Cry Me A River

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1

Financial Disclosures 8/16/2025 Ben Gaddie, OD

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

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

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Financial Disclosures-Justin Schweitzer, OD

- Alcon
- AbbiVie
- Bausch and Lomb
- Sight Sciences
- Dompe
- Zeiss
- Tarsus
- Sun
- Bruder
- LKC
- Glaukos
- Visus
- Reichert
- MediPrint
- Harrow
- Thear
- Viatris

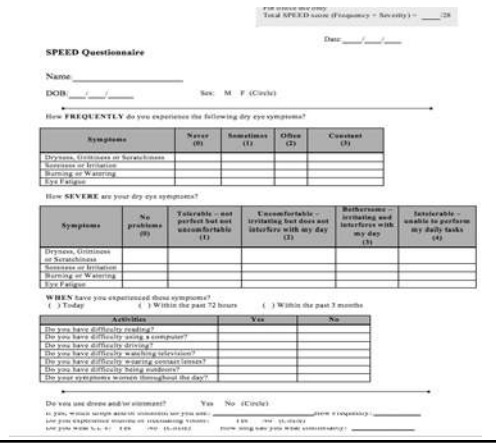
3

4

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*)

5


SPEED Questionnaire

Name _____

DOB: ___/___/____ Sex: M F (Circle)

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

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

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

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

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

Activities	Yes	No
Do you have difficulty reading?		
Do you have difficulty using a computer?		
Do you have difficulty driving?		
Do you have difficulty watching television?		
Do you have difficulty wearing contact lenses?		
Do you have difficulty being outdoors?		
Do your symptoms worsen throughout the day?		

Do you use drops and/or ointment? Yes No (Circle)

6

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***

7

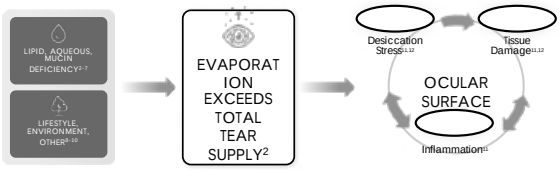
Basic Ocular Surface Principles

- 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

8

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):ST83. 4. Arita R, et al. *Am J Ophthalmol.* 2016;169:125-137. 5. Alkhamees A, et al. *Clin Exp Optom.* 2020;103(4):456-473. 6. Kawashima M, et al. *Adv Ther.* 2017;34(3):732-753. 7. Tsubota K, et al. *Ocul Surf.* 2017;15:65-76. 8. Wolffsohn JS, et al. *Ocul Surf.* 2021;21:58-63. 9. Wang MTM, et al. *Cont Lens Anterior Eye.* 2021;44(6):101409. 10. Al-Mohaseb 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.* 2021;21:145-156. | DED, dry eye disease.

9

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

12

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

13

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

14

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

15

Diagnostic Testing in Ocular Surface Disease

- Osmolarity
- MMP-9
- Vital Dyes

16

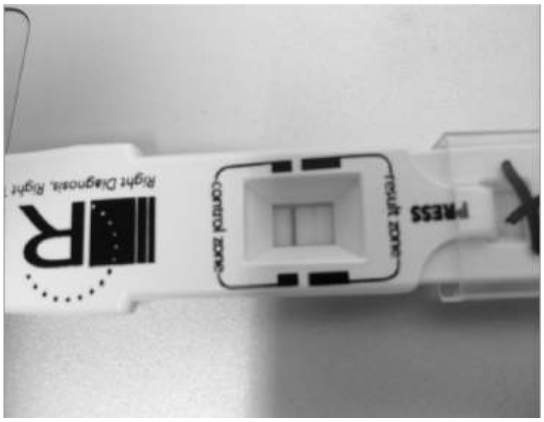
Limit of Detection

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

POSITIVE TEST RESULT
MMP-9 ≥ 40 ng/ml

NEGATIVE TEST RESULT
MMP-9 < 40 ng/ml

17



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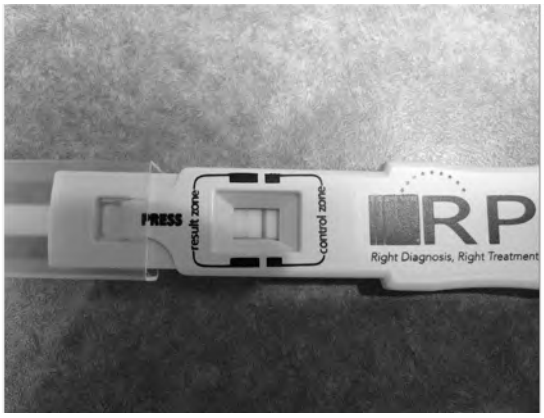

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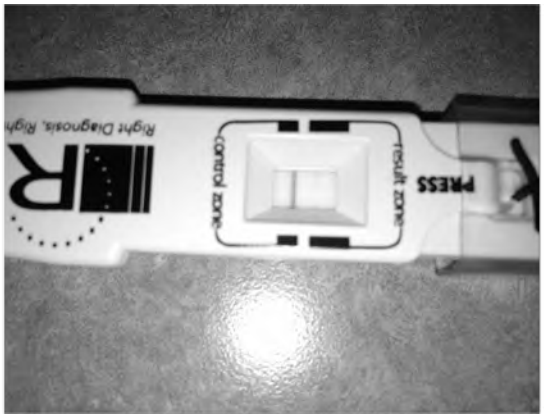


20

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

21

22

23

Hyperosmolarity in Dry Eye Diagnosis

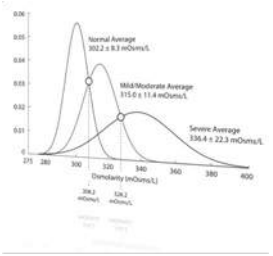
Dry Eye Diagnosis

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

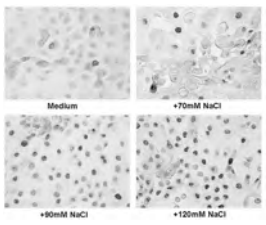


24

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**



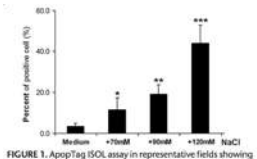


FIGURE 1. ApopTag ISOL assay in representative fields showing the increased ISOL-positive apoptotic cells in corneal epithelial cultures exposed to high-osmolarity saline-added media (+70, 90, or 120 mM NaCl) for 24 hours, compared with cells cultured in normal medium. The percentage of positive cells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

Liu H. Invest Ophthalmol Vis Sci. 2008;50:3671–3679

25

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

27

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.[3]

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

29

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.

30

So Let's Start with MGD

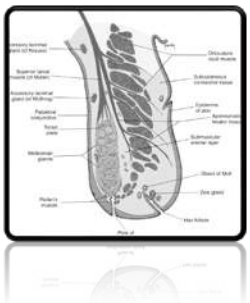
- Meibography
- Expression
- Treatment
  - Medical
  - Procedural
  - OTC
  - Neutraceutical

31

Meibomian Gland Anatomy

Meibomian gland function is regulated by:

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



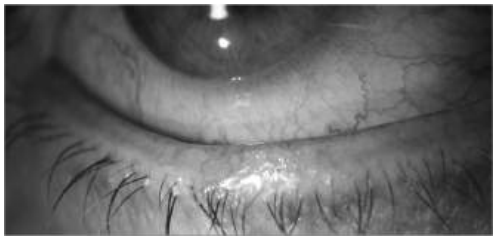
http://www.slideserve.com/lana-mccall/tear-film-lacrimal-and-meibomian-glands

32

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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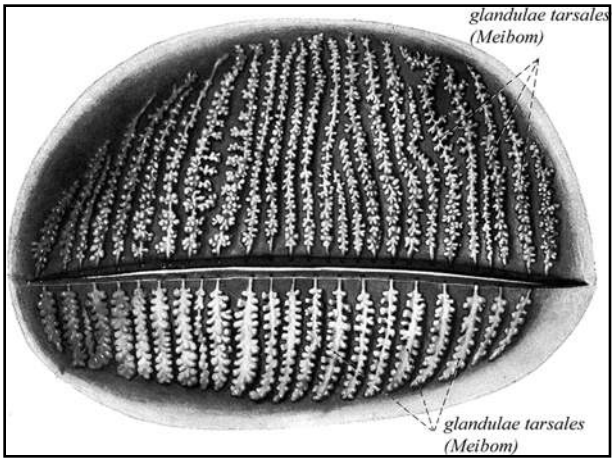

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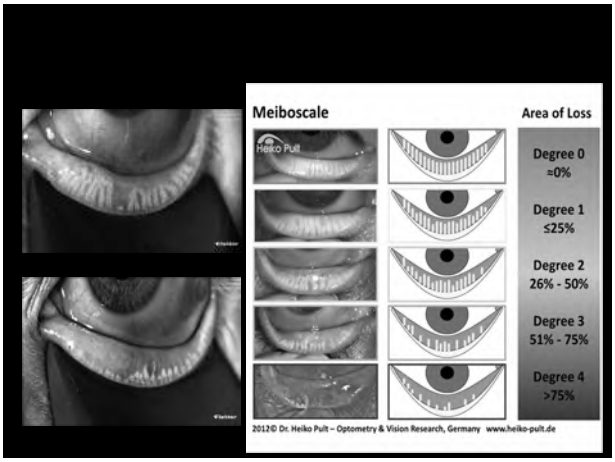

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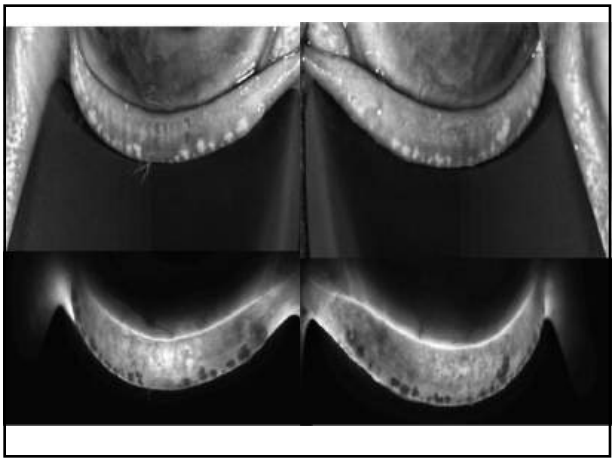

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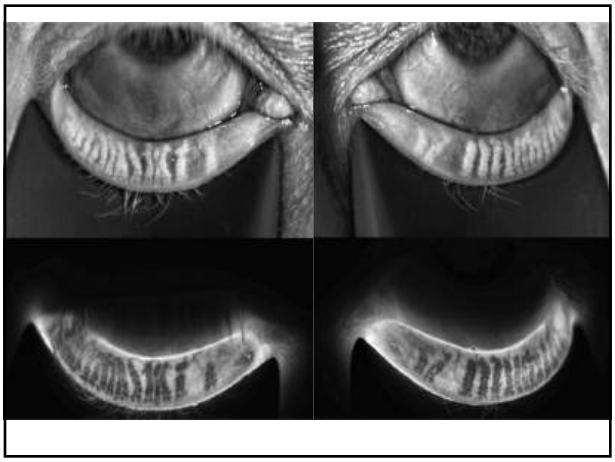


38

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.

48

Newer Ocular Surface Treatments

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

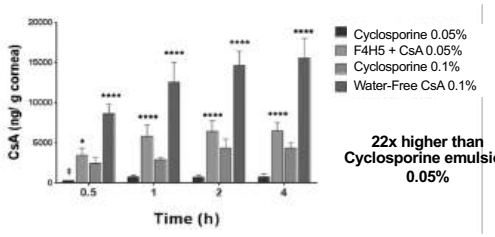
52

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

53

Ex-vivo Corneal Permeability of Cyclosporine
in Porcine Eyes

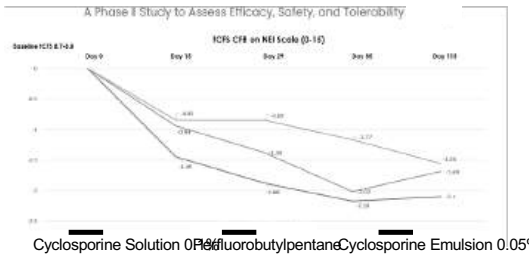


22x higher than Cyclosporine emulsion 0.05%

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

54

Water-Free Cyclosporine 0.1% Phase II Study



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

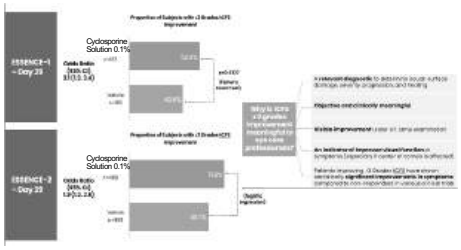
55

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

56

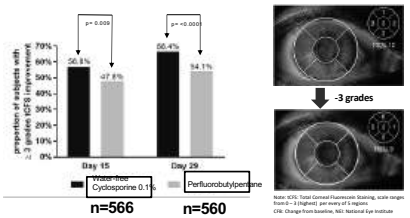
Water-Free CsA 0.1% demonstrated significantly meaningful tCFS improvement in ESSENCE-1 and ESSENCE-2



[1] ARVO 2018, Poster: Kröser S, et al., [2] Agarwal P, et al. Int J Pharm. 2018 Mar; [3] Sheppard JD, et al. Cornea. 2021 Oct; [4] Akpek EK, et al. JAMA Ophthalmol. 2023 Apr

57

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



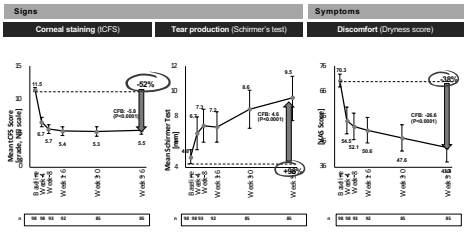
Note: tCFS: Total Corneal Fluorescein Staining, scale ranges from 0 – 3 (highest), per every of 5 regions
CFB: Change from baseline, NEI: National Eye Institute

[1] ARVO 2018, Poster: Kröser S, et al., [2] Agarwal P, et al. Int J Pharm. 2018 Mar; [3] Sheppard JD, et al. Cornea. 2021 Oct; [4] Akpek EK, et al. JAMA Ophthalmol. 2023 Apr

58

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.

Note: Analysis shows mean change from baseline with p-value for the difference in least square means. tCFS: Total Corneal Fluorescein Staining, DED: Dry Eye Disease, CFB: Change From Baseline.
1) Akpek E, et al. Submitted to AJO.

59

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%)

60

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)

61

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

KEY INCLUSION 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

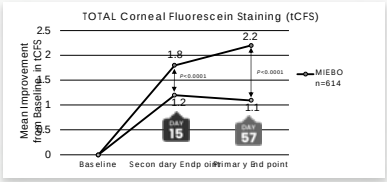
KEY EXCLUSION CRITERIA

- 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

62

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

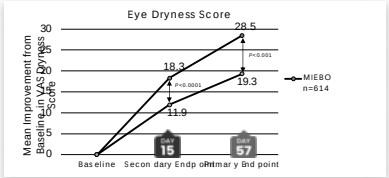


Pooled data | tCFS Grading Scale: 0-15 (0-3 in each of 5 areas) | Mean Baseline = 6.9 | At day 57, Mean (SD) CFB GOBI: –2.0 (2.6) for MIEBO (n=289) vs –1.0 (2.7) for saline (n=279) (*P*<0.001) | MOJAVE: –2.3 (2.8) for MIEBO (n=302) vs –1.1 (2.9) for saline (n=296) (*P*<0.001)

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

63

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

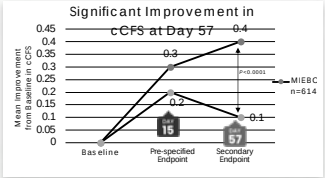


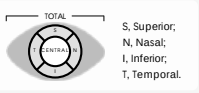
Pooled data | Visual analog scale: 0-100 (0=no discomfort, 100=maximal discomfort) | Mean Baseline, MIEBO = 65.6; Mean Baseline, Saline = 65.5 | At Day 57, Mean (SD) CFB
GOBI: –27.4 (27.9) for MIEBO (n=289) vs –19.7 (26.7) for saline (n=279) (*P*<0.001) | MOJAVE: –29.5 (28.6) for MIEBO (n=302) vs –19.0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

64

Significant Improvement in Central Corneal Staining at Day 57





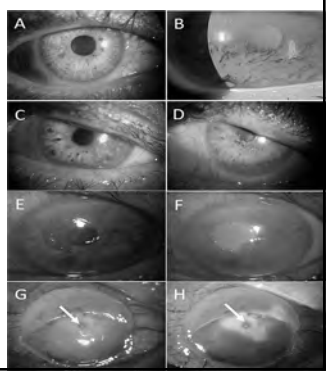
Pooled analysis (above): Mean baseline cCFS = 1.1 for MIEBO and control. cCFS grading scale: 0-3. Across GOBI and MOJAVE, 614 patients received MIEBO and 603 patients received control with 591 and 575, respectively, assessed on Day 57. | GOBI: Mean (SD) CFB –0.4 (0.8) for MIEBO (n = 289) vs –0.1 (0.9)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

65

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.



66

Case Overview

Patient Details
46 YOF presents for dry eye exam

Referral
Self referred

Visual Acuity
VA: 20/200 OD, 20/60 OS PHH OU

PHI: "Severe dry eye" that has become incapacitating, difficult to work, tried everything and nothing seems to be helping

67

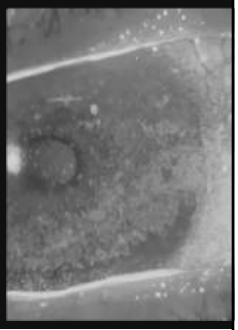
A cornea that looks like this is a patient with severe dry eye disease?

68

Additional Questions

Ocular History

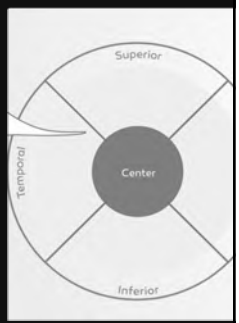
The patient's ocular history is an important consideration in understanding the context of their severe dry eye condition. Gathering details about any prior eye injuries, surgeries, or other relevant medical events can provide valuable insights.



69

Cornea Sensitivity Testing

Evaluating corneal sensitivity is a crucial step in assessing the severity of neurotrophic keratitis (NK) and determining the appropriate treatment approach.



70

Testing Corneal Sensitivity: A Key Step in Diagnosing NK

Cotton Wisp Test

QUALITATIVE

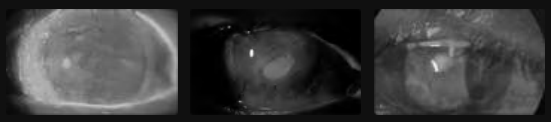
Examples include cotton swab, cotton wisp, dental floss, and tip of a tissue. Basic scoring systems may be developed using simple tests for sensation. Descriptive scales range from normal to hypoesthesia to anesthesia.

QUANTITATIVE

The Cochet-Bonnet esthesiometer is often used in basic research and clinical trial settings to quantitatively measure corneal sensitivity. While more precise, it may have limitations for general clinical practice.

71

The Mackie Classification Represents One Way to Assess NK Progression



STAGE 1 (Mild)
Punctate epithelial keratopathy (PEK)

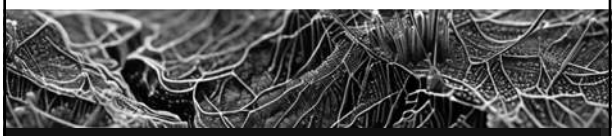
STAGE 2 (Moderate)
Persistent epithelial defect (PED)

STAGE 3 (Severe)
Corneal ulcer

NK Is a Degenerative Disease

- Some vision loss can potentially be seen in all stages of NK
- If untreated, moderate NK progresses to severe disease with associated risks of profound vision loss resulting from scarring and corneal perforation

72



NK Treatment Options

Topicals
- artificial tears
- Corticosteroids
- autologous serum eye drops
- Antibiotics
- OXERVATE (cenegermin-bbtj ophthalmic solution 0.002% \[20 mcg/mL\])

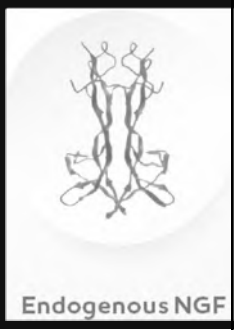
In-Office Procedures
- therapeutic contact lenses
- punctal occlusion
- non-surgical eyelid closure
- amniotic membranes
- tissue adhesives

Surgical Intervention
- Tarsorrhaphy
- conjunctival flap
- corneal transplant
- direct neurotization
- sutured amniotic membrane transplantation (AMT)

73

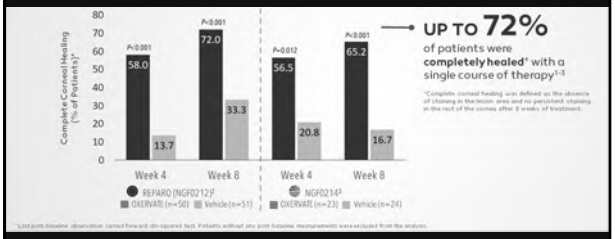
Cenegermin, the Active Ingredient in OXERVATE, Is Structurally Identical to Endogenous NGF in the Ocular Tissues

- Cenegermin is the active ingredient in the drug OXERVATE
- Cenegermin is structurally identical to endogenous NGF (nerve growth factor) found naturally in the ocular tissues.



74

Cenegermin 0.002% Efficacy at 8 Weeks



75

Long-term Efficacy of OXERVATE

80%
Remained Healed at Week 48
of patients who achieved complete corneal healing* in Study NGF0212/REPARO were still healed 48 weeks after completing one 8-week OXERVATE treatment cycle

72.0%
Week 8
Complete Corneal Healing (% of Patients)

33.3%
Week 4
Complete Corneal Healing (% of Patients)

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

(*complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment)

76

- Cross-linked hyaluronic acid gel that allows patient's eyes to be bathed in their own natural tears
- Customized for each individual patient
- Provides a full fill of the canalicular system
- Lasts for 6 months
- In-office procedure reimbursed through existing CPT code (68761)

78

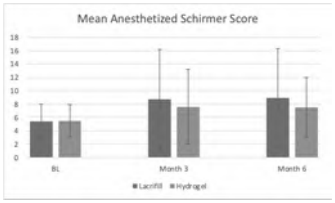
US FDA Clinical Trial Summary

- n = 157
- Subjects with anesthetized Schirmer score ≤ 10 mm, Ocular Surface Disease Index (OSDI) score ≥ 23, presence of corneal staining and patent bilateral lacrimal drainage systems were randomized in a 2:1 ratio to LACRIFILL (n = 99) or a hydrogel plug (n = 52).
- Primary endpoint at 3 months; gel removed by irrigation at 6 months
- 510(k) Clearance December 2022

79

Schirmer Score

Greater Increase in Schirmer with LACRIFILL



80

Adverse Events Generally Consistent with Dry Eye Syndrome

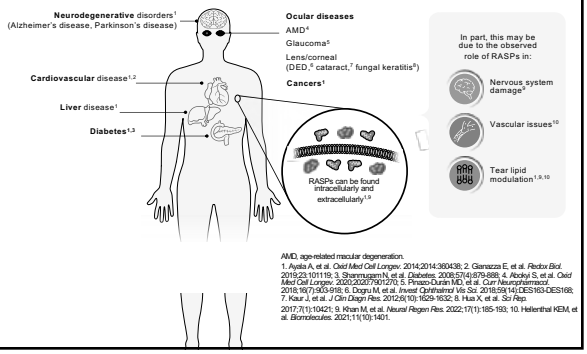
	CANALICULAR GEL (n=103)	CONTROL (n=54)
Adverse Events	%	%
Corneal Staining	36.9	40.7
Ocular Pain	9.7	0
Presumed Dacryocystitis	0.97	0
Conjunctivitis	4.9	1.9
Allergic Blepharoconjunctivitis	0.97	0
Epiphora	7.8	5.6

For further information please refer to the approved Information For Use available at lacrifill.com/instructions-for-use/

81

82

RASPs play a role in the etiology of many diseases

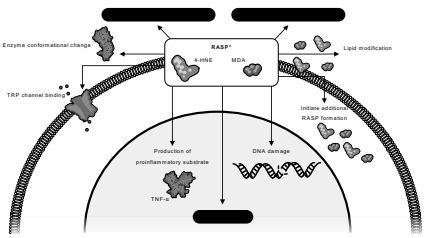


AMD, age-related macular degeneration.
1. Ayala A, et al. *Oxid Med Cell Longev.* 2014;2014:360438; 2. Gianazza E, et al. *Redox Biol.* 2019;23:101119; 3. Shanmugam N, et al. *Diabetes.* 2008;57(4):879-888; 4. Abokyi S, et al. *Oxid Med Cell Longev.* 2020;2020:7901270; 5. Pinazo-Duran MD, et al. *Curr Neuropharmacol.* 2018;16(7):903-918; 6. Dogru M, et al. *Invest Ophthalmol Vis Sci.* 2018;59(14):DES163-DES168; 7. Kaur J, et al. *J Clin Diagn Res.* 2012;6(10):1625-1632; 8. Hua X, et al. *Sci Rep.* 2017;7(1):10421; 9. Khan M, et al. *Neural Regen Res.* 2022;17(1):185-193; 10. Hellenthal KEM, et al. *Biomolecules.* 2021;11(10):1401.

83

In DED, RASPs exert damaging effects via a multipronged mechanism[1-5]

RASPs act to **amplify and perpetuate the oxidative stress cascade**



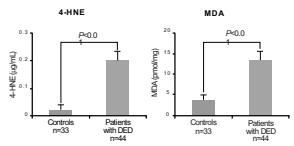
*4-HNE and MDA shown as examples of the most commonly studied RASP. TRP, transient receptor potential.
1. Hellenthal KEM, et al. *Biomolecules.* 2021;11(10):1401; 2. Scarpellini C, et al. *Int J Mol Sci.* 2023;24(1):731; 3. Raghavan S, et al. *J Leukoc Biol.* 2012;92(5):1055-1067; 4. Bu J, et al. *Antioxidants (Basel).* 2024;13(4):422; 5. Pohl EE, et al. *Molecules.* 2016;26(4):941.

84

RASP expression is associated with DED severity and meibomian gland damage

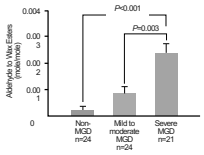
RASPs in tears[1]

RASPs are elevated in tears of individuals with DED vs controls



Meibum lipid composition[2]

Aldehyde* to wax ester ratio increases with MGD severity



*Aldehydes detected using NMR analysis of meibum composition; aldehydes (near 9.8 ppm) were detected in the non-MGD (n=2), mild to moderate MGD (n=7), and severe MGD (n=9) cohorts.
MGD, meibomian gland dysfunction; NMR, nuclear magnetic resonance.
1. Choi W, et al. *Curr Eye Res*. 2016;41:1143-1149. 2. Nagar S, et al. *Invest Ophthalmol Vis Sci*. 2023;64(10):22.

85

Acoltremon (AR-15512) Ophthalmic Solution 0.003%

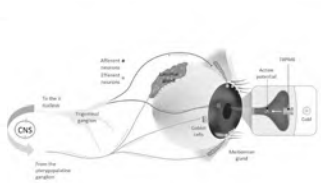
A drug candidate containing acoltremon, a TRPM8 agonist

WHAT IS TRPM8?

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

WHY TRPM8 AS A TARGET FOR DRY EYE?

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



Acoltremon ophthalmic solution 0.003% is an investigational drug that has not been approved for any indication in any country; therefore, its safety and efficacy have not been established.

1. Guerrero-Moreno A, Baudouin C, Melik Parsadaniantz S, Réaux-Le Goazigo A. *Front Cell Neurosci*. 2020;14:610342. 2. McCoy DD, Knowlton WM, McKemy DD. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(6):R1378-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(8):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.

86

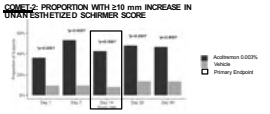
Acoltremon (AR-15512) Ophthalmic Solution 0.003%

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

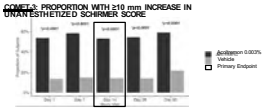
Enrollment	931 dry eye subjects completed COMET-2 and -3 studies
Primary Unanesthetized Schirmer Test	• Higher % of subjects with ≥ 10 mm increase in unanesthetized Schirmer Test scores on Day 14 with acoltremon 0.003% (ACO) compared to vehicle • Similar results seen on Day 1 and Day 90 (secondary endpoints)
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

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



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



87

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/NCT05493111. Accessed September 24, 2024.

Acoltremon ophthalmic solution 0.003% is an investigational drug that has not been approved for any indication in any country; therefore, its safety and efficacy have not been established.

88

TRPM8 as a Potential Therapeutic Target

Acoltremon[1-3]	IVW-1001[4,5]
TRPM8 agonist	TRPM8 agonist
Instilled as a drop on the ocular surface	Applied over upper eyelid
Completed phase 3 studies	Initiating phase 1/2 studies

Acoltremon and IVW-1001 are investigational drugs and have not been approved for commercialization.
TRPM8, transient receptor potential melastatin 8
1. https://clinicaltrials.gov/study/NCT05360966. Accessed March 27, 2024. 2. https://clinicaltrials.gov/study/NCT05285644. Accessed March 27, 2024. 3. Wirta DL, et al. Ocul Surf. 2022;26:166-173. 4. IVW-1001 phase 1/2 in subjects with dry eye disease. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT04408638. Accessed July 25, 2024. 5. Liang, BG et al. Chancer. Invest. Ophthalmol. Vis. Sci. 2024;65(7):5763.

25

89

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.

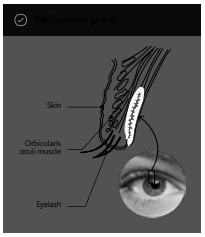
AZR-MD-001 is a keratolytic ointment dosed 2x per week @ bedtime directly to the meibomian glands

90

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**

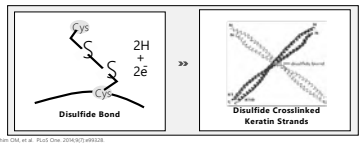


[1]Green-Church KB, et al. Invest Oph Vis Sci. 2011 Mar 30;52(4):1979-93. [2]Blackie CA, et al. Cornea. 2010;29(12):1313-45. [3]Knop E, et al. Invest Ophthalmol Vis Sci. 2011;52(4):1938-78.
[4]Butovich IA Prog Retin Eye Res. 28 (6): 463–498 [5]Tsai, PS, et al. Br J Ophthalmol. 90 (3): 372–7 [6]Jester JV, et al. Invest Ophthalmol Vis Sci. 1989;30(5):927-935.

91

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.

92

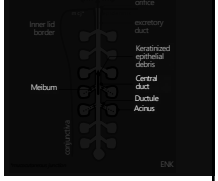
93

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

- **Increased meibum viscosity is also a leading pathogenesis of MGD[1]**
  - Keratin deeper in the gland may contribute to dysfunction
  - Acinar cells deep down in the gland may produce abnormal amounts of keratin
  - Released from the acini into the central ducts, **keratinized epithelial debris** (keratin strands crosslinked linked by strong disulfide bonds) increases the normal melting point of meibum.[2] Resulting in **altered meibum quality and thickness**

Meibum Viscosity

Meibomian Gland



[1]Knop E, et al. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1938-78 [2]Ong, et al. Curr Eye Res. 1991;10:1113-1119.

94

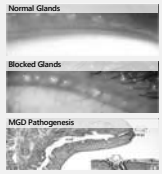
Keratinization may be present in multiple places in the Meibomian gland: Gland

- **Hyperkeratinization at the gland orifice is a leading pathogenesis of MGD[1]**

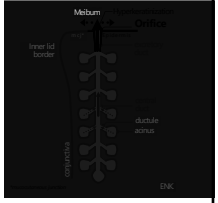
Keratin formation is a natural process
- Keratin is produced and sheds at physiological rates to confer its protective role while not accumulating in excess

At the gland orifice on the lid margin:
- Hyperproliferation may produce excess keratin (directly related to an oil-producing gland)
- Terminal Duct Obstruction: Stress at the lid margin results in excess keratinization and excess keratin may block the glands and restricts outflow of meibum

Gland Orifice



Meibomian Gland



[1] Knop E, et al. Ophthalmologe 2009;106:872–833 2 Knop E, et al. Invest Ophthalmol Vis Sci. 2011;52(4):1938-78.8.

95

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

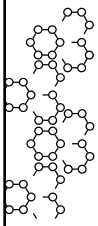
- Similar to the lid margin, secretory gland hyperkeratinization plays an important role in various skin disorders
- Comedonal lesions in acne are inspissated hair follicles, filled with corneocytes, sebum, and other debris
- Keratolytic treatments are used to shed dead corneocytes, loosen the sebum plug, and prevent the formation of inflammatory papules and pustules

Acne – Keratin Plug	Blocked Meibomian Glands	Closed Comedones	Comedonal Acne
			

96

Triple Mechanism of Action

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



DECREASE meibomian gland hyperkeratinization of ducts and orifices

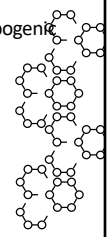
Keratostatic

LOOSEN meibomian gland blockages

Keratolytic

INCREASE secretion of meibomian gland lipids

Lipogenic



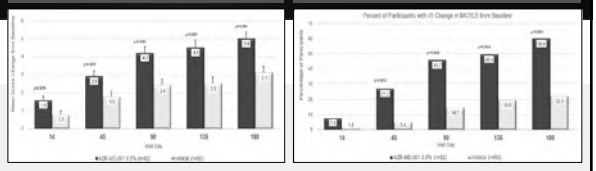
97

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

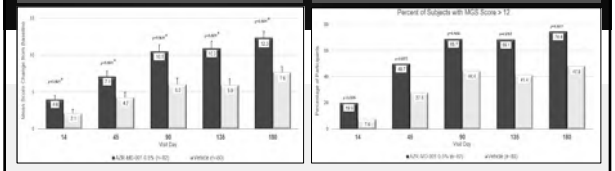
98

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

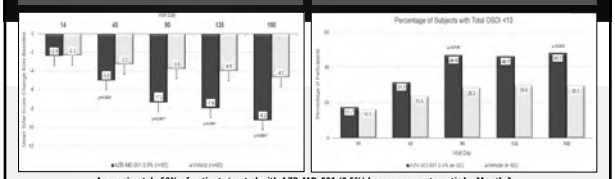
99

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

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

Reduction in Symptoms
Statistically Significant Difference from Control

% of Asymptomatic Patients
Clinically Significant Difference from Control



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

p-values completed using LS mean difference from baseline
p<0.05 change from baseline compared to vehicle

MCID for OSDI: 4.5 – 7.0 for Mild to Moderate Disease.
Miller KL, et al. Minimal Clinically Important Difference for the Ocular Surface Disease Index. Arch Ophthalmol. 2010;128(1):94-101.

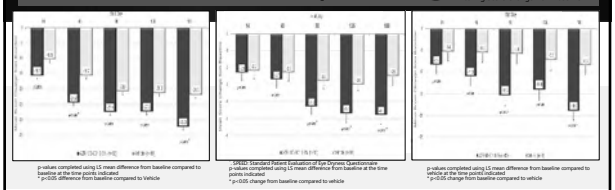
100

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

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

Statistically Significant Improvement in Eye Dryness
SPEED[1] Score Change from Baseline

Statistically Significant Decreased Itching
Itching Score Change from Baseline



p-values completed using LS mean difference from baseline compared to baseline at the time points indicated
p<0.05 difference from baseline compared to Vehicle

1. SPEED: Standard Patient Evaluation of Eye Dryness Questionnaire
p-values completed using LS mean difference from baseline at the time points indicated
* p<0.05 change from baseline compared to vehicle

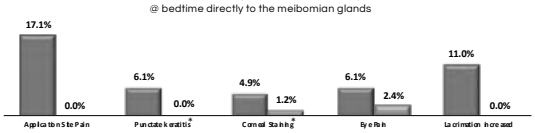
p-values completed using LS mean difference from baseline compared to vehicle at the time point indicated
* p<0.05 change from baseline compared to vehicle

101

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



* Defined as associated with an increase in corneal staining of ≥ 2 grades

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

101

102

AZR-MD-001 Clinical Data Review:

AZR-MD-001 Phase 6-month clinical trial results

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)

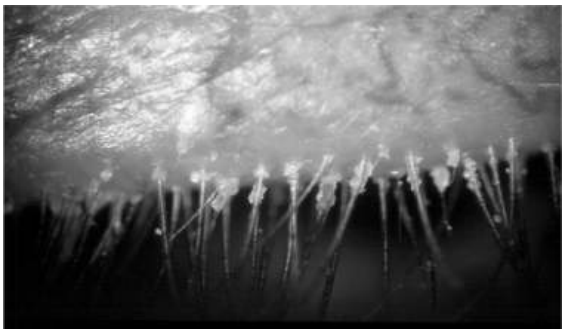
102

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!

103

Anterior Blepharitis



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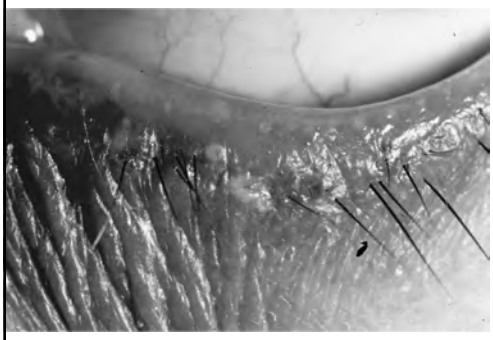
105



106

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

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)

107

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

108

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, İstanbul, Turkey

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

109

INVESTIGATION

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

Ezgi Aktaş Karabay *, Aslı Aksu Çerman

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

110

> 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 †, 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

111

Rosacea

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

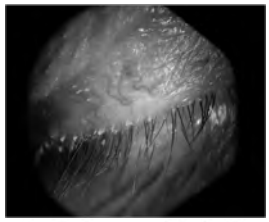
Zhao YE, Wu LP, Peng Y, Cheng H. Retrospective analysis of the association between Demodex infestation and rosacea. Arch Dermatol 2010;146:896Y902.

112

Demodex Has Been Linked to Rosacea and Blepharitis

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

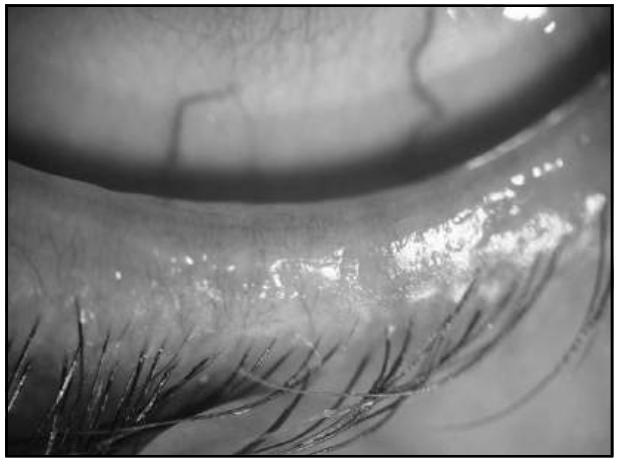
Skin Rosacea



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

113



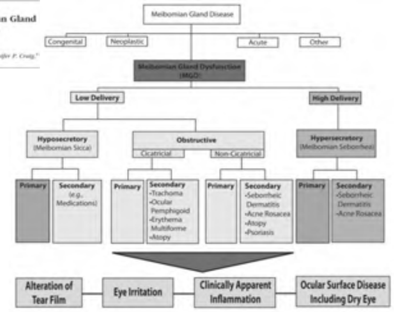
114

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

115

Classifications of MGD

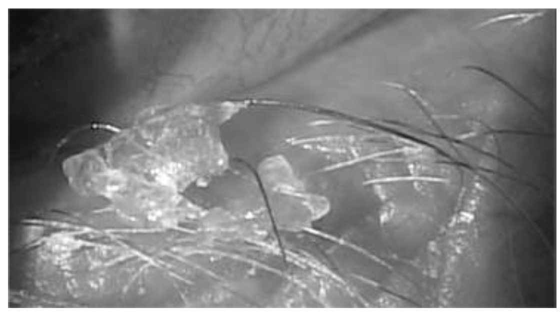


IOVS, 2011

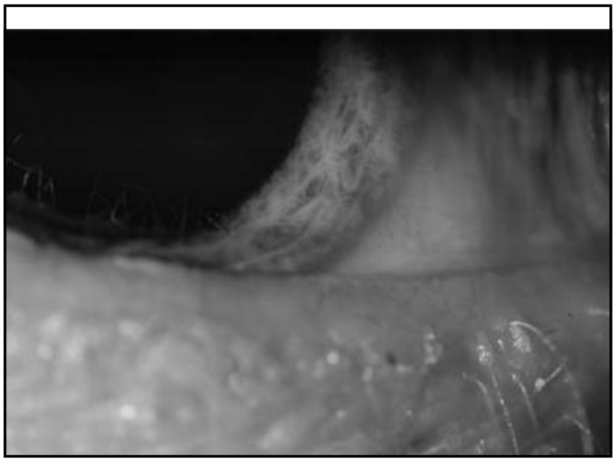
116

Seborrheic Blepharitis

117



118

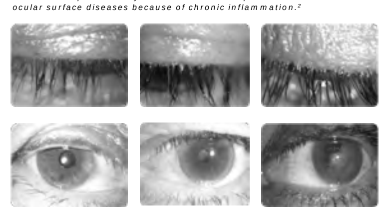


119

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



All data and images courtesy of Roberto Gonzalez-Salinas, MD.

References: 1. Aumond S, Bitton E. The eyelash follicle features and 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). 2018;10:57-63.

120

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

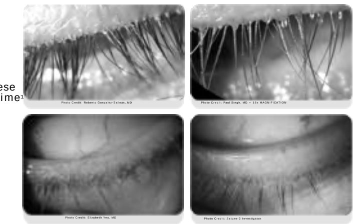


Photo Credit: Roberto Gonzalez-Salinas, MD

Photo Credit: Paul Singh, MD + 16x MAGNIFICATION

Photo Credit: Elizabeth Yeu, MD

Photo Credit: Saturn-2 Investigator

References: 1. O'Dell L, Dierker DS, 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).* 2018;10:57-63.

121

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

122

What We Really DON'T Know:

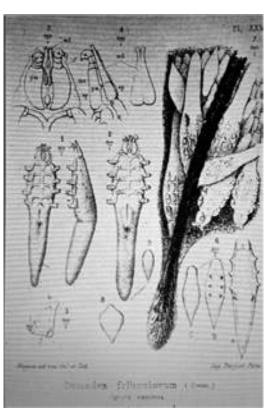
- What is the true prevalence of Demodex?
- How much Demodex results in symptoms
- How much "symptom" is needed to treat
- Which percentage of dry eye is really lipid layer evaporation vs. mucin deficiency
- What is an effective and enduring treatment for MGD?
- What is an effective and enduring treatment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

123

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?

124



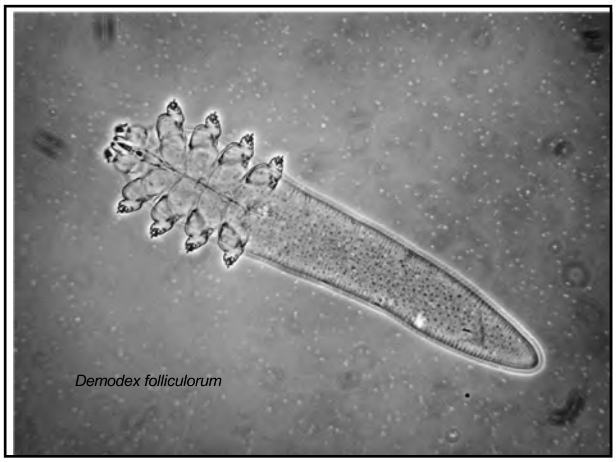
HANDBOOK OF MEDICAL ENTOMOLOGY

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

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

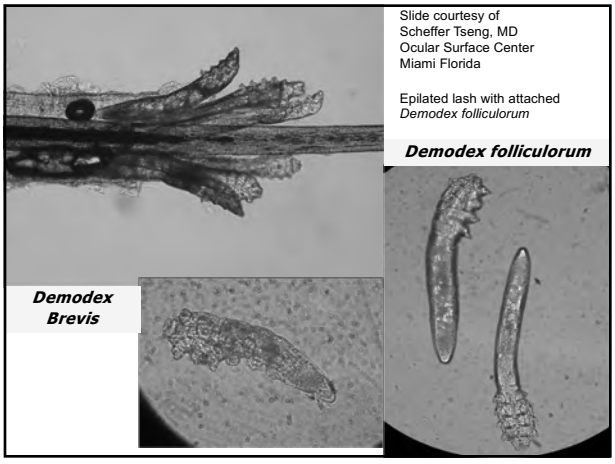
1915

125



Demodex folliculorum

126



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

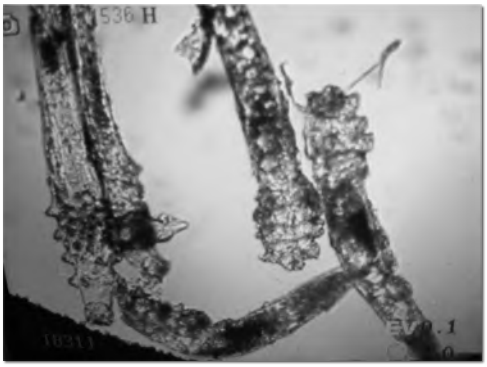
Epilated lash with attached
Demodex folliculorum

Demodex folliculorum

127

don't forget cover slips and slides

128

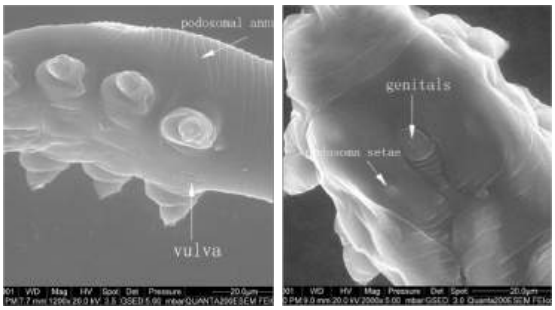


129

130

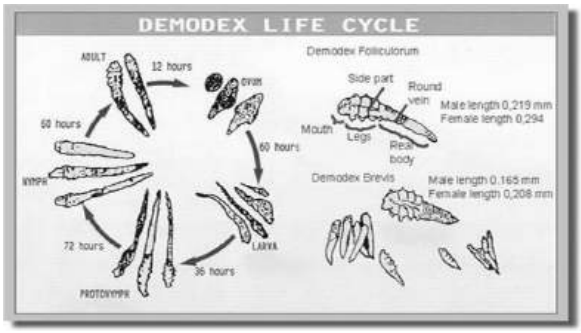
The Sexes

Fig. 3, Fig. 4



132

Demodex Life Cycle



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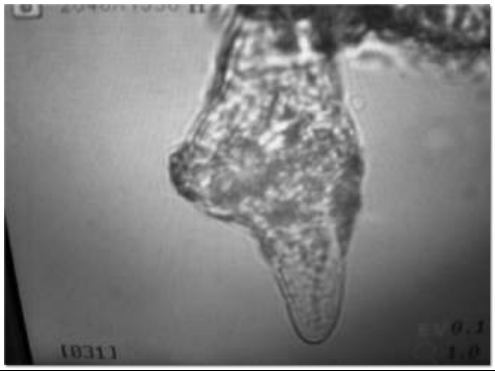


134

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.

135

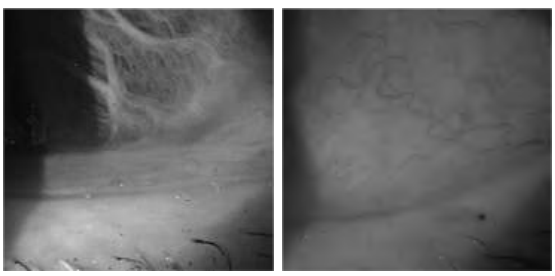
Symptoms of Demodex

- 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

136

Redundant Conjunctival Folds

137



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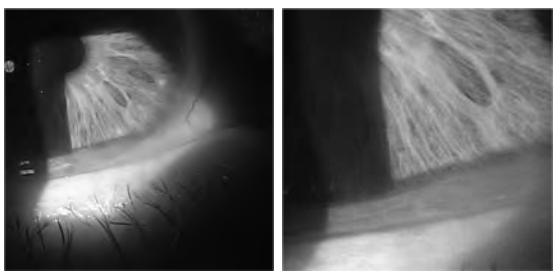

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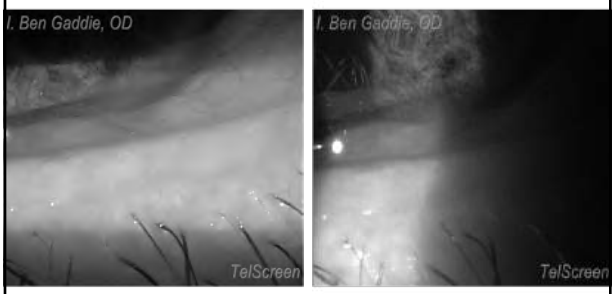


140

2. Slit lamp evaluation

141

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.

142

Cylindrical dandruff

143

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

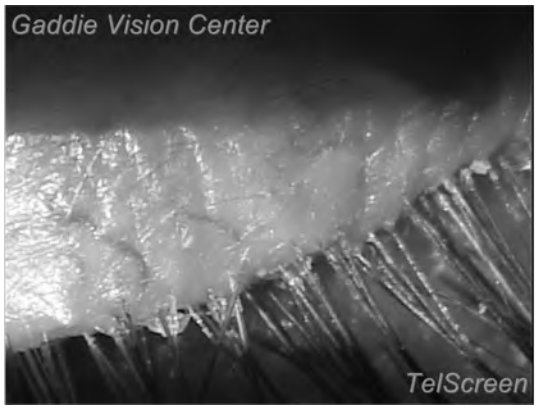
- Regurgitated undigested material combined with epithelial cells, keratin, mite eggs, and digestive enzymes, which cause irritation[3,4]
- Translucent, waxy plugs typically at base of lashes[3]

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):3089-3094. 2. Kaemsuwan, N., et al. Prevalence of ocular demodicosis among patients at Tertiary Care Center, Bangkok, Thailand. *Int J Ophthalmol* 2017; 10(1): 122-127. 3. Zhang AC, Muntz A, Wong MYM, Craig JP, Downie LE. Ocular Demodex: a systematic review of the clinical literature. *Ophthalmic Physiol Opt*. 2020;40:389-411. 4. Nicholls S, Oakley CL, Tan A, Vote BJ. Demodex species in human ocular disease: new clinicopathological aspects. *Int Ophthalmol*. 2017;37(1):359-412.

144

145



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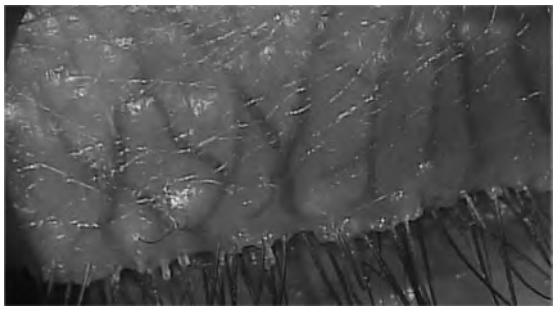

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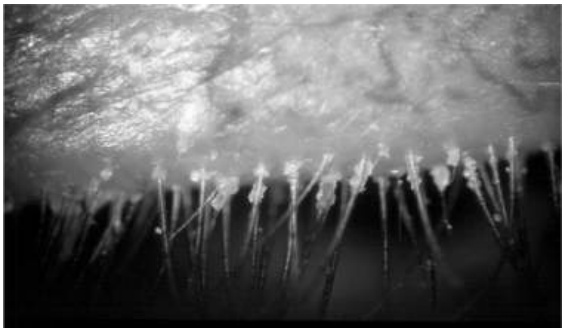

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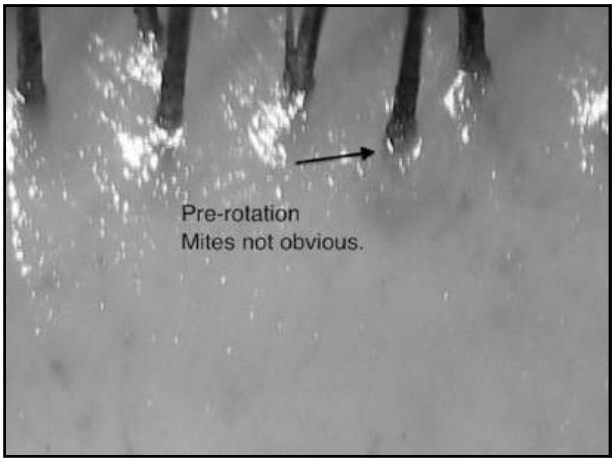

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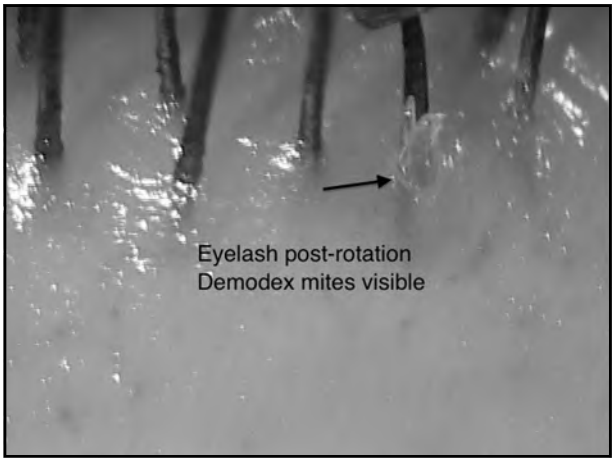

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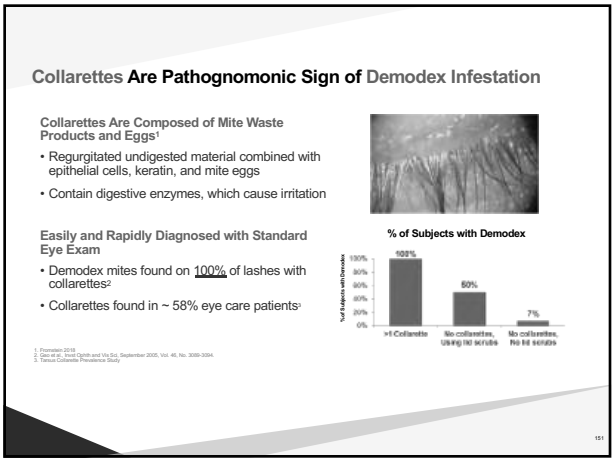
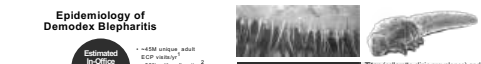


151

Blepharitis Is a Large and Underserved Market in Eye Care

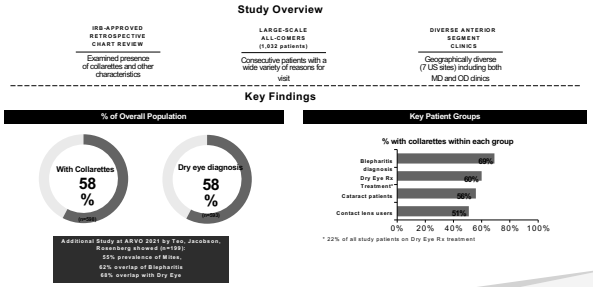


Large Patient Population with Significant Disease Impact	**Titan** (collarette clinic prevalence) and **Atlas** (disease impact) studies demonstrate high prevalence of disease and significant burden on patients
Significant Head Start on Diagnosis	2.1M ICD-10 **Blepharitis** Dx's/yr[6]
Blepharitis Routinely Causes	Eyelids to become red, irritated and itchy, with debris on the eyelashes.[7]
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[8]
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]

1. Allied Epidemiology 2019; 2(4):E8. 2019. 2. Tulsa collected prevalence study. 3. IMS Report 2019. Special Issue 2011; Vol 52: 2. 4. American Optometric Association Following Survey September 4, 2019, July 2020. 7. Wise... Ophthalmic Epidemiology. 19(2): 65–74. 2012.
5. Kunimoto, Charles Data Analysis. 6. Statista. Market Research Key Drop Report. 2019. 7. Tarsavage M. Review Analysis. 8. Wilson M. Demodex sp. as a Potential Cause of the Inflammation of the Ocular Surface. Wiley Online Library. Received: Nov 10, 2019; 2019:00:00

152

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



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

153

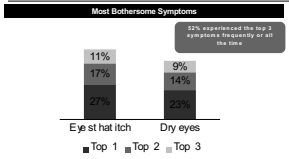
Atlas Study Reveals Symptomatic and Psychosocial Burden of *Demodex* Blepharitis: 80% Report Negative Impact on Daily Life

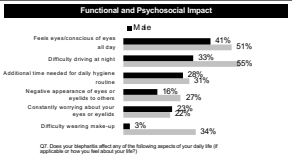
- Multicenter, observational study of patients pre-screened for the Saturn-1 pivotal trial
- Evaluated the clinical and patient reported impact of *Demodex* blepharitis (interim analysis of 311 patients)
  - Presence of *Demodex* mites (at least 1 mite per lash)
  - Presence of collarettes (> 10, upper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





154

155

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.**
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.

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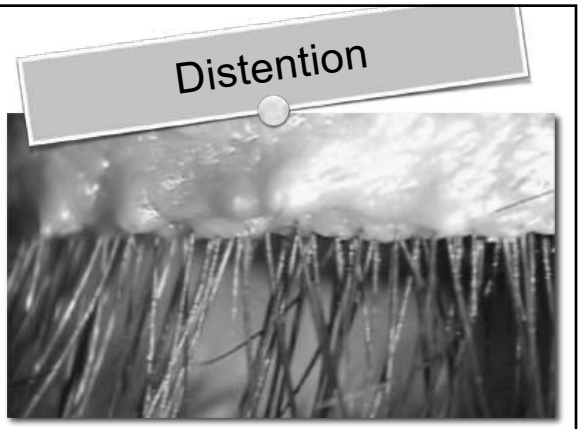
156



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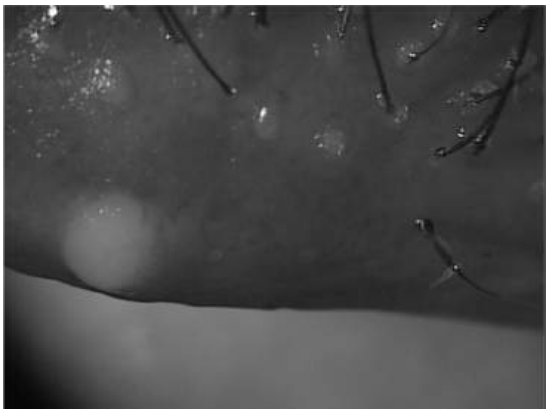

158

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]✉

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 *Demodex* Expert Panel on Treatment and Eyelid Health (DEPTH). Following 3 surveys, experts agreed that DB is chronic ($n = 11$) and recurrent ($n = 12$) and is often misdiagnosed. Consensus was achieved regarding inflammation driving symptoms (median = 7; range 7–9), collarettes as the most common sign ($n = 10$) and pathognomonic for DB (median = 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

160

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

162

Collarettes **Can Be Easily Missed on the** Upper Lid!

Patient 1, Looking straight on

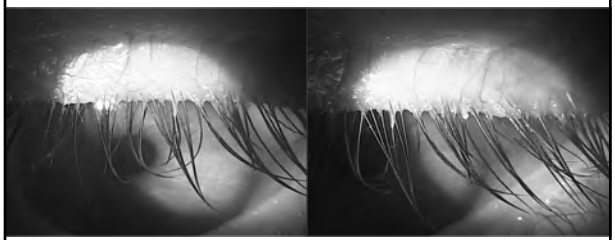
Patient 1, Looking straight on, with lid lift

c/o E. Yeu, MD, 1.0 mag

163

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

164

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

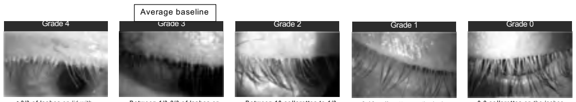
- **Efficacy:** All pre-specified primary, secondary, and exploratory endpoints were met
  - Primary Endpoint: Complete Collarette Cure **p < 0.0001**
  - Clinically Meaningful Collarette Cure (Grade 0 or 1) **p < 0.0001**
  - Secondary Endpoint: Mite Eradication **p < 0.0001**
  - Secondary Endpoint: 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

168

Collarette Grading Scale Used in Saturn-1

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

Average baseline



Grade 4	Grade 3	Grade 2	Grade 1	Grade 0
• **>2/3 of lashes** on lid with collarettes • Approximately 150 collarettes/lid	• **Between 1/3-2/3 of lashes** on lid with collarettes • Approximately 100 collarettes/lid	• **Between 10 collarettes to 1/3 of lashes** on lid with collarettes • Approximately 50 collarettes/lid	• **3-10 collarettes** on the lashes	• **0-2 collarettes** on the lashes • Cure of collarettes

Photos are images taken of patients in Saturn-1 with the corresponding collarette grade.

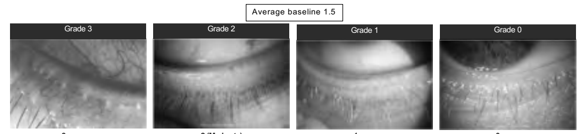
169

169

Lid Margin Erythema Scale Used in Saturn-1

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

Average baseline 1.5



3 (Severe)* | 2 (Moderate) | 1 (Mild) | 0 (None)

Hosseini K, Bourque LB, Hays RD. Development and evaluation of a measure of patient-reported symptoms of blepharitis. Health and Quality of Life Outcomes 2018;16:11 May 2018. Drug Design, Development and Therapy Volume 12:1269-1279

*Image reproduced with permission from Jiang et al. Efficacy of intra-meibomian gland injection of the anti-VEGF agent bevacizumab for the treatment of meibomian gland dysfunction with lid-margin vascularity, Drug Design, Development and Therapy 2018:12 1269-1279, © Dove Medical Press Limited. Grades 0, 1, and 2 images are from patients in Saturn-1.

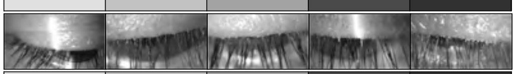
Photos are images taken of patients in Saturn-1 with the corresponding collarette grade.

170

170

Assessing Severity of *Demodex* Blepharitis: Collarettes*

Collarette grade (nonlinear)				
0	1	2	3	4
0 to 2 lashes/eyelid with collarettes	3 to 10 lashes/eyelid with collarettes	>10 to <1/3 (~50)*,† lashes/eyelid with collarettes	≥1/3 to <2/3 (~100)*,† lashes/eyelid with collarettes	≥2/3 (~150)*,† lashes/eyelid with collarettes



†Per a randomized, controlled, double-masked, phase 2b/3 clinical trial of 421 patients with *Demodex* blepharitis.

Yeu E et al. *Cornea*. 2022. Ahead of print. doi:10.1097/ICO.0000000000003097

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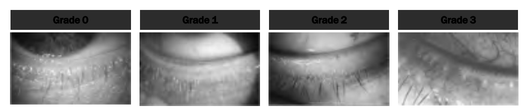
171

171

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



0 (None) | 1 (Mild) | 2 (Moderate) | 3 (Severe)

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.[2]

*Per the Saturn-1 trial. This was a randomized, controlled, double-masked, phase 2b/3 clinical trial of 421 patients with *Demodex* blepharitis.

1. Yeu E et al. *Cornea*. 2022. Ahead of print. doi:10.1097/ICO.0000000000003097. 2. Jiang X et al. *Drug Des Dev Ther*. 2018;12:1269-1279.

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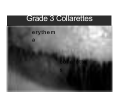
172

172

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



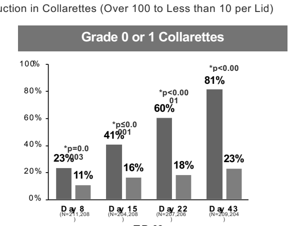
Photos are images taken of patients in Saturn-1

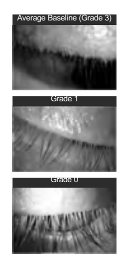
173

173

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)





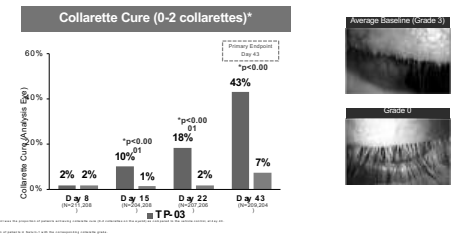
Photos are images taken of patients in Saturn-1 with the corresponding collarette grade.

174

174

Primary Endpoint of Complete Collarette Cure Achieved

Regulatory Endpoint of Complete Collarette Cure Observed by Week 2



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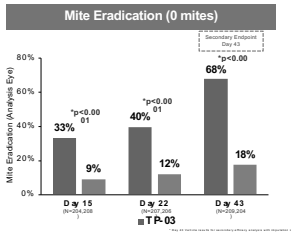
Secondary Endpoint of Mite Eradication Rate Achieved

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



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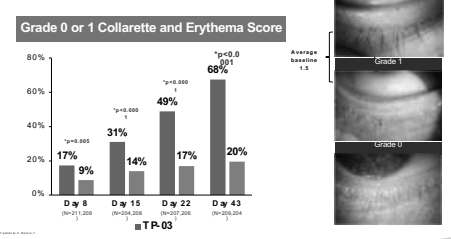
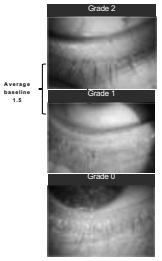
Clinically Meaningful Composite Cure

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

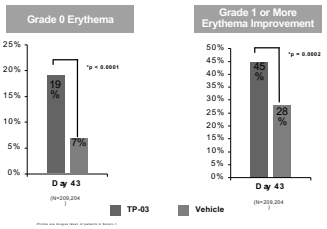


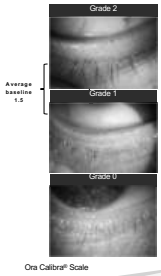


177

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

179

Adverse Event Summary

Treatment related ocular AEs occurring at rate of ≥ 1% in active group

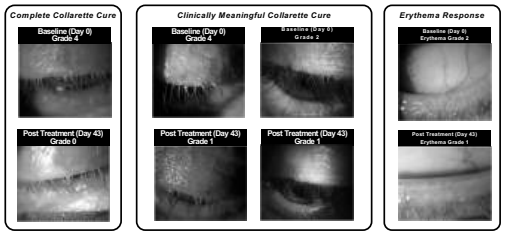
– Summary of Adverse Events occurring at any time during trial

	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

180

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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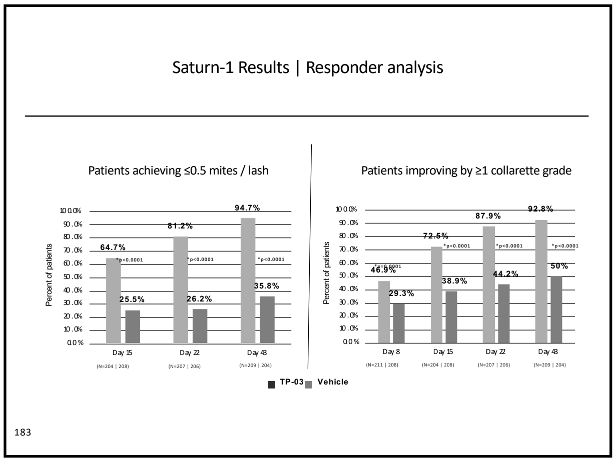

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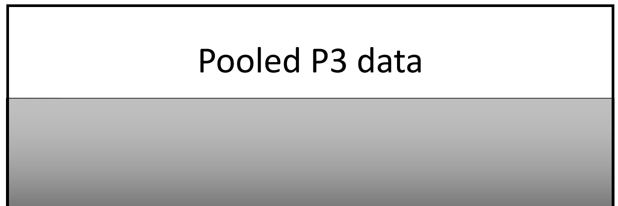
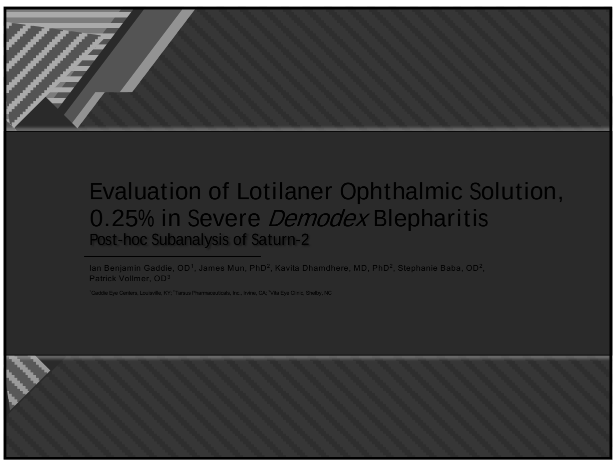


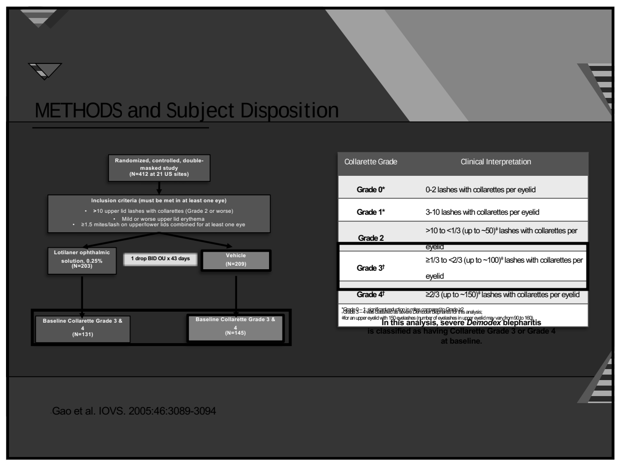
	Saturn-1 (Pivotal Phase 2b/3)	Saturn-2 (Pivotal Phase 3) N=412	Combined Pivotal Data
Primary Endpoint: Complete Collarette Cure	44% vs. 7% (p<0.0001)	56% vs. 13% (p<0.0001)	50% vs. 10%
Clinically Meaningful Collarette Cure (Grade 0 or 1)	81% vs. 23% (p<0.0001)	89% vs. 33% (p<0.0001)	85% vs 28%
Mite Eradication	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

184



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

185



METHODS and Subject Disposition
Randomized, controlled, double-masked study (N=412 at 21 US sites)
Inclusion criteria (must be met in at least one eye)
>10 upper lid lashes with collarettes (Grade 2 or worse)
Mild or worse upper lid erythema
≥1.5 mites/lash on upper/lower lids combined for at least one eye
Lotilaner ophthalmic solution, 0.25% (N=203)
1 drop BID OU x 43 days
Vehicle (N=209)
Baseline Collarette Grade 3 & 4 (N=131)
Baseline Collarette Grade 3 & 4 (N=145)

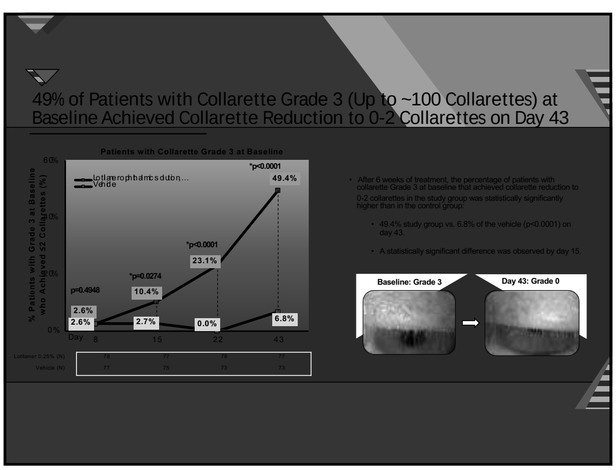
Collarette Grade	Clinical Interpretation
Grade 0*	0-2 lashes with collarettes per eyelid
Grade 1*	3-10 lashes with collarettes per eyelid
Grade 2	>10 to <1/3 (up to ~50)‡ lashes with collarettes per eyelid
Grade 3†	≥1/3 to <2/3 (up to ~100)‡ lashes with collarettes per eyelid
Grade 4†	≥2/3 (up to ~150)‡ 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;
‡for an upper eyelid with 150 eyelashes (number of eyelashes in upper eyelid may vary from 90 to 160)

In this analysis, severe *Demodex* blepharitis is classified as having Collarette Grade 3 or Grade 4 at baseline.

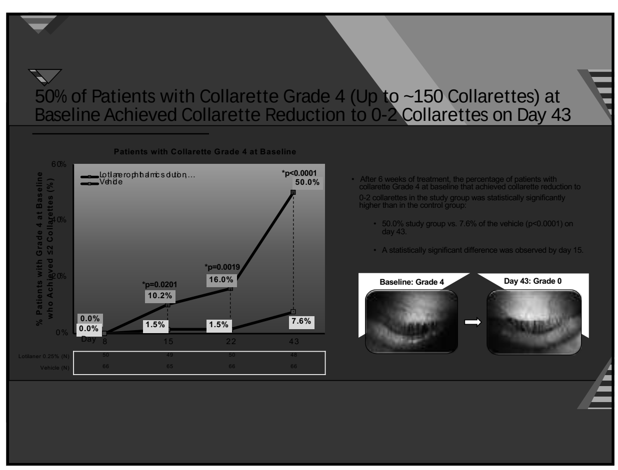
Gao et al. IOVS. 2005:46:3089-3094

186



49% of Patients with Collarette Grade 3 (Up to ~100 Collarettes) at Baseline Achieved Collarette Reduction to 0-2 Collarettes on Day 43
Patients with Collarette Grade 3 at Baseline
% Patients with Grade 3 at Baseline who Achieved ≤2 Collarettes (%)
p=0.4948
*p=0.0274
*p<0.0001
*p<0.0001
2.6%
2.6%
10.4%
2.7%
23.1%
0.0%
49.4%
6.8%
Day 8 15 22 43
Lotilaner 0.25% (N) 78 77 78 77
Vehicle (N) 77 75 73 73
• 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.
Baseline: Grade 3
Day 43: Grade 0

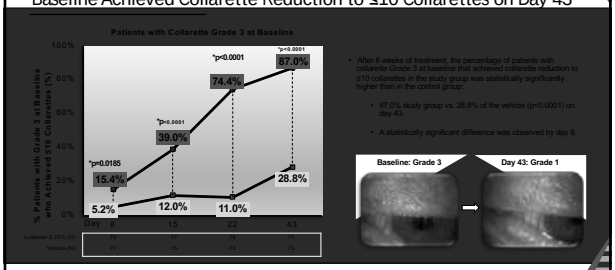
187



50% of Patients with Collarette Grade 4 (Up to ~150 Collarettes) at Baseline Achieved Collarette Reduction to 0-2 Collarettes on Day 43
Patients with Collarette Grade 4 at Baseline
% Patients with Grade 4 at Baseline who Achieved ≤2 Collarettes (%)
*p=0.0201
*p=0.0019
*p<0.0001
0.0%
0.0%
10.2%
1.5%
16.0%
1.5%
50.0%
7.6%
Day 8 15 22 43
Lotilaner 0.25% (N) 50 49 50 48
Vehicle (N) 66 65 66 66
• 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.
Baseline: Grade 4
Day 43: Grade 0

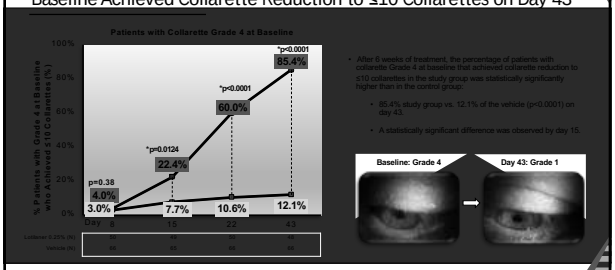
188

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



189

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



190

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

191

192

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

193

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

194

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

195

% 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

196

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

197

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

198

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

199

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

200

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

206

207

208

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

209

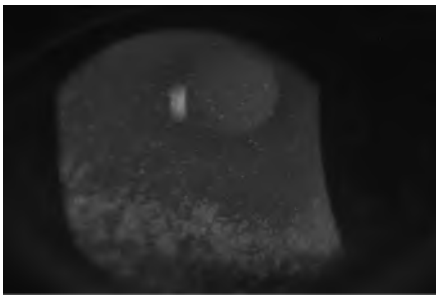
210

Case

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

211

212

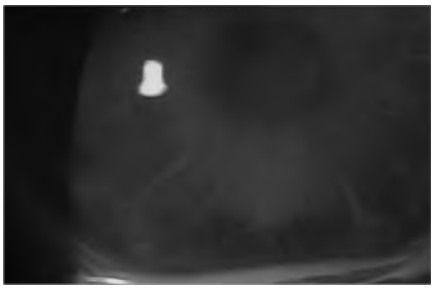


213

Case

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

214



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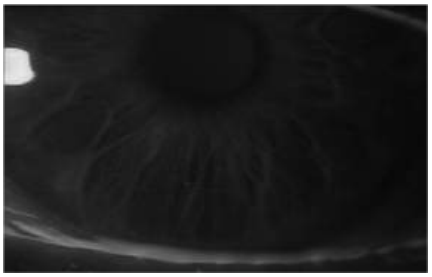


216

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%

217

Case 1

218

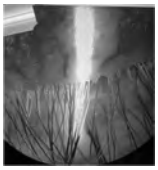
29-year-old WF with complaints of fluctuating vision, irritated eyes, and some redness. She owns a flower business, but states this has never been a problem in the past. I am tired of wearing my contact lenses and is interested in refractive surgery.

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

219

SPEED: 6/28
BCVA: 20/15 OD 20/15 OS
MRX: -3.50 OU
IOP: 12 OD 12 OS
MMP-9 Testing: Positive OU
Osmolarity: 300 OD 322 OS

SLEx:
Lids/Lashes: See photo's; Minimal meibum secretions noted
Conjunctiva/Sclera: Trace injection noted OU, no staining
Cornea: Clear; TBUT: 7 seconds OU
A/C: Deep and Quiet OU
Iris: Flat OU
Lens: Normal



220

Case Considerations

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

221

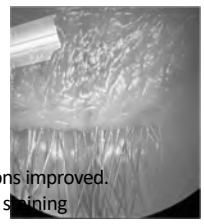
What I Did

1. Heat and gland clearing treatment in clinic OU
2. Start loteprednol bid x 1 month OU
3. Start lotilaner bid OU x 6 weeks OU
4. At home maintenance
5. RTC in 6 weeks for a recheck

222

Patient states VA seems better.
BCVA: 20/15 OD 20/15 OS
IOP: 14 OD 14 OS
Osmolarity: 300 OD 300 OS

SLEx:
Lids/Lashes: See photo; Meibum secretions improved.
Conjunctiva/Sclera: Clear, no injection or staining
Cornea: Clear; TBUT: >10 seconds OU
A/C: Deep and Quiet OU
Iris: Flat OU
Lens: Normal



223

Case 2

224

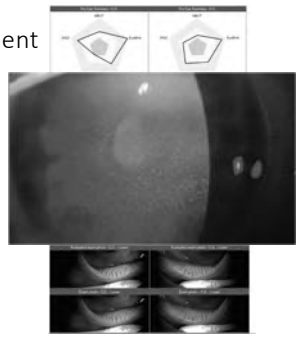
- **75-year-old Caucasian male**
  - **Not good with my drops**
  - **VA seems to change**
- **Referred for GLC Eval**
- **PEHX: SLT x 2**
- **BCVA**: 20/20 -1 OU
- TMAX: 30 mmHg OU
- Medications:
  - Latanoprost 1 x a day
  - Timolol 1 x a day

- **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)

225

Ocular Surface Assessment

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



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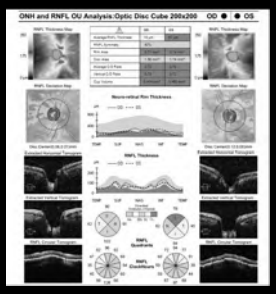

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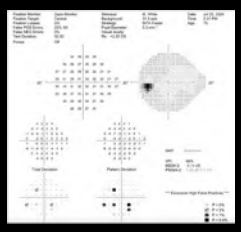
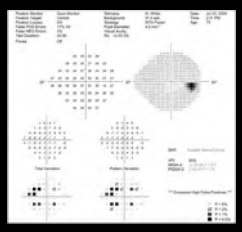


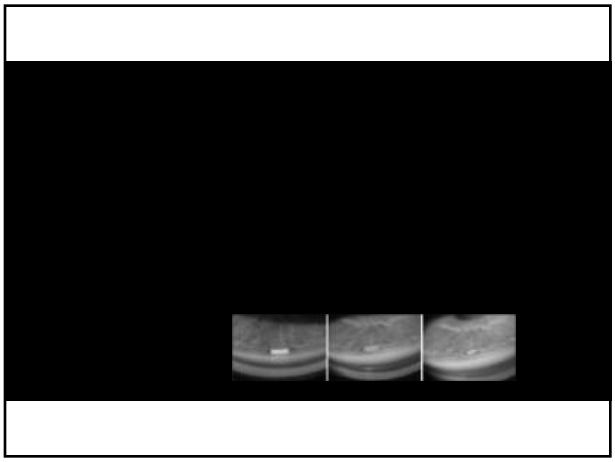


228

Treatment Considerations

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

229



230

Case 3

231

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

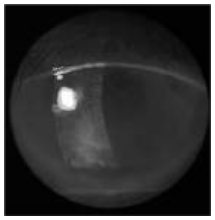
- 61-year-old female – Also noticed that her vision fluctuates; is worse as the day goes on; spends 4 to 6 hours a day on a computer or tablet
- Patient does not smoke, run a ceiling fan, or rub her eyes

- 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

232

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:

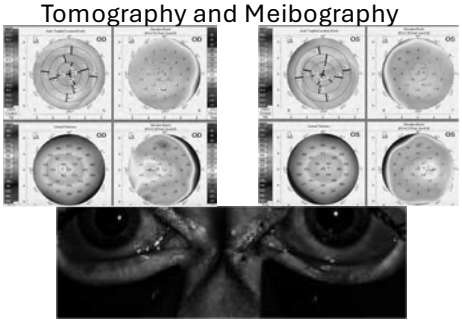
- Lids/Lashes: Minimal meibum secretions, slightly opaque, low tear meniscus
- Conjunctiva/Sclera: Clear, no injection noted OU, no significant staining
- Cornea: 2+ to 3 diffuse punctate epithelial erosions (PEEs) OU (see image); TBUT: < 5 seconds OU
- A/C: Deep and quiet OU
- Iris: Flat OU
- Lens: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

Posterior Segment:

- Unremarkable

233

Tomography and Meibography



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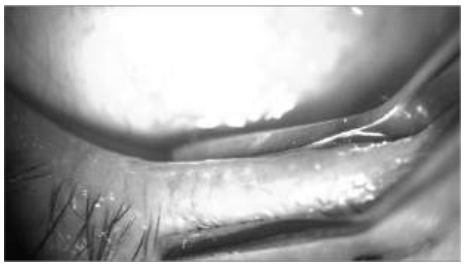


235

Case Conclusion: 6-Week Follow-Up

Intervention:

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

236

Acoltremon (AR-15512) Ophthalmic Solution 0.003%

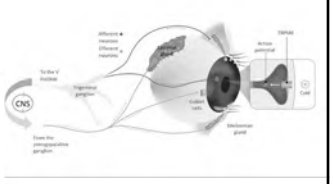
TRPM8 agonist

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;14:610342. 2. McCoy DD, Knowlton WM, McKemy DD. *Am J Physiol Regul Integr Comp Physiol.* 2011;300(6):R1278-R1287. 3. Hosta H and Meng ID. *Invest Ophthalmol Vis Sci.* 2010;51(6):3069-3076. 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.

237

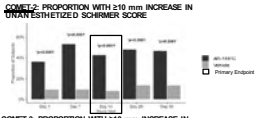
Acoltremon (AR-15512) Ophthalmic Solution 0.003%

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

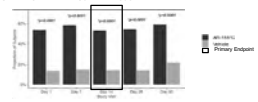
Enrollment	931 dry eye subjects completed COMET-2 and -3 studies
Primary Unanesthetized Schirmer Test	• Higher % of subjects with ≥ 10 mm increase in unanesthetized Schirmer Test scores on Day 14 with acoltremon 0.003% (ACO) compared to vehicle • Similar results seen on Day 1 and Day 90 (secondary endpoints)
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

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



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



238

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/NCT05493111. Accessed September 24, 2024.

239

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.

240