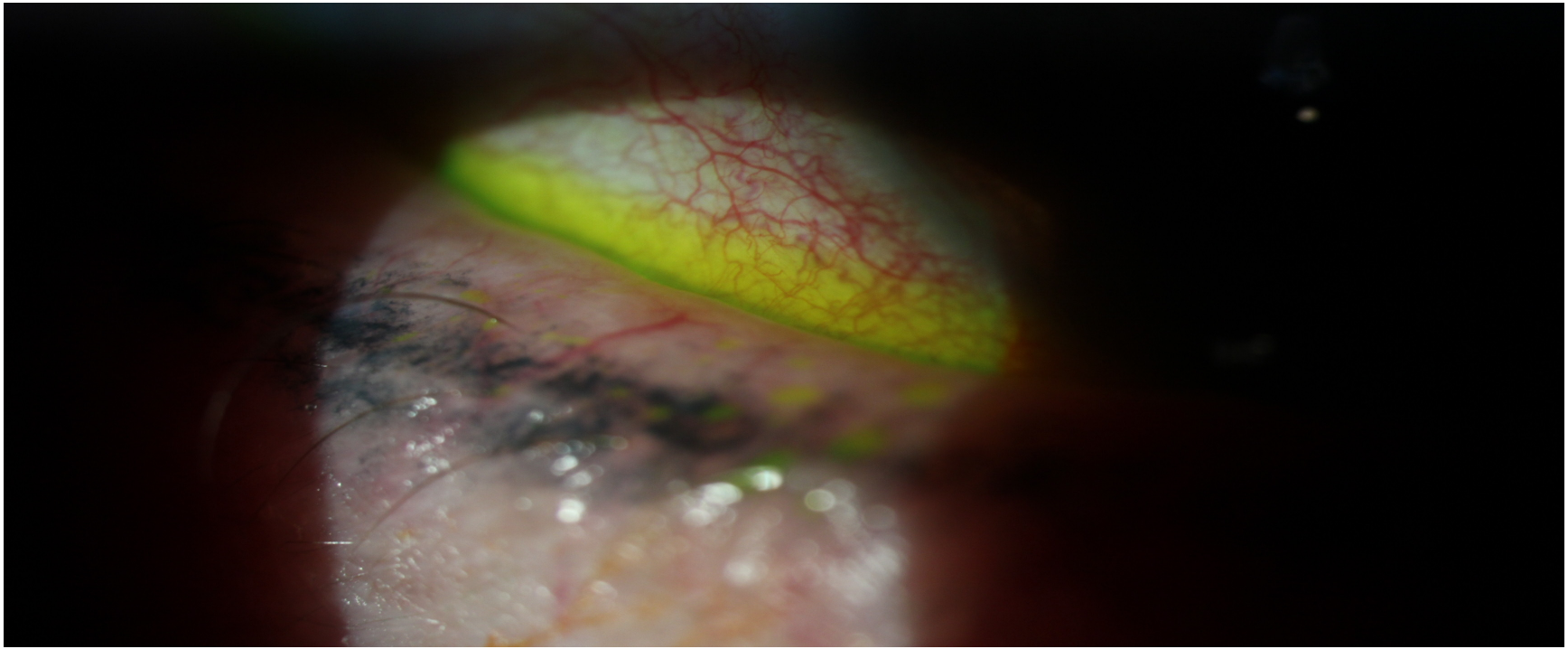


Moderate

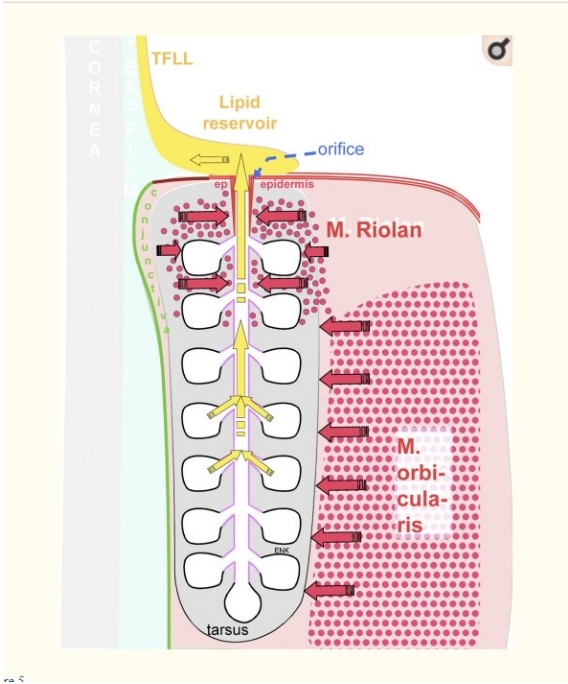


Severe





MG function



- Secretory Acini feed meibum into central duct
- Epithelial ingrowth into gland forms orifice
- Lid margin is among the thinnest skin in the body
- Gland is set up for natural blink to most efficiently express gland

Treatment challenges

- The natural tear layer of meibum is incredibly thin to function properly (adding excessive artificial lipid does not help)
- Inflamed glands will solidify the meibum (lipid chemical change) – increasing the melting point above body temperature.
- Stagnant glands will not clear themselves – need to be actively evacuated
- Steroids only provide temporary relief of inflammation
- Glands do not regenerate once they atrophy

Diagnostic expression?????

- Not practical as patient's eyelid is not laterally compressed on normal blink. Compressing the eyelid has no practicality to normal blink.

- Glands are often capped with keratin, so pushing on them will not produce anything anyway

- Inflamed glands will not usually express without heat

Why do warm compresses and lid scrubs have such limitations?

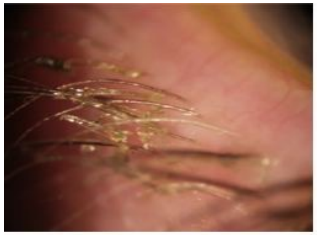
- All dry eye is inflammatory in nature.
  - Heat increases inflammation

- Majority of meibomian gland patients have lid margin telangiectasia or thinned lid margin skin
  - Heat causes vasodilation and increased vascular permeability of inflammatory factors into surrounding tissue and gland
  - These lid margins also inflame further with mechanical abrasion or compression

MGD Treatment Options

- Topical azithromycin
- cyclosporine
- Lid hygiene- scrubs, foams, sprays
- Warm compresses
- Oral Doxycycline, azithromycin PO
- Antibiotic/steroid combination drops/ointments
- Lid/Gland Expression
- IPL/BBL
- Omega 3 Supplementation
- Gland Ductal Probing
- Thermal Pulsation System/Other
- Neurostimulation

Microblepharoexfoliation



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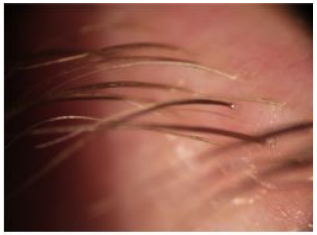

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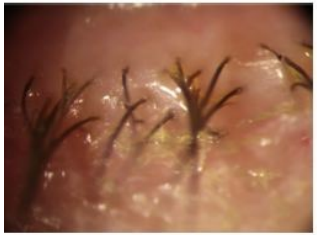

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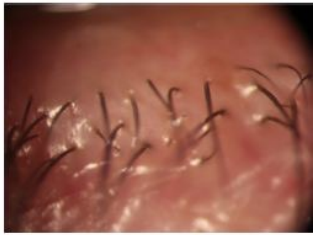

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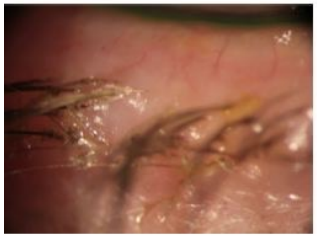

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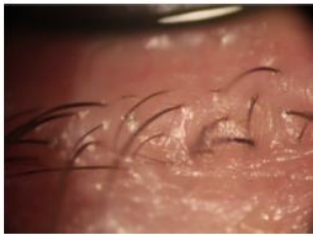

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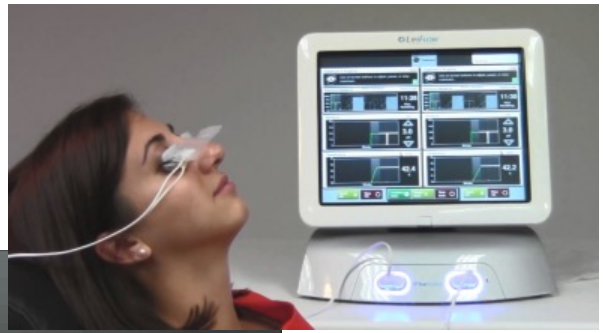
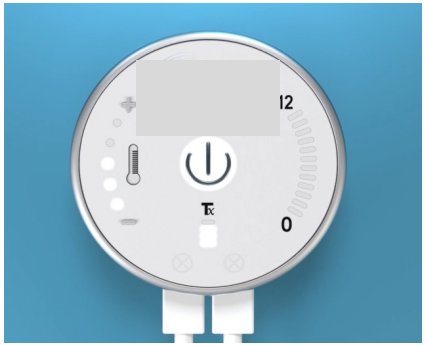
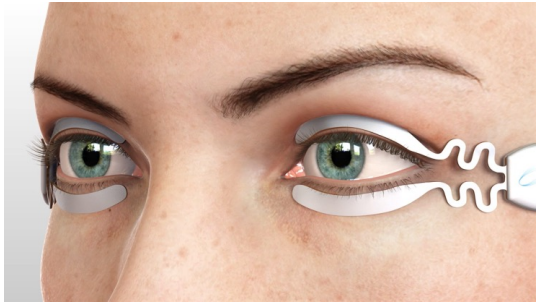
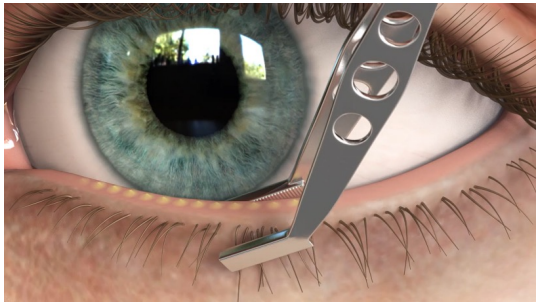
Thermal Pulsation Treatment



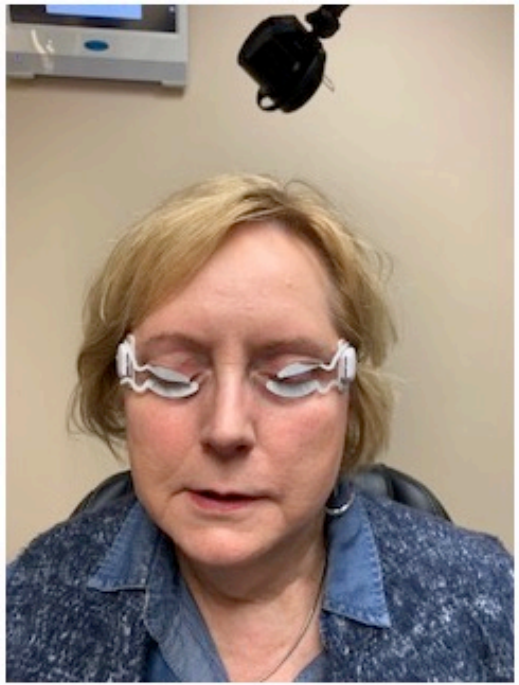






Procedure

1. Place iLid Devices on patient's lower and upper lids
2. Heat delivered to eyelids while patient's eyes remain open and blinking
3. Clear: lower and upper lids



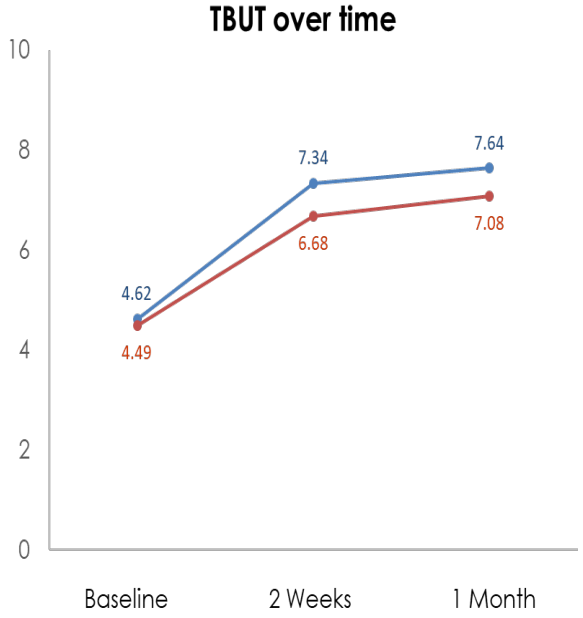
A Novel, Targeted, Open Eye, Thermal Therapy and Meibomian Gland Clearance in the Treatment of Dye Eye:

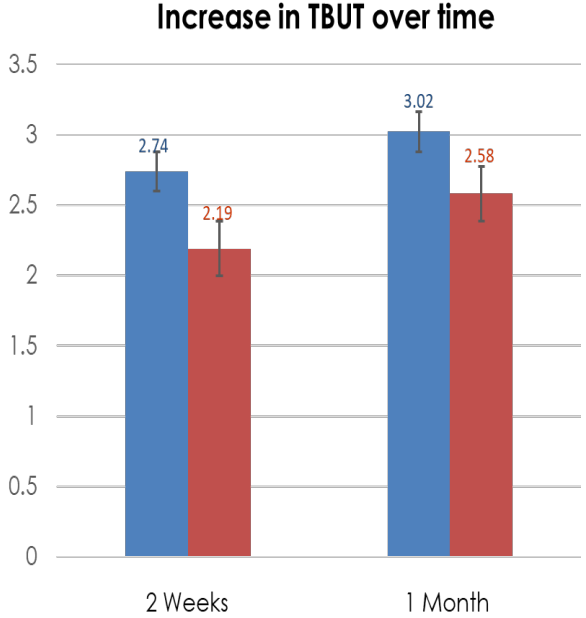
A Randomized Controlled Investigator masked Trial (OLYMPIA)

Jennifer M. Loh, MD, ABO; William B. Trattler, MD, ABO; Kavita P. Dhamdhere, MD, PhD; Marc R. Bloomenstein, OD; John A. Hovanesian, MD; Mitchell A. Jackson, MD, ABO; Bobby Saenz, OD

Presented by Jennifer M. Loh, MD, ABO; ASCRS May 16, 2020

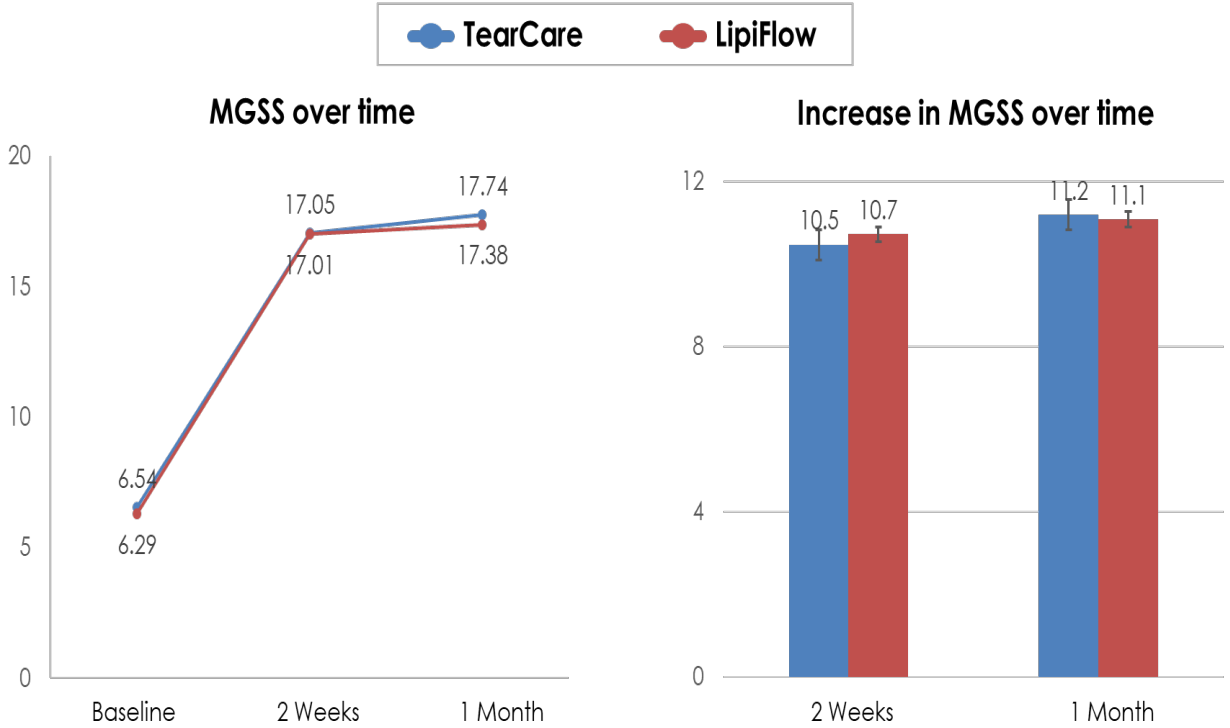
Primary Endpoint: Tear Film Break-Up Time (TBUT)





- Statistically significant increase ($p<0.0001$)in mean TBUT in both groups at all f/u time points
- **TearCare is non-inferior to LipiFlow**

Primary Endpoint: Meibomian Gland Secretion Score (MGSS)



- Statistically significant increase ($p<0.0001$)in mean MGSS in both groups at all f/u time points
- **TearCare is non-inferior to LipiFlow**

Conclusions

TearCare successfully met non-inferiority objective v. LipiFlow

- ✓ 82% of TearCare subjects had clinically meaningful improvements in OSDI
- ✓ Symptoms-OSDI, SANDE, Eye Dryness Score
- ✓ Signs- TBUT, MGSS, Conjunctival and Corneal staining, Glands Yielding any liquid, Glands Yielding clear liquid

A **greater proportion** of patients in **TearCare** group showed clinically **meaningful symptomatic relief** compared to LipiFlow group

- ✓ 72% of TearCare vs 59% for LipiFlow subjects improved by at least 1 OSDI category
- ✓ 22% less use of lubricant drops throughout the study follow up in TearCare group

Thermal Pulsation
1 Week / 1 Month Study Design[1]

Study Objective:
to assess changes in meibomian gland function and evaporative dry eye symptoms after treatment

Study Design:
non-randomized, open-label, multisite trial

Subjects:
30 subjects

- **Primary endpoints**
  MGS and TBUT
- **Secondary endpoint**
  SPEED score and OSDI symptom scores

Assessed pre-treatment, and at 1 week and 1 month post-treatment

MGS, meibomian gland score; OSDI, Ocular Surface Disease Index; SPEED, Standard Patent Evaluation of Eye Dryness; TBUT, tear breakup time.

Reference: 1. Alcon data on file, 2017.

Thermal Pulsation Delivered Significant Improvements in 1 Week[1]

Significant improvements seen
1 week after treatment

Meibomian Gland Score (*P*<0.0001)

315% improvement

Medial, temporal, nasal regions all improved

Tear break-up time (*P*<0.0001)

71% improvement

SPEED Questionnaire (*P*<0.0001)

53% improvement

Improvement in all 8 sub-scores

OSDI Score (*P*=0.0003)

58% improvement

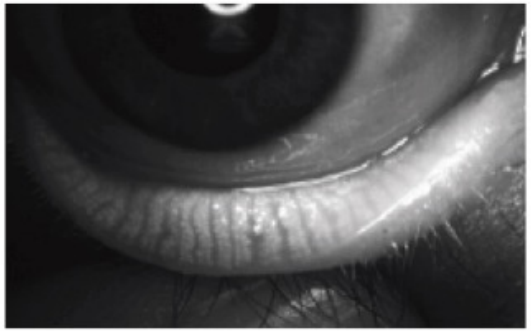
All improvements **maintained at 1 month**

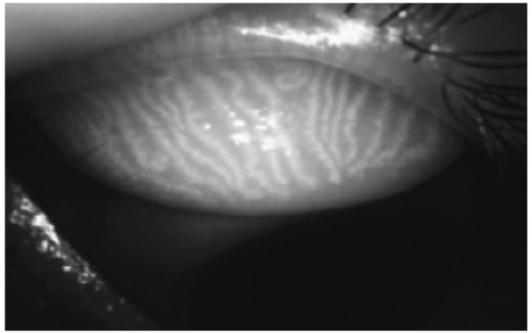
MGD, meibomian gland dysfunction; OSDI, Ocular Surface Disease Index; SPEED, Standard Patent Evaluation of Eye Dryness.

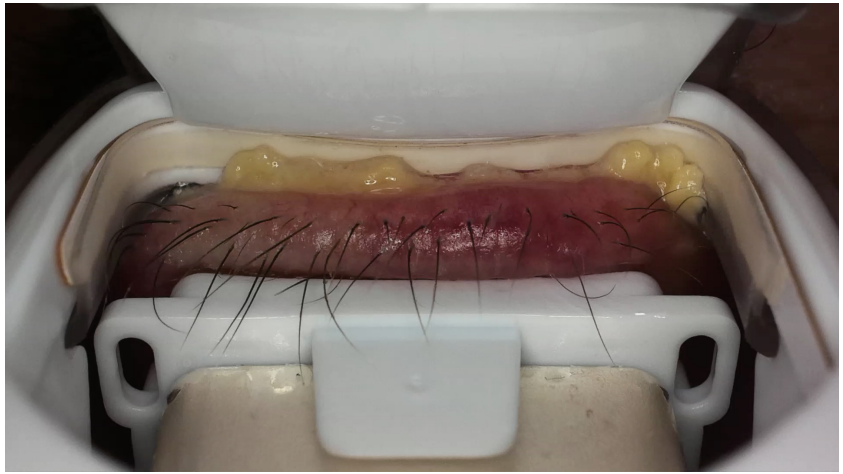
In a prospective, open-label, multicenter study of patients ≥18 years with MGD (n=30).

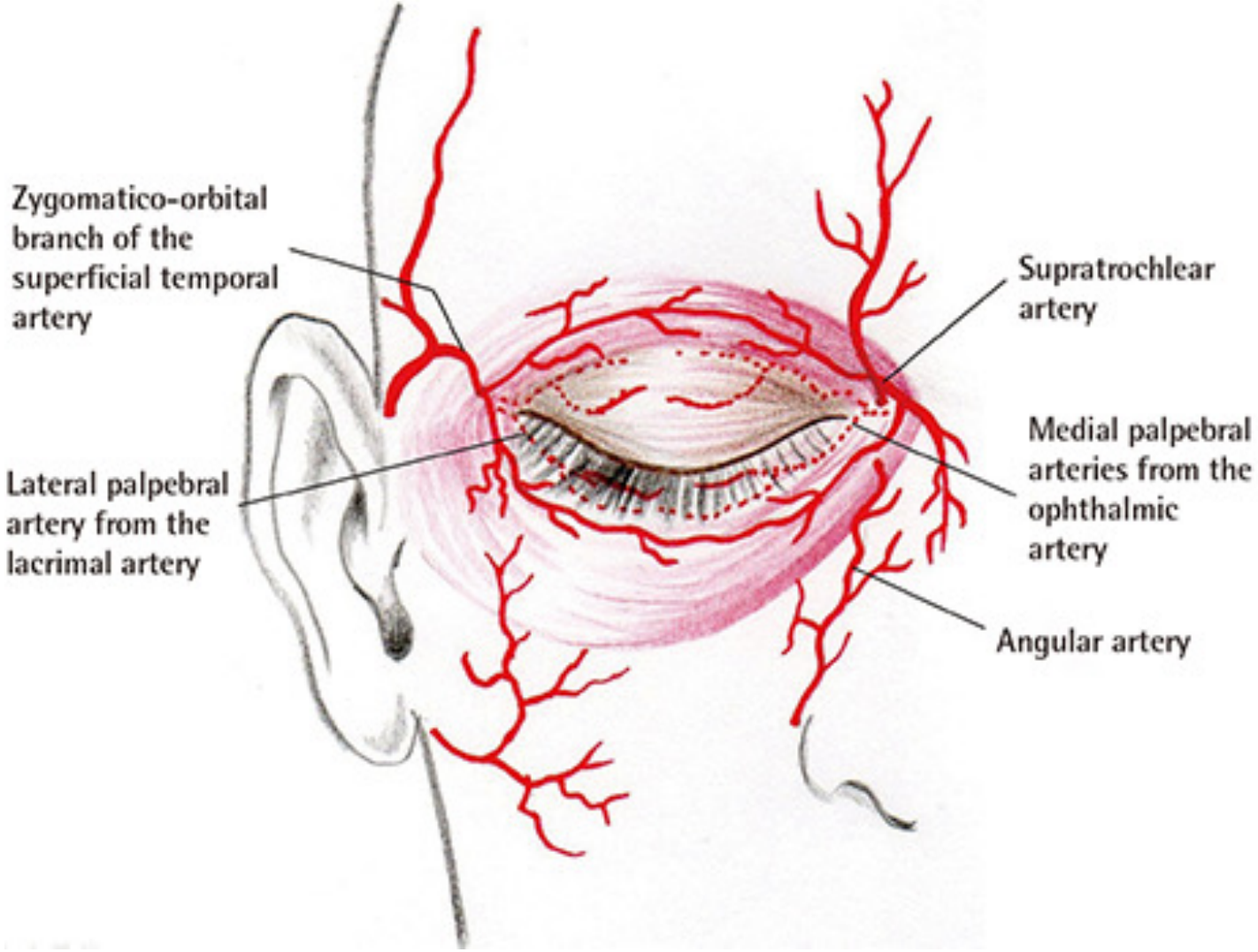
*8-item questionnaire that scores patient experience of dry eye before and after a treatment. Total SPEED score calculated through sum of all 8 items; total score value can vary from 0–28, with higher score indicating worse experience of dry eye.

Reference: 1. Alcon data on file, 2017.








Zygomatico-orbital branch of the superficial temporal artery
Supratrochlear artery
Lateral palpebral artery from the lacrimal artery
Medial palpebral arteries from the ophthalmic artery
Angular artery

IPL for Dry Eye?

The specific mechanism of action is not well understood but is believed to be partially due to the thermal heating of the meibum coupled with the therapeutic effects of treating superficial telangiectasia.


Stellar Optima
Lumenis
M22
Lumenis

Initial FDA approved IPL

- Designed for full face

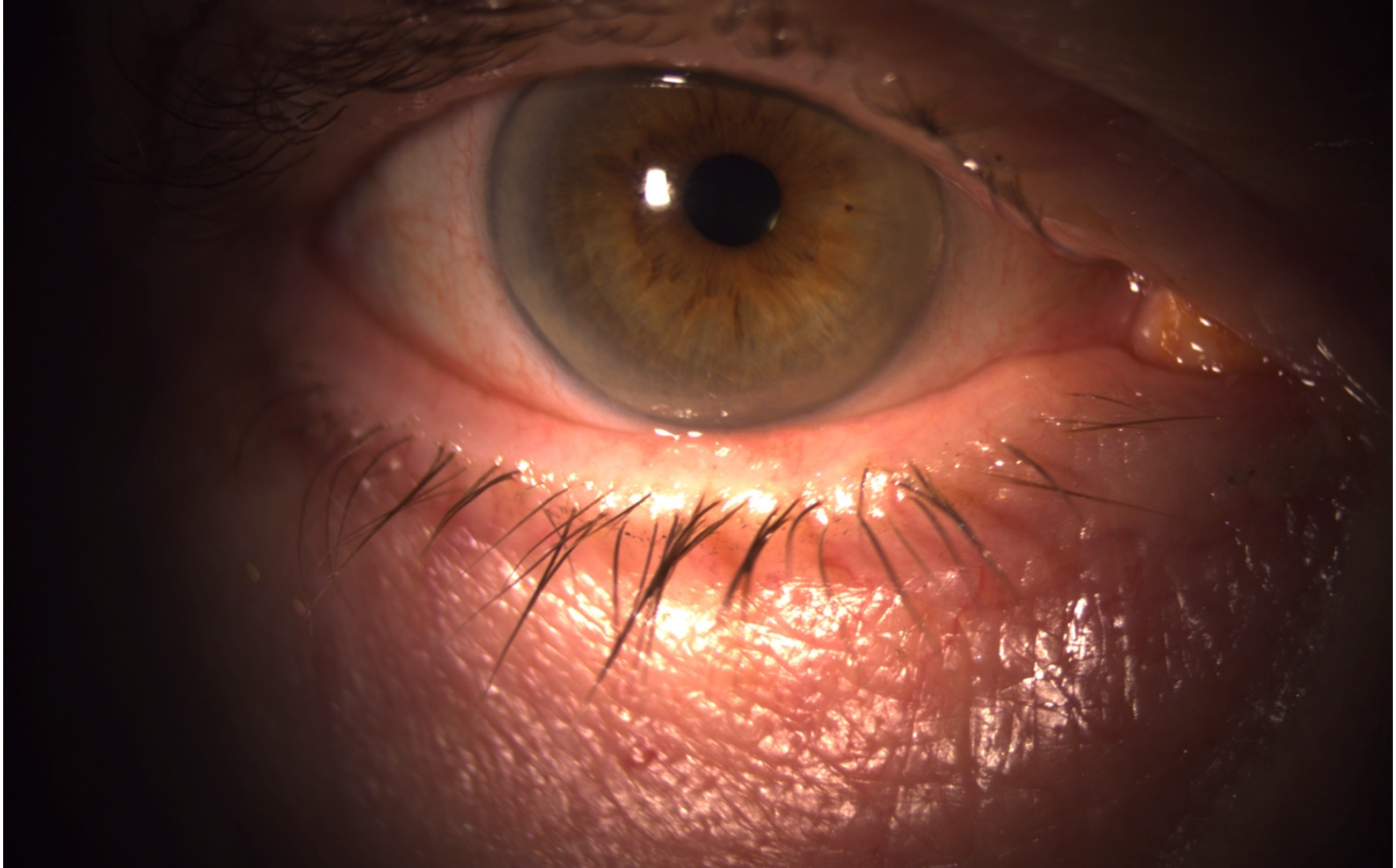
New approved unit

- Better for around eyes

New handpiece


Stellar Optima

WITH SO MANY OPTIONS FOR IN-OFFICE THERAPY, HOW DO YOU DECIDE WHICH ONE?



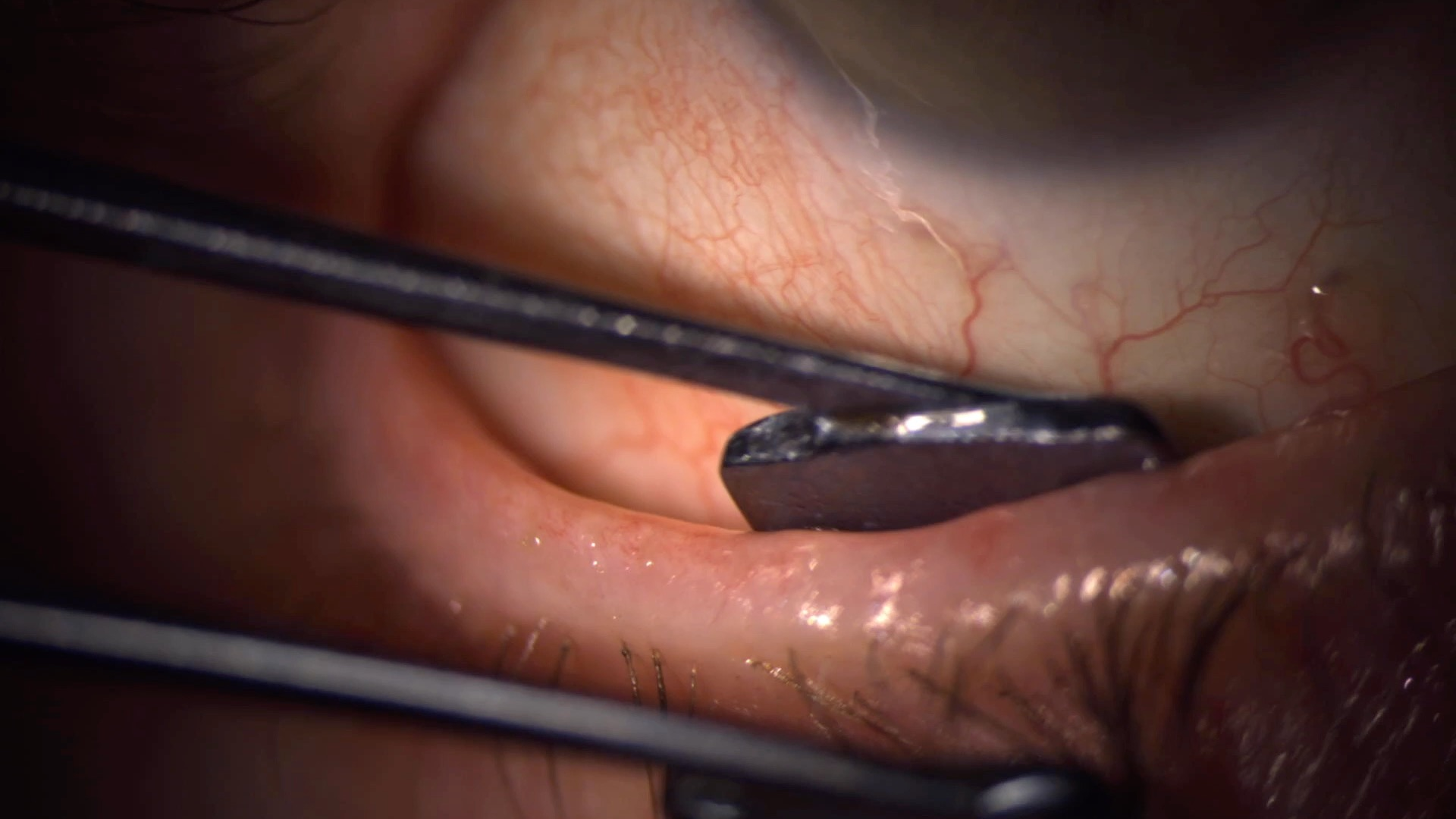
DX

- Ocular rosacea
- Evaporative dry eye
- Mild loss loss of lower lashes

Treatment

- Topical steroid gtts TID OU
- HOCL applied to lid margins BID
- Order Tear Care
- NO MORE WARM COMPRESS TX – Need to avoid heat to lid margins

Post Treatment Gland Expression



Neurotrophic Keratitis: Etiology

1. Infectious: HSV, VZV, leprosy
2. CN V palsy
   - Surgery for trigeminal neuralgia, neoplasia (acoustic neuroma), aneurysm, facial trauma, congenital, familial dysautonomia (Riley-Day syndrome), Goldenhar-Gorlin syndrome, Möbius syndrome, familial corneal hypesthesia
3. Topical medications: anesthetic abuse
4. Iatrogenic: LASIK/PRK, corneal incisions (RK, AK), contact lens wear, scleral bands, vitrectomy and photocoagulation to treat DM retinopathy[1,2]
5. Chemical and physical burns
6. Systemic: DM, multiple sclerosis, Vit A deficiency
7. Increasing age, chronic DED[3]

1. Banerjee PJ. JAMA ophthalmology 2014;132:750-2.
2.Tinley CG, Eye 2009;23:1819-23
3. Ocul Surf. 2007 Apr;5(2):75-92.

Neurotrophic Keratitis: Classification

Mackie classification

- Stage I is characterized by hyperplasia and/or irregularity of the epithelium, evolving to punctate keratopathy, corneal edema, neovascularization, stromal scarring.
- Stage II is defined by a recurrent or persistent epithelial defects or a PED without stromal thinning.
- Stage III: stromal involvement leads to corneal ulcer, melting and perforation

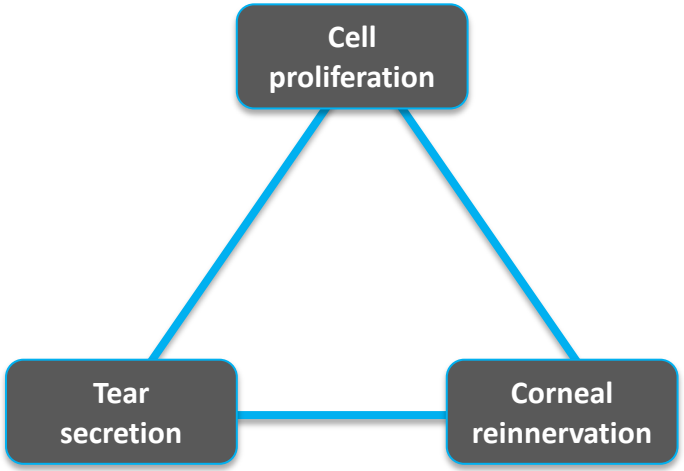
Mackie IA. Neuroparalytic keratitis. Current Ocular Therapy. Philadelphia, PA: WB Saunders; 1995:452-4.

Endogenous nerve growth factor (NGF) and its role in NK

Neurotrophic keratitis (NK) is a result from impaired trigeminal corneal innervation

- ↓ Lacrimation and blink reflex
- ↓ Epithelial cell vitality, metabolism, mitosis
- ↓ Epithelial trophism and repair
- ↑ Stromal and intracellular edema
- ↓ Microvilli
- ↓ Development of the basal lamina

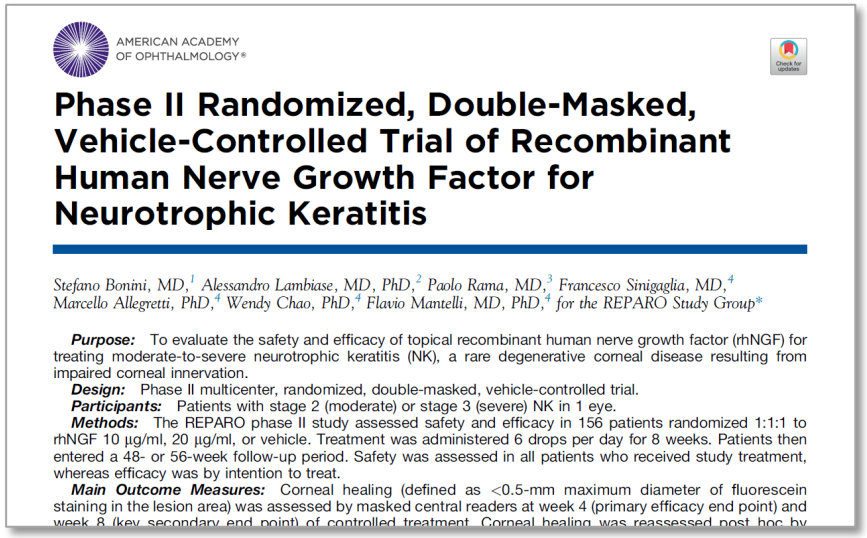
Endogenous NGF maintains corneal integrity by three mechanisms



Nerve damage → loss of corneal sensitivity → NK

Mastropasqua et al. (2017) J Cell Physiol 232:717-24

cenegermin-bkbj 20 mcg/ml was approved by FDA in August 2018



AMERICAN ACADEMY OF OPHTHALMOLOGY®

Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

*Stefano Bonini, MD,[1] Alessandro Lambiase, MD, PhD,[2] Paolo Rama, MD,[3] Francesco Sinigaglia, MD,[4] Marcello Allegretti, PhD,[4] Wendy Chao, PhD,[4] Flavio Mantelli, MD, PhD,[4] for the REPARO Study Group**

Purpose: To evaluate the safety and efficacy of topical recombinant human nerve growth factor (rhNGF) for treating moderate-to-severe neurotrophic keratitis (NK), a rare degenerative corneal disease resulting from impaired corneal innervation.
Design: Phase II multicenter, randomized, double-masked, vehicle-controlled trial.
Participants: Patients with stage 2 (moderate) or stage 3 (severe) NK in 1 eye.
Methods: The REPARO phase II study assessed safety and efficacy in 156 patients randomized 1:1:1 to rhNGF 10 µg/ml, 20 µg/ml, or vehicle. Treatment was administered 6 drops per day for 8 weeks. Patients then entered a 48- or 56-week follow-up period. Safety was assessed in all patients who received study treatment, whereas efficacy was by intention to treat.
Main Outcome Measures: Corneal healing (defined as <0.5-mm maximum diameter of fluorescein staining in the lesion area) was assessed by masked central readers at week 4 (primary efficacy end point) and week 8 (key secondary end point) of controlled treatment. Corneal healing was reassessed post hoc by

- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older
- Available for ordering since January 2019
- Developed by Dompé pharmaceuticals, available through specialty pharmacy

Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.

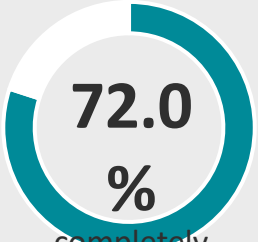
After 8 weeks of treatment, 6 times daily

In the majority of patients across two clinical studies (cenegermin ophthalmic solution 0.002%) was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

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

European patients with NK in one eye

NCT01756456

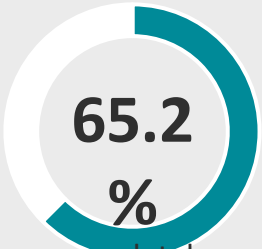


Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147



Vehicle response rate 16.7%

Of patients who healed after one 8-week course of treatment…

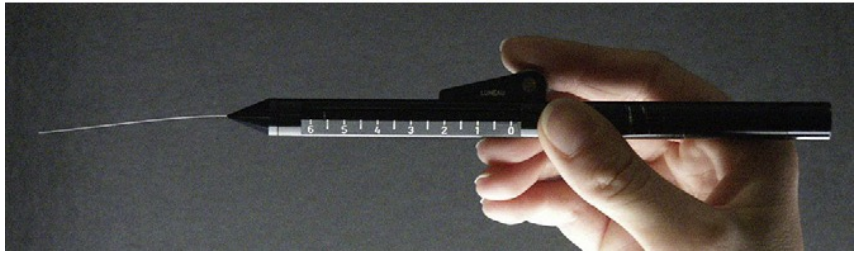
80%

Remained healed for one year*

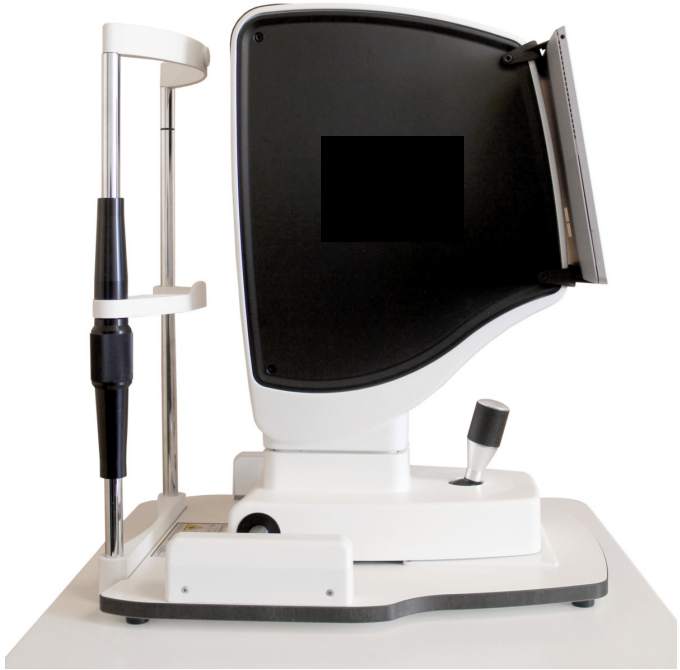
*Based on REPARO, the study with longer follow-up

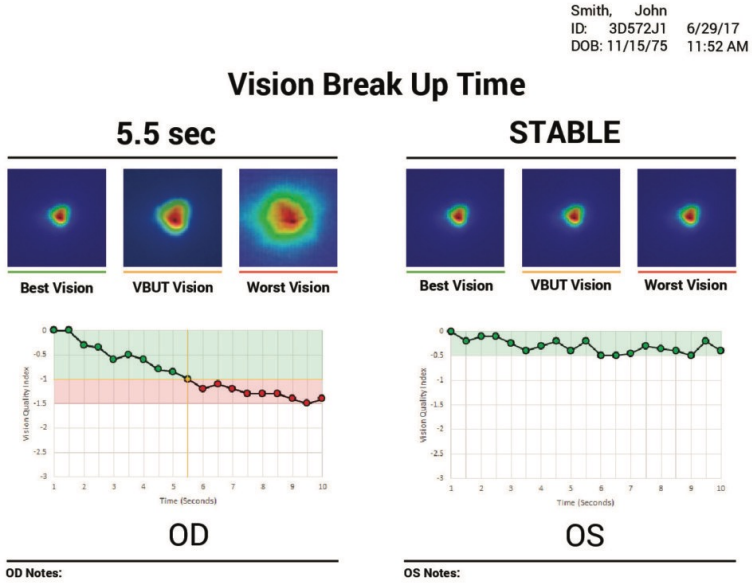
1. Bonini S, Lambiase A, Rama P *et al. Ophthalmology* 2018;125:1332-1343.
2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017.

K Sensitivity



Tear Film Analysis

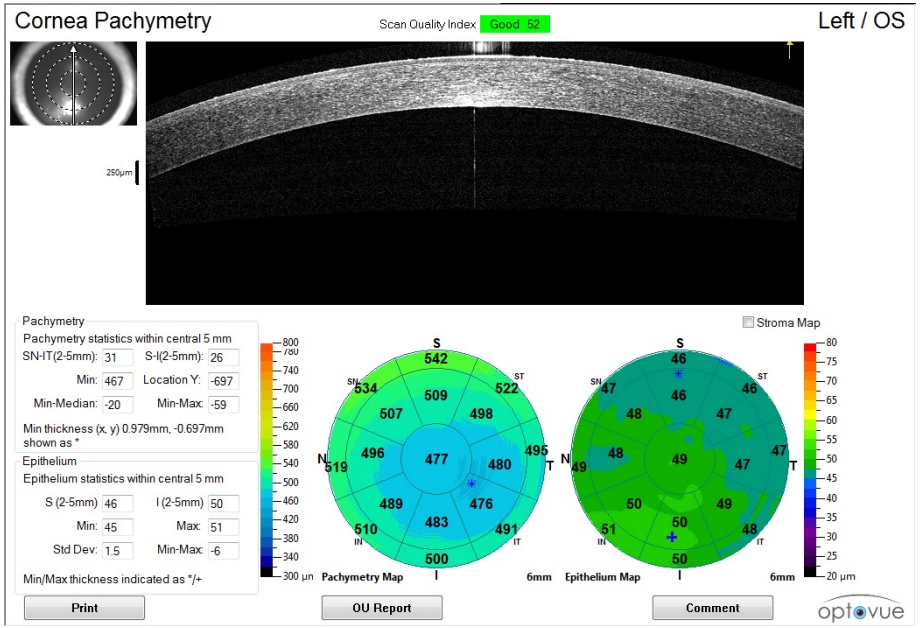




Epi-Mapping

- Quantitative measurements of the epithelial and stromal layers of the cornea

- Indications
  - Refractive surgery
  - Keratoconus
  - Dry eye disease



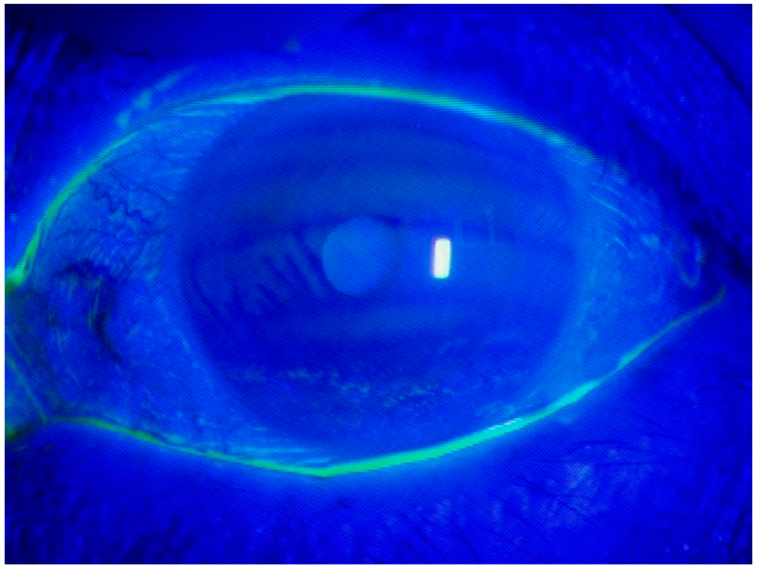
Rocha KM, Straziota CP, Stutling RD, et. Al. Spectral-Domain OCT Analysis of Regional Epithelial Thickness Profiles in Keratoconus, Postoperative Corneal Ectasia, and Normal Eyes. *J Refract Surg.* 2013 Mar; 29(3): 173-179.

Li Y, Tan O, and Huang D. Corneal epithelial thickness mapping in Normal and keratoconic eyes with fourier-domain optical coherence tomography. *Investigative Ophthalmology & Visual Science.* April 2010, Vol.51, 5819.

PHARMACEUTICAL ADVANCEMENTS TO EFFECTIVELY MANAGE OSD

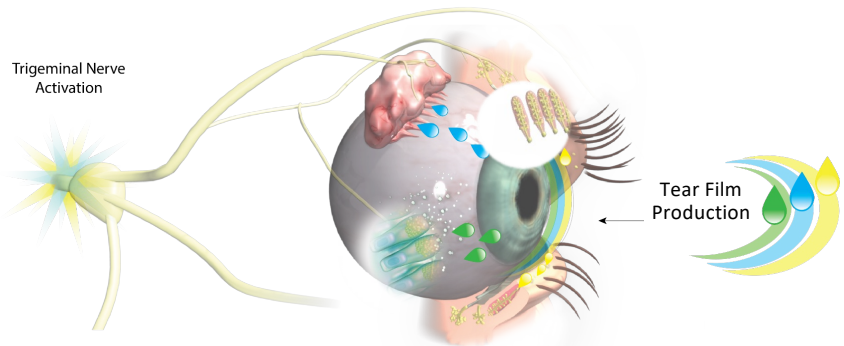
WHAT IS YOUR BASIC TREATMENT FOR OCULAR SURFACE DISEASE?

ARE YOU A STEROID OR CYCLOSPORINE OR LIFITEGRAST GUY?



The Parasympathetic Nervous System (PNS) Is a Critical Regulator of the Lacrimal Functional Unit (LFU) and a Healthy Tear Film

The **parasympathetic nervous system** regulates the Lacrimal Functional Unit (LFU) and Tear Film Production via the Trigeminal Nerve **accessible within the nose**



[1] Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. *Cornea*. 1997 Nov;16(6):645–8.
[2] van der Werf, F. R. A. N. S., Baljet, B., Prins, M. A. A. R. T. E. N., & Otto, J. A. (1996). Innervation of the lacrimal gland in the cynomolgous monkey: a retrograde tracing study. *Journal of anatomy,* 188(Pt 3), 591.
[3] LeDoux, M. S., Zhou, Q., Murphy, R. B., Greene, M. L., & Ryan, P. (2001). Parasympathetic innervation of the meibomian glands in rats. *Investigative ophthalmology & visual science*, 42(11), 2434-2441.
[4] Dartt, D. A., Mccarthy, D. M., Mercer, H. J., Kessler, T. L., Chung, E. H., & Zieske, J. D. (1995). Localization of nerves adjacent to goblet cells in rat conjunctiva. *Current eye research*, 14(11), 993-1000.

Disruptive Approach to Treating Dry Eye Disease Based on Neuroscience and Role of the LFU

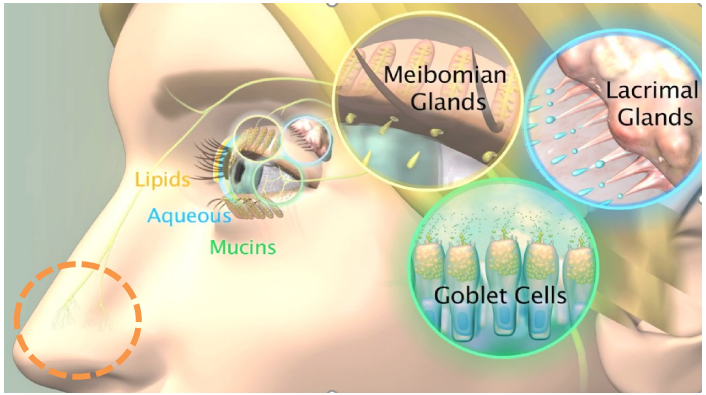
Ideal Compound

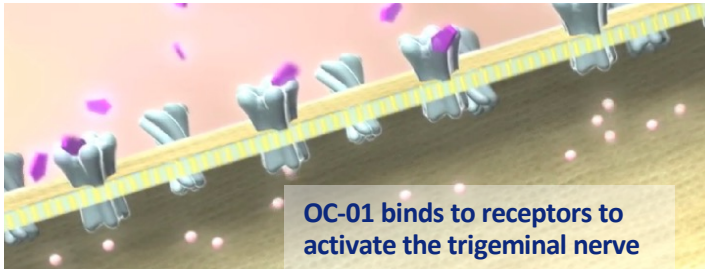
Novel Mechanism of Action

The trigeminal nerve is **accessible within the nasal cavity** and can be activated by stimulating **Nicotinic acetylcholine receptors** (nAChR)

OC-01 **nAChR Agonist with Unique Receptor Activation Profile**

- Nasal Spray Solution
- Multi Dose Preservative Free
- 50µl volume (Standard is 120µl)
- BID Dosing
- 30 Day Supply

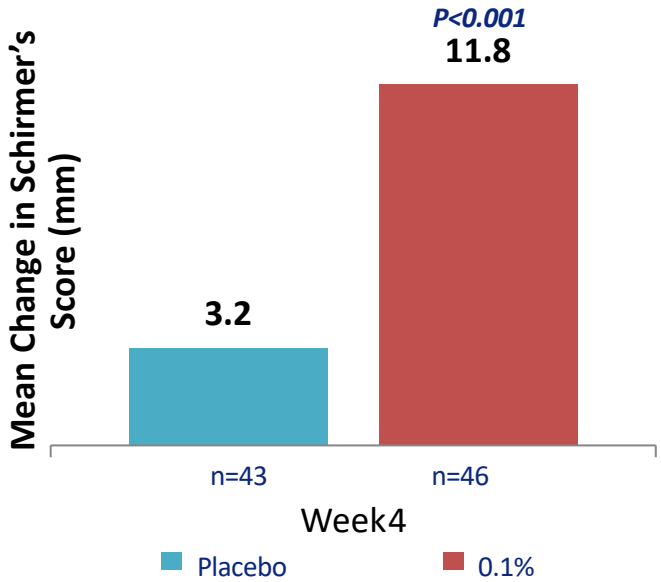




OC-01 Demonstrated Statistically Significant Improvement in Signs and Symptoms of Dry Eye Disease (DED)

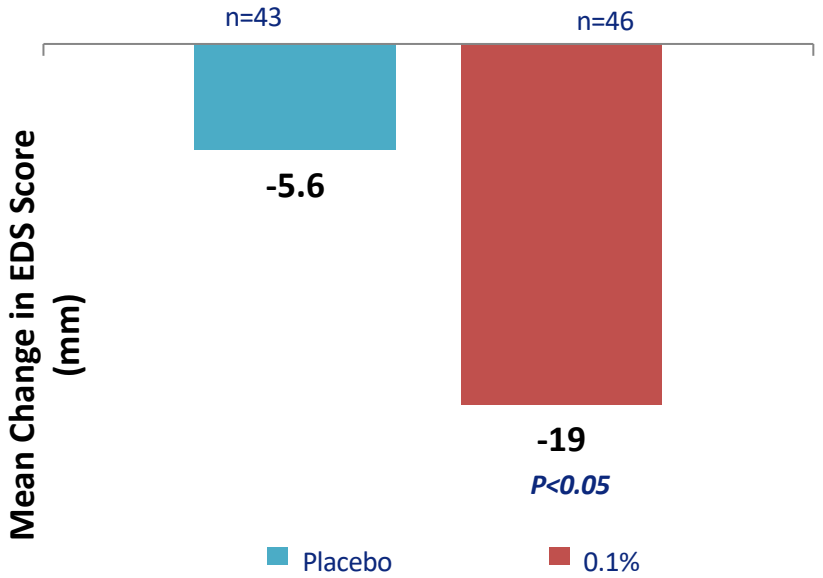
Mean Change from Baseline in Schirmer's Score – Week 4

Primary Sign Endpoint



Mean Change from Baseline in Eye Dryness Score (EDS) – Week 4

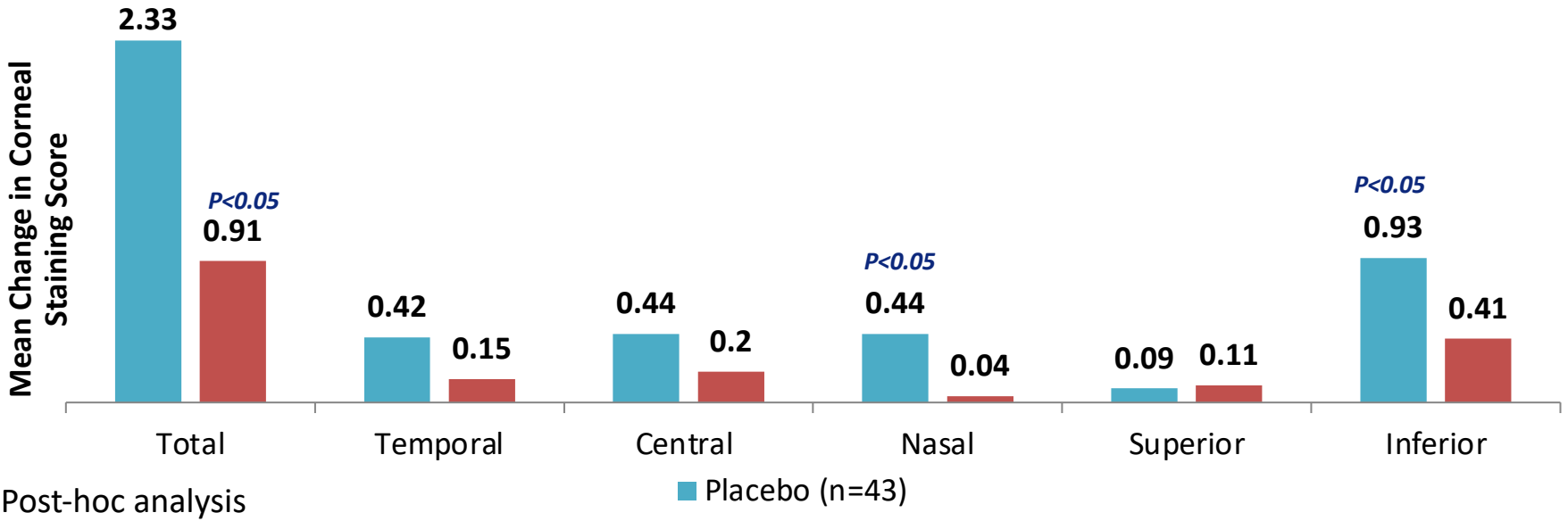
Secondary Symptom Endpoint



ITT-observed population
ANCOVA, Least Squares means

OC-01 Demonstrated Significant Difference from Placebo in Mean Change in Corneal Staining in Total, Nasal and Inferior Regions

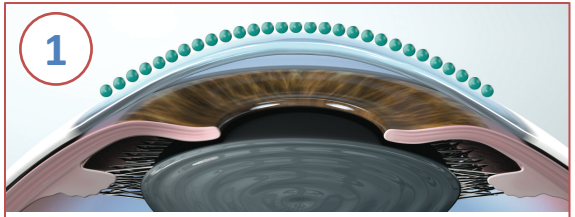
Mean Change from Baseline in Cornea Staining Score – 0.1% @ Week 4



* Post-hoc analysis
** Subject to QC and formal statistical analysis
ITT-observed population
ANCOVA, Least Squares means

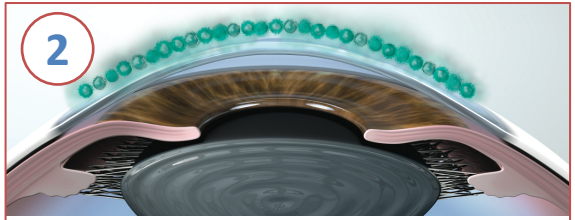
WHERE DO STEROIDS FIT IN YOUR TREATMENT ALGORITHM?

LOTEMAX® SM UTILIZES SM TECHNOLOGY™: RAPID DISSOLUTION WITH SUBMICRON PARTICLES FOR EFFICIENT PENETRATION



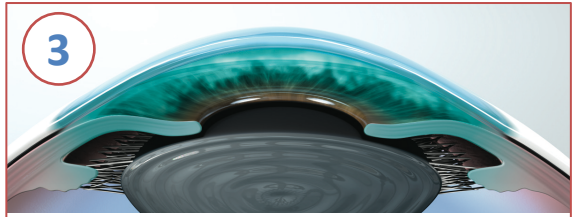
ADHERENCE

Similar to LOTEMAX® GEL, polycarbophil helps enhance widespread coverage and prolong exposure on the ocular surface to maximize absorption potential[1,2]



RAPID DISSOLUTION

Submicron particles have more surface area exposed to tears, driving rapid drug dissolution. In an in vitro assay, ~80% of maximum dissolved loteprednol etabonate was attained at 30 sec[2,3]



PENETRATION

LOTEMAX® SM efficiently penetrates, with ~2x greater penetration to the aqueous humor than LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5%[2]

Clinical significance of these preclinical data has not been established

1. Coffey MJ, et al. *Clin Ophthalmol*. 2013;7:299-312. **2.** Cavet ME, et al. *J Ocul Pharmacol Ther.* 2019. doi: 10.1089/jop.2018.0136. [Epub ahead of print]. **3.** Data on file, Bausch & Lomb Incorporated.

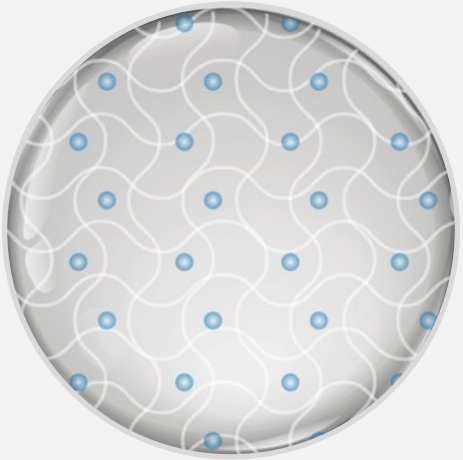
DESIGNED TO ADHERE TO THE OCULAR SURFACE

Non-settling in the Bottle

Polycarbophil provides the gel structure to the formulation to prevent sedimentation of loteprednol etabonate

Adaptive Viscosity in the Tear Film

- Electrolytes in the tear film convert the gel into a viscous liquid by decreasing polycarbophil swelling
- During blinking, high shear force causes the solution to have relatively low viscosity, allowing for easy spreading over the surface of the eye
- Between blinks, low shear force causes the solution to have a relatively higher viscosity, which increases the ocular surface contact time



Polycarbophil gel matrix with encapsulated drug

Polycarbophil helps enhance widespread coverage and prolong exposure on the ocular surface through adaptive viscosity

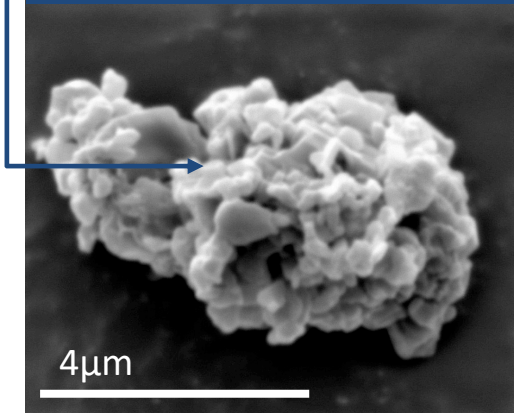
Coffey MJ, DeCory HH, Lane SS. *Clin Ophthalmol*. 2013;7:299-312.

SUBMICRON PARTICLES ARE ~80% SMALLER THAN LOTEMAX® GEL[1]

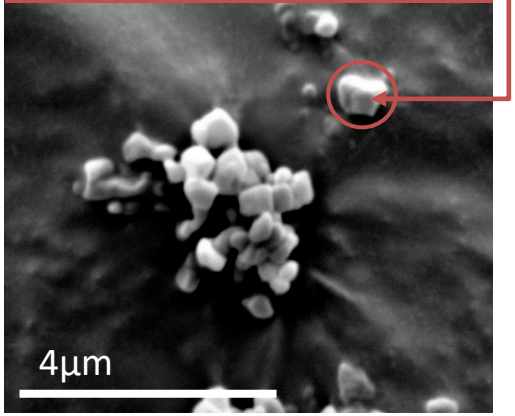
LOTEMAX® GEL[2]

Median particle diameter
~3 to 5 microns

Micron Sized LE Particles in LOTEMAX® GEL[3]



Submicron Sized LE Particles in LOTEMAX® SM[3]



LOTEMAX® SM[2]

Median particle diameter
~0.4 to 0.6 microns

LOTEMAX® SM particles are stabilized by poloxamer 407 and hypromellose[2,4,5]

~3.8 to 9.5 fold increase in total surface area[3]

1. Fong R, et al. *J Cataract Refract Surg*. 2018;44(10):1220-1229. **2.** c**4.** Moghimi SM, et al. *Trends Biotechnol*. 2000;18(10):412-420. **5.** LOTEMAX SM [prescribing information]. Bausch & Lomb Incorporated.

SMALLER PARTICLES LEAD TO EFFICIENT PENETRATION

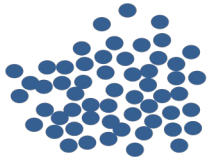
Smaller Drug Particle Size for Faster Dissolution[1,2]

Large drug particles

Slow Dissolution

Lower concentration of dissolved drug in tears

Less drug penetration into ocular tissues



Small drug particles

Fast Dissolution

Higher concentration of dissolved drug in tears

More drug penetration into ocular tissues

A smaller particle size allows for a larger surface area to be exposed to the tear film[1]

Fast dissolution maximizes the amount of dissolved drug available for penetration[2]

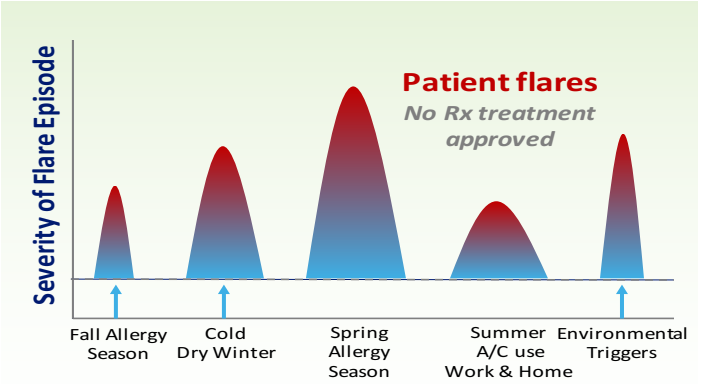
Clinical significance of these preclinical data has not been established

1. Khadka P, et al. *Asn J of Pharm Sci*. 2014;9(6):304-316. **2.** Ghate D, et al. *Expert Opin Drug Deliv*. 2006;3(2):275-287.

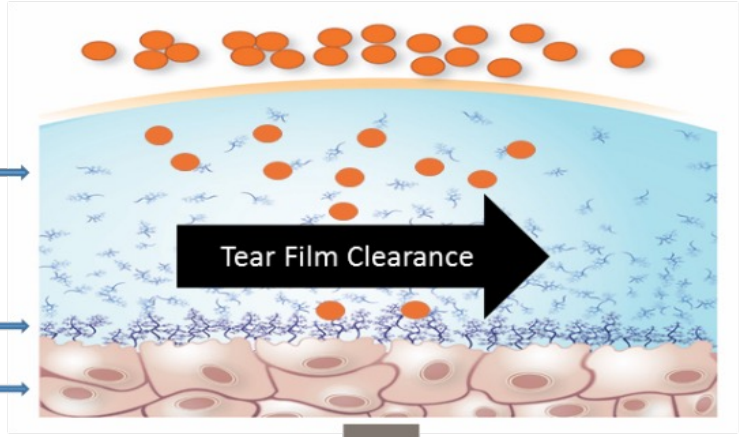
Loteprednol 0.25% in MPP for Dry Eye Flares

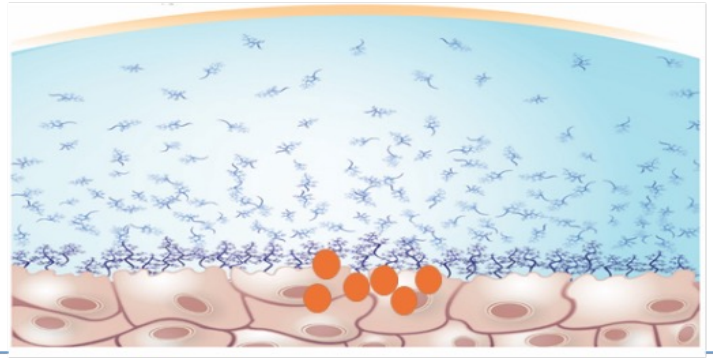
- Loteprednol etabonate 0.25% in the AMPPLIFY™ nanosuspension is ~300 nm
  - Traditional loteprednol etabonate (LE) suspension 6,000 nm
  - Current LE concentrations 0.5% and 0.2%

- FDA Approved on 10/27/2020



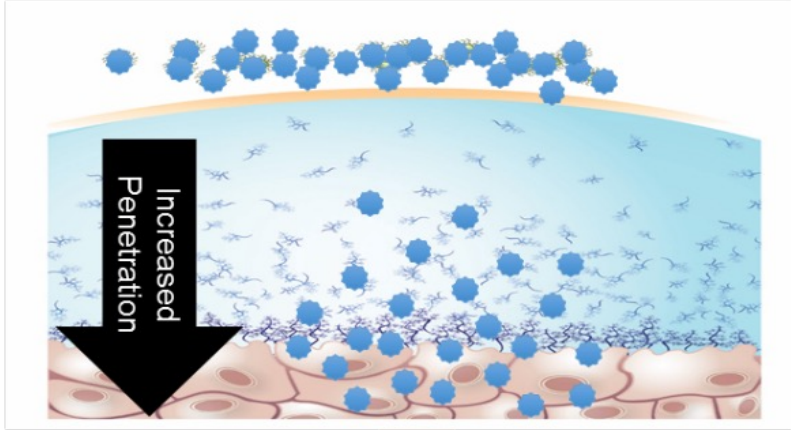
Traditional Suspension Eye Drop

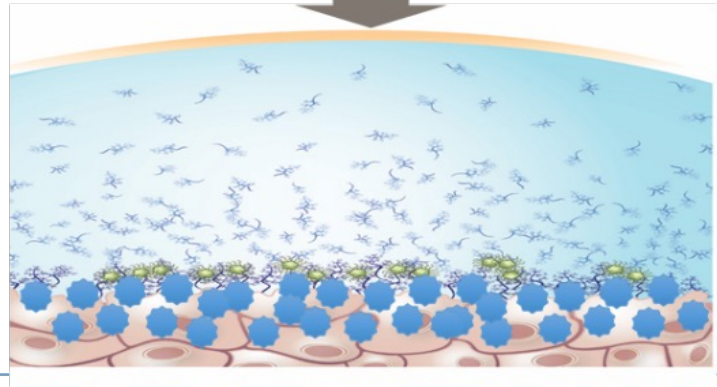




Traditional suspension eye drops adhere to the mucins and are rapidly cleared with the tears via blinking

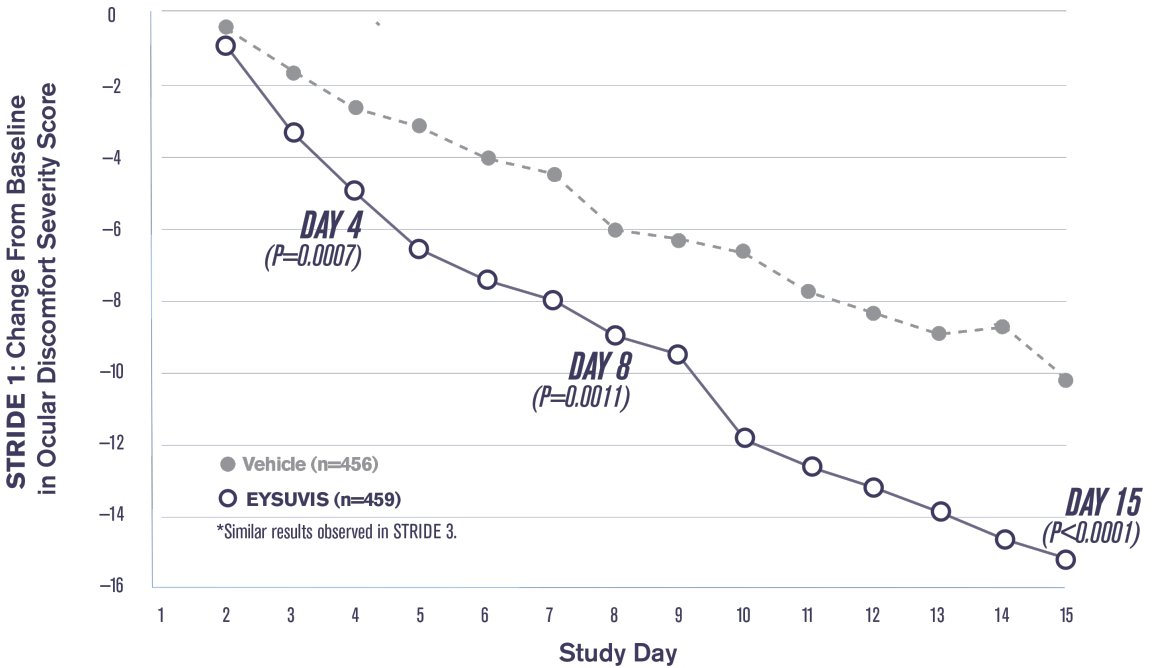
Kala MPPs





MPPs move freely through tear mucins into the membrane-bound mucins, allowing increased penetration and more even coating of target tissues

Demonstrated Rapid Onset of Symptom Relief



Daily OCULAR DISCOMFORT Scores from STRIDE 1 Phase 3 Trial[1,2*]

(DAYS 4, 8, AND 15 WERE PRESPECIFIED ENDPOINTS)

(Inverted scale; lowering of Ocular Discomfort Severity Score from baseline indicates improvement.)

The safety and efficacy of EYSUVIS was assessed in 4 multicentered, randomized, double-masked, placebo-controlled trials (one Phase 2 and three Phase 3 trials, STRIDE 1, STRIDE 2, and STRIDE 3) in 2871 patients with documented Dry Eye. Patients received either EYSUVIS or vehicle 4 times a day for at least 2 weeks. Day 8 and Day 15 were prespecified efficacy endpoints in STRIDE 1, STRIDE 2, and STRIDE 3; Day 4 was also a prespecified endpoint for STRIDE 1. *P* values for Day 8 and Day 15 were analyzed on the days following Day 7 and Day 14 using the 3-day mean prior to Day 8 (Days 5, 6, and 7) and the 3-day mean prior to Day 15 (Days 12, 13, and 14) compared with the 3-day mean prior to Day 1 (baseline). The *P* value for Day 4 was analyzed using the single-day data compared with the 3-day mean prior to Day 1 (baseline). The daily ocular discomfort severity score (ODS) change from baseline data presented here are derived comparing the single-day data from each time point to the 3-day mean prior to Day 1 (baseline).[1]

Reference: 1. Data on file. Kala Pharmaceuticals. Watertown, MA. **2.** Holland E et al. Presented at AAO2020; Nov 13-15, 2020; virtual meeting.

Safety of KPI-121 Ophthalmic Suspension 0.25% in Patients with Dry Eye Disease: A Pooled Analysis of Four Multicenter, Randomized, Vehicle-Controlled Studies

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[1]Virginia Eye Consultants, Norfolk VA; [2]University of Alabama School of Optometry, Birmingham AL; [3]Canyon City Eyecare, Azusa CA; [4]Kentucky Eye Institute, Lexington KY; [5]Kala Pharmaceuticals, Watertown MA

Abstract

Purpose: To evaluate the safety of KPI-121 0.25%, a nanoparticle suspension of loteprednol etabonate with proprietary Mucus-Penetrating Particle (MPP) technology, in subjects with dry eye disease (DED) in pooled analysis of four (one Phase 2 and three Phase 3) multicentered randomized clinical trials.

Methods: A total of 2868 adult DED subjects (≥18 yrs) across one Phase 2 and three Phase 3 clinical trials (Phase 2, STRIDE 1, STRIDE 2, STRIDE 3) were randomized to either KPI-121 0.25% or vehicle four times daily (QID) for at least two weeks. A total of 1430 subjects were treated with KPI-121 0.25% and 1438 with vehicle following a 2-week vehicle run-in period. Main safety assessments were adverse events (AE) and intraocular pressure (IOP). Other safety assessments included best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, and dilated ophthalmoscopy. Safety data across the four trials was pooled for analysis.

Results: AEs were reported with low incidence overall (12.9% in the KPI-121group and 10.4% in the vehicle group). Instillation site pain was the most common AE, reported by 5.2% of subjects in the KPI-121 0.25% group and 4.4% of subjects in the vehicle group. IOP elevations were observed with low incidence, 0.6% and 0.3% of subjects in the KPI-121 and vehicle groups, respectively. No serious treatment-related AEs were reported. Assessments of BCVA, biomicroscopy, and ophthalmoscopy showed no clinically meaningful differences between treatment groups.

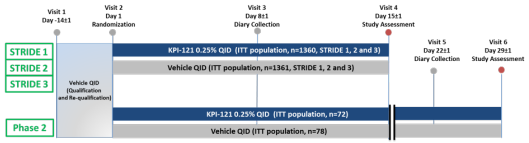
Conclusion: In all four trials, KPI-121 0.25% appeared to be safe and well-tolerated when dosed QID for up to 4 weeks in DED subjects. The incidence of IOP elevation, a known side effect with topical corticosteroids, was similar between the KPI-121 0.25% and vehicle arms.

Key Design Elements

- A total of 2,871 subjects were enrolled which included 150 subjects in the Phase 2 trial from 9 investigative sites, 915 subjects in STRIDE 1 from 55 investigative sites, 905 subjects in STRIDE 2 from 58 investigative sites, and 901 subjects from 82 investigative sites in STRIDE 3.
- The randomized population for STRIDE 3 included 3 subjects who previously participated in STRIDE 2 therefore the safety population includes 2868 subjects. From these, 1430 subjects were treated with KPI-121 0.25% QID and 1438 subjects were treated with vehicle QID.
- **Key entry criteria:**
  - Documented clinical diagnoses of DED in both eyes.
  - Ongoing DED as defined by criteria associated with:
    - Corneal fluorescein staining using the National Eye Institute (NEI) scale
    - Bulbar conjunctival hyperemia as assessed using the CCLRU scale
    - Unanesthetized Schirmer Test score
    - Ocular discomfort severity (ODS) score using modified SANDE
- **Safety** was monitored based on adverse events (AEs), changes in intraocular pressure (IOP), evaluations of biomicroscopy, visual acuity, and dilated ophthalmoscopy.

Study Design and Demographics

KPI-121 0.25% Clinical Trial Design



Summary of Demographic Characteristics by Trial (ITT Population)

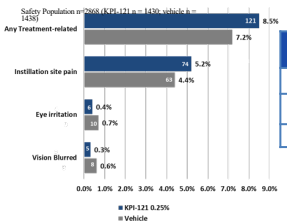
	Phase 2 Trial		STRIDE 1		STRIDE 2		STRIDE 3	
	KPI-121 0.25% (N = 74)	Vehicle (N = 77)	KPI-121 0.25% (N = 455)	Vehicle (N = 456)	KPI-121 0.25% (N = 452)	Vehicle (N = 453)	KPI-121 0.25% (N = 447)	Vehicle (N = 454)
Age (years) Mean (SD)	56.3 (17.17)	54.9 (12.29)	58.1 (15.41)	58.3 (14.66)	59.1 (14.48)	59.3 (15.01)	57.6 (15.26)	57.3 (15.53)
emale, n (%)	53 (72.6)	61 (79.2)	367 (80.0)	359 (78.7)	332 (73.5)	354 (78.1)	339 (75.8)	330 (72.7)
Race, n (%) White	54 (74.0)	63 (81.8)	362 (78.9)	361 (79.2)	345 (76.3)	352 (77.7)	348 (77.9)	341 (75.1)
Black/Africa n-American	10 (13.7)	8 (10.4)	69 (15.0)	71 (15.6)	58 (12.8)	54 (11.9)	71 (15.9)	73 (16.1)
Asian	3 (4.1)	4 (5.2)	18 (3.9)	18 (3.9)	39 (8.6)	35 (7.7)	26 (5.8)	37 (8.1)
Other Race	6 (8.2)	2 (2.6)	10 (2.2)	6 (1.3)	10 (3.1)	12 (2.7)	2 (0.4)	3 (0.7)

Safety Results

Number (%) of Subjects Reporting AEs by Category

	KPI-121 0.25% (n = 1430)	Vehicle (n = 1438)
Any AEs	185 (12.9)	150 (10.4)
Ocular AEs	135 (9.4)	126 (8.8)
Severe AEs	8 (0.6)	1 (0.1)
AEs related to treatment	121 (8.5)	103 (7.2)
AEs leading to discontinuation of study treatment	10 (0.7)	5 (0.3)
Serious AEs	7 (0.5)	1 (0.1)
Deaths	0	0

Number (%) of Subjects Reporting Treatment-related Adverse Event by >0.3% of subjects



Number (%) of Subjects Reporting Common (≥1% in Either Group) AEs (Integrated Safety Population)

System Organ Class Preferred Term	KPI-121 0.25% (n = 1430)	Vehicle (n = 1438)
No. (%) of subjects reporting any AE	185 (12.9)	150 (10.4)
General disorders and administration site conditions	82 (5.7)	69 (4.8)
Instillation site pain	74 (5.2)	63 (4.4)

Number (%) of Subjects Reporting AEs Leading to Permanent Withdrawal of Study Treatment (Integrated Safety Population)

No. (%) of subjects reporting any:	KPI-121 0.25% QID (n=1430)	Vehicle QID (n=1438)
AE leading to permanent withdrawal of study treatment	10 (0.7%)	5 (0.3%)
Conjunctival hyperemia	1 (0.1%)	0
Conjunctival edema	1 (0.1%)	0
Corneal infiltrates	0	1 (0.1%)
Eye irritation	0	1 (0.1%)
Eye pruritus	1 (0.1%)	0
Ocular hyperemia	1 (0.1%)	0
Vision blurred	0	1 (0.1%)
Herpes zoster	0	1 (0.1%)
Nasopharyngitis	0	1 (0.1%)
Eyelid injury	0	1 (0.1%)
Hip fracture	1 (0.1%)	0
Palpitations	1 (0.1%)	0
Nausea	0	1 (0.1%)
Instillation site pain	1 (0.1%)	0
Cholelithiasis	1 (0.1%)	0
Drug hypersensitivity	1 (0.1%)	0
Blood pressure increased	1 (0.1%)	0
Neck pain	1 (0.1%)	0
Headache	1 (0.1%)	0
Delusional disorder, unspecified type	1 (0.1%)	0
Schizoaffective disorder	1 (0.1%)	0
Dyspnea	1 (0.1%)	0
Rash	1 (0.1%)	0

Observed IOP (mmHg) in the study and fellow eyes (Integrated Safety Population)

		Study Eye		Fellow Eye	
		KPI-121 0.25% (N = 1430)	Vehicle (N = 1438)	KPI-121 0.25% (N = 1430)	Vehicle (N = 1438)
Baseline[a, b]		1430	1438	1430	1438
n (SD)	Mea	14.9 (2.54)	14.9 (2.54)	15.0 (2.51)	14.9 (2.48)
Max	Min,	7, 21	7, 21	8, 21	7, 21
Day 15, n		1411	1430	1411	1430
n (SD)	Mea	15.2 (2.65)	14.8 (2.56)	15.3 (2.61)	14.9 (2.51)
Max	Min,	8, 30	7, 25	9, 30	7, 24
Day 29[b, c]		72	78	72	78
n (SD)	Mea	15.6 (3.12)	15.1 (2.80)	15.6 (2.77)	15.3 (2.70)
Max	Min,	10, 30	8, 22	10, 27	9, 22

Number (%) of subjects with Increased IOP Measurements Compared with Baseline (BL) at any Postbaseline Visit, by Category & Eye

	Study Eye		Fellow Eye	
	KPI-121 0.25% (n = 1430)	Vehicle (n = 1438)	KPI-121 0.25% (n = 1430)	Vehicle (n = 1438)
>5 mmHg increase from BL	30 (2.1%)	22 (1.5%)	33 (2.3%)	20 (1.4%)
>5 mmHg increase from BL and ≥21 mmHg measurement	9 (0.6%)	3 (0.2%)	8 (0.6%)	4 (0.3%)
≥10 mmHg increase from BL	4 (0.3%)	0	3 (0.2%)	1 (0.1%)
≥10 mmHg increase from BL and ≥21 mmHg measurement	3 (0.2%)	0	2 (0.1%)	1 (0.1%)

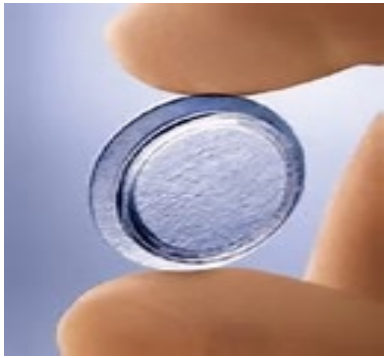
Conclusions

- KPI-121 0.25% is a novel formulation of loteprednol etabonate (LE) utilizing Kala's AMPPLIFY™ Mucus Penetrating Particle (MPP) Technology.
- The most frequently reported treatment-related AE was instillation site pain, reported by 5.2% of subjects in the KPI-121 0.25% group and 4.4% of subjects in the vehicle group.
- The discontinuation rate due to adverse events was low, at 0.7% (10/1430) for the KPI-121 0.25% group.
- In the KPI-121 0.25% and vehicle groups, respectively, 0.7% and 0.3% of subjects experienced a > 5 mmHg increase from baseline resulting in an IOP measurement of ≥ 21 mmHg in 1 or both eyes at any postbaseline visit.
- KPI 121 0.25% QID for up to 29 days appeared safe and well-tolerated. No unexpected adverse events in all four trials. The incidence of treatment-related adverse events was comparable between the KPI-121 0.25% and vehicle arms.
- IOP profile was similar between KPI-121 0.25% and the vehicle arms. Less than 1% of subject experienced IOP elevation defined by increase of >5mmHg from baseline resulting in a measurement ≥21 mmHg.
- Most ocular treatment emergent adverse events (TEAEs) were local to instillation site and mild or moderate in severity.
- No serious ocular TEAE was reported or observed in either treatment arm.

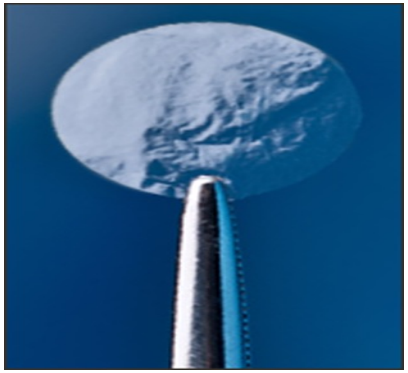
Acknowledgement

Special thanks to Mary Bearkland, Donna Bezner, and Jean Ricci members of Kala Clinical Operation Team.

Amniotic Membranes



Cryopreserved



Dry Membrane

Dry Membrane

Drops

Hindawi
Journal of Ophthalmology
Volume 2017, Article ID 6404918, 10 pages
https://doi.org/10.1155/2017/6404918

Clinical Study

Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease

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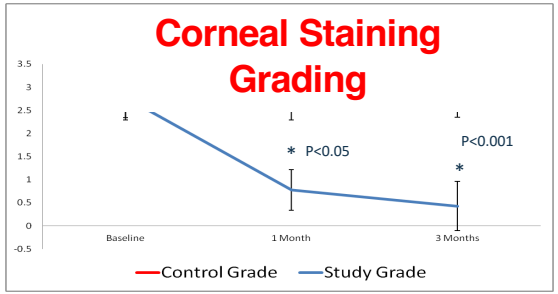
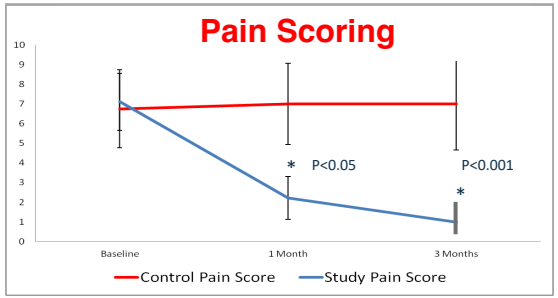
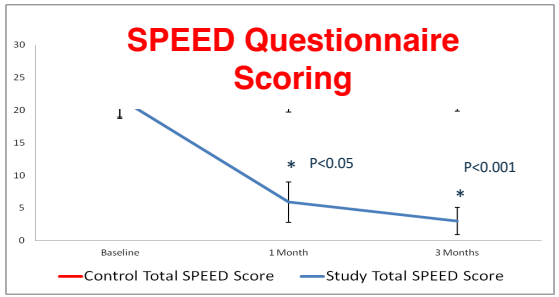
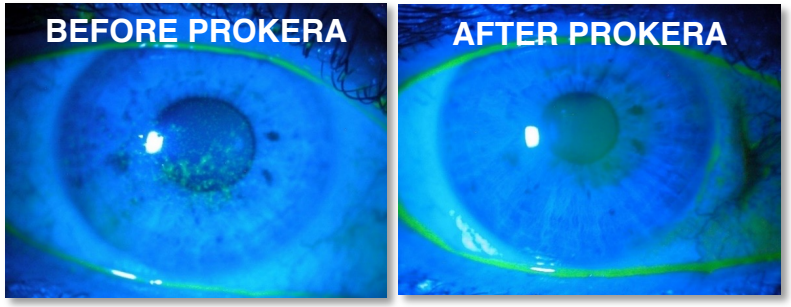
[5]*Research Institute of Ophthalmology, Cairo, Egypt*
[6]*Boston Image Reading Center, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA*
[7]*Center for Translational Ocular Immunology, Department of Ophthalmology, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA*
[8]*Wang Vision Institute, Nashville, TN, USA*

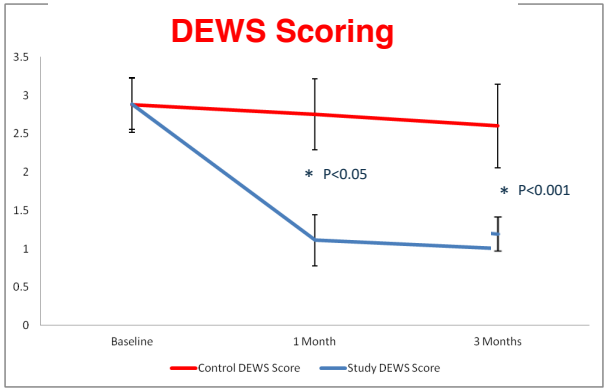
Improvements in Clinical Signs and Symptoms



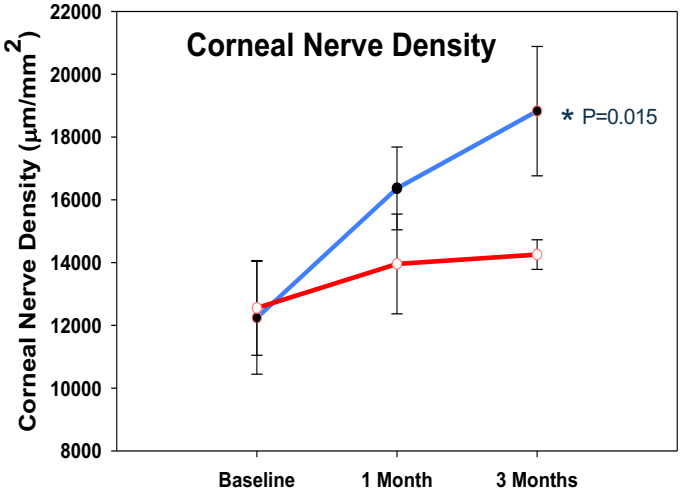


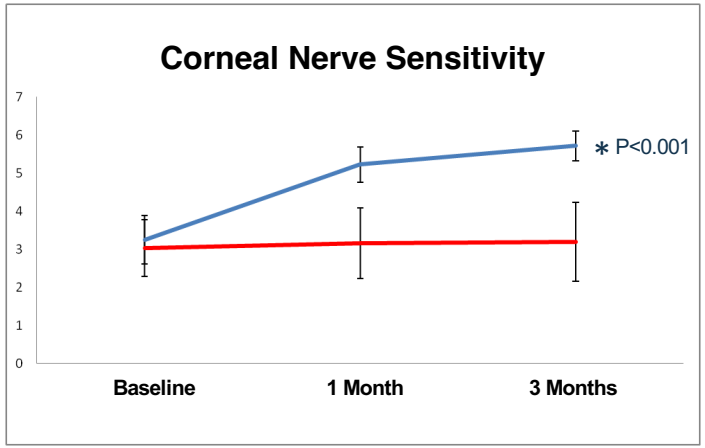




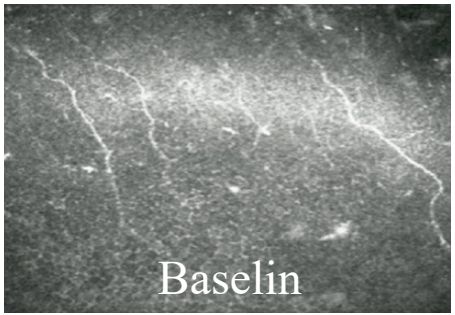


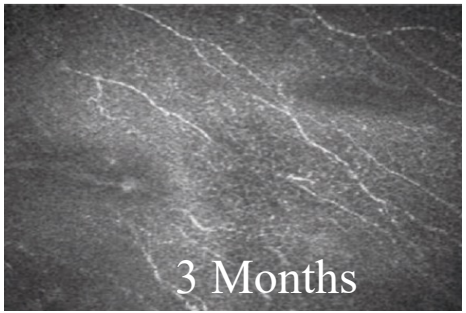
Improvements in Corneal Nerve Density & Sensitivity





Control Measurement Study Measurement

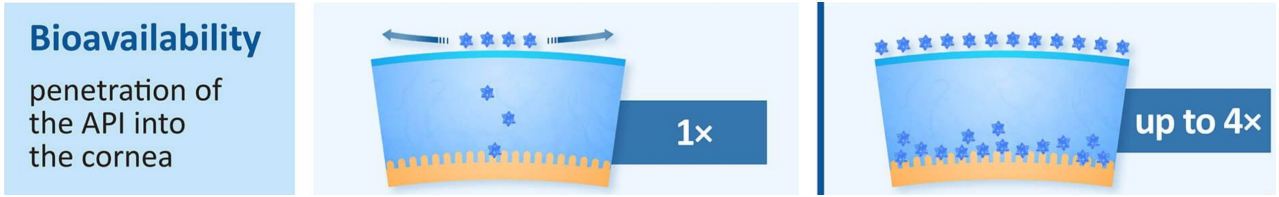


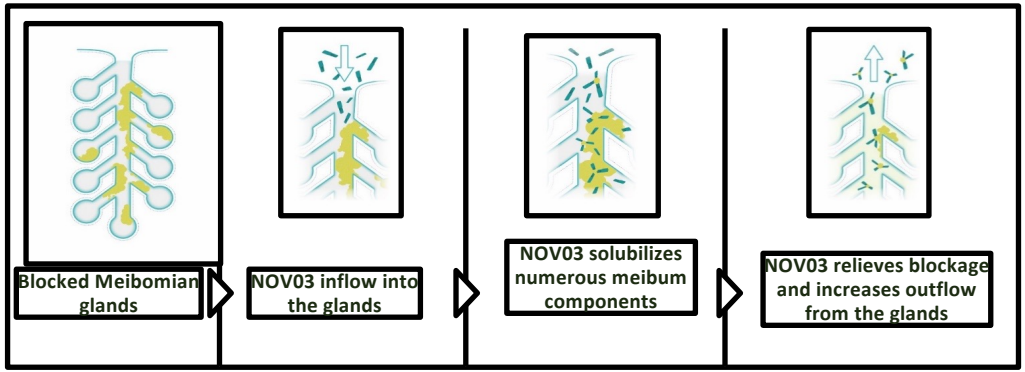


Dry Eye Pipeline

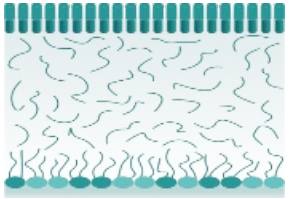
- Dry eye
  - OC-01 - nicotinic acetylcholine receptor (nAChR) agonist
  - Reproxalap ophthalmic solution (0.25%)
- MGD
  - Cyclosporine 0.1%
  - AZR-MD-001 - Treatment for Lipid Deficiency and associated Dry eye
- Demodex
  - TP-03 – Lotilaner

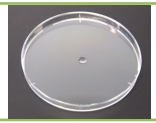
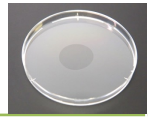
NOV03 Perfluorohexyloctane - Dual Mode of Action





NOV03 Perfluorohexyloctane



	Water-based Technologies	NOV03
Drop Size	**~ 40–50µL** (Blink reflex activated) 	**< 12 µL** (Blink reflex not activated) 
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** **No vision blurring**

A Randomized Clinical Study (SEECASE) to Assess Efficacy, Safety, and Tolerability of NOV03 for Treatment of Dry Eye Disease

Joseph Tauber, MD, David L. Wirta, MD,† Kenneth Sall, MD,‡ Parag A. Majmudar, MD,§ Daniela Willen, PhD,¶ and Sonja Krösser, PhD,¶ for the SEECASE study group*

Purpose: NOV03 has a unique dual mode of action to address dry eye disease (DED) associated with meibomian gland dysfunction. SEECASE evaluated the efficacy, safety, and tolerability of NOV03 at 2 dosing regimens compared with a saline comparator in patients with DED.

Methods: SEECASE was a prospective, multicenter, randomized, double-masked, saline-controlled clinical study. A total of 336 DED patients [tear film breakup time ≤5 seconds, abnormal meibum secretion, total corneal fluorescein staining (tCFS) score of $4 \leq X \leq 11$ (National Eye Institute scale), Schirmer of ≥5 mm] were randomized in a 2:2:1:1 manner to NOV03 4 times daily (QID), NOV03 twice daily (BID), saline BID, and saline QID, respectively. The primary efficacy endpoint was tCFS staining at 8 weeks for both regimens. Secondary endpoints included visual analog scales and the Ocular Surface Disease Index questionnaire for symptom assessment.

Results: The study met its primary endpoint, change from baseline of tCFS over control, for both dosing regimens QID and BID ($P < 0.001$ and $P = 0.009$, respectively). NOV03 also showed pronounced improvement in various symptoms. For the Eye Dryness Score, changes from baseline were statistically significant compared with those of the control at week 8 [$P < 0.001$ (QID) and $P = 0.002$ (BID)]. Benefits on tCFS and symptoms started at 2 weeks after start of treatment and were maintained over the study duration. The effects were dosing schedule dependent. NOV03 was well tolerated with instillation site reactions below 3% in both treatment regimes.

Conclusions: The SEECASE study demonstrated that NOV03 improves signs and symptoms in patients with highly symptomatic evaporative dry eye disease.

Key Words: dry eye disease, keratoconjunctivis sicca, meibomian gland dysfunction, perfluorohexyloctane, clinical trial, clinical study

(*Cornea* 2020;00:1–9)

Dry eye disease (DED) is one of the most common ocular surface disorders, and meibomian gland dysfunction (MGD) is considered as a key component in the pathogenesis of dry eye.[1] The role of meibomian glands is secretion of lipids that form the outermost layer of the tear film; these lipids spread easily, promoting stability and reducing tear evaporation. MGD is characterized by gland obstruction and quantitative and/or qualitative changes in meibum secretion that contributes to the evaporative loss of the tear film and, thus, leading to evaporative DED.[2]

Epidemiological and clinical evidence suggest that most DED is evaporative in nature.[3] Lemp et al[4] reported ~60% to 80% of DED patients having evaporative DED. For evaporative DED associated with MGD, treatment options are currently limited. The principle goal of all treatments for MGD is to increase the quality and quantity of meibomian expressate. Physical therapies such as eyelid hygiene, warm compresses, intense pulsed light, thermal pulsation system (LipiFlow), or lid expression aim to increase lipid outflow[5] whereas lipid containing artificial tears and emulsions aim to substitute the lipid layer.[6] Substitution of the lipid layer, however, is challenging given its complex structure.[7,8]

NOV03 is an investigational drug in the United States; it is a preservative-free, sterile ophthalmic solution with a unique dual mode of action that affects known abnormalities in the lipid layer and meibomian glands. The sole ingredient of NOV03 is the inert and anhydrous semifluorinated alkane perfluorohexyloctane (F6H8). NOV03 rapidly spreads across the ocular surface because of its low surface/interfacial tension and interacts with the lipophilic part of the tear film, forming a layer at the tear film–air interface. The result of this is prevention of evaporation of the aqueous phase of the tears.[9,10] In addition, NOV03 penetrates meibomian glands, where it has been reported to interact with and dissolve the altered, viscous meibum in the glands.[11] In Europe, Australia,

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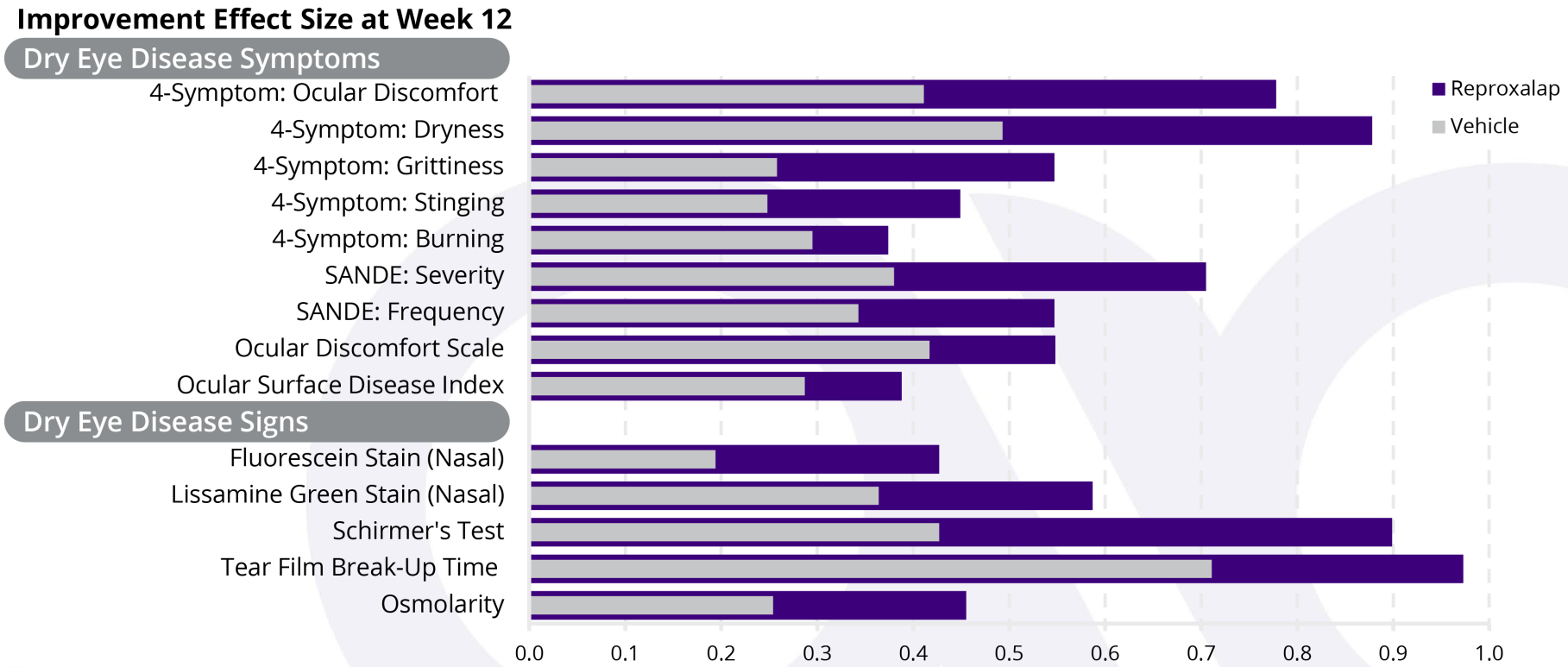
Reactive Aldehyde Species

- Reactive molecules that covalently bind to cellular biomolecules, disrupting their function and activating pro-inflammatory mediators. RASP are formed by a variety of processes, including lipid peroxidation, alcohol oxidation, polyamine and glucose metabolism.

- Levels of RASP are generally observed to be elevated in ocular and systemic inflammatory disease, and thus represent therapeutic targets for immune-modulation

- RASP is a pre-cytokine pro-inflammatory mediator that is elevated in the tears of patients with dry eye disease, and correlates with dry eye disease symptoms and signs.

Broad Drug Activity Across All Measured Dry Eye Disease Symptoms and Signs in Phase 2b Clinical Trial Supports Differentiated Product Profile



Average improvement effect size across both eyes for Schirmer's Test, Tear Film Break-Up Time, and Osmolarity
Topical ocular reproxalap has been studied in over 1,000 patients thus far with no observed safety concerns; mild instillation site irritation is the most commonly reported adverse event in clinical trials.

SANDE = Symptom Assessment in Dry Eye
Improvement Effect size = Change from Baseline / Standard Deviation at Baseline
Source: Reproxalap 0.25% DED Phase 2b clinical trial results

THANK YOU!!

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