Cry Me A River

Ben Gaddie, O.D. FAAO
Gaddie Eye Centers
Louisville, KY
2-hour COPE APPROVED

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Experience EXPO With Us!

- Vision Stage – *Tangerine Ballroom – Room WF1*
  Our Vision Stage sessions feature free, promotional content for all attendees.
- Vision Series - *Thursday 3/12 and Friday 3/13*
  Grab a bite to eat and continue learning over *Breakfast 8:30-9:30am* or *Lunch 12:00-1:00pm*!* Listen to industry leaders as they address the latest clinical innovations in a relaxed and collaborative environment.
  **Open to Optometrists only. Not for Credit. Meals offered on first-come, first-serve basis. Education Badge required.*
- Exhibit Hall Hours
  Thursday, March 12 9:30am – 6:00pm
  Friday, March 13 9:30am – 6:00pm
  Saturday, March 14 9:30am – 3:00pm
  · Conferee Cafe – Exhibit Hall – Booth 2902
  · Education Lounge - Level 2 - Conference Area Tangerine Ballroom – Room WF2

vision expo

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Financial Disclosures Ben Gaddie 12/16/2025

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

- Tarsus-Consultant, Clinical Trials
- Bausch and Lomb-Consultant
- Topcon-Consultant
- Harrow-Consultant
- MediPrint-Shareholder/Consultant
- Orasis-Scientific Advisory Board
- Glaukos-Consultant
- Heru-Consultant
- Balance Ophthalmics-Consultant
- Sydnexis-Consultant
- Azura-Consultant
- Ocusoft-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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Basic Ocular Surface Principles

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

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Excessive Evaporation Triggers A Vicious Cycle

When tear evaporation exceeds supply, loss of homeostasis follows[1,2]

1. Bron AJ, et al. Ocul Surf. 2017;15(3):438-510. 2. McMonnies CW. Eye Vis (Lond). 2020;7:6. 3. Covita A, et al. Invest Ophthalmol Vis Sci. 2019;60(9):6783. 4. Arita R, et al. Am J Ophthalmol. 2016;169:125-137. 5. Alkhamees 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. Al-Mohaiseb Z, et al. Clin Ophthalmol. 2021;15:3811-3820. 11. Pflugfelder SC, et al. Ophthalmology. 2017;124(11):S4-S13. 12. Zhang R, et al. Ocul Surf. 2022;23:145-156. | DED, dry eye disease.

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Basic Ocular Surface Principles

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

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Basic Ocular Surface Principles

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

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Basic Ocular Surface Principles

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

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Basic Ocular Surface Principles

- Before 2023, we only had steroids and 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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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

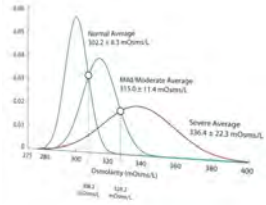
Dry Eye Diagnosis

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**

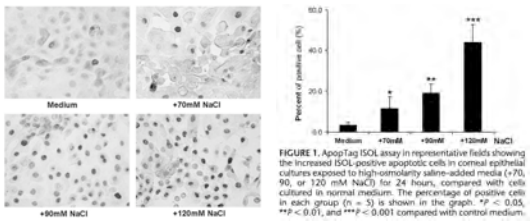

FIGURE 1. ApopTag ISOL assay in representative fields showing the increased ISOL-positive apoptotic cells in corneal epithelial cultures exposed to high-osmolarity saline-added media (+70, 90, or 120 mM NaCl) for 24 hours, compared with cells cultured in normal medium. The percentage of positive cells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

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

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

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

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Tear Osmolarity in the Diagnosis and Management of Dry Eye Disease

MICHAEL A. LEMP, ANTHONY 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 92 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 306 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, 34%; 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 CHRONICLY PHOOTHTHIC 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.[4]

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,[5] 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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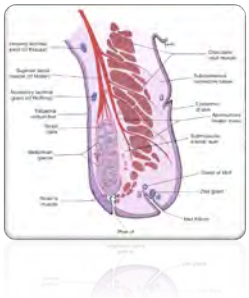
Meibomian Gland Anatomy

Meibomian gland function is regulated by:

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



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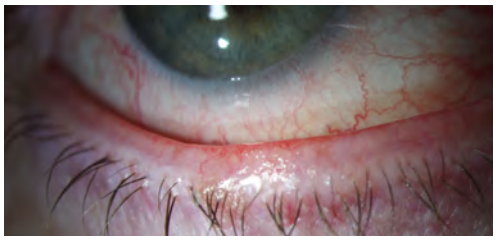
What is MGD?

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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Thermal expression

- TearCare
- iLux
- LipiFlow

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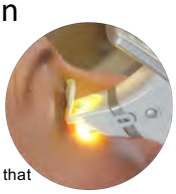
TFI/iLux Thermal expression



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-

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

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Vectored thermal pulsation

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

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Case

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- **75-year-old Caucasian male**
  - **Not good with my drops**
  - **VA seems to change**
- **Referred for GLC Eval**
- **PEHX: SLT x 2**
- **BCVA**: 20/20 -1 OU
- TMAX: 30 mmHg OU
- Medications:
  - **Latanoprost 1 x a day**
  - **Timolol 1 x a day**

- **IOP**: 17 mm Hg OD; 17 mm Hg OS
- **C/D**: 0.60/0.60 OD 0.70/0.70 OS
- **Pachymetry**: 553 OD; 543 OS
- **Corneal hysteresis**: 8.0 OD 7.4 OS
- **Gonioscopy**: Open to CB OU w/ trace pigment in TM
- SLE: See next slide (s)
- **VF's** – See next slide(s)
- **OCT's** – See next slide(s)
- ONH – See next slide(s)

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Treatment Considerations

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

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Case – 6 weeks after insertion

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

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Case

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

- 61-year-old female – Also noticed that her vision fluctuates; is worse as the day goes on; spends 4 to 6 hours a day on a computer or tablet
- Patient does not smoke, run a ceiling fan, or rub her eyes

- Past medical history: Unremarkable
- Systemic medications: Amitriptyline
- Allergies: NKDA
- Family medical history: Age-related macular degeneration (grandmother)
- Social history: No smoking, teacher, no eye rubbing

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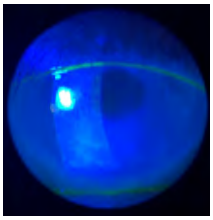
Examination

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



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

Posterior Segment:
- Unremarkable

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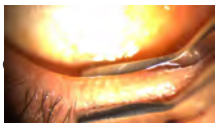
Case Conclusion: 6-Week Follow-Up

Intervention:



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

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Newer Ocular Surface Treatments

- Perfluorohexylocatane (Miebo)
- Perfluorobutylpentane + Cyclosporine .1% (Veyve)
- Lotaliner (Xdemvy)
- Acoltremon (Tryptry)
- Varenicline (Tyrvaya)

- Pharmacies???

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Semifluorinated Alkanes (SFAs) in Medicine and Eye Care

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

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Cyclosporine .1% in SFA

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

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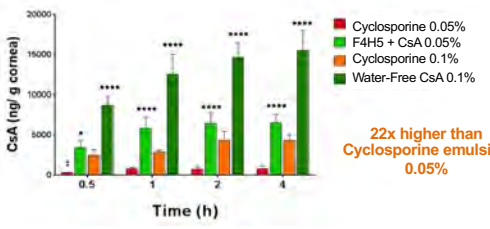
Ex-vivo Corneal Permeability of Cyclosporine
in Porcine Eyes



22x higher than Cyclosporine emulsion 0.05%

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

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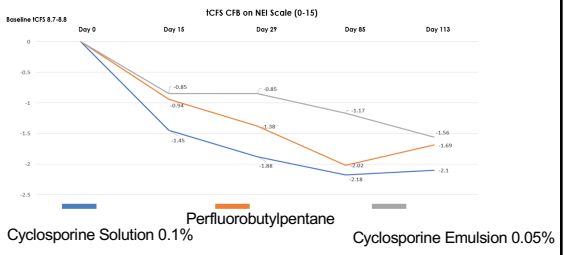
Water-Free Cyclosporine 0.1% Phase II Study

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



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

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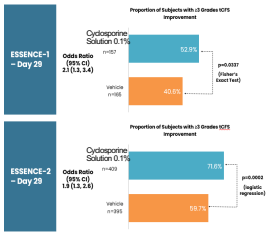
Water-Free CsA 0.1% demonstrated significantly meaningful tCFS improvement in ESSENCE-1 and ESSENCE-2



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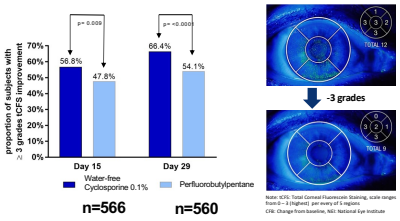
Majority of Patients See Clinically Significant Improvement from Water-free Cyclosporine 0.1% Therapy Within 2 Weeks



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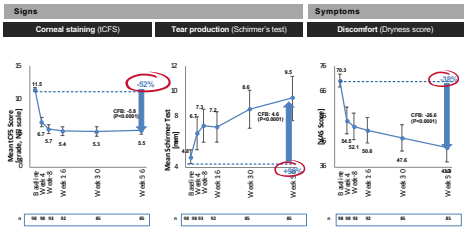
ESSENCE 2-OLE: 12-Month Sign and Symptom Improvement

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



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

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

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

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Perfluorohexyloctane (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*. 2023;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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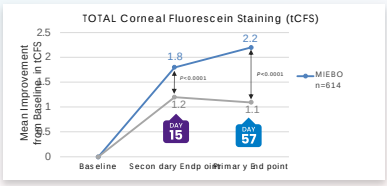
Rapid and Sustained Improvement in Total Corneal Staining as Early as Day 15 Through Day 57



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

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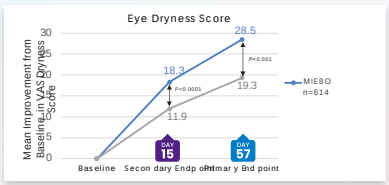
Rapid and Sustained Relief of Eye Dryness as Early as Day 15 Through Day 57

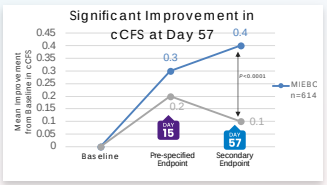


Pooled data | Visual analog scale: 0-100 (0=no discomfort, 100=maximal discomfort) | Mean Baseline, MIEBO = 65.6; Mean Baseline, Saline = 65.5 | At Day 57, Mean (SD) CFB GOBI: –27.4 (27.9) for MIEBO (n=289) vs –19.7 (26.7) for saline (n=279) (*P*<0.001) | MOJAVE: –29.5 (28.6) for MIEBO (n=302) vs –19.0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

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

65

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*. 2023;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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Acoltremon (AR-15512) Ophthalmic Solution 0.003%

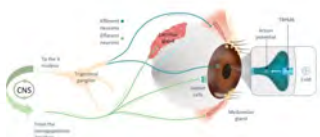
TRPM8 agonist

WHAT IS TRPM8?

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

WHY TRPM8 AS A TARGET FOR DRY EYE?

- TRPM8 receptors are stimulated by ocular surface cooling and increased tear osmolarity associated with tear evaporation to regulate basal tear production[3-6]



1. Guerrero-Moreno A, Baudouin C, Melik Parsadaniantz S, Réaux-Le Goazigo A. *Front Cell Neurosci*. 2020;14:610543. 2. McCoy DD, Knowlton WM, McKemy DD. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(6):R1278-R1287. 3. Hirata H and Meng ID. *Invest Ophthalmol Vis Sci*. 2010;51(8):3963-3970. 4. Belmonte C, Gallar J. *Invest Ophthalmol Vis Sci*. 2011;52(6):3888-3892. 5. Parra A, Madrid R, Echevarria D, et al. *Nat Med*. 2010;16(12):1396-1399. 6. Quallo T, Vastani N, Horridge E et al. *Nat Commun*. 2015; 6: 7150.

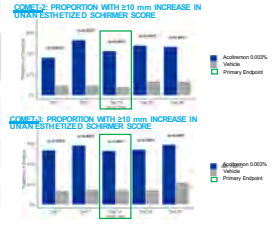
67

Acoltremon (AR-15512) Ophthalmic Solution 0.003%

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

Enrollment	931 dry eye subjects completed COMET-2 and -3 studies
Primary **Unanesthetized Schirmer Test**	• Higher % of subjects with ≥ 10 mm increase in unanesthetized Schirmer Test scores on Day 14 with acoltremon 0.003% (ACO) compared to vehicle • Similar results seen on Day 1 and Day 90 (secondary endpoints)
Key Secondary **SANDE Score**	• Change from baseline in SANDE scores were greater with ACO on Day 28 in COMET-2 (P=0.0138); numerically greater with ACO in COMET-3 (P=0.1321)
Exploratory **Ocular Staining**	• Change from baseline in total corneal and total conjunctival staining were observed at Day 7 through Day 90
Adverse Events	• ACO was well-tolerated, and there were no reported serious ocular adverse events

Primary endpoint met in both phase 3 (COMET) trials



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Summary

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

1. https://clinicaltrials.gov/study/NCT05285644. Accessed September 24, 2024. 2. https://clinicaltrials.gov/study/NCT05360966 Accessed September 24, 2024.
3. https://clinicaltrials.gov/study/NCT05463111. Accessed September 24, 2024.

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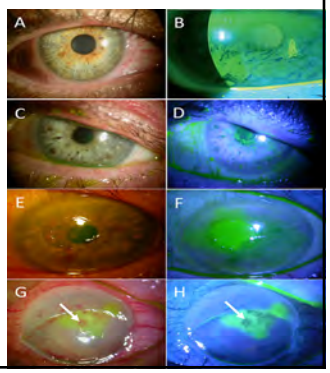
Cenegermin for NK

- 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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Pipeline and Pending Approvals

- RASP Inhibitor-Abbvie/Alderya
- Eyelid Health
  - Azura
  - Tarsus
- SFA's
  - Lifitegrast + Miebo

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AZR-MD-001

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

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

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

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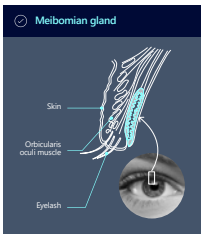
Meibomian Glands

Meibomian glands which secrete meibum[1] are modified sebaceous glands

- **Normal meibum is a clear liquid at body temperature**
- **Lubricate the ocular surface during blinking and protect against tear evaporation.[1,2,3]**
- **Meibum consists of a complex mixture of various *proteins*, lipids, and other components[1]**
  - More than 90 different ***proteins*** identified in the meibum[5]
  - 100s of different species of lipids, most of which are wax and cholesteryl esters[4]
  - Indirect immunofluorescence determined keratin proteins expressed in humans meibomian glands in the normal eye[6]
- **Keratins are helical structural *proteins* present in the meibum**



[1]Green-Church KB, et al. Invest Oph Vis Sci. 2011 Mar 30;52(4):1973-93. [2]Blackie CA, et al. Cornea. 2010;29(12):1323-45. [3]Knop E, et al. Invest Ophthalmol Vis Sci. 2011;52(4):1938-78.
[4]Butovich IA Prog Retin Eye Res. 28 (6): 418–498. [5]Tiffany JM, et al. Br J Ophthalmol. 60 (2): 172–7. [6]Jester JV, et al. Invest Ophthalmol Vis Sci. 1989;30(5):927-935.

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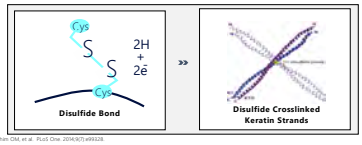
Disulfide Bond Formation
Production of protein aggregates

- **Oxidative stress contributes to the pathology of MGD[1] and the formation of aberrant disulfide bonds**
- **Aberrant disulfide bonds leads to formation of excess keratin aggregates in unwanted locations**
- **Keratin protein release in the absence of crosslinking won't lead to the formation of keratin aggregates**



[1]Ibrahim OM, et al. PLoS One. 2014;9(7):e99328.

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

Similar to the lid margin, secretory gland hyperkeratinization plays an important role in various skin disorders

Comedonal lesions in acne are inspissated hair follicles, filled with corneocytes, sebum, and other debris

Keratolytic treatments are used to shed dead corneocytes, loosen the sebum plug, and prevent the formation of inflammatory papules and pustules

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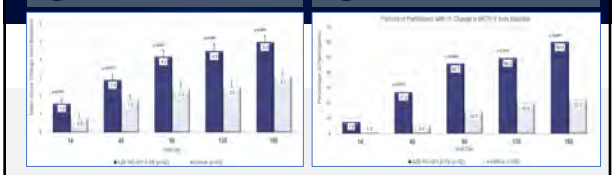
AZR-MD-001 Shows Statistically Significant Improvement in MGYLS Sign

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

Number of Open Glands
Statistically Significant Difference from Control

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



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

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

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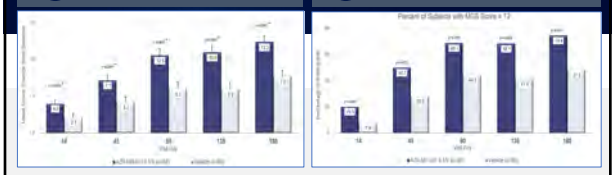
AZR-MD-001 Shows Statistically Significant Improvement in MGS Sign

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

Quality of Meibum
Statistically Significant Difference from Control

% of Patients with Normal Meibum
Clinically Significant Difference from Control



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

1. Meibomian gland secretion
p-values completed using LS mean difference from baseline at the time points indicated
* p<0.05 change from baseline compared to vehicle

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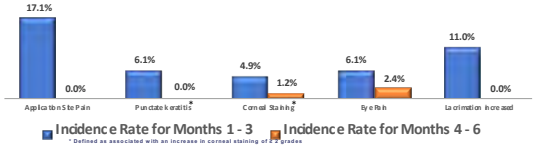
Reduction of TEAEs (≥5%) Over Time for AZR-MD-001 0.5%

Safety Data Set

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



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

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AZR-MD-001 Clinical Data Review:

Trial Efficacy
- **U.S. Regulatory requirements achieved**
- 3-mo. Co-Primary Endpoints met statistical significance and clinically meaningful benefit for 0.5% over vehicle[1]
- 6-mo. Further improvement in **all signs and symptoms** with continued use through 6-months
  - Durability of effect strengthens US filling and supports an ex-US regulatory strategy

Restored Gland Function
- **61.7%** of patients had their glands opened to a normal level[2] at 6-mo.
- **75%** of patients had their meibum quality return to normal levels[3] at 6-mo.

Improved Patient Symptoms
- **54.7%** of patients became asymptomatic as measured by Total OSDI[©] at 6-mo.
- Improved tear stability – Over a 2 second improvement in Tear Break Up Time maintained from Month 3 onward
- **Significantly improved patient symptoms** across multiple patient-reported outcome measures (SPEED, average VAS, Eye Dryness, Eye Discomfort, Ocular Itch)

1. In a single study in ITT population (all randomized patients)
2. MGYLS responder rate; p=0.0005 compared to vehicle at month 3; improvement from baseline of 4.2 glands (p<0.0001)
3. MGS responder rate; p=0.0069 compared to vehicle at month 3; improvement form baseline of 10.5 (p<0.0001)

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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!

TFOS DEWS II - Diagnostic Methodology

1. Introduction
2. Goals of the Diagnostic Methodology Subcommittee
3. Definition of dry eye disease (DED)
4. Classification of sub-categories of dry eye disease (DED)
5. Diagnostic considerations
6. Recommendations of appropriate tests for diagnosis and assessment of dry eye
7. Monitoring dry eye disease progression and management
8. Clinical protocol for dry eye diagnostic test battery
9. Differential diagnosis & comorbidities
10. Emerging technologies
11. Summary and conclusions
12. Financial disclosures
13. Acknowledgements
14. References
15. Tables
16. Questionnaire Forms (DEQ-5 & OSDI)

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6.8.1.1 Anterior

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

6.8.1.2 Posterior

6.8.1.2.1 Lid wiper 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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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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Available online 12 February 2020

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INVESTIGATION

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

Ezgi Aktaş Karabay *, Aslı Aksu Çerman

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J Clin Exp Dermatol. 2009 Dec;34(8):e616–20. doi: 10.1111/j.1365-2230.2009.03343.x. Epub 2009 May 22

Is Demodex folliculorum an aetiological factor in seborrhoeic dermatitis?

Y Karincaoglu, B Tepe, B Kalayci, M Atambay, M Sayhan

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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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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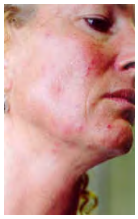
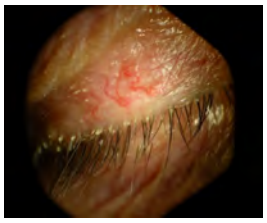
Demodex Has Been Linked to Rosacea and Blepharitis

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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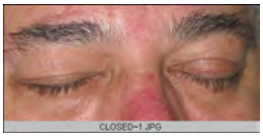
Demodex Infestation is Associated with Floppy Eyelid Syndrome (4)

- 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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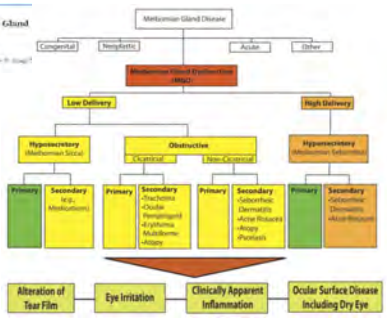
Classifications of MGD

The International Workshop on Meibomian Gland Dysfunction: Report of the Definition and Classification Subcommittee



IOVS, 2011

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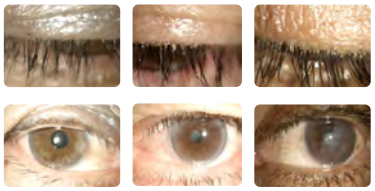
Lid health directly impacts the ocular surface[1]

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

Examples of *Demodex* blepharitis conjunctival/corneal disease



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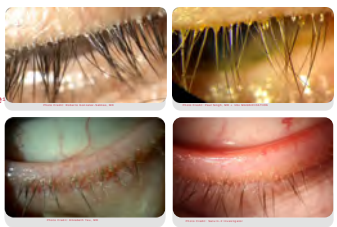
Demodex blepharitis (DB) can be seen and experienced by your patients

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[1]

- 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



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

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

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Symptoms of Demodex

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

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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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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

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):3089-3096. 2. Kheirkhawan, N., et al. Prevalence of ocular demodicosis among patients at Tertiary Care Center, Bangkok, Thailand. *Int J Ophthalmol* 2017; 10(1): 123-127. 3. Zhang AC, Muntz A, Wang MTM, Craig JP, Downie LE. Ocular Demodex: a systematic review of the clinical literature. *Ophthalmol Physiol Opt*. 2020;40:366-401. 4. Nicholls S, 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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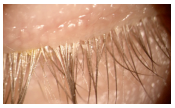
Collarettes Are Pathognomonic Sign of Demodex Infestation

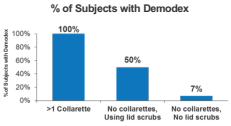
Collarettes Are Composed of Mite Waste Products and Eggs[1]

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

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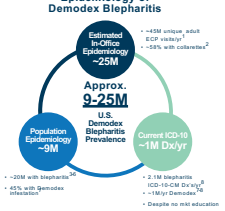
Blepharitis Is a Large and Underserved Market in Eye Care

Epidemiology of Demodex Blepharitis



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.[1]
Blepharitis Can Lead to	Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the cornea[4]
Concomitant Dry Eye	Significant overlap in **Dry Eye** patients. Demodex prevalent in ~69% of DE patients[5]
Blepharitis and Surgery	Important factor for maximizing surgical outcomes: 67% of **Cataract Patients** have Demodex blepharitis[9]
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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Titan Study Confirms Widespread Collarette Prevalence in ECP Clinic Patients and Key Patient Segments

Study Overview

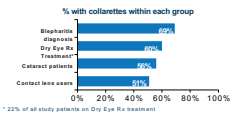
IRB-APPROVED RETROSPECTIVE CHART REVIEW	LARGE-SCALE ALL-COMERS (1,032 patients)	DIVERSE ANTERIOR SEGMENT CLINICS
Examined presence of collarettes and other characteristics	Consecutive patients with a wide variety of reasons for visit	Geographically diverse (7 US sites) including both MD and OD clinics

Key Findings

% of Overall Population

Additional Study at AEVO 2021 by Teo, Jacobson, Rosenberg showed (n=195):
55% prevalence of Mites,
62% overlap of Blepharitis
68% overlap with Dry Eye

Key Patient Groups



Trattler et al. Clin Ophthalmol. 2022; 16: 1153–1164.

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

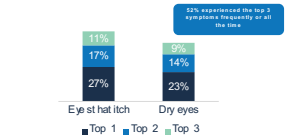
- Multicenter, observational study of patients pre-screened for the Saturn-1 pivotal trial
- Evaluated the clinical and patient reported impact of *Demodex* blepharitis (interim analysis of 311 patients)
  - Presence of *Demodex* mites (at least 1 mite per lash)
  - Presence of collarettes (> 10, upper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

51% Experienced signs and symptoms > 4 yrs

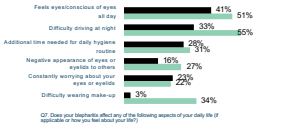
58% Never diagnosed with blepharitis

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

Most Bothersome Symptoms



Functional and Psychosocial Impact



Q7. Does your blepharitis affect any of the following aspects of your daily life (if applicable or how you feel about your life?)

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Clinical Manifestations of *Demodex* Blepharitis

Disorders of eyelashes[1,2]
Infestation of the lash follicles may lead to collarettes.

Conjunctival inflammation[1,2]
Lid margin inflammation may spread over to the conjunctiva.

Lid margin inflammation[1,2]
Severe lid margin inflammation can be caused by mechanical blockage.

Corneal manifestations[1,2]
***D. brevis* is commonly associated with inflammation that spreads to the cornea, causing marginal infiltrates.[2]**
The cytoskeleton of mites may act as a foreign body and create a granulomatous reaction that is implicated in chalazia.

Meibomian gland dysfunction[1,2]
Blockage leads to filling, swelling, and many enlarged glands (cysts) or infection.

BG

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

www.nature.com/eye

ARTICLE OPEN

Check for updates

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

Brandon D. 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]✉

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 Treatment 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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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
[a]Mite visualization NOT necessary to diagnose	2	1–8

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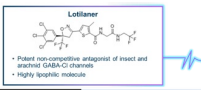
TP-03 is a Novel Therapeutic Designed to Eradicate Demodex Mites and Treat Demodex Blepharitis



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

*BID means twice per day

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Extensive Clinical Trial Program for TP-03

Study	# of Subjects	Effectiveness Endpoints	Study Highlights	Status
PoC: Mercury	80 mites	Ex-vivo mite death count	Ex-vivo mite testing	Completed ✓
P2a: Mars	15 – Single arm	Collarette grade Mite density	28-day BID dosing	Completed ✓
P2b: Jupiter	60 – 1:1	1° – 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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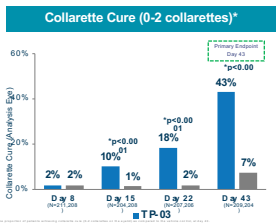
Primary Endpoint of Complete Collarette Cure Achieved

Regulatory Endpoint of Complete Collarette Cure Observed by Week 2



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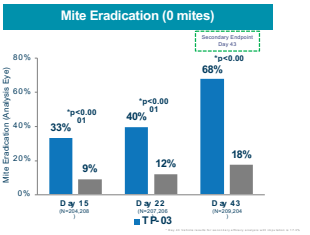
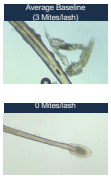
Secondary Endpoint of Mite Eradication Rate Achieved

Complete Mite Eradication Observed by Week 2

68% of Patients Experienced Complete Eradication at Week 6 (Secondary Endpoint)





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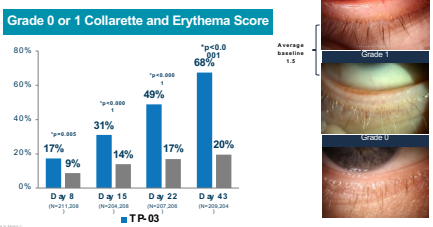
Clinically Meaningful Composite Cure

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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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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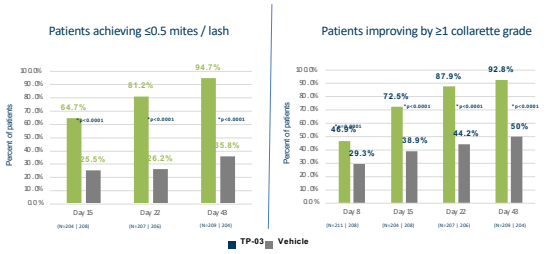
Saturn-1 Results | Responder analysis



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Pooled P3 data

	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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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[3]

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

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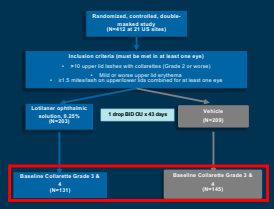
METHODS and Subject Disposition



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

is classified as having Collarette Grade 3 or Grade 4 at baseline.

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

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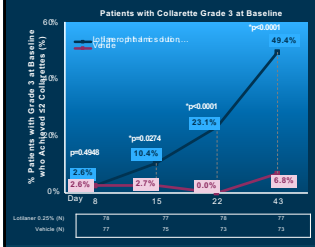
49% of Patients with Collarette Grade 3 (Up to ~100 Collarettes) at Baseline Achieved Collarette Reduction to 0-2 Collarettes on Day 43



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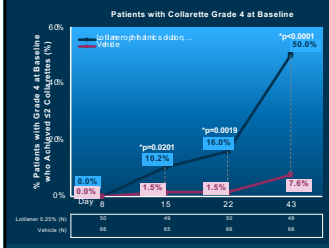
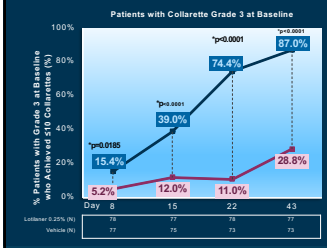
50% of Patients with Collarette Grade 4 (Up to ~150 Collarettes) at Baseline Achieved Collarette Reduction to 0-2 Collarettes on Day 43



- 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.

166

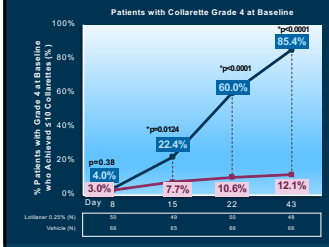
87% of Patients with Collarette Grade 3 (Up to ~100 Collarettes) at Baseline Achieved Collarette Reduction to ≤10 Collarettes on Day 43



- 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.

167

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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Phase 2b Lotilaner MGD Data

- Two Studies
  - 1 with lotilaner 0.25%
  - 1 with vehicle
- Two Arms
  - TID
  - BIG
- Time points
  - Day 43
  - Day 85

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Grading Scales and VAS

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

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Meibomian Gland Secretion Scores

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

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

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

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

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

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Fluctuating Visual Acuity

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

175

Itching

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

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Burning

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

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Redness

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

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Case

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

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Case

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

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Case

- Lids look much improved
  - 2 collarettes each lid (grade 0)
  - VA improved to 20/25 OD and OS
  - Speed down to 12
- Significant residual SPK OU
  - Symptoms still persist of DED,
    - SFA + Cyclosporine .1% due to persistent SPK
      - BID OU
  - RTC 4-6 weeks

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Case

- 1 month follow up
  - BCVA 20/20 OD and OS
  - Quality of vision is improved
  - Resumed CL wear successfully

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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%
- Persistent symptoms after this, I usually try tryptyr

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