The Ocular Surface Diseases: Inflammation, Evaporation and Infestation

Ben Gaddie, O.D. FAAO
Chief Medical Officer
Keplr Vision
Gaddie Eye Centers
Louisville, KY

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Financial Disclosures 11/5/2023

- Tarsus-Consultant, Clinical Trials
- Ocusoft-Advisory Board
- Bausch and Lomb-Consultant

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

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

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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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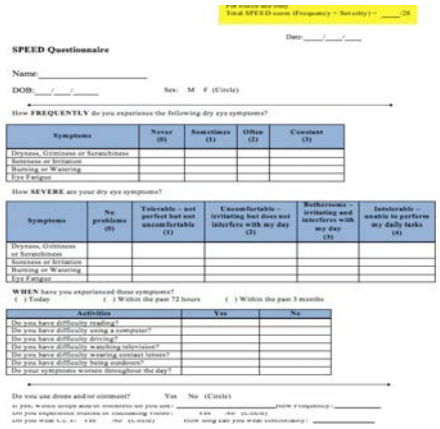

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Basic Ocular Surface Principles

- Despite the statistics that are constantly repeated, 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]

1. Bron AJ, et al. *Ocul Surf*. 2017;15(3):438-510. 2. McMonnies CW. *Eye Vis (Lond)*. 2020;7:6. 3. Costa A, et al. *Invest Ophthalmol Vis Sci*. 2019;60(9):6793. 4. Arita R, et al. *Am J Ophthalmol*. 2016;169:125-137. 5. Alshammeri S, et al. *Clin Exp Optom*. 2020;103(4):469-473. 6. Kawashima M, et al. *Adv Ther*. 2017;34(3):732-743. 7. Tsubota K, et al. *Ocul Surf*. 2017;15:65-76. 8. Wolffsohn JS, et al. *Ocul Surf*. 2021;21:59-63. 9. Wang MTM, et al. *Cont Lens Anterior Eye*. 2021;44(6):101409. 10. Ashkenazi I, et al. *Clin Ophthalmol*. 2021;15:3811-3820. 11. Pflugfelder SC, et al. *Ophthalmology*. 2017;124(11S):S4-S13. 12. Zhang R, et al. *Ocul Surf*. 2021;21:145-159. | DED, dry eye disease

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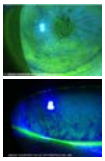
In Aqueous Deficiency, Tear Evaporation Exceeds Available Supply

With low aqueous volume, **tear film integrity may be disrupted rapidly between blinks**, even with a normal lipid layer

Aqueous deficiency may be associated with

- Reduced tear meniscus[2,3]
- Slower tear turnover[2]
- Tear film instability[4,5]
- Ocular surface staining[5]



1. McMonnies CW. *Eye Vis (Lond)*. 2020;7:6. 2. Alshammeri S, et al. *Clin Exp Optom*. 2020;103(4):469-473. 3. Wang Y, et al. *Transl Vis Sci Technol*. 2022;11(3):15. 4. Eom Y, et al. *Jpn J Ophthalmol*. 2021;65(2):261-270. 5. Kawashima M, et al. *Adv Ther*. 2017;34(3):732-743.

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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
  - 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 immunomodulaters
  - 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

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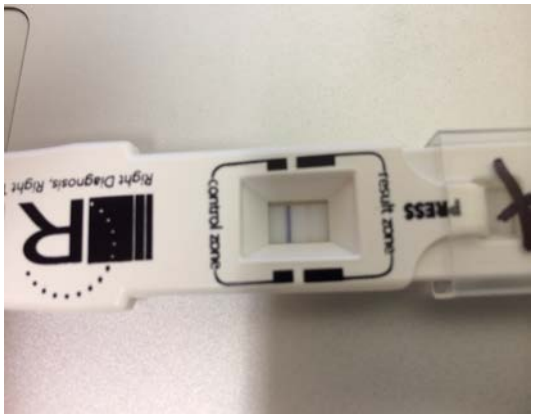

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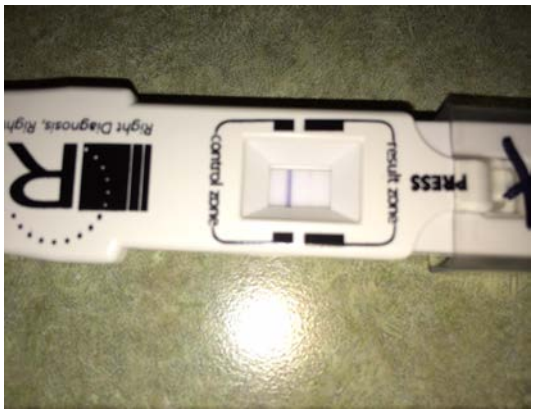

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Tear Film Osmolarity

- 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

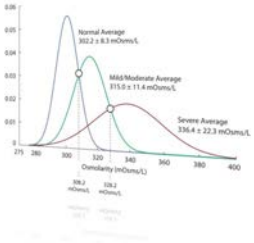
Dry Eye Diagnosis

Santosh Khanal,[1] Alan Tomlinson,[1] Angus McFadyen,[2] Charles Diaper,[3] and Kannu Ramaesh[4]

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/iovs.07-0635



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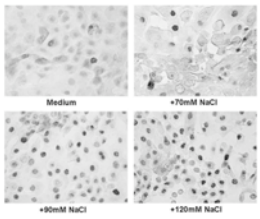
Hyperosmolarity & Ocular Surface

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**



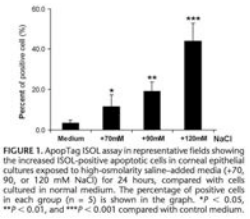


FIGURE 1. ApopTag ISOL assay in representative fields showing the increased ISOL-positive apoptotic cells in corneal epithelial cultures exposed to high-osmolarity saline–added media (+70, 90, or 120 mM NaCl) for 24 hours, compared with cells cultured in normal medium. The percentage of positive cells 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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Tear Hyperosmolarity

- Hyperosmolarity stimulates a cascade of inflammatory events on the ocular surface
  - IL-1alpha
  - TNF-alpha
  - MMP 9
- Can lead to surface cell apoptosis, including the goblet cells

Reference: DEWS Report 2007-The Ocular Surface

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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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Prevalence of Abnormal Tear Film Quality in Contact Lens Wearers

- 273 consecutive CL subjects across 7 OD sites
- Subject discomfort symptoms and tear osmolarity measured
- Abnormal osmolarity in 59% (161/273)
  - Symptomatic: 70%
- Symptomatic: 68.9% (188/273)
  - Abnormal osmolarity: 60.1%
    - (3/5 symptomatic CL wearers have abnormal osmolarity)
- 85 patients were asymptomatic and 54.6% (48/85) had abnormal osmolarity

Parameter	Normal Osm (n= 112)	Abnormal Osm (n=161)
Age (yrs)	37.4 ± 12.4	39.0 ± 14
Gender	M 38 F 74	M 53 F 108
Osmolarity (mOsm/L)	295.3 ± 7.6	315.3 ± 19.2
Inter eye diff (mOsm/L)	3.8 ± 2.6	19.1 ± 15.4
Symptomatic (≥ 3)	75 (67.0%)	113 (70.2%)
Median # of symptoms	4	6

Bowling E, Bloomenstein M, Gaddie I, Clay G, Harrell M, Ward J, Brimer C. Prevalence of Abnormal Tear Film Quality and Stability Measured by Abnormal Tear Osmolarity Among Contact Lens Wearers, presented at American Academy of Optometry; Anaheim, Calif.; Nov. 8-13, 2015.

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Tear Osmolarity in the Diagnosis and Management of Dry Eye Disease

MICHAEL A. LEMP, ANTHONY J. BRON, CHRISTOPHE BAUDOUIN, JOSÉ M. BENÍTEZ DEL CASTILLO, DAVID GEFFEN, JOE TAUBER, GARY N. FOULKS, 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 82 years of age. Bilateral tear osmolarity, tear film break-up time (TBUT), corneal 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 mOsms/L, whereas the most specific was found at 315 mOsms/L. At a cutoff of 312 mOsms/L, tear hyperosmolarity exhibited 73% sensitivity and 92% specificity. By contrast, the other common tests exhibited either poor sensitivity (corneal staining, 54%; conjunctival staining, 60%; meibomian gland grading, 61%) 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,[4] 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.[2] Further, microliter volumes are not available

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TABLE 1. Sensitivity and Specificity of Objective Clinical Signs of Dry Eye Disease[a]

Test	Cutoff	Sensitivity (n = 224)	Specificity (n = 75)
Osmolarity	>311 mOsms/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.
[a]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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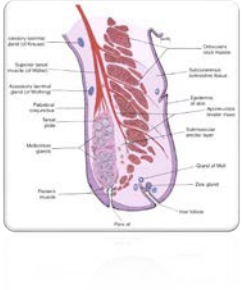
Meibomian Gland Anatomy

Meibomian gland function is regulated by:

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



http://www.slideserve.com/tana-mccall/tear-film-lacrimal-and-meibomian-glands

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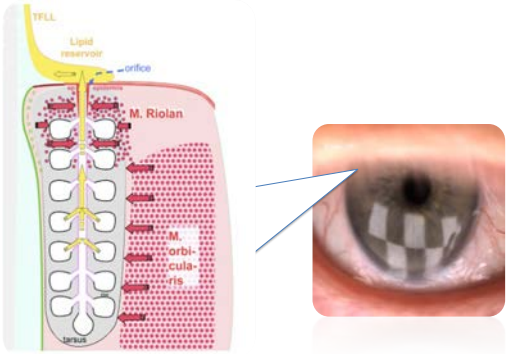

Courtesy of Dr. David Kading

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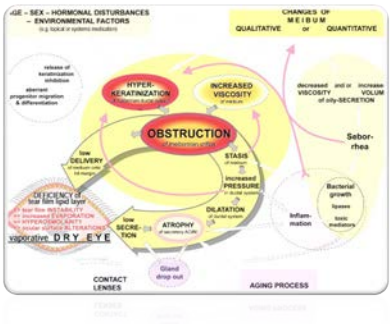

From: The International Workshop on Meibomian Gland Dysfunction: Executive Summary
Invest. Ophthalmol. Vis. Sci.. 2011;52(4):1922-1929. doi:10.1167/iovs.10-6997a

ARVO | JOURNALS

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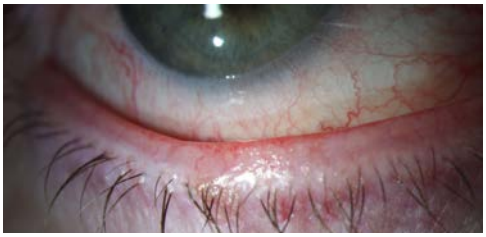
What is MGD?

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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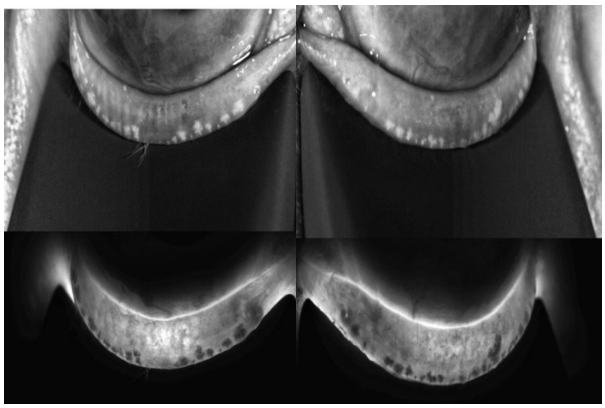

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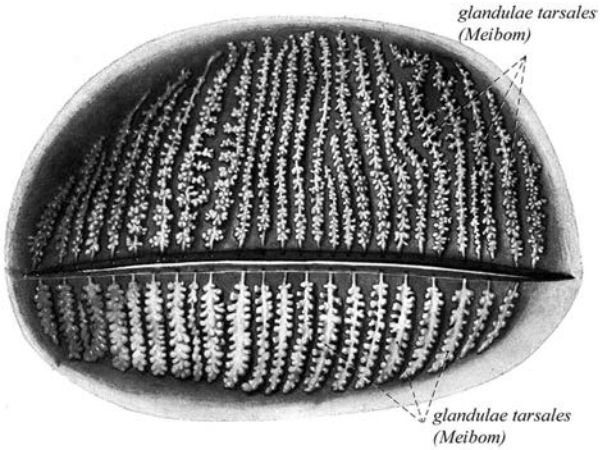

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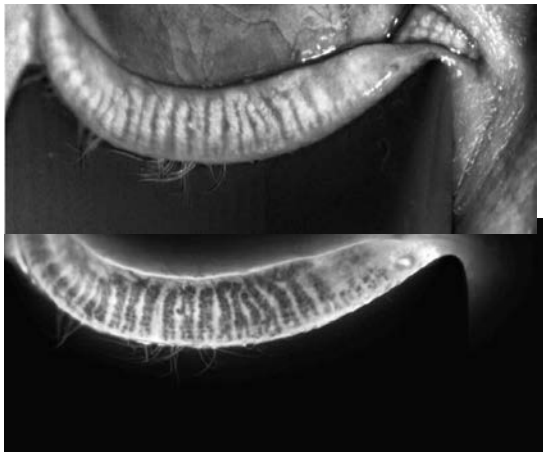

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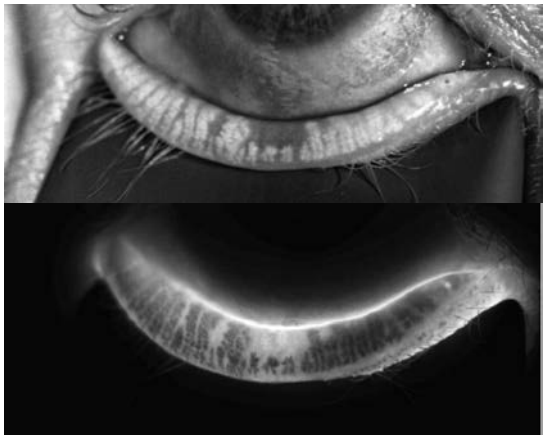

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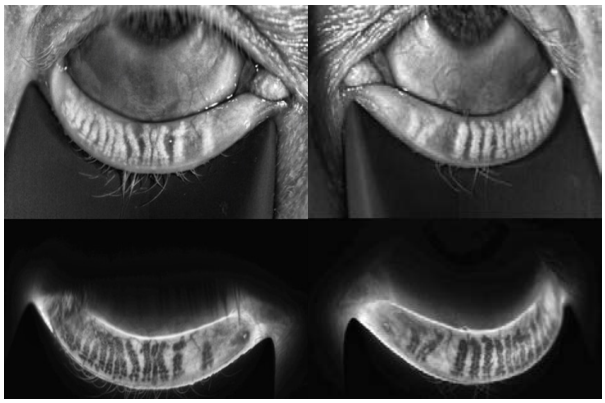

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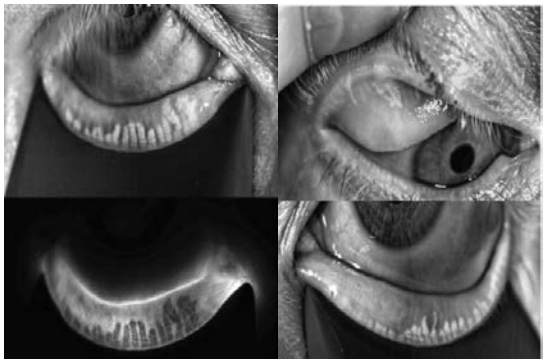

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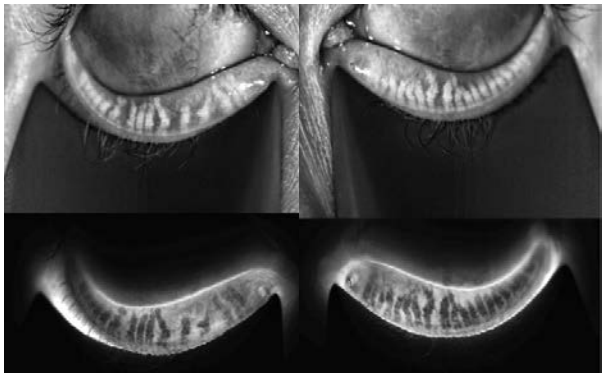

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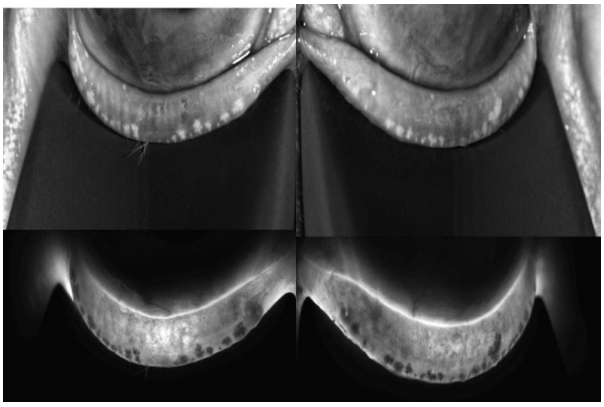

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OCuSOFT® Thermal 1-Touch™

Localized Heat Therapy

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Unique Features

- Low Corneal Pressure
- 100% Portable
- Treats All 4 Eyelids Simultaneously
- Fits All Face Shapes & Sizes
- Can be Administered by Staff

"EASY AS PUTTING ON GLASSES"

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Three Preset Times and Temperature Modes

Temperature Setting	Maximum Time	Eyelid Tissue Temperature Post Treatment
High	10 Minutes	43-44˚C (110˚F)
Medium	15 Minutes	41-42˚C (108˚F)
Low	30 Minutes	39-40˚C (103˚F)

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Thermal expression

- TearCare
- iLux
- LipiFlow
- Ocusoft Thermal 1 Touch

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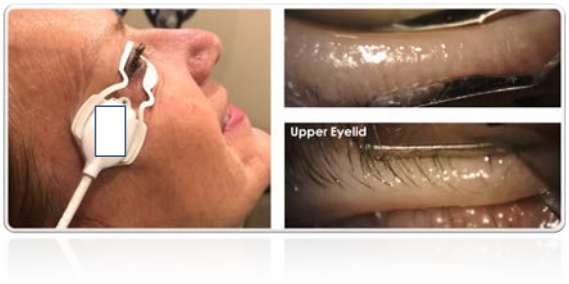
Thermal expression



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Thermal expression

TearCare Pilot Study
Initial 6-month data published in Clinical Ophthalmology, April 2018

Purpose: Preliminary Assessment of the Long-Term Safety & Effectiveness of the TearCare System in the Treatment of the Signs & Symptoms of Dry Eye Disease

- Single Center, prospective, randomized, controlled trial
- 24 Subjects followed for 6 months
  - 12 TearCare subjects
  - 12 Warm Compress subjects (5 minutes daily for 1 month)
- All 12 original TearCare subjects were re-treated at 7 months and followed for another 6 months

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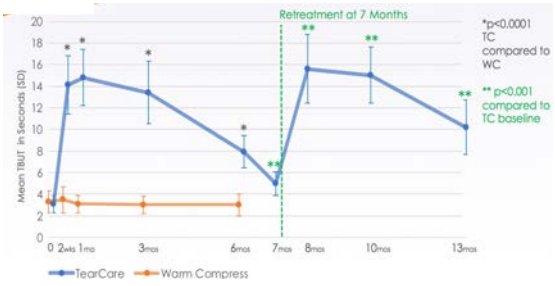
TearCare Thermal expression



TearCare Pilot Study
Initial 6-month data published in Clinical Ophthalmology, April 2018

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TearCare Thermal expression

TearCare Pilot Study
Initial 6-month data published in Clinical Ophthalmology, April 2018

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TFI/iLux Thermal expression

- Magnifier allows for visualization of glands during treatment
- Warms the eyelid tissue within a therapeutic target
- Applies compression to express meibum
- Amount of heat and pressure control of the user

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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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TFI/iLux Thermal expression

Non-Inferiority of MGD Treatment Relative To LipiFlow[1]

Meibomian Gland Score (MGS) Significantly Improved From Baseline at Week 2 and Week 4 After Treatment With iLux

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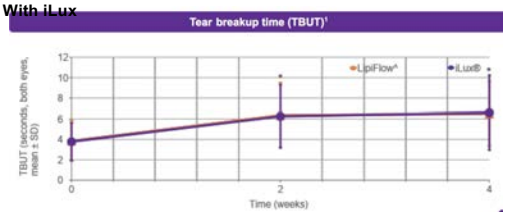
TFI/iLux Thermal expression

Tear Breakup Time (TBUT) Significantly Improved From Baseline at Week 2 and Week 4 After Treatment With iLux



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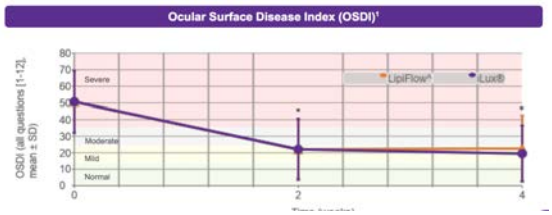
TFI/iLux Thermal expression

Ocular Surface Disease Index (OSDI) Significantly Improved From Baseline at Week 2 and Week 4 After



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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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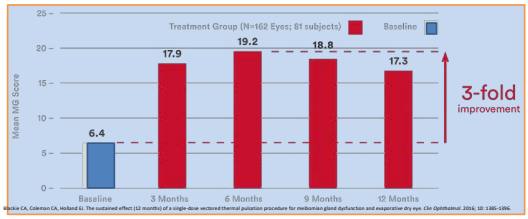
Lipiflow Vectored thermal pulsation

12-Month Cohort with 1 LipiFlow Treatment.

For the 86% of treatment group subjects who received one LipiFlow® treatment, a sustained mean improvement in meibomian gland function was observed from Baseline (6.4 ± 3.7) to 12 Months (17.3 ± 9.1) (p<0.0001).



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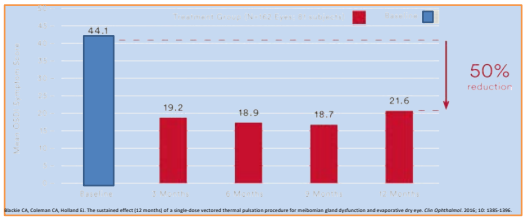
Lipiflow Vectored thermal pulsation

1 Treatment was Effective for 1 Year in Most Patients.[1]

LipiFlow: Improves dry eye symptom score. For 86% of treatment group subjects who received only one LipiFlow treatment, a sustained mean improvement in dry eye symptom score was observed from Baseline (44.1 ± 20.4) to 12 Months (21.6 ± 21.3) (p<0.0001).[1]



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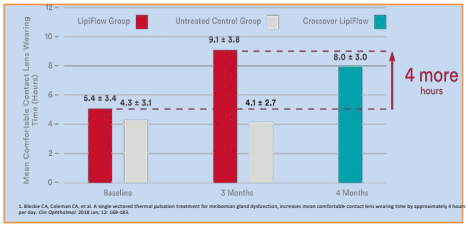
Lipiflow Vectored thermal pulsation

LipiFlow: Increased Patient Comfortable Contact Lens Wear Time by Approximately 4 Hours on Average per day, Doubling Pre-treatment Findings[1]

LipiFlow group had a significantly greater mean increase in comfortable lens wear time than control from baseline to 3 months (p<0.0001).



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Intense Pulse Light

- Non-laser high intensity light source
- High-output flashlamp to produce broad wavelength of non-coherent light
- Light pulse produced by electrical current passing through a xenon gas-filled chamber
- Energy pulse goes through a sapphire or quartz block
- Operator controls: duration, intensity and spectral distribution

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Intense Pulse Light

Three main chromophores:

- Hemoglobin
- Water
- Melanin

http://www.lumidermaskincare.com/content/cosmetics/science.html

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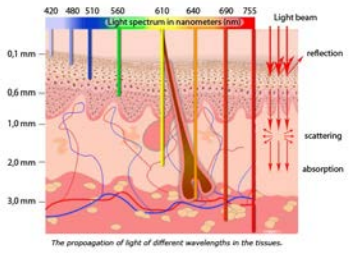
Intense Pulse Light



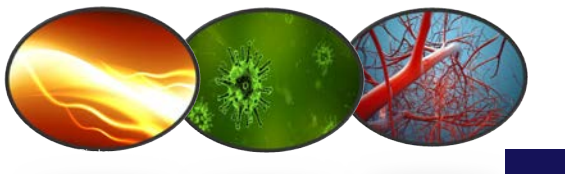
The propoagation of light of different wavelengths in the tissues.

62

Intense Pulse Light

Proposed Mechanism of Action:

- Thermal response
- Decreased bacterial load
- Telangiectasia reduction at lid margin



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IPL AND "THE LITERATURE"

- Lei Y, Peng J, Liu J, Zhong J. Intense pulsed light (IPL) therapy for meibomian gland dysfunction (MGD)-related dry eye disease (DED): a systematic review and meta-analysis. Lasers Med Sci. 2022 Dec 19;38(1):1. doi: 10.1007/s10103-022-03690-1. PMID: 36534219.


ORIGINAL ARTICLE

Intense pulsed light (IPL) therapy for meibomian gland dysfunction (MGD)–related dry eye disease (DED): a systematic review and meta-analysis

Yahui Lei[1] · Jing Peng[2] · Jiayan Liu[1] · Jingxiang Zhong[1,3]

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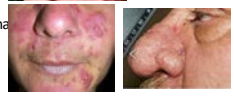
Historically Rosacea (a chronic skin condition) was classified into 4 subtypes: New system is 2 Diagnostic Phenotypes

- Erythematoustelangiectatic
- Papulopustular
- Phymatous
- Ocular

- Fixed centrofacial erythema
- Phymatous changes
  - Papules & Pustules
  - Flushing
  - Telangiectasia
  - Ocular Manifestations



Gallo RL, Granstein RD, Kang S, et al. Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol* 2017 Oct 28. pii: S0190-9622(17)32297-1. doi: 10.1016/j.jaad.2017.08.037.

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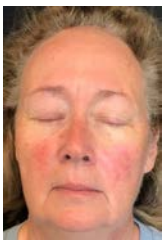
Erythematous-Flushing, Telangiectasia



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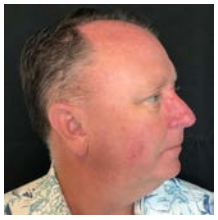
Papulopustular-Papules and pustules



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IPL Treatment

- Face
- Neck
- Décolleté
- Hands
- Up to Fitzpatrick IV-very carefully!

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Skin Assessment

- Fitzpatrick Skin Type
- Amounts of Target Chromophore and Competing Chromophore
  - What's a Chromophore?
    - Water, Pigment, Oxyhemaglobin
- Any active sun or lamp exposure
- Ethnicity
- Thickness of skin
- Overall skin health
- Medical history
- Medication Review
- **THIS NEEDS TO BE DONE BEFORE EVERY TREATMENT**

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Contraindications

- Treatment should not be attempted on patients with the following conditions in the treatment area:
  - Active infections
  - Dysplastic nevi
  - Significant concurrent skin conditions or any inflammatory skin conditions
  - Active cold sores, open lacerations or abrasions
  - Chronic or cutaneous viral, fungal, or bacterial diseases
  - Exposure to sun, remaining suntan or artificial tanning in the 3-4 weeks pre-op plan
  - Tattoos
- Treatment should not be attempted on patients with a history of skin cancer or pre-cancerous lesions on the treatment area

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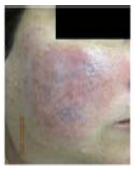
Pulse Durations

- **Pulse durations** are selected to slowly heat vessels to coagulation while avoiding purpura. This allows patients to return to normal activities quickly rather than suffering from purpura for one or two weeks. (PDL-Pulse Dye Laser is notorious for this)



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Energy Levels

- **Energy levels** (fluence in J/cm2) are governed by clinical response. If tissue reactions do not occur, fluence levels may be increased by 1 J/cm2 (Lumenis One) or 2 J/cm2 (VascuLight SR or Quantum IPL [Lumenis, Inc.]). A good rule of thumb is to use mild to moderate erythema as the treatment end point. (If target is pigment-1-2 shades darker)
- Vessels should blur or disappear-no purple

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Treatment Aggressiveness

- Less Aggressive
  - Higher cut-off filter
  - Lower fluence
  - Higher pulses
  - Longer delay
  - Eg. 590 nm, Triple pulse, 6 m/s delay, 4 ms
- More Aggressive
  - Lower cut-off filter (meaning treat longer wavelengths and more superficial treatment)
  - Higher fluence
  - Shorter Delay
  - Fewer Pulses
  - Eg. 515 nm, single pulse, 4 ms

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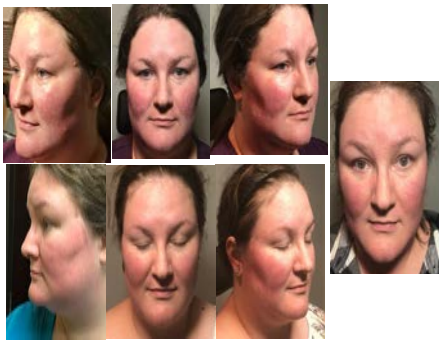

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Treatment Settings
Treating deep & large to smaller & more superficial

- First Pass I did: medium to deep depth 590 nm, triple pulse, 3ms-30 ms 20 J/cm ^{2}
- 2nd pass Shallow depth 560 nm, triple pulse, 3.0ms 25ms 18 J/cm^2
- Toyos settings over V2 with double pass
  590 filter, triple pulse 6.0 msec pulse, 50msce rest, 12 J/cm^2
- Eyelids-Periman Protocol **LASER Grade Corneal Shields!**
  Small rectangle light guide 3 pulses per lid with double pass,
  Stay 2 mm away from the lash line (Total 24 pulses)
  590 filter, triple pulse 5.0 msec pulse, 50msec rest,10-14 J/cm^2

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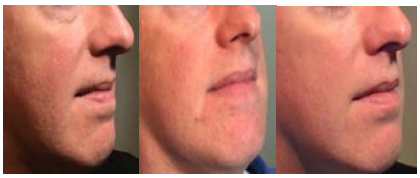
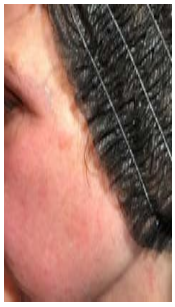
After 3 treatments



- First Pass is medium to deep depth (590 nm)
- Triple pulse 3.5 ms PD, 25ms D, 21J/cm^2
- Second pass was 560 nm, triple pulse, 3.5ms, 20 ms and 19 J/cm^2
- Toyos settings over V2 with double pass
  - 590 filter, triple pulse 6.0 msec pulse, 50ms rest, 12 J/cm^2
- Eyelids-Periman Protocol **LASER Grade Corneal Shields!**
  Small rectangle light guide 3 pulses per lid with double pass,
  Stay 2 mm away from the lash line (Total 24 pulses)
  590 filter, triple pulse 5.0 msec pulse, 50msce rest.10-14 J/cm^2

76



Lentinges-Spot Treat with 6mm circle
- Pigment Lesion Menu
- Type II
- Lentigines
- Light
- Epidermal
- 515 nm filter, Single Pulse, 4.0 msec pulse, 19.0 J/cm^2
- Clinical endpoint the pigment will **Immediately** turn darker-Salmon colored

Telangiectasia's-Spot treat with 6 mm circle
- Vascular Lesion Menu
- Skin Type II
- Circle
- Facial Telang
- Shallow or Medium
- Vacular Filter, Double Pulse, 3.5 ms 15 ms 28 J/cm^2
- Clinical endpoint-Vessel vaporizes-very satifsfying☺

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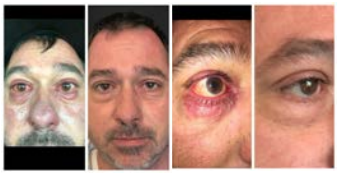
Ectopic Dermatitis



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Intense Pulse Light

Analysis of Cytokine Levels in Tears and Clinical Correlations After Intense Pulsed Light Treating Meibomian Gland Dysfunction

Purpose: To investigate the change from baseline of inflammatory markers in tears of dry eye disease (DED) subjects owing to MGD after IPL and MG expression compared to sham and correlations with OSD parameters

All of the inflammatory markers declined in value compared to baselines.

- IL-17A and IL-6 showed statistically significant decreases
- PGE2 showed statistically significant decreases compared to sham at week 12
- The study results suggest that IPL can significantly reduce inflammatory [illegible] after IPL

Analysis of Cytokine Levels in Tears and Clinical Correlations After Intense Pulsed Light Treating Meibomian Gland Dysfunction. RuixingLiuaBeiRongaPingTubYunTangaWenjingSongaRolandoToyoscMelissaToyoscXiaomingYang. American Journal of Ophthalmology Volume 183, November 2017, Pages 81-90

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How does IPL actually work? What is it doing to the tissues?

- Photocoagulation
- Photoimmunomodulation
- Photomodulation
- Photothermolysis
- Photosanitization

Emerging strategies for the diagnosis and treatment of MGD: Proceedings of the OCEAN group meeting. *Ocular Surface* 2017;15:179-191

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Newer Ocular Surface Treatments and Procedures

- Perfluorohexylocatane (Miebo)
- Perfluorobutylpentane + Cyclosporine .1% (Veyve)
- Lotaliner (Xdemvy)

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Perfluorohexylocatane (Miebo) Demonstrated Consistent Results Across Clinical Trials

Two phase 3 studies evaluating the safety and efficacy of MIEBO for the treatment of DED

- Multicenter
- Randomized
- Double-masked

100% of participants had DED and clinical signs of MGD

GOBI N=597 | MOJAVE N=620

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

614 participants received MIEBO

OUTCOMES

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

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100% of Patients in the Trial Had DED and Clinical Signs of MGD

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
≥6 month self-reported history of DED tCFS score 4 to 11 Total MGD score ≥3 Based on secretion of 5 central glands on lower eyelid Each scored from 0 to 3 0 = normal 1 = thick yellow/whitish particulate 2 = paste 3 = no expression/occluded	Active blepharitis Contact lens wear Recent history of punctal plugs or MGD procedure Use of topical steroids, other Rx DED drugs, serum tears, or glaucoma medications Other dry eye products (incl. artificial tears) or TrueTear™ device

Tauber J, et al. Ophthalmology. 2022;130(5):516-524. Sheppard JD, et al. *Am J Ophthalmol*. 2023;252:265-274. | DED, dry eye disease; MGD, meibomian gland dysfunction; tCFS, total corneal fluorescein staining score

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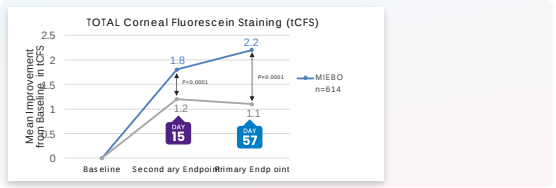
Rapid and Sustained Improvement in Total Corneal Staining as Early as Day 15 Through Day 57



Pooled data | tCFS Grading Scale: 0-15 (0-3 in each of 5 areas) | Mean Baseline = 6.9 | At day 57, Mean (SD) CFB GOBI: –2.0 (2.6) for MIEBO (n=289) vs –1.0 (2.7) for saline (n=279) (*P*<0.001) | MOJAVE: –2.3 (2.8) for MIEBO (n=302) vs –1.1 (2.9) for saline (n=296) (*P*<0.001)

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

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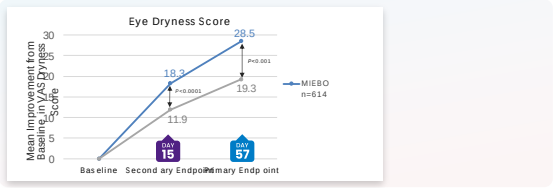
Rapid and Sustained Relief of Eye Dryness as Early as Day 15 Through Day 57



Pooled data | Visual analog scale: 0-100 (0=no discomfort, 100=maximal discomfort) | Mean Baseline, MIEBO = 65.6; Mean Baseline, Saline = 65.5 | At Day 57, Mean (SD) CFB GOBI: –27.4 (27.9) for MIEBO (n=289) vs –19.7 (26.7) for saline (n=279) (*P*<0.001) | MOJAVE: –29.5 (28.6) for MIEBO (n=302) vs –19.0 (27.2) for saline (n=296) (*P*<0.001)

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

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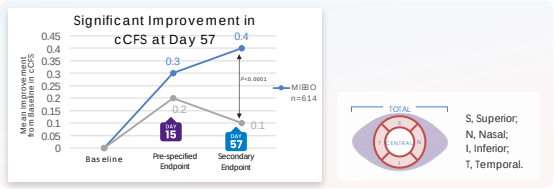
Significant Improvement in Central Corneal Staining at Day 57



Pooled analysis (above): Mean baseline cCFS = 1.1 for MIEBO and control. cCFS grading scale: 0-3. Across GOBI and MOJAVE, 614 patients received MIEBO and 603 patients received control with 591 and 575, respectively, assessed on Day 57. | GOBI: Mean (SD) CFB –0.4 (0.8) for MIEBO (n = 289) vs –0.1 (0.9) for control (n = 279) (*P*<0.001) at Day 57. MOJAVE: Mean (SD) CFB -0.4 (0.8) for MIEBO (n = 302) vs –0.1 (0.9) for control (n = 296) (*P*<0.001) at Day 57

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

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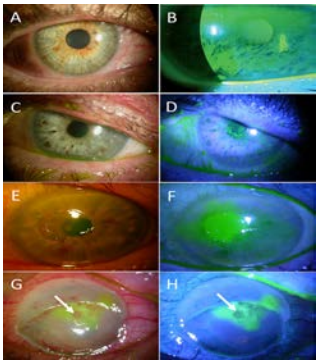
Cenegermin for NK

- 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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Neurostimulation

- Neurostimulation results in endogenous tear production, giving patients a way to manage their DED and gain relief immediately. Specifically, the device targets the trigeminal nerve, which controls the lacrimal functional unit (LFU). This is important because the LFU is responsible for the lacrimal gland and accessory glands, as well as goblet cells degranulating and meibomian gland function.
- Patients that desire a drop-free, drug-free therapy are great candidates, as well as anyone using artificial tears. There is nothing artificial about the tears the body produces on it's own. Since the technology stimulates ALL glands both aqueous-deficient and evaporative benefit.
- Utilize the in-office demo of the unit to create a wow effect and allow patients to experience it for themselves prior to purchase.

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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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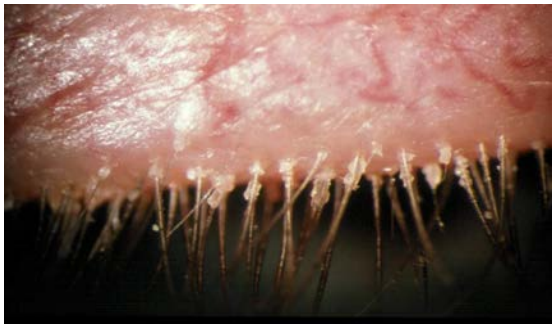
Anterior Blepharitis



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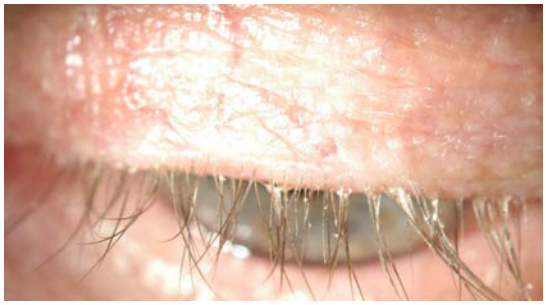

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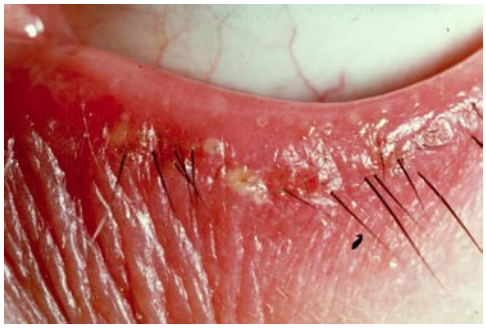

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TFOS DEWS II - Diagnostic Methodology

James S. Wolffsohn, FCOptom, PhD1,*Correspondence information about the author FCOptom, PhD James S. WolffsohnEmail 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, Preeya K. Gupta, MD, Paul Karpecki, OD, Sihem Lazreg, MD, Heiko Pult, 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

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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 epitheliopathy (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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9.2 Anterior blepharitis

Inflammation of the eyelids can result from infection by, or allergic reaction to, external agents. The clinical features of blepharitis include redness, exanthema, sores, eschar, swelling, and bullous formation. Blepharitis is classified according to its anatomic location. Anterior blepharitis affects the base of the eyelashes, eyelash follicles, and/or eyelid skin. Inflammation of follicles is categorized as marginal blepharitis, whereas that of eyelid skin is blepharo-dermatitis. The pathogenesis of anterior blepharitis is infectious or noninfectious in nature, and so the location and cause of the condition should be considered for diagnosis [523]. Clinical features of anterior blepharitis often overlap those of DED [524]. Recurrent or persistent blepharitis can cause DED, thus observation of the eyelid is important for adequate diagnosis of DED. The tear meniscus, tear film breakup time and pattern, foamy discharge and debris in the tear film should be observed [524], along with the eyelid position (i.e., ectropion and entropion), eyelid closure (i.e., lagophthalmos), blink response and the anterior eyelid margin (noting any collarettes around eyelashes). Staphylococcal or seborrheic anterior blepharitis are linked to ADDE [482,524] in 50–75% of cases [525,526], perhaps due to the decreased tear volume supporting less lysozyme or immunoglobulins [526]. Definitive diagnosis is made by identification of the responsible microorganism or allergen. There are no specific clinical diagnostic tests for blepharitis. However, cultures of the eyelid margins may be indicated for patients who have recurrent anterior blepharitis with severe inflammation as well as for patients who are not responding to therapy [524].

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9.3 Demodex

Demodex mites are common elongated microscopic ectoparasites that live on the surface of the human body. Demodex infestation is related to age with 84% of the population at age 60 and 100% of those older than 70 years exhibiting Demodex infestation [527]. Demodex can spread from the face to the eyelids, perhaps leading to blepharitis and also rosacea [527–530], which may be the link between DED and meibomian gland dysfunction [528,531–533]. However Demodex infestation can also be found in asymptomatic patients [529]. Contact lens wearers do not show higher rates of Demodex infestation than non-wearers, but the relationship with DED symptoms and signs has not been investigated [534]. Two species, Demodex folliculorum and Demodex brevis have been identified in human eyelids [529,535,536]. Demodex folliculorum are typically found in the lash follicles of the eyelids, whereas Demodex brevis burrow deep into sebaceous and meibomian glands. Sebum is thought to be their main food source and Demodex mites may consume follicular and glandular epithelial cells, which may lead to direct damage of the lid margin [529]. Demodex mites can cause blepharitis by carrying bacteria on their surface including streptococci and staphylococci [529,537]. Also the protein inside the Demodex mites and their waste products may trigger inflammatory responses, likely via a delayed hypersensitivity or an innate immune response [538]. Demodex-based lid margin inflammation may result in blepharoconjunctivitis [529]. Proper treatment of ocular demodicosis may resolve blepharoconjunctivitis in adults [529,539], however its role in children remains unclear [529]. Severe cases of demodex with inflamed lid margins can affect the cornea [529,540].

Demodex can sometimes be observed in situ with high magnification slit lamp microscopy, on epilated lashes using standard light microscopy or using more advanced techniques, such as IVCM [329,440,528,529,541]. Liu et al. [529] recommend the following clinical procedure based on a comprehensive literature review:

1. Clinical history: high index of suspicion when blepharitis, conjunctivitis or keratitis in adult patients or blepharoconjunctivitis or recurrent chalazia in young patients are refractory to conventional treatments, or when there is madarosis or recurrent trichiasis.
2. Slit-lamp examination: typical cylindrical dandruff at the root of eyelashes.
3. Microscopic confirmation: detection and counting of Demodex eggs, lavae and adult mites on epilated lashes.

To avoid epilating eyelashes it has also been reported that Demodex leave the follicle and are visible by slit lamp microscopy after gentle tension is applied to the lash and the lash manually rotated with forceps, encouraging exodus of the mites and allowing the lash to "scrape out" Demodex deep within the follicle [542]. As Demodex infestation can also occur in non-DED patients [527], its diagnostic contribution is limited.

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An Bras Dermatol. 2020;95(2):187–193

Anais Brasileiros de Dermatologia

INVESTIGATION

Demodex folliculorum infestations in common facial dermatoses: acne vulgaris, rosacea, seborrheic dermatitis☆,☆☆

Ezgi Aktaş Karabay *, Aslı Aksu Çerman

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

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INVESTIGATION

Demodex folliculorum infestations in common facial dermatoses: acne vulgaris, rosacea, seborrheic dermatitis☆,☆☆

Ezgi Aktaş Karabay *, Aslı Aksu Çerman

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

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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 Karincaoglu [1], B Tepe, B Kalayci, 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 5 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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Allergy

Demodex mites
Link to allergic conjunctivitis
Increase secretion cytokine (IL-17)
Stimulates inflammatory or allergic reactions
Resulting ocular surface damage.

Koo H, Kim TH, Kim KW. et.al. Ocular surface discomfort and demodex: effect of tea tree oil eyelid scrub in demodex blepharitis. J Korean Med Sci. 2012 Dec;27(12):1574-9.

Kim JT, Lee SH, Chun YS, Kim JC. Tear cytokines and chemokines in patients with Demodex blepharitis. Cytokine. 2011;53:94–99.

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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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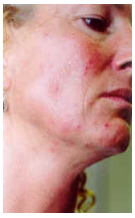
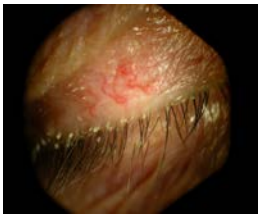
Demodex Has Been Linked to Rosacea and Blepharitis

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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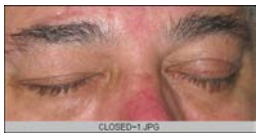
Demodex Infestation is Associated with Floppy Eyelid Syndrome (4)

- floppy, rubbery and easily everted upper eyelids
- lacrimal gland prolapse
- ptosis/lash ptosis
- dematochalasis
- eye lid hyperpigmentation.
- papillary conjunctivitis.
- squamous metaplasia and keratinization in meibomian glands/gland dysfunction
- lax lids have diminished lipid production
- associated with obstructive sleep apnea



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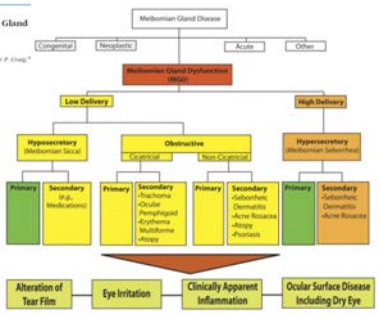
Classifications of MGD



IOVS, 2011

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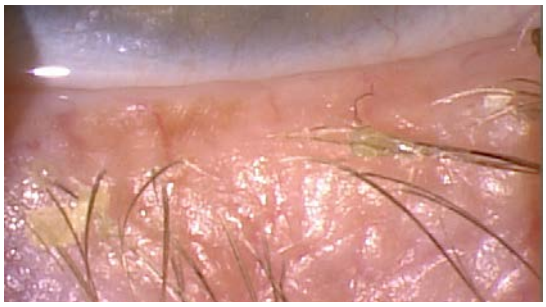
Seborrheic Blepharitis



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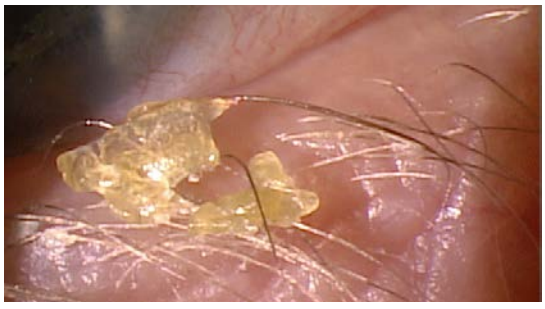

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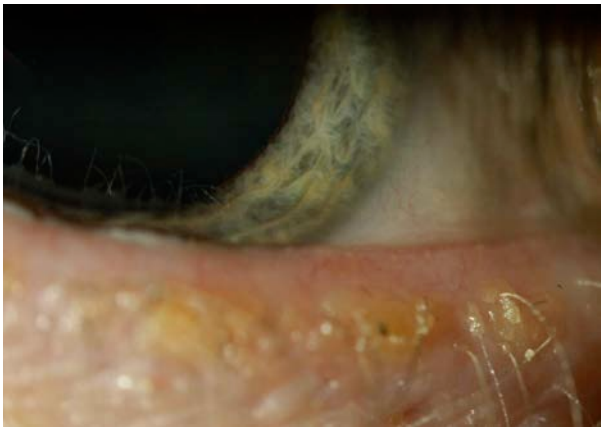

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Rosacea

- Erythema
- Telangiectasia
- Pustules
- Prominent sebaceous glands
- Rhinophyma

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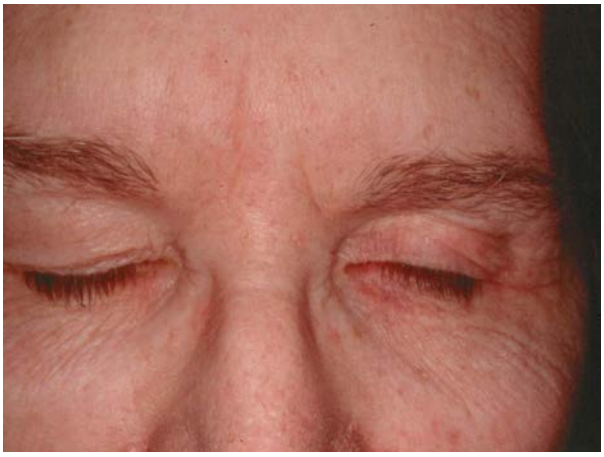

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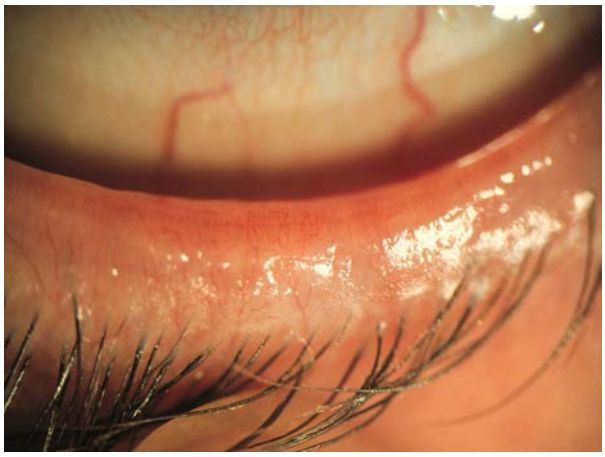

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What Do We Know?

- 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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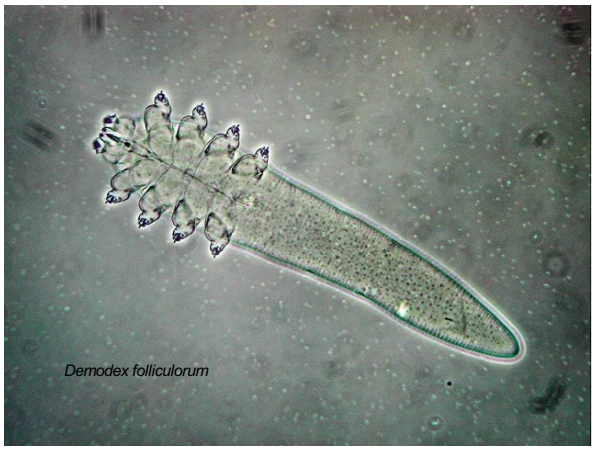

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Slide courtesy of
Scheffer Tseng, MD
Ocular Surface Center
Miami Florida

Epilated lash with attached *Demodex folliculorum*

Demodex folliculorum

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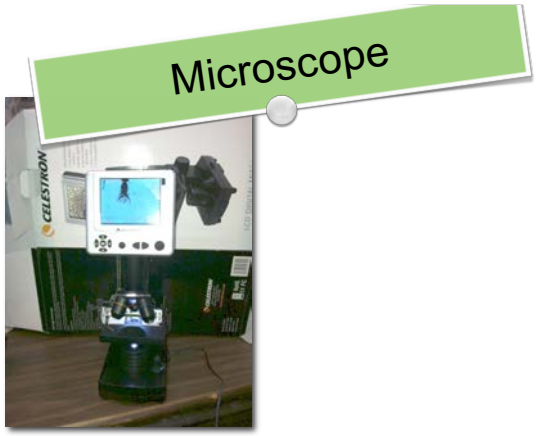

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Demodex

Tip sheet

Drop cover slip first, then add emulsion drop at the side

Show and tell

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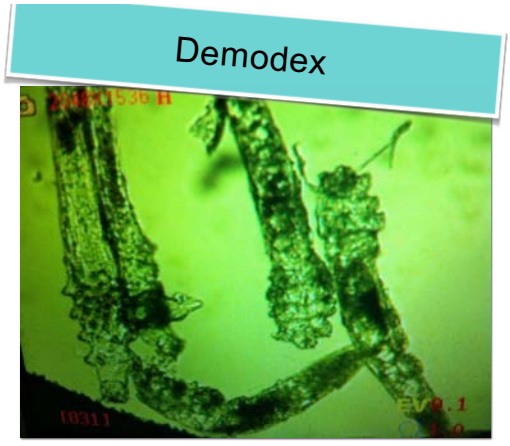

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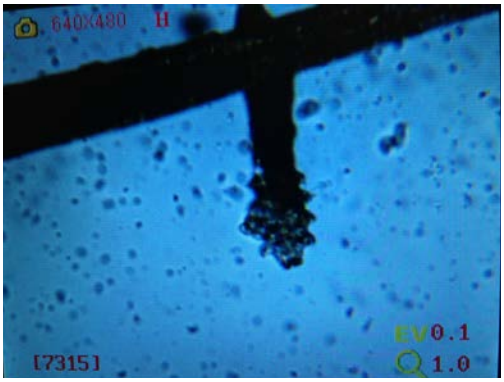

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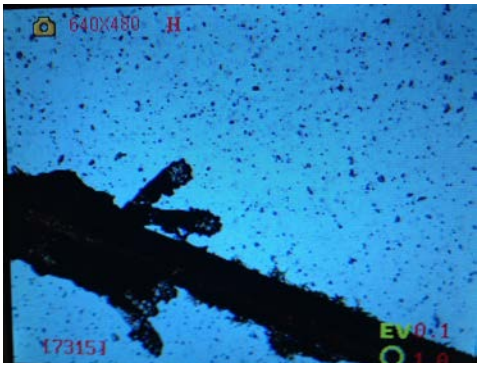

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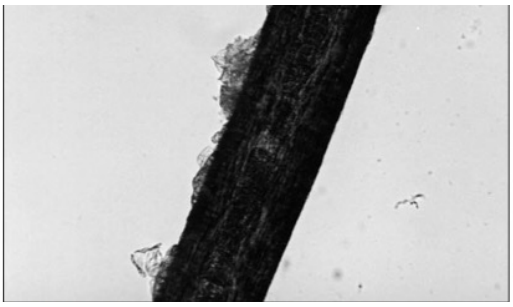

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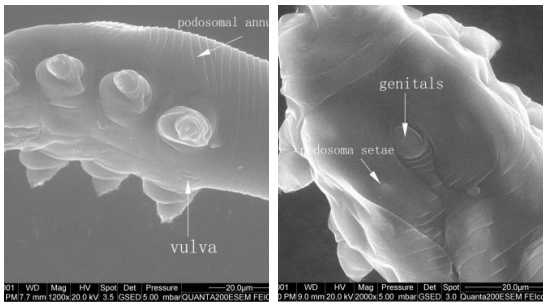
The Sexes

Fig. 3, Fig. 4



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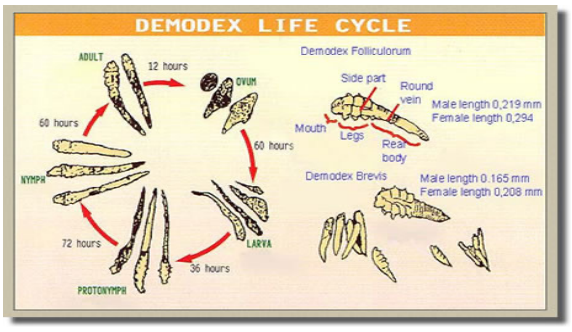
Demodex Life Cycle



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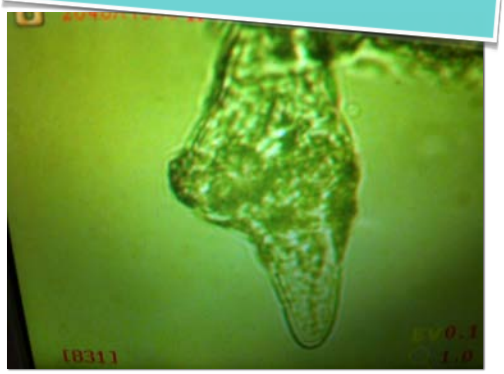
Demodex



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Clinical history

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

Hom MM, Mastrota KM, Schachter SF. 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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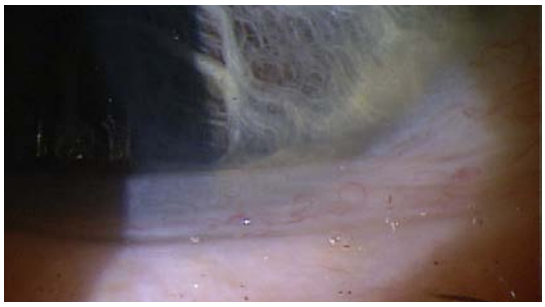
Redundant Conjunctival Folds



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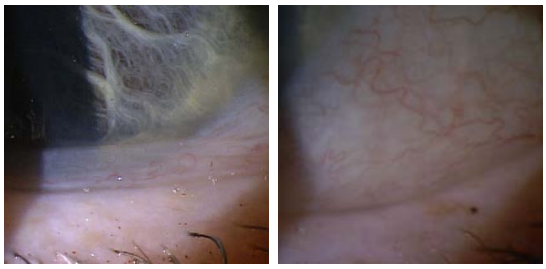

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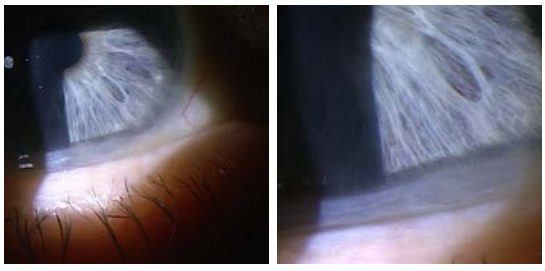

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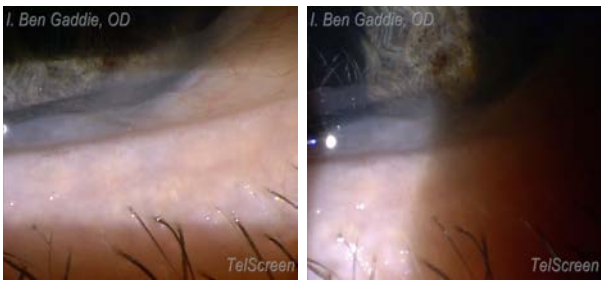

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2. Slit lamp evaluation

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Cylindrical dandruff

"Cylindrical dandruff was pathognomonic for the presence of demodex infestation."

Gao YY. Di Pascuale MA. Li W. et.al. High Prevalence of Demodex in Eyelashes with Cylindrical Dandruff. Invest. Ophthalmol. Vis. Sci. 2005;46(9):3089-3094.

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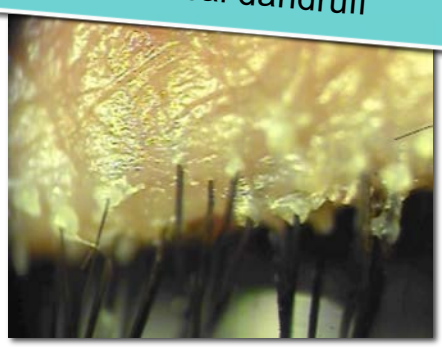
Cylindrical dandruff



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Collarettes Are the Pathognomonic Sign of *Demodex* Blepharitis

Confirming the presence of **collarettes** can be used to confidently make a diagnosis

- In a clinical study, ***Demodex* mites, detected via epilation, were found on 100% of lashes with collarettes**[1]
- In another clinical study, ***Demodex* mites, detected via molecular technique (PCR), were found on 100% of lashes with collarettes**[2]

Collarettes are composed of mite waste and eggs

- Regurgitated undigested material combined with epithelial cells, keratin, mite eggs, and digestive enzymes, which cause irritation[3,4]
- Translucent, waxy plugs typically at base of lashes[3]

Photos courtesy of Elizabeth Yeu, MD, Paul Singh, MD, Paul Karpecki, OD. Used with permission.

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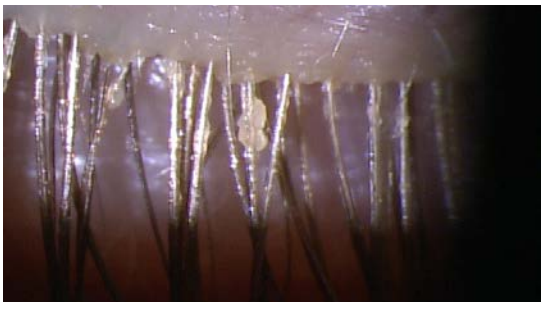
1. Gao YY, Di Pascuale MA, Li W, et al. High prevalence of Demodex in eyelashes with cylindrical dandruff. Invest Ophthalmol Vis Sci. 2005;46(9):3089-3094. 2. Kheirkhah A, Casas V, Li W, et al. Corneal manifestations of ocular demodex infestation. Am J Ophthalmol. 2007;143(4):640-643. 3. Nicholls SG, Oakley CL, Tan A, Vote BJ. Demodex species in human ocular disease: new clinicopathological aspects. Int Ophthalmol. 2017;37(1):303-312.



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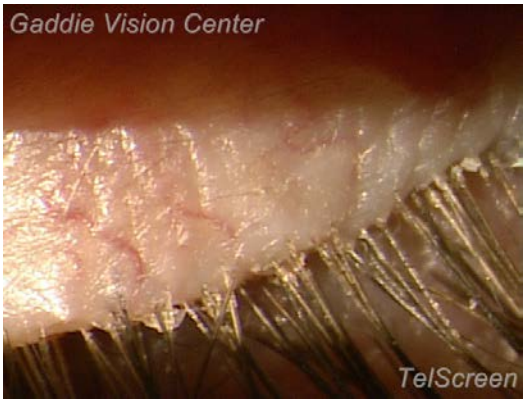

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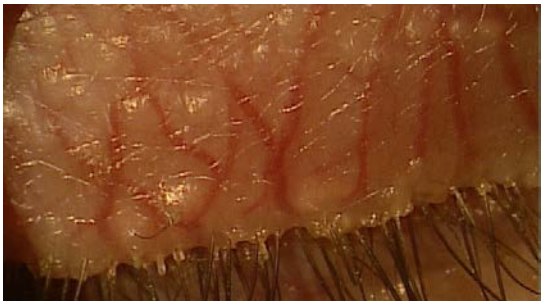

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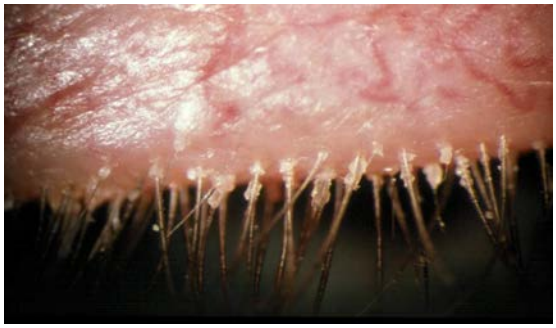

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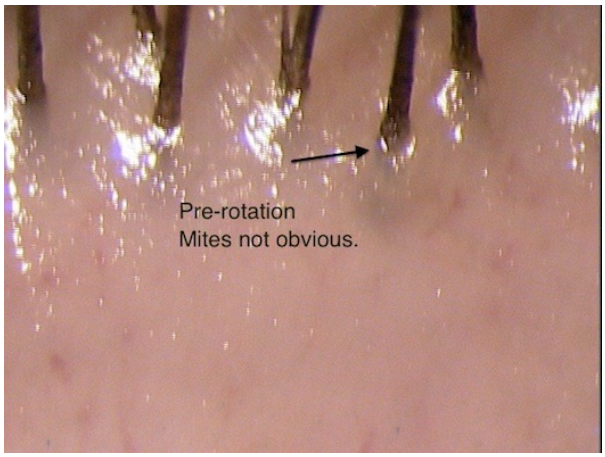

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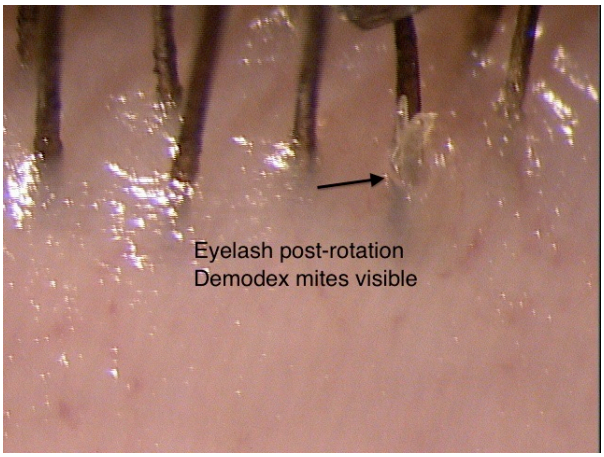

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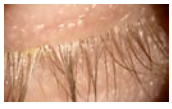
Collarettes Are Pathognomonic Sign of Demodex Infestation

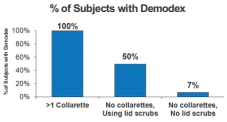
Collarettes Are Composed of Mite Waste Products and Eggs[1]

- 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. Potential 2016
2. Donnenfeld, Ophthalmology and Vis Sci, September 2005, Vol. 46, No. 3089-3094.
3. Tarsus Collarette Prevalence Study

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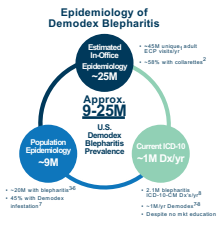
Blepharitis Is a Large and Underserved Market in Eye Care



Large Patient Population with Significant Disease Impact	**Titan** (collarette clinic prevalence) and **Atlas** (disease impact) studies demonstrate high prevalence of disease and significant burden on patients
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.[9]
Blepharitis Can Lead to	Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the cornea[9]
Concomitant Dry Eye	Significant overlap in **Dry Eye** patients. Demodex prevalent in ~69% of DE patients[3]
Blepharitis and Surgery	Important factor for maximizing surgical outcomes: 67% of **Cataract Patients** have Demodex blepharitis[6]
Contact Lens Drop-out	Studies have shown a direct correlation between Demodex blepharitis and **Contact Lens** intolerance[10]
Prescription Treatment	None; 81% of patients currently seeking treatment[11]

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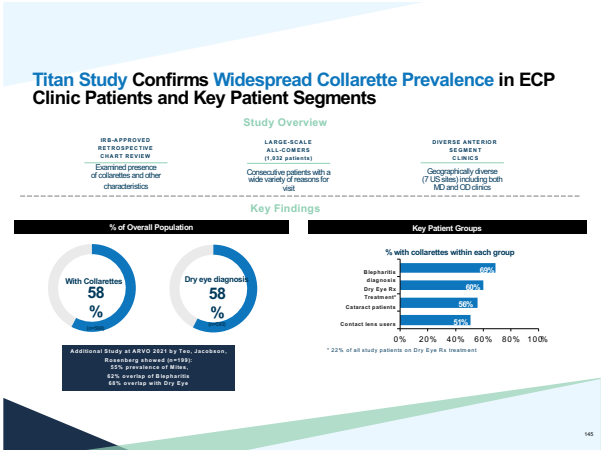

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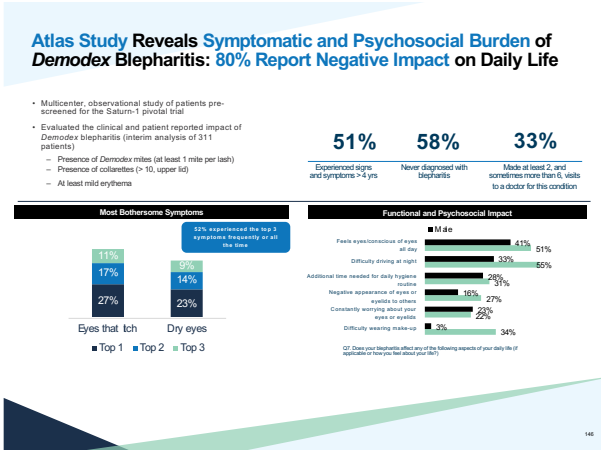

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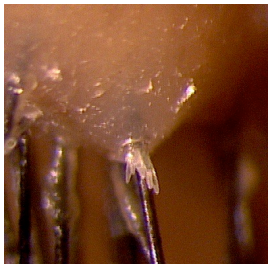

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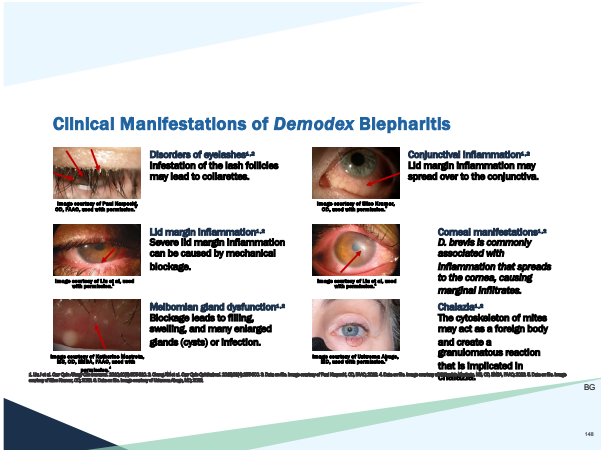

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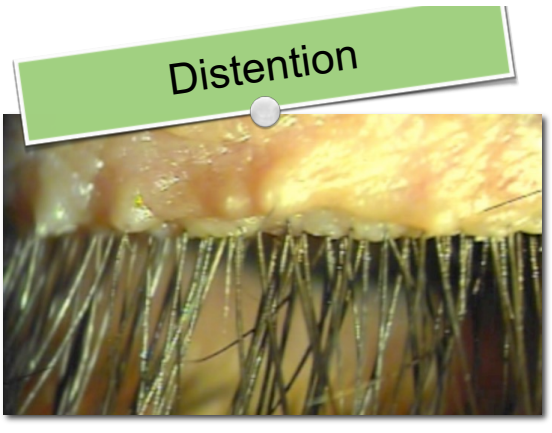

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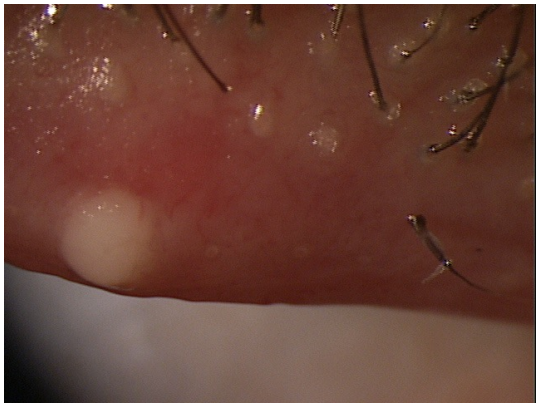

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

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ARTICLE OPEN

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

Brandon D. Ayres[1], Eric Donnenfeld[2], Marjan Farid[3], Ian Benjamin Gaddie[4], Preeya K. Gupta[5,6], Edward Holland[7], Paul M. Karpecki[8], Richard Lindstrom[9], Kelly K. Nichols[10], Stephen C. Pflugfelder[11], Christopher E. Starr[12] and Elizabeth Yeu[13,14]

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 panellists agreed. Questions were randomized, and results of each survey informed the following survey.
RESULTS: Twelve practitioners comprised the **D**emodex **E**xpert **P**anel on **T**reatment and Eyelid **H**ealth (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 = 9; range 8–9), and itching as the most common symptom ($n = 12$). Panellists 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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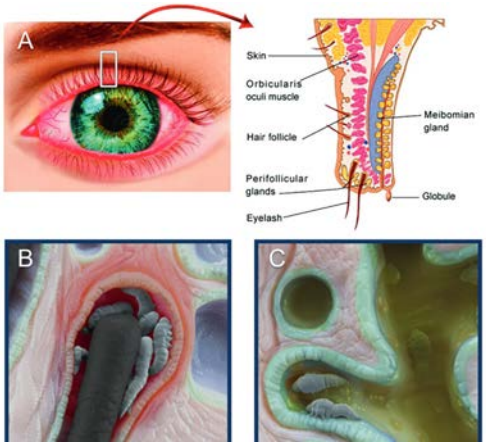

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Table 1. Key areas of consensus on scaled questions.

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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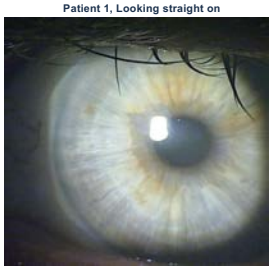
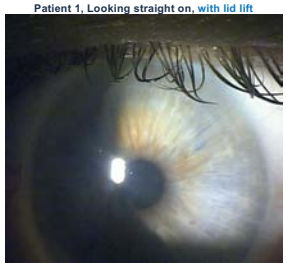
Collarettes Can Be Easily Missed on the Upper Lid!

Patient 1, Looking straight on



Patient 1, Looking straight on, with lid lift



c/o E. Yeu, MD, 1.0 mag

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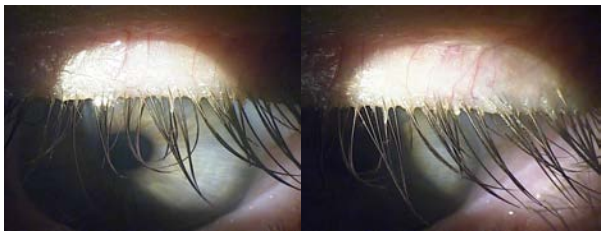
Collarettes Can Be Easily Seen on the Upper Lid when Patient Looks DOWN

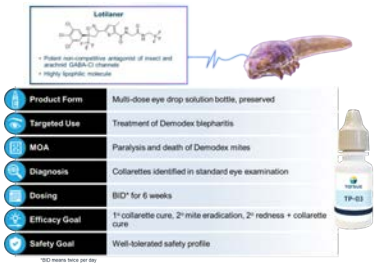
Patient : Diffuse collarettes, misdirected and missing lashes



c/o E. Yeu, MD, 1.0 mag

156

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



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

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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° – Collarette grade 2° - Mite density	28-day BID dosing; RCT	Completed
P2a: Io	18	1° – Collarette cure 2° - Mite eradication	Crossover of Jupiter control arm subjects; 42-day BID dosing	Completed
P2b: Europa	54 – 1:1	1° – Collarette cure 2° - Mite eradication 2° – Redness composite	42-day BID dosing; RCT	Completed
P2b/3: Saturn-1	421 – 1:1	1° – Collarette cure 2° - Mite eradication 2° – Redness composite	**Pivotal registration study** 42-day BID dosing; RCT	Completed
P3: Saturn-2	418 – 1:1	1° – Collarette cure 2° - Mite eradication 2° – Redness composite	**Pivotal registration study** 42-day BID dosing; RCT	Initiated May 2021

Two Pivotal Trials

Same formulation of TP-03 as expected in the Saturn trials | Represents pivotal trial

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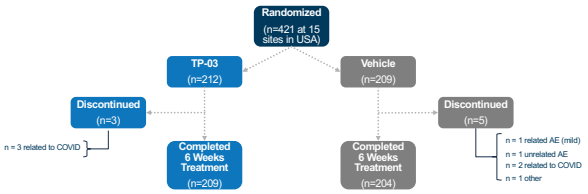
Saturn-1 Patient Enrollment and Follow-up

6 Week Treatment and Follow-up, twice a day drop without any touching or wiping of lid margin



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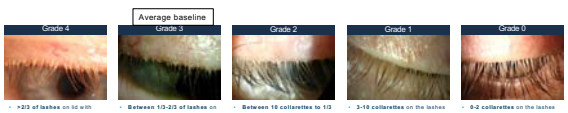
Saturn-1: All Primary and Secondary Endpoints Were Met and TP-03 was Well Tolerated

- **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 ≤ 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

160

Collarette Grading Scale Used in Saturn-1

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



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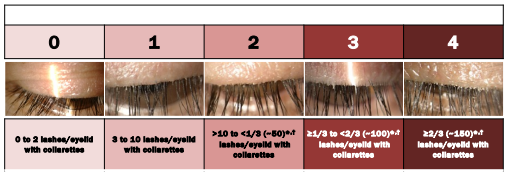
Lid Margin Erythema Scale Used in Saturn-1

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

162

Assessing Severity of *Demodex* Blepharitis: Collarettes*



BG

163

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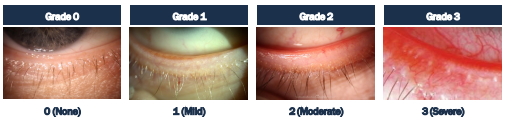
Assessing Severity of *Demodex* Blepharitis: Lid Erythema[1,*]



Images for Grades 0, 1, and 2 are from patients in the Saturn-1 trial. The image for Grade 3 has been reproduced with permission from Jiang et al.[1]

*Per the Saturn-1 trial. This was a randomized, controlled, double-masked, phase 3b/4 clinical trial of 411 patients with *Demodex* blepharitis.

BG

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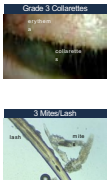
Saturn-1 Baseline Characteristics

	TP-03	Vehicle
Age	66.1	67.8
Female %	58	56
Collarette Score	2.8	2.8
Mite Density	3.2	3.2
Erythema Score	1.5	1.5



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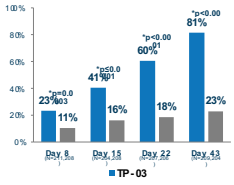
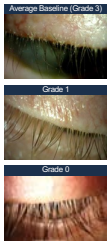
Clinically Meaningful Collarette Cure

Clinically Meaningful Collarette Cure Observed by Week 1
Over 90% Avg. Reduction in Collarettes (Over 100 to Less than 10 per Lid)





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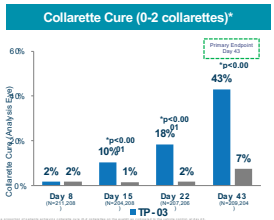
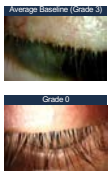
Primary Endpoint of Complete Collarette Cure Achieved

Regulatory Endpoint of Complete Collarette Cure Observed by Week 2





167

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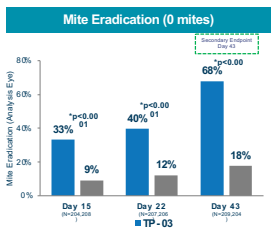
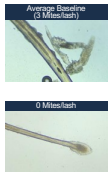
Secondary Endpoint of Mite Eradication Rate Achieved

Complete Mite Eradication Observed by Week 2
68% of Patients Experienced Complete Eradication at Week 6 (Secondary Endpoint)





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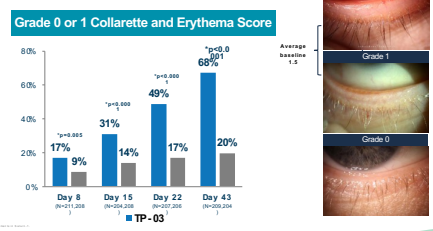
Clinically Meaningful Composite Cure

Clinically Meaningful Composite Cure Improvements Observed by Week 2
68% of Patients Experienced a Grade 0 or 1 Collarette and Erythema Score



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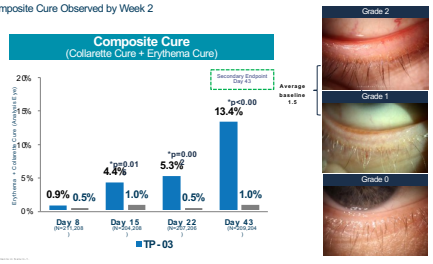
Secondary Endpoint of Complete Composite Cure Achieved

Endpoint of Complete Composite Cure Observed by Week 2



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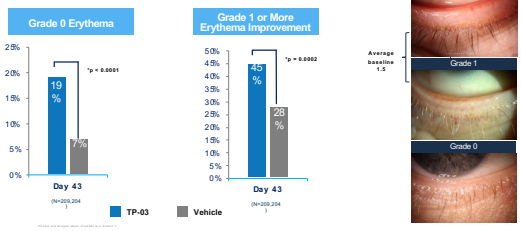
Erythema Cure and Response

19% of Patients Experienced Complete Erythema Cure at Day 43
45% of Patients Experienced Erythema Improvement at Day 43



Ora Calibra® Scale

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Adverse Event Summary

Treatment related ocular AEs occurring at rate of ≥ 1% in active group
– Summary of Adverse Events occurring at any time during trial

	TP-03 (n=212)	Vehicle (n=209)
Instillation site pain/burning/stinging	25 (11.8%)	16 (7.7%)
Instillation site pruritis	3 (1.4%)	7 (3.3%)
Visual acuity reduced	3 (1.4%)	5 (2.4%)
Eye pain	3 (1.4%)	2 (1.0%)
Eye discharge	3 (1.4%)	1 (0.5%)
AE Severity	All Mild	One moderate AE All other AEs mild

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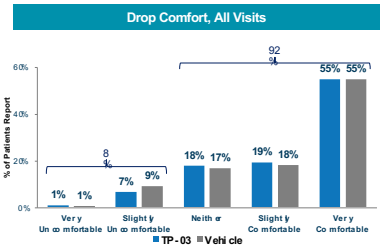
TP-03 Was Well Tolerated With 92% of Patients Reporting TP-03 to Be Neutral to Very Comfortable



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Improvements Seen Post Treatment Have Significant Clinical Impact

Cure rates and clinically meaningful effects validate the opportunity to benefit a large proportion of patients

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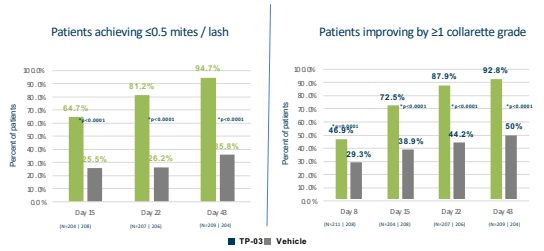
Saturn-1 Results | Responder analysis



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Evaluation of Lotilaner Ophthalmic Solution, 0.25% in Severe *Demodex* Blepharitis

Post-hoc Subanalysis of Saturn-2

Ian Benjamin Gaddie, OD[1], James Mun, PhD[2], Kavita Dhamdhere, MD, PhD[2], Stephanie Baba, OD[2], Patrick Vollmer, OD[2]

[1]Gaddie Eye Centers, Louisville, KY; [2]Tarsus Pharmaceuticals, Inc., Irvine, CA; [3]Vita Eye Clinic, Shelby, NC

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Financial Disclosures

- Ian Benjamin Gaddie
  Tarsus: Consultant, Orasis, Allergan, Bausch and Lomb, Sun Pharma
- James Mun
  Tarsus: Employee
- Kavita Dhamdhere
  Tarsus: Employee
- Stephanie Baba
  Tarsus: Employee
- Patrick Vollmer
  Tarsus: Consultant, Research

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BACKGROUND and PURPOSE

- *Demodex* blepharitis has a high prevalence of 58% among all patients visiting eye care clinics in the US.[1] However, the condition is often under- or misdiagnosed and ineffectively managed due to the lack of targeted treatments.[2]
- On July 24th, 2023, the Food and Drug Administration approved the first therapeutic treatment for *Demodex* blepharitis: lotilaner ophthalmic solution, 0.25%.
- Saturn-2 is the phase 3 pivotal, prospective, randomized, vehicle-controlled clinical trial that evaluated the efficacy and safety of a 6-week treatment with lotilaner ophthalmic solution, 0.25% in patients with *Demodex* blepharitis.[3]
  - Among all patients enrolled in Saturn-2, those with severe *Demodex* blepharitis (Grade 3-4) at baseline were included in this post-hoc subanalysis.

Purpose:
This post-hoc analysis evaluated the patients with severe *Demodex* blepharitis at baseline in Saturn-2 who achieved collarette reduction to 0-2 collarettes (Grade 0) or to ≤10 collarettes (Grade 0-1) after 6-week treatment with lotilaner ophthalmic solution, 0.25%.

1. Trattler W et al. *Clin Ophthalmol*. 2022;16:1153-1164; **2.** Rhee MK et al. *Eye Contact Lens*. 2023;10.1097; **3.** Gaddie IB et al. *Ophthalmology*. 2023;S0161-6420(23)00392-5;

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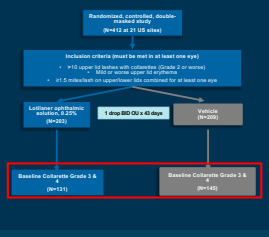
METHODS and Subject Disposition



Collarette Grade	Clinical Interpretation
Grade 0*	0-2 lashes with collarettes per eyelid
Grade 1*	3-10 lashes with collarettes per eyelid
Grade 2	>10 to <1/3 (up to ~50)[†] lashes with collarettes per eyelid
Grade 3[†]	≥1/3 to <2/3 (up to ~100)[†] lashes with collarettes per eyelid
Grade 4[†]	≥2/3 (up to ~150)[†] lashes with collarettes per eyelid

*Grade 0– 1 significant reduction in mites compared to Grade ≥2
†Grade 3– 4 was classified as severe Demodex blepharitis for this analysis;
#On an upper eyelid with 150 eyelashes (number of eyelashes on upper eyelid may vary from 50 to 150).

Subjects with ≥10 lashes with collarettes (Grade 2 or worse) is classified as having Collarette Grade 3 or Grade 4 at baseline.

Gao et al. IOVS. 2005;46:3089-3094

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RESULTS
Baseline Characteristics of Severe *Demodex* Blepharitis Patients

Baseline Characteristics	Lotilaner ophthalmic solution, 0.25% (N=131)	Vehicle (N = 145)
Age in years, mean (SD)	65.5 (15.0)	66.5 (13.5)
Sex, n (%)		
Male	69 (52.7)	78 (53.8)
Female	62 (47.3)	67 (46.2)
Race, n (%)		
White	118 (90.1)	129 (89.0)
Non-White	13 (9.9)	16 (11.0)
Collarette grade, n (%)		
3	80 (61.1)	77 (53.1)
4	51 (38.9)	68 (46.9)

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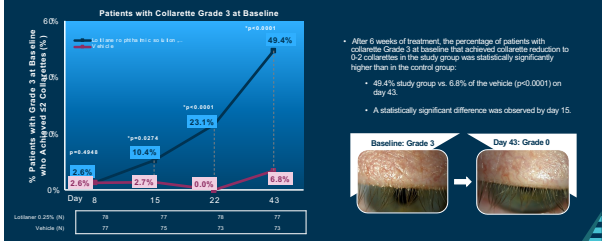
49% of Patients with Collarette Grade 3 (Up to ~100 Collarettes) at Baseline Achieved Collarette Reduction to 0-2 Collarettes on Day 43



- After 6 weeks of treatment, the percentage of patients with collarette Grade 3 at baseline that achieved collarette reduction to 0-2 collarettes in the study group was statistically significantly higher than in the control group:
  - 49.4% study group vs. 6.8% of the vehicle (p<0.0001) on day 43.
  - A statistically significant difference was observed by day 15.

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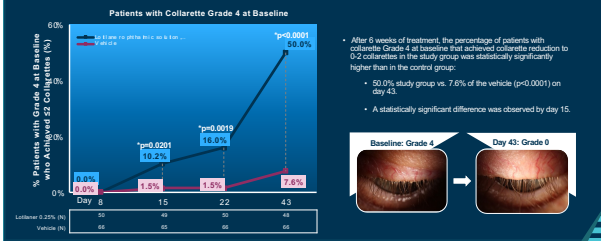
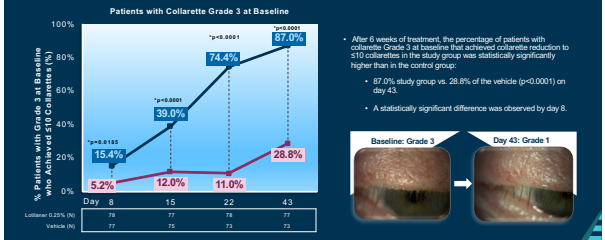
50% of Patients with Collarette Grade 4 (Up to ~150 Collarettes) at Baseline Achieved Collarette Reduction to 0-2 Collarettes on Day 43



- After 6 weeks of treatment, the percentage of patients with collarette Grade 4 at baseline that achieved collarette reduction to 0-2 collarettes in the study group was statistically significantly higher than in the control group:
  - 50.0% study group vs. 7.6% of the vehicle (p<0.0001) on day 43.
  - A statistically significant difference was observed by day 15.

182

87% of Patients with Collarette Grade 3 (Up to ~100 Collarettes) at Baseline Achieved Collarette Reduction to ≤10 Collarettes on Day 43



- After 6 weeks of treatment, the percentage of patients with collarette Grade 3 at baseline that achieved collarette reduction to ≤10 collarettes in the study group was statistically significantly higher than in the control group:
  - 87.0% study group vs. 28.8% of the vehicle (p<0.0001) on day 43.
  - A statistically significant difference was observed by day 8.

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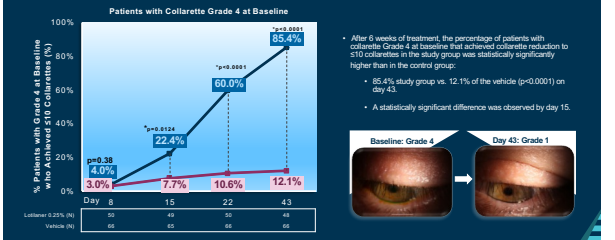
85% of Patients with Collarette Grade 4 (Up to ~150 Collarettes) at Baseline Achieved Collarette Reduction to ≤10 Collarettes on Day 43



- After 6 weeks of treatment, the percentage of patients with collarette Grade 4 at baseline that achieved collarette reduction to ≤10 collarettes in the study group was statistically significantly higher than in the control group:
  - 85.4% study group vs. 12.1% of the vehicle (p<0.0001) on day 43.
  - A statistically significant difference was observed by day 15.

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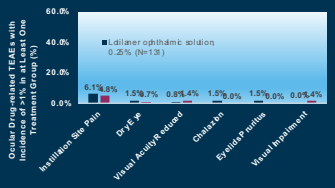
Safety Measures



- The drug-related ocular treatment-emergent adverse events (TEAEs) were similar in the study and vehicle groups.
- No serious drug-related ocular adverse events were observed.
- No safety concerns in the study or vehicle group for measures including intraocular pressure, endothelial cell density, and corneal staining.

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CONCLUSIONS

- Lotilaner ophthalmic solution, 0.25% was recently approved by the Food and Drug Administration on July 24, 2023, for the treatment of *Demodex* blepharitis in humans.
- Its safety and efficacy profile in patients with *Demodex* blepharitis has been previously reported in multiple phase 2 and 3 clinical trials.
- In this post-hoc subanalysis on severe *Demodex* blepharitis patients from the Saturn-2 prospective, controlled clinical trial:
  - More than 49% of patients with severe *Demodex* blepharitis (Grade 3-4 collarettes) at baseline achieved collarette reduction to 0-2 collarettes at the conclusion of treatment (43 days), compared to 8% or less in the vehicle control group.
  - More than 85% of patients with severe *Demodex* blepharitis (Grade 3-4 collarettes) at baseline achieved collarette reduction to ≤10 collarettes at the conclusion of treatment (43 days), compared to 29% or less in the vehicle control group.
  - Most adverse events were mild with no serious ocular treatment-related adverse event. Instillation site pain was the most commonly reported treatment-related ocular adverse event.

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Two Successful Pivotal Trials with Consistency Across Endpoints

Consistency and High Statistical Significance Expected to Result in Definitive Standard of Care Therapy for Demodex Blepharitis

	Saturn-1 N=421 (Pivotal Phase 2b/3)	Saturn-2 N=412 (Pivotal Phase 3)	Combined N=833 Pivotal Data
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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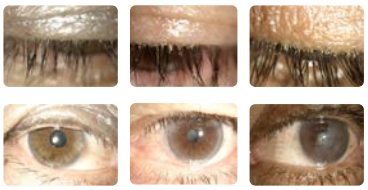
Lid health directly impacts the ocular surface[1]

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

Examples of *Demodex* blepharitis conjunctival/corneal disease



References: 1. Aumond S, Bitton E. The eyelash follicle feature: oral anomalies: a review. J Optom. 2018;11(4):211-222. 2. Fromstein SR, Harthan JS, Patel J, Opitz DL. Demodex blepharitis: clinical perspectives. Clin Optom(Auckl). 2016;8:57-62.

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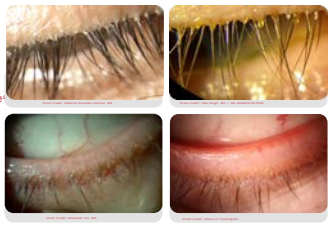
Demodex blepharitis (DB) can be seen and experienced by your patients

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[1]:
  - Dry eye
  - Lid itching
  - Irritation

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

- Clinical consequences may include[2]:
  - Dry eye
  - Red, itchy, or irritated eyelids
  - Missing or misdirected eyelashes
  - Inflammation of the conjunctiva and lid margin
  - Recurrent chalazia



References: 1. O'Dell L, Donker GS, Devries DK, et al. Psychosocial impact of *Demodex* blepharitis. Clin Ophthalmol. 2022;16:2979-2987. 2. Fromstein SR, Harthan JS, Patel J, Opitz DL. Demodex blepharitis: clinical perspectives. Clin Optom(Auckl). 2016;8:57-62.

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A Note On Lid Hygiene

- I do prescribe lid scrubs (commercially available) immediately following completion of the Lotaliner 6-week treatment
- New evidence that skin oil (thinks seb derm) can seep into lids/ocular surface and not mix well, accelerating evaporation
- Products containing Hypochlorous Acid may help with some of the skin oil/meibomian clashing
  - I am considering for all my seb derm patients

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Current/Previous Treatment methods for Demodex

- Topical Ivermectin
- Topical Tea Tree Oil
  - Ocusoft Demodex kit
  - Cliradex premedicated towelettes
  - Blephadex towelettes or foam
  - Terpinol-4 Active ingredient in TTO
- Other homemade concoctions?
  - Macadamia Nut oil

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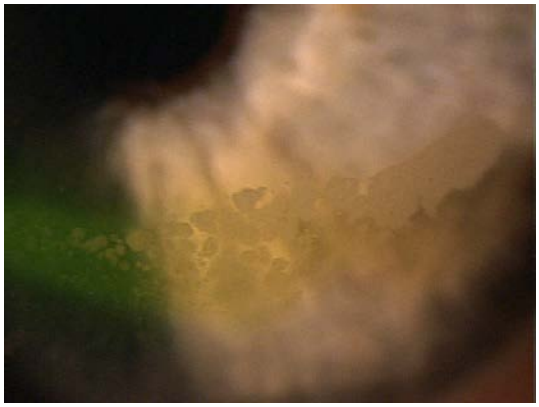

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Ointments

- Do ointments have any efficacy in treating demodex?
- Erythromycin
- Gentamycin
- Tobradex Ung
- Lotemax Ung
- Pilo ung?

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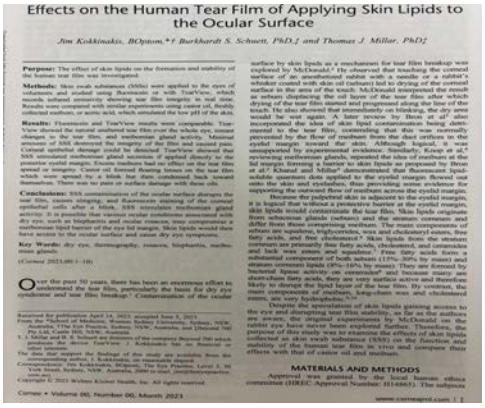
Skin Oils



Effects on the Human Tear Film of Applying Skin Lipids to the Ocular Surface

Jim Kokkinakis, BOptom,*† Burkhardt S. Schuett, PhD,‡ and Thomas J. Millar, PhD‡

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Last thoughts…

Although their pathogenic potential remains unclear, the ubiquitous pilosebaceous mite *Demodex* (generally considered a saprophryte) overpopulation should be considered as cause in recalcitrant cases of blepharitis/conjuctivitis/corneal pathology.

Demodex brevis induced pathological changes in the meibomian gland function/lipid layer is implicated in evaporative dry eye/ocular surface disease.

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Gaddie Current Protocol

- **Think SPEED!! All 3 of the below work w/in 2 weeks!**
- If I have a work-up and see corneal staining, my immediate go to is perflourohexyloctane TID OU
- If I have a work-up and see cylindrical dandruff, my immediate go to is Lotaliner
- If I have aqueous deficient patient, I will reach for Perfluorobutylpentane + Cyclosporine .1%

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