Advances in Ocular Surface Disease Management

COPE#71296-AS

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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

2

NP Dry Eye Evaluation

- 58 YOWF presents for evaluation of dry eyes OU. It started about 8 years ago and symptoms are constant and severe. Both eyes burn, water constantly, are red all the time, and gritty feeling in the morning. She suffers from allergies uses OTC allergy meds and nasal sprays. Suffers from light sensitivity and decrease in vision. Previously tried lifitegrast and cyclosporine 0.05% but it didn't help at all. Pt stopped using make-up but it didn't change anything. Pt is taking OTC artificial tears TID OU.
- Pt Hx: Allergies, HTN
- Meds: Diphyhydramine, ibuprofen, lisinopril, montelukast

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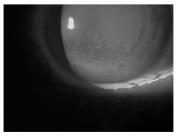
Clinical Exam

- SPEED 25
- BCVA:
  - OD +0.50+0.50X170 20/20
  - OS +0.50DS 20/20
- Tear Oz: 319/ 326
- MMP-9: + OU
- SLE: Mild blepharitis, granular secretions, 1+ injection,2+ Lissamine green, 2+ diffuse SPK, 4sec TBUT
- Schirmers 5/4



***What's Your Working Diagnosis???

4

Goals for Treatment

- Improve symptoms??
- Improve MGD??
- Reduce inflammation??

5

Management Options?

- Since we agree that Mrs. Smith has a diagnosis of DED
  - How would you proceed with therapy for her?
  - When would you see her back?
  - What criteria would you use to monitor improvement?

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What Did I Do?

- Loteprednol 1.0% BID OU
- Nutraceuticals BID OU
- PF ATs qid OU
- Heat mask
- Continue montelukast 10mg PO
- Sjogrens testing
- Consider plugs at next visit
- Refer to dry eye counselor to discuss Lid Renewal Package (Lid Wipes / Microblepharoexfoliation / thermal pulsation)
- F/U????? Tests????

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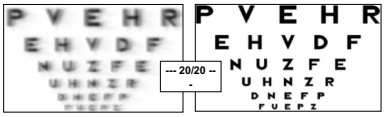
Better Comfort and Quality of Vision

- 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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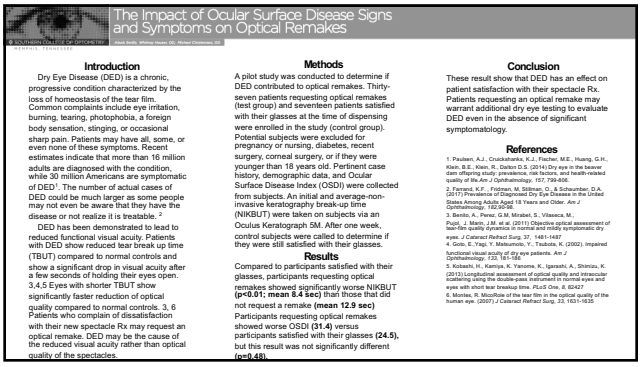

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Dry Eye Practice Optimization

- Patients Win: Diagnostic Accuracy
- Insurers Win: Targeted Therapy
- Doctors Win: Practice Growth
- Practices Win: Income Diversification

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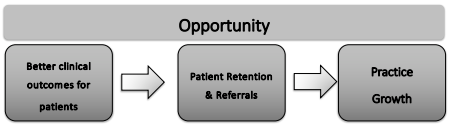
Dry Eye Market Overview

- **>30 Million** Americans suffer from 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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Dry Eye Supplements
Fail to Address the Underlying Cause

Beard B. Boston Foundation for Sight Survey. Report Back to the Community. *Boston Foundation for Sight*. July 15, 2010. www.bostonsight.org.

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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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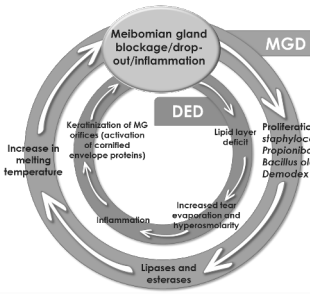
Mechanism of disease



- Lipids from meibomian glands necessary for ocular surface health and 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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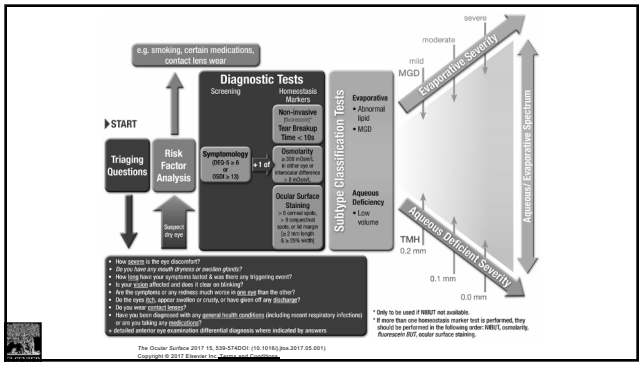

The Ocular Surface 2017 15, 539-574DOI: (10.1016/j.jtos.2017.05.001)
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Improving the Screening, Diagnosis, and Management of Dry Eye Disease

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, 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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Contact Lens Considerations

- Contact lens wearers with unexplainable reduced wearing time had MGD[1]
- CL wear accelerates MGD[2,3]
- 60% of CL wearers had MGD[4]

1. Henriquez AS, Korb DR. Meibomian glands and contact lens wear. Br J Ophthalmol. 1981 Feb;65(2):108-11.
2. Ong BL. Relation between contact lens wear and Meibomian gland dysfunction. Optom Vis Sci 1994;71:208-10.
3. Arita R, Itoh K, Inoue K, Kuchiba A, Yamaguchi T, Amano S. Contact lens wear is associated with decrease of meibomian glands. Ophthalmology 2009;116:379-84.
4. Machalińska A, et al. Comparison of Morphological and Functional Meibomian Gland Characteristics Between Daily Contact Lens Wearers and Nonwearers. Cornea. 2015 Sep;34(9):1098-104.

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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

23

Surgical Considerations

- Approximately 10–20% of post-LASIK patients may suffer from chronic dry eye disease with more severe discomfort after LASIK[1]
- Cataract Patients: 59% (n-233) had MGD[2]
- 62.3% had TBUT < 5 sec[3]

1. Ambrósio R Jr, Tervo 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. Algamadi et al. Epidemiology of Meibomian Gland Dysfunction in an Elderly Population. Cornea. 2016 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 (PHACO) 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

VanDusen, BS,
MD

Results: There were 120 patients (69% women), mean age 69.5 years ± 8.4 (SD). Abnormal osmolarity 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 (osmolarity 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.

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 time[3]
  - Possibly worse with femtosecond laser-assisted cataract surgery[4]
  - Possibly grooved incision[5]
  - Medication toxicities
- No relationship to incision location

1. Ishrat S., Nema N, Chandravanshi SCL. Saudi J Ophthalmol. 2019 Jan-Mar;33(1):34-40.
2. Iglesias E, Galor A, et al. Cornea. 2018 Jul;37(7):893-898.
3. Kohli P, Handa U, et al. Int Ophthalmol. 2019 Jun;39(6):1345-1353.
4. Yu Y, Yao K,et al. J Cataract Refract Surg. 2015 Dec;41(12):2614-23.
5. Cho YK, Kim MS. Korean J Ophthalmol. 2009 Jun;23(2):65-73.

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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 postoperatively[8]
- 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 KE, Seo KY, et al. Am J Ophthalmol. 2014 Jun;157(6):1144-1150.
7. Park Y, Hwang HB, Kim HS. PLoS One. 2016 Oct 3;11(10):e0152460.
8. El Ameen A, Pisella PJ, et al. \ J Fr Ophtalmol. 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 surgery[9]
  - 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. Hanyuda 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 device[1]
- While asthenopia, glare, and accommodative difficulty are all aspects of CVS, dry eye appears to contribute to a major component of symptoms reported[2]
- 74.3% of VDT users had MGD[3]

1. The Vision Council. TVC DigitEYEted Report 2013.
http://www.thevisioncouncil.org/consumers/\/media/ResearchReports/dec2014/TVCDigitEYEtedReport2013.pdf. Accessed 01/01/2014.
2. Blehm CS, Vishnu S, Khattak A, et al. Computer vision syndrome: a review. Surv Ophthalmol 2005;50:253-62.
3. Fenga C Aragona P Cacciola A . Meibomian gland dysfunction and ocular discomfort in video display terminal workers. Eye. 2008;22:91–95.

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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, Budenz D, et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. Cornea. 2010;29:618-621

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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, Budenz D, et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. Cornea. 2010;29:618-621

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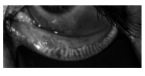
Glaucoma Considerations

- Glaucoma medications significantly elevate the risk and progression of MGD[1]
- Preservative and dry eye[2]



1. Arita R, Itoh K, Maeda S, et al. Comparison of the long-term effects of various topical antiglaucoma medications on meibomian glands. Cornea. 2012 Nov 31(11): 1228-34.
2. Baudouin, C, Labbe, A, Liang, H, et. Al Preservatives in eyedrops: The good, the bad and the ugly, Progress in Retinal and Eye Research, Volume 29, Issue 6, July 2010, Pages 312-334

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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 singulair, 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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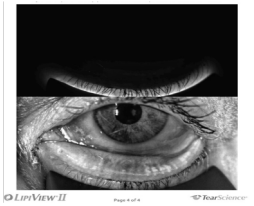
Early to Moderate Structural Changes to Meibomian Glands



Advanced Gland Atrophy / Dropout

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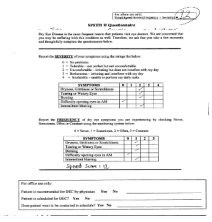
Post Treatment

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 osmolarity
    - Order inflammadry
    - SPEED Questionnaire

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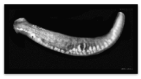
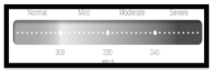
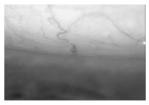
Point of Care Testing



Dynamic Meibomian Imaging

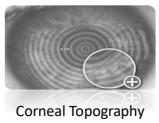


Osmolarity

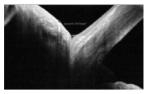


LIPCOF

MMP-9



Corneal Topography



AS-OCT

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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

LEWIS 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. InflammaDry Package Insert-English, Canada, Rapid Pathogen Screening, Inc. 5.Huang Y, Cheng Q, Jiang C, et al. Clin Dev Immunol 2013; 6. Klein D, Pinchuk N, Schrader S, Geerling G.

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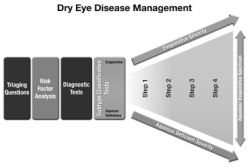
POC Diagnostics Guide Treatments

- Evaluate structure and function of MG
- Presence of inflammation???
  - Rx drops?? Punctal Plugs?? TCN??
- Are additional therapies needed??



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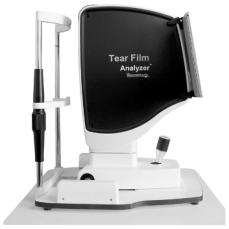
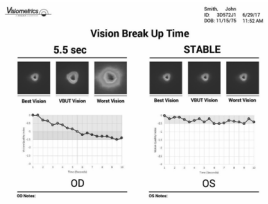
Tear Film Analyzer





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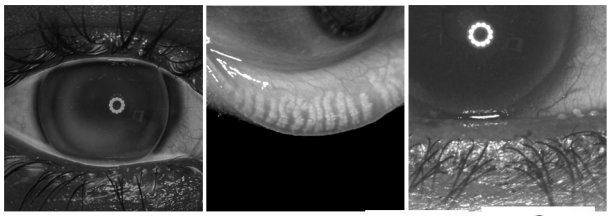
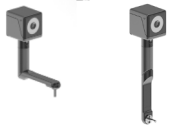


MX2 Images

MX2 Convertible Form Factor



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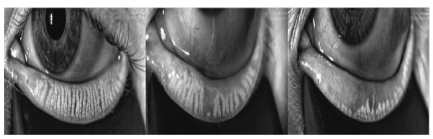
LipiScan™

PROACTIVE CARE

REACTIVE CARE



Duct dilation, atrophy and dropout

Severe atrophy and dropout

Don't forget to look at function too!!!

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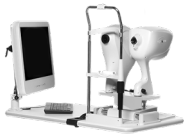
Epi-Mapping

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



Rocha KM, Straniota 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.
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 SR19.

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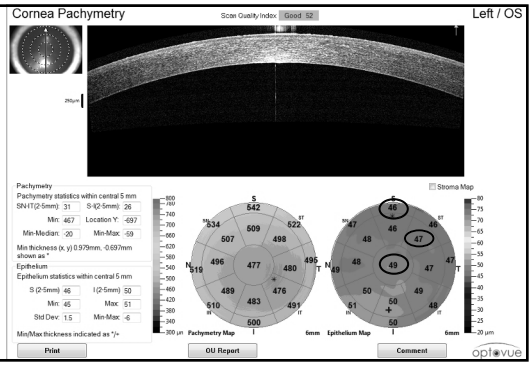
Dry Eye



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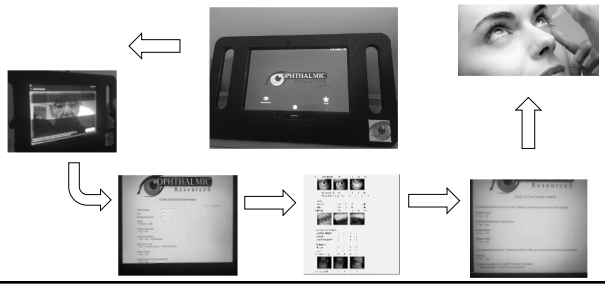
The Ophthalmic Resources System



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Treatment Strategies in 2020

- 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 2020: 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 and meibomian gland expression for anterior blepharitis and posterior blepharitis
  - Motorized/mechanical devices[2]
  - Thermal and thermal pulsation[3]
  - Intraductal probing[4]
  - Intense pulsed light[5]

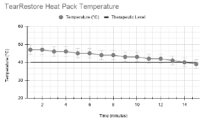
1. Gao YY, et al. *Cornea*. 2007;26(2):136-143; 2. Korb DR, Blackie CA. *Cornea*. 2013;32(12):1554-15
3. Lane SS, et al. *Cornea*. 2012;31(4):396-404; 4. Maskin SL. *Cornea*. 2010;29(10):1145-1152;
5. Craig JP, et al. *Invest Ophthalmol Vis Sci*. 2015;56(3):1965-1970.

47

TearRestore The First Open-Eye Warm Compress

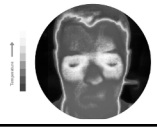
Effective & Consistent Heat

TearRestore supplies therapeutic heat (>40C) for a minimum of ten minutes every use. This ensures patients and doctors an effective treatment every time.



Unique Convenience & Natural Expression

TearRestore's 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.



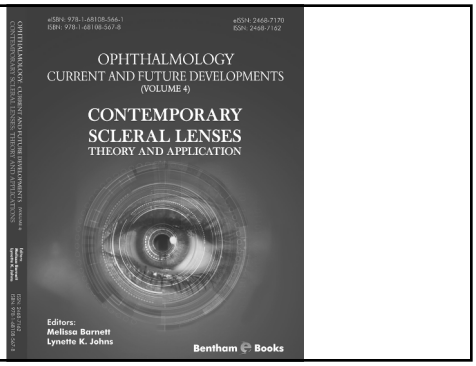
TearRestore

48

Treatment Strategies in 2020

- 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

49

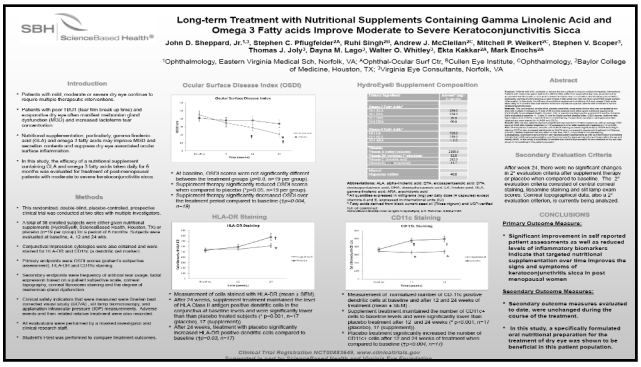


50

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

51



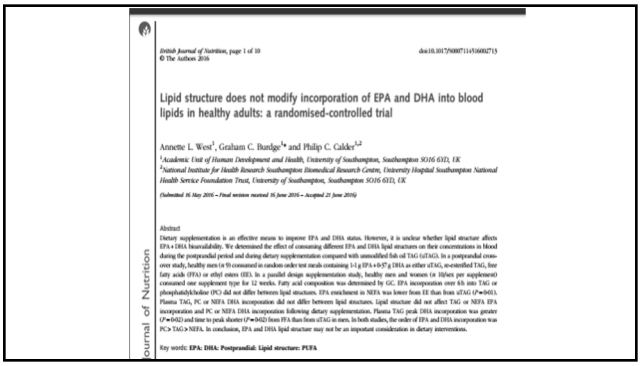
52

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.

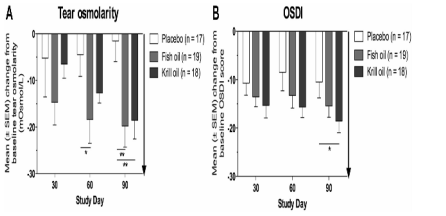
Donnenfeld ED, Holland, EJ, Bucci FA, et. Al. 2015

53



54

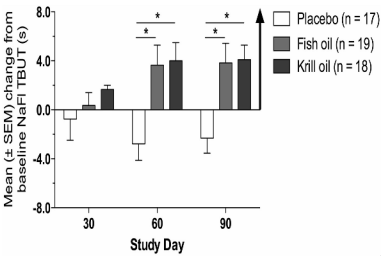
A Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Two Forms of Omega-3 Supplements for Treating Dry Eye Disease



Ophthalmology 2017 124, 43-52DOI: (10.1016/j.ophtha.2016.09.023)
Figure 1
Deinema, LA, Algis, JV, Chinn, YW. Ophthalmology Volume 124, Issue 1, Pages 43-52 (January 2017)

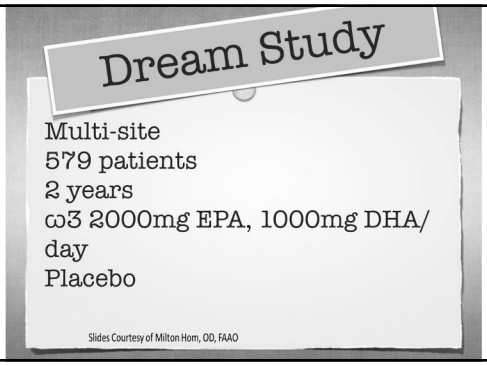
55

Figure 2



Ophthalmology 2017 124, 43-52DOI: (10.1016/j.ophtha.2016.09.023)

56



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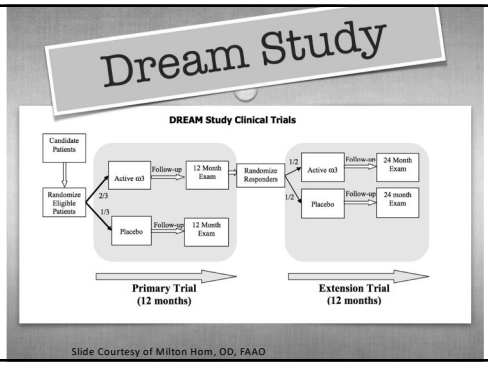

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Results

- No significant difference between fish / olive oil groups
- However, **both groups** improved significantly in primary endpoint of symptoms (plus secondary endpoints of corneal / conj staining, TBUT)
- Olive oil may not have been best choice for study
- There's been much confusion over findings

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What does this mean to clinicians?

- We should all make effort to educate ourselves on research – headlines often get it wrong
- Fish oil may be beneficial, but may not be the only option we should consider
- Other omegas (e.g. GLA), and nutrients have clinical evidence in OSD, weren't examined in DREAM

60

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 Schrimer'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

61

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%

1. Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.

Please see Important Safety Information on slide 4 and full Prescribing Information available at this presentation. 62

CONFIDENTIAL – NOT FOR DISTRIBUTION

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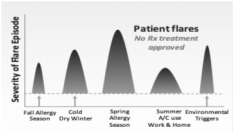
Loteprednol 0.25% in MPP for Dry Eye Flares

- 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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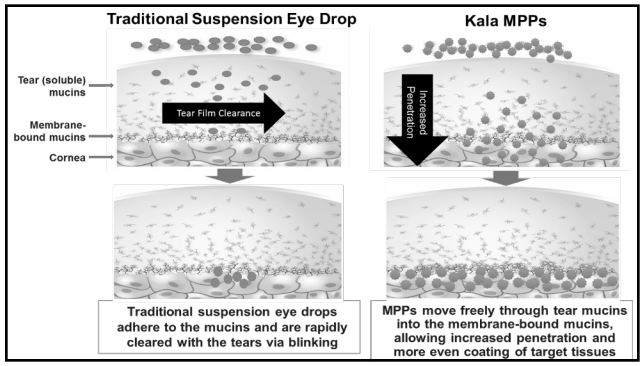

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Totality of Data Demonstrates Efficacy for Signs and Symptoms of DED

KPI-121 0.25% Results and Key Findings				
		Phase II	**STRIDE 1**	**STRIDE 2**
SIGN	Variable	Conjunctival Hyperemia (CH)	Conjunctival Hyperemia (CH)	Conjunctival Hyperemia (CH)
	P	0.0090	<0.0001	<0.0001
SYMPTOM	Variable	Ocular Discomfort Severity (ODS)*	Ocular Discomfort Severity (ODS)	Ocular Discomfort Severity (ODS)
	P	0.0489**	<0.0001	0.1289

Primary Endpoints with statistical significance

Secondary Endpoint of the Phase II Trial; **Using the STRIDE 1/2 statistical analysis plan

65

KPI-121 0.25% Demonstrated Similar IOP Profile to Placebo in Both Trials

Mean IOP

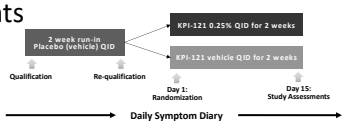
	STRIDE 1		STRIDE 2	
	KPI-121 0.25% Mean (SD) in mmHg (n=459)	Vehicle Mean (SD) in mmHg (n=456)	KPI-121 0.25% Mean (SD) in mmHg (n=453)	Vehicle Mean (SD) in mmHg (n=452)
Day 1	14.9 (2.57)	15.3 (2.52)	14.9 (2.53)	14.9 (2.48)
Day 15	15.1 (2.67)	14.9 (2.68)	15.0 (2.65)	14.6 (2.41)

Number of Patients with IOP Increase > 5 mmHg Leading to IOP ≥ 21 mmHg

STRIDE 1		STRIDE 2		COMBINED	
KPI-121 0.25%	Vehicle	KPI-121 0.25%	Vehicle	KPI-121 0.25%	Vehicle
2/455 (0.4%)	2/453 (0.4%)	5/448 (1.1%)	0/448 (0.0%)	7/903 (0.8%)	2/901 (0.2%)

66

STRIDE 3 Design Focus on Symptom Endpoints



Key Aspects of STRIDE 3 Study Design:

- Similar design to STRIDE 1 and 2
- Specific modifications made to inclusion/exclusion criteria to address key factors which are expected to improve the probability of success
- Independent primary endpoints of Day 15 Ocular Discomfort in ITT population and severe subgroup
  - Achieving either endpoint should satisfy symptom requirement
- Study ongoing and topline results anticipated in Q4 2019

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Stride 3 Results

- STRIDE 3 met both of its primary and key secondary endpoints:
  - Prespecified primary: statistical significance achieved for ODS (Ocular Discomfort Severity) in the overall ITT population (p=0.0002) and a subset of subjects with more severe baseline discomfort (p=0.0007).
  - Prespecified key secondary: statistical significance achieved for conjunctival hyperemia at day 15 (p<0.0001) and ODS at day 8 in the ITT population (p=0.0282).
- The STRIDE 3 results replicated both the primary symptom endpoint results from the STRIDE 1 and the primary sign endpoint results from Phase II, STRIDE 1 and STRIDE 2.
- KPI-121 0.25% was well tolerated with adverse event and IOP elevation rates similar to those of the vehicle in all trials

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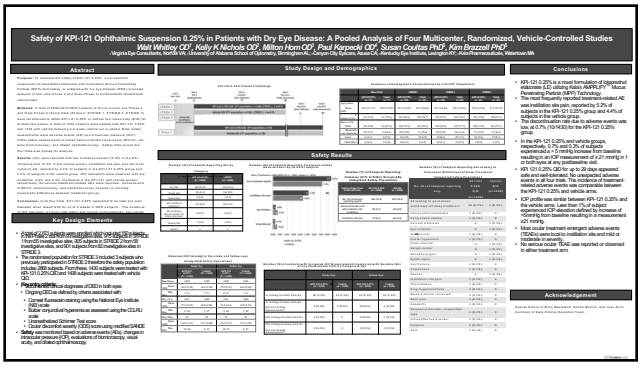
Safety of KPI-121 Ophthalmic Suspension 0.25% in Patients with Dry Eye Disease: A Pooled Analysis of Four Multicenter, Randomized, Vehicle-Controlled Studies

Walt Whitley OD[1], Kelly N Nichols OD[2], Milton Hom OD[3], Paul Karpecki OD[4], Susan Coultas PhD[5], Kim Brazzell PhD[6]

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

Abstract

Study Design and Demographics

Conclusions

Safety Results

Key Design Elements

Acknowledgement

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Neurotrophic Keratitis: Etiology

1. Infectious: HSV, VZV, leprosy
2. CN V palsy
   - Surgery for trigeminal neuralgia, neoplasia (acoustic neuroma), aneurysm, facial trauma, congenital, familial dysautonomia (Riley-Day syndrome), Goldenhar-Gorlin syndrome, Möbius syndrome, familial corneal hypesthesia
- 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 DED[3]

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

70

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.

71

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

Neurotrophic keratitis (NK) is a result from impaired trigeminal corneal innervation	Endogenous NGF maintains corneal integrity by three mechanisms
↓ Lacrimation and blink reflex	Cell proliferation
↓ Epithelial cell vitality, metabolism, mitosis	
↓ Epithelial trophism and repair	
↑ Stromal and intracellular edema	Tear secretion — Corneal reinnervation
↓ Microvilli	
↓ Development of the basal lamina	

Nerve damage ⇨ loss of corneal sensitivity ⇨ NK

Mastropasqua et al. (2017) J Cell Physiol 232:717-26

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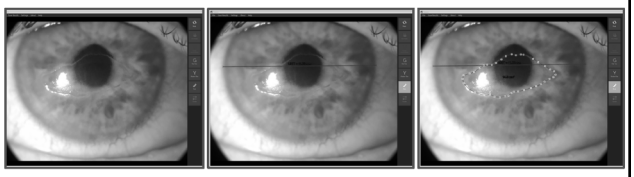
CASE STUDY: JOHN GELLES



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

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SPARCA

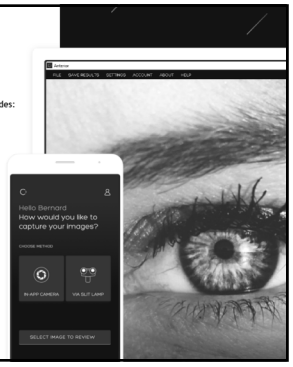
Award-winning ocular analysis - AOS Anterior software

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 Wratten 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)



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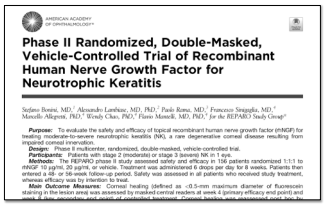
cenegermin-bkbj 20 mcg/ml was approved by FDA in August 2018



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

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

Purpose: To evaluate the safety and efficacy of topical recombinant human nerve growth factor (rhNGF) for healing moderate-to-severe neurotrophic keratitis (NK), a rare degenerative corneal disease resulting from impaired corneal innervation.

Design: Phase II multicenter, randomized, double-masked, vehicle-controlled trial.

Participants: Patients with stage 2 (moderate) or stage 3 (severe) NK in 1 eye.

Methods: The REPARO phase II study assessed safety and efficacy in 156 patients randomized 1:1:1 to rhNGF 10 μg/ml, 20 μg/ml, or vehicle. Treatment was administered 6 drops per day for 8 weeks. Patients then entered a 48- or 56-week follow-up period. Safety was assessed in all patients who received study treatment, whereas efficacy was by intention to treat.

Main Outcome Measures: Corneal healing (defined as <0.5-mm maximum diameter of fluorescein staining in the lesion area) was assessed by masked central readers at week 4 (primary efficacy end point) and week 8 (key secondary end point of combined treatment. Corneal healing was assessed post hoc in

- 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.

75

Study Conclusions

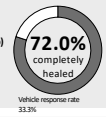
Up to 72% of patients achieved complete corneal healing;
80% of healed patients were recurrence free after 1 year*

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



Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)
U.S patients with NK in one or both eyes
NCT02227147

Vehicle response rate 16.7%

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

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

76

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.

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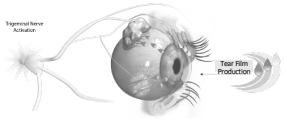
The Parasympathetic Nervous System (PNS) Is a Critical Regulator of the Lacrimal Functional Unit (LFU) and a Healthy Tear Film

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



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

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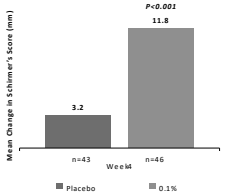
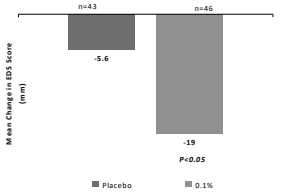
OC-01 Demonstrated Statistically Significant Improvement in Signs and Symptoms of Dry Eye Disease (DED)

Note: The CAE was ***not*** used for this measurement.

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



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



ITT-observed population
ANCOVA, Least Squares means

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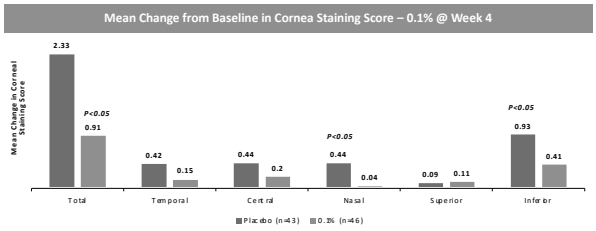
OC-01 Demonstrated Significant Difference from Placebo in Mean Change in Corneal Staining in Total, Nasal and Inferior Regions



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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

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ONSET-2 Top Line Results

- Primary endpoint: Statistically significant improvement in percentage of subjects gaining ≥ 10mm 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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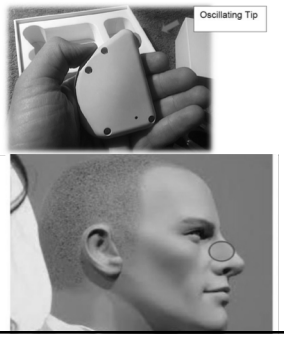
FDA Label

INDICATION FOR USE

The iTEAR100 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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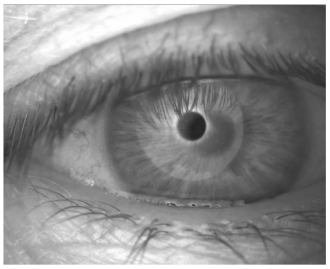
Immediate TEAR Response and Meibum Secretion



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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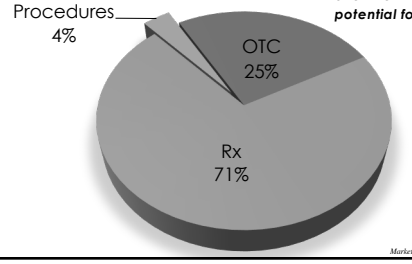
Procedures Currently Represent 4% of all US Dry Eye Revenue

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

A Randomized Controlled Investigator masked Trial (OLYMPIA)

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

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

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

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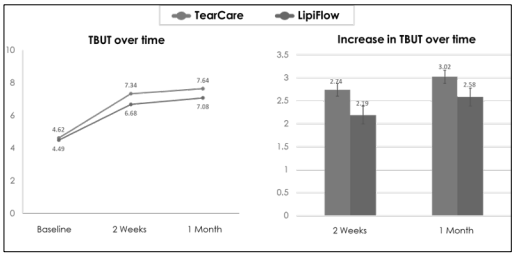
Primary Endpoint: Tear Film Break-Up Time (TBUT)



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

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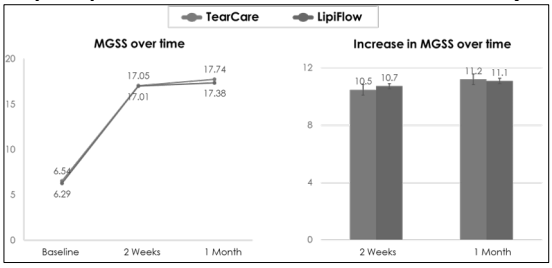
Primary Endpoint: Meibomian Gland Secretion Score (MGSS)



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

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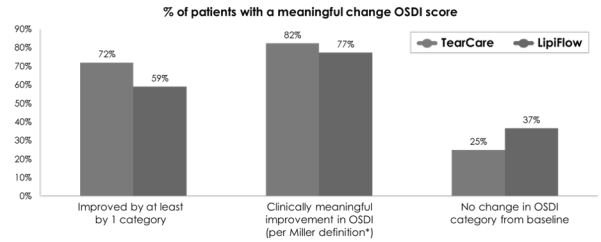
A greater proportion of showed meaningful symptom relief*



72% of TearCare vs 59% for LipiFlow subjects improved by at least 1 ***QSDI*** category

*per Miller definition

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In-Office MGD Treatment

Handheld iLux® 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**

iLux® 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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Clin Ophthalmol. 2020; 14: 459–418.
Published online 2020 Feb 12. doi: 10.2147/OPTH.S234008
PMCID: PMC7024784
PMID: 32109987

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

Jerrold L Turbert,[1] James Owen,[2] Marc Bloomenstein,[3] John Heuninckx,[4] and Kevin A Buchanan[5]

Abstract

Go to: ⓒ

Purpose

To compare the effects of eyelid treatment with the iLUX MGD Treatment System and the LipiFlow Thermal Pulsation System on objective and subjective parameters of meibomian gland function and symptoms.

Patients and Methods

In this randomized, open-label, controlled, multicenter clinical trial, both eyes of 142 patients aged ≥18 years with Ocular Surface Disease Index (OSDI) scores ≥23, total meibomian gland scores (MGS) ≤12 in the lower eyelid of each eye, and tear break-up time (TBUT) <10 s were randomized 1:1 to iLUX or LipiFlow treatment, with stratification by test center. The primary effectiveness endpoints were changes to total MGS (masked) and TBUT from baseline to 4 weeks. The secondary effectiveness endpoint was changed in OSDI score from baseline to 4 weeks.

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 18.9 ± 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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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

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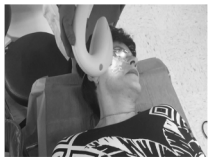
Intense Pulsed Light

- 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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Clinical Ophthalmology
Dovepress
CLINICAL TRIAL REPORT

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

This article was published in the following Dove Press journal:
Clinical Ophthalmology
2 May 2017
Number of times this article has been viewed

Steven J Dell[1]
Ronald N Gasser[2]
Sheila C Barbarino[3]
Derek N Cunningham[3]

[1]Dell Laser Consultants, Austin, TX, [2]Gasser Eye Center, Beverly Hills, CA, USA

Purpose: The aim of this study was to estimate the efficacy of intense pulsed light (IPL), followed by meibomian gland expression (MGX), for reducing the number and severity of signs and symptoms of dry eye disease (DED) secondary to meibomian gland dysfunction (MGD).
Patients and methods: In a prospective study conducted in two sites, 40 subjects (80 eyes) with moderate to severe MGD were enrolled. Major inclusion criteria consisted of at least two of the following measures being compatible with DED in both eyes: tear breakup time (TBUT), meibomian gland score (MGS), corneal fluorescein staining (CFS), Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire, and tear film osmolarity (TFO). Enrolled patients underwent four treatment sessions, 3 weeks apart. Each treatment included the administration of 10–15 pulses of IPL on the cheeks and nose, followed by MGX of the upper and lower eyelids. TBUT, MGS, CFS, SPEED, TFO, and lipid layer thickness (LLT) were measured at baseline (BL) and at 9, 12, and 15 weeks after BL.
Results: Due to different staining methods used for TBUT measurements, TBUT and CFS were analyzed separately for each site. From BL to the final followup, the number of signs compatible with DED decreased from 3.3±0.1 to 1.4±0.1. TBUT improved by +85% (n=18; $P<0.0001$) and +425% (n=22; $P<0.0001$) for sites 1 and 2, respectively. SPEED, MGS, and CFS improved by −55% (n=40; $P<0.0001$), −36% (n=40; $P<0.0001$), and −68% (n=36; $P<0.0001$), respectively. In 20 eyes with abnormally elevated TFO at BL, TFO improved by −7% (n=20; $P<0.05$). LLT did not change (n=38; $P=0.88$).
Conclusion: In subjects with moderate to severe MGD, IPL combined with MGX reduced the number and severity of symptoms and signs of DED. Except for LLT, all examined outcome measures significantly improved after 15 weeks. These results support the efficacy of IPL + MGX in relieving both signs and symptoms of DED secondary to MGD.
Keywords: dry eye, meibomian gland dysfunction, intense pulsed light

Video abstract

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Radiofrequency

- **ThermiEyes™:**
  - 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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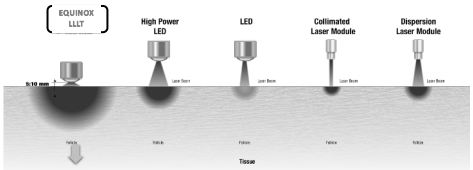
LLLT & LED Technology



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

OphthalmologyTimes › 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 15, 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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From The Ophthalmolgy Times Article

Application of LLLT therapy resulted in improvement in the tear film break-up time in more than 90% of patients with dry eye disease.

The results are similar to those reported previously in patients treated with intense pulsed light (IPL) treatment.

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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
- Semi-permanent occlusion
  - Silicone or thermal labile acrylic polymers
  - May last for several months
- Permanent occlusion
  - Silicone plugs
  - Thermal / laser cautery
  - May extrude or migrate out of the puncta over time
- 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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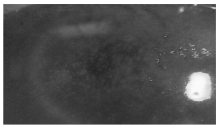
Current Uses for Topical Biologics for OSD

- 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



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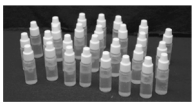
Autologous Serum

- 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

Benefits

- Preservative free and innately allergy free
- Adverse events rare
- Improvement in symptomology
- Demonstrated improvement in staining (Tsubota – SS pts)

Complications

- Cost – no insurance coverage
- Frequent blood draw
- Availability of labs to make ASED
- Strict handling

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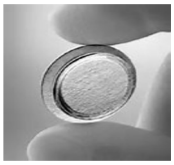
Amniotic Membranes



Cryopreserved Membranes

Dry Membranes

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Amniotic Membrane

- Amnion is innermost layer of placenta and contains components that produce factors in proliferation/differentiation, help decrease infection, and increase membrane integrity
  - Collagens
  - Fibronectin
  - Laminin
  - Fibroblasts
  - Growth factors – Nerve Growth Factor
- Suppress TGF-beta, myofibroblasts to limit scarring/haze while promoting epithelial healing and tissue reconstruction
- Sequesters inflammatory cells
  - This leads to membrane breakdown

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Pros and Cons of Amniotic Membrane Modalities

Cryopreserved
- Self-retaining on cornea
- Higher levels of regenerative complex HC-HA/PTX3
- Shorter storage life – requires refrigeration
- Potential discomfort from symblepharon ring
  - Avoid with filtering procedures

Dehydrated
- Longer storage life – room temperature
- No ring = better comfort
- Frequent slippage
- Requires bandage lens to maintain position

*****For all amniotic membranes, RCTs limited**

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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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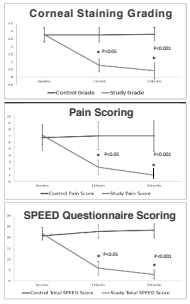
Improvements in Clinical Signs and Symptoms



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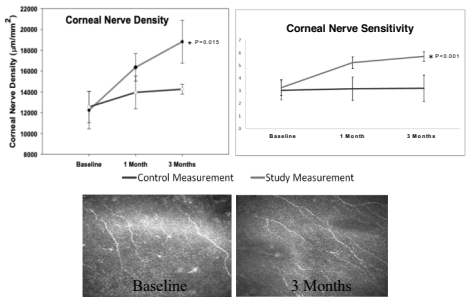
Improvements in Corneal Nerve Density & Sensitivity



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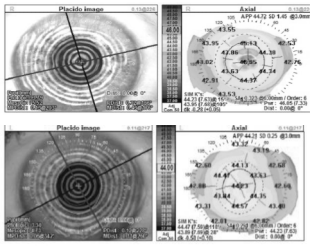
Cryopreserved Self-retaining AMT

Pre-tx

Post Tx (placed for 5 days)



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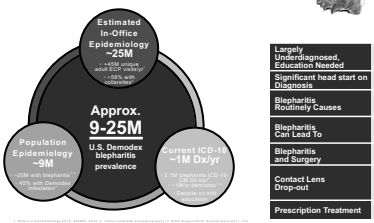
Blepharitis is a Large and Underserved Market in Eye Care

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[6]
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[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 [5,10]
Prescription Treatment	None

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Demodex is an Underlying Cause of Blepharitis

2 Species of Mites Contribute to Blepharitis

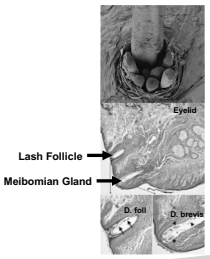
- *Demodex folliculorum*: eyelash follicles
- *Demodex brevis*: meibomian glands in eyelid

***Demodex* Implicated in 45% of Blepharitis Cases**

- Meta-analysis of 11 studies and 4,741 pts[1]

Demodex Overgrowth Causes Disease in 3 Ways

1. Mechanical: overcrowding, obstruction, eyelash loss, irritation
2. Chemical: digestive enzymes and waste
3. Bacterial: inflammation from surface/gut bacteria



1. Zhao - Ophthalmic Epidemiology, 19(2), 95–102, 2012

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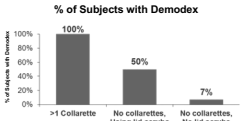
Collarettes Are Pathognomonic Sign of Demodex Infestation

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

- 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 collarettes[2]
- Collarettes found in ~ 58% eye care patients[3]



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

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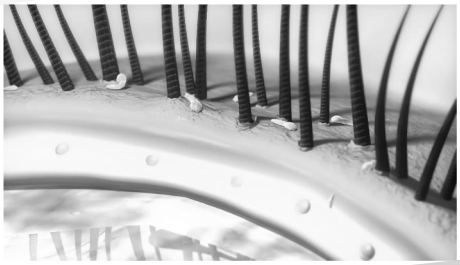
TP-03 is Designed to Eradicate Demodex Mites and Treat Demodex Blepharitis



***Not FDA Approved

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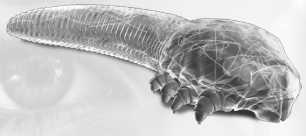
TP-03 is a Novel Therapeutic Designed to Eradicate Demodex Mites and Treat Demodex Blepharitis

TP-03 is designed to paralyze the mite nervous system through parasite-specific GABA inhibition



***Not FDA Approved

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TP-03 is a Novel Drug Designed to Treat Demodex Blepharitis by Eradicating Mites and Collarettes[1]

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	1º collarette cure, 2º mite eradication, 2º redness + collarette cure
Safety Goal	Well-tolerated safety profile

*BID means twice per day

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

***Not FDA Approved

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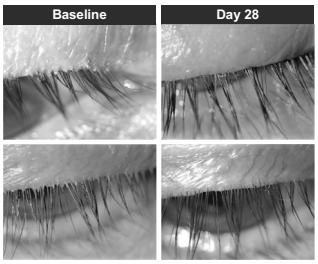
Cure of Collarettes with BID Use of TP-03

***Not FDA Approved



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TP-03 for Demodex Blepharitis

- Single-arm, open-label study that evaluated the safety and efficacy of TP-03 in 15 participants with Demodex Blepharitis over 28 days
- **Collarette Score:** The mean grade showed statistically significant improvement from baseline to day 14 and had a 2-grade improvement overall on a 4-point scale
- **Mite Eradication:** The average mites/lash showed statistically significant improvement from baseline to day 14 and had a 10-fold improvement from baseline
- No treatment-related adverse events were reported

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Teprotumumab

- Approved based on the results of two studies (Study 1 and 2) consisting of a total of 170 patients with active thyroid eye disease who were randomized to either receive study drug or a placebo
- Greater than 2mm reduction in proptosis
  - Study 1 71% vs. 20%
  - Study 2 83% vs. 10%
- Most common adverse reactions include muscle spasm, nausea, alopecia (hair loss), diarrhea, fatigue, hyperglycemia (high blood sugar), hearing loss, dry skin, dysgeusia (altered sense of taste) and headache

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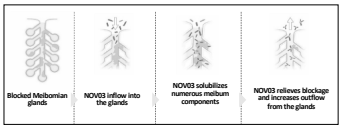
NOV03 Perfluorohexyloctane - Dual Mode of Action



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NOV03 Perfluorohexyloctane

	Water-based Technologies	NOV03
Drop Size	~ 40–50µL (Blink reflex activated)	< 12 µL (Blink reflex not activated)
Drug Residual Time	Brief 3–5 min	Long ~ 240 min
Spreading	High surface tension hinders spreading	Fast spreading Film forming properties
Other features	Usually Preserved	Preservative free No vision blurring

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NOV03 – Dual Mode of Action

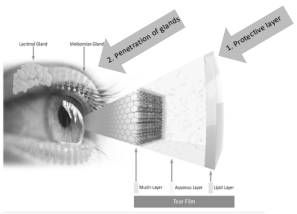
Phase 3: ESSENCE-2

0.1% CsA in EyeSol

Water-free

Preservative Free

Penetration of meibomian glands and potentially solubilizing blocked Meibum



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

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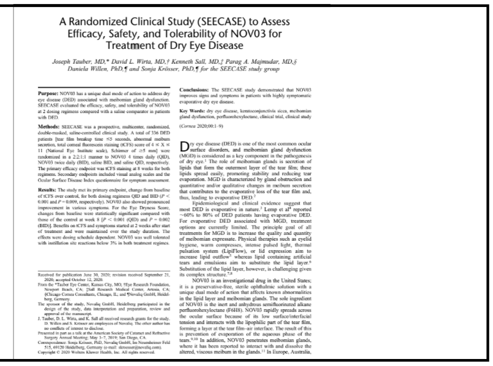

A Randomized Clinical Study (SEECASE) to Assess Efficacy, Safety, and Tolerability of NOV03 for Treatment of Dry Eye Disease

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

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

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

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

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

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

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

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

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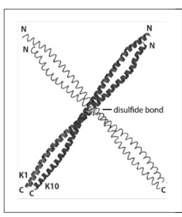
TARGETING ABERRANT KERATIN

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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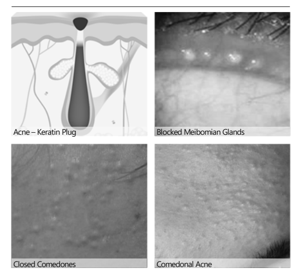
WHAT ARE KERATOLYTICS?

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"

[redacted]

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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.

[redacted]

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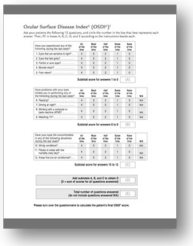
Call to Action – Implement Now

- 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


Ocular Surface Disease Index® (OSDI®)

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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

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