What's In The Bottle?
New Rx Therapies for DED

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Disclosures - Damon Dierker, OD, FAAO

- Aerie - A
- Alcon - A/C/S
- Allergan - A/C/R/S
- ArcticDx - R
- Avellino Lab - A
- Azura - A
- Bausch & Lomb - A/C/S
- Bio-Tissue - A/C/R/S
- Carl Zeiss Meditec - A
- Dompe - S
- Dry Eye Boot Camp - Founder
- Eyes On Dry Eye - Co-Founder
- Eyevance - A/C/S
- Genentech - A
- Glaukos - A/C/S
- Gyroscope - R
- Johnson & Johnson - C
- Kala - A/C/S
- Lumenis - C/S
- MacuHealth - S
- MacuLogix - A/C/S
- Notal Vision - A/C/R/S
- NovaBay - C
- Novartis - A/C/S
- NuSight Medical - C
- Ocular Therapeutix - A/R
- Ocuphire - A
- OcuTerra - A
- Optovue - S
- Oyster Point Pharma - A/C/R/S
- Quidel - A/C
- RVL Pharmaceuticals - A/C/S
- ScienceBased Health - A/C/S
- Scope - C
- Shire - A/C/S
- Sight Sciences - A/C/R/S
- Sun Pharma - A/S
- Tarsus - A/C/R
- Thea Pharmaceuticals - A/C
- Trukera Medical - Chief Medical Advisor, Optometry

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Varenicline

Dry Eye Disease

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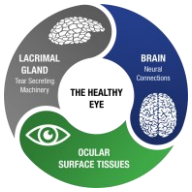
Unmet Need – Dry Eye Disease

Tear Production is Regulated through a Neural Feedback Loop

- Lacrimal Functional Unit
  - Ocular Surface Tissues
  - Lacrimal Gland
  - Neuronal Connections - sensory and motor
- Healthy tear film provides a smooth optical surface to optimize vision
- LFU maintains ocular surface comfort and epithelial cell health
- Tear film homeostasis involves maintaining stability of all layers of the tear film



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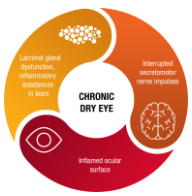
Unmet Need – Dry Eye Disease

DED is initiated by desiccating stress and perpetuated by a vicious circle of ocular surface inflammation

Tear film evaporation leads to hyperosmolarity and ocular surface damage

LFU is disrupted and a loss of homeostasis occurs



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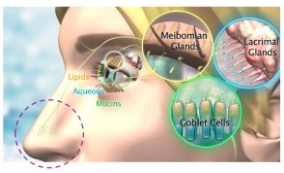
Parasympathetic Nervous System Controls Tear Film Homeostasis

The trigeminal nerve provides the pathway for parasympathetic stimulation of the Lacrimal Functional Unit (LFU) to promote complete natural tear film

The trigeminal nerve is accessible within the nasal cavity and can be activated by stimulating nicotinic acetylcholine receptors (nAChR)



34% of basal tear production is due to inhaling air through the nose[1]

[1]Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. Cornea. 1997;16(6):645-648.

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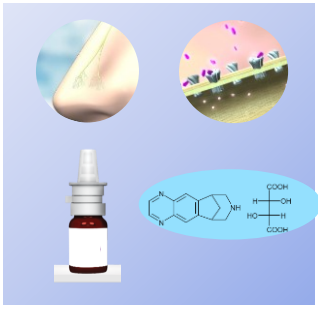
OC-01 (varenicline)

- Preservative-free intranasal spray containing the selective nicotinic acetylcholine receptor agonist, varenicline
- Binds to receptors located on the trigeminal nerve, which is readily accessible within the anterior portion of the nasal cavity, to open ion channels and depolarize the nerve
- Nerve is activated, and lacrimal functional unit is stimulated to produce natural tears



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Tyrvaya – What's In The Bottle?

- Active Ingredient – varenicline 0.03 mg
- Indication – treatment of the signs and symptoms of dry eye disease
- Dosing – one spray in each nostril twice daily
- Contraindications – none
- Warnings - none
- Adverse events
  - Sneezing (82%)
  - Cough/throat irritation/nose irritation (5-16%)

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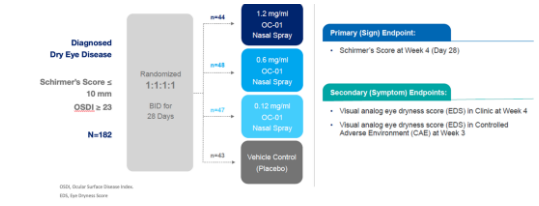
ONSET-1: OC-01 Phase 2b Study Design

Multicenter, Randomized, Double-Masked, Vehicle-Controlled Clinical Trial to Evaluate the Safety and Efficacy of OC-01 Intranasal Spray on Signs and Symptoms of DED



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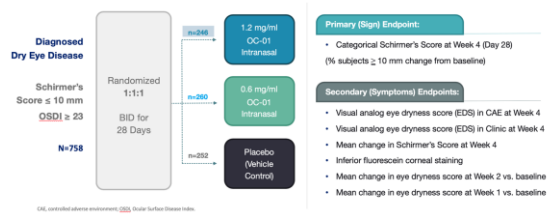
ONSET-2: Phase 3 Study Design

Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy and Safety of OC-01 Intranasal on the Signs and Symptoms of Dry Eye Disease



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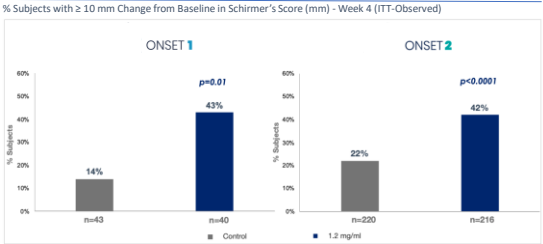
ONSET-1 and ONSET-2: Statistically Significant Improvement in Signs

% Subjects with ≥ 10 mm Change from Baseline in Schirmer's Score (mm) - Week 4 (ITT-Observed)



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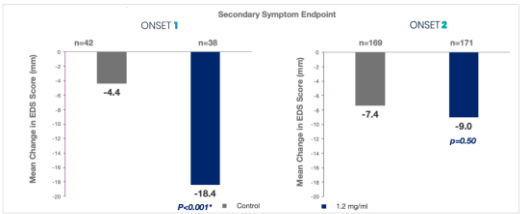
ONSET-1 and ONSET-2: Change in Eye Dryness in CAE

Mean Change in Eye Dryness Score in CAE (5 minutes post administration) vs. Baseline (Day 1)
Measured at Week 3 (ONSET-1) or Week 4 (ONSET-2)



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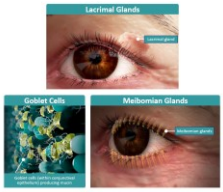
Clinical Applications

- Patients with signs/symptoms of DED:
  - Any dry eye subtype
  - Failed or incomplete response to traditional dry eye therapies
  - Side effects from topical prescription medications
  - Trouble instilling eye drops
  - Want less dependence on drops
  - Contact lens patients



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Perfluorohexyloctane

Dry Eye Disease

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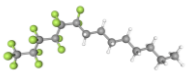
NOV03 - Perfluorohexyloctane

- Perfluorohexyloctane
  - ✓ Water-free, preservative-free
  - ✓ Long-lasting lubricant
  - ✓ Potent inhibitor of evaporation



	Water-based Technologies	NOV03
Drop Size	~ 40–50µL	11 µL
Drug Residual Time	Brief 3–5 min	Long ~ 240 min
Spreading	High surface tension hinders spreading	Fast spreading Film-forming properties
Other Features	Usually preserved	Preservative-free Blink reflex not activated No vision blurring

1. Kröser S, et al. *Invest Ophthalmol Vis Sci.* 2018;59:2656. 2. Broniatowski M, et al. *J Phys Chem B* 2004;108:13403-13411. 3. Liu X, et al. *Bull Chem Soc Jpn.* 2018;91(5):846-857. 4. Gaines G Jr. *Langmuir* 1991;7(12):3054-3056. 5. Meinert H, et al. *Eur J Ophthalmol.* 2000;10(3):189-197. 6. Borchmann et al. *Invest Ophthalmol Vis Sci.* 2022;63:1525 – A0250.

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Miebo – What's In The Bottle?

- Active Ingredient – perflourohexyloctane
- Indication – treatment of the signs and symptoms of dry eye disease
- Dosing – one drop in each eye four times daily
- Contraindications – none
- Warnings - none
- Adverse events
  - Blurred vision (<4%)

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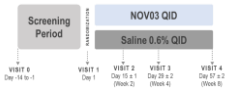
Phase 3 Program - GOBI and MOJAVE

- Multicenter, randomized, double-masked, hypotonic saline (0.6%)-controlled trials in subjects with DED associated with MGD[1,2]
- Subjects ≥18 years old with self-reported history of DED in both eyes
- Subjects randomized 1:1 to NOV03 or saline 1 drop QID in both eyes for 8 weeks
- Primary outcomes:
  - CFB in tCFS (NEI scale) at Day 57
  - CFB in VAS dryness score at Day 57
- Secondary outcomes:
  - CFB in dryness score (VAS) at Day 15
  - CFB in tCFS (NEI scale) at Day 15
  - CFB of VAS burning/stinging at Day 57
  - CFB in central corneal fluorescein staining (cCFS) at Day 57
- Safety outcomes:
  - Ocular and non-ocular AEs, best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure, dilated fundoscopy



Abbreviations: CFB, change from baseline; tCFS, total corneal fluorescein staining; cCFS, central corneal fluorescein staining ; VAS, visual analog scale; QID, four times a day

Tauber J, Berdy GJ, Wirta DL, Kröser S, Vittitow JL. Presented at the 2022 American Society of Cataract and Refractive Surgeons annual meeting, April 22-26, 2022.
Sheppard JD, Kurata FK, Epitropoulos A, Kröser S, Vittitow J. *Invest Ophthalmol Vis Sci.* 2022;63:1531.

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GOBI and MOJAVE - Demographics

	GOBI		MOJAVE	
	NOV03 (n=303)	Saline (n=294)	NOV03 (n=311)	Saline (n=309)
Mean Age (years)	60.3	61.6	53.3	53.8
Sex				
Male	27.7%	27.2%	19.6%	23.0%
Female	72.3%	72.8%	80.4%	77.0%
Race				
Asian	11.2%	9.5%	11.6%	8.7%
Black	17.5%	18.7%	7.4%	6.5%
White	70.0%	69.4%	78.5%	82.5%
Other	1.3%	2.4%	2.6%	2.3%
Ethnicity				
Hispanic or Latino	14.2%	17.3%	20.3%	21.0%
Not Hispanic or Latino	85.8%	82.7%	79.7%	79.0%

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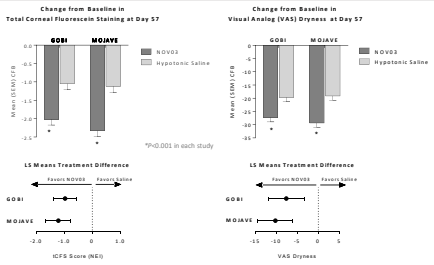
Primary Efficacy - *Both* Sign and Symptom Endpoints Met



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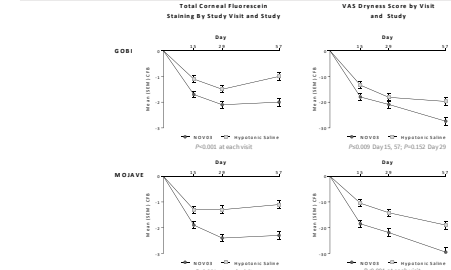
Key Secondary Endpoints - Improvements as Early as Day 15



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Sheppard JD, Kurata FK, Epitropoulos A, Krösser S, Vittitow J. *Invest Ophthalmol Vis Sci.* 2022;63:1531.

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NOV03 was Well-Tolerated

GOBI	NOV03 (n=303) n (%)	SALINE (n=294) n (%)
Subjects with ≥ 1 ocular study eye AE	25 (8.3)	15 (5.1)
Most common study eye AEs*		
Blurred Vision	9 (3.0)	1 (0.3)

*Incidence >1% in either treatment group

MOJAVE	NOV03 (n=311) n (%)	SALINE (n=309) n (%)
Subjects with ≥ 1 ocular study eye AE	30 (9.6)	30 (9.7)
Most common study eye AEs*		
Blepharitis	5 (1.6)	1 (0.3)
Blurred Vision	4 (1.3)	1 (0.3)
Conjunctival Hyperemia	4 (1.3)	5 (1.6)
Conjunctival Papillae	4 (1.3)	5 (1.6)
Eye Discharge	1 (0.3)	3 (1.0)
Eye Pain	1 (0.3)	3 (1.0)

*Incidence >1% in either treatment group.

- Few subjects experienced non-ocular AEs
  - None of the non-ocular AEs were considered related to treatment
- Other safety assessments were unremarkable (BCVA, biomicroscopy, IOP, fundoscopy)

Tauber J, Berdy GJ, Wirta DL, Krösser S, Vittitow JL. Presented at the 2022 American Society of Cataract and Refractive Surgeons annual meeting, April 22-26, 2022.
Sheppard JD, Kurata FK, Epitropoulos A, Krösser S, Vittitow J. *Invest Ophthalmol Vis Sci.* 2022;63:1531.

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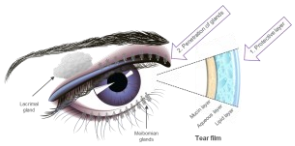
Clinical Applications

- Patients with signs/symptoms of DED:
  - Any dry eye subtype
  - Primary therapy
  - Adjunctive therapy
- Consider in any case where evaporation > total tear supply



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Lotilaner

Demodex Blepharitis

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DEMODEX BLEPHARITIS | A PERVASIVE AND DAMAGING EYE DISEASE

- **Blepharitis is the inflammation of the eyelids** causing irritation and redness
- **69% of blepharitis cases are due to *Demodex* infestation leading to *Demodex* blepharitis[1-4]**
  - *Demodex* mites are implicated in other diseases of the lid and lid margin, including blepharitis and meibomian gland dysfunction[2,3]
  - *Demodex* mites are associated with acne vulgaris, folliculitis, rosacea, seborrheic dermatitis, perioral and scalp hair loss, and basal cell carcinoma[1,2]
- ***Demodex folliculorum* and *Demodex brevis*** are the only 2 species found in humans[5]
  - The life cycle of the *Demodex* mite is approximately 14 to 18 days from the egg to the larval stage followed by the adult stage[5]
  - The life span of the mite is limited outside the living body; direct contact is required for transinfestation[5]

D. folliculorum

0.3-0.4 mm length
Colonizes the base of the lash follicle[5]

D. brevis

0.1 mm length
Colonizes the meibomian gland[5]

1. Mayo Clinic. Accessed June 28, 2022. https://www.mayoclinic.org/diseases-conditions/blepharitis/symptoms-causes/syc-20370160 2. Zhang AC et al. *Ophthalmol Physiol Opt.* 2020;40(4):389-432. 3. Frizenschaf N et al. *Clin Optom (Auckl).* 2018;10:57-63. 4. Tarkkan W et al. *Clin Ophthalmol.* 2021;15:2113-2118. 5. Liu J et al. *Ann Parasitol.* 2017;63(1):1-23.

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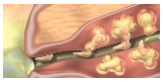
DEMODEX BLEPHARITIS | MECHANISMS OF DISEASE

Image courtesy of Laura M. Periman, MD, used with permission.[1]



MECHANICAL

- Lash distension occurs as *Demodex* mites attach to follicles[2-4]
- *Demodex* mites deposit debris and digestive enzymes, causing further irritation to the eyelid margin[4,5]

BACTERIAL

- *Demodex* mites can contribute to blepharitis by carrying bacteria on their exterior surface that may elicit immune responses[3,6-7]

CHEMICAL

- *Demodex* mites have been associated with altered meibum composition[8]
- Debris from *Demodex* mites can potentially lead to chronic inflammation and degeneration of conjunctival tissue[9]

1. Data on file. Images courtesy of Laura M. Periman, MD; 2022. 2. Zhang AC et al. *Ophthalmol Physiol Opt*. 2020;40(4):389-432. 3. Liu J et al. *Curr Opin Allergy Clin Immunol*. 2010;10(5):505-510. 4. Gao YY et al. *Invest Ophthalmol Vis Sci*. 2009;50(8):3694-3699. 5. Zhu W et al. *Front Microbiol*. 2018;9:2078. 6. Li et al. *Ophthalmology*. 2010;117(5):870-877. 7. Gao Y et al. *Transl Vis Sci Technol*. 2020;10(14):5. 8. Tarkowski M et al. *Biomed Res Int*. 2020;2958109.

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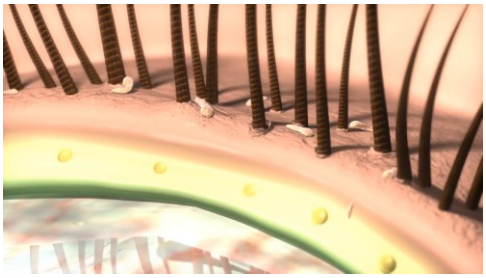

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CLINICAL MANIFESTATIONS OF *DEMODEX* BLEPHARITIS

Images courtesy of Paul Karpecki, OD, used with permission.

Disorders of Eyelashes[1,2]

Infestation of the lash follicles can result in collarettes and may lead to malalignment, trichiasis, and madarosis

Images courtesy of Paul Karpecki, OD, used with permission.

Meibomian Gland Dysfunction[1,2]

Blockage leads to filling, swelling, and many enlarged glands (cysts) or infection. Chalazia are common granulomatous responses

Lid Margin Inflammation[1,2]

Severe lid margin inflammation can be caused by mechanical blockage and a delayed host immune hypersensitivity reaction

Images courtesy of Paul Karpecki, OD, used with permission.

Conjunctival Inflammation[1,2]

Without proper hygiene, lid margin inflammation may spread over to the conjunctiva producing a condition known as blepharoconjunctivitis

Corneal Manifestations[1,2]

D. brevis is commonly associated with inflammation that spreads to the cornea, causing sight-threatening corneal lesions, superficial vascularization, marginal infiltrates, phlyctenule-like lesions, opacity, and/or nodular scars

1. Liu J et al. *Curr Opin Allergy Clin Immunol*. 2010;10(5):505-510. 2. Zhang AM et al. *Curr Opin Ophthalmol*. 2020;31(4):299-306.

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Collarettes Are Pathognomonic Sign of Demodex Infestation

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

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

Easily and Rapidly Diagnosed with Standard Eye Exam

- Demodex mites found on 100% of lashes with collarettes[2]
- Collarettes found in ~ 58% eye care patients[3]

Patient looking straight ahead

Patient looking down, **exposing base of lashes and collarettes**

Images courtesy of Elizabeth Yeu, MD, used with permission.

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

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DEMODEX BLEPHARITIS CAN BE DIAGNOSED DURING SLIT LAMP EXAMINATION

Collarettes are hardened excretions around the base of the eyelashes visible during slit lamp examination[1-3]

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 ahead[4]

Patient looking straight ahead

Patient looking down, **exposing base of lashes and collarettes**

Images courtesy of Elizabeth Yeu, MD, used with permission.[4]

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. Zhang AC et al. *Ophthalmol Physiol Opt*. 2020;40(4):389-432. 2. Gao YY et al. *Invest Ophthalmol Vis Sci*. 2009;50(7):3288-3295. 3. Fromstein SR et al. *Clin Optom (Auckl)*. 2018;10:57-63. 4. Cotliar J. & Refractive Surgery Today. Accessed June 29, 2022. https://crstoday.com/articles/oct-2021/impact-of-demodex-blepharitis-and-importance-of-early-detection. 5. Data on file. Image courtesy of Elizabeth Yeu, MD; 2022.

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TP-03 is a Novel Drug Designed to Treat Demodex Blepharitis by Eradicating Mites and Collarettes[1]

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	1º collarette cure, 2º mite eradication, 2º redness + collarette cure
Safety Goal	Well-tolerated safety profile

*BID means twice per day

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

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Xdemvy – What's In The Bottle?

- Active Ingredient – lotilaner 0.25%
- Indication – treatment of Demodex blepharitis
- Dosing – one drop in each eye twice daily for 6 weeks
- Contraindications – none
- Warnings - none
- Adverse events
  - Instillation site stinging and burning (10%)

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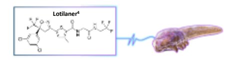
MECHANISM OF ACTION OF TP-03 (Lotilaner Ophthalmic Solution, 0.25%)

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 reside[3]



Product form[5]
Preserved (sorbate) multidose eye drop solution in bottle

Dosing[5]
Twice daily for 6 weeks

FDA, Food and Drug Administration; GABA, gamma aminobutyric acid.

1. Dailymed Credelio. Accessed June 28, 2022. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=427f2ebc-ce24-452b-bbb3-43d4ef8b63b0 **2.** Gonzalez-Salinas R et al. *J Ophthalmol.* 2021:3862684. **3.** LianBio. Accessed June 28, 2022. https://www.globenewswire.com/news-release/2022/05/03/2434549/0/en/LianBio-Partner-Tarsus-Pharmaceuticals-Announces-Positive-Topline-Data-from-Second-Pivotal-Trial-of-TP-03-for-the-Treatment-of-Demodex-Blepharitis.html
4. ChemSrc Lotilaner. Accessed June 28, 2022. https://www.chemsrc.com/en/cas/1369852-71-0_1262257.html **5.** Yeu E et al. *Cornea.* 2022; In Press.

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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

Efficacy goal
1° collarette cure rate,
2° mite eradication,
2° redness + collarette cure rate

Safety goal
Well-tolerated safety profile

1°, primary; 2°, secondary; NDA, New Drug Application.
Data on file. Tarsus Pharmaceuticals Incorporated; 2022

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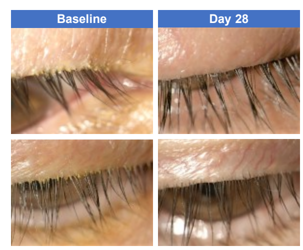
Cure of Collarettes with BID Use of TP-03



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CyclaSol

Dry Eye Disease

Eye Surgeons of Indiana

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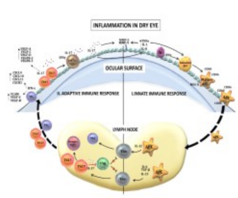
Cyclosporine in DED – Mechanism of Action



- Inactives T cells
- Inhibits release of inflammatory cytokines
- Prevents apoptosis of conjunctival epithelial cells
- Induces apoptosis of activated T cells

Tsubota K, Pflugfelder SC, Liu Z, Baudouin C, Kim HM, Messmer EM, Kruse F, Liang L, Carreno-Galeano JT, Rolando M, Yokoi N, Kinoshita S, Dana R. Defining Dry Eye from a Clinical Perspective. Int J Mol Sci. 2020 Dec 4;21(23):9271
Periman LM, Mah FS, Karpecki PM. A Review of the Mechanism of Action of Cyclosporine A: The Role of Cyclosporine A in Dry Eye Disease and Recent Formulation Developments. Clin Ophthalmol. 2020 Dec 2;14:4187-4200

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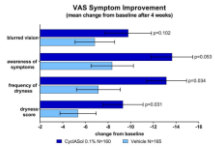
CyclASol (cyclosporine 0.1%)

- First-of-a-kind topical treatment of cyclosporine
- Cyclosporine is soluble in the excipient perfluorobutylpentane allowing for its improved bioavailability and better efficacy on the target tissue
- Contains no oils, no surfactants and is preservative-free due to the novel carrier
- Provides additional clinical benefits for patients, such as improved tolerability and decreased visual disturbances
- Each drop 20 µl in size

A Water-free 0.1% Cyclosporine A Solution for Treatment of Dry Eye Disease: Results of the Randomized Phase 2B/3 ESSENCE Study



Sheppard JD, Wirta DL, McLaurin E, Boehmer BE, Ciolino JB, Meides AS, Schlüter T, Ousler GW, Usner D, Kröscer S. A Water-free 0.1% Cyclosporine A Solution for Treatment of Dry Eye Disease: Results of the Randomized Phase 2B/3 ESSENCE Study. Cornea. 2021 Oct 1;40(10):1290-1297.

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Vevye – What's In The Bottle?

- Active Ingredient – cyclosporine 0.1%
- Indication – treatment of the signs and symptoms of dry eye disease
- Dosing – one drop in each eye twice daily
- Contraindications – none
- Warnings - none
- Adverse events
  - Instillation site reactions (8%)

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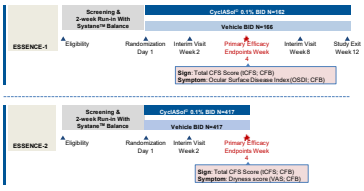
ESSENCE-1 and ESSENCE-2 Trial Designs



Two large scale, controlled trials to assess the efficacy, safety, and tolerability of CyclASol for the treatment of dry eye disease

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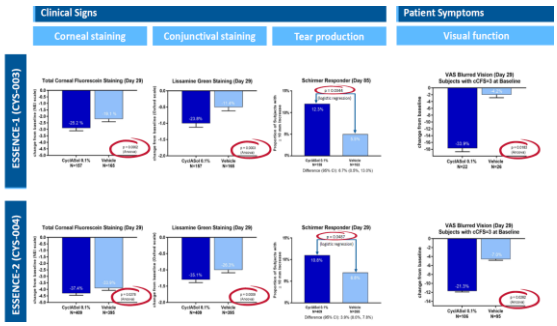

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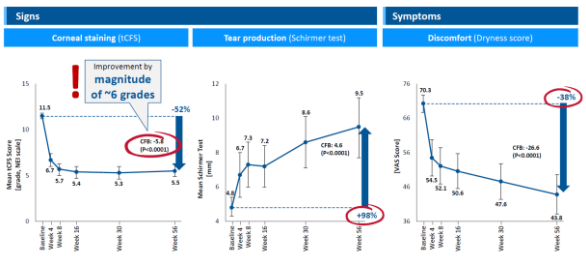
Clinical Benefit over 52 Weeks



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Safety and tolerability profile

All AEs	ESSENCE-1 CyclASol® 0.1%	ESSENCE-1 Vehicle	ESSENCE-2 CyclASol® 0.1%	ESSENCE-2 Vehicle
Number of TEAEs	72	71	82	96
Number of subjects with at least one TEAE	46 (28.4%)	44 (26.5%)	71 (16.8%)	73 (17.8%)
Number of treatment-emergent SAEs	0 (0.0%)	3 (1.8%)	2 (0.5%)	3 (0.7%)
Number of subjects discontinued treatment due to an AE	3 (1.9%)	0 (0.0%)	2 (0.5%)	3 (0.7%)
Ocular AEs				
Number of TEAEs	31	23	68	75
Number of subjects with at least one ocular TEAE	20 (12.3%)	14 (8.4%)	57 (13.5%)	62 (15.1%)
Ocular AEs occurring in more than 2% of patients				
Visual acuity reduced	5 (3.1%)	3 (1.8%)	7 (1.7%)	13 (3.2%)
Instillation site pain/pruritus				
• Mild	4 (2.5%)	2 (1.2%)	42 (9.9%)	35 (8.5%)
• Moderate	0	0	1 (0.2%)	1 (0.2%)
• Severe	0	0	0	0
Vision blurred	2 (1.2%)	4 (2.4%)	2 (0.5%)	2 (0.5%)

CyclASol and its novel vehicle were generally safe and well tolerated with minimal reports of TEAEs similar between treatment groups

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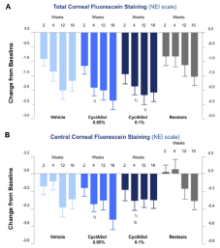
Phase-2 study (CYS-002): tCFS and cCFS



(1) Statistically significant vs. Restasis (P 0.05) in analysis of covariance (ANCOVA);
(2) Statistically significant vs. Vehicle (P 0.05) in ANCOVA.

Wirta et. al. 2018
https://doi.org/10.1016/j.ophtha.2019.01.024

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Thank You!

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