

## Blepharitis: The Biggest Unmet Need in Eyecare

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## Financial Disclosures: Ben Gaddie, OD

- Consultant
  - Allergan
  - Bausch and Lomb
  - Tarsus
  - Ocusoft

## What Is Blepharitis?

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

### TFOS DEWS II - Diagnostic Methodology

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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
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16. Questionnaire Forms (DEQ-5 & OSDI)

#### 6.8.1.1 Anterior

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

#### 6.8.1.2 Posterior

##### 6.8.1.2.1 Lid wiper epithelopathy (LWE)

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

#### 9.2 Anterior blepharitis

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

**9.3 Demodex**

Demodex mites are common elongated microscopic ectoparasites that live on the surface of the human body. Demodex infestation is related to age with 84% of the population at age 40 and 100% of those older than 70 years exhibiting Demodex infestation [527]. Demodex can spread from the face to the eyelids, perhaps leading to blepharitis and also rosacea [527-530], which may be the link between DED and meibomian gland dysfunction [528,531-533]. However Demodex infestation can also be found in asymptomatic patients [529]. Contact lens wearers do not show higher rates of Demodex infestation than non-wearers, but the relationship with DED symptoms and signs has not been investigated [534]. Two species, Demodex folliculorum and Demodex brevis have been identified in human eyelids [529,535,536]. Demodex folliculorum are typically found in the lash follicles of the eyelids, whereas Demodex brevis burrow deep into sebaceous and meibomian glands. Sebum is thought to be their main food source and Demodex mites may consume follicular and glandular epithelial cells, which may lead to direct damage of the lid margin [529]. Demodex mites can cause blepharitis by carrying bacteria on their surface including streptococci and staphylococci [529,537]. Also the protein inside the Demodex mites and their waste products may trigger inflammatory responses, likely via a delayed hypersensitivity or an innate immune response [538]. Demodex-based lid margin inflammation may result in blepharoconjunctivitis [529]. Proper treatment of ocular demodicosis may resolve blepharoconjunctivitis in adults [529,539], however its role in children remains unclear [529]. Severe cases of demodex with inflamed lid margins can affect the cornea [529,540].

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

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

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

An Bras Dermatol. 2020;65(2):187-191



**INVESTIGATION**

**Demodex folliculorum infestations in common facial dermatoses: acne vulgaris, rosacea, seborrheic dermatitis**<sup>1,2,3</sup>

Ezgi Aktaş Karabay<sup>1</sup>, Ashi Aksu Çerman<sup>2</sup>

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Received 18 March 2019; accepted 26 August 2019  
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**KEYWORDS:** Acne vulgaris; Demodex; Seborrheic dermatitis; Rosacea

**Abstract:** Demodex mites are found on the skin of many healthy individuals. Demodex mites in high numbers are considered to play a pathogenic role. This study aims to investigate the demodex infestation rates in patients with the three most common facial dermatoses: acne vulgaris, rosacea and seborrheic dermatitis. Methods: The prospective observational study included 127 patients (88 acne vulgaris, 41 with rosacea and 41 with seborrheic dermatitis) and 17 healthy controls. The presence of Demodex was revealed by epilation and the eyelashes were taken from the patients and control groups. Results: In terms of gender and age, no significant difference was found between the patients and controls ( $p > 0.05$ ). Demodex infestation rates were significantly higher in patients than in controls ( $p < 0.001$ ). Demodex infestation rates were significantly higher in the rosacea group than in the acne vulgaris and seborrheic dermatitis groups and controls ( $p = 0.001$ ,  $p = 0.001$ ,  $p < 0.001$ , respectively). Demodex infestation was found to be significantly higher in the acne vulgaris and seborrheic dermatitis groups than in controls ( $p = 0.001$  and  $p = 0.001$ , respectively). No difference was observed between the acne vulgaris and seborrheic dermatitis groups in terms of demodicosis ( $p = 0.394$ ). Conclusion: Small sample size is a limitation of the study. The lack of a diagnostic scoring system in the diagnosis of Demodex infestation is another limitation.

**Results:** In terms of gender and age, no significant difference was found between the patients and controls ( $p > 0.05$ ). Demodex infestation rates were significantly higher in patients than in controls ( $p = 0.001$ ). Demodex infestation rates were significantly higher in the rosacea group than in the acne vulgaris and seborrheic dermatitis groups and controls ( $p = 0.001$ ;  $p = 0.024$ ;  $p = 0.001$ , respectively). Demodex infestation was found to be significantly higher in the acne vulgaris and seborrheic dermatitis groups than in controls ( $p = 0.001$  and  $p = 0.001$ , respectively). No difference was observed between the acne vulgaris and seborrheic dermatitis groups in terms of demodicosis ( $p = 0.294$ ).

**The rapid effect of pulsed dye laser on demodex density of facial skin**

Ragej Ertay<sup>1</sup>, Ozan Yaman<sup>2</sup>, M Reyat Akkuş<sup>3</sup>, Emin Özü<sup>3</sup>, Abdüvki<sup>1</sup>, Yılmaz Ulaş<sup>1</sup>, Kemal Özyurt<sup>1</sup>, Mustafa Atasoy<sup>1</sup>

Affiliations + expand  
PMID: 29883220 DOI: 10.1080/14764172.2018.1481509

**Abstract**

**Background:** Recently, treatment with acaricides, which is aimed at reducing excessive proliferation of demodex mites, has gained popularity due to its providing a significant improvement in the symptoms of diseases, such as rosacea, seborrheic dermatitis, and perioral dermatitis. The effect of IPL on demodex mites was reported in skin biopsy specimens in three patients; however, to the best of our knowledge, no study exists to date, which evaluates the effect of pulsed dye laser (PDL) on demodex density (Dd) in larger patient group. We aim here in to observe the Dd before and after PDL therapy with two different skin biopsy techniques.

**Material and methods:** Thirty-one patients diagnosed with rosacea were included in the study who received PDL treatment. Dds which were measured by using both the SSSB (standardized skin surface biopsy) and CTM (cellulophane tape method) techniques before and after 3 weeks of PDL therapy were evaluated.

**Results and discussion:** The Dd of patients before PDL treatment was 13.0 (interquartile range (IQR): 5.0-28.0) and after 3 weeks of PDL treatment it was 6.0 (IQR: 2.0-12.0) with SSSB. After PDL treatment, the Dd was significantly lower than pretreatment the Dd ( $p < 0.002$ ). The present study shows that PDL significantly reduced Dd in facial skin with one session.

**Keywords:** Demodex; cellulophane tape method; demodex density; pulsed dye laser; standardized skin surface biopsy.

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 seborrheic dermatitis?**

Y Karıncaoğlu<sup>1</sup>, B Tepe, B Kalaycı, M Atambay, M Seyhan

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

**Abstract**

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

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

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

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

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

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**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 may have either direct or indirect role in the aetiology of SD.

**Similar articles**

## Allergy

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

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

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


## 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.

## Demodex Has Been Linked to Rosacea and Blepharitis

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



**Skin Rosacea**





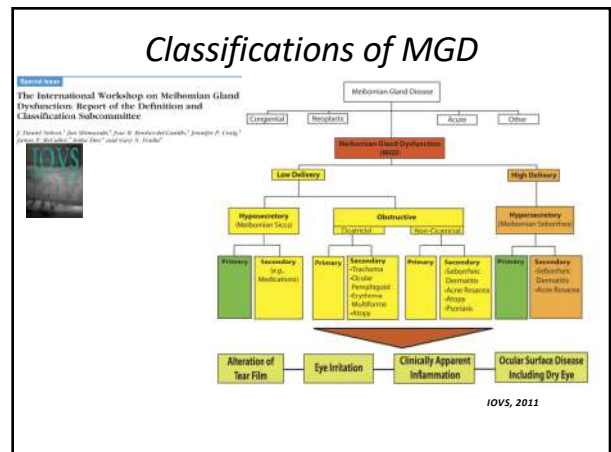
**Ocular Rosacea, Blepharitis**

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

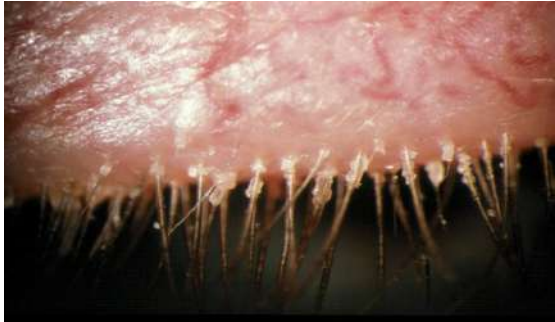
## Demodex Infestation is Associated with Floppy Eyelid Syndrome (4)

- 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



Anterior Blepharitis



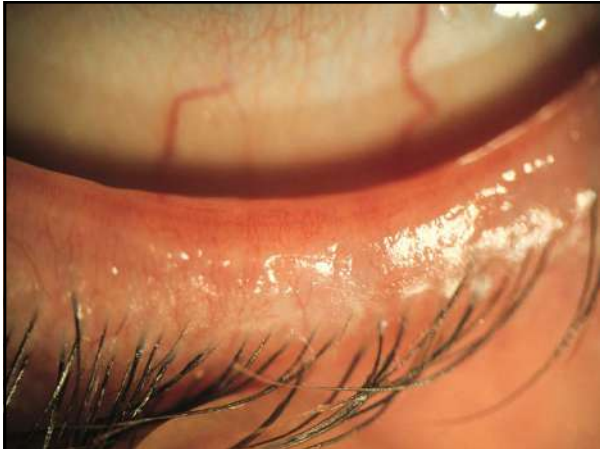
Seborrheic Blepharitis





## Rosacea

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



### What Do We Know?

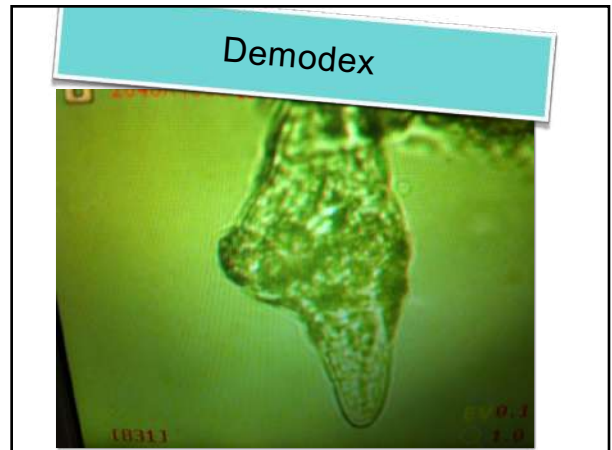
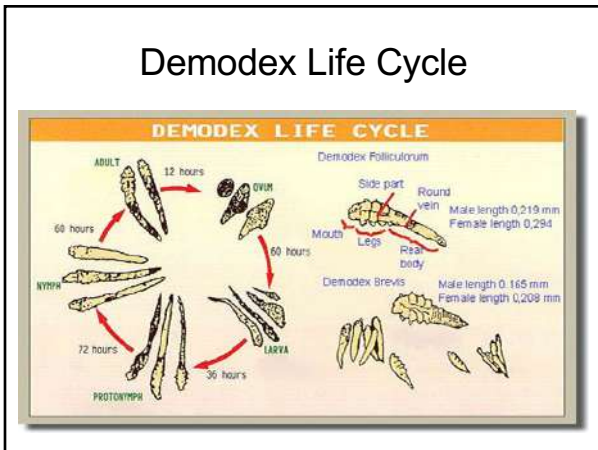
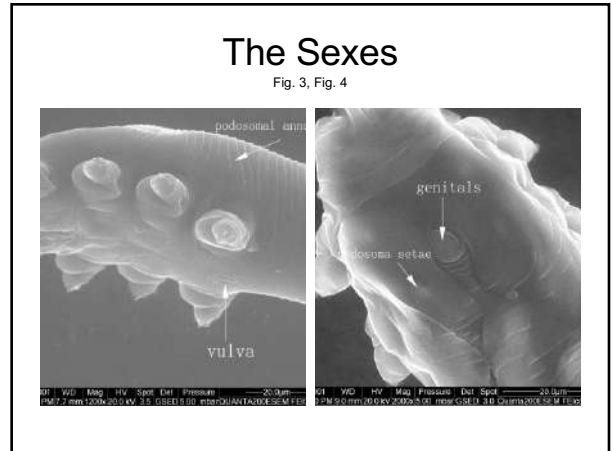
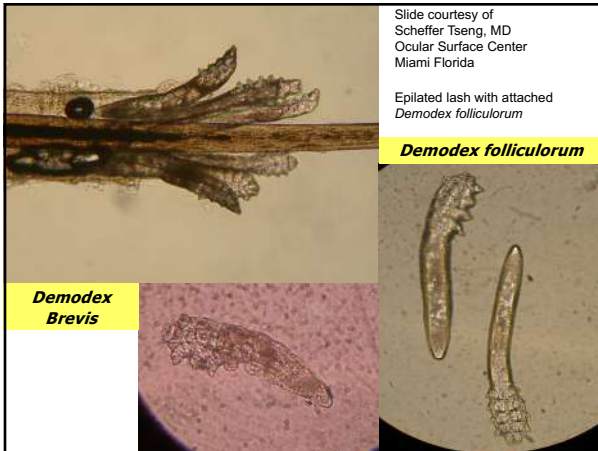
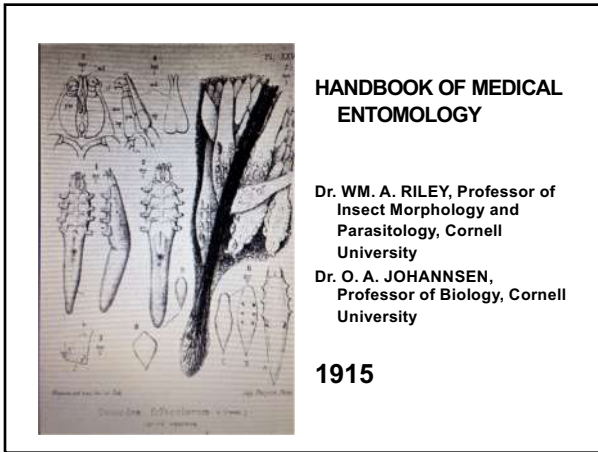
- Blepharitis and MGD are extremely common
- Demodex is extremely common
- Lid disease is a common cause of evaporative dry eye
- Rosacea is a common cause of MGD
- Demodex is a common cause of Rosacea
- What we thought was anterior blepharitis is probably Demodex
- Ocular allergy symptoms overlap dry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

### 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?

### 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?



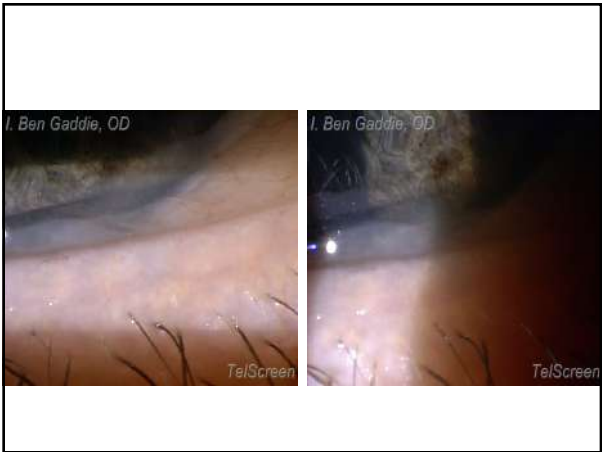
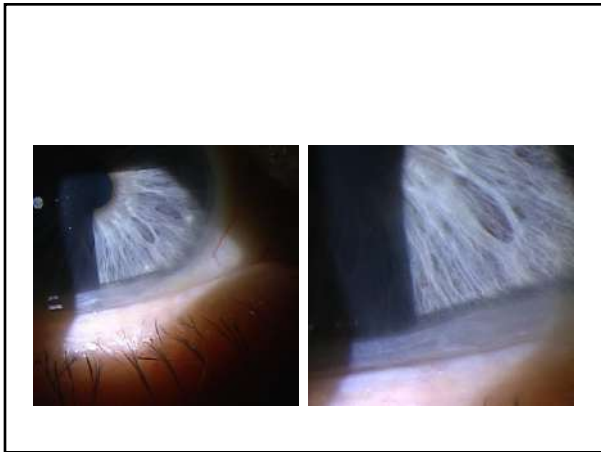
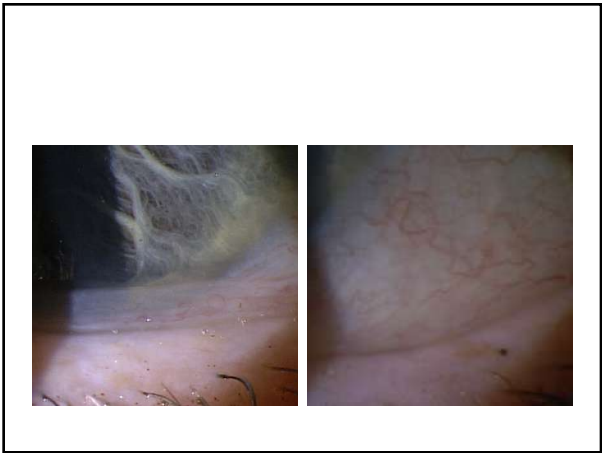
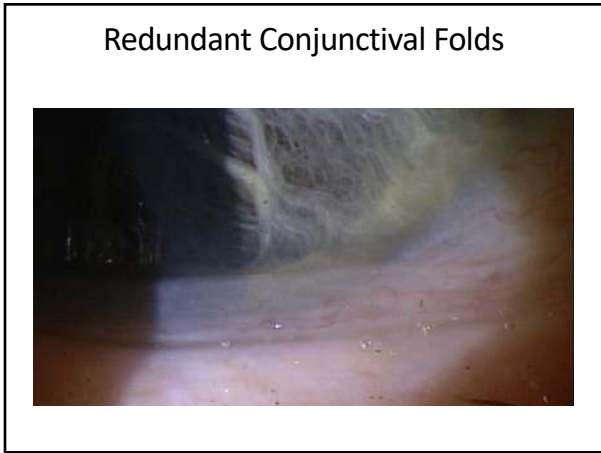
## Clinical history

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.

## 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



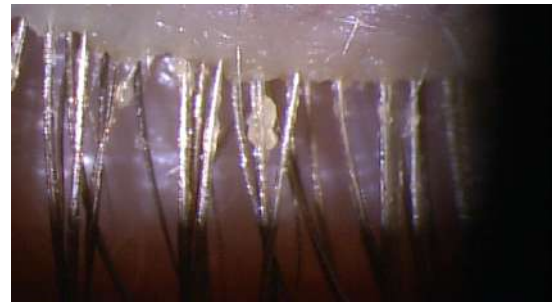
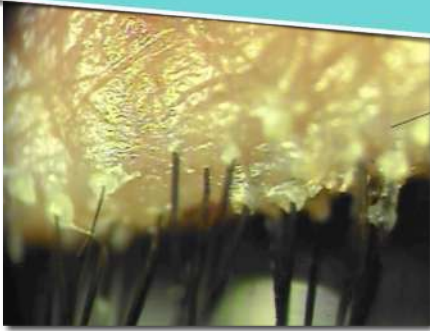
## 2. Slit lamp evaluation

### Cylindrical dandruff

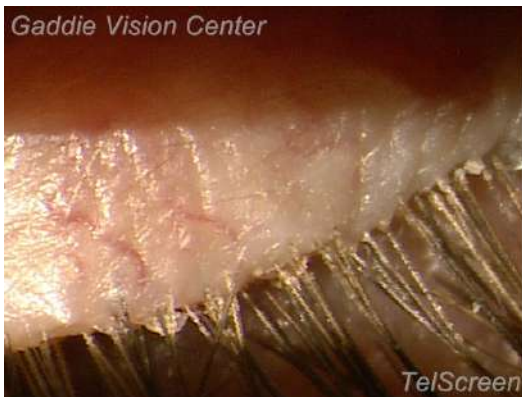
“Cylindrical dandruff was pathognomonic for the presence of demodex infestation.”

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.

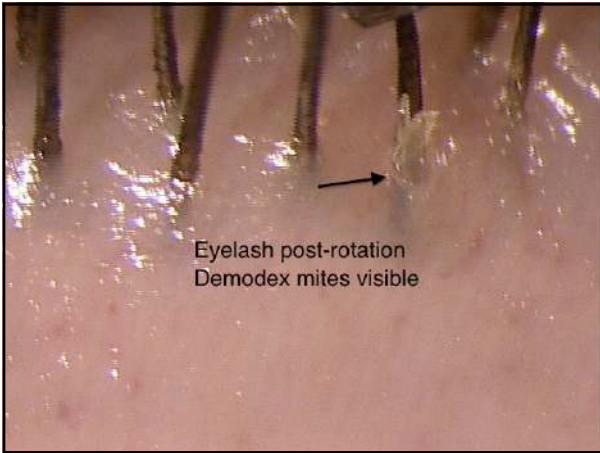
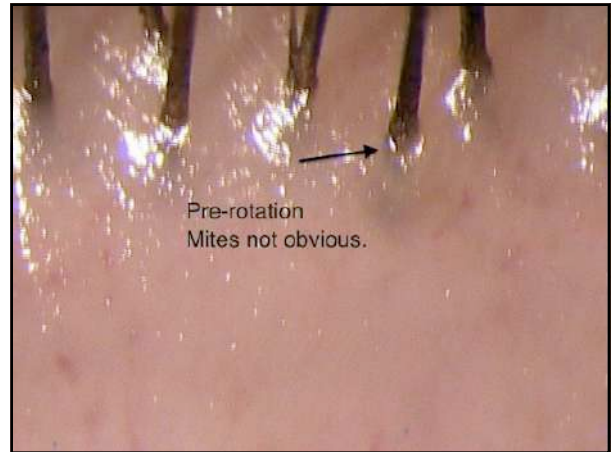
### Cylindrical dandruff



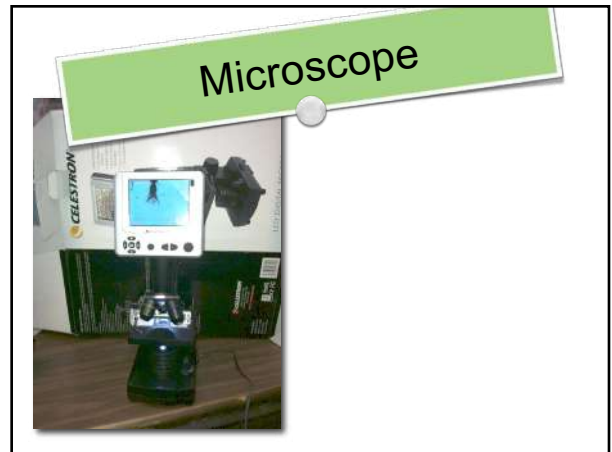
Gaddie Vision Center





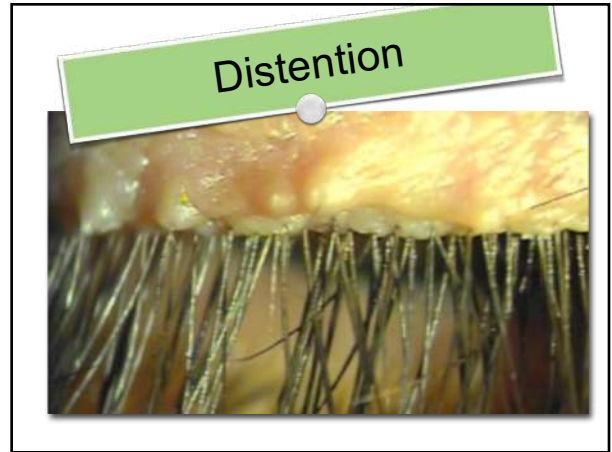
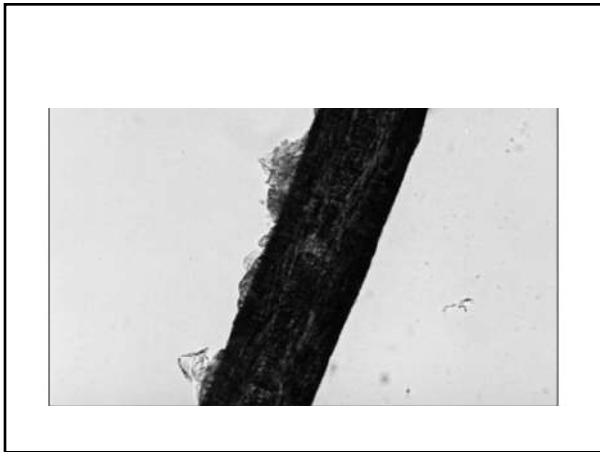
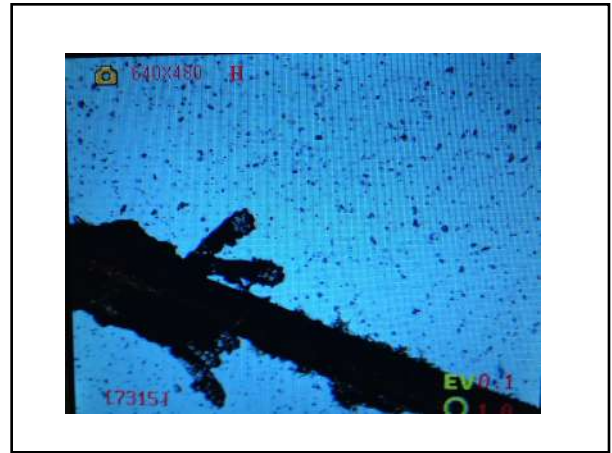
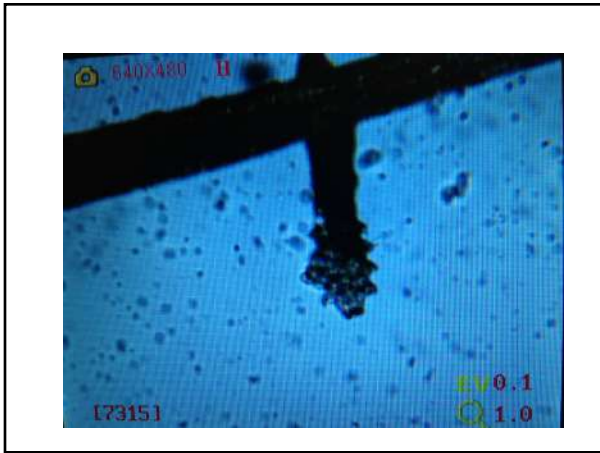
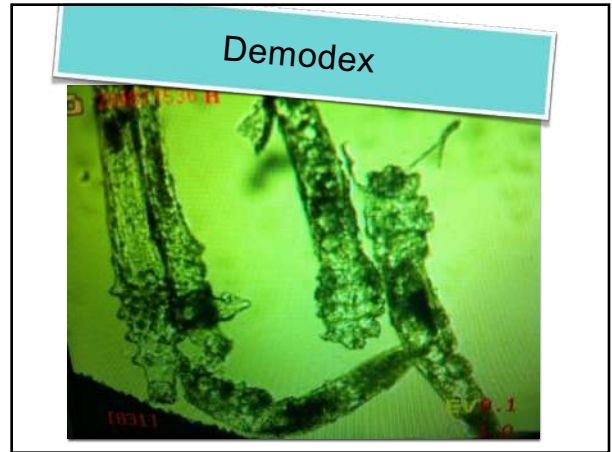


3. Epilate and microscope



### Demodex

Tip sheet  
Drop cover slip first, then add emulsion drop at the side  
Show and tell





### Blepharitis Is a Large and Underserved Market in Eye Care

**Epidemiology of Demodex Blepharitis**

- Estimated In-Clinic Epidemiology ~25M
- U.S. Demodex Blepharitis Prevalence ~9-25M
- Population Epidemiology ~9M
- Current ICD-10 ~1M Dx/yr

~25M with blepharitis<sup>34</sup>  
~65% with Demodex blepharitis<sup>35</sup>

~45M unique visits ECP clinics<sup>36</sup>  
~55% with collarettes<sup>37</sup>

**Large Patient Population with Significant Disease Impact**

**Significant Head Start on Diagnosis**

**Blepharitis Routinely Causes**

**Blepharitis Can Lead to**

**Concomitant Dry Eye**

**Blepharitis and Surgery**

**Contact Lens Drop-out**

**Prescription Treatment**

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

2.1M ICD-10 Blepharitis Dx/yr<sup>38</sup>

Eyelids to become red, itchy and itchy, with debris on the eyelashes<sup>39</sup>

Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the corner<sup>40</sup>

Significant overlap in Dry Eye patients. Demodex prevalent in ~65% of U.S. patients<sup>41</sup>

Important factor for missing surgical outcomes: 67% of Cataract Patients have Demodex Blepharitis<sup>42</sup>

Questionnaire driven a direct correlation between Demodex Blepharitis and Contact Lens Intolerance<sup>43</sup>

Note: 81% of patients currently seeking treatment<sup>44</sup>

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

**Study Overview**

- IRB APPROVED RETROSPECTIVE CHART REVIEW
- LARGE-SCALE ALL-COMERS (ECP) ANALYSIS
- DIVERSE ANTERIOR SEGMENT CLINICS

Examined presence of collarettes and other characteristics

Consecutive patients with a wide variety of reasons for visit

Geographically diverse (7 US sites) including both MD and O.D. clinics

**Key Findings**

**% of Overall Population**

With Collarettes **58%**

Dry eye diagnosis **58%**

**Key Patient Groups**

% with collarettes within each group

Blepharitis diagnosis	~85%
Dry Eye Rx Treatment <sup>45</sup>	~75%
Cataract patients	~70%
Contact lens users	~65%

Additional Study of ARVO 2021 by Van Jacobson, Rosenberg showed (n=189):  
55% prevalence of blepharitis, 62% overlap of blepharitis 64% overlap with Dry Eye

\* 22% of study patients on Dry Eye Rx treatment

### 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)

**51%**

Experienced signs and symptoms > 4 yrs

**58%**

Never diagnosed with blepharitis

**33%**

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

**Most Bothersome Symptoms**

81% experienced the top 3 symptoms frequently or all of the time

Eyes that itch	11%
Dry eyes	17%
Top 1	27%
Top 2	14%
Top 3	9%

**Functional and Psychosocial Impact**

Mite

Feels eyes/eyelashes of eyes all day	41%
Difficulty driving at night	33%
Additional time needed for daily hygiene routine	26%
Negative appearance of eyes or unable to smile	16%
Constantly worrying about your eyes or eyelids	27%
Difficulty wearing make-up	3%
34%	

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

### Collarettes Are Pathognomonic Sign of Demodex Infestation

**Collarettes Are Composed of Mite Waste Products and Eggs<sup>1</sup>**

- Regurgitated undigested material combined with epithelial cells, keratin, and mite eggs
- Contain digestive enzymes, which cause irritation

**Easily and Rapidly Diagnosed with Standard Eye Exam**

- Demodex mites found on **100%** of lashes with collarettes<sup>2</sup>
- Collarettes found in ~ 58% eye care patients<sup>3</sup>

**% of Subjects with Demodex**

>1 Collarette	100%
No collarettes, Using lid scrubs	60%
No collarettes, No lid scrubs	7%

1. Pomeroy 2013  
2. Grewell, Invest Ophthalmol Vis Sci, September 2010, Vol. 51, No. 20, 2038-2044  
3. Titus-Collamer, Prevalence Study

### 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

### 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

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

**Levamisole**  
 1. Potent and selective antagonist of host and parasite (GABA<sub>A</sub>) channels  
 2. Highly lipophilic molecule

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

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

### Extensive Clinical Trial Program for TP-03

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

Two Pivotal Trials

### Saturn-1 Patient Enrollment and Follow-up

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

Discontinued (n=3)      Completed 6 Weeks Treatment (n=209)

Randomized (n=421 at 15 sites in USA)

TP-03 (n=212)      Vehicle (n=209)

Discontinued (n=5)      Completed 6 Weeks Treatment (n=204)

n = 3 related to COVID

n = 1 related AE (mild)  
n = 1 unrelated AE  
n = 2 related to COVID  
n = 1 other

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

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



### Collarette Grading Scale Used in Saturn-1

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

Grade 4	Average baseline Grade 3	Grade 2	Grade 1	Grade 0
<ul style="list-style-type: none"> <li>&gt;20 of lashes on lid with collarettes</li> <li>Approximately 150 collarettes/lid</li> </ul>	<ul style="list-style-type: none"> <li>Between 10-20 of lashes on lid with collarettes</li> <li>Approximately 100 collarettes/lid</li> </ul>	<ul style="list-style-type: none"> <li>Between 10 collarettes to 10 of lashes on lid with collarettes</li> <li>Approximately 50 collarettes/lid</li> </ul>	<ul style="list-style-type: none"> <li>3-10 collarettes on the lashes</li> </ul>	<ul style="list-style-type: none"> <li>0-2 collarettes on the lashes</li> <li>Cure of collarettes</li> </ul>

### Lid Margin Erythema Scale Used in Saturn-1

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

Grade 3 (Severe)	Average baseline 1.5 Grade 2 (Moderate)	Grade 1 (Mild)	Grade 0 (None)

### 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

### 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)

Day	TP-03 (%)	Vehicle (%)
Day 8	11%	23%
Day 15	41%	16%
Day 22	60%	18%
Day 43	81%	23%

### Primary Endpoint of Complete Collarette Cure Achieved

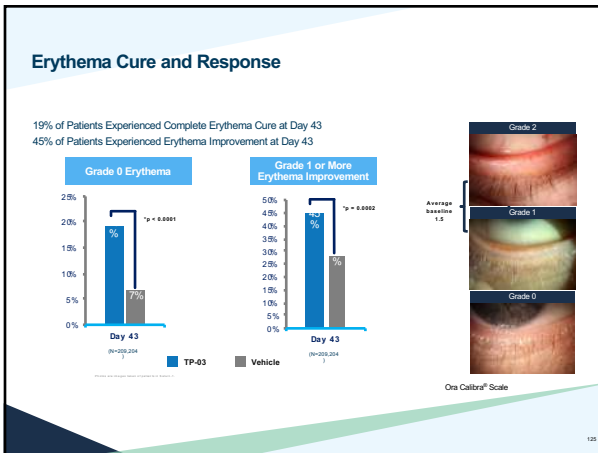
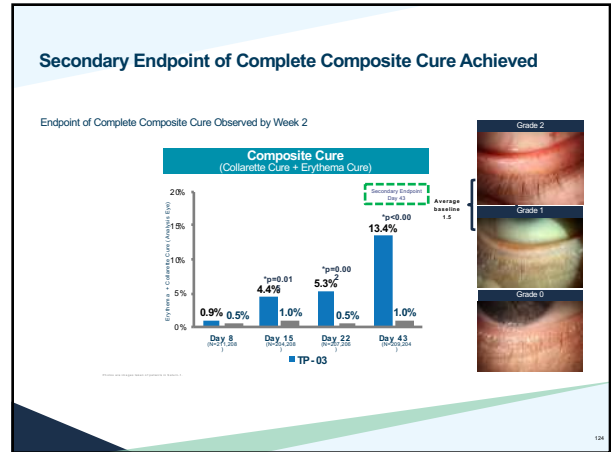
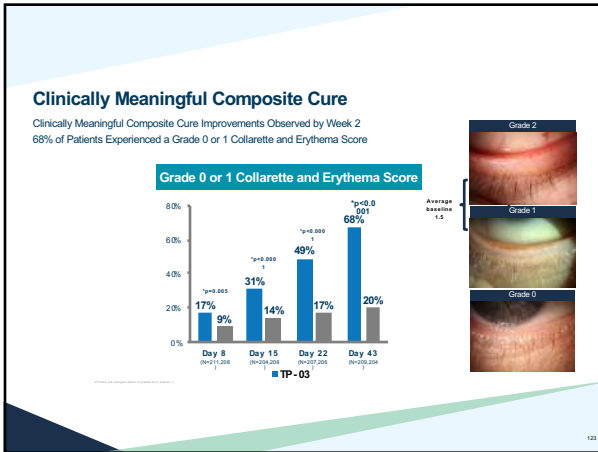
Regulatory Endpoint of Complete Collarette Cure Observed by Week 2

Day	TP-03 (%)	Vehicle (%)
Day 8	2%	2%
Day 15	10%	1%
Day 22	18%	2%
Day 43	43%	7%

### 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)

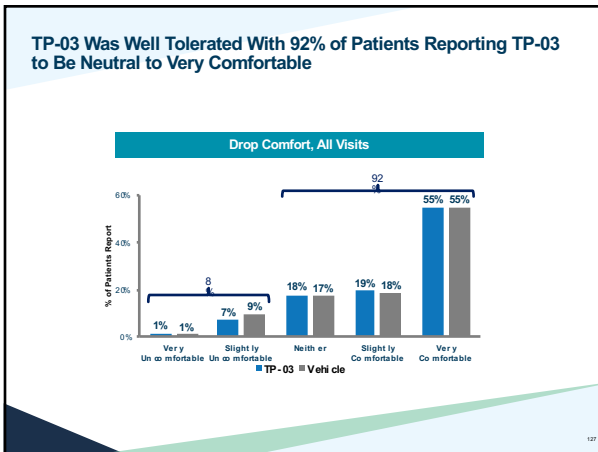
Day	TP-03 (%)	Vehicle (%)
Day 15	33%	9%
Day 22	40%	12%
Day 43	68%	18%



### Adverse Event Summary

Treatment related ocular AEs occurring at rate of  $\geq 1\%$  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



### Improvements Seen Post Treatment Have Significant Clinical Impact

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

**Complete Collarette Cure**

**Clinically Meaningful Collarette Cure**

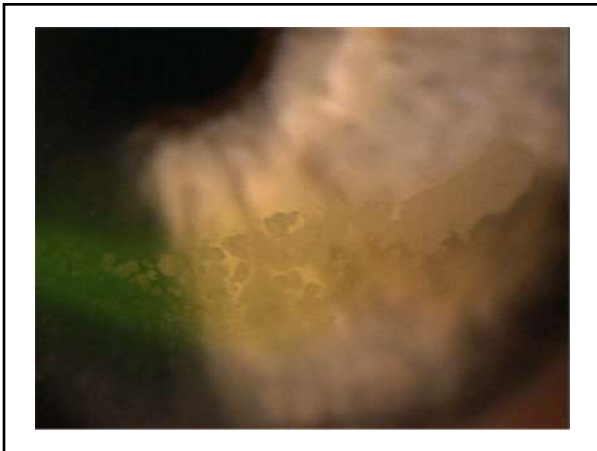
**Erythema Response**

### Current/Previous Treatment methods for Demodex

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

### In Office Treatment

- I find about 50% of patients find some symptomatic relief with one month use of Cliradex at home
- Patients with heavy scruff may need an in office treatment to remove scruff (Blephex) or TTO will never get to the target.
- Typically doing 2 different in office TTO, rarely third
- Maintenance on Cliradex; range QD to Q 1-3 x week



### Treatment Goal:

- NOT to eradicate 100%
- Want to knock down the “load” and reduce symptoms
- Like to see some visible reduction in cylindrical dandruff
- Improve redness profile of eye, lid and face

### Ointments

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

### Last thoughts...

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

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

