

## Demodex Diaries

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## Disclosures Koetting

\*All relevant financial conflicts have been mitigated

- ▶ Ocular Therapeutics
- ▶ Glaukos
- ▶ Horizon
- ▶ Quidel
- ▶ Eyevance/Santen
- ▶ Ivantis
- ▶ Orasis
- ▶ Claris Bio
- ▶ Aldeyra
- ▶ Dompe
- ▶ RVL
- ▶ Oyster Point
- ▶ Allergan
- ▶ Alcon
- ▶ Visus
- ▶ Thea
- ▶ Bruder
- ▶ Glaukos
- ▶ B & L
- ▶ Twenty/Twenty
- ▶ Myze
- ▶ Azura
- ▶ Scope
- ▶ Iveric Bio

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Dear Diary,

Today I learned about this little bug that does nothing but cause trouble. Let me tell you all about it!

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## Demodex Mites

- ▶ Most common ectoparasite on humans
  - ▶ Likes pilosebaceous follicles and sebaceous glands
    - ▶ most often found on face
- ▶ Associated with acne vulgaris, folliculitis, rosacea, seborrheic dermatitis, peri-oral and scalp hair loss and basal cell carcinoma
- ▶ Implicated in diseases of the lid and lid margin, blepharitis and MGD - can lead to recurrent chalazia, pterygia and blepharokeratitis



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### Who Do They Choose?

- ▶ In short almost everyone
- ▶ Found in 10% of skin biopsies
  - ▶ 12% of follicles
- ▶ Prevalence in adults varies between 23-100%
- ▶ Increased prevalence with age
  - ▶ Highest at 20-30 YOA
  - ▶ Sebum secretion at highest
- ▶ Older age increased rate
  - ▶ Demodectic blepharitis
  - ▶ Skin changes
  - ▶ <5 YOA
  - ▶ Increased bacteria on skin D/D (itching etc)
- ▶ Passes to newborns with close physical contact after birth
  - ▶ Genetics of the mites?
- ▶ More common in males vs females
- ▶ Rosacea and demodex rosacea and other predisposing conditions

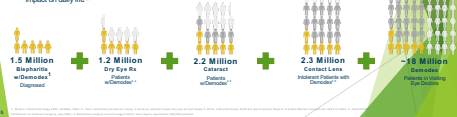
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### Demodex Blepharitis Is a Large and Underserved Market in Eye Care

#### 25 Million

#### Demodex Blepharitis Patients in the U.S.

- Demodex blepharitis is caused by infestation of Demodex mites
- Characterized by collarettes leading to eyelid margin inflammation, redness, and ocular irritation
- Patients suffer from eyelid itching/burning, blurred vision, and negative impact on daily life<sup>1,2</sup>

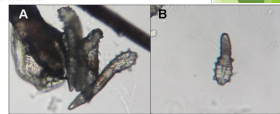


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### The Two Contenders

#### ▶ Two species affect the eye

- *Demodex folliculorum*
  - ▶ ~0.3 to 0.4 mm in length
  - ▶ found in clusters around the lash root and lash follicle
  - ▶ feeds on sebum and follicular epithelial cells
  - ▶ Most often found on face
- *Demodex brevis*
  - ▶ 0.15-2mm in length
  - ▶ more solitary
  - ▶ prefers the meibomian glands.



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### Such a Cute Little Bugger

- ▶ Both species are semi-translucent elongated body with 2 segments
- ▶ Eight short clawed legs
  - ▶ Move at a rate of 8-16mm/h
  - ▶ Usually during the night
- ▶ Body covered with scales to help anchor into the hair follicle
- ▶ Pin like mouth arts to eat skin cells, oils bacteria
- ▶ Bright light causes them to receded into follicle

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### Tell Me More!

- ▶ Life cycle
  - ▶ Mating takes place in follicle opening
  - ▶ Eggs laid inside hair follicles or sebaceous glands
  - ▶ Larvae hatch after 3-4 days
    - ▶ Develop into adults in 7 days
  - ▶ 14 day life cycle
  - ▶ Total lifespan is several weeks
  - ▶ Dead mites decompose inside follicle or sebaceous gland

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### Trouble Making

- ▶ Some remain asymptomatic
- ▶ Itching
- ▶ Burning
- ▶ Tearing
- ▶ Telangiectasia
- ▶ Lid margin thickening

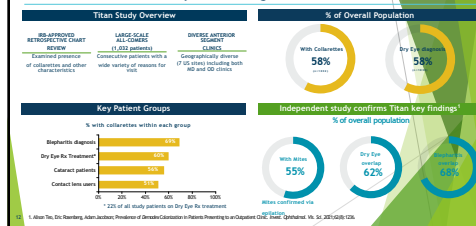
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### Do they cause OSD to worsen?

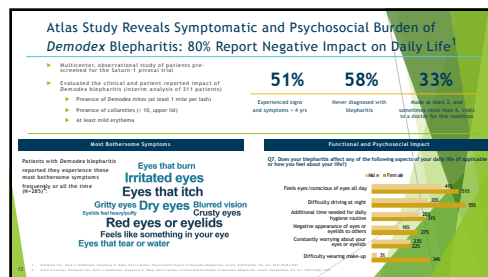
- ▶ Plausible action mechanism infestation involves causing direct damage, acting as a vector for bacteria, and inducing hypersensitivity.
  - ▶ Consume epithelial cells at the hair follicle, resulting in follicular distention.
  - ▶ Microabrasions caused by the mite claws further induce epithelial hyperplasia and reactive hyperkeratinization
  - ▶ *D. brevis* burrows deep into the meibomian glands
    - ▶ Mechanically blocking the orifices of the meibomian glands
    - ▶ Chitinous exoskeleton may act as a foreign body and cause granulomatous reactions,
      - ▶ may be a potential cause of chalazia and MGD
  - ▶ Demodex mites carry concomitant bacteria such as *Streptococci* and *Staphylococci* on their surface
    - ▶ *Bacillus oleronius* inside their abdomen
  - ▶ Proteins inside the mites and their debris or waste may trigger host inflammatory responses through delayed hypersensitivity or innate immune responses

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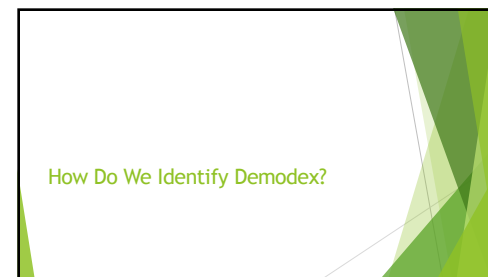
### Titan Study Confirms Widespread Collarette Prevalence in ECP Clinic Patients and Key Patient Segments



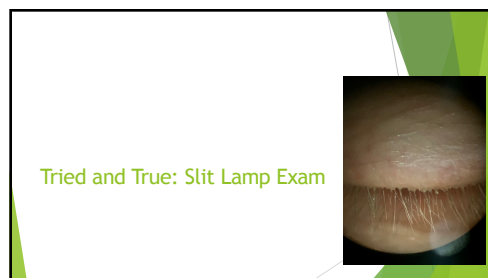
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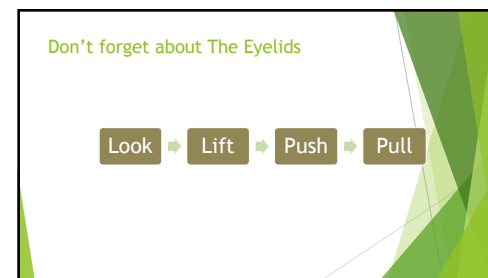
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### Grade the lid and gland appearance

- ▶ Any pitting?
- ▶ Any capping?
- ▶ Any lid structure abnormality?

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### Express the glands

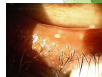
- ▶ Cotton tip applicator
- ▶ Your clean finger
- ▶ Gland expressor
- ▶ Meibomian gland evaluator (J&J)
- ▶ Just do it!



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### Meibomian gland compression

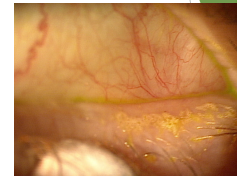
- ▶ Grade expressibility
- ▶ Meibum quality can be described as clear, cloudy, granular or inspissated, grading as follows:
  - ▶ Grade 1: olive oil, clear
  - ▶ Grade 2: turbid, cloudy
  - ▶ Grade 3: cloudy with debris
  - ▶ Grade 4: toothpaste-like, or inspissated



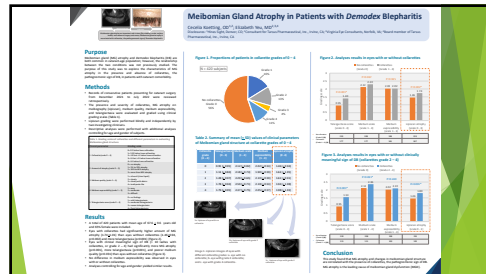
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### Blepharitis

- ▶ Saponification
- ▶ Lid margin debris
- ▶ Lid margin biofilm
- ▶ Collarettes at base of lashes
- ▶ Telangiectasia
- ▶ Lid margin thickening



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**Collarettes Are the Pathognomonic Sign of Demodex Blepharitis**

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

- In a clinical study, *Demodex* mites were found on 100% of lashes with collarettes<sup>1</sup>

Collarettes are composed of mite waste and eggs

- Regurgitated undigested material combined with epithelial cells, keratin, mite eggs, and digestive enzymes, which cause irritation<sup>2,3</sup>
- Translucent, waxy plugs typically at base of lashes<sup>2</sup>

Photos courtesy of Elizabeth Hershberg, MD. Visit: [www.demodex.com](http://www.demodex.com)

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**Clinical Pearl:** Have your patient look down to better identify demodex collarettes.

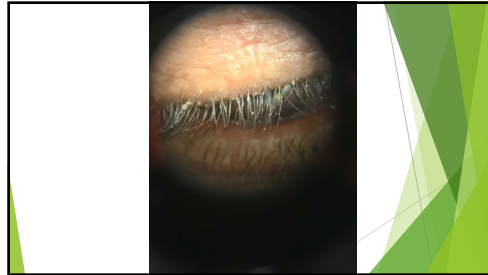
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**Asking Your Patient to Look Down During a Slit Lamp Exam Can Reveal Diffuse Collarettes and Misdirected or Missing Lashes**

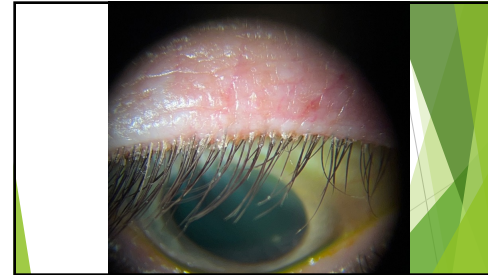
All that is needed to confidently diagnose Demodex blepharitis is a slit lamp.

Photos courtesy of Elizabeth Hershberg, MD.

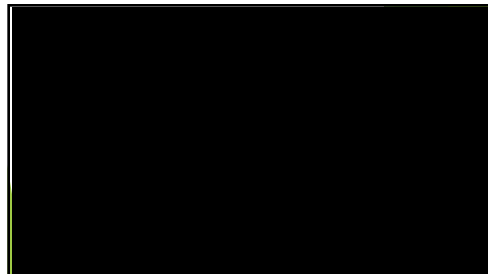
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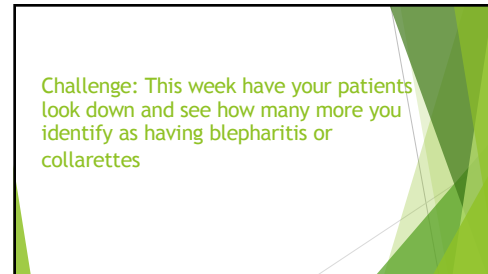
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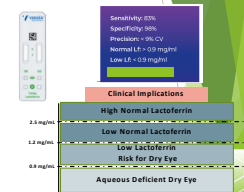
Tickle test?  
Whirl and twirl?  
Microscope with camera?

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### T-POC Lactoferrin Testing Is it Aqueous Deficient or Evaporative Disease?

Benefits of testing Lactoferrin levels in the tear film:

- Low Lactoferrin levels (<1.2 mg/ml) directly correlate to DED caused by aqueous deficiency
- Severity of DED can be determined by the Lactoferrin level
- Lactoferrin < 0.9 mg/ml has 72% sensitivity and 95% specificity for Sjogren's Disease
- Low Lactoferrin levels indicate DED with increased surgical risk
- Low Lactoferrin levels may indicate the cause of contact lens intolerance
- Changes in Lactoferrin levels may show the efficacy of the prescribed treatment
- Lactoferrin levels are normal, and not reduced, in the setting of meibomitis related rosacea



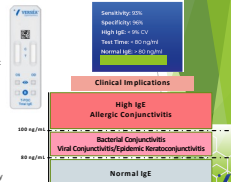
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### T-POC IgE Testing Is There An Allergic Component?

Benefits of testing IgE levels in the tear film:

- Presence of IgE indicates the diagnosis of allergic conjunctivitis (seasonal, perennial, atopic, and vernal)
- Levels of IgE increase with the severity of the allergic response
- IgE testing can help differentiate allergic conjunctivitis from DED and viral conjunctivitis
- Elevated IgE causes tear film instability
- Changes in IgE levels may show the efficacy of prescribed treatment

IgE value is < 80 ng/mL (33 kIU), there is a 95.7% probability that the patient does not have an ocular allergy  
IgE value is > 80 ng/mL, there is a 92.9% probability that this elevated IgE is indicative of an ocular allergy



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So Fresh and So Clean  
Demodex treatment

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## My Personal Regimen



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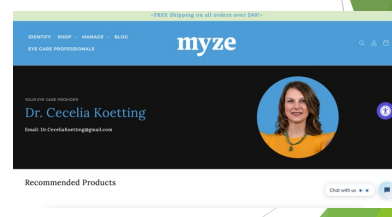
## In office sales vs Third party online

- ▶ Office size, foot print
- ▶ Decision making ability
- ▶ Profits to you?
  - ▶ In office sales
  - ▶ Amazon
  - ▶ Direct from manufacturer
  - ▶ DryEyeRescue
  - ▶ NEW Myze



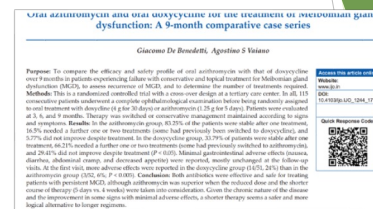
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## Helpmyze.com



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## Oral Azithromycin vs Oral Doxycycline for MGD



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### Take away

- ▶ Doxy 4 weeks 400mg vs Azithromycin 125mg for 5 days
- ▶ Both Doxycycline and Azithromycin found effective and safe for MGD
- ▶ Azithromycin superior for reduced dose and duration of therapy
- ▶ Evaluated at 3, 6, 9 months post tx
  - ▶ 33% Doxy patients stable after 1 tx
  - ▶ 83% Azith patients stable after 1 tx

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### Topical Azithromycin in DuraSite

- ▶ Known antibacterial and anti-inflammatory aspects of topical azithromycin 1% in DuraSite
- ▶ Results from early studies in subjects with chronic blepharitis (both anterior and posterior) are encouraging, although the results are limited by the study designs
- ▶ Difficulty obtaining?

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### Positive for demodex or suspected

- ▶ Everything previously discussed
- ▶ Lid scrubs, ointments or sprays containing
  - ▶ Tea tree oil and derivatives
  - ▶ Manuka honey
  - ▶ Okra extract
- ▶ Facial outbreaks
  - ▶ Ivermectin, permethrin
  - ▶ Oral metronidazole and dilute topical camphor oil

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### Tea Tree Oil

- ▶ Demodex mites are resistant to a wide range of antiseptic agents, including 75% alcohol, 10% povidone iodine, and erythromycin.
- ▶ *In vitro* microscopic observation for 150 min, Gao et al.<sup>14</sup> found that *D. folliculorum* can be dose-dependently killed by TTO.
- ▶ TTO not only cleanses CD from the eyelash roots, but also stimulates the embedded mites to migrate out to the skin. Apart from Demodex eradication, TTO exerts actions that are antibacterial,<sup>15</sup> antifungal,<sup>16</sup> and anti-inflammatory.

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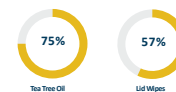
### But is Tea Tree Oil also causing damage?

- Few studies suggest this, but others support that it doesn't. . . . .
- But we do know it is IRRITATING !

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### Titan Study Also Revealed Tea Tree Oil and Lid Wipes Are Ineffective at Treating Demodex Blepharitis<sup>1</sup>

High percentage of collarettes observed in patient populations using tea tree oil and lid wipes



- Over the counter eye care treatments can also lead to ocular stinging/burning, driving discontinuation in many patients
- Tea tree oil toxicity may extend to human meibomian gland epithelial cells<sup>2</sup>
- There are currently no U.S. FDA approved therapeutics for Demodex blepharitis

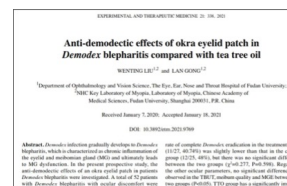
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### Okra Extract

- How Okra works?
  - Okra has been reported to exert anti-oxidative and anti-inflammatory effects by suppressing the Akt-mediated NF- $\kappa$ B pathway
  - Akt-mediated NF- $\kappa$ B pathway has been demonstrated to serve an important role in dry eye and blepharitis
  - Due to the curative and medicinal effects of okra, it could be speculated that okra may confer therapeutic effects in patients with blepharitis and dry eye.

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### Okra Extract



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## Results

- Changes in the parameters were compared between the treatment group and control group after 1 and 3 months of treatment.
- The average survival time in the okra group was  $115.25 \pm 11.87$  min, which was significantly lower compared with the average ST of  $378.75 \pm 37.94$  min in the blank group ( $P < 0.01$ ).
- After 3 months of okra eyelid patch treatment, the Demodex count was significantly reduced from  $10.15 \pm 4.53$  to  $1.30 \pm 1.41$  ( $P < 0.01$ ) and the OSDI score of the patients was reduced by  $16.84 \pm 10.17$  ( $P < 0.01$ ).
- There was no significant difference in the Demodex count ( $P = 0.716$ ) and OSDI ( $P = 0.873$ ) between the treatment and control groups.
- Okra eyelid patch treatment is able to significantly eradicate ocular Demodex as well as markedly alleviate ocular symptoms. Due to causing less irritation than TTO, the okra eyelid patch may be more suitable for sensitive patients with Demodex blepharitis.

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## Manuka Honey

- Natural honey is well known for its anti-inflammatory and antimicrobial properties.
- Theory is because it has low pH, high osmolality, hydrogen peroxide content, as well as non-peroxide constituents, including methylglyoxal (MGO).
- In recent years, New Zealand native Mānuka honey (*Leptospermum scoparium*) has received particular interest as a potential treatment for blepharitis.
- Has higher concentration of methylglyoxal (MGO) than other honeys

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## Study 2020

- Fifty-three participants with clinical signs of blepharitis
- The MHME eye cream (Manuka Health New Zealand) was applied to the closed eyelids of one eye (randomized) overnight for 3 months.
- Visual acuity, ocular surface characteristics, symptoms and tear film parameters were assessed at baseline, day 30, and day 90. Eyelid swab microbiology cultures were evaluated at baseline and day 90.
- Results
  - Topical overnight application of the MHME eye cream effected significant improvements in ocular surface symptomatology, tear film stability and lipid layer thickness, and reduced lid margin staining, ocular Demodex and bacterial loads.

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## In Office Blepharo-exfoliation



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### Intense Pulsed Light (IPL)

- ▶ Helps to reduce mean Demodex mite density
- ▶ Improves ocular surface
- ▶ Limitations
  - ▶ Cost to obtain unit
  - ▶ Cost to patient, not covered by insurance
  - ▶ Is contraindicated for certain skin tones

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### Other Dermatology Treatments

- ▶ Ivermectin
  - ▶ Topical or oral
  - ▶ Improves signs and symptoms, reduces mite density
  - ▶ Limitation is hypersensitivity rxns and drug interaction along with more severe side effects with oral use
- ▶ Metronidazole
  - ▶ Broad anti-inflammatory and antiparasitic
  - ▶ Improves signs and symptoms and reduces mite density
  - ▶ Similar problems with more severe side effects with oral use

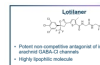
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New Topical Treatment Option Coming  
SOON!-Submitted to FDA

NOW HERE!!

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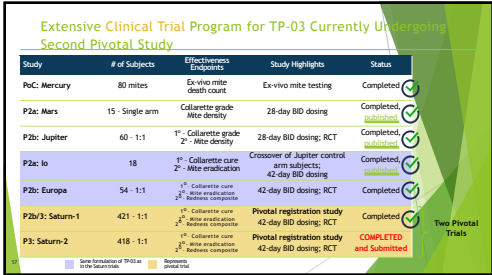
### XDEMVY is a Novel Therapeutic Designed to Eradicate *Demodex* Mites and Treat *Demodex* Blepharitis



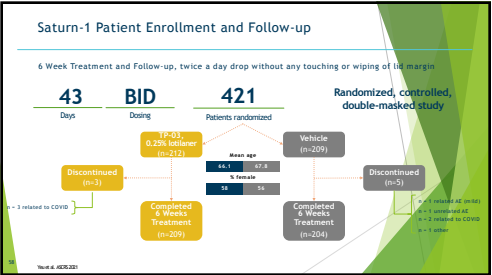
The lipophilic nature of the drop enables it to flow into the lash follicle. No scrubbing/rubbing was permitted in clinical trials.

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

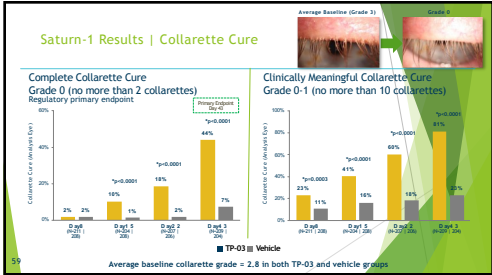
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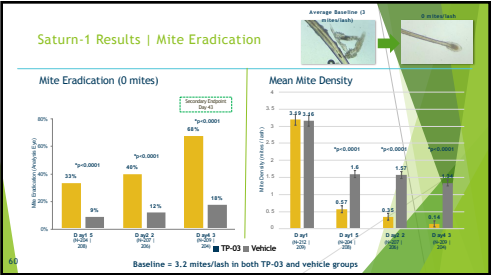
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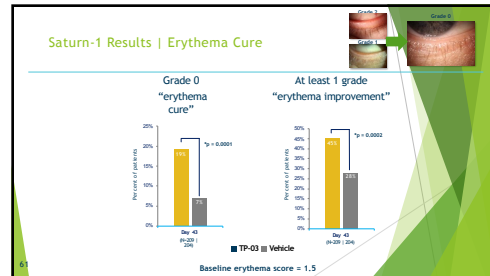
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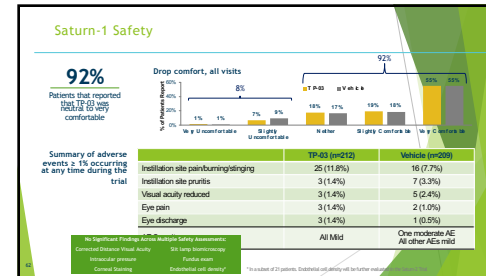
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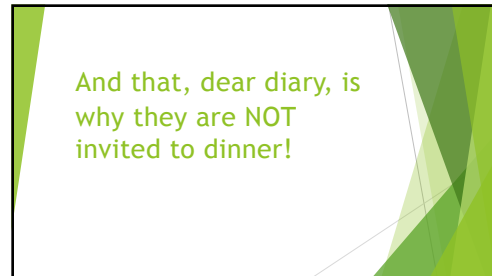


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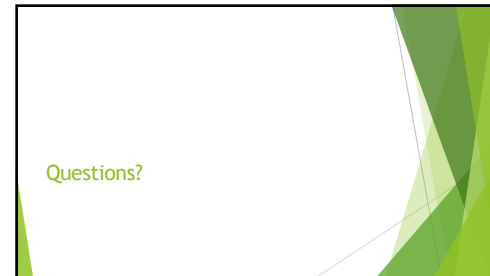


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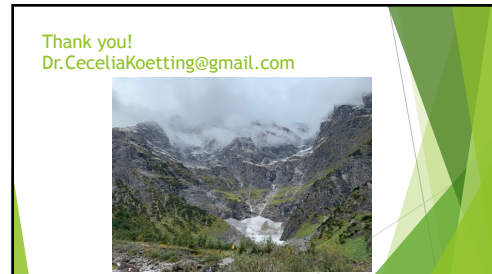




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