

Innovations in Ocular Surface Disease to Maximize Patient Outcomes COPE#77297-TD

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Today's Objectives

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

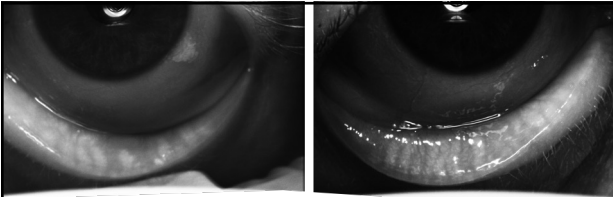
- Discuss current and future technologies in Ocular Surface Disease
- Consider how this technology will benefit your patients and your practice
- Consider would it change your diagnosis or treatment

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Case Example

- 84 yowf presents for a dry eye follow up OU with MMP-9 testing. Constant and moderate symptoms. Vision fluctuates daily. Been on cyclosporine 0.05% off and on for >2 years. Tried plugs in the past but they fell out.
- Oc Hx: PCIOL OU 2018, styes OS, amblyopia OD
- Med Hx: rosacea, HTN, osteoarthritis, asthma, high cholesterol
- Meds: amlodipine, lisinopril, montelukast, albuterol
- Allergies: KNMA

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Examination

- VAccOD 20/150 OS 20/25
- SPEED Score: 24
- SLE: 2+ MGD / Cloudy secretions / No telangiectasia / 2+ SPR
- IOP 13/13
- IFD: Neg OU
- C/D: 0.3 OU
- Anything else we should check?

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- Assessment
 - H16.223 KCS / non-sjogrens
 - H02.88A MGD, Right Upper and Lower Lids
 - H02.88B MGD, Left Upper and Lower Lids
- Plan
 - Start loteprednol etabonate 0.25% TID OU
 - Heat mask 5 min/day
 - Hypochlorous acid qd
 - Omega supplements
 - Prescribe thermal pulsation

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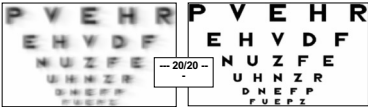
Follow Up 4-6 weeks

- Symptoms have improved dramatically since drops and thermal pulsation procedure
 - VAcc: OD20/150 OS 20/30+3
 - SLE: 2+MGD / improved expression / Clear cornea
 - IOP: 15/15
- Assessment
 - Improve S/Sx of KCS / MGD
- Plan
 - Finish loteprednol 0.25%
 - Continue heat mask, hypochlorous acid, Ats TID
 - Follow up 4-6 months, MMP9

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Better Comfort and Quality of Vision

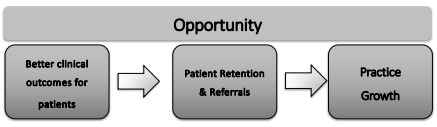
- Tear film abnormalities result in a significant reduction in quality of vision and patient satisfaction
- Due to this, proper ocular surface treatment is critical to outcomes.



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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: 2023 Comprehensive Report on the Global Dry Eye Products Market

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Potential Mechanisms for BAK-Induced DED¹

- Goblet cells**
 - Goblet cells, which contribute to tear film stability and immune defenses through production of soluble mucins, have been shown to decrease in density in the presence of BAK or BAK-containing timodol
- Mucous layer**
 - In human corneal and limbal epithelial cells, MUC1 and MUC16 were reduced after exposure to BAK
 - After exposure to 0.01% BAK for 5 or 15 minutes, transmission electron microscopy showed a change in the mucous layer in human corneal-limbal epithelial cells
 - After extended exposure to 0.01% BAK for 60 minutes, the mucous layer was destroyed
- Tear film**
 - Since BAK is a tensioactive compound, it acts as a detergent on the lipid layer of the tear film
 - Cumulative amounts of BAK have been shown to disrupt the tear film, as measured by an increase in tear film osmolality
 - Not only does a weakened tear film produce dry eye symptoms and corneal damage, but it may also promote inflammatory mediators throughout the ocular surface
 - This may result in increased corneal epithelial permeability, and the use of artificial tears containing BAK would further aggravate dry eye
- Corneal epithelium**
 - A major effect of BAK on the corneal epithelium is disruption of the barrier function
 - Although tissue defenses may be able to counteract some of the toxicity caused by BAK in patients with and without glaucoma, there is a higher level of toxicity caused by BAK in patients with existing DED
- Proinflammatory effects**
 - BAK may increase the expression of receptors to chemokines and cytokines, and has been shown to cause a direct release of inflammatory cytokines
 - In patients with glaucoma, there was an overexpression of inflammation-related markers, including ICAM-1, interleukin (IL)-6, IL-8, IL-10, CCR4 or CCR5, and patients who received multiple therapies and preserved eye drops had an increase in these markers

1. Gomes JAP, Azar DT, Baubouk C, et al. TDS DED's etiologic regimen. Ocul Surf. 2017;15(3):142-148.

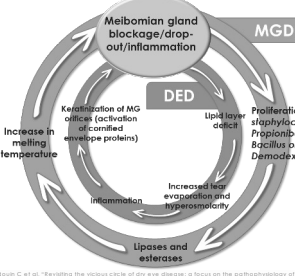
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TFOS DEWS II Definition

*“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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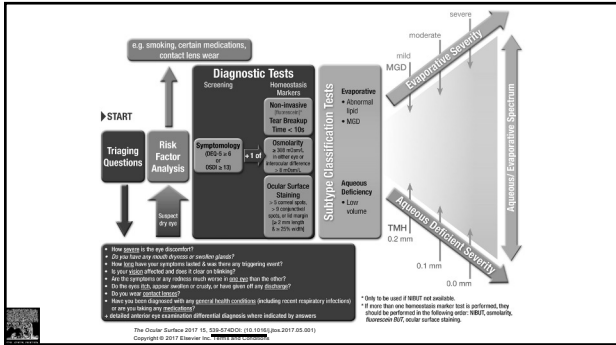
Mechanism of disease



- Lipids from meibomian glands necessary for ocular surface health and integrity¹
- Blocked meibomian glands lead to gland dilation, atrophy, low secretion, gland dropout and compromised tear film¹
- Meibomian gland health is integral to a healthy tearfilm²

1. Baubouk C et al. "Revisiting the vicious cycle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction". Br J Ophthalmol. Vol 100(3), pp 300-304. 2. Dry eye management: keeping the ocular surface microenvironment hot J Allergy Clin Immunol. 2017; 138:1718.

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Improving the Screening, Diagnosis, and Management of Dry Eye Disease

2014 Dry Eye Summit

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Consensus on Screening Questions


- 1) Do your eyes ever feel dry or uncomfortable?
- 2) Are you bothered by changes in your vision throughout the day?
- 3) Are you ever bothered by red eyes?
- 4) Do you ever use or feel the need to use drops?



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Consensus on Baseline Diagnostic Options for Entry Level Dry Eye Disease

1. Eyelid exam
2. Staining
3. Tear film instability



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Consensus on Baseline Management

1. For all patients:
 - A. Ocular lubrication
 - B. Lid hygiene
 - C. Nutrition
2. Topical anti-inflammatories

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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
- 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, Burns W, et al. TFOS DEWS II Epidemiology Report. *Ocular Surf*. 2017;15:334-365.
Gomes JAV, Azev DO, Baudouin C, et al. TFOS DEWS II Etiology Report. *Ocular Surf*. 2017;15:311-336.

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Contact Lens Considerations

- Contact lens wearers with unexplainable reduced wearing time had MGD¹
- CL wear accelerates MGD^{2,3}
- 60% of CL wearers had MGD⁴
- CANDEES Study: 50.1% CL experience DE vs. 27.1% Non CL wear

1. Moshirfar A, Korb D. Meibomian glands and contact lens wear. *W J Ophthalmol*. 1993 Feb;6(2):109-11.
2. Ong H. Relation between contact lens wear and Meibomian gland dysfunction. *Optom Vis Sci*. 1996;73:209-10.
3. Goto K, Sato K, Hirose K, Kashiwa A, Yamaguchi T, Sano S. Contact lens wear is associated with decrease of meibomian glands. *Ophthalmology*. 2009;116:379-84.
4. Washida A, et al. Comparison of Morphological and Functional Meibomian Gland Characteristics Between Daily Contact Lens Wearers and Nonwearers. *Cornea*. 2015. DOI:10.1097/ICO.0000000000000246.

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Focus on Dry Eye Prevalence

• Cataract Surgery	77%
• Penetrating Keratoplasty	60%
• Lasik	27%
• Glaucoma Surgery	78%
• Blepharoplasty	26%

Trattler, ASCRS CME Supplement, 2013
Sheppard, WCC, 2015
Azuma, BMC Research Notes, 2014
Leung, Journal of Glaucoma, 2008
Prischmann, JAMA Facial Plastic Surgery, 2013

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Surgical Considerations

- Approximately 10–20% of post-LASIK patients may suffer from chronic dry eye disease with more severe discomfort after LASIK¹
- Cataract Patients: 59% (n=233) had MGD²
- 62.3% had TBUT < 5 sec³

1. Ambrosio R Jr, Tava T, Wilson SE. LASIK-associated dry eye and neurotrophic epitheliopathy: pathophysiology and strategies for prevention and treatment. *J Refract Surg*. 2008; 24:396-407.
2. Aligned et al. Epidemiology of Meibomian Gland Dysfunction in an Elderly Population. *Cornea*. 2015 Jun;35(6):731-5.
3. Trattler WB, Reilly CD, Goldberg DF, et al. Cataract and Dry Eye: Prospective Health Assessment of Cataract Patient Ocular Surface (PHACOS) Study. Paper presented at: ASCRS Symposium and Congress, May 25-29, 2011; San Diego, CA.

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ARTICLE

Prevalence of ocular surface dysfunction in patients presenting for cataract surgery evaluation

Results: There were 120 patients (69% women), mean age 69.5 years ± 8.4 (SD). Abnormal osmolality was found in 68 patients (56.7%), and abnormal MMP-9 in 76 patients (63.3%). Clinical findings showed that 47 patients (39.2%) had positive corneal staining on presentation, 9 patients (7.5%) had epithelial basement membrane dystrophy, and 2 patients (1.6%) had Salzmann nodules. Questionnaire data showed 54 (54.0%) of 100 patients reported symptoms suggestive of ocular surface dysfunction. In the asymptomatic group of 46 patients, 39 (85%) had at least 1 abnormal tear test (osmolality or MMP-9) and 22 (48%) had both tests abnormal. **Overall, 96 (80%) of 120 patients had at least 1 abnormal tear test** result suggestive of ocular surface dysfunction and 48 patients (40%) had 2 abnormal results.

VanDusen, BS, MD

J Cataract and Refractive Surgery 2018

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Cataract Surgery and Dry Eye

- Incidence: 42% eyes at 1 week follow-up, up to 1/3 of patients after 3 months after surgery^{1, 2}
- Etiology:
 - Decreased goblet cell density, age, duration of exposure to microscope light and effective phacoemulsification time³
 - Possibly worse with femtosecond laser-assisted cataract surgery⁴
 - Possibly grooved incision⁵
 - Medication toxicities
- No relationship to incision location

1. Mohr S, Neme N, Chandrasekhar SCL, Saudi J Ophthalmol. 2019 Jan-Mar;33(1):34-40.
2. Ignatov C, Collier A, et al. *Cornea*. 2016 Jul;35(7):993-998.
3. Kashi H, Haseki S, et al. *Br J Ophthalmol*. 2019 Jun;103(6):1345-1353.
4. Lu Y, Yao X, et al. *J Cataract Refract Surg*. 2015 Dec;41(12):2014-23.
5. Cho WK, Kim HJ. *Korean J Ophthalmol*. 2009 Jun;23(2):167-73.

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Cataract Surgery and Dry Eye

- Meibomian gland function can be affected after cataract surgery
 - Meibomian gland function may worsen with or without structural changes after cataract surgery^{6,7}
 - Alterations in MG expressibility and TBUT persist for up to 3 months postoperatively⁸
- Pre-existing DED is a significant risk factor for post-op DED!⁷
 - Compared with the no dry eye group, dry eye group revealed significantly higher post-op ocular symptom scores, lower TBUT, higher lid margin abnormalities, meibum quality and expressibility scores.

6. Han HK, Seo KY, et al. *J Ophthalmol*. 2014 Jun;15(76):1144-1150.
7. Park Y, Heung HB, Kim HG. *PLoS One*. 2016 Oct 3;11(10):e0152460.
8. El Ameen A, Psoeila PJ, et al. *J Fr Ophthalmol*. 2018 May;41(5):e173-e180.

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Cataract Surgery and Dry Eye

- Persistent DED > 3 months can occur in up to 1/3 of patients!^{2,9}
 - Persistent tear instability and corneal epitheliopathy were found > 5 months after cataract surgery⁹
 - Pre-existing DED is a significant risk factor for persistent post-op DED
 - High OSDI and 1 month post-op low TBUT, low MG orifice obstruction scores, and increased MG dropout are risk factors for persistent DED!¹⁰

9. Hanayada A, Negishi K, et al. *J Clin Med*. 2019 Feb 7;8(2).
10. Choi YJ, Kim TI, et al. *Cornea*. 2018 Jun;37(6):734-739.

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Effect of Tear Osmolarity on Repeatability of Keratometry for Cataract Surgery Planning


- Significantly more variability in average K and anterior corneal astigmatism was observed in the hyperosmolar group, with significant resultant differences in IOL power calculations. Variability was not significantly different when subjects were grouped by self-reported dry eye. Measurement of tear osmolarity at the time of cataract surgery planning can effectively identify patients with a higher likelihood of high unexpected refractive error resulting from inaccurate keratometry.

Epitropoulos, Alice T. et al. *Journal of Cataract & Refractive Surgery*, Volume 41, Issue 8, 1672 - 1677

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Digital Devices

- Approximately 65 percent spend between three to nine hours per day in front of a digital device¹
- While asthenopia, glare, and accommodative difficulty are all aspects of CVS, dry eye appears to contribute to a major component of symptoms reported²
- 74.3% of VDT users had MGD³



1. The Vision Council. *The Digital Eye Report 2013*. <http://www.thevisioncouncil.org/consumers/media/ResearchReports/2014/TheDigitalEyeReport2013.pdf>. Accessed 01/02/2014.
2. Blumenthal CS, Vishnu S, Khattak A, et al. Computer vision syndrome: a review. *Surv Ophthalmol* 2005;50:253-62.
3. Feng C, Wang Y, Cao Z, et al. Meibomian gland dysfunction and ocular discomfort in video display terminal workers. *Exp*. 2008;22:95-96.
4. https://www.researchgate.net/publication/319133090_prevalence_of_digital_eye_sickness_in_video_display_terminal_workers

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According to Fechtner, What is the Prevalence of Ocular Surface Complaints in Patients with Glaucoma?



- 28%
- 38%
- 48%
- 58%

Fechtner, RD, Godfrey DG, Buderer D, et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. *Cornea*. 2010;29:638-621

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Glaucoma Considerations

- Glaucoma medications significantly elevate the risk and progression of MGD¹
- Preservative and dry eye²

1. Aizu K, Saito Y, Wada S, et al. Comparison of the long-term effects of various topical antiglaucoma medications on meibomian glands. *Cornea*. 2012 Nov 11;31(11):1229-34.
2. Kozanich, C, Lubbo, A, Sang, M, et al. Preservatives in eye drops: The good, the bad and the ugly. *Progress in Retinal and Eye Research*, Volume 29, Issue 4, July 2010, Pages 313-334

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76YOWF – Present for follow up for Glaucoma and dry eye disease

- Compliant with drops OU. Vision has been blurry and eyes irritated more in the past few months
 - Previous treated with topical azithromycin
 - Current Ocular Meds: Restasis BID OU, latanoprost qhs OU
 - Numerous systemic meds including singlair, synthroid
- SPEED Score: 25
- Tear Osmolarity 308 / 315
- SLE: 2+ MGD OD / 3+ MGD OS / 1+ SPK OU
 - Cloud secretions OU
 - MG Structure: See images
- IOP: 14/13

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Post Treatment

6 Weeks Post Treatment



- Post Tx Osmolarity
 - 300/299
- Post Thermal Pulsation Management
 - Heat masks qhs OU
 - Omega po as directed
 - Cyclosporine 0.05% BID OU
 - Lipid based tear BID OU
 - Latanoprost qhs OU
 - F/u 3 months dry eye
 - Order tear osmolality
 - Order MMP 9
 - SPEED Questionnaire

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Biomarkers vs. Conventional Diagnostics

Test	Sensitivity	Specificity	Positive Predictive Value (PPV)
Schirmer I <10mm ⁵	83%	68%	31%
TBUT <10sec ⁶	72%	62%	25%
Staining, rose bengal ¹	25%	90%	31%
Osmolarity >308 mOsm/L ^{3,3}	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. Srinivasan et al. 2007. Ocul Surf. 2007;5(2):108-12. 2. Sedgwick et al. 2008. Ophthalmol. 2008;115(12):2125-30. 3. Saitou et al. 2004. Invest Ophthalmol Vis Sci. 2004;45(12):4125-30. 4. Saitou et al. 2004. Invest Ophthalmol Vis Sci. 2004;45(12):4125-30. 5. Saitou et al. 2004. Invest Ophthalmol Vis Sci. 2004;45(12):4125-30. 6. Saitou et al. 2004. Invest Ophthalmol Vis Sci. 2004;45(12):4125-30. 7. Saitou et al. 2004. Invest Ophthalmol Vis Sci. 2004;45(12):4125-30.

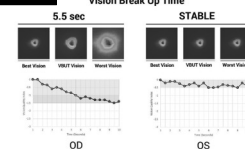
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Tear Film Analyzer



Vision Break Up Time


5.5 sec STABLE



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Epi-Mapping

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

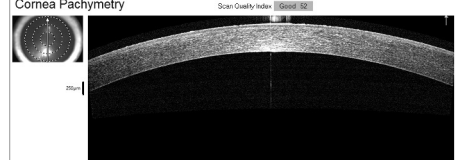


Rocha RM, Strazielle CP, Stulting RD, et al. Spectral-Domain OCT Analysis of Regional Epithelial Thickness Profiles in Keratoconus, Postoperative Corneal Ectasia, and Normal Eyes. J Refract Surg. 2013 Mar; 29(3): 173-179. 1. Y. Tanaka and H. H. Corneal epithelial thickness mapping in Normal and keratoconic eyes with Fourier-domain optical coherence tomography. Investigative Ophthalmology & Visual Science. April 2010, Vol 51, 5813.

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Cornea Pachymetry

Left / OS

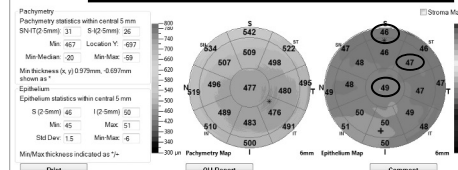


Dry Eye

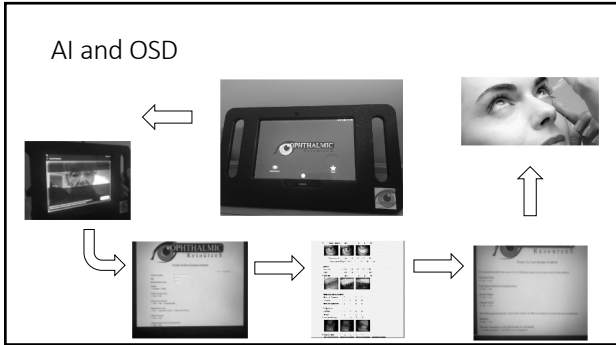
Pachymetry statistics within central 5 mm
 SNR(TP 5mm): 31 S-IQ 5mm: 26
 Min: 467 Location Y: 497
 Max: 507 Min-Max: 40
 Mean: 488
 Min-Max: 49
 Max Dev: 15 (x, y) 0.97mm, 0.697mm
 at least as

Epithelium statistics within central 5 mm
 S (p 5mm): 46 I (p 5mm): 50
 Min: 45 Max: 51
 Min-Max: 6
 Min Dev: 1.5 Min-Max: 6

Max thickness indicated as 71



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Treatment Strategies in 2022

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

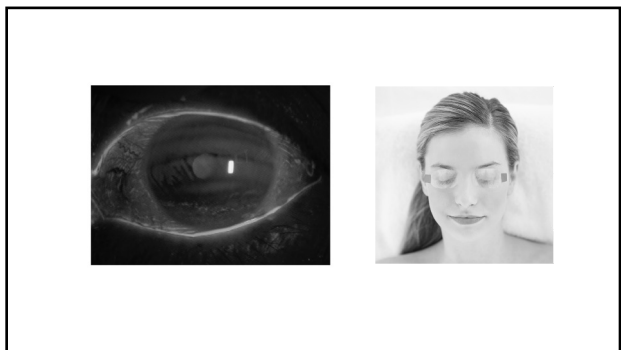
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Treatment Strategies in 2022: Lid Margin Disease Management

- **Warm compress and lid massage**
 - Difficult to maintain adequate temperature; poor compliance
- **Lid scrubs**
 - Commercial soap scrubs
 - Tea tree oil in *Demodex* mite infestation¹
- **In-office lid margin cleansing and meibomian gland expression for anterior blepharitis and posterior blepharitis**
 - Motorized/mechanical devices²
 - Thermal and thermal pulsation³
 - Intraductal probing⁴
 - Intense pulsed light⁵

1. Gao YF, et al. *Cornea*. 2007;26(2):136-143. 2. Korb DR, Blakeie CA. *Cornea*. 2013;32(12):1554-1557. 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.

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The First Open-Eye Warm Compress

Effective & Consistent Heat
 [Product] supplies therapeutic heat (>40°C) for a minimum of ten minutes every use. This ensures patients and doctors an effective treatment every time.

Unique Convenience & Natural Expression
 [Product] design utilizes anatomical norms to target the eyelids while avoiding the globe. This permits the user to see and blink throughout treatment, resulting in improved compliance and natural meibomian gland expression.

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Innovative treatment for the MGD patient

- Precise Moist Heat, On Demand
- Gentle Cleaning With Sodium Hyaluronate & coconut extracts

Designed to Help Improve Patient Compliance

- ✓ Simple, Easy To Use as Part of Existing Daily Routine
- ✓ Fast – Works in seconds; For Only 4-6 Mins/Day
- ✓ Individually Wrapped For Use Anywhere
- ✓ Eliminates Need to Use Multiple Products

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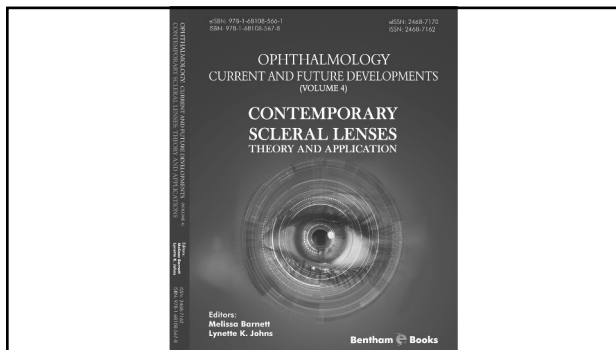
Maintains > 40°C/104°F for 7 minutes, 15 seconds with an average mean temp of 45°C/113°F

Device Average Temps (n=30)	Mean
Max or peak temperature	47.7°
Seconds to reach 40°C	15.7
Duration above 40°C	7 min, 15 sec
Mean temperature above 40°C	45°
Seconds to reach 38°C	12.6
Duration above 38°C degrees	8 min, 25 sec
Mean temperature above 38°	44.1°

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- ### Treatment Strategies in 2022
- Anti-inflammatory agents
 - Topical corticosteroids
 - Topical cyclosporine A emulsion (CSA) 0.05% and 0.09%
 - Topical lifitegrast, 5%
 - Oral tetracyclines or macrolides
 - Topical azithromycin
 - Amniotic membrane products: anti-inflammatory and promote wound healing
 - Neurostimulation
 - Intranasal neurostimulation
 - Extranasal neurostimulation

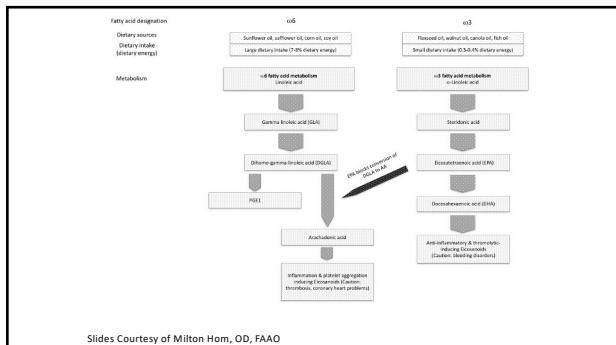
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- ### Oral Medications for Dry Eye
- Nutritional supplements
 - 1,000 mg BID of Omega-3 Fish Oil
 - Rx
 - 4g per day po
 - Indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia
 - Oral pilocarpine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

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

John D. Stimpers, et al., Stephen C. Pflugfelder, Rishi Singh, Andrew J. McClellan, Michael P. Weikert, Stephen V. Scooter, Thomas J. Jony, Danya M. Lago, Walter O. Whittier, Bala Kishan, Mark Brocher

¹Ophthalmology, Eastern Virginia Medical School, Norfolk, VA, ²Central Coast Eye Care, ³Coastal Eye Institute, ⁴Ophthalmology, Baylor College of Medicine, Houston, TX, ⁵Virginia Eye Consultants, Norfolk, VA

Introduction: Patients with moderate to severe dry eye continue to require topical treatment. Nutritional supplements containing gamma linolenic acid (GLA) and omega-3 fatty acids (omega-3) may improve dry eye symptoms. This study evaluated the efficacy of a nutritional supplement containing GLA and omega-3 fatty acids in improving dry eye symptoms.

Methods: A total of 48 patients with moderate to severe dry eye were enrolled in a randomized, controlled, prospective study. The study was conducted in a tertiary care ophthalmology clinic. The study was conducted in a tertiary care ophthalmology clinic. The study was conducted in a tertiary care ophthalmology clinic.

Results: The study showed that patients who received the nutritional supplement had significantly improved dry eye symptoms compared to the control group. The study showed that patients who received the nutritional supplement had significantly improved dry eye symptoms compared to the control group.

Conclusion: The study demonstrated that the nutritional supplement containing GLA and omega-3 fatty acids significantly improved dry eye symptoms in patients with moderate to severe keratoconjunctivitis sicca.

Keywords: Dry eye, nutritional supplement, gamma linolenic acid, omega-3 fatty acids, keratoconjunctivitis sicca.

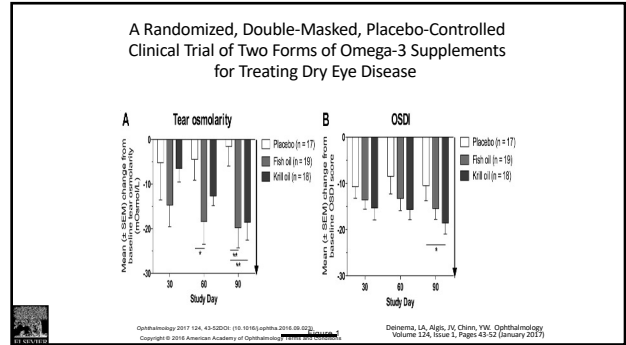
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Effect of Oral Re-Esterified Omega-3 Nutritional Supplementation on Dry-Eye Disease: Double-Masked Randomized Placebo-Controlled Study

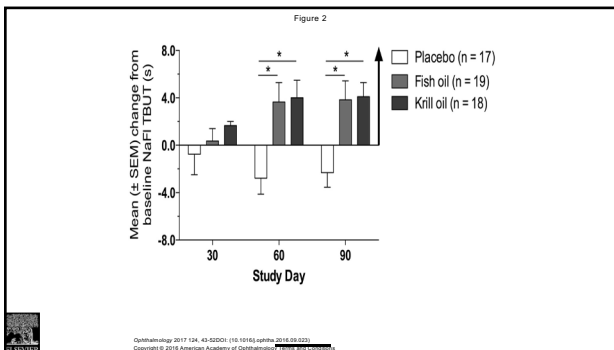
- 105 patients with dry eye disease
 - Four capsules (2 gm) once a day containing 1680mg EPA and 560mg DHA (PRN Dry Eye Omega Benefits) for 3 months or four capsules of placebo.
 - All patients underwent a screening, baseline, 6 week and 12 weeks visit.
 - On each visit patients were tested for tear 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

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Cyclosporine ophthalmic solution

- A nanomicellar formulation of cyclosporine 0.09%
- In this 12 week, multicenter, randomized, double-masked, vehicle controlled Phase 3 confirmatory study, 744 dry eye patients were treated either with OTX-101 or its vehicle.
 - Met primary endpoint of Schirmer's Score ($p < 0.0001$)
 - The demonstration of efficacy at 12 weeks is earlier than other drugs approved for dry eye in the same class.
- FDA Approved 8/16/18

52

Advanced NCell™ Technology Helps Increase Ocular Penetration of CsA

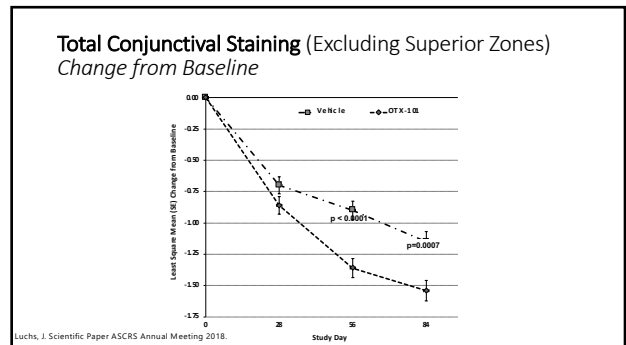
A single-dose, preclinical study of a CsA 0.05% formulation with NCell™ technology vs a commercially available CsA ophthalmic emulsion 0.05%

3X higher corneal absorption

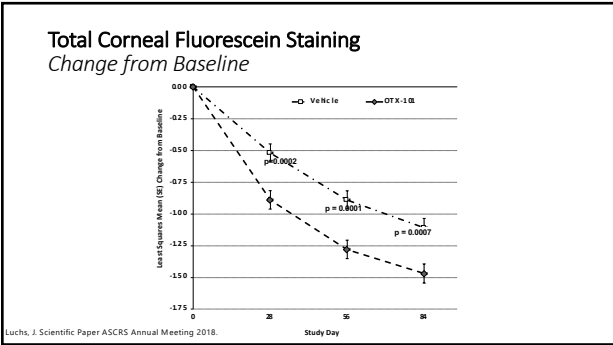
1.6X higher conjunctival absorption

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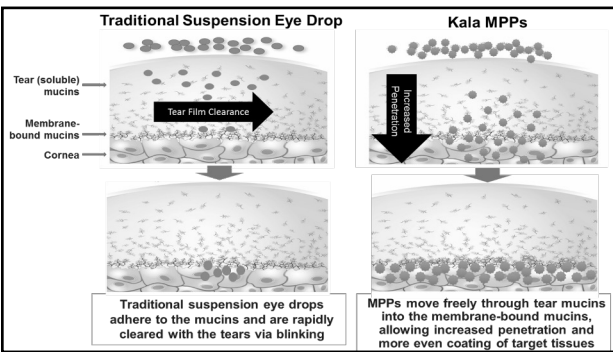
55

Loteprednol 0.25% in MPP for Dry Eye Flares

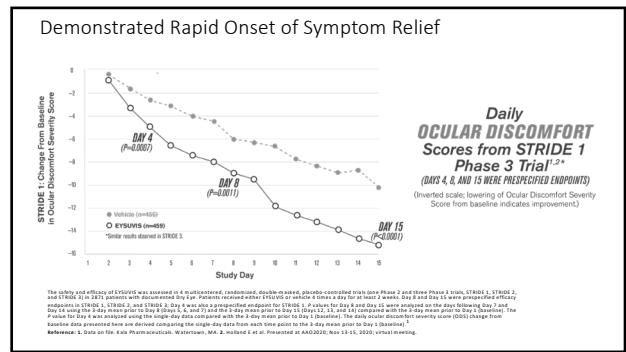
- Loteprednol etabonate 0.25% in the AMPPLIFY™ nanosuspension is ~300 nm
- Traditional loteprednol etabonate (LE) suspension 6,000 nm
- Current LE concentrations 0.5% and 0.2%

- FDA Approved on 10/27/2020

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

Abstract	Study Design and Demographics	Conclusions
Background: KPI-121 is a novel ophthalmic suspension... Methods: Safety was assessed in four multicenter, randomized, vehicle-controlled studies... Results: KPI-121 was well-tolerated... Conclusions: KPI-121 is safe and effective.	Study Design: Four multicenter, randomized, vehicle-controlled studies. Demographics: Mean age 58.7 years, 79% female.	Conclusions: KPI-121 was well-tolerated... Adverse Events: No serious adverse events... Significance: KPI-121 is safe and effective.

59

Neurotrophic Keratitis: Etiology

- Infectious: HSV, VZV, leprosy
- 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
- Topical medications: anesthetic abuse
- Iatrogenic: LASIK/PRK, corneal incisions (RK, AK), contact lens wear, scleral bands, vitrectomy and photocoagulation to treat diabetic retinopathy^{1,2}
- Chemical and physical burns
- Systemic: DM, multiple sclerosis, Vit A deficiency
- Increasing age, chronic DED³

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

60

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 JA. Neurotrophic keratitis. Current Ocular Therapy, Philadelphia, PA: WB Saunders; 1995:452-4.

61

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

```

graph TD
    NGF[Endogenous NGF] --> CP[Cell proliferation]
    NGF --> TS[Tear secretion]
    NGF --> CR[Corneal reinnervation]
    CP --- CR
    TS --- CR
    
```

Nerve damage → loss of corneal sensitivity → NK

Mastrorillo et al. (2017) Cell Physiol 202:737-04

62

CASE STUDY:

- **Original**
- **HVID**
 - Known measurement
 - Select units
- **Defect Area**
 - Measure the surface area of the defect in selected units

63

Award-winning ocular analysis - AOS Anterior software

Analyse any digital image of the ocular surface using any one of three modes:

- Bulbar redness grading
- Lid redness grading
- Fluorescein punctate count

Features of the application:

- Digital Written filter
- Digital ruler
- Digital extraction
- Digital enhancement
- Image cropping tool
- Automated grading on objective scale
- PDF file generator for reporting
- Mobile image capture application (HIPPA compliant)

64

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

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

Basilio S, Lamba A, Kana P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology 2018;125:1342-1349.

- 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

65

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

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

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

European patients with NK in one eye

NCT02735456

VALIDATED REPORT 93.3%

72.0% completely healed

In the majority of patients across two clinical studies (cenegermin bkbj 20 mcg/ml), was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

Study NGF0214 (N=24 per group)

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

NCT02277447

VALIDATED REPORT 93.7%

65.2% completely healed

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

*Validated Report (N=100) study with longest follow-up

66

66

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

Did you know?

34% of basal tear production is due to inhaled air through the nasal passage¹

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

¹Gupta A, Hejtle T, Pflugfelder SC. Nasoc lacrimal stimulation of aqueous tear production. *Cornea*. 1997 Nov;16(8):648-51.

²van der Werf F, de A, Li, S., Jajic, B., Price, M, A, R, T, Li, H., & O'Neil, J, A. (1998). Innervation of the lacrimal gland in the cynomolgus monkey: a retrograde tracing study. *Journal of neurocytology*, 27(10), 591.

³Wong, M, S., Zhou, G., Murphy, R, B., Greene, M, L., & Ryan, P. (2001). Parasympathetic innervation of the meibomian glands in rats. *Investigative ophthalmology & visual science*, 42(11), 2434.

⁴Curt, D, A., McCarthy, D, M., Menor, H, J., Kessler, T, L., Chung, E, H., & Zeleke, J, D. (1995). Localization of nerves adjacent to goblet cells in rat conjunctiva. *Current eye research*, 14(11), 993-1000.

67

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

Note: The CAE was used for this measurement.

Mean Change from Baseline in Schirmer's Score – Week 4 (Primary Sign Endpoint)

Group	n	Mean Change (mm)
Placebo	43	3.2
OC-01	46	11.8

P<0.001

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

Group	n	Mean Change (mm)
Placebo	43	-5.6
OC-01	46	-19

P<0.05

ITT-observed population ANCOVA, Least Squares means

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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

Region	Placebo (n=43)	OC-01 (n=46)
Total	2.33	0.31
Temporal	0.42	0.15
Central	0.44	0.2
Nasal	0.44	0.04
Superior	0.09	0.11
Inferior	0.93	0.41

P-values: Total (P<0.05), Central (P<0.05), Inferior (P<0.05)

69

OC-01 is Well Tolerated with Zero Ocular Side Effects

Adverse Events Potentially Related to OC-01 >5% of subjects

Occurred at least once after any installation	OC-01 (0.1%) (n=48)	Placebo (n=43)
Sneeze	38 (79)	0
Cough	6 (13)	0
Throat irritation	7 (15)	0
Instillation site irritation	8 (17)	0
Pharynx dysaesthesia	4 (8)	0

- All events transient and self-limiting immediately following administration
- All events mild (94%) or moderate (4%) in severity. No severe events.
- No ocular adverse events; Side effects consistent with that of any nasal spray (sneeze, cough, irritation)

On Track for Initiating Phase 3 in 2019

70

ONSET-2 Top Line Results

- Primary endpoint: Statistically significant improvement in percentage of subjects gaining ≥ 10 mm on Schirmer's Score in both doses tested (0.6 mg/ml and 1.2 mg/ml) as compared to control (p<0.0001). Consistent outcome with ONSET-1
- Statistically significant improvement in mean change in Schirmer's Score in both doses tested as compared to control (p<0.0001). Consistent outcome with ONSET-1
- Eye Dryness Score measured in the normal clinic environment demonstrated SS improvement as compared to control in the 1.2 mg/ml dose group at Week 4 (p<0.009) and as early as Week 2 (p=0.002)
- Most common AE was sneeze, which was predominantly transient and mild

***Possible FDA NDA Submission 2nd half 2020

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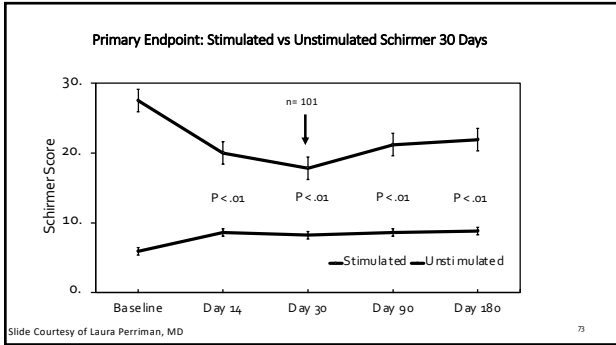
FDA Label

INDICATION FOR USE

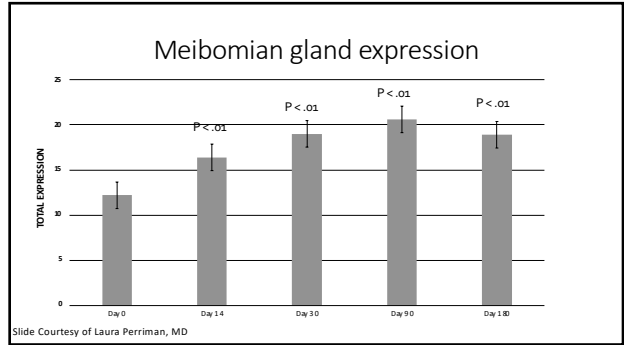
The Neurostimulator™ is an electromechanical nerve stimulator device, indicated for temporary use (up to 30 days) to increase acute tear production during vibratory stimulation of the external nasal nerve in adults, under prescription of an eyecare provider.

Slide Courtesy of Laura Perriman, MD

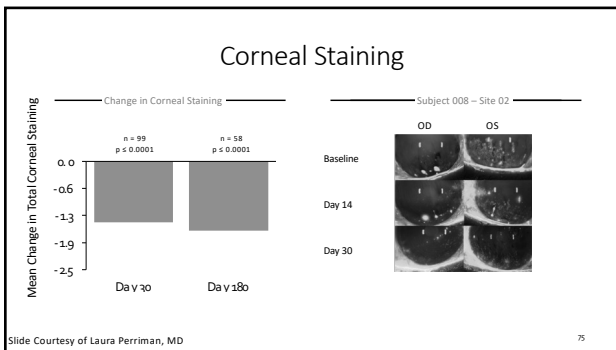
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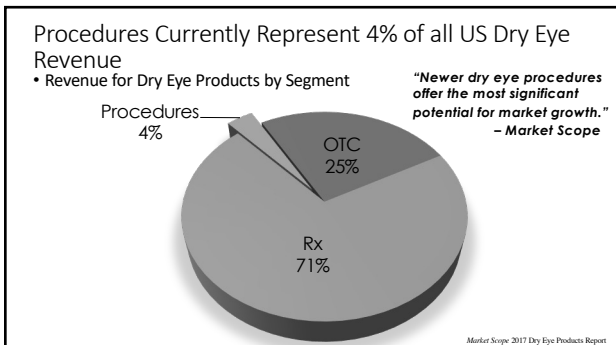
Summary

- Array of positive endpoints reflects broad mechanism of action of neuromodulation
- Effective for improving Schirmers scores, fluorescein staining and meibomian gland scores
- Immediate, intermediate and long term benefits to the ocular surface
- Strong safety profile
- High value addition to the dry eye armamentarium

FDA approved May 1, 2020

Slide Courtesy of Laura Perriman, MD

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

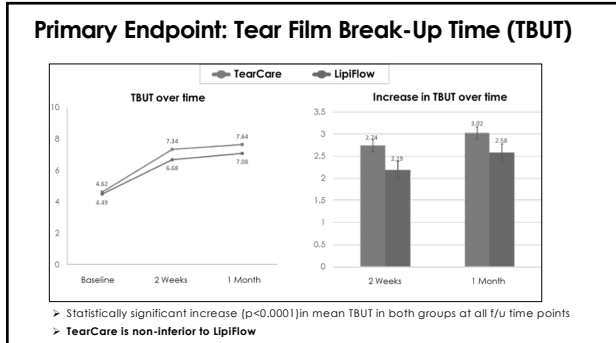
A Randomized Controlled Investigator masked Trial (OLYMPIA)

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

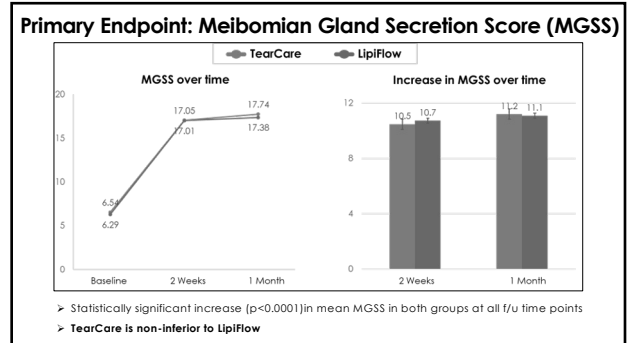
Presented by Jennifer M. Loh, MD, ABO; ASCRS May 16, 2020

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

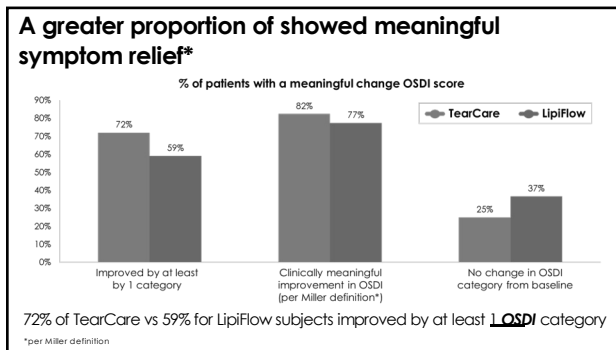
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In-Office MGD Treatment

Handheld Thermal Pulsation device

- Magnifier allows the user to view the eyelid margin
- Warms the eyelid tissue within a therapeutic target range to melt the meibum blocking the orifices, then applies compression to express the melted meibum through the orifices
- Amount of heat and pressure is under direct control of the user

Smart Tip

- Sterile, single-patient-use disposable tip
- Inner and outer pads are covered with a soft, biocompatible silicone material
- Contains precision temperature sensors that continually monitor inner and outer eyelid temperature and ensure therapeutic heat levels during treatment

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03/08/2022, 09:01:14 AM
 Published online 2022 Feb 12, doi: 10.1093/ptj/ptj/abq008

PROCEEDINGS
 PAPER

Comparison of the iLUX and the LipiFlow for the Treatment of Meibomian Gland Dysfunction and Symptoms: A Randomized Clinical Trial

Joseph T. Taylor,¹ James Chen,² Neil B. Rosenblatt,³ John H. Johnson,⁴ and Mark A. Dubowitz⁵

Abstract

Results

Both devices significantly improved effectiveness outcomes, with no differences between the two devices. At the 4-week visit, mean MGS, TBUT, and OSDI scores improved at least 16.9 ± 11.5 , 2.6 ± 3.2 s, and 28.0 ± 22.8 , respectively, across treatment groups and treated eyes. Four device/procedure-related events occurred in the iLUX group, compared with none in the LipiFlow group, but there were no device-related adverse events that involved changes in lid margins, eyelids, or lash integrity. Corneal staining, intraocular pressure, and visual acuity did not differ in the two groups.

Conclusion

Both treatments produced significant improvements in meibomian gland function and symptoms. For all effectiveness measures, there were no statistically significant differences between the two treatments.

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Does Not Cause Excessive Heating of the Eye

• An open-label safety study found no sign of excessive heating of the cornea, outer eyelid, or surrounding surface!*

• Standard optometric assessments of the cornea and subjects' vision demonstrated no corneal damage and minimal impact on vision!*

Tissue Site	Pre-heating temperature (°C)	Post-heating temperature (°C)	Change in temperature (°C)
Corneal	Maximum: 36.9 Mean: 36.0 ± 0.6	Maximum: 38.8 Mean: 37.7 ± 0.5	+1.8
Outer eyelid	Maximum: 37.4 Mean: 36.5 ± 0.5	Maximum: 40.6 Mean: 38.5 ± 0.8	+3.2
Surrounding surface	Maximum: 37.6 Mean: 36.8 ± 0.5	Maximum: 39.7 Mean: 38.2 ± 0.7	+2.1

* Heating performed in the medial-nasal and medial-temporal zones in the upper and lower eyelids of each eye for 90 seconds in each case

Reference: 1. Humber DR, Kasperli PM, Owen J. Safety parameters of a handheld infrared heating and compression device for management of Meibomian gland dysfunction. Presented at the ASGS/AGS Annual Meeting, April 13-17, 2016, Washington, DC.

84

Handheld MGD Thermal Pulsation System 1 Week / 1 Month Study Design¹

- 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

MGD, meibomian gland dysfunction. Reference 1. Alcon data on file, 2011.

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Thermal Pulsation System Delivered Significant Improvements in 1 Week in a Clinical Study¹

Significant improvements seen
1 week after treatment

Meibomian Gland Score (P<0.0001)	Tear break-up time (P<0.0001)	SPEED Questionnaire (P<0.0001)	OSDI Score (P<0.0003)
315% improvement <small>Medial, temporal, nasal regions all improved</small>	71% improvement	55% improvement <small>Improvement in all 8 sub-scores</small>	58% improvement

All improvements maintained at 1 month

In a prospective, open-label, multicenter study of patients ≥18 years with MGD (n=30).
*In some questionnaires that assess 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.
MGD, meibomian gland dysfunction; OSDI, Ocular Surface Disease Index; SPEED, Standard Patient Evaluation of Eye Dryness.
Reference 1. Alcon data on file, 2011.

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Safety of in 1 Week / 1 Month Study

In the non-randomized clinical study of the handheld MGD Thermal Pulsation System¹

- No adverse events or serious adverse events reported!**
- Pain scores increased post treatment, but returned to pre-treatment values one day post treatment!
- 1 week post treatment pain scores were significantly lower than pretreatment values (both eyes, P<0.0001)**
- No clinically significant changes in IOP occurred immediately post-treatment or throughout follow-up!**
- No change in lid abnormalities associated with treatment!**

In a prospective, open-label, multicenter study of patients ≥18 years with MGD (n=30).
MGD, meibomian gland dysfunction; OSDI, Ocular Surface Disease Index.
Reference 1. Alcon data on file, 2011.

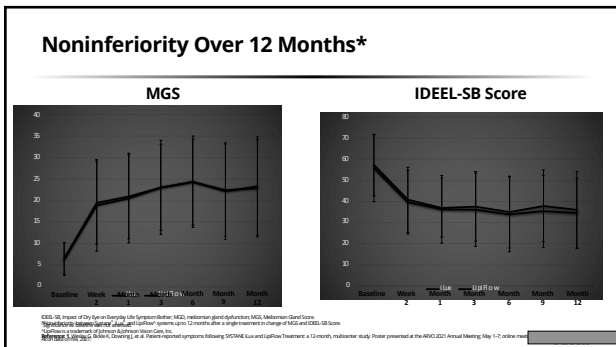
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Phase 4, 12-Month Follow-Up Study of Handheld Thermal Pulsation

- Study Objective:** compare meibomian gland function and impact of dry eye symptoms on patient everyday life over 12 months of follow-up after treatment with Systane® iLux® and Lipiflow[®]
- Study Design:** prospective, randomized, parallel group, investigator-masked, multicenter, noninferiority study
- Subjects:** 236 subjects with MGD
- Endpoints:** MGS, IDEEL-SB, TBUT
- Assessed at baseline, 2 weeks and 1, 3, 6, 9, and 12 months

IDEEL-SB, Impact of Dry Eye on Everyday Life Symptom Burden; MGD, meibomian gland dysfunction; MGS, Meibomian Gland Score; TBUT, tear breakup time.
Reference 1. Hwang J, et al. Secondary end points: patient reported symptoms following SYTAME Lux and Lipiflow Treatment: a 12-month, randomized study. Poster presented at the AAO 2021 Annual Meeting, May 1-5, 2021, Orlando, FL. Abstract 208. (Aug 2021).

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At Home Treatment

- Stimulates the meibomian gland's opening using a disposable tip made of a soft silicone material to remove biofilm and scurf
- At-home lid treatment

90

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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Clinical Ophthalmology

PROSPECTIVE EVALUATION OF INTENSE PULSED LIGHT AND MEIBOMIAN GLAND EXPRESSION EFFICACY ON RELIEVING SIGNS AND SYMPTOMS OF DRY EYE DISEASE DUE TO MEIBOMIAN GLAND DYSFUNCTION

Steven J. Dell¹, Ronald N. Gassner², David C. Barshatzky³, Derek N. Cunningham⁴

¹Optical Laser, Cosmetics, Irvine, CA, CAUSA
²Optical Laser, Cosmetics, Irvine, CA, CAUSA
³Optical Laser, Cosmetics, Irvine, CA, CAUSA
⁴Optical Laser, Cosmetics, Irvine, CA, CAUSA

Abstract: The aim of this study was to evaluate the efficacy of intense pulsed light (IPL) delivered by meibomian gland expression (MGE) in reducing the number and severity of signs and symptoms of dry eye disease (DED) secondary to meibomian gland dysfunction (MGD).

Methods and results: In a prospective study conducted in two sites, 40 subjects with severe MGD were treated with IPL. Signs and symptoms were measured at baseline and at 1, 2, 4, 8, and 12 weeks post-treatment. Significant improvements were observed in the following parameters: tear film break-up time (TFI), meibomian gland score (MGS), central keratinized staining (CKS), modified Foster's U index score of fluorescein (FUS) punctate keratitis, and tear film osmolarity (TFOS). Significant patients achieved four significant outcomes: 3 weeks post-treatment included the administration of 0.02% cyclosporine (CYC) on the study and visit, followed by MGE of the upper and lower eyelids. MGS, MGS, CKS, FUS, TFOS, and Tear Layer Thickness (TLT) were measured at baseline, 1, 2, 4, 8, and 12 weeks after IPL.


Results: Due to different testing methods used for TFOS measurements, TFOS and CYC were analyzed separately for each site. From 10 to 12 weeks following the number of signs and symptoms with DED decreased from 1,300 to 1,400. TFOS improved by 20%, MGS, meibomian gland score (MGS) improved by 20%, CKS improved by 20%, FUS improved by 20%, TFOS improved by 20%, and TLT improved by 20%. These results support the efficacy of IPL + MGE in relieving both signs and symptoms of DED secondary to MGD.

Keywords: Dry eye, meibomian gland dysfunction, intense pulsed light

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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

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Photobiostimulation

Red light is absorbed in the cellular mitochondria and stimulates ATP production leading to an increased cellular action and enhanced cell vitality.

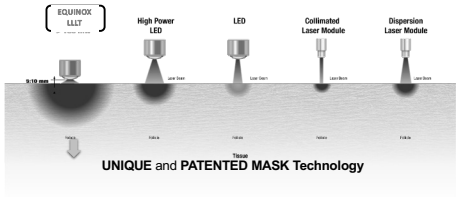
The 633 nm emitted light is potentially absorbed by fibroblasts, with a subsequent increase in the speed and efficiency of neo-collagen synthesis. Turnover of aged collagen and elastin fibers results from light stimulation of metalloproteinases (MMP's).



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LLLT & LED Technology



UNIQUE and PATENTED MASK Technology

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Advanced Technology

- Computer Driven
- Select Level of MGD 1-4 = Calculates correct Energy and Time (15min Max)
- Apply Comfortable Mask
- Both Eyes/Lids Treated Simultaneously
- Automated Treatment Starts & Stops with Countdown Timer
- Visible Results Possible for Patient after 1st Treatment

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Ophthalmology Times
CUTTING-EDGE ADVANCEMENTS

Ophthalmology Times • Ophthalmology • Drug Therapy • Ophthalmology

Red light technology increases tear break-up time in dry eye patients

More than 90% of subjects report improvement in symptoms in study

November 25, 2015 | By Lynda Charters, Rolando Toyos MD

Take-home message: Treatment with red light technology resulted in a significant improvement in the tear break-up time in the vast majority of patients. This may be a future light treatment for the improvement of dry eye disease in patients with meibomian gland dysfunction.

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Like With Lasers – Color Matters

BLUE LIGHT:
Purification action. The blue light is recognized to be the ideal wavelength to solicit porphyrins to obtain a bacteriostatic effect with a consequent **elimination of bacteria**

YELLOW LIGHT:
Specific action on the lymphatic system. The yellow light stimulates cell's metabolism promoting a **de-toxifying action** to relief swelling conditions.

RED LIGHT:
Stimulates production of collagen and elastin. Through the **EQUINOX LLLT®** technology, the red light is absorbed by mitochondria and **stimulates ATP increasing cellular action, enhancing it's activity.**

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Indications for Punctal Occlusion

- Dry Eye symptoms
- For treatment of ocular dryness secondary to contact lens use
- To enhance the efficacy of topical ocular medications
- After surgery to prevent complications due to dry eye
- Dry eye component of conjunctivitis, keratitis, corneal ulcer, pterygium, blepharitis, red lid margins, recurrent chalazion, corneal erosion, filamentary keratitis and other eye diseases.

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Types of Occlusion

- Temporary occlusion
 - Collagen plugs
 - Dissolve within 4 – 7 days
- Permanent occlusion
 - Silicone plugs
 - Thermal / laser cautery
 - May extrude or migrate out of the puncta over time
- Semi-permanent occlusion
 - Silicone or thermal labile acrylic polymers
 - May last for several months
- Partial occlusion
 - Used when total occlusion is too much
 - Designed with an interior channel (.008 inches) to limit the drainage of tears

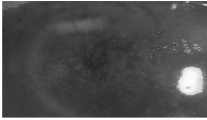
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Current Uses for Topical Biologics for OSD

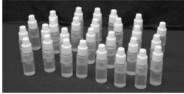
- Persistent epithelial defects
 - Neurotrophic keratopathy
 - Exposure keratopathy
- Recalcitrant dry eye
- Filamentary keratitis
- Corneal ulcers
- Herpetic keratitis
- Steven-Johnson's Syndrom
- Keratoneuralgia
- Recurrent corneal erosion
- Limbal stem cell deficiency



101

Autologous Serum

- Blood drawn via 18 gauge needle – 40 mL blood collected into blood tubes
- Blood set aside to clot at room temperature for two hours, then centrifuged at 5600 rpm for 10 minutes
- Serum filtered to remove fibrin strands before mixing with saline
- Typically start with 20% AS up to 50%
- Unopened bottles stored in freezer up to 3 months; open bottles in refrigerator for 48 hours
 - Potential for safe refrigerator storage for up to 1 month



Source: Review of Optometry

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Healing factors in Autologous Serum

- Vitamin A
- Lysozyme
- Transforming Growth Factor-beta
- Fibronectin
- Substance P
- Insulin-like growth factor-1
- Nerve growth factor

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Benefits and Pitfalls of Autologous Serum

<p>Benefits</p> <ul style="list-style-type: none"> • Preservative free and innately allergy free • Adverse events rare • Improvement in symptomology • Demonstrated improvement in staining (Tsubota – SS pts) 	<p>Complications</p> <ul style="list-style-type: none"> • Cost – no insurance coverage • Frequent blood draw • Availability of labs to make ASED • Strict handling
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Amniotic Membranes

Cryopreserved Dry Membrane Dry Membrane Drops

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Hindawi
Journal of Ophthalmology
Volume 2017, Article ID 404918, 10 pages
https://doi.org/10.1155/2017/404918

Clinical Study

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

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Improvements in Clinical Signs and Symptoms

Corneal Staining Grading: Control (solid line) vs Study (dashed line). P < 0.05, P < 0.001.

Pain Scoring: Control (solid line) vs Study (dashed line). P < 0.05, P < 0.001.

SPEED Questionnaire Scoring: Control (solid line) vs Study (dashed line). P < 0.05, P < 0.001.

DEWS Scoring: Control (solid line) vs Study (dashed line). P < 0.05, P < 0.001.

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Improvements in Corneal Nerve Density & Sensitivity

Corneal Nerve Density: Control (solid line) vs Study (dashed line). P = 0.015.

Corneal Nerve Sensitivity: Control (solid line) vs Study (dashed line). P < 0.001.

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Blepharitis is a Large and Underserved Market in Eye Care

Epidemiology of Demodex Blepharitis

Not fully Undiagnosed, Education Needed	~50% of all patients in the eye clinic have collarettes ¹ but current impression of only 30-35% of blepharitis cases
Significant HEAR STAY on Diagnosis	2.1M ICD-10 blepharitis Dx/yr ²
Blepharitis Routinely Causes	Eye lids 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 ⁴
Blepharitis and Surgery	Important factor for maximizing surgical outcomes: 67% of cataract patients have Demodex blepharitis ⁵
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. ^{6,7,8}
Prescription Treatment	None

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Collarettes Are Pathognomonic Sign of Demodex Infestation

Collarettes Are Composed of Mite Waste Products and Eggs¹

- Regurgitated undigested material combined with epithelial cells, keratin, and mite eggs
- Contain digestive enzymes, which cause irritation

Easily and Rapidly Diagnosed with Standard Eye Exam

- Demodex mites found on **100%** of lashes with collarettes²
- Collarettes found in ~ **58%** eye care patients³

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TP-03 is Designed to Eradicate Demodex Mites and Treat Demodex Blepharitis

***Not FDA Approved

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TP-03 is a Novel Drug Designed to Treat Demodex Blepharitis by Eradicating Mites and Collarettes

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

*BID means twice per day
© TP-03 Product profile based on Saturn-1 Trial Design
***Not FDA Approved

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Cure of Collarettes with BID Use of TP-03

***Not FDA Approved

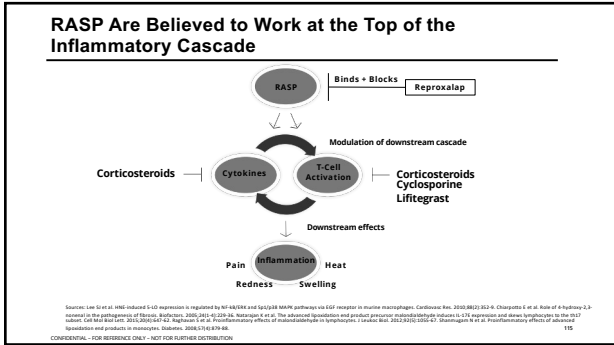
Baseline	Day 28

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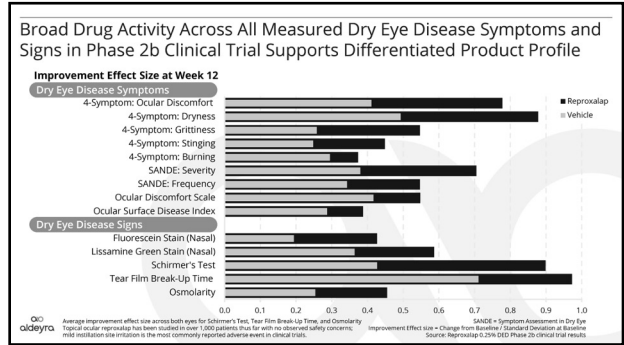
Reactive Aldehyde Species

- 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 immunomodulation
- 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.

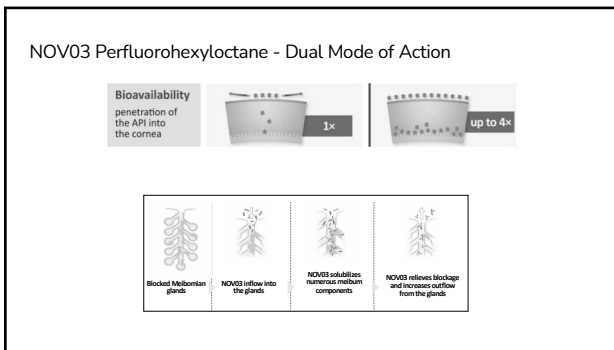
114



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NOV03 has been Evaluated in Several Small Clinical Studies in the EU

- Steven P, Scherer D, Krösser S, Beckert M, Cursiefen C, Kaercher T. Semifluorinated alkane eye drops for treatment of dry eye disease—A prospective, multicenter noninterventional study. *J Ocular Pharmacol Ther* 2015;31(8):498-503. <https://pubmed.ncbi.nlm.nih.gov/26296040/>
- Steven P, Augustin AJ, Geerling G, et al. Semifluorinated alkane eye drops for treatment of dry eye disease due to meibomian gland disease. *J Ocul Pharmacol Ther* 2017;33(9):678-685. <https://pubmed.ncbi.nlm.nih.gov/28922088/>
- Eberwein P, Krösser S, Steven P. Semifluorinated alkane eye drops in chronic ocular graft-versus-host disease: A prospective, multicenter, noninterventional study. *Ophthalm Res.* 2020;63:50-58.
- Garhofer G, Schmidt D, Werkmeister RM, et al. Influence of perfluorohexyloctane containing eye drops on tear film thickness in patients with mild to moderate dry eye disease. *Invest Ophthalmol Vis Sci.* 2018;59(9):941. <https://iovs.arvojournals.org/article.aspx?articleid=2689663&resultClick=1>

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

Joseph Toubou, MD, David J. Wills, MD, P. Gnanasekar, MD, P. Pong, J. Majumdar, MD, J. Daniels Wilson, PhD, S. Srinivasan, PhD, R. P. Singh, MD for the SEECASE study group

Purpose: NOV03 has a unique dual mode of action to address the underlying cause of dry eye disease (DED) by restoring the meibomian gland function. The purpose of this study was to evaluate the efficacy, safety, and tolerability of NOV03 in the treatment of DED.

Methods: SEECASE was a prospective, randomized, controlled, parallel-group study. A total of 200 patients were randomized to receive either NOV03 or vehicle. The primary efficacy endpoint was the change in the mean tear film break-up time (TFBT) at 12 weeks. Secondary endpoints included the change in the mean tear film break-up time (TFBT) at 4 and 8 weeks, the change in the mean tear film break-up time (TFBT) at 12 weeks, and the change in the mean tear film break-up time (TFBT) at 12 weeks.

Results: The study met its primary endpoint, showing a statistically significant increase in TFBT at 12 weeks for the NOV03 group compared to the vehicle group. Secondary endpoints were also met, showing a statistically significant increase in TFBT at 4 and 8 weeks for the NOV03 group compared to the vehicle group. The study was well-tolerated, with no significant differences in adverse events between the two groups.

Conclusion: This study demonstrated that NOV03 is an effective and safe treatment for DED. The unique dual mode of action of NOV03, which addresses the underlying cause of DED, provides a differentiated product profile compared to other treatments. The study was well-tolerated, with no significant differences in adverse events between the two groups.

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TARGETING ABBERRANT 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

Trank, et al. Journal of Investigative Dermatology 2007, Volume 127, No. 10. | Trank et al. Molecular Basis 2009, 9, 801-810

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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 comedocytes, sebum, and other debris
- Keratolytic treatments are used to shed dead comedocytes, 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

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AZR-MD-001 Phase 2 program—Study design and overview

- Multicentre, randomized, double masked vehicle controlled clinical trial to evaluate safety and efficacy of signs and symptoms of meibomian gland dysfunction

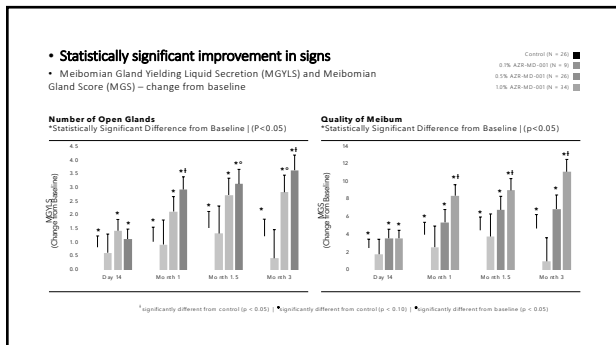
Primary Sign Endpoints

- Change from baseline to month 3 in MGSL
- Change from baseline to month 3 in MGYSL
- Either can serve for approval

Primary Symptom Endpoints

- Change from baseline to month 3 in total OSDI
- Change from baseline to month 3 in Eye Dryness VAS

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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 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