

Mastering the Ocular Surface: Eye Lid Health

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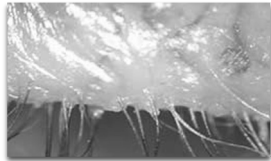
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DOUGLAS K DEVRIES, OD
DISCLOSURES
ANY CONFLICTS HAVE BEEN MITIGATED

Ailigan - Advisory Board and Speakers Bureau	Alcon - Advisory Board and Speakers	Aura Advisory	Aescula Tech	Bio-Tissue Speakers Bureau and Advisory Board	Bruder - Advisory Board	Novartis - Advisory Board and Speakers Bureau	B & L - Advisory Board and Speakers	Compex - Advisory and Speakers	TheraMox - Advisory	Sub - Advisory and Speakers	Vision Advisory	Versar Advisory	Cosentis Advisory Board	Tealab Advisory Board	Sight Science Advisory and Speaker	RVL Advisory Board	Oyster Point Advisory and Speaker	Truvis Advisory	Science Based Health Advisory and Speaker	Sun Advisory and Speaker	Ophthalmic Resources Partner	Crisis Advisory	Johnson & Johnson Vision Advisory and Speaker	Summit Advisory and Speaker
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Blepharitis
= lid inflammation

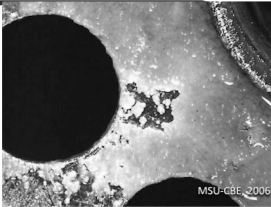


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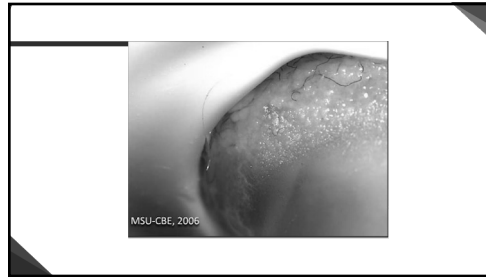
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BLEPHARITIS - DEBS

UPPER EYELID: TARSAL ANATOMY

Cheng-Hua Chen, 2016/10/10/2016/10/2016

Hypothetical Theory of DEBS

```

    graph TD
        A[DEBS] --> B[Meibomian Gland Dysfunction]
        A --> C[Chronic Inflammation]
        A --> D[Malnutrition]
        A --> E[Genetic Predisposition]
        A --> F[Environmental Factors]
        B --> G[Meibomian Gland Dysfunction]
        C --> H[Chronic Inflammation]
        D --> I[Malnutrition]
        E --> J[Genetic Predisposition]
        F --> K[Environmental Factors]
    
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QUORUM-SENSING GENE ACTIVATION 1968

John Woodland "Woody" Hastings, (March 24, 1927 – August 6, 2014)
 Professor of Molecular and Cellular Biology at Harvard University
 Increase in population densities causes production of virulence factors

- Exotoxins
- Lipases
- Superantigens...toxic shock syndrome

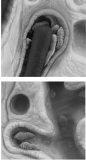
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DEMODEX BLEPHARITIS | A PERSISTENT AND DAMAGING EYE DISEASE

Blepharitis is the inflammation of the eyelids causing irritation and redness

D. folliculorum
0.3-0.4 mm length
Colonizes the base of the lash follicle^{1,2}

D. brevis
0.1 mm length
Colonizes the meibomian gland²



1. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
2. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
3. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.

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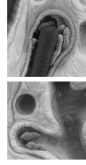
DEMODEX BLEPHARITIS | A PERSISTENT AND DAMAGING EYE DISEASE

69% of blepharitis cases are due to Demodex infestation leading to Demodex blepharitis¹⁻⁴

- Demodex mites are implicated in other diseases of the lid and lid margin, including blepharitis and meibomian gland dysfunction^{2,3}

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0.1 mm length
Colonizes the meibomian gland²



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3. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
4. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.

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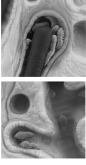
DEMODEX BLEPHARITIS | A PERSISTENT AND DAMAGING EYE DISEASE

Demodex folliculorum and Demodex brevis are the only 2 species found in humans⁵

- The life cycle of the Demodex mite is approximately 14 to 18 days from the egg to the larval stage followed by the adult stage⁵
- The life span of the mite is limited outside the living body; direct contact is required for transinfestation⁵

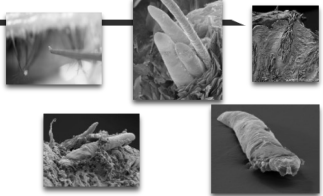
D. folliculorum
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4. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
5. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.

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BIOFILM IS A POLYSACCHARIDE
Perfect food source for a Demodex infestation

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DEMODEX BLEPHARITIS | MECHANISMS OF DISEASE

MECHANICAL


- Lash distension occurs as Demodex mites attach to follicles^{1,4}
- Demodex mites deposit debris and digestive enzymes, causing further irritation to the eyelid margin^{1,5}

MECHANICAL

- Demodex mites can contribute to blepharitis by carrying bacteria on their exterior surface that may elicit immune responses^{1,2,7}

CHEMICAL


- Demodex mites have been associated with altered meibum composition⁸
- Debris from Demodex mites can potentially lead to chronic inflammation and degeneration of conjunctival tissue⁹



1. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
2. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
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5. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
6. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
7. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
8. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
9. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.

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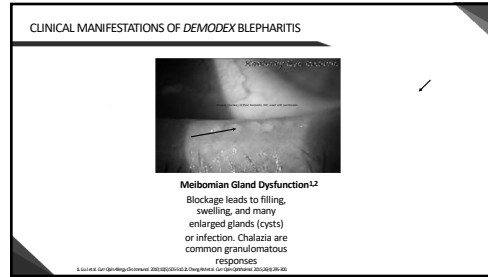
CLINICAL MANIFESTATIONS OF DEMODEX BLEPHARITIS



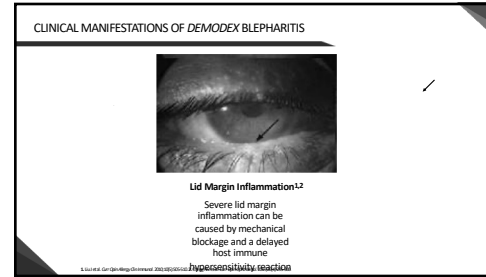
Disorders of Eyelashes^{1,2}
Infestation of the lash follicles can result in collarettes and may lead to malalignment, trichiasis, and madarosis

1. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.
2. Hachisu, A. et al. 2002. <http://www.ncbi.nlm.nih.gov/pubmed/12481018>.

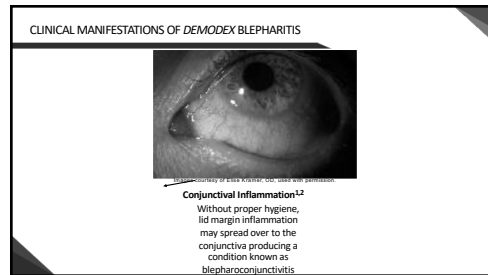
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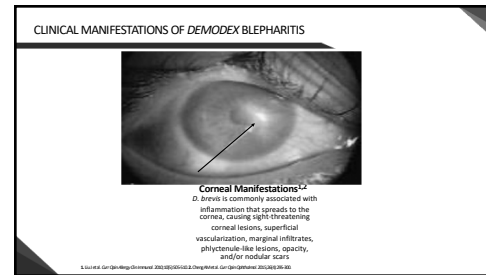
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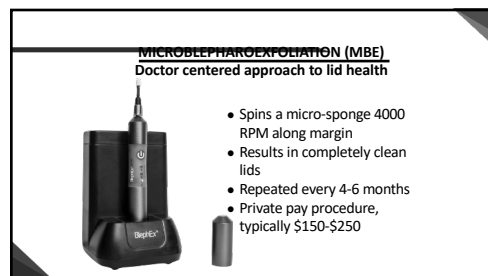
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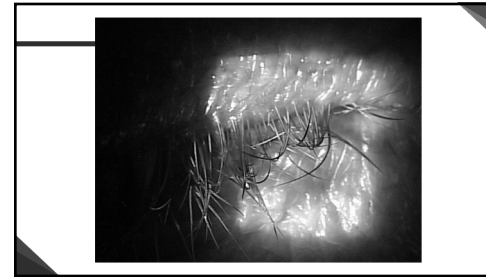
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COLLARETTES ARE A PATHOGNOMONIC SIGN OF DEMODEX BLEPHARITIS

Collarettes, or cylindrical dandruff, are composed of mite waste products and eggs¹

- Collarettes are translucent, solidified exudative excretions that form a cylindrical collar that cuffs around the base of the eyelash follicle^{1,3}
- Collarettes are displaced along the shaft of the lash as it grows, and they are also displaced due to bacterial overgrowth⁴

1. Jiang H et al. Ophthalmic Pharmacol Ther. 2015;31(4):301-312. 2. Gao H et al. Invest Ophthalmol Vis Sci. 2015;56(10):3081-3086. 3. Kormanik SR et al. Clin Ophthalmol. 2016;9(7):1210-1212. 4. Bhatnagar V. JAMA Ophthalmol. 2015;33(10):1301-1302. 5. Kormanik SR et al. Clin Ophthalmol. 2016;9(7):1210-1212.

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COLLARETTES ARE A PATHOGNOMONIC SIGN OF DEMODEX BLEPHARITIS

- Collarettes are displaced along the shaft of the lash as it grows, and they are also displaced due to bacterial overgrowth⁴
- Collarettes are composed of regurgitated undigested mite waste combined with epithelial cells, keratin, mite eggs, and secreted proteases and lipases that cause irritation³
- **100%** of patients with collarettes have Demodex blepharitis^{2,5}

1. Jiang H et al. Ophthalmic Pharmacol Ther. 2015;31(4):301-312. 2. Gao H et al. Invest Ophthalmol Vis Sci. 2015;56(10):3081-3086. 3. Kormanik SR et al. Clin Ophthalmol. 2016;9(7):1210-1212. 4. Bhatnagar V. JAMA Ophthalmol. 2015;33(10):1301-1302. 5. Kormanik SR et al. Clin Ophthalmol. 2016;9(7):1210-1212.

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DEMODEX BLEPHARITIS CAN BE DIAGNOSED DURING SLIT LAMP EXAMINATION

- Collarettes are hardened excretions around the base of the eyelashes visible during slit lamp examination¹⁻³
- Collarettes can be identified when the base of lashes on the upper lid are exposed as the patient **looks down**⁴
- Collarettes may be missed during a slit lamp exam even with a lid lift if a patient is looking straight ahead⁴

1. Jiang H et al. Ophthalmic Pharmacol Ther. 2015;31(4):301-312. 2. Gao H et al. Invest Ophthalmol Vis Sci. 2015;56(10):3081-3086. 3. Kormanik SR et al. Clin Ophthalmol. 2016;9(7):1210-1212. 4. Bhatnagar V. JAMA Ophthalmol. 2015;33(10):1301-1302.

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DEMODEX BLEPHARITIS CAN BE DIAGNOSED DURING SLIT LAMP EXAMINATION

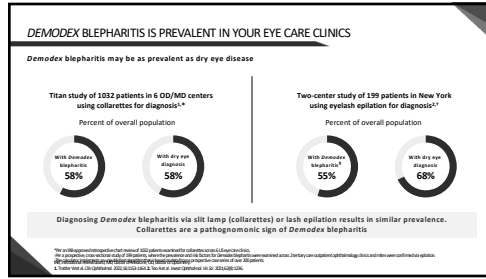
Patients looking straight ahead

Patients looking down, exposing base of lashes and collarettes

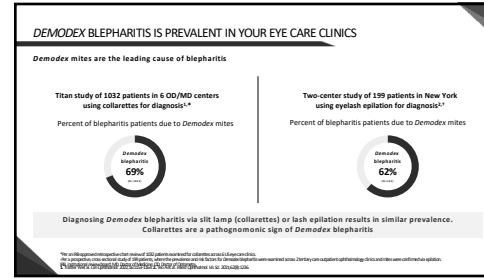
Asking a patient to look down during a slit lamp examination can reveal diffuse collarettes and misdirected or missing lashes that are strong signs of Demodex blepharitis

1. Jiang H et al. Ophthalmic Pharmacol Ther. 2015;31(4):301-312. 2. Gao H et al. Invest Ophthalmol Vis Sci. 2015;56(10):3081-3086. 3. Kormanik SR et al. Clin Ophthalmol. 2016;9(7):1210-1212. 4. Bhatnagar V. JAMA Ophthalmol. 2015;33(10):1301-1302.

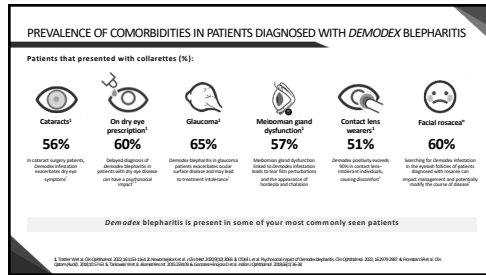
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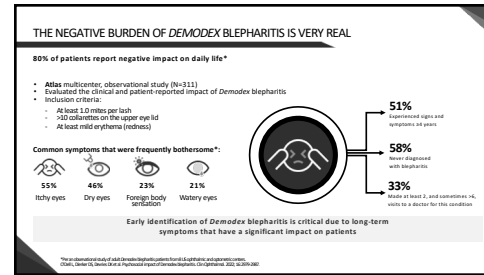
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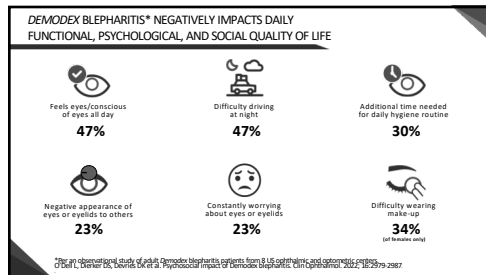
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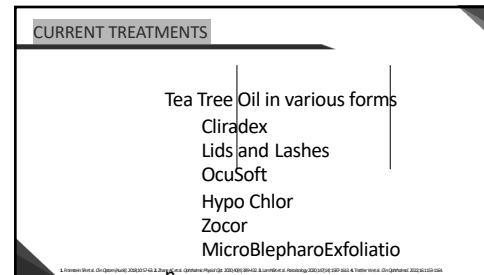
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MECHANISM OF ACTION OF TP-03 (Lotilaner Ophthalmic Solution, 0.25%)

TP-03: Lotilaner ophthalmic solution 0.25% (Tarsus Pharmaceuticals, Inc.)

- Lotilaner functions as a noncompetitive antagonist of mite and arachnid GABA-gated chloride channels^{1,2}
- Directly paralyzes the mite nervous system through parasite-specific GABA inhibition, leading to death^{1,2}
- The lipophilic nature of the drop suggests its ability to flow into the oily sebum of the lash follicle where the mites reside³

NOTE: Currently not FDA approved, in development and for investigational use only. There are currently no FDA-approved therapeutics for Demodex blepharitis.

Product form⁴
Preserved (orabate) multidose eye drop solution in bottle

Dosing⁴
Twice daily for 6 weeks

1. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 2. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 3. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 4. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist.

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SATURN-1 AND SATURN-2 | PIVOTAL CLINICAL STUDIES OF TREATMENT FOR DEMODEX BLEPHARITIS

Consistent cures and responses demonstrated in 2 pivotal trials, the largest clinical program for Demodex blepharitis, involving 833 patients

- The primary and all secondary endpoints (collarette cure, mite eradication, lid erythema) met with high statistical significance
- Clinically and statistically significant effects seen as early as **2 weeks**
- Very high responder rate to TP-03: **96%** of patients improved at least 1 collarette grade; **89%** achieved a clinically meaningful cure
- NDA submission expected in 2H 2022**

Efficacy goal
1st collarette cure rate, 2nd mite eradication, 3rd erythema + collarette cure rate

Safety goal
Well-tolerated safety profile

1. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 2. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 3. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 4. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist.

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COLLARETTE SCALE USED TO DETERMINE SEVERITY OF DEMODEX BLEPHARITIS

Grades 2-4 Indicate Clinically Significant Disease

GRADE 4	GRADE 3	GRADE 2
• 2/3 of lashes on lid with collarettes	• Between 1/3 to 2/3 of lashes with collarettes	• Between 1/3 collarettes to 1/3 of lashes on lid with collarettes
• Approximately 100 collarettes/lid*	• Approximately 100 collarettes/lid*	• Approximately 10 collarettes/lid*

Grades 0-1 Indicate Clinically Meaningful Cure

GRADE 1	GRADE 0
• 0 to 1/3 collarettes on the lashes	• 0 to 2 collarettes on the lashes
• 0 or sparse erythema	• Complete cure of collarettes

Chances of Demodex infestation increase with >10 collarettes/lid^{1,2}

AVERAGE BASELINE = GRADE 3 FOR SATURN-1 and SATURN-2 STUDIES^{3,4}

1. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 2. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 3. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 4. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist.

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LID ERYTHEMA SCALE USED IN SATURN-1 AND SATURN-2 STUDIES

GRADE 3	GRADE 2	GRADE 1	GRADE 0
3 [Severe] ¹	2 [Moderate]	1 [Mild]	0 [None]

AVERAGE BASELINE = 1.0 FOR SATURN-1 and SATURN-2 STUDIES

1. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 2. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 3. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 4. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist.

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SATURN-1 and SATURN-2 BASELINE CHARACTERISTICS

	Saturn-1 ¹		Saturn-2 ²	
	TP-03	Vehicle	TP-03	Vehicle
No. of Patients	212	209	203	209
Age (yrs)	66.1	67.8	64	65
Female %	58	56	48	49
Collarette Score	2.8	2.8	2.9	3.0
Mites/Lash	3.2	3.2	3.2	3.4
Erythema Score	1.5	1.5	1.6	1.6

Grade 3 = ~100 collarettes/lid

3 mites/lash

1. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 2. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist.

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PRIMARY ENDPOINT OF COMPLETE COLLARETTE CURE (≤2 COLLARETTES) ACHIEVED

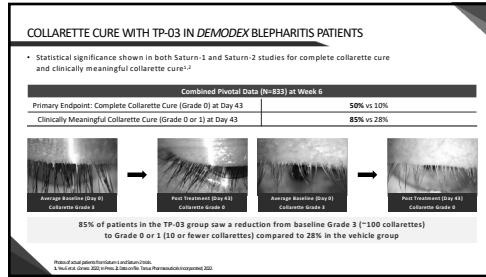
Saturn-1: Collarette Cure (≤2 collarettes)^{1,*}

Saturn-2: Collarette Cure (≤2 collarettes)^{1,*}

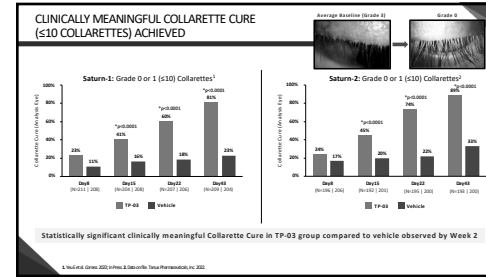
Regulatory endpoint of statistically significant Complete Collarette Cure in TP-03 group compared to vehicle observed by Week 2

1. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist. 2. Lotilaner (TP-03) is a novel, potent, and selective GABA-gated chloride channel antagonist.

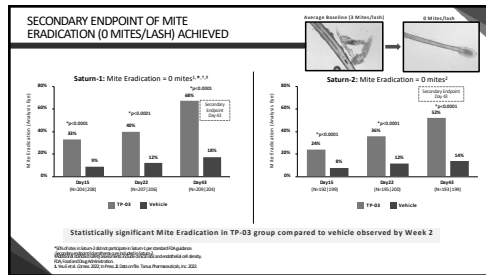
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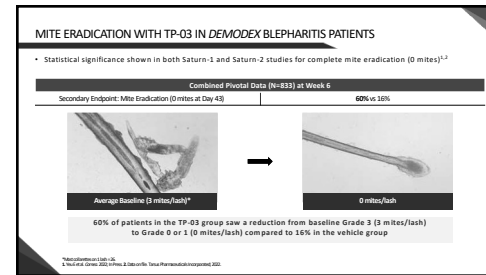
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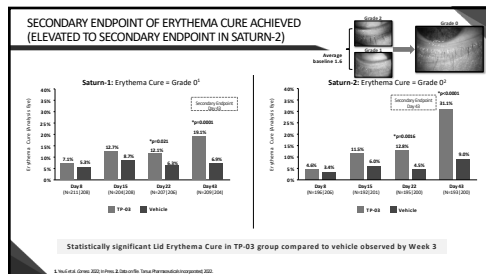
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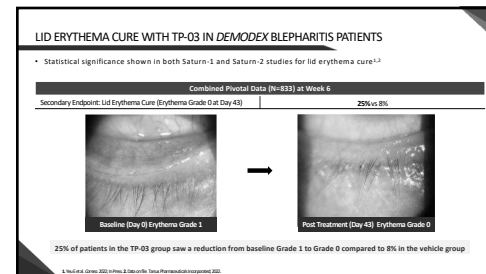
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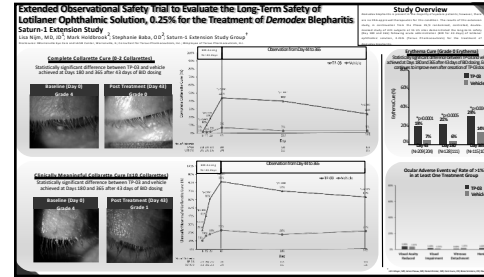
OCULAR ADVERSE EVENT SUMMARY

- Overall there were low rates of ocular AEs across both studies

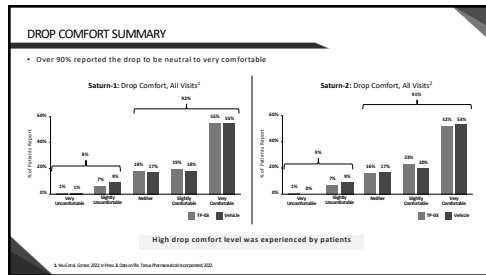
Saturn-1: Treatment-Related Ocular AE Rates 21% ¹		Saturn-2: Treatment-Related Ocular AE Rates 21% ²	
	TR-01 (n=212)	Vehicle (n=209)	
Instillation Site Pain/Burning/Stinging	25 (11.8%)	16 (7.7%)	Instillation Site Pain/Burning/Stinging
Instillation Site Pruritus	3 (1.4%)	7 (3.3%)	Instillation Site Pruritus
Visual Acuity Reduced	3 (1.4%)	5 (2.4%)	Visual Acuity Reduced
Eye Pain	3 (1.4%)	2 (1.0%)	Eye Pain
Eye Discharge	3 (1.4%)	1 (0.5%)	Eye Discharge
Dry Eye	0	1 (0.5%)	Dry Eye
AE Severity	All mild	1 moderate All others mild	AE Severity
			2 moderate All others mild

All AEs were mild or moderate

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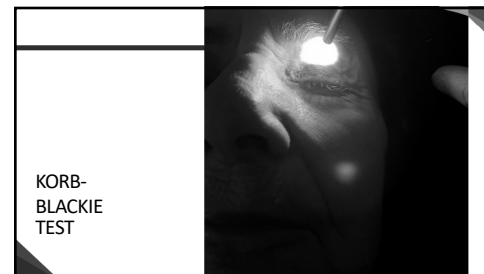
- ### DEMODEX BLEPHARITIS KEY TAKEAWAYS
- Demodex mites may be present in 69% of all blepharitis cases
 - It is a disease that is often misdiagnosed and underdiagnosed
 - Demodex blepharitis is prevalent in cataract, dry eye, and contact lens wearers and has a substantial impact on the quality of life of patients, including pain, irritation, and clinical burden
 - Establishing the root cause (the Demodex mite) rather than just addressing symptoms is crucial
 - Current options for managing Demodex blepharitis do not eradicate mites and are poorly tolerated
 - Confidently and definitively diagnose Demodex blepharitis by looking for collarettes
 - Look for collarettes by having every patient look down during a slit lamp examination
 - Provide patient education and understand their current struggles with comfort and lid hygiene compliance
 - TR-01, if approved, may be an emerging safe and effective treatment for Demodex blepharitis, which has demonstrated patient comfort and shows effective collarette cure, mite eradication and erythema cure in 2 pivotal studies
- #### WHAT CAN WE ALL DO?
- Look for collarettes during every slit lamp exam – collarettes are the pathognomonic sign of Demodex blepharitis
 - Share images of collarettes with your peers to equip them with knowledge to properly diagnose Demodex blepharitis

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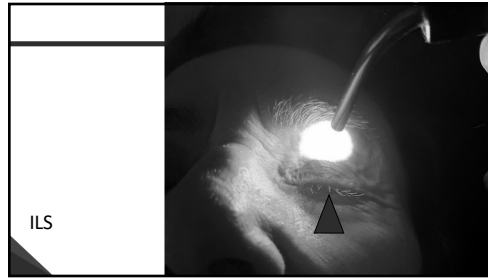
MOST IMPORTANT QUESTION TO ASK:

Do you have morning symptoms?

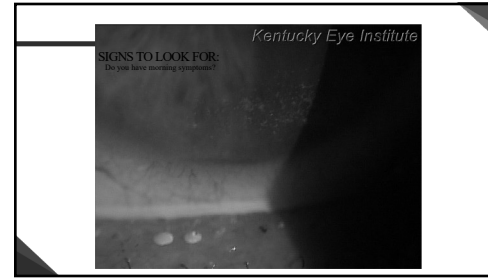
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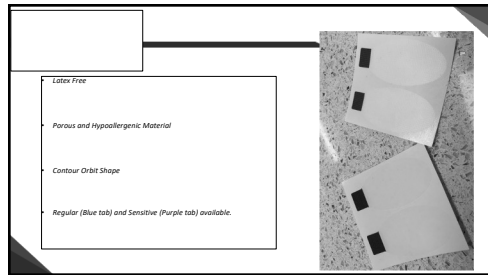
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