

Cry Me A River

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Financial Disclosures Ben Gaddie 12/16/2025

****All relevant relationships have been mitigated****

- Tarsus-Consultant, Clinical Trials
- Bausch and Lomb-Consultant
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- MediPrint-Shareholder/Consultant
- Orasis-Scientific Advisory Board
- Glaukos-Consultant
- Heru-Consultant
- Balance Ophthalmics-Consultant
- Sydnexis-Consultant
- Azura-Consultant
- Ocusoft-Consultant

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Dry Eye can cause more than discomfort. Over time, it can also steal your vision.

Talk to your Gaddie Eye Centers team about their customized approach to diagnosing and treating this common condition with drops, diet, and oral medications.

Common causes of Dry Eye Syndrome (DES)

- Dry environment/low humidity
- Prolonged reading/staring at a computer screen
- Household plastics and video games
- Hormonal changes
- Contact lenses
- Surgery and certain medications

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Symptoms-Be Proactive! Don't wait on the patient to volunteer

- OSDI
- SPEED (Standardized Patient Evaluation of Eye Dryness and Ocular Surface Disease Index-*TearScience*)
- DEQ-5 (The Dry Eye Questionnaire-*Chalmers et al*)

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Total SPEED score (Frequency x Severity) = 28

Date: / /

SPEED Questionnaire

Name: _____
DOB: / / Sex: M F (Circle)

How **FREQUENTLY** do you experience the following dry eye symptoms?

Symptoms	Never (0)	Sometimes (1)	Often (2)	Constant (3)
Dryness, Grittiness or Scratchiness				
Burning or Irritation				
Burning or Itching				
Eye Fatigue				

How **SEVERE** are your dry eye symptoms?

Symptoms	No problems (0)	Tolerable - not perfect but not uncomfortable (1)	Uncomfortable - irritating but does not interfere with my day (2)	Bothersome - irritating and interferes with my day (3)	Intolerable - unable to perform my daily tasks (4)
Dryness, Grittiness or Scratchiness					
Burning or Irritation					
Burning or Itching					
Eye Fatigue					

WHEN have you experienced these symptoms?
 Today Within the past 72 hours Within the past 3 months

Symptoms	Yes	No
Do you have difficulty reading?		
Do you have difficulty using a computer?		
Do you have difficulty driving at night?		
Do you have difficulty washing mirrors?		
Do you have difficulty wearing contact lenses?		
Do you have difficulty being outdoors?		
Do your symptoms worsen throughout the day?		

Do you use drops and/or ointment? Yes No (Circle)
 If yes, please specify brand or generic: _____
 If you experience trouble on reinserting lenses: Yes No (Circle) _____
 Are you using any eye drops or ointment? Yes No (Circle) _____

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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?

Recommendations from the *Dry Eye Summit 2014*

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Basic Ocular Surface Principles

- Despite the statistics that are constantly regurgitated, not all dry eye is due to MGD
 - When you have evaporative, it can be caused from one of three factors
 - MGD
 - Goblet cell deficiency
 - Blinking/shearing/tear turnover
 - Not everyone with evaporative dry eye has MGD!
 - Think about the new drug Miebo, it adds a monolayer and prevents evaporation without doing a thing to meibomian glands

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Excessive Evaporation Triggers A Vicious Cycle

When tear evaporation exceeds supply, loss of homeostasis follows^{1,2}



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Basic Ocular Surface Principles

- When examining someone with dry eye signs and symptoms, I pay attention to the following:
 - Lids/Lashes
 - Demodex/Seb dermatitis/margin redness
 - Consider lotaliner and lid scrubs
 - Telengectasia
 - Lid closure
 - May need night mask/ointment
 - MGD/Gland eval
 - Thermal Treatment/IPL

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Basic Ocular Surface Principles

- Cornea
 - Peripheral scarring
 - Can be demodex related
 - Punctate keratitis
 - Where? Inferior, central, all over?
 - Consider exposure vs evaporation
 - NK?
 - Endothelium/other dystrophies?
 - Staining, primarily NaFL for me..
 - Consider steroid vs. newer perfluorohexyloctane/butane containing agents
 - Consider amniotic membranes
 - Stem cell deficiency

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Basic Ocular Surface Principles

- Conjunctiva
 - Stain, primarily with LG
 - If positive, consider cyclosporine given MOA and results in this area from P3 clinical trials
 - Conjunctivalchalasis
 - Consider Amniotic graft transplant or conjunctivalplasty
- Osmolarity/MMP9
 - Measure with TearLab
 - MMP 9 measurement
 - If Osmo is out of range, good reason to consider anti-inflammatory as initial treatment

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Basic Ocular Surface Principles

- Before 2023, we only had steroids and immunomodulators
 - Cyclosporine
 - Liftegrast
 - Steroids
- Downside, it takes 2-6 months to have a symptom relief (except steroids)
- Side effects (burning, stinging, taste aversion) certainly limit adherence to medication

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Diagnostic Testing in Ocular Surface Disease

- Osmolarity
- MMP-9
- Vital Dyes

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Limit of Detection

Normal levels of MMP-9 in human tears ranges from 3-41 ng/ml

POSITIVE TEST RESULT

MMP-9 \geq 40 ng/ml

NEGATIVE TEST RESULT

MMP-9 $<$ 40 ng/ml



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Tear Film Osmolarity

- Tear Hyperosmolarity
 - Central mechanism in ocular surface inflammation, damage and symptoms
 - Also causes the compensatory events such as reflex lacrimation
 - Arises as a result of water evaporation from ocular surface
 - From low aqueous tear flow or increased evaporation
 - Maybe from both?

DEWS Report 2007

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Hyperosmolarity in Dry Eye Diagnosis

Dry Eye Diagnosis

Santosh Khanal,¹ Alan Tomlinson,¹ Angus McFadyen,² Charles Diaper,³ and Kannu Ramaesh⁴

PURPOSE. To determine the most effective objective tests, applied singly or in combination in the diagnosis of dry eye disease.

METHODS. Two groups of subjects—41 with dry eye and 32 with no ocular surface disease—had symptoms, tear film quality, evaporation, tear turnover rate (TTR), volume and osmolarity, and meibomian gland dropout score assessed.

CONCLUSIONS. Tear osmolarity is the best single test for the diagnosis of dry eye, whereas a battery of tests employing a weighted comparison of TTR, evaporation, and osmolarity measurements derived from discriminant function analysis is the most effective. (*Invest Ophthalmol Vis Sci.* 2008;49:1407-1414) DOI:10.1167/iov.07-0635

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Hyperosmolarity & Ocular Surface

Hyperosmolarity-Induced Apoptosis in Human Corneal Epithelial Cells Is Mediated by Cytochrome c and MAPK Pathways

*Lihui Luo, MD,**† De-Quan Li, MD, PhD,* and Stephen C. Pflugfelder, MD**

FIGURE 1. ApoptTag BCL assay in representative fields showing the increased BCL-positive apoptotic cells in corneal epithelial cultures exposed to high-osmolarity saline-added media (70, 90, or 120 mM NaCl) for 24 hours, compared with cells cultured in normal medium. The percentage of positive cells in each group (n = 5) is shown in the graph. **P < 0.05, ***P < 0.01, and ****P < 0.001 compared with control medium.

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Osmolarity in the Diagnosis of Dry Eye Disease

Clinical Test	PPV
Osmolarity	87%
Schirmers	31%
TBUT	25%
Staining	31%
Meniscus Height	33%

- Osmolarity is the “gold standard” test for Dry Eye
 - 45 years peer reviewed research
 - Osmolarity has been added to definition of Dry Eye
 - Global marker of Dry Eye, indicating a concentrated tear film

Source: DEWS Report, Ocular Surface April 2007 Vol 5 No 2. © Tomlinson A, et al., IOVS 47(10) 2006

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Tear Osmolarity in the Diagnosis and Management of Dry Eye Disease

MICHAEL A. LEMP, ANTHONY L. BRON, CHRISTOPHE BAUDOIN, JOSÉ M. BENÍTEZ DEL CASTILLO, DAVID GEFFEN, JOE TAUBER, GARY N. FOULKES, JAY S. PEPOSE, AND BENJAMIN D. SULLIVAN

PURPOSE. To evaluate the use of tear osmolarity in the diagnosis of dry eye disease.

DESIGN. A prospective, observational case series to determine the clinical usefulness of tear osmolarity and commonly used objective tests to diagnose dry eye disease.

METHODS. A multicenter, 10-site study consisting of 314 consecutive subjects between 18 and 62 years of age. Bilateral tear osmolarity, tear film break-up time (TBUT), conjunctival staining, conjunctival staining, Schirmer test, and meibomian gland grading were performed. Diagnostic performance was measured against a composite index of objective measurements that classified subjects as having normal, mild or moderate, or severe dry eye. The main outcome measures were sensitivity, specificity, area under the receiver operating characteristic curve, and intereye variability.

RESULTS. Of the 6 tests, tear osmolarity was found to have superior diagnostic performance. The most sensitive threshold between normal and mild or moderate subjects was found to be 308 mOsm/L, whereas the most specific was found at 315 mOsm/L. At a cutoff of 312 mOsm/L, tear hyperosmolarity exhibited 73% sensitivity and 92% specificity. By contrast, the other common tests exhibited either poor sensitivity (conjunctival staining, 54%; conjunctival staining, 60%; meibomian gland grading, 63%) or poor specificity (tear film break-up time, 45%; Schirmer test, 51%). Tear osmolarity also had the highest area under the receiver operating characteristic curve (0.89). Intereye differences in osmolarity were found to correlate

DRY EYE DISEASE IS A COMMONLY ENCOUNTERED condition in clinical practice and affects up to 20% of the population in North America.¹ The knowledge base concerning its pathogenesis, classification, and characteristics has grown considerably over the last 15 years, but its diagnosis, particularly in the early or mild stages, has been hampered by the lack of objective tests with sufficient sensitivity and specificity, adequate repeatability, ease of performance, and suitability for the clinical practice setting.² In addition, although symptoms of ocular irritation are common, there is a lack of correlation between signs and symptoms, particularly in mild dry eye disease, rendering symptoms alone unreliable for diagnosis and determination of disease severity.³ Moreover, there is a lack of consensus on the clinical usefulness of individual objective tests in the diagnosis of dry eye disease.² An increase in tear osmolarity is a hallmark of dry eye disease and is thought to be the central mechanism in the pathogenesis of ocular surface damage in the disease, as noted in the Dry Eye Workshop Report.⁴ Tear osmolarity has been reported to be the single best marker for dry eye disease,¹ but measurement has been limited to laboratory instruments requiring large microliter volumes, collection and manipulation of the tear specimens induce reflex tearing in most subjects, and collected specimens can be concentrated by evaporative loss during handling and collection.⁵ Further, microdialysis volumes are not available in many dry eye patients. The current study was undertaken

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TABLE 1. Sensitivity and Specificity of Objective Clinical Signs of Dry Eye Disease*

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

TBUT = tear film break-up time.
 *Cutoff values were located at the intersection between normal subjects and the entire subset of dry eye patients.

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- ### So Let's Start with MGD
- Meibography
 - Expression
 - Treatment
 - Medical
 - Procedural
 - OTC
 - Neutraceutical

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Meibomian Gland Anatomy

Meibomian gland function is regulated by:

- Androgens
- Estrogens
- Progestins
- Retinoic acid
- Growth factors
- Neurotransmitters

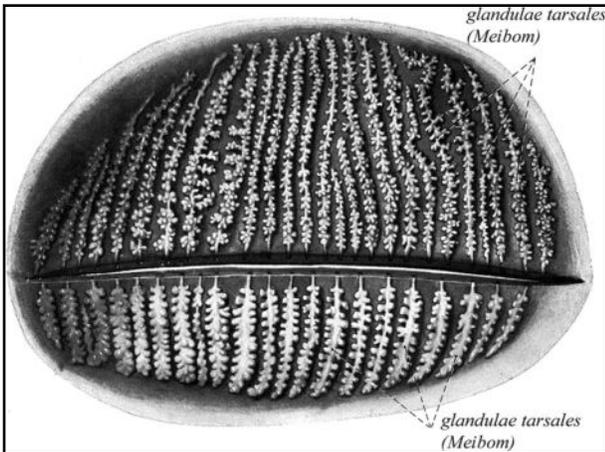
http://www.elsevier.com/locate/jcr.2011.01.001 and meibomian-gland

31

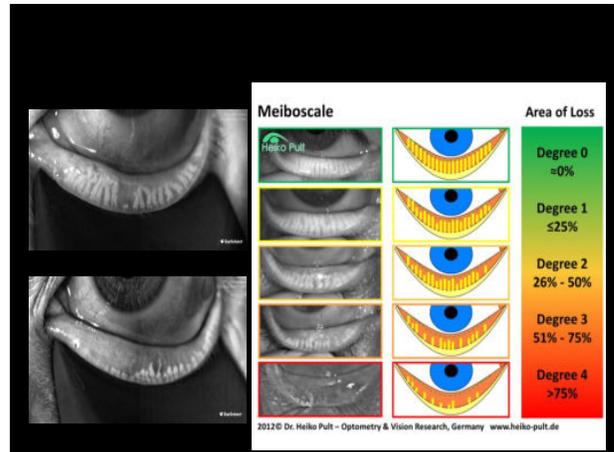
What is MGD?

The Workshop defined MGD as follows:
Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.

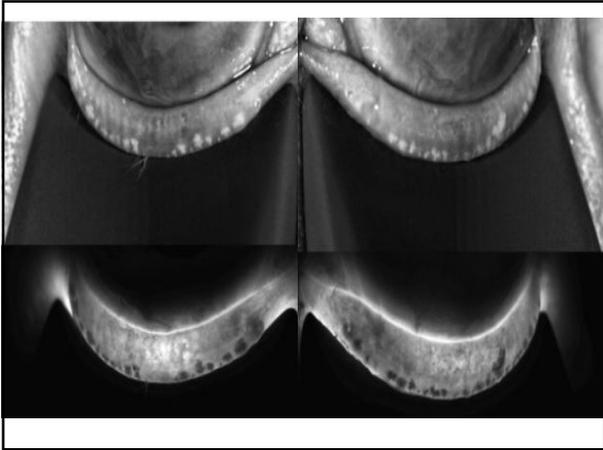
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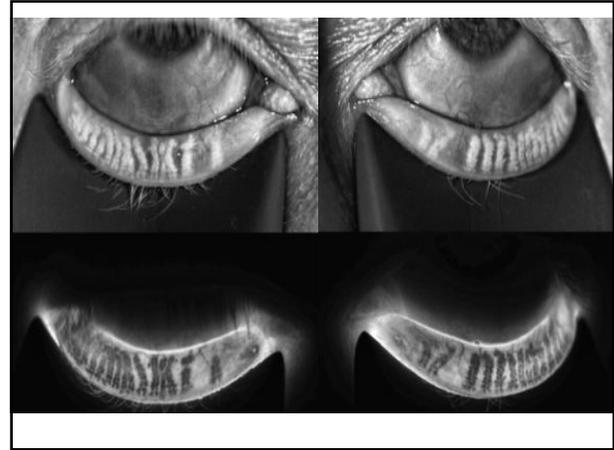
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Thermal expression

- TearCare
- iLux
- LipiFlow

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Thermal expression

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TFI/iLux Thermal expression

Purpose: To compare the changes in Meibomian gland function and evaporative dry eye (EDE) symptoms after treatment with iLux and LipiFlow

- Randomized, open-label, multisite clinical trial that enrolled 142 subjects from 8 study sites.
- Subjects were randomized for bilateral treatment in a 1:1 ratio between the iLux® treatment group and the LipiFlow group.
- Primary and secondary efficacy endpoints were assessed at baseline and 2 and 4 weeks post-treatment.

Hardten DR, Schanzlin JD, Dishler JG, et al. Comparison of a Handheld Infrared Heating and Compression Device for Treatment of Meibomian Gland Dysfunction to a Thermal Pulsation Device. Presented at the Annual Meeting of the American Society of Cataract and Refractive Surgery (ASCRS); April 13-17, 2018; Washington, D.C.

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Vectored thermal pulsation

- LipiFlow provides an automated 12-minute in-office procedure.¹
- LipiFlow liquefies obstructed meibum and pushes it up and out of the gland orifices
- Heat and pressure LipiFlow applies to the glands are regulated by redundant sensors.

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Case

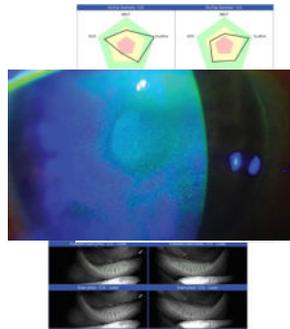
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- **75-year-old Caucasian male**
 - Not good with my drops
 - VA seems to change
 - **Referred for GLC Eval**
 - **PEHX: SLT x 2**
 - **BCVA: 20/20 -1 OU**
 - **TMAX: 30 mmHg OU**
 - **Medications:**
 - Latanoprost 1 x a day
 - Timolol 1 x a day
- **IOP:** 17 mm Hg OD; 17 mm Hg OS
 - **C/D:** 0.60/0.60 OD 0.70/0.70 OS
 - **Pachymetry:** 553 OD; 543 OS
 - **Corneal hysteresis:** 8.0 OD 7.4 OS
 - **Gonioscopy:** Open to CB OU w/ trace pigment in TM
 - **SLE:** See next slide (s)
 - **VF's** – See next slide(s)
 - **OCT's** – See next slide(s)
 - **ONH** – See next slide(s)

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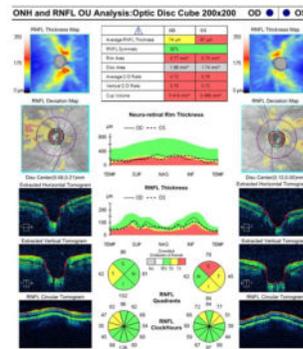
Ocular Surface Assessment

Speed Score: 9/28
 Tear Osmolarity:
 OD: 308
 OS: 315
 MMP-9: Positive OU
 Lids: Normal, (-) blepharitis
 Meibomian glands:
 Normal gland secretion



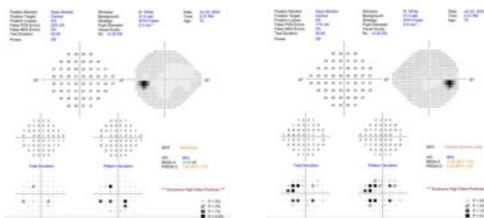
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OCT



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Visual Field



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Treatment Considerations

1. Must Treat the Dryness!
2. Glaucoma Treatment?
 - Monitor
 - Glaucoma Drops
 - SLT
 - Drug Delivery
 - Surgical Intervention

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Case – 6 weeks after insertion

- IOP: 15 mmHg OD, 16 mmHg OS
- No drops
 - Drops stopped at time of insertion
- Plan
 - Follow up 3-4 months for repeat glaucoma testing



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Case 3

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"I always struggle with dryness, irritated, and burning eyes. I have never done eye drops before."

- 61-year-old female – Also noticed that her vision fluctuates; is worse as the day goes on; spends 4 to 6 hours a day on a computer or tablet
- Patient does not smoke, run a ceiling fan, or rub her eyes
- Past medical history: Unremarkable
- Systemic medications: Amitriptyline
- Allergies: NKDA
- Family medical history: Age-related macular degeneration (grandmother)
- Social history: No smoking, teacher, no eye rubbing

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Examination

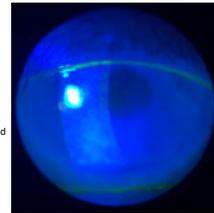
- SPEED: 10/28
- BCVA: 20/25 OD, 20/30 OS
- IOP: 13 mm Hg OD, 15 mm Hg OS
- MMP-9: Positive OU
- Osmolarity: 288 mOsm/L OD; 305 mOsm/L OS

Slitlamp Examination:

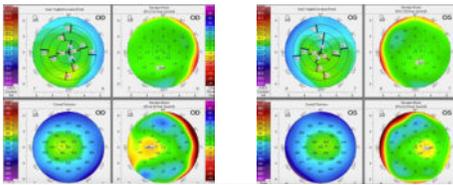
- Lids/Lashes: Minimal meibum secretions, slightly opaque, low tear meniscus
- Conjunctiva/Sclera: Clear, no injection noted OU, no significant staining
- Cornea: 2+ to 3 diffuse punctate epithelial erosions (PEEs) OU (see image); TBU: < 5 seconds OU
- A/C: Deep and quiet OU
- Iris: Flat OU
- Lens: Trace NS OU

Posterior Segment:

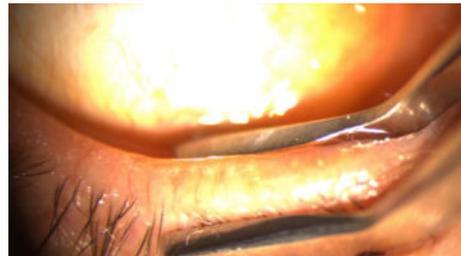
- Unremarkable



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Case Conclusion: 6-Week Follow-Up

Intervention:

1. Heat and gland clearing (see vid)
2. Perfluorobutylpentane + Cyclosporine 0.1%
3. Placed punctal plugs
4. 6-week follow-up



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Newer Ocular Surface Treatments

- Perfluorohexylocatane (Miebo)
- Perfluorobutylpentane + Cyclosporine .1% (Vevye)
- Lotaliner (Xdemvy)
- Varenicline (Tyrvaya)

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Semifluorinated Alkanes (SFAs) in Medicine and Eye Care

- Perfluorohexyloctane
- Perfluorobutylpentane
- Retinal gas tamponade
- SFA's easily facilitate lipophilic and hydrophobic compounds into the cornea and conjunctiva
- Free of oils, surfactants, or preservatives with superior spreading properties
- No pH, no osmolarity
- Currently FDA approved SFA compounds
 - F4H5 and F6H8

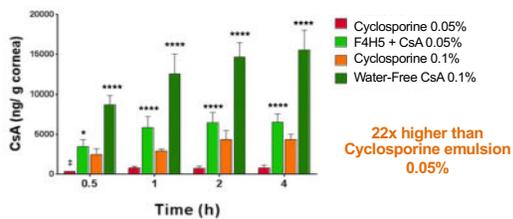
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Cyclosporine .1% in SFA

- Trade Name: Vevye, Harrow Pharmaceuticals
- Many types of SFA compounds
 - Some penetrate and act as drug carriers for poorly soluble drugs
 - Others act as coating agents to prevent evaporation
 - There is some overlap

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Ex-vivo Corneal Permeability of Cyclosporine in Porcine Eyes

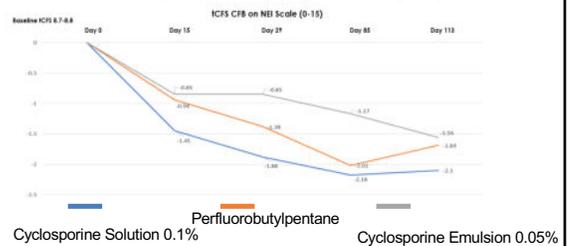


See Supplemental Tables for topical delivery of Cyclosporine A. P. Agrawal, D. Schmitt, J. B. Gierke, L. D. Superficial Ulceration/Ocular Therapeutics Unit, Department of Ophthalmology, New York University School of Medicine, New York, NY; Department of Ophthalmology, University of Bonn, Bonn, Germany

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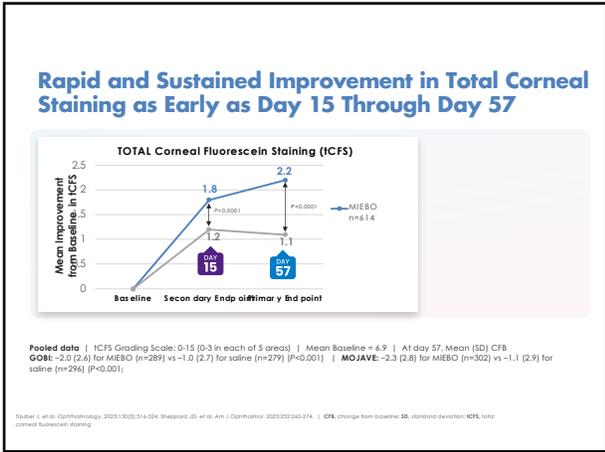
Water-Free Cyclosporine 0.1% Phase II Study

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

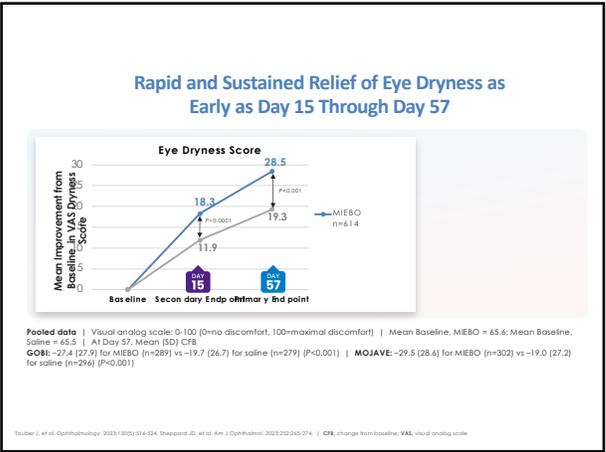


Wells J, et al. Clinical Phase II Study to Assess Efficacy, Safety and Tolerability of Water-Free Cyclosporine Formulation for Treatment of DED. Ophthalmology 2018

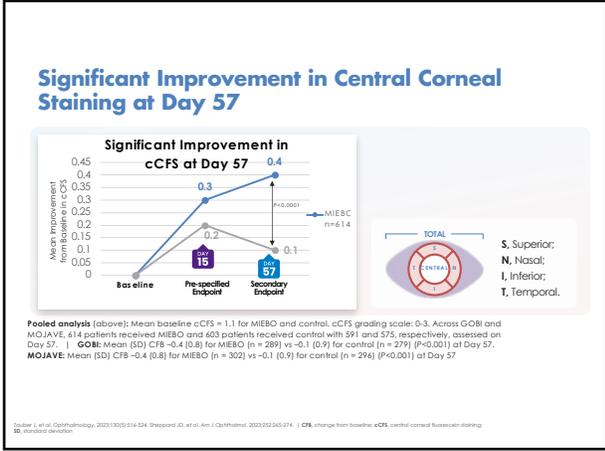
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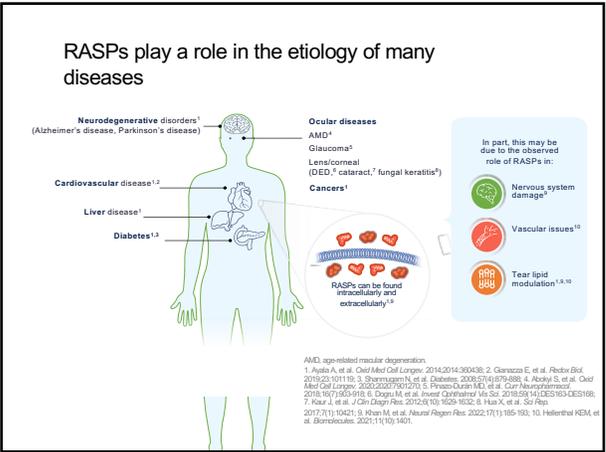
Cenergermin for NK

- Known commercially as Oxervate (Dompe), this 0.002% topical solution contains a recombinant form of human nerve growth factor, whose receptors in the anterior segment of the eye to support corneal innervation and integrity.
- It is prescribed for patients who have neurotrophic keratitis, a rare disease that can progress to corneal scarring and vision loss. It is dosed 6 x day for 8 weeks.

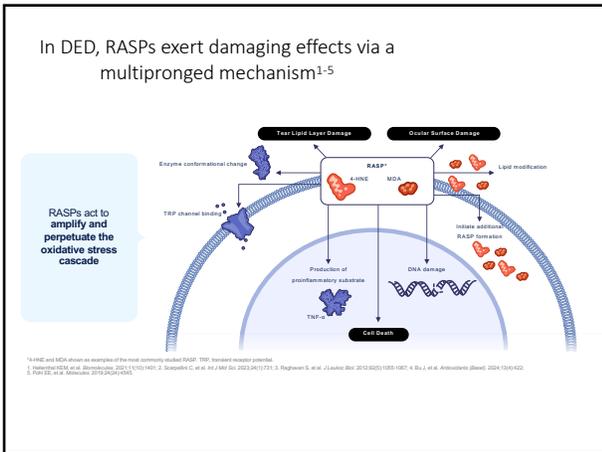
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- ### Pipeline and Pending Approvals
- AR512-Alcon
 - RASP Inhibitor-Abbvie/Alderya
 - Eyelid Health
 - Azura
 - Tarsus

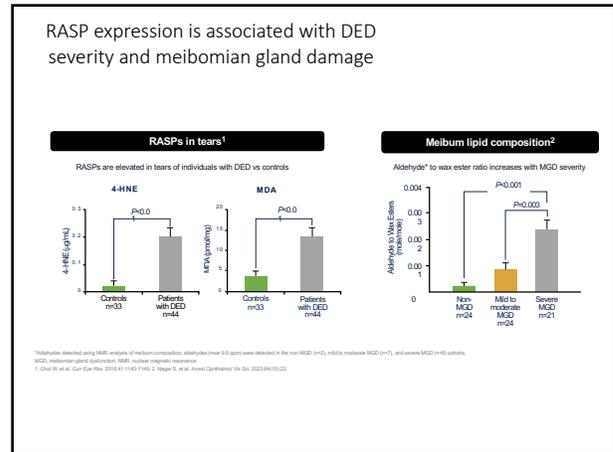
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Acotrelmon (AR-15512) Ophthalmic Solution 0.003% A drug candidate containing acotrelmon, a TRPM8 agonist

WHAT IS TRPM8?

- Transient receptor potential melastatin 8 (TRPM8)
- Expressed on trigeminal sensory nerve terminals in corneal epithelium
- Principal cold-sensitive TRP receptor^{1,2}

WHY TRPM8 AS A TARGET FOR DRY EYE?

- TRPM8 receptors are stimulated by ocular surface cooling and increased tear osmolarity associated with tear evaporation to regulate basal tear production^{3,4}

1. Gagnon-Nelson A, Beaudouin C, Munn-Chandrasekhar S, Shetty S, et al. *Front Cell Neurosci* 2020;14:152421. 2. Mitsuura CD, Akita Y, et al. *Mol Cell Neurosci* 2011;46(1):129-37. 3. Hoshikawa M, et al. *Antioxidants* 2021;10(10):1601. 4. Savelbergh C, et al. *JAMA Netw J* 2023;24(1):71-3.

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Acotrelmon (AR-15512) Ophthalmic Solution 0.003%

Acotrelmon is a potent and selective TRPM8 agonist that activates the trigeminal nerve to stimulate tear production

Enrollment 931 dry eye subjects completed COMET-2 and -3 studies

Primary Unanesthetized Schirmer Test

- Higher % of subjects with ≥ 10 mm increase in unanesthetized Schirmer Test scores on Day 14 with acotrelmon 0.003% (ACO) compared to vehicle
- Similar results seen on Day 1 and Day 90 (secondary endpoints)

Key Secondary SANDE Score

- Change from baseline in SANDE scores were greater with ACO on Day 28 in COMET-2 (P=0.0138), numerically greater with ACO in COMET-3 (P=0.1321)

Secondary Ocular Staining

- Change from baseline in total corneal and total conjunctival staining were observed at Day 7 through Day 90

Adverse Events

- ACO was well-tolerated, and there were no reported serious ocular adverse events

Primary endpoint met in both phase 3 (COMET) trials

COMET-2: PROPORTION WITH ≥ 10 mm INCREASE IN UNANESTHETIZED SCHIRMER SCORE

COMET-3: PROPORTION WITH ≥ 10 mm INCREASE IN UNANESTHETIZED SCHIRMER SCORE

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Summary

- Acotrelmon 0.003% increased tear production in a large proportion of subjects in both pivotal phase 3 studies^{1,2}
 - The primary endpoint, proportion of subjects with a ≥ 10 -mm increase in unanesthetized Schirmer score at day 14, was met in both phase 3 studies, COMET-2 and COMET-3 (P<0.0001)
 - Tear production was observed as early as after the first dose and continued through day 90
- The efficacy of acotrelmon 0.003% was supported by^{1,2}:
 - DED symptom reduction:** Improvements in global SANDE scores were statistically significantly greater than vehicle scores in COMET-2 and within the pooled analysis and directionally in favor of acotrelmon 0.003% in COMET-3
 - Ocular surface staining:** As exploratory endpoints, reductions in total corneal and total conjunctival staining was observed in both individual studies as well as in the pooled analysis
- Acotrelmon 0.003% was well tolerated by subjects over the 90-day duration of both pivotal studies^{1,2}
 - The only ocular treatment-emergent adverse event with $>2.5\%$ incidence was mild instillation site burning/tingling, which was reported in $\leq 51\%$ of subjects receiving acotrelmon 0.003%
 - In COMET-4, burning/tingling was reported to be transient, with $\sim 86\%$ of subjects who experienced the sensation reporting a duration of 1 minute or less³

1. https://clinicaltrials.gov/study/NCT02289544. Accessed September 24, 2024. 2. https://clinicaltrials.gov/study/NCT03360966. Accessed September 24, 2024. 3. https://clinicaltrials.gov/study/NCT03600111. Accessed September 24, 2024.

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TRPM8 as a Potential Therapeutic Target

Acotrelmon ¹⁻³	IWW-1001 ^{4,5}
TRPM8 agonist	TRPM8 agonist
Instilled as a drop on the ocular surface	Applied over upper eyelid
Completed phase 3 studies	Initiating phase 1/2 studies

Acotrelmon and IWW-1001 are investigational drugs and have not been approved for commercialization.
 TRPM8, transient receptor potential melastatin 8.
 1. https://clinicaltrials.gov/study/NCT02289544. Accessed March 27, 2024. 2. https://clinicaltrials.gov/study/NCT03360966. Accessed March 27, 2024. 3. https://clinicaltrials.gov/study/NCT03600111. Accessed March 27, 2024. 4. https://clinicaltrials.gov/study/NCT03600111. Accessed March 27, 2024. 5. https://clinicaltrials.gov/study/NCT03600111. Accessed March 27, 2024.

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AZR-MD-001

AZR-MD-001 is positioned to be the first and only pharmaceutical therapy to treat meibomian gland dysfunction (MGD) by:

- improving the meibum quality and quantity,
- restoring meibomian gland function, and
- treating evaporative dry eye signs & symptoms.

AZR-MD-001 is a keratolytic ointment dosed 2x per week @ bedtime directly to the meibomian glands

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Meibomian Glands

Meibomian glands which secrete meibum¹ are modified **sebaceous** glands

- **Normal meibum is a clear liquid at body temperature**
- **Lubricate the ocular surface during blinking and protect against tear evaporation.^{1,2,3}**
- **Meibum consists of a complex mixture of various proteins, lipids, and other components¹**
 - More than 90 different **proteins** identified in the meibum¹
 - 100s of different species of lipids, most of which are wax and cholesteryl esters⁴
 - Indirect immunofluorescence determined keratin proteins expressed in humans meibomian glands in the normal eye⁵
- **Keratins are helical structural proteins present in the meibum**

Meibomian gland

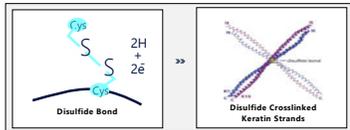
Labels: Skin, Orbicularis oculi muscle, Eyelash

Green-Church KB, et al. Invest Ophthalmol Vis Sci. 2011 Mar; 52(3):1079-81. Blocker CA, et al. Cornea. 2010;29(2):183-41. Kropf S, et al. Invest Ophthalmol Vis Sci. 2015;56(18):18-26. Mollnes IB, et al. Invest Ophthalmol Vis Sci. 2015;56(18):18-26. You JS, et al. J Ophthalmol. 2012; 17(1): 1-7. Sauer JL, et al. Invest Ophthalmol Vis Sci. 1988;29(1):17-25.

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Disulfide Bond Formation
Production of protein aggregates

- **Oxidative stress contributes to the pathology of MGD¹ and the formation of aberrant disulfide bonds**
- **Aberrant disulfide bonds leads to formation of excess keratin aggregates in unwanted locations**
- **Keratin protein release in the absence of crosslinking won't lead to the formation of keratin aggregates**



Israrath Chai, et al. PLoS One. 2014;9(7):e102028

79

Keratinization may be present in multiple places in the Meibomian gland:

- **Increased meibum viscosity is also a leading pathogenesis of MGD¹**
- **Keratin deeper in the gland may contribute to dysfunction**
- **Acinar cells deep down in the gland may produce abnormal amounts of keratin**
- **Released from the acini into the central ducts, keratinized epithelial debris (keratin strands crosslinked linked by strong disulfide bonds) increases the normal melting point of meibum.² Resulting in altered meibum quality and thickness**

Meibomian Gland

Labels: Meibum, Keratinized epithelial debris, Central duct, Ductule, Acinus, Sebaceous gland, Meibomian gland

Kropf S, et al. Invest Ophthalmol Vis Sci. 2011 Mar; 52(3):1078-79. Qing, et al. Curr Eye Res. 1991;10:113-119.

80

Keratinization may be present in multiple places in the Meibomian gland:

- **Hyperkeratinization at the gland orifice is a leading pathogenesis of MGD¹**
- **Keratin formation is a natural process**
 - Keratin is produced and sheds at physiological rates to confer its protective role while not accumulating in excess
- **At the gland orifice on the lid margin:**
 - Hyperproliferation may produce excess keratin (directly related to an oil-producing gland)
 - Terminal Duct Obstruction: Stress at the lid margin results in excess keratinization and excess keratin may block the glands and restricts outflow of meibum

Gland Orifice

Labels: Normal Glands, Blocked Glands, MGD Pathogenesis

Meibomian Gland

Labels: Meibum, Hyperkeratinization, Orifice, Inner lid border, acini, central duct, ductule, acinus, Meibomian gland

Kropf S, et al. Ophthalmology. 2008;116(8):1872-1877. Kropf S, et al. Invest Ophthalmol Vis Sci. 2015;56(18):18-26.

81

What are keratolytics?
Agents that soften skin through the process of breaking down keratin shed the skin epithelium or horny outer layer

- **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**

Acne - Keratin Plug

Blocked Meibomian Glands

Closed Comedones

Comedonal Acne

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Triple Mechanism of Action

AZR-MD-001 is a potent keratolytic/keratostatic with lipogenic activity:



DECREASE
meibomian gland
hyperkeratinization
of ducts and orifices

Keratostatic



LOOSEN
meibomian
gland blockages

Keratolytic



INCREASE
secretion of meibomian
gland lipids

Lipogenic

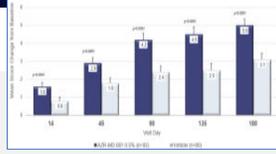
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AZR-MD-001 Shows Statistically Significant Improvement in MGYS Sign

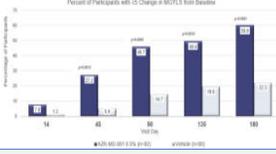
Meibomian Gland Yielding Liquid Secretion (MGYS) in target population; change from baseline

Number of Open Glands
Statistically Significant Difference from Control



% of Patients with Normal Open Glands
Clinically Significant Difference from Control

Percent of Participants with ≥ 5 Change in MGYS from Baseline



AZR-MD-001 (0.5%) show a significant treatment response vs. control for MGYS

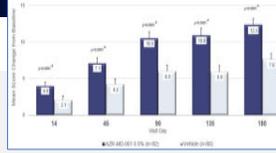
p-values computed using LS mean percentage compared to vehicle at the time points indicated

84

AZR-MD-001 Shows Statistically Significant Improvement in MGS Sign

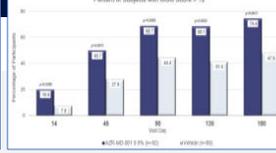
Meibomian Gland Score (MGS) in target population; change from baseline

Quality of Meibum
Statistically Significant Difference from Control



% of Patients with Normal Meibum
Clinically Significant Difference from Control

Percent of Subjects with MGS Score ≥ 12



AZR-MD-001 (0.5%) show a significant treatment response vs. control for MGS

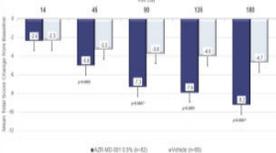
p-values computed using LS mean difference from baseline at the time points indicated
p-values computed using LS mean difference from baseline at the time points indicated

85

AZR-MD-001 Shows Statistically Significant Improvement in Symptoms for OSDI[®]

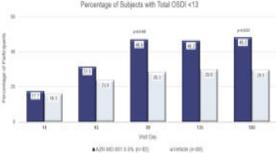
Total Ocular Surface Disease Index (OSDI) in target population; change from baseline

Reduction in Symptoms
Statistically Significant Difference from Control



% of Asymptomatic Patients
Clinically Significant Difference from Control

Percentage of Subjects with Total OSDI ≤ 13



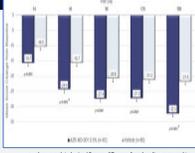
Approximately 50% of patients treated with AZR-MD-001 (0.5%) became asymptomatic by Month 3

p-values computed using LS mean difference from baseline
Miller et al. Meibomian Gland Lipid Secretion in Ocular Surface Disease: An Update. 2010;13(2):105-115

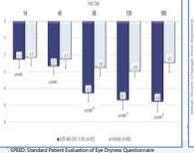
86

AZR-MD-001 Shows Statistically Significant Improvement in Symptoms across multiple symptom measures

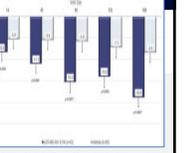
Statistically Significant Improvement in Eye Dryness
Eye Dryness (VAS) Change from Baseline



Statistically Significant Improvement in Eye Dryness
OSDI[®] Score Change from Baseline



Statistically Significant Decreased Itching
Itching Score Change from Baseline



p-values computed using LS mean difference from baseline compared to baseline at the time points indicated
p-values computed using LS mean difference from baseline at the time points indicated
p-values computed using LS mean difference from baseline compared to vehicle
p-values computed using LS mean difference from baseline at the time points indicated
p-values computed using LS mean difference from baseline compared to vehicle

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Reduction of TEAEs ($\geq 5\%$) Over Time for AZR-MD-001 0.5% Safety Data Set

AZR-MD-001 is a keratolytic ointment dosed 2x per week @ bedtime directly to the meibomian glands



Incidence Rate for Months 1 - 3 **Incidence Rate for Months 4 - 6**

* Defined as associated with an increase in conjunctival staining of 2+ grades

At month 6, most (96%) TEAEs in the AZR-MD-001 0.5% group were Mild to Moderate in severity and only two additional subjects (2.4%) discontinued for AEs

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AZR-MD-001 Clinical Data Review:

- U.S. Regulatory requirements achieved**
- 3-mo. Co-Primary Endpoints met statistical significance and clinically meaningful benefit for 0.5% over vehicle¹
- 6-mo. Further improvement in **all signs and symptoms** with continued use through 6-months
 - Durability of effect strengthens US filing and supports an ex-US regulatory strategy

Trial Efficacy

- Restored Gland Function**
 - 61.7% of patients had their glands opened to a normal level² at 6-mo.
 - 75% of patients had their meibum quality return to normal levels³ at 6-mo.
- Improved Patient Symptoms**
 - 54.7% of patients became asymptomatic as measured by Total OSDI[®] at 6-mo.
 - Improved tear stability – Over a 2 second improvement in Tear Break Up Time maintained from Month 3 onward
 - Significantly improved patient symptoms across multiple patient-reported outcome measures (SPEED, average VAS, Eye Dryness, Eye Discomfort, Ocular Itch)

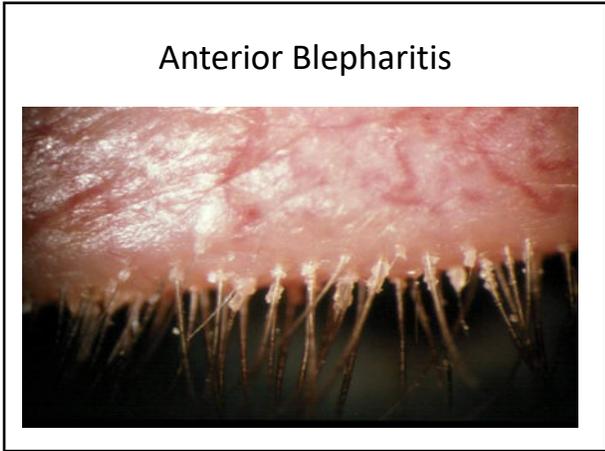
1. In a single study in IT population (all randomized patients)
 2. MCG responder rate (p<0.005) compared to vehicle at month 3. Improvement from baseline of 4.2 (p<0.009)
 3. MCG responder rate (p<0.006) compared to vehicle at month 3. Improvement from baseline of 0.5 (p<0.006)

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What Is Blepharitis?

- Traditionally taught it is either anterior or posterior
- Anterior blepharitis was traditionally caused by bacterial overgrowth, staph endotoxin etc
- Posterior blepharitis was eventually referred to as Meibomian Gland Dysfunction
- I think they got it all wrong, TFOS/DEWS agrees with me!

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TFOS DEWS II - Diagnostic Methodology

James S. Wolffsohn, FCOptom, PhD¹; Correspondence information about the author FCOptom, PhD James S. Wolffsohn Email the author FCOptom, PhD James S. Wolffsohn, Reiko Arita, MD, PhD, Robin Chalmers, OD, Ali Djalilian, MD, Murat Dogru, MD, PhD, Kathy Dumbleton, MCOptom, PhD, Preetiya K. Gupta, MD, Paul Karpecki, OD, Sihem Larregu, MD, Hideo Fujit, MSc (Optom), PhD, Benjamin D Sullivan, PhD, Alan Tomlinson, FCOptom, DSc, Louis Tong, FRCS, PhD, Edoardo Villani, MD, Kyung Chul Yoon, MD, PhD, Lyndon Jones, FCOptom, PhD, Jennifer P. Craig, MCOptom, PhD

- Introduction
- Goals of the Diagnostic Methodology Subcommittee
- Definition of dry eye disease (DED)
- Classification of sub-categories of dry eye disease (DED)
- Diagnostic considerations
- Recommendations of appropriate tests for diagnosis and assessment of dry eye
- Monitoring dry eye disease progression and management
- Clinical protocol for dry eye diagnostic test battery
- Differential diagnosis & comorbidities
- Emerging technologies
- Summary and conclusions
- Financial disclosures
- Acknowledgements
- References
- Tables
- Questionnaire Forms (DEQ-5 & OSDI)

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6.8.1.1 Anterior

Anterior eyelid features, such as anterior blepharitis and demodex blepharitis, are differential diagnoses and comorbidities of DED rather than diagnostic criteria and therefore are discussed in Section 9.

6.8.1.2 Posterior

6.8.1.2.1 Lid wiper epithelopathy (LWE)

A small portion of the marginal conjunctiva of the upper and lower lid acts as a wiping surface to spread the tear film over the ocular surface [379,380]. This contacting surface at the lid margin has been termed the 'lid wiper' [379]. The normal lid wiper is rich in goblet cells [381], and appears to be the most sensitive conjunctival tissue of the ocular surface [382]. Lid wiper staining with dyes such as fluorescein and lissamine green, which occurs principally in DED patients [298,299,379,383,384], has been termed lid

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INVESTIGATION

Demodex folliculorum infestations in common facial dermatoses: acne vulgaris, rosacea, seborrheic dermatitis^{1,2,3,4}

Ezgi Aktaş Karabay ^{1,2,3,4}, Aşlı Aksu Çerçman ^{1,2,3,4}

Department of Dermatology and Venereology, Faculty of Medicine, Bahçeşehir University, Istanbul, Turkey

Received 18 March 2019; accepted 26 August 2019
Available online 12 February 2020

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Department of Dermatology and Venereology, Faculty of Medicine, Bahçeşehir University, Istanbul, Turkey

Received 18 March 2019; accepted 26 August 2019
Available online 12 February 2020

Abstract

Background: Demodex mites are found on the skin of many healthy individuals. Demodex mites in high densities are considered to play a pathogenic role.

Objective: To investigate the association between Demodex infestation and the three most common facial dermatoses: acne vulgaris, rosacea and seborrheic dermatitis.

Methods: This prospective, observational case-control study included 127 patients (42 with acne vulgaris, 42 with rosacea and 43 with seborrheic dermatitis) and 77 healthy controls. The presence of demodexes was evaluated by standardized skin surface biopsies in both the patient and control groups.

Results: In terms of gender and age, no significant difference was found between the patients and controls ($p=0.385$). Demodex infestation rates were significantly higher in patients than in controls ($p<0.001$). Demodex infestation rates were significantly higher in the rosacea group than acne vulgaris and seborrheic dermatitis groups and controls ($p<0.001$, $p=0.004$, $p<0.001$, respectively). Demodex infestation was found to be significantly higher in the acne vulgaris and seborrheic dermatitis groups than in controls ($p<0.001$ and $p=0.001$, respectively). No difference was observed between the acne vulgaris and seborrheic dermatitis groups in terms of demodexes ($p=0.294$).

Conclusion: Small sample size is a limitation of the study. The lack of an objective scoring system in the diagnosis of Demodex infestation is another limitation.

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> Clin Exp Dermatol. 2009 Dec;34(8):e516-20. doi: 10.1111/j.1365-2230.2009.03343.x. Epub 2009 May 22.

Is Demodex folliculorum an aetiological factor in seborrhoeic dermatitis?

Y Karıncaoğlu ¹, B Tepe, B Kalaycı, M Atambay, M Seyhan

Affiliations + expand
PMID: 19486039 DOI: 10.1111/j.1365-2230.2009.03343.x

Abstract

Background: Seborrhoeic dermatitis (SD) is a common inflammatory skin disease for which no single cause has been found, although many factors have been implicated. The mite Demodex folliculorum (DF) is most commonly seen in the pilosebaceous unit in humans. SD is located in areas that are rich in sebaceous glands, which are also preferred by DF.

Aims: To compare the number of DF parasites in patients with clinical SD and in healthy controls, and to investigate any possible relationship between the number of DF mites and the presence of SD.

Methods: The study comprised 38 patients with SD and 38 healthy controls. Standard random and lesion-specific sampling was performed in the group of patients with SD, whereas standard random sampling only was performed for controls.

Results: Demodex folliculorum sampling was positive in 19 patients (50%) and 6 controls (13.1%). Mean DF density was 8.16 +/- 10.1/cm(2) (range 0-40) and 1.03 +/- 2.17/cm(2) (1-7) in patient and control groups, respectively. The differences between groups for DF positivity and mean DF density were significant ($P=0.001$ for each). DF was found in 13 lesional areas in the patient group, but in only 5 areas in the control group ($P=0.031$).

Conclusions: The number of DF mites was significantly higher in both lesional and nonlesional areas of patients with SD. This suggests that, when other aetiological causes are excluded, DF

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Rosacea

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

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

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Demodex Has Been Linked to Rosacea and Blepharitis

Slide courtesy of Scheffer Tseng, MD
The Ocular Surface Center, Miami Florida

Skin Rosacea **Ocular Rosacea, Blepharitis**

Coston, 1967, English, 1971, English & Nutting, 1981, Heacock, 1986, Fulk & Clifford, 1990, Fulk et al, 1996, Kamoun et al. 1999, Morfin, 2003

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Lid health directly impacts the ocular surface¹

Demodex blepharitis may contribute to development of ocular surface diseases because of chronic inflammation.²



Examples of Demodex blepharitis conjunctival/corneal disease

References: 1. Kurotori, S. et al. The eyelid follicular flora and its relation to ocular surface disease. 2018; 2018:1-10. 2. Farnsworth, J. et al. Demodex blepharitis: ocular surface disease. 2018; 2018:1-10.

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Demodex blepharitis (DB) can be seen and experienced by your patients

The ATLAS study was the first prospective, multicenter, observational study of 311 adults with Demodex blepharitis to evaluate the impact of the disease.¹

- Commonly reported symptoms:
 - Dry eye
 - Lid itching
 - Irritation

52% of patients experienced these symptoms frequently or all the time

- Clinical consequences may include:
 - Dry eye
 - Red, itchy, or irritated eyelids
 - Missing or misdirected eyelashes
 - Inflammation of the conjunctiva and lid margin
 - Recurrent chalazia



References: 1. O'Neil, J. et al. The epidemiology of Demodex blepharitis. 2018; 2018:1-10. 2. Farnsworth, J. et al. Demodex blepharitis: ocular surface disease. 2018; 2018:1-10.

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What Do We Know?

- Blepharitis and MGD are extremely common
- Demodex is extremely common
- Lid disease is a common cause of evaporative dry eye
- Rosacea is a common cause of MGD
- Demodex is a common cause of Rosacea
- What we thought was anterior blepharitis is probably Demodex
- Ocular allergy symptoms overlap dry eye and MGD symptoms

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What We Really DON'T Know:

- What is the true prevalence of Demodex?
- How much Demodex results in symptoms
- How much "symptom" is needed to treat
- Which percentage of dry eye is really lipid layer evaporation vs. mucin deficiency
- What is an effective and enduring treatment for MGD?
- What is an effective and enduring treatment for Demodex?

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What We Really DON'T Know:

- Could there be a socioeconomic predisposition to demodex?
- Are autoimmune systemic conditions associated with blepharitis?
- Are there differences in prevalence rates by ethnicity or gender?

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HANDBOOK OF MEDICAL ENTOMOLOGY

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

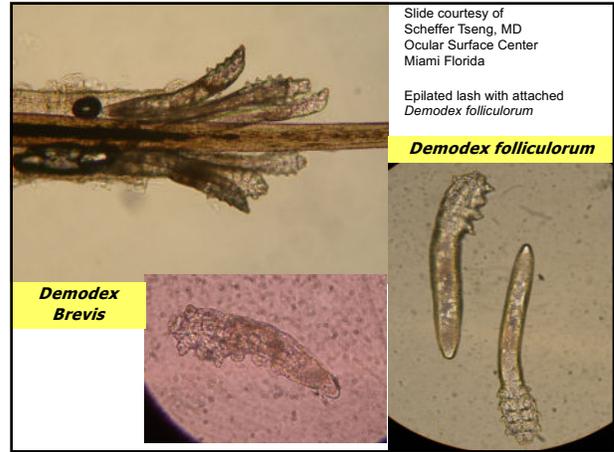
Dr. O. A. JOHANNSEN, Professor of Biology, Cornell University

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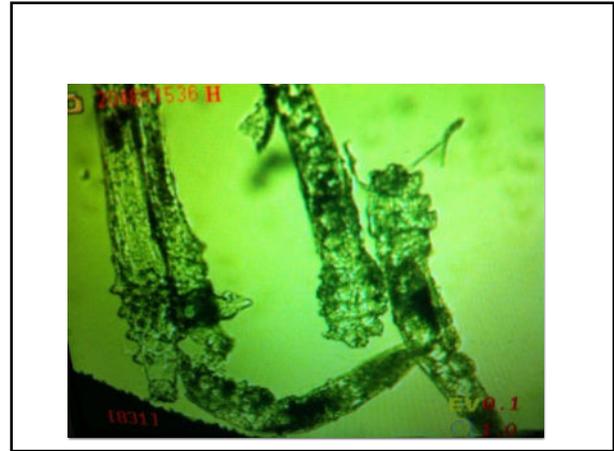
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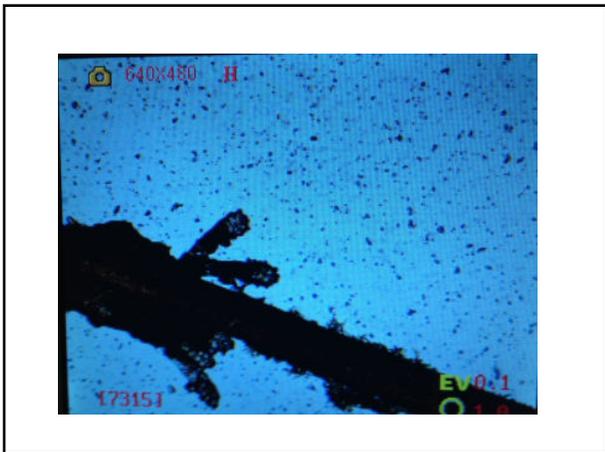
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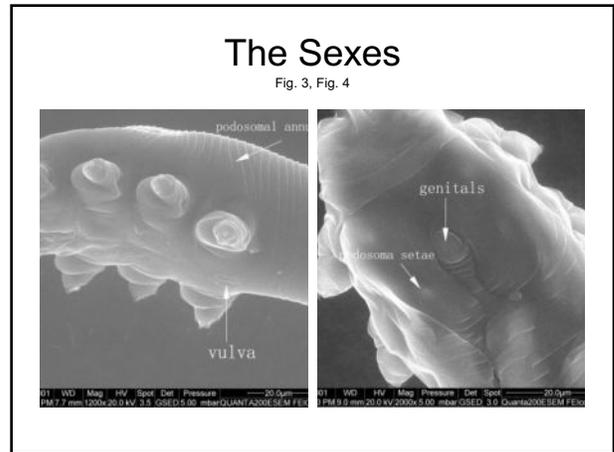
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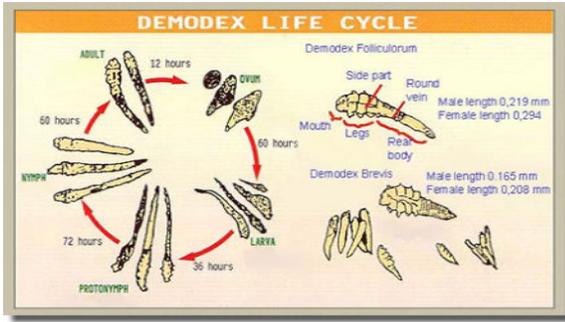


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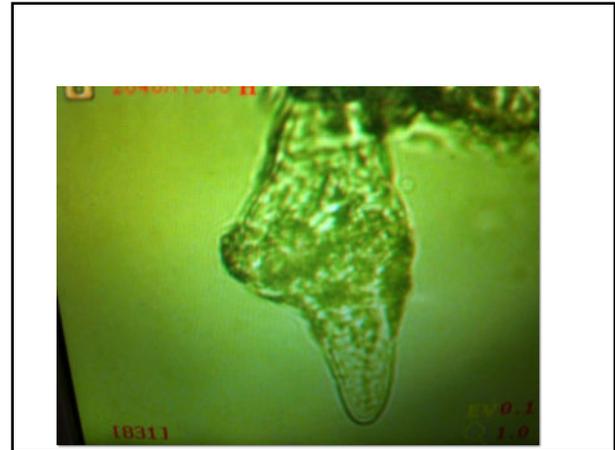


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Demodex Life Cycle



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Symptoms:

Itch, burning, foreign body sensation, crusting, redness, blurry vision

[Hom MM](#), [Mastrota KM](#), [Schachter SE](#), Demodex. *Optom Vis Sci.* 2013 Jul;90(7):e198-205.

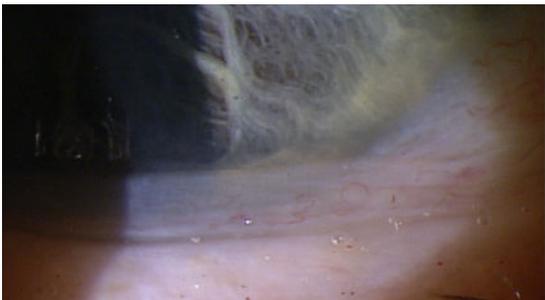
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Symptoms of Demodex

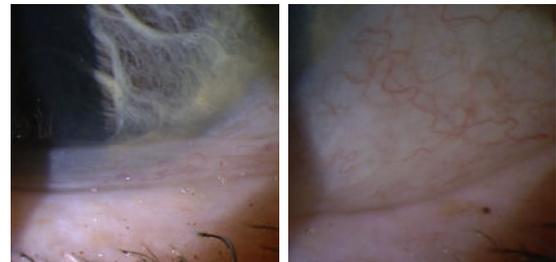
- Eyelid itching
- Ocular itching
- Facial itching
- Thickened, red lids seen
 - Personal observation: Exacerbated in PGA pts
- **Watering, often chronic**
- Eyelash loss
- Chronic redness of conjunctiva
- Coexists with OSD and MGD symptoms

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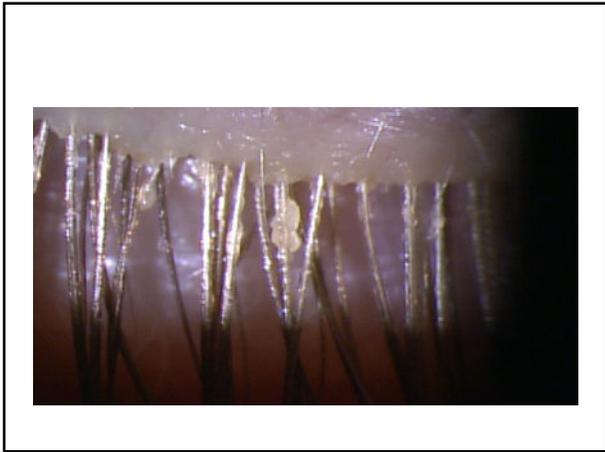
Redundant Conjunctival Folds



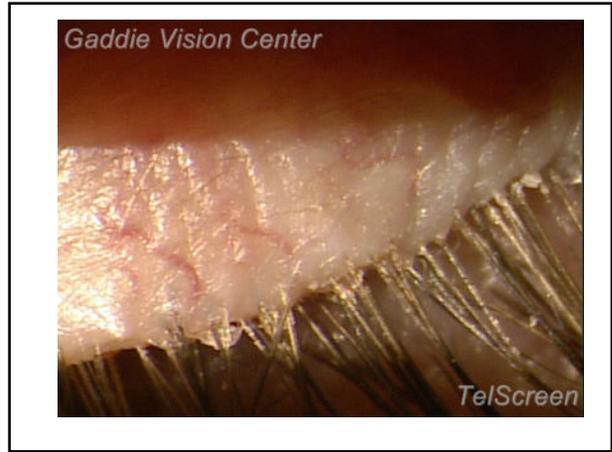
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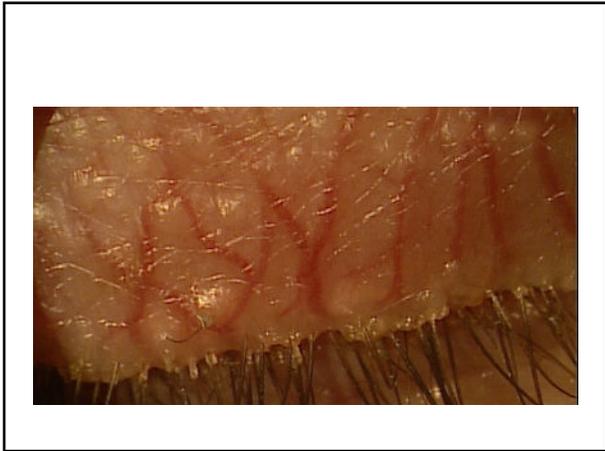
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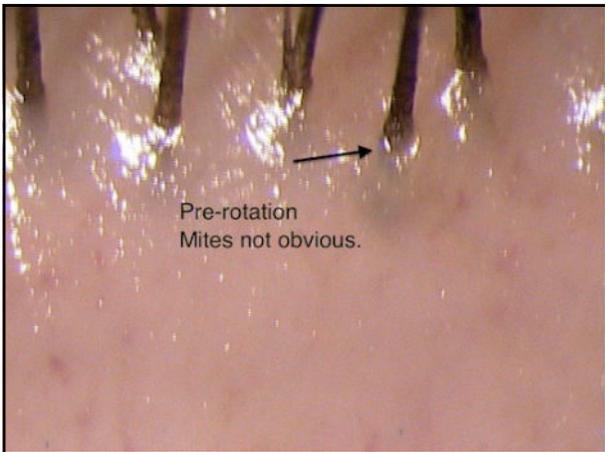
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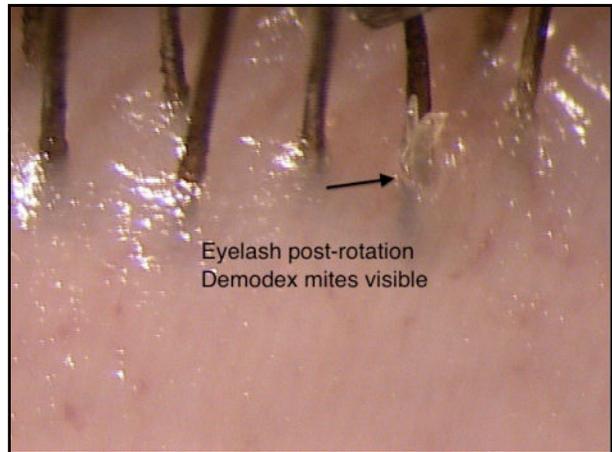
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Collarettes Are Pathognomonic Sign of Demodex Infestation

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

% of Subjects with Demodex

Collarette Status	% of Subjects with Demodex
>1 Collarettes	100%
No collarettes, Using lid scrubs	50%
No collarettes, No lid scrubs	7%

1. Trantler 2019
2. Chan et al. Invest Ophthalmol Vis Sci. September 2005; Vol. 46, No. 20:3920-3924.
3. Demodex Prevalence Study

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Blepharitis Is a Large and Underserved Market in Eye Care

Epidemiology of Demodex Blepharitis

- Estimated In-Office Epidemiology ~25M
- Population Epidemiology ~9M
- U.S. Demodex Blepharitis Prevalence ~1M Dx/yr
- Current ICD-10 ~1M Dx/yr
- ~45M unique adult eye visits¹
- ~15% with collarettes²
- ~200M with blepharitis³
- 45% with Demodex infestation⁴
- ~2.1M blepharitis ICD-10-CM Dx visits⁵
- ~1.8M eye visits⁶
- Despite no mild education

Large Patient Population with Significant Disease Impact

- Significant Head Start on Diagnosis
- Blepharitis Routinely Causes
- Blepharitis Can Lead to
- Concomitant Dry Eye
- Blepharitis and Surgery
- Contact Lens Drop-out
- Prescription Treatment

Titan (collarette clinic prevalence) and Atlas (disease impact) studies demonstrate high prevalence of disease and significant burden on patients

- Yields to become red, itchy and itchy, with debris on the eyelashes⁷
- Evids to become red, itchy and itchy, with debris on the eyelashes⁸
- Blepharitis Routine Causes Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the cornea⁹
- Significant overlap in Dry Eye patients. Demodex prevalent in ~69% of DE patients¹⁰
- Important factor for misdiagnosing surgical outcomes: 87% of Colarrete Patients have Demodex Blepharitis¹¹
- Studies have shown a direct correlation between Demodex Blepharitis and Contact Lens Intolerance¹²
- None; 81% of patients currently seeking treatment¹³

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Titan Study Confirms Widespread Collarette Prevalence in ECP Clinic Patients and Key Patient Segments

Study Overview

- IRB-APPROVED RETROSPECTIVE CHART REVIEW: Examined presence of collarettes and other characteristics
- LARGE-SCALE ALL-COMERS (1,832 PATIENTS): Consecutive patients with a wide variety of reasons for visit
- DIVERSE ANTERIOR SEGMENT CLINICS: Geographically diverse (7 US sites) including both MD and OD clinics

Key Findings

- % of Overall Population**
 - With Collarettes: 58%
 - Dry eye diagnosed: 58%
- Key Patient Groups**
 - Blepharitis diagnosis: 69%
 - Dry eye Rx: 66%
 - Treatment: 66%
 - Contact patient: 61%
 - Contact lens wear: 51%

Additional Study at ARVO 2021 by Drs. Jacobson, Rosenberg showed (n=199):
 65% prevalence of mites, 62% overlap of blepharitis 45% overlap with Dry Eye

Trantler et al. *Clin Ophthalmol*. 2022; 16: 1153-1164.

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Atlas Study Reveals Symptomatic and Psychosocial Burden of Demodex Blepharitis: 80% Report Negative Impact on Daily Life

- Multicenter, observational study of patients pre-screened for the Saturn-1 pivotal trial
- Evaluated the clinical and patient reported impact of Demodex blepharitis (interim analysis of 311 patients)
 - Presence of Demodex mites (at least 1 mite per lash)
 - Presence of collarettes (> 10, upper lid)
 - At least mild erythema

51% Experienced signs and symptoms > 4 yrs

58% Never diagnosed with blepharitis

33% Made at least 2, and sometimes more than 6, visits to a doctor for this condition

Most Bothersome Symptoms

- Eye at hat itch: 11% (Top 1), 17% (Top 2), 27% (Top 3)
- Dry eyes: 9% (Top 1), 14% (Top 2), 23% (Top 3)
- 82% experienced the top 3 symptoms frequently or all the time

Functional and Psychosocial Impact

- Feels symptomatic of eyes at day: 41%
- Difficulty doing at night: 51%
- Additional time needed for daily hygiene routine: 33%
- Negative appearance of eyes at day: 29%
- Consistently worrying about your eyes at night: 27%
- Difficulty wearing make-up: 22%
- Difficulty: Does your blepharitis affect any of the following aspects of your daily life if applicable or how you feel about your life? 34%

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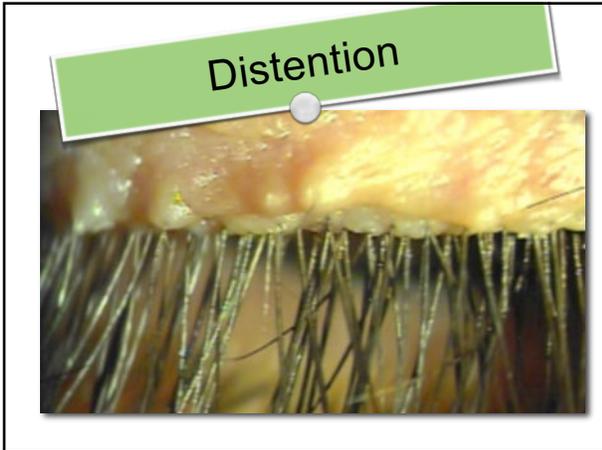


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Clinical Manifestations of Demodex Blepharitis

- Disorders of eyelashes^{1,2}**: Infestation of the lash follicles may lead to collarettes.
- Lid margin inflammation^{1,2}**: Severe lid margin inflammation can be caused by mechanical blockage.
- Melibrosian gland dysfunction^{1,2}**: Blockage leads to filling, swelling, and many enlarged glands (cysts) or infection.
- Conjunctival inflammation^{1,2}**: Lid margin inflammation may spread over to the conjunctiva.
- Corneal manifestations^{1,2}**: *D. brevis* is commonly associated with inflammation that spreads to the cornea, causing marginal keratitis. The cytolysis of mites may act as a foreign body and create a granulomatous reaction that is implicated in trichiasis.

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The ROYAL COLLEGE of OPHTHALMOLOGISTS www.nature.com/eye

ARTICLE OPEN [Check for updates](#)

Clinical diagnosis and management of *Demodex* blepharitis: the Demodex Expert Panel on Treatment and Eyelid Health (DEPTH)

Brandon D. Ayres¹, Eric Dornheim², Marjan Farid³, Ian Benjamin Gaddie⁴, Freya K. Gupta⁵, Edward Hellanz⁶, Paul M. Karpecki⁷, Richard Lindstrom⁸, Kelly K. Nichols⁹, Stephen C. Pflugfelder¹⁰, Christopher E. Stan¹¹ and Elizabeth Yu¹²

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BACKGROUND: Twelve ocular surface disease experts convened to achieve consensus about Demodex blepharitis (DB) using a modified Delphi panel process.

METHODS: Online surveys were administered using scaled, open-ended, true/false, and multiple-choice questions. Consensus for questions using a 1 to 9 Likert scale was predefined as median scores of 7–9 and 1–3. For other question types, consensus was achieved when 8 of 12 panelists agreed. Questions were randomized, and results of each survey informed the following survey.

RESULTS: Twelve practitioners comprised the Demodex Expert Panel on Treatment and Eyelid Health (DEPTH). Following 3 surveys, experts agreed that DB is chronic ($n = 11$) and recurrent ($n = 12$) and is often misdiagnosed. Consensus was achieved regarding inflammation driving symptoms (median = 7; range 7–9), collarettes as the most common sign ($n = 10$) and pathognomonic for DB (median = 8; range 8–9), and itching as the most common symptom ($n = 12$). Panelists agreed that DB may be diagnosed based on collarettes, mites, and/or patient symptoms ($n = 10$) and felt that patients unresponsive to typical therapies should be evaluated for DB ($n = 12$). Consensus about the most effective currently available OTC treatment was not reached.

CONCLUSIONS: The Delphi methodology proved effective in establishing consensus about DB, including signs, symptoms, and diagnosis. Consensus was not reached about the best treatment or how to grade severity. With increased awareness, eyecare practitioners can offer DB patients better clinical outcomes. A follow-up Delphi panel is planned to obtain further consensus surrounding DB treatment.

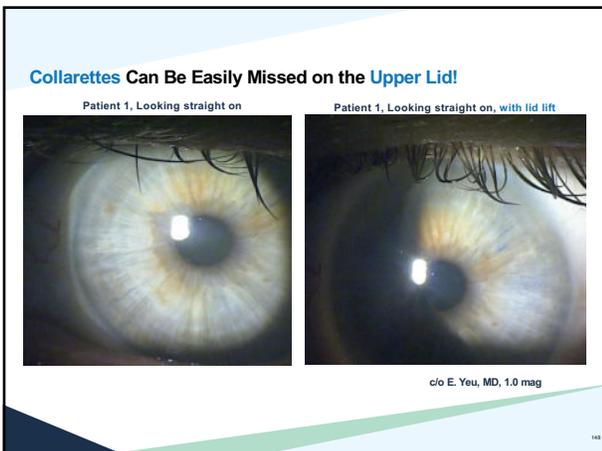
Eye: <https://doi.org/10.1038/s41433-023-02500-4>

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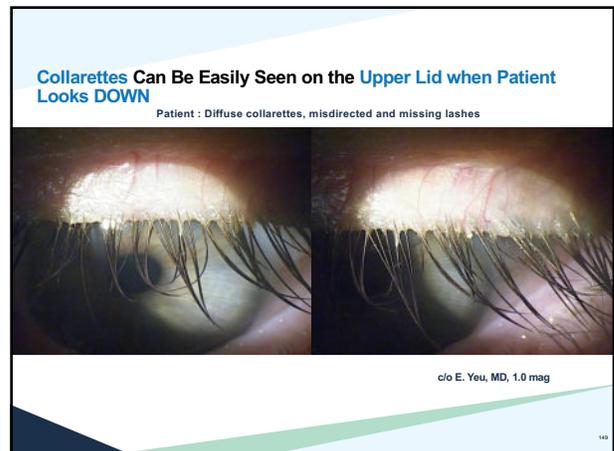
Table 1. Key areas of consensus on scaled questions.

Area of consensus	Median score	Range
Collarettes are pathognomonic for Demodex blepharitis	9	8–9
Epilation is not necessary	9	5–9
Number of mites correlates with density and severity of collarettes	9	4–9
Demodex blepharitis may cause insecurity about appearance	8	6–9
Number of mites correlates with symptom severity	8	6–9
Restoring balance to the ocular ecology is the key to managing Demodex infestation	8	5–9
More itching is seen in dry eye disease with Demodex blepharitis vs. Demodex blepharitis alone	8	5–9
Demodex blepharitis patients may have secondary ocular infections	7.5	2–9
Contact lens intolerance correlates with Demodex infestation	7	7–9
Demodex mites and their byproducts such as chitin and digestive enzymes trigger the inflammatory cascade	7	7–9
Inflammation drives symptoms in Demodex blepharitis	7	7–9
Itching is caused by non-histamine pathways	7	4–9
Lash loss only occurs with severe Demodex blepharitis	7	1–9
Mite visualization NOT necessary to diagnose	2	1–8

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

Lutiferin

• Patent non-competitive antagonist of itraconazole
• Highly lipophilic molecule



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

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Extensive Clinical Trial Program for TP-03

Study	# of Subjects	Effectiveness Endpoints	Study Highlights	Status
PoC: Mercury	80 mites	Ex-vivo mite death count	Ex-vivo mite testing	Completed
P2a: Mars	15 – Single arm	Collarette grade Mite density	28-day BID dosing	Completed
P2b: Jupiter	60 – 1:1	1 st – Collarette grade 2 nd – Mite density	28-day BID dosing; RCT	Completed
P2a: Io	18	1 st – Collarette cure 2 nd – Mite eradication	Crossover of Jupiter control arm subjects; 42-day BID dosing	Completed
P2b: Europa	54 – 1:1	1 st – Collarette cure 2 nd – Mite eradication	42-day BID dosing; RCT	Completed
P2b/3: Saturn-1	421 – 1:1	1 st – Collarette cure 2 nd – Mite eradication 2 nd – Redness composite	Pivotal registration study 42-day BID dosing; RCT	Completed
P3: Saturn-2	418 – 1:1	1 st – Collarette cure 2 nd – Mite eradication 2 nd – Redness composite	Pivotal registration study 42-day BID dosing; RCT	Initiated May 2021

} Two Pivotal Trials

Same formulation of TP-03 as explored in the Saturn trial

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Saturn-1: All Primary and Secondary Endpoints Were Met and TP-03 was Well Tolerated

- Efficacy:** All pre-specified primary, secondary, and exploratory endpoints were met
 - Primary Endpoint: Complete Collarette Cure $p < 0.0001$
 - Clinically Meaningful Collarette Cure (Grade 0 or 1) $p < 0.0001$
 - Secondary Endpoint: Mite Eradication $p < 0.0001$
 - Secondary Endpoint: Composite Lid Erythema and Collarette Complete Cure $p < 0.0001$
 - Clinically Meaningful Composite Lid Erythema and Collarette Cure $p < 0.0001$
 - Erythema Cure $p = 0.0001$ and Erythema Response $p = 0.0002$
 - Rapid Cures: Improvements Seen in 2 Weeks $p \leq 0.0149$ in Primary and Secondary Endpoints
- Safety:** TP-03 was well-tolerated, with safety profile similar to vehicle
 - All TP-03-related AE's were mild with no treatment related discontinuations
 - 92% of patients reported the drop to be neutral to very comfortable

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Collarette Grading Scale Used in Saturn-1

Non-linear scale for counting collarettes performed by each site investigator

Grade 4

>25 of lashes on lid with collarettes
Approximately 150 collarettes/lid

Average baseline
Grade 3

Between 10-20 of lashes on lid with collarettes
Approximately 100 collarettes/lid

Grade 2

Between 5-10 collarettes on lid of lashes on lid with collarettes
Approximately 50 collarettes/lid

Grade 1

3-10 collarettes on the lashes

Grade 0

0-2 collarettes on the lashes
Cure of collarettes

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Lid Margin Erythema Scale Used in Saturn-1

Established and validated scale used in blepharitis studies, performed by each investigator

Grade 3

3 (Severe)*

Grade 2

2 (Moderate)

Grade 1

1 (Mild)

Grade 0

0 (None)

Average baseline 1.5

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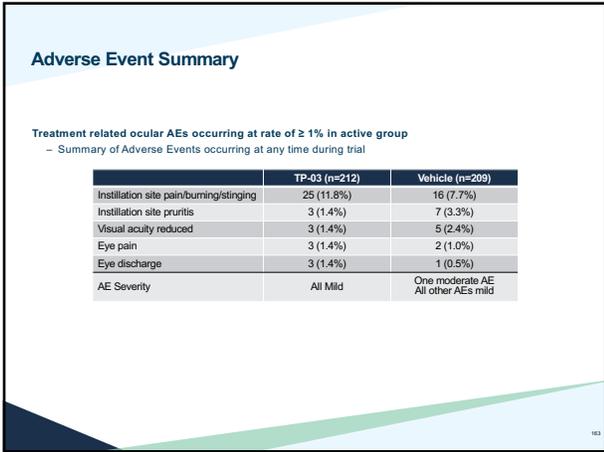
Assessing Severity of Demodex Blepharitis: Collarettes*

0	1	2	3	4
0 to 2 lashes/eyelid with collarettes	3 to 10 lashes/eyelid with collarettes	>10 to <4/3 (~80)*†	≥1/3 to <4/3 (~100)*†	≥2/3 (~150)*†

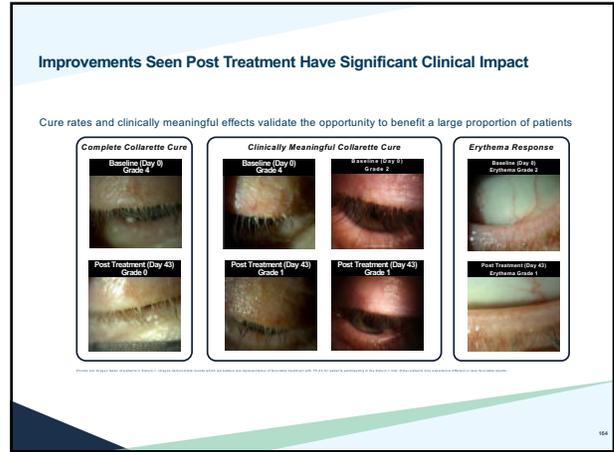
*Mild, moderate, and severe grades are based on the number of lashes with Demodex blepharitis.

†Based on 2000 lashes per eyelid.

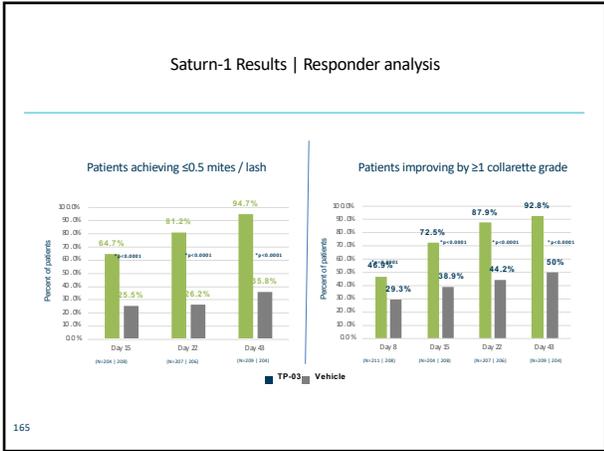
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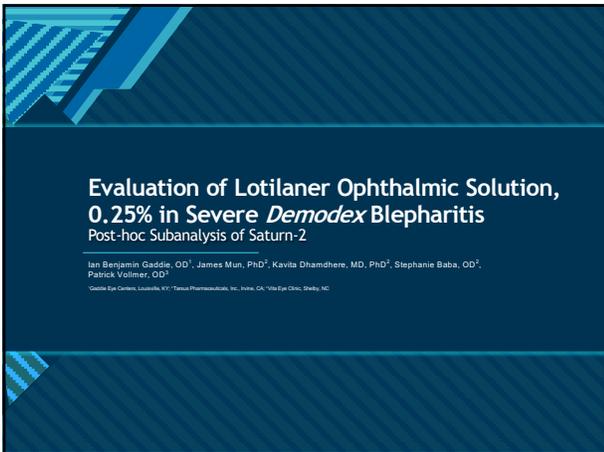


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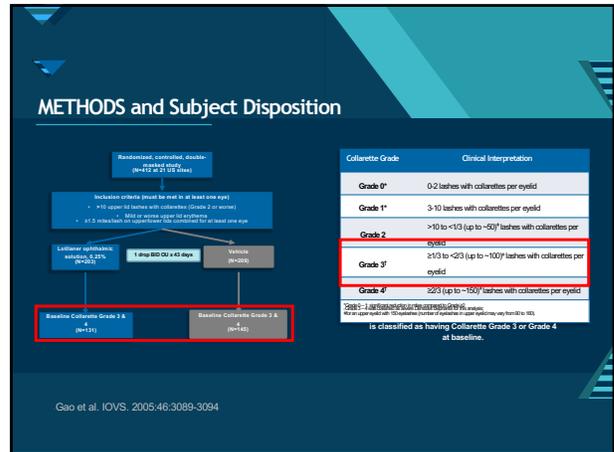
Pooled P3 data

	Saturn-1 (Pivotal Phase 2b/3) N=421	Saturn-2 (Pivotal Phase 3) N=412	Combined Pivotal Data N=833
Primary Endpoint: Complete Collarette Cure	44% vs. 7% (p<0.0001)	56% vs. 13% (p<0.0001)	50% vs. 10%
Clinically Meaningful Collarette Cure (Grade 0 or 1)	81% vs. 23% (p<0.0001)	89% vs. 33% (p<0.0001)	85% vs. 28%
Mite Eradication	68% vs. 18% (p<0.0001)	52% vs. 14% (p<0.0001)	60% vs. 16%
Lid Erythema Cure	19% vs. 7% (p<0.0001)	31% vs. 9% (p<0.0001)	25% vs. 8%
Safety	Generally safe and well tolerated	Generally safe and well tolerated	Generally safe and well tolerated

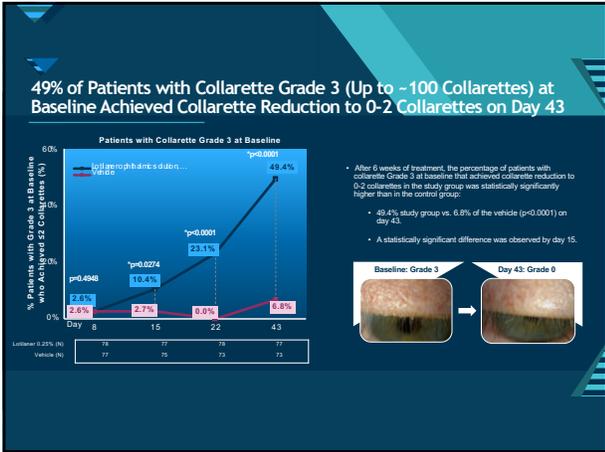
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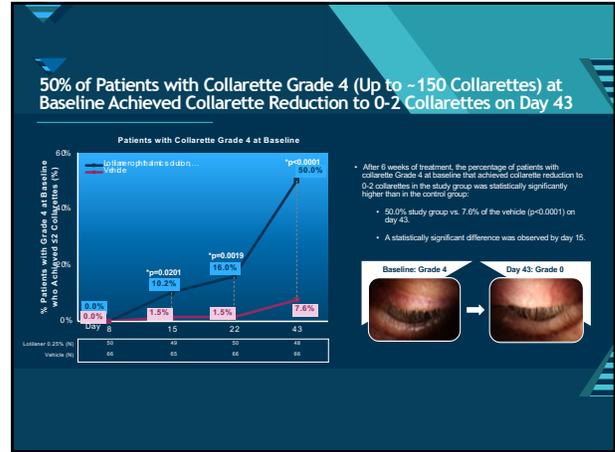
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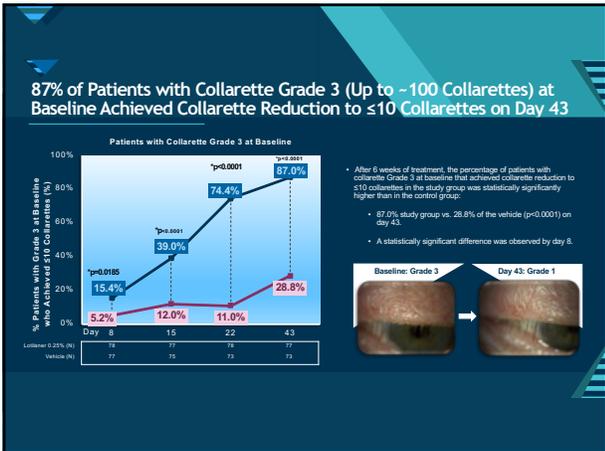
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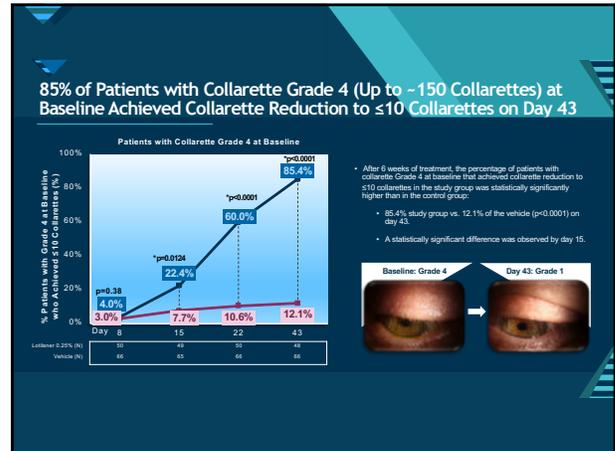
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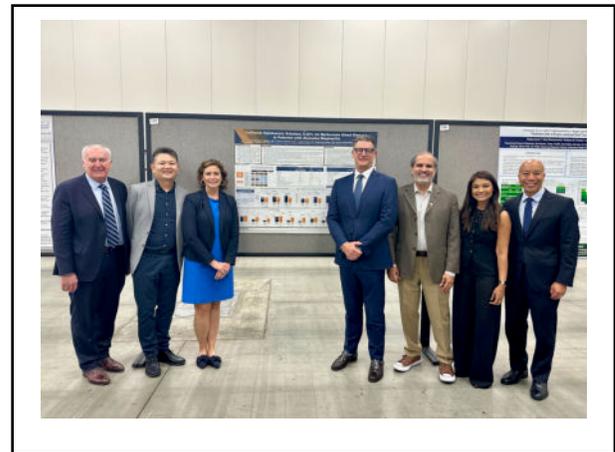
171



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- ### Phase 2b Lotilaner MGD Data
- Two Studies
 - 1 with lotilaner 0.25%
 - 1 with vehicle
 - Two Arms
 - TID
 - BIG
 - Time points
 - Day 43
 - Day 85

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Grading Scales and VAS

- Meibum Quality Score Scale
 - Grade 3= Clear Liquid Secretion
 - Grade 2= Cloudy Liquid Secretion
 - Grade 1= Opaque liquid to toothpaste
 - Grade 0= No secretion
 - 15 central lower glands studied
 - Perfect function= 45 (GRADE 3 X 15=45)
- Visual Analog Score (VAS)
 - Patient grades symptoms on a scale of 1 to 100
 - Example: Fluctuating Vision score of 60= 60% of the time patient has fluctuating vision

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Meibomian Gland Secretion Scores

- Baseline was a score of 22 in both studies
 - Day 43= 27.8 Lotilaner vs. 23.3 vehicle
- Day 85= 33.2 Lotilaner vs. 23.1 vehicle

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Number of Glands Secreting Any Liquid (grade 2 or 3)

- 15 central glands=15 is perfect score
- Baseline both groups=7.1 glands
- Day 43= 10.7 lotilaner vs. 8.2 vehicle
- Day 85= 12.7 lotilaner vs. 7.6 vehicle

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% of Patients Achieving >3 Glands With Improvement to Grade 3

- Day 43=44.7% Lotilaner vs. 17.6% vehicle
- Day 85=78.9% Lotilaner vs. 18.1% vehicle

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Fluctuating Visual Acuity

- Visual Analog Score up to 100
- Baseline=46.5 Lotilaner vs. 51.9 vehicle
- Day 43=22.2 Lotilaner vs. 40.1 vehicle
- Day 85=13.1 Lotilaner vs. 30.8 vehicle

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Itching

- Visual Analog Score up to 100
- Baseline= 47.0 Lotilaner vs. 52.8 vehicle
- Day 43= 16.9 Lotilaner vs. 42.6 vehicle
- Day 85= 11.4 Lotilaner vs. 40.5 vehicle

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Burning

- Visual Analog Scale up to 100
- Baseline= 35.4 Lotilaner vs. 46.0 vehicle
- Day 43= 20.0 Lotilaner vs. 34.1 vehicle
- Day 85= 10.5 Lotilaner vs. 31.6 vehicle

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Redness

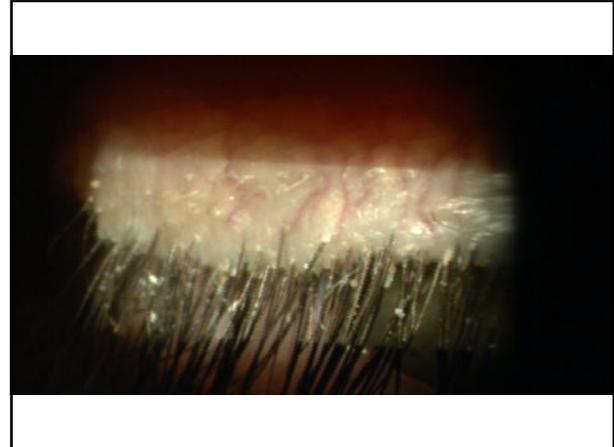
- Visual Analog Scale up to 100
- Baseline= 43.6 Lotilaner vs. 42.5 vehicle
- Day 43= 18.6 Lotilaner vs. 38.9 vehicle
- Day 85= 12.2 Lotilaner vs. 32.6 vehicle

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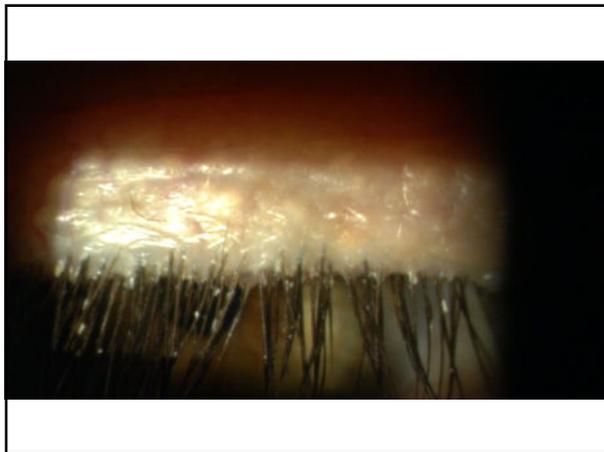
Case

- 56 YOWF presenting for comprehensive exam
 - Red, itchy eyelids and fluctuating vision
 - Stopped wearing her contact lenses due to blurry vision
 - VA BCVA 20/25-1 OD and 20/25-1 OS
 - SPEED Score 21/28
- Current medications:
 - Flaxseed oil, Flonase, Retaine MGD
- Previous/Failed Therapies
 - FreshKote for SPK
 - Lotemax
 - Cyclosporine
 - Liftegrast
- Previous procedures-Lipiflow, iLux

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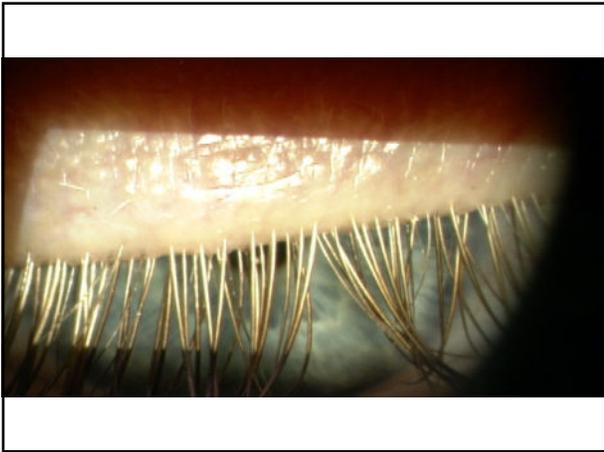


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Case

- Diagnosis?
 - Demodex Blepharitis, Grade 4 (over 150 lashes with collarettes)
- Start Lotilaner 0.25% BID OU x 6 weeks
- RTC 6-8 weeks for follow up

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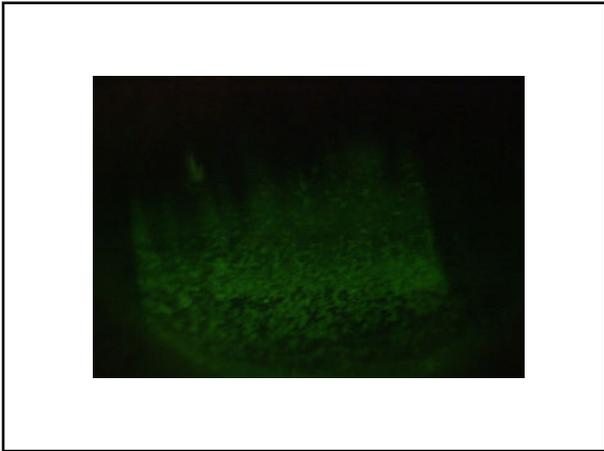


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Case

- Lids look much improved
 - 2 collarettes each lid (grade 0)
 - VA improved to 20/25 OD and OS
 - Speed down to 12
- Significant residual SPK OU
 - Symptoms still persist of DED,
 - SFA (perfluorohexyloctane) due to persistent SPK
 - QID (BID-TID w Contact lens wear)
 - RTC 4-6 weeks

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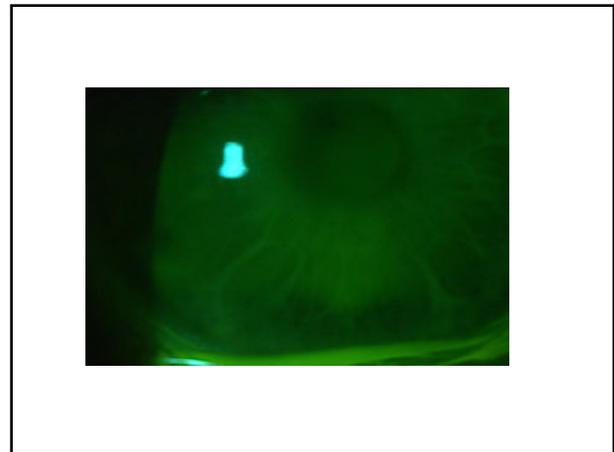


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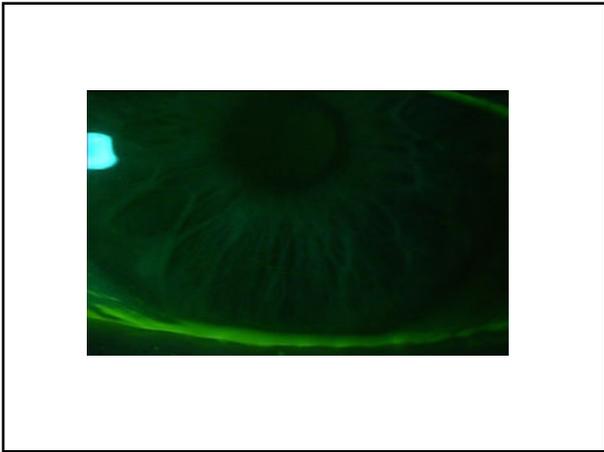
Case

- 1 month follow up
 - BCVA 20/20 OD and OS
 - Quality of vision is improved
 - Resumed CL wear successfully
- Decreased to BID OU while wearing CL's

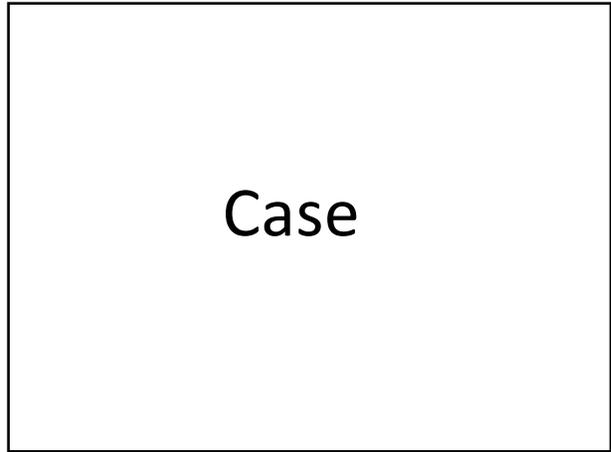
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29-year-old WF with complaints of fluctuating vision, irritated eyes, and some redness. She owns a flower business, but states this has never been a problem in the past. I am tired of wearing my contact lenses and is interested in refractive surgery.

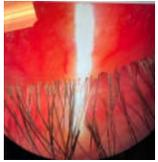
PMHx: Unremarkable
 POHx: Contact Lenses x 14 years
 Systemic Meds: None
 Topical Meds: AT's off and on
 Allergies: NKDA
 FMHx: None
 Social Hx: Nothing to report



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SPEED: 6/28
 BCVA: 20/15 right eye (OD), 20/15 left eye (OS)
 MRX: -3.50 both eyes (OU)
 IOP: 12 mmHg right eye (OD), 12 mmHg left eye (OS)
 MMP-9 Testing: Positive in both eyes (OU)
 Osmolarity: 300 right eye (OD), 322 left eye (OS)

SLE:
 Lids/Lashes: Refer to photos; minimal meibum secretion observed.
 Conjunctiva/Sclera: Mild injection present in both eyes, no staining detected.
 Cornea: Clear; Tear Break-Up Time (TBUT): 7 seconds in both eyes.
 Anterior Chamber (A/C): Deep and quiet in both eyes.
 Iris: Flat in both eyes.
 Lens: Normal appearance.




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Case Considerations

- OK To Proceed Refractive Surgery?
- How do you educate this patient?
- Treatment Considerations?

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What Was Done

1. Performed heat and gland clearing treatment in both eyes at the clinic
2. Initiated loteprednol twice daily for 1 month in both eyes
3. Began lotilaner twice daily for 6 weeks in both eyes
4. Provided instructions for home maintenance
5. Scheduled return to clinic in 6 weeks for follow-up evaluation

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- The patient reports that their vision appears better.
- Best Corrected Visual Acuity (BCVA):
- 20/15 in both right eye (OD) and left eye (OS)
- Intraocular Pressure (IOP): 14 mmHg in both OD and OS
- Osmolarity: 300 in both OD and OS

- SLEx:
- Lids/Lashes: See attached photo; Meibum secretions have improved.
- Conjunctiva/Sclera: Clear with no signs of injection or staining.
- Cornea: Clear; Tear Break-Up Time (TBUT): greater than 10 seconds in both eyes
- Anterior Chamber (A/C): Deep and quiet in both eyes
- Iris: Flat in both eyes
- Lens: Normal

