Candid Conversations: Ocular Surface Disease COPE#94460-TD

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What's your Why for Dry Eye?

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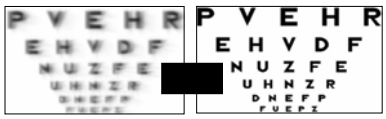
Better Comfort and Quality of Vision

- Tear film abnormalities result in a significant reduction in quality of vision and patient satisfaction
- Due to this, proper ocular surface treatment is critical to outcomes.



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Dry Eye Market Overview

- **>44 Million** Americans suffer from symptoms of dry eye disease
- **$3.8 Billion** spent on dry eye symptom relief annually in the U.S. alone
- **Most frequently encountered disease state** by eye care professionals

Market Scope **2013 Comprehensive Report on the Global Dry Eye Products Market**

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Impact of MGD on Patient Quality of Life

- DED can:
  - Impair patients' physical and mental well-being
  - Leave individuals less productive at work and less able to enjoy their hobbies and social activities
- Patients have compared the impact of moderate to severe DED to that of a hip fracture or severe angina!

Sheppard J et al. *Ann Med*. 2023;55(1):241-252.

5

5

TFOS DEWS II Definition

*"Dry eye is a multifactorial disease of the ocular surface characterized by a **loss of homeostasis** of the tear film, and accompanied by **ocular symptoms**, in which tear film **instability** and **hyperosmolarity**, ocular surface **inflammation** and damage, and **neurosensory abnormalities** play etiological roles."*

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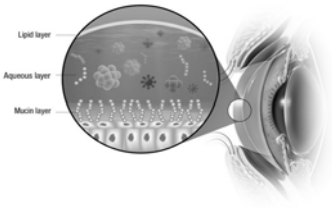
Importance of Healthy Tear Film

- Provides a smooth optical surface for normal vision
- Maintains ocular surface comfort
- Protects from environmental and infectious insults
- Maintains ocular surface epithelial cell health

The tear film is composed of 3 layers:



Stern et al. In: Pflugfelder et al, eds. *Dry Eye and Ocular Surface Disorders*. 2004.

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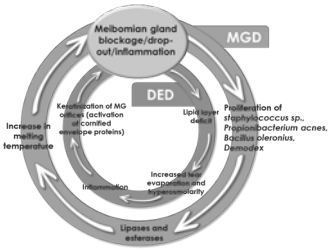
Mechanism of Disease



- Lipids from meibomian glands necessary for ocular surface health and integrity[1]
- Blocked meibomian glands lead to gland dilation, atrophy, low secretion, gland dropout and compromised tear film[1]
- Meibomian gland health is integral to a healthy tearfilm[2]

1. Baudouin C et al, "Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction". Br J Ophthalmol. Vol 100(3), pp 300-306. 2. Dry eye management: targeting the ocular surface microenvironment. Int J Mol Sci. 2017; 18: E1398

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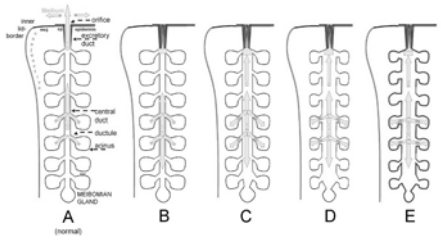
Meibomian Gland Pathology

Obstructive MGD leads to progressive ductal dilatation and acinar atrophy



Knop E et al. *Ophthalmologe*. 2009;106(11):980-987.

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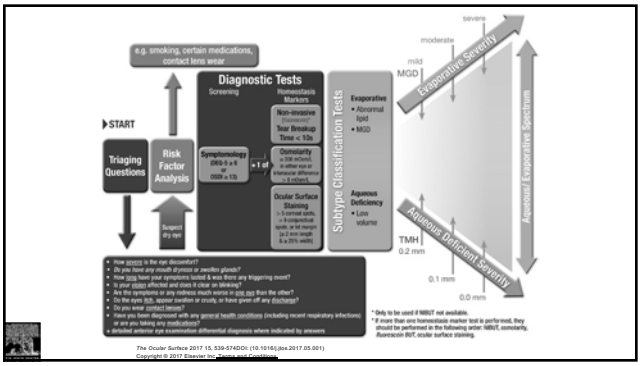

The Ocular Surface 2017 15, 539-574DOI: (10.1016/j.jtos.2017.05.001)
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Who Should We Evaluate?

- Everyone!
- Symptomatic patients
- CL patients
- Conditions associated with OSD
  - Medication
  - Ocular disease
  - Systemic disease

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Risk Factors for Dry Eye Disease

- Age
- Sex
- Medications
  - Anti-everything
  - Ocular medications
- Hormonal deficiency
- Environment
  - Geography
  - Temperature
- Diet
- Systemic conditions
  - Hypertension
  - Rosacea, Atopy,
  - Androgen deficiency
  - SLE
  - Sjogrens
  - Many more
- Ophthalmic surgery
- Contact lens wear
- Digital device use

Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II Epidemiology Report. *Ocular Surf*. 2017;15:334-365.
Gomes JAP, Azar DT, Baudouin C, et al. TFOS DEWS II iatrogenic report. *Ocular Surf*. 2017;15:511-538.

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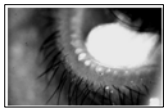
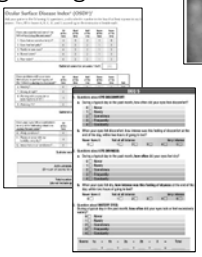
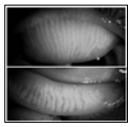
Approaches for Diagnosing MGD

- Patient questionnaire
- Tear osmolarity
- MMP-9
- Meibography
- Lashes
- Lid margin expressibility, quality, and quantity
- Corneal and conjunctival staining
- TBUT
- Corneal sensitivity
- Lid seal







TBUT, tear breakup time.

From Tomlinson A et al. *Invest Ophthalmol Vis Sci.* 2011;52(4):2006-2049.

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What's New in Dry Eye Diagnostics?

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Biomarkers vs. Conventional Diagnostics

Test	Sensitivity	Specificity	Positive Predictive Value (PPV)
Schirmer I <10mm[1]	83%	68%	31%
TBUT <10sec[1]	72%	62%	25%
Staining, rose bengal[1]	25%	90%	31%
Osmolarity >308 mOsms/L[2,3]	75-95%	88%	87%
MMP-9 ≥40 ng/ml[4]	85%	94%	97%
Lactoferrin <0.9 mg/ml	83%	98%	Not available
Conv'l Sjögren's biomarkers[5]	40-60%	40-60%	Not available
New Sjögren's markers[7]	95%	95%	Not available

1.DEWS Report, 2007. Ocul Surf 2007;5(2):108-52. 2. Sullivan BD, Whitmer D, Nichols KK, et al. Invest Ophthalmol Vis Sci 2010;51(12):6125-30. 3. TearLab Osmolarity Test, Package Insert. 4. Inflammad Dry Package Insert-English, Canada, Rapid Pathogen Screening, Inc. 5.Huang Y, Cheng Q, Jiang C, et al. Clin Dev Immunol 2013. 6. Finis D, Pischel N, Schrader S, Geerling G.

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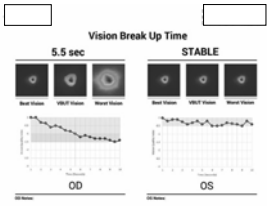
Tear Film Analyzer



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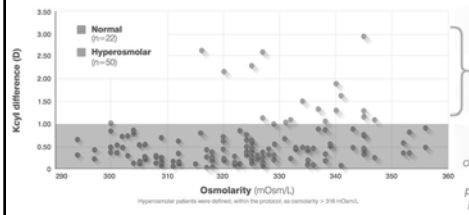
Why Osmolarity Matters



>1D variability in preoperative keratometry in nearly 1 out of 5 patients with hyperosmolarity

"Measurement of tear osmolarity at the time of cataract surgery planning can effectively identify patients with a ***higher likelihood of high unexpected refractive error...***"

Epitropoulos AT et al. J Cataract Refract Surg. 2015 Aug;41(8):1672-7

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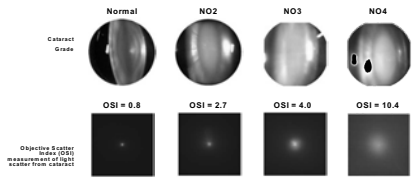
Quantifying Light Scatter



Artal P. PLoS One. 2011 Feb 4;6(2):e16823.

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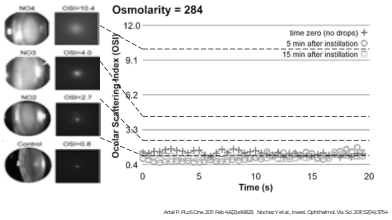
Light Scatter in a Normal Patient



Artal P. PLoS One. 2011 Feb 4;6(2):e16823; Nichez Y et al., Invest. Ophthalmol. Vis. Sci. 2015;52(4):3754

Artal P. PLoS One. 2011 Feb 4;6(2):e16823; Artal P. Data on File 2023

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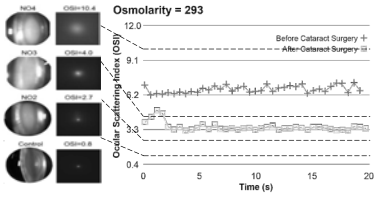
Light Scatter in a Cataract Patient



Artal P. PLoS One. 2011 Feb 4;6(2):e16823; Artal P. Data on File 2023

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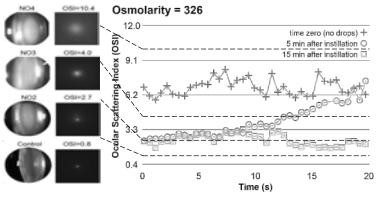
Light Scatter in a Hyperosmolar Patient



Artal P. PLoS One. 2011 Feb 4;6(2):e16823; Artal P. Data on File 2023

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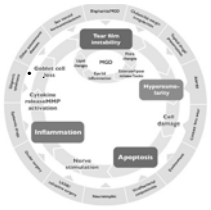
Corneal Esthesiometer



- CEB is an electromedical device for corneal sensitivity assessment through controlled air pulses as stimuli
- It is the first non-invasive and portable corneal esthesiometer

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Corneal Esthesiometer

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

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T-POC Quantitative Testing Platform

Used to improve patient care in the areas of:

- Dry eye disease (DED)
- Ocular allergy
- Ocular surgery, incl Cataract and LASIK

With T-POC in your practice, patients can be diagnosed, treated, and monitored directly within your practice

- Quantitative IgE and Lactoferrin results delivered within minutes
- MMP-9 completing development

Requires ≤ 1 µl tear sample from each eye

1. RAPID
2. REPEATABLE
3. REPRODUCIBLE
4. REIMBURSABLE

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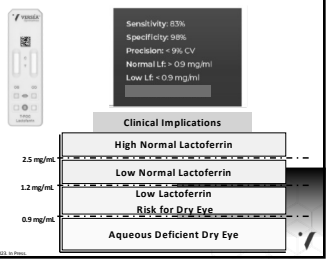
T-POC Lactoferrin Testing

Is it Aqueous Deficient or Evaporative Disease?

Benefits of testing Lactoferrin levels in the tear film:

- Low Lactoferrin levels (<1.2 mg/ml) directly correlate to DED caused by aqueous deficiency
- Severity of DED can be determined by the Lactoferrin level
- Lactoferrin ≤ 0.9 mg/ml has 72% sensitivity and 95% specificity for Sjogren's Disease
- Low Lactoferrin levels indicate DED with increased surgical risk
- Low Lactoferrin levels may indicate the cause of contact lens intolerance
- Changes in Lactoferrin levels may show the efficacy of the prescribed treatment
- Lactoferrin levels are normal, and not reduced, in the setting of meibomitis related rosacea



Chester T, et al How can we best diagnose severity levels of dry eye disease: Current perspectives. Clinical Ophthalmology. 2023. In Press.

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T-POC IgE Testing

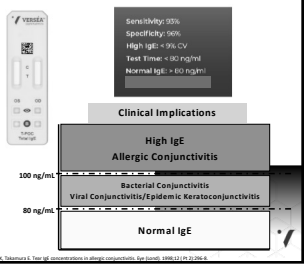
Is There An Allergic Component?

Benefits of testing IgE levels in the tear film:

- Presence of IgE indicates the diagnosis of allergic conjunctivitis (seasonal, perennial, atopic, and vernal)
- Levels of IgE increase with the severity of the allergic response
- IgE testing can help differentiate allergic conjunctivitis from DED and viral conjunctivitis
- Elevated IgE causes tear film instability
- Changes in IgE levels may show the efficacy of prescribed treatment

IgE value is < 80 ng/mL (33 kIU), there is a 95.7% probability that the patient does not have an ocular allergy

IgE value is > 80 ng/mL, there is a 92.9% probability that this elevated IgE is indicative of an ocular allergy



Chester T, et al How can we best diagnose severity levels of dry eye disease: Current perspectives. Clinical Ophthalmology. 2023. In press. Nomura K, Takamura E. Tear IgE concentrations in allergic conjunctivitis. Eye (Lond). 1998;12 (Pt 2):296-8.

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Epi-Mapping

- Quantitative measurements of the epithelial and stromal layers of the cornea
- Indications
  - Refractive surgery
  - Keratoconus
  - Dry eye disease

Rocha KM, Stratiotia 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.

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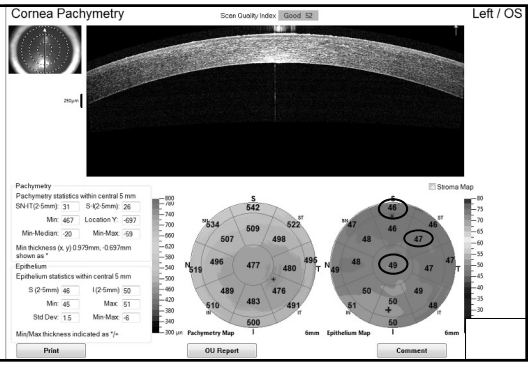
Dry Eye



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Comprehensive DRY EYE Assessment

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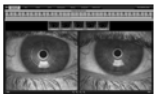
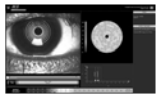
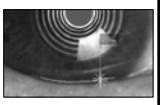
Comprehensive Data Gathering



AUTO INTERFEROMETRY
- Automatically evaluates the quantity and quality of the lipid component of the tear film
- Reporting the Lipid Layer Thickness (LLT) measurement (15 nm through 160 nm classified through the Guillon Scale[1])

AUTO NIBUT – NON-INVASIVE
- Average of more than one value
- Graph documents tear film trend stability during the video
- Topography documents all breaking of the tear film over time

AUTO BLINK EVALUATION
- Automatically evaluates blink quality, delivering a completeness of blink score
- Evaluate Blink Quality of contact lens wearers to identify low blink rate or incomplete blinking for dry eye symptoms or ocular surface staining.

AUTO TEAR MENISCUS HEIGHT MEASUREMENT
- Automatically identifies tear meniscus analyzing hundreds of points to determine the height measurement
- No relying on technician to perform measurements

Patient-friendly traffic light results

15 Seconds Per Eye

1 Guillon JP. Use of the Tearscope Plus and attachments in the routine examination of the marginal dry eye contact lens patient. *Adv Exp Med Biol*. 1998;438:859-867. doi:10.1007/978-1-4615-5359-5_121

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Meibography & 3D Meibography

Automatic Lid & Gland Detection

Patients can have meibomian gland loss with no dry eye symptoms

2 Arita R, Minoura I, Morishige N, et al. Development of Definitive and Reliable Grading Scales for Meibomian Gland Dysfunction. *Am J Ophthalmol*. 2016;169:125-137. doi:10.1016/j.ajo.2016.06.026

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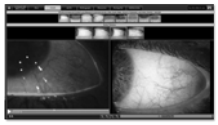
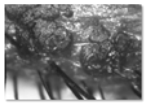
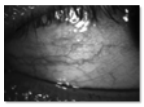
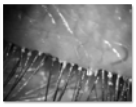
External Documentation

Fluorescein, Lissamine Green Imaging, Demodex, Blepharitis, Cylindrical Dandruff
- Document demodex brevis mites
- Providing Staining Assessment of the cornea, conjunctiva, and lid margins classified through the relevant grading scales
- Evaluate and monitor appearance of eye lid lashes and edge margins, skin texture

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Clearly documented evidence save consultation time

Quick Snap-Shot View
- Provides an immediate view of all test results.
- Using the familiar Green-Yellow-Red traffic light grading display guides patients through the status of their disease state
- Encourages compliance and improves conversion rates for premium services (IPL, LipiFlow, etc.)
- Improve acceptance of ocular surface treatment requirements prior to cataract and refractive surgery.

If a patient can't see what you see, they won't convert to treatment.

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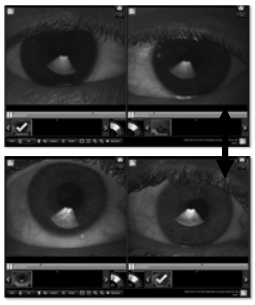
Help patients understand their disease state



Compare Before & After Treatment Images

- Encourages patients to continue their treatments
- Aids in the conversion of premium services like IPL, LipiFlow, etc.

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CASE STUDY 1

70YOWF Presents for DM Evaluation

- Blurry, fluctuating vision OU and worse since last visit one year ago. Itching, burning, redness. Takes OTC gel drops PRN and baby shampoo qhs. HgA1c unknown
- **LEE**: 1.5 years
- **Oc Hx**: Dry eye for 3 years with punctal occlusion, Phaco OS
  - Failed Meds: Cyclosporine, lifitegrast
- **Med Hx**: Depression, HTN, Angina, DM, Seasonal allergies, Asthma
- **Meds**: Albuterol, Buspirone, Doexpine, duloxetine, Fosamax, januvia, atorvastatin, micardis, nitroglycerin, pantoprazole, pramipexole, montelukast, valacyclovir, wellbutrin
- **Allergies**: beta blockers, PCN, phenytoin sodium, sulfa

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CASE STUDY 1

EXAMINATION

BCVA
- OD 20/40-2 PH 20/25
- OS 20/40 PH 20/30-

MR
- OD -0.75 + 0.25 x 005 20/40-
- OS -1.75 + 0.50 x 180 20/50

Lensometry
- OD -1.25 + 1.50 x 178
- OS -2.50 + 2.00 x 155

SPEED: 12 / 28

SLE
- Lids: Clear expression
- K:
  - 1+ABMD OU
  - TBUT 5 sec
- Lens:
  - OD 1+ NS
  - OS PCIOL
- No DR / CSME

What else would you like to know?

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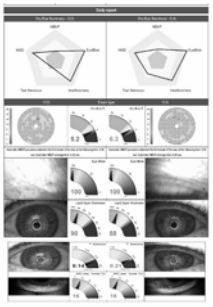
CASE STUDY 1

What about osmolarity and MMP-9?

What type of dry eye?

How should we treat?



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CASE STUDY 1

Treatment Plan
- Moist Heat mask qd
- PHFO QID OU
- F/u 4-6 weeks, SPEED, Tear osmolarity

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AI and Dry Eye

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What is your Treatment Algorithm?

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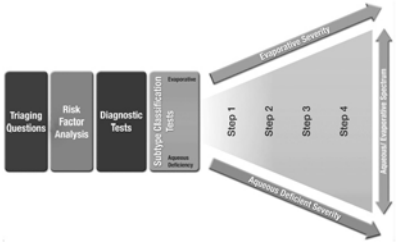
TFOS DEWS II Diagnostic Methodology



Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf 2017;15:539-74.

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TFOS DEWS II Management and Therapy Algorithm

- ***Step 1*** - patient education; environmental modifications; dietary recommendations; and home treatment with lid hygiene, warm compresses, and lubricating eye drops.
- ***Step 2*** comprises management with prescription medications, including topical steroids, cyclosporine, LFA-1, secretagogues, and topical or oral antibiotics. Punctal plugs, MGD Tx, IPL
- ***Step 3*** includes oral secretagogues, bandage or scleral contact lenses, and autologous serum eyedrops.
- ***Step 4*** is reserved for refractory DED that may require long-term topical corticosteroids, amniotic membrane grafting, or surgical intervention such as permanent punctal occlusion, tarsorrhaphy, and other eyelid procedures.

Jones L et al. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15(3):575-628.

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CEDARS DE Algorithm

Accessed on https://www.ophthalmologymanagement.com/newsletters/ocular-surface-news-for-mds/february-27,-2019

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ASCRS DE Algorithms

- **Step 1.** Noninvasive refractive preop measurements
  - Keratometry, topography, optical biometry, aberrometry, etc.
- **Step 2.** OSD screening battery
  - Pre-op questionnaire
  - Objective signs - osmolarity and inflammatory marker testing
- **Step 3.** Look, Lift, Push, Pull, Stain
- **Step 4.** OSD ruled in or out
  - If ruled in, determine visual significance

Starr, Christopher E. et al. An algorithm for the preoperative diagnosis and treatment of ocular surface disorders. Journal of Cataract & Refractive Surgery, Volume 45, Issue 5, 669 – 684 2019

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Treatment Strategies in 2025

- Lubricants
  - Tears (emulsions, solutions), gels, ointments, sustained-release formulation
  - Ingredients
    - Hyaluronic acid, Carboxymethylcellulose (CMC), Lipid-based
- Nutrition
  - Oral essential fatty acids
  - Vitamin A ointment
  - Lutein, xeazanthin, curcurminoids, vitamin D

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Treatment Strategies in 2025: Lid Margin Disease Management

- Warm compress and lid massage
  - Difficult to maintain adequate temperature; poor compliance
- Lid scrubs
  - Commercial soap scrubs
  - Tea tree oil in *Demodex* mite infestation[1]
- In-office lid margin cleansing / meibomian gland procedures
  - Motorized/mechanical devices[2]
  - Thermal and thermal pulsation[3]
  - Intraductal probing[4]
  - Intense pulsed light[5]

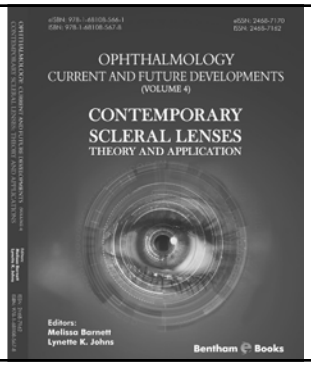
1. Gao YY, et al. *Cornea*. 2007;26(2):136-143; 2. Korb DR, Blackie CA. *Cornea*. 2013;32(12):1554-15
3. Lane SS, et al. *Cornea*. 2012;31(4):396-404; 4. Maskin SL. *Cornea*. 2010;29(10):1145-1152;
5. Craig JP, et al. *Invest Ophthalmol Vis Sci*. 2015;56(3):1965-1970.

47

Treatment Strategies in 2025

- Anti-inflammatory agents
  - Topical corticosteroids
  - Topical cyclosporine A emulsion (CSA) 0.05%, 0.09%, 0.10%
  - Topical lifitegrast, 5%
  - Oral tetracyclines or macrolides
  - Topical azithromycin
- Amniotic membrane products: anti-inflammatory and promote wound healing
- Neurostimulation
  - Intranasal neurostimulation
  - Extranasal neurostimulation

48

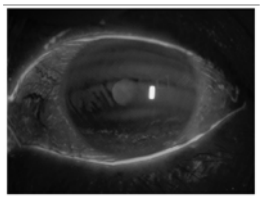


49

What Needs Exist in Dry Eye for 2024 and Beyond?

50

Nocturnal Lagophthalmos



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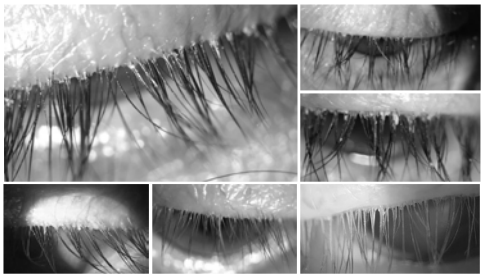
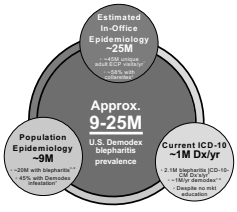


52

Epidemiology of Demodex Blepharitis



Largely Underdiagnosed, Education Needed	~ 58% of all patients in the eye clinic have collarettes[2] but current impression of only 10-15% of blepharitis cases
Significant head start on Diagnosis	2.1M ICD-10 Blepharitis Dx's/yr[3]
Blepharitis Routinely Causes	Eyelids to become red, irritated and itchy, with debris on the eyelashes[3]
Blepharitis Can Lead To	Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the cornea[3]
Blepharitis and Surgery	Important factor for maximizing surgical outcomes: 67% of cataract patients have Demodex blepharitis[4]
Contact Lens Drop-out	#1 reason people discontinue contact lens wear is discomfort. Studies have shown a direct correlation between Demodex blepharitis and CL intolerance[3,10]
Prescription Treatment	None

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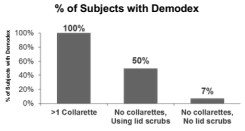
Collarettes Are Composed of Mite Waste Products and Eggs[1]

Easily and Rapidly Diagnosed with Standard Eye Exam



1. Fromstein 2018
2. Gao et al., Invest Ophth and Vis Sci, September 2005, Vol. 46, No. 3089-3094.
3. Tarsus Collarette Prevalence Study

54

Lotilaner ophthalmic solution 0.25%

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

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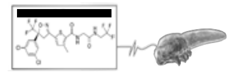
MECHANISM OF ACTION

Lotilaner ophthalmic solution 0.25%

- Lotilaner functions as a noncompetitive antagonist of mite and arachnid GABA-gated chloride channels[1,2]
- Directly paralyzes the mite nervous system through parasite-specific GABA inhibition, leading to death[1,2]
- The lipophilic nature of the drop suggests its ability to flow into the oily sebum of the lash follicle where the mites reside[3]



Product form[5]
Preserved (sorbate) multidose eye drop solution in bottle

Dosing[5]
Twice daily for 6 weeks

FDA, Food and Drug Administration; GABA, gamma aminobutyric acid.

1. Dailymed Credelio. Accessed June 28, 2022. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=427f2ebc-ce24-452b-bbb3-43d4ef8b63b0 **2.** Gonzalez-Salinas R et al. *J Ophthalmol*. 2021:3862684. **3.** LianBio. Accessed June 28, 2022. https://www.globenewswire.com/news-release/2022/05/03/2434549/0/en/LianBio-Partner-Tarsus-Pharmaceuticals-Announces-Positive-Topline-Data-from-Second-Pivotal-Trial-of-TP-03-for-the-Treatment-of-Demodex-Blepharitis.html
4. ChemSrc Lotilaner. Accessed June 28, 2022. https://www.chemsrc.com/en/cas/1369852-71-0_1262257.html **5.** Yeu E et al. *Cornea*. 2022; In Press.

56

SATURN-1 and SATURN-2 | PIVOTAL CLINICAL STUDIES OF TREATMENT FOR *DEMODEX* BLEPHARITIS

Consistent cures and **responses** demonstrated in **2 pivotal trials,** the largest clinical program for *Demodex* blepharitis, involving **833 patients**

The primary and all secondary endpoints (collarette cure, mite eradication, lid erythema) met with high statistical significance

Clinically and statistically significant effects seen as early as **2 weeks**

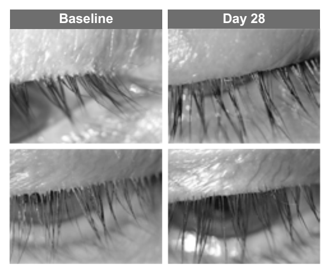
Very high responder rate to TP-03: **96%** of patients improved at least 1 collarette grade; **89%** achieved a clinically meaningful cure

Efficacy goal
1° collarette cure rate, 2° mite eradication, 2° redness + collarette cure rate

Safety goal
Well-tolerated safety profile

57

Cure of Collarettes with BID Use



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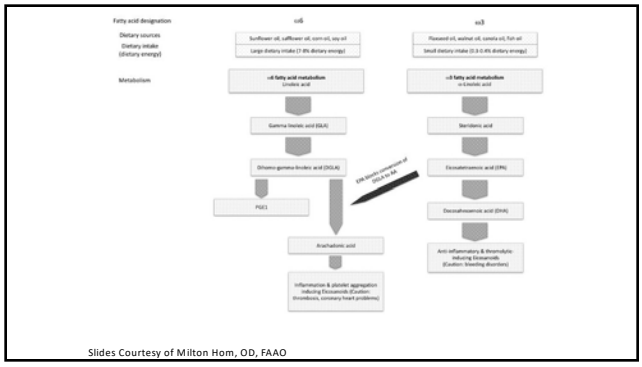
Where Do Nutracueticals fit in?

59

Oral Medications for Dry Eye

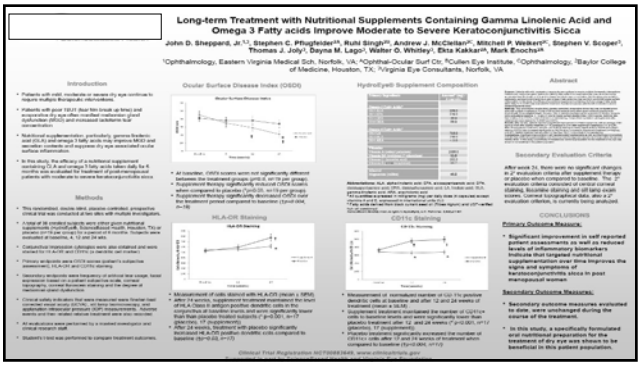
- Nutritional supplements
  - 1,000 mg BID of Omega-3 Fish Oil
- Rx
  - 4g per day po
  - Indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia
- Oral pilocarpine
  - Salagen®: 5 mg qid for dry mouth
  - Evoxac®: 30 mg tid for dry mouth

60



Slides Courtesy of Milton Hom, OD, FAAO

61



Long-term Treatment with Nutritional Supplements Containing Gamma Linolenic Acid and Omega 3 Fatty acids Improve Moderate to Severe Keratoconjunctivitis Sicca

John D. Sheppard, Jr.[1,2], Stephen C. Pflugfelder[3,4], Ruhi Singh[3,4], Andrew J. McClellan[3,4], Mitchell P. Weikert[3,4], Stephen V. Scope[1], Thomas J. Joly[1], Dayna M. Lago[1], Walter O. Whitley[1], Ekta Kakkar[3,4], Mark Enochs[3,4]

[1]Ophthalmology, Eastern Virginia Medical Sch, Norfolk, VA, [2]Ophthal-Ocular Surf Ctr, [3]Cullen Eye Institute, [4]Ophthalmology, [5]Baylor College of Medicine, Houston, TX, [6]Virginia Eye Consultants, Norfolk, VA

Introduction

Ocular Surface Disease Index (OSDI)

HydroEye® Supplement Composition

Abstract

Methods

HLA-DR Staining

CD11c Staining

Secondary Evaluation Criteria

CONCLUSIONS

Primary Outcome Measure:

Secondary Outcome Measure:

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Effect of Oral Re-Esterified Omega-3 Nutritional Supplementation on Dry-Eye Disease: Double-Masked Randomized Placebo-Controlled Study

- 105 patients with dry eye disease
  - Four capsules (2 gm) once a day containing 1680mg EPA and 560mg DHA (PRN Dry Eye Omega Benefits) for 3 months or four capsules of placebo.
  - All patients underwent a screening, baseline, 6 week and 12 weeks visit.
  - On each visit patients were tested for tear osmolarity, MMP-9, fluorescein corneal staining, Schirmer's testing, and OSDI. On the screening exam and week 12 evaluation patients had their omega index tested.
- This study demonstrated that oral consumption of re-esterified omega-3 fatty acids (1680 mg EPA and 560 mg DHA once daily for 12 weeks) is an effective treatment of dry eye disease and results in a statistically significant improvement in tear osmolarity, OSDI, tear break up time and omega index levels.

Donnenfeld ED, Holland, EJ, Bucci FA, et. Al. 2015

63

Latest Proprietary Blend of Antioxidant Ingredients for Dry Eye

Integrative Actives

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

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

Curcuminoids **200 mgs**

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

Vitamin D3 **600 IU**

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

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

1. Cristaldi M, et al. *Appl Sci* (2022) 12(3):1268. 2. Bian Q, et al. *Free Radic Biol Med* (2012) 53 (6):1298-307. 3. Castro-Castaneda CR, et al. *Nutrients* (2022) 14(23):5014. 4. Davis BM, et al. *Sci Rep* (2018) 8(1):11068. 5. Gorimanipalli B, et al. *Indian J Ophthalmol* (2023) 71(4):1127-34. 6. Hwang JS, et al. *Cornea* (2019) 38(3):304-10. 7. Najjaran M, et al. *Clin Exp Optom* (2023) 106(3):257 62.

64

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

Addressing dry eyes from the inside out*§

MMP-9 Positivity

Promoting healthy tear production*§

Schirmer Test Score, OU

Reducing patient discomfort in 2 to 4 weeks*

OSDI Total Score

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

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

§ Based on a clinical study

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

65

Are You a Cyclosporine or Lifitegrast or Varenicline or Loteprednol or Fluoromethalone or Dexamethasone Guy?

66

What Happens Beyond Cyclosporine 0.05%? Unveiling Phase 4 Study of Patients Switching to 0.09%

Study design: Single arm, phase 4, 12-week, multicenter study of 124 adults with inadequately controlled DED on current Restasis therapy[1,2]

Co-primary endpoints: Corneal fluorescein staining (CFS) (signs) and mSANDE (symptoms)[3]

Inclusion Criteria[3]
Clinical diagnosis of DED & treatment on Restasis for ≥3 months
BCVA of ≥20/200 mSANDE score of ≥40
Total CFS ≥6 or CFS in an individual zone ≥2 at baseline

Exclusion Criteria[3]
Previous history of failure on Restasis
Discontinued/switched to different immunomodulatory

Patients were on 0.05% for >38 months before switching to 0.09%[2]

Patients received **1 drop 2x** daily of 0.09% in each eye[1]

BCVA=best corrected visual acuity; CFS=corneal fluorescein staining; DED=dry eye disease; mSANDE=modified Symptom Assessment in Dry Eye.
1. Johnston, J. Effect of OTX-101 0.09% on corneal staining and SANDE scores in patients with dry eye disease uncontrolled on cyclosporine ophthalmic emulsion 0.05%. Abstract presented at American Academy of Optometry 2023; October 12, 2023; New Orleans, LA. **2.** Data on file. Cranbury ,NJ: Sun Pharmaceutical Industries, Inc. **3.** Effect of CEQUA in Subjects with Dry Eye Disease, ClinicalTrials.gov identifier NCT04357795. Updated Sept 09, 2022. Accessed August 29, 2023. https://www.clinicaltrials.gov/study/NCT04357795. 67

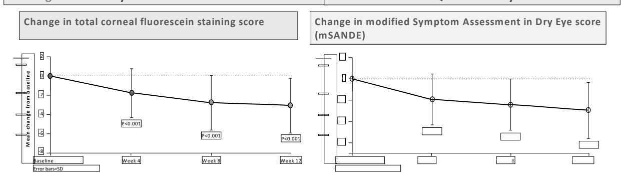
67

Demonstrated Improvements As Early as Week 4 After Switching from 0.05% to 0.09%

FOR THE MAJORITY OF PATIENTS

Statistically significant improvements in total corneal staining seen as early as week 4 & continued to week 12[1]

Most reported their eyes felt more comfortable* after 4 weeks of CEQUA than they did with Restasis[1]



*Less dryness and irritation.
BCVA=best corrected visual acuity; CFS=corneal fluorescein staining; DED=dry eye disease; mSANDE=modified Symptom Assessment in Dry Eye.
1. Johnston, J. Effect of OTX-101 0.09% on corneal staining and SANDE scores in patients with dry eye disease uncontrolled on cyclosporine ophthalmic emulsion 0.05%. Abstract presented at American Academy of Optometry 2023; October 12, 2023; New Orleans, LA. 68

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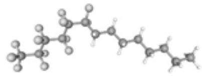
NOV03-Perfluorohexyloctane

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



	Water-based Technologies	NOV03
Drop Size	~ 40–50µL	11 µL
Drug Residual Time	Brief 3–5 min	Long ~ 240 min
Spreading	High surface tension hinders spreading	Fast spreading Film forming properties
Other features	Usually preserved	Preservative free Blink reflex not activated No vision blurring

1. Krösser S, et al. *Invest Ophthalmol Vis Sci.* 2018;59:2656. 2. Broniatowski M, et al. *J Phys Chem B* 2004;108:13403-13411. 3. Liu X, et al. *Bull Chem Soc Jpn.* 2018;91(5):846-857. 4. Gaines G Jr. *Langmuir* 1991;7(12):3054-3056. 5. Meinert H, et al. *Eur J Ophthalmol.* 2000;10(3):189-197. 6. Borchmann et al. *Invest Ophthalmol Vis Sci.* 2022;63:1525 – A0250. 69

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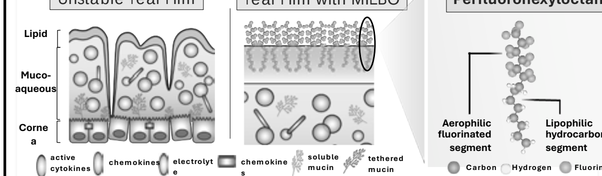
Forms A Monolayer at the Air-liquid Interface

EXPECTED TO REDUCE TEAR EVAPORATION



The exact mechanism of action of Perfluorexlyoctane in DED is not known

70 1. Owiklik L. *Biochimica et Biophysica Acta.* 2016;1858:2421-2430. 2. Willcox MDP, et al. *Ocul Surf.* 2017;15(3):366-403. 3. Liu X, et al. *Bull Che Soc Jpn.* 2018;91(5):846-857. 4. Broniatowski M, et al. *J Phys Chem B.* 2004;108:13403-11.

70

perfluorohexyloctane Demonstrated Consistent Results Across Clinical Trials

Two phase 3 studies evaluating the safety and efficacy of MIEBO for the treatment of DED
- **Multicenter**
- **Randomized**
- **Double-masked**

100% of participants: DED & clinical signs of MGD
GOBI N=597 | MOJAVE N=620

Participants randomized 1:1 to MIEBO or saline (control) QID
614 participants received MIEBO

Outcomes
- Change from baseline in total corneal fluorescein staining (tCFS) at Days 15 (secondary) and 57 (primary)
- Change from baseline in visual analog scale (VAS) dryness score at Days 15 (secondary) and 57 (primary)

MIEBO. Package Insert. Bridgewater, NJ: Bausch + Lomb Americas, Inc.; 2023. 71
DED, dry eye disease; MGD, meibomian gland dysfunction; QID, four times a day; tCFS, total corneal fluorescein staining; VAS, visual analog scale

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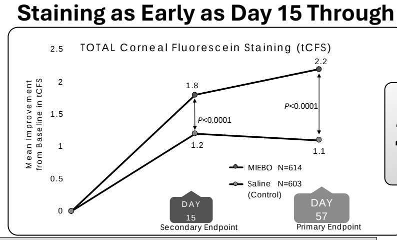
Rapid and Sustained Improvement in Total Corneal Staining as Early as Day 15 Through Day 57



2x IMPROVEMENT vs control in total corneal staining at Day 57

Pooled data | tCFS Grading Scale: 0-15 (0-3 in each of 5 areas) Mean Baseline = 6.9

At day 57, Mean (SD) CFB
GOBI: –2.0 (2.6) for MIEBO (n=289) vs –1.0 (2.7) for saline (n=279) (*P*<0.001)
MOJAVE: –2.3 (2.8) for MIEBO (n=302) vs –1.1 (2.9) for saline (n=296) (*P*<0.001)

72 Tauber J, et al. *Ophthalmology.* 2022;130(5):516-524. Sheppard JD, et al. *Am J Ophthalmol.* 2023;252:265-274. | CFB, change from baseline; SD, standard deviation; tCFS, total corneal fluorescein staining

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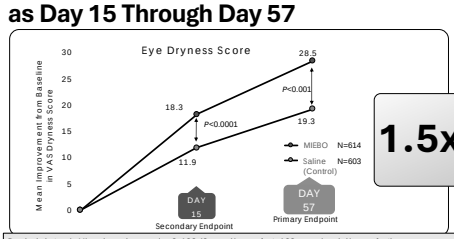
Rapid and Sustained Relief of Eye Dryness as Early as Day 15 Through Day 57



1.5x **IMPROVEMENT** vs control in eye dryness at Day 57

Pooled data | Visual analog scale: 0-100 (0=no discomfort, 100=maximal discomfort)
Mean Baseline, MIEBO = 65.6; Mean Baseline, Saline = 65.5

At Day 57, Mean (SD) CFB
GOBI: −27.4 (27.9) for MIEBO (n=289) vs −19.7 (26.7) for saline (n=279) (*P*<0.001)
MOJAVE: −29.5 (28.6) for MIEBO (n=302) vs −19.0 (27.2) for saline (n=296) (*P*<0.001)

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Tauber J, et al. *Ophthalmology*. 2022;130(5):516-524. Sheppard JD, et al. *Am J Ophthalmol*. 2023;252:265-274.
CFB, change from baseline; VAS, visual analog scale

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Excellent Tolerability Profile

In 2 pivotal clinical studies of >1200 patients
(>600 treated with perfluorohexyloctane**)**

0	0.2%	0.5%	2.1%
Serious ocular AEs	*Low rate of discontinuation due to AEs*	Low rate of burning or stinging	One ocular AE with an incidence ≥ 2% (blurred vision)

Discontinuation rates for MIEBO were comparable to control (pooled: 0.2% vs 0.5%; GOBI: 0.3% vs 1.0%; MOJAVE: 0% vs 0%)
Pooled incidences of instillation site pain, such as burning or stinging occurred in 0.5% of patients; 1.0% in the GOBI study and no reported incidences in the MOJAVE study
The most common ocular AE was blurred vision, which was mostly mild and transient. Blurred vision (pooled: 2.1%; GOBI: 3.0%; MOJAVE: 1.3%) and conjunctival redness (pooled: 0.8%; GOBI: 0%; MOJAVE: 1.3%) were reported in 1%-3% of individuals

74

1. Tauber J, et al. *Ophthalmology*. 2022;130(5):516-524. 2. Sheppard JD, et al. *Am J Ophthalmol*. 2023;252:265-274. 3. Data on File. Bausch + Lomb Incorporated. AE, adverse event

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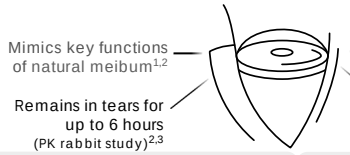
perfluorohexyloctane Inhibits Evaporation



Mimics key functions of natural meibum[1,2]

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

Promotes healing on the ocular surface[4-6]

May reduce friction[5,7]

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

Exact mechanism of action in DED is not known

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

The clinical significance of this data has not been established.

1. Vittitow J, et al. *Curr Ther Res*. 2023; S0011-393X(23)00013-9. 2. Sheppard JD, Nichols KK. *Ophthalmol Ther*. 2023;12(3):1397-1418. 3. Krösser S, et al. *Invest Ophthalmol Vis Sci*. 2018;59:2656. 4. MIEBO. Prescribing Information. Bausch & Lomb, Inc; 2023. 5. Tauber J, et al. *Ophthalmology*. 2022;130(5):516-524. 6. Sheppard JD, et al. *Am J Ophthalmol*. 2023;252:265-274. 7. Schmidl D, et al. *J Ocul Pharmacol Ther*. 2020;36(3):154-161. | DED, dry eye disease; PK, pharmacokinetics

75

Water-free cyclosporine 0.1% ophthalmic solution

- The only cyclosporine indicated for the treatment of the signs and symptoms of dry eye disease
- Free of oils, surfactants, or preservatives with superior spreading properties
- No pH, no osmolarity

Semifluorinated alkane vehicle		Perfluorobutylpentane (PFBP) Vehicle
Spreading and API penetration	 **~22x**	PFBP delivered ~22x more CsA vs a commercially available CsA emulsion (0.05%)
Surface residence time	 **8hrs**	PFBP resides in tears for up to 8 hours (PK rabbit study).*
Comfort	 **99.8%**	of patients experienced no or mild instillation site pain[3,4]

*The clinical significance of this has not been established
Note: * development name of the water-free ophthalmic cyclosporin solution, 0.1 % in perfluorobutylpentane.
[1] ARVO 2018, Flöter Krösser S, et al. [2] Agarwal P, et al. Int J Pharm. 2019 Mar. [3] Sheppard JD, et al. Cornea. 2021 Oct; [4] Akpek SK, et al. JAMA Ophthalmol. 2023 Apr

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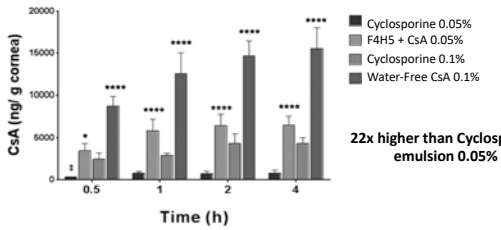
Ex-vivo Corneal Permeability of Cyclosporine

in Porcine Eyes



22x higher than Cyclosporine emulsion 0.05%

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

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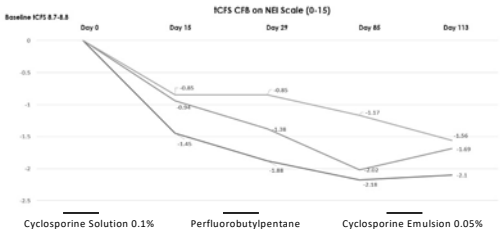
Water-Free Cyclosporine 0.1% Phase II Study

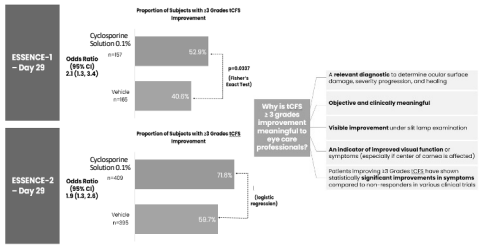
A Phase II Study to Assess Efficacy, Safety, and Tolerability



Wirta D, et al. Clinical Phase II Study to Assess Efficacy, Safety and Tolerability of Waterfree Cyclosporine Formulation for Treatment of DED. Ophthalmology 2019.

78

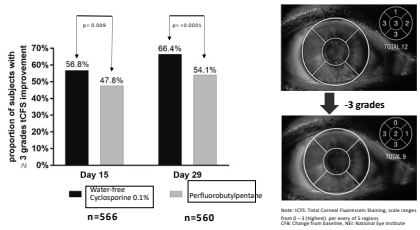
Water-Free CsA 0.1% demonstrated significantly meaningful tCFS improvement in ESSENCE-1 and ESSENCE-2



[1] ARVO 2018, Poster: Kröser S, et al., [2] Agarwal P, et al. . Int J Pharm. 2018 Mar; [3] Sheppard JD, et al. Cornea. 2021 Oct; [4] Akpek EK, et al. JAMA Ophthalmol. 2023 Apr

79

Majority of Patients See Clinically Significant Improvement from Water-free Cyclosporine 0.1% Therapy Within 2 Weeks



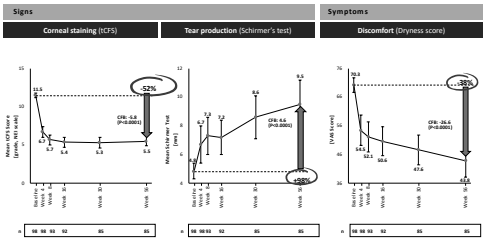
Note: tCFS: Total Corneal Fluorescein Staining, scale ranges from 0 – 3 (highest) per every of 5 regions
CFB: Change from baseline, NEI: National Eye Institute

[1] ARVO 2018, Poster: Kröser S, et al., [2] Agarwal P, et al. . Int J Pharm. 2018 Mar; [3] Sheppard JD, et al. Cornea. 2021 Oct; [4] Akpek EK, et al. JAMA Ophthalmol. 2023 Apr

80

ESSENCE 2-OLE: 12-Month Sign and Symptom Improvement

Water-free CsA 0.1% maintained clinical benefit over more than 12 months in both sign and symptom improvements for DED patients



1 patient discontinued treatment due to an adverse event (mild stinging) in the 56-week study.

Note: Analysis shows mean change from baseline with p-value for the difference in least square means. tCFS: Total Corneal Fluorescein Staining, DED: Dry Eye Disease, CFB: Change From Baseline.
1) Akpek E, et al. Submitted to AJO.

81

Water-free CsA 0.1% with its SFA vehicle (perfluorobutylpentane) was safe and well-tolerated with minimal reports of TEAEs between treatment groups

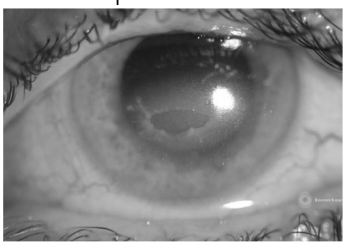
	ESSENCE-1		ESSENCE-2		OLE
All AEs	CsA 0.1% N= 162	Vehicle N= 166	CsA 0.1% N= 423	Vehicle N= 411	CsA 0.1% N= 200
Number of subjects with at least one TEAE	46 (28.4%)	44 (26.5%)	71 (16.8%)	73 (17.8%)	97 (48.5%)
Number of subjects with treatment-emergent SAEs	0 (0.0%)	3 (1.8%)	2 (0.5%)	3 (0.7%)	4 (2.0%)
Number of subjects discontinued treatment due to an AE	3 (1.9%)	0 (0.0%)	2 (0.5%)	3 (0.7%)	3 (1.5%)
Ocular AEs					
Number of subjects with at least one ocular TEAE	20 (12.3%)	14 (8.4%)	57 (13.5%)	62 (15.1%)	55 (27.5%)
Number of subjects with at least one treatment related ocular TEAE	9 (5.6%)	5 (3.0%)	46 (10.9%)	44 (10.7%)	20 (10%)
Ocular AEs occurring in more than 2% of patients					
Visual acuity reduced	5 (3.1%)	3 (1.8%)	7 (1.7%)	13 (3.2%)	6 (3.0%)
Instillation site pain/pruritus					
• Mild	4 (2.5%)	2 (1.2%)	42 (9.9%)	35 (8.5%)	13 (6.5%)
• Moderate	0	0	1 (0.2%)	1 (0.2%)	0
• Severe	0	0	0	0	0
Vision blurred	2 (1.2%)	4 (2.4%)	2 (0.5%)	2 (0.5%)	2 (1%)

82

Where does Neurotropic Keratitis Fit in?

83

Neurotropic Keratitis Definition



- Degenerative corneal disease
- Damage to the trigeminal nerve (cranial nerve V)
- Loss of corneal sensation
- Breakdown of the corneal epithelium
- Impaired corneal healing
- Persistent epithelial defect → corneal ulceration → stromal melting and perforation

Hallmark: decreased sensation, decreased or no pain

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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.

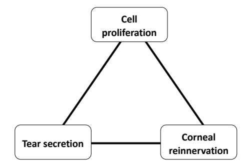
85

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

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

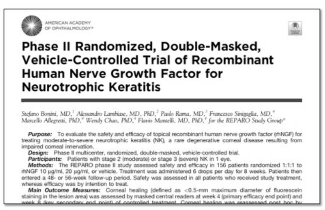


Nerve damage ➡ loss of corneal sensitivity ➡ NK

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

86

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

- 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.

87

Study Conclusions

Up to 72% of patients achieved complete corneal healing;

80% of healed patients were recurrence free after 1 year*

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.

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%

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

88

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.

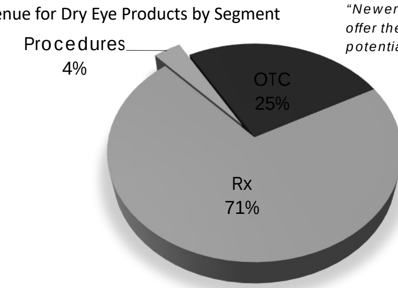
88

Let's Talk about MGD Procedures

89

Procedures Currently Represent 4% of all US Dry Eye Revenue

- Revenue for Dry Eye Products by Segment



"Newer dry eye procedures offer the most significant potential for market growth."
– Market Scope

Market Scope 2017 Dry Eye Products Report

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SHAMIR MEDICAL CENTER · TEL AVIV UNIVERSITY · RAMBAM Health Care Campus · TECHNION Israel Institute of Technology

Dry Eye Disease Management Via Technological Methods - a Systematic Review and Network Meta-analysis

Dror Ben Ephraim Noyman[1] MD, Clara C. Chan[2] MD, Itamar Achvi[3] MD, Or Yosefi[4] MD, Michael Mimouni[1] MD, Margarita Safir[5] MD

1-Ophthalmology Department, Rambam Health Care Campus, Ruth Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

2-Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario, Canada.

3- Ophthalmology Department, Meir Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

4- Department of Military Medicine, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel.

5- Ophthalmology Department, Yitzhak Shamir Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

WE HAVE NO FINANCIAL INTEREST TO DISCLOSE

91

DISCUSSION

- In this study, all examined DED parameters (TBUT, CFS, meibomian gland secretion and total symptoms) showed significant improvement with TearCare+MGX and IPL-based treatments at 1 and 3 months.
- IRPL, Lipiflow, MGP and transcutaneous electronic stimulation showed improvement of some but not all DED parameters.
- The single study assessing TearCare which was included for analysis had a potential conflict of interests- results should be interpreted with caution.

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Sahara RCT Background

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

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

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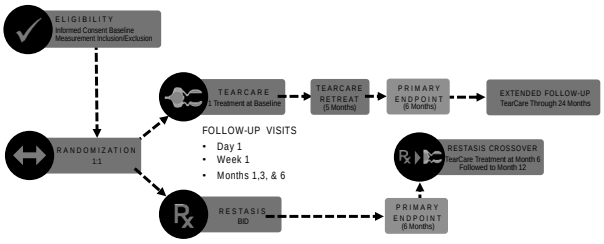
Study Design



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Conclusions

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

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Intense Pulsed Light

- 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

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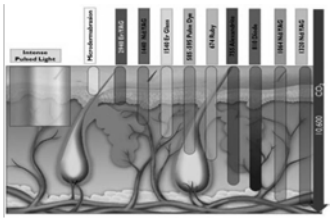
Intense Pulsed Light (IPL)

Effects via photo-

- -coagulation
- -immunomodulation
- -biomodulation
- -thermolysis
- -sanitization



Slide Courtesy of Selina McGee, OD, FAAO

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Peer-Reviewed Literature on IPL for MGD/DED

Authors	Year	P/R	Publication	N	Key Findings
Seo KY et al	2018	P	*Cont Lens Anterior Eye.* 41(5):430-435.	17	OSDI, TBUT, NIBUT, staining, LM vascularity, meibum quality, meibomian expressibility
Arita R et al	2018	P	Cornea. 37(12):1566-1571.	31	SPEED, TBUT, NIBUT, interferometric pattern, meibum grade, lid margin abnormality score, CFS
Yue Y et al.	2018	P	*Curr Eye Res.* 43(3):308-313.	35	OSDI, TBUT, MGE, MG morphology (confocal)
Rong B et al.	2017	P	*Zhonghua Yan Ke Za Zhi.* 53(9):675-681.	44	MGYSS, SPEED, TBUT, staining, meibography
Liu R et al.	2017	P	*Am J Ophthalmol.* 183:81-90.	44	IL-17A, IL-6, PGE2, MGYCS (clear secretions)
Dell SJ	2017	P	*Clin Ophthalmol.* 11:1167-1173.	40	TBUT, SPEED, osmolarity, staining, MG score
Albietz JM et al	2017	P	*Clin Exp Optom.* 101(1):23-33.	26	OSDI, Ocular Comfort Index, AFT use, TBUT, staining
Gupta PK et al.	2016	R	*Can J Ophthalmol.* 51(4):249-253.	100	Lid margins, MG flow, meibum quality, TBUT, OSDI, eyelids
Vegunta S et al.	2016	R	*Cornea.* 35(3):318-322.	35	SPEED2, MGE (liquid secretions)
Jiang X et al.	2016	P	*J Ophthalmol.* 2016:1910694.	40	TBUT, TMH, staining, lid margin, MGA, meibography
Toyos R et al.	2016	P	*J Clin Exp Ophthalmol.* 7(6):619.	16	Tear film osmolarity

Slide Courtesy of Selina McGee, OD, FAAO

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Peer-Reviewed Literature on IPL for MGD/DED

Authors	Year	P/R	Publication	N	Key Findings
Craig JP et al.	2015	P	*Invest Ophthalmol Vis Sci.* 56(3):1965-1970.	28	Lipid layer grade, NIBUT, tear evap. rate, TMH, VAS, SPEED
Vora GK et al.	2015	R	*Curr Opin Ophthalmol.* 26(4):314-318.	37	TBUT, lid margins, eyelids, MG oil flow, meibum quality, OSDI
Toyos R et al.	2015	R	*Photomed Laser Surg.* 33(1):41-46.	78	TBUT, patient satisfaction, meibum quality, lid margin
Vegunta S et al.	2014	R	ARVO, published in *Invest Ophthalmol Vis Sci.* 55:2018	43	SPEED2, MGE
Shen L et al.	2015	R	ARVO PN 4441/PBN A0067	9	SPEED2, OSDI, MGE, Schirmer test, staining, TBUT, lipid tear film analysis, TMH, meibography
Kim et al.	2015	R	ARVO PN 6193/PBN C0264	53	OSDI
Craig et al.	2015	P	ARVO PN 6193/PBN C0265	28	Lipid layer grade, NIBUT
Shen JF	2014	R	ARVO, published in *Invest Ophthalmol Vis Sci.* 55:2017	5	SPEED2, OSDI, MGE, Schirmer test, staining, TBUT, lipid tear film analysis, TMH, meibography
Gupta	2014	R	ASCRS	37	Lid margin edema & vascularity, facial telangiectasia, meibum quality, OSDI, TBUT, oil flow score
Toyos R	2013	R	ARVO, published in *Invest Ophthalmol Vis Sci.* 54:966	91	TBUT, self-satisfaction, physician-judged improvement

Slide Courtesy of Selina McGee, OD, FAAO

99

Radiofrequency

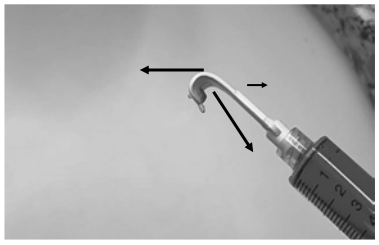
- FDA cleared (K130689) and indicated for use in dermatological and general surgical procedures for electrocoagulation and hemostasis; creation of lesions in nerve tissue.
- Associated with improving skin laxity and wrinkle reduction using a **Radio Frequency Thermistor Heating Device**

Slide Courtesy of Drs. Christensen and Hauser

100

Irrigating Eyelid Retractor

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



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Study Design

Randomized Controlled Trial of Patients with Dry Eye Disease & Positive MMP-9 via POC Testing (n=88)

Device rinse with 15mL of irrigating solution n=46

Standard rinse with 15mL of irrigating solution n=42

Three Hours Post-Rinse
Primary Endpoint: Change in MMP-9 POC Testing
Secondary Endpoint: Percentage of patients negative MMP-9

1 week & 4-12 weeks Post-Rinse
Exploratory EPs: Percentage of patients negative MMP-9 in Device Arm; Results of CDES-Q*

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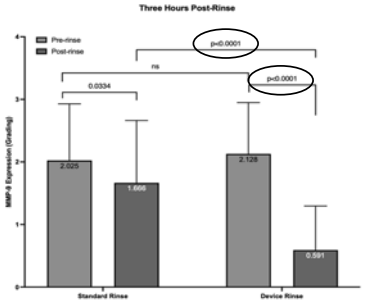
Results—Primary Endpoint

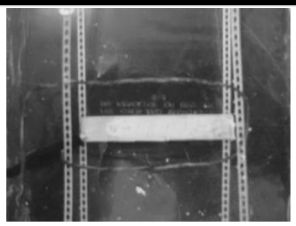


Paired t-test: decreased MMP-9 expression in both standard and device groups with greater attenuation in the device rinse group.

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

103

Biofilm has an Achilles heel



Courtesy Montana State University Center for Biofilm Engineering

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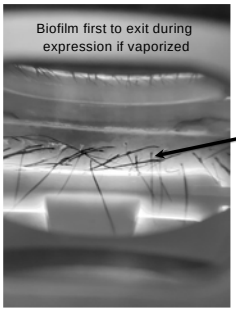
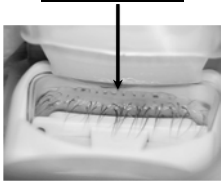
The doctor uses a device to deliver a 6 volt current (equivalent of 2 AA batteries) through a specialty contact lens that is harmonically tuned to blow apart the bonds of a bacterial polysaccharide biofilm

105



Vaporizes Intraglandular Biofilm in Less than One Minute

Granules of polysaccharide compare to melted Crisco



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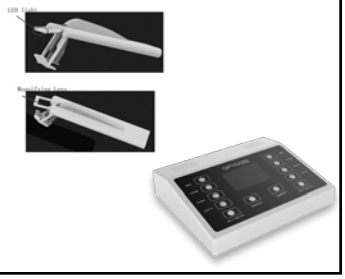
Regular Exfoliation Vaporization Vibratory Expression

- Monthly In-Office
  - Exfoliate
  - Vaporize
  - Heat / Vibrate express
- At-Home
  - Home treatment



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With so many options for in-office therapy, how do you decide which one?

108

What are Your Clinical Pearls to Increase Conversions?

109

How and When do you performing punctal occlusion?

110

- 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)

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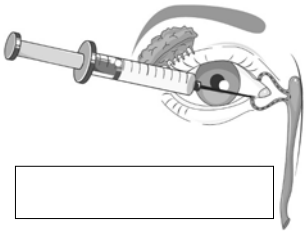
Instructions for Use

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



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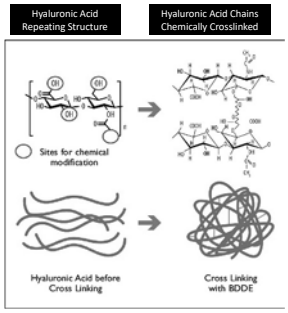
Intricate Crossing of Hyaluronic Acid Chains to Create Gels



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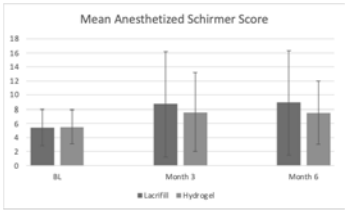
Fast & Effective Dry Eye Relief: Schirmer Score

Greater Increase in Schirmer with LACRIFILL



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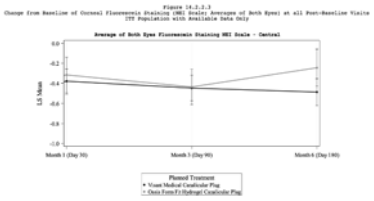
Fast & Effective Dry Eye Relief: Corneal Staining

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



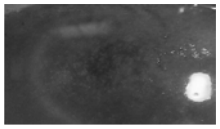
115

When do you use a Cryopreserved vs. Dry Amniotic Membrane?

116

Current Uses for Topical Biologics for OSD

- Persistent epithelial defects
  - Neurotrophic keratopathy
  - Exposure keratopathy
- Recalcitrant dry eye
- Filamentary keratitis
- Corneal ulcers
- Herpetic keratitis
- Steven-Johnson's Syndrom
- Keratoneuralgia
- Recurrent corneal erosion
- Limbal stem cell deficiency



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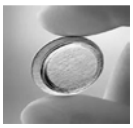
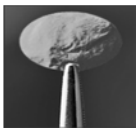
Amniotic Membranes



Cryopreserved



Dry Membrane

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

Hindawi

Clinical Study

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

Thomas John,[1,2] Sean Tighe,[3,4] Hosam Sheha,[3,4,5] Pedram Hamrah,[6,7] Zeina M. Salem,[6,7] Anny M. S. Cheng,[3,4] Ming X. Wang,[8] and Nathan D. Rock[8]

[1]*Thomas John Vision Institute, Tinley Park, Cook County, IL, USA*
[2]*Loyola University at Chicago, Maywood, Chicago, IL, USA*
[3]*Ocular Surface Center and TissueTech, Inc., Miami, FL, USA*
[4]*Florida International University Herbert Wertheim College of Medicine, Miami, FL, USA*
[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*

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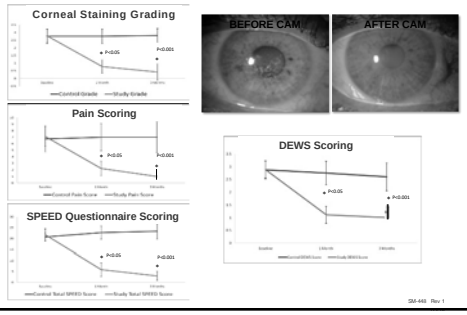
Improvements in Clinical Signs and Symptoms



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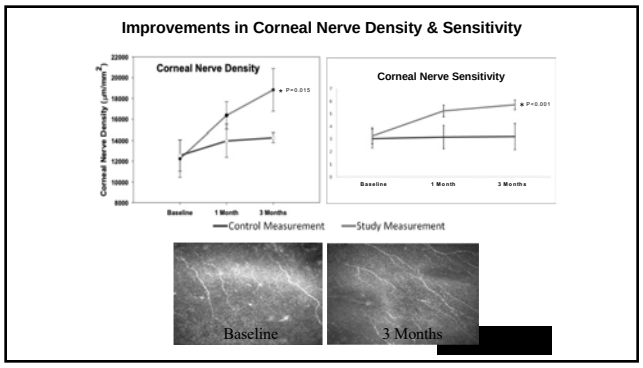

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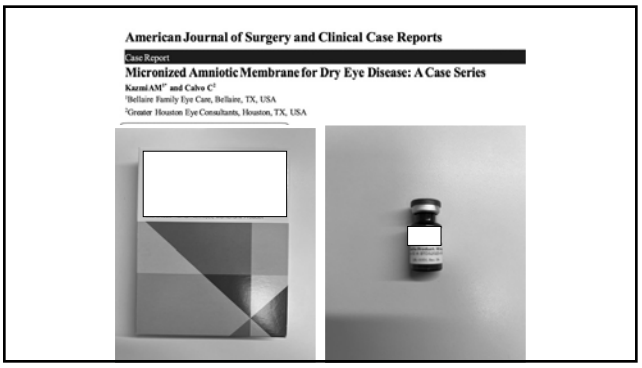

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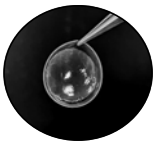
Cryopreserved Membrane w/BCL



- Hydrated CAM
- Ringless
- Adhesion Property[1]
- Room Temperature Storage
- Size (∅): 12 mm

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So What's in the Pipeline now??

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Activating Natural Tear Production via Trigeminal Nerve

1. Green BG. *Chem Senses*. 2012;37:201-206. 2. Meng ID, Kurose M. *Exp Eye Res*. 2013;117:79-87. 3. Zhang M, et al. *Sig Trans Target Ther*. 2023;8:261.

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Nasal Activation of the Trigeminal Nerve

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

1. Alzohairy MA, et al. *Clin Ophthalmol*. 2016;10:1695-1701. 2. Arendt-Nielsen L, et al. *Curr Rheumatol Rep*. 2018;20:48. 3. Wirta O, et al. *Cornea*. 2022;41:1207-1216. 4. Wirta O, et al. *Ophthalmology*. 2022;129:379-387.

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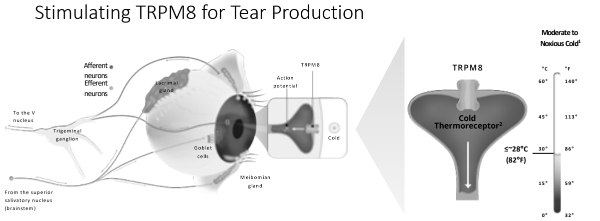
Stimulating TRPM8 for Tear Production



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

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

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

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TRPM8 as a Potential Therapeutic Target

Acoltremon[1-3]***	IVW-1001[4,5]
TRPM8 agonist	TRPM8 agonist
Instilled as a drop on the ocular surface	Applied over upper eyelid
Completed phase 3 studies	Initiating phase 1/2 studies

*** PDUFA decision date of April 2, 2025

*****Not FDA Approved**

Acoltremon and IVW-1001 are investigational drugs and have not been approved for commercialization.
TRPM8, transient receptor potential melastatin 8

1. https://clinicaltrials.gov/study/NCT05360966. Accessed March 27, 2024. 2. https://clinicaltrials.gov/study/NCT05285644. Accessed March 27, 2024. 3. Wirta DL, et al. Ocul Surf. 2022;26:166-173. 4. IVW-1001 phase 1/2 in subjects with dry eye disease. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT06400459. Accessed July 25, 2024. 5. Liang, BG et al. *Disease. Invest. Ophthalmol. Vis. Sci.* 2024;65(7):5763.

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Summary: TRPM8 Is a Regulator of Tear Production

Unmet Need

- A novel mechanism to help manage a multifactorial disease[1]

Altered Tear Volume and Composition

- Sustains and perpetuates the DED cycle[1]
- Can be caused by dysfunction in tear-secreting glands or in the neuronal circuits regulating these glands[1]

Neuromodulation

- Leverages the LFU to quickly replenish tear components[2]
- Current option requires nasal delivery[3]

Corneal TRPM8 Receptors

- Regulate tear production by detecting evaporative cooling on the ocular surface[2]
- Being investigated as a target for increasing tear production[4-6]

DED, dry eye disease; LFU, lacrimal functional unit; TRPM8, transient receptor potential melastatin 8

1. Craig JP, et al. *Ocul Surf.* 2017;15(4):802-812. 2. Belmonte C and Gallar J. *Invest Ophthalmol Vis Sci.* 2011;52:3888-3892. 3. Tyrvaya (varenicline solution nasal spray) [prescribing information]. Princeton, NJ: Oyster Point Pharma; 2021. 4. Study Evaluating the Safety and Efficacy of AR-15512 (COMET-2) https://clinicaltrials.gov/study/NCT05285644. Accessed March 27, 2024. 5. Study Evaluating the Safety and Efficacy of AR-15512 (COMET-3). Accessed March 27, 2024. 6. IVW-1001 phase 1/2 in subjects with dry eye disease. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT06400459. Accessed July 25, 2024

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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.

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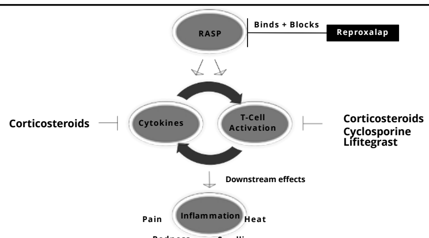
RASP Are Believed to Work at the Top of the Inflammatory Cascade



Sources: Lee SJ et al. HNE-induced 5-LO expression is regulated by NF-kB/ERK and Sp1/p38 MAPK pathways via EGF receptor in murine macrophages. Cardiovasc Res. 2010;88(2):352-9. Chiarpotto E et al. Role of 4-hydroxy-2,3-nonenal in the pathogenesis of fibrosis. Biofactors. 2005;24(1-4):229-36. Natarajan K et al. The advanced lipoxidation end product precursor malondialdehyde induces IL-17E expression and skews lymphocytes to the th17 subset. Cell Mol Biol Lett. 2015;20(4):647-62. Raghavan S et al. Proinflammatory effects of malondialdehyde in lymphocytes. J Leukoc Biol. 2012;92(5):1055-67. Shanmugam N et al. Proinflammatory effects of advanced lipoxidation end products in monocytes. Diabetes. 2008;57(4):879-88.

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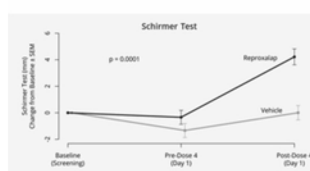
In TRANQUILITY-2, Both Primary Endpoints Were Achieved



≥10 mm Schirmer Test Responder Analysis

	Reproxalap (n=181)	Vehicle (n=180)
≥10 mm increase in tear production post-Dose 4 on Day 1	25%	8%
Odds ratio (95% confidence interval)*	2.6 (1.7, 4.1)	
p-value* versus vehicle	< 0.0001	

Consistent with prior trials, no clinically significant safety signals were observed.

aldeyra

*****Not FDA Approved**

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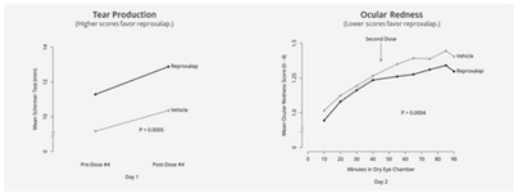
In the Dry Eye Disease Crossover Trial, Both Primary Endpoints Were Statistically Significant in Favor of Reproxalap over Vehicle



***Not FDA Approved**

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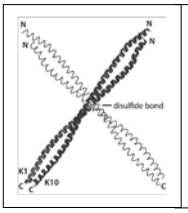
TARGETING ABERRANT KERATIN
Unblocking Glands and Disruption of Keratin Plaques Within Meibum Matrix



- Keratins are helical structural proteins that make up hair, nails, and skin
- Extremely resilient and insoluble
- Disulfide bond cross linking hardens structures to give strength and durability

Thermal denaturing
Disulfide bonds are comparatively strong and require considerable thermal energy to break, >144 °C

Chemical denaturing
Readily achieved chemically with a mild disulfide bond disrupting agent, i.e. keratolytic

[1] Bunick, et al. Journal of Investigative Dermatology 2017, Volume 137, 142-150. [2] Istrate et al. Macromol. Biosci. 2009, 9, 805–812

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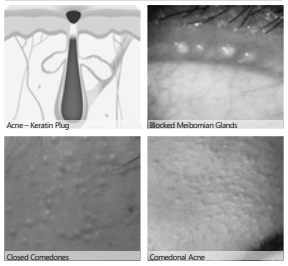
WHAT ARE KERATOLYTICS?
Agents that soften and shed the skin epithelium or horny outer layer of skin through the process of breaking down keratin

- Similar to the lid margin, secretory gland hyperkeratinization plays an important role in various skin disorders
- Comedonal lesions in acne are inspissated hair follicles, filled with corneocytes, sebum, and other debris
- Keratolytic treatments are used to shed dead corneocytes, loosen the sebum plug, and prevent the formation of inflammatory papules and pustules



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KERATOLYTICS
Taking a Dermatological Approach to treating Ocular Surface Diseases

A variety of keratolytics are used to treat dermatological issues

- Urea
- BHA (Salicylic acid)
- AHA (fruit acids, glycolic acid)
- Selenium Sulfide (SeS2)

Topical retinoids convey a concentration-dependent reduction in comedonal lesions, much like selenium sulfide in the treatment of MGD

The Meibomian gland can be regarded as a "hair follicle without a hair shaft"

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AZR-MD-001 (SELENIUM SULFIDE)
Triple MOA for the treatment of MGD

A potent keratolytic, with a unique MoA compared to traditional keratolytic agents, such as urea, AHA and BHA

Keratostatic | Keratolytic | Lipogenesis

AZR-MD-001 TRIPLE MOA
Decrease meibomian gland hyperkeratinization of ducts and orifices, loosen meibomian gland blockages, and increase secretion of meibomian gland lipids

[1] Data on file, Azura Ophthalmics. [2] Data on file, Azura Ophthalmics.

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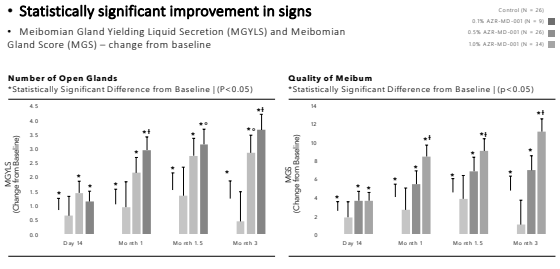
- **Statistically significant improvement in signs**
- Meibomian Gland Yielding Liquid Secretion (MGYLS) and Meibomian Gland Score (MGS) – change from baseline



[4] significantly different from control (p < 0.05) ; ♦significantly different from control (p < 0.10) ; ♦significantly different from baseline (p < 0.05)

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And Many Many More…

- OTX-CSI
- Chronic DE - SURF-100
  - Mycophenolate sodium and betamethasone sodium phosphate
- Acute/episodic dry eye - SURF-200
  - Betamethasone
- ST-100
- Visomitin
- Lacriprep
- Tanfanercept
- Cenergermin 0.002%
- Tanfanercept
- GLK-301 – pilocarpine
- RGN-259 – Tß4
- TRPM8
- Topical Azithromycin
- CBt-006
- \

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Call to Action – Implement Now

- Screening questionnaire
- Blink rate
- Tear meniscus
- Tear film osmolarity
- Tear film break up time
- Ocular surface staining
- Schirmer / Red Thread Test
- Lid Evaluation
  - Lid and MG morphology
  - MG Expression
- Tear interferometry
- Presence of MMP-9

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Conclusions

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

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Thank You!

wwhitley@cvphealth.com

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