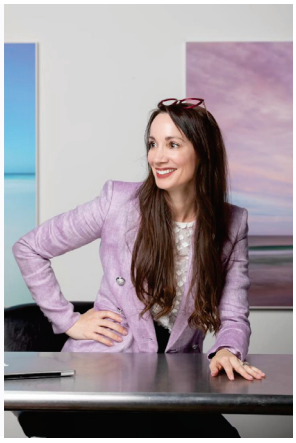
New Technologies in Dry Eye

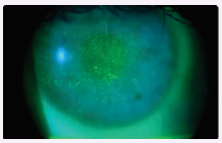
Selina R. McGee, OD, FAAO, presents the latest advancements in the field of dry eye treatment and management.



First things first

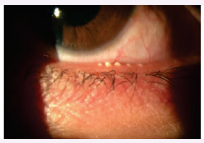
1. Establish a **baseline** understanding of the patient's dry eye symptoms and ocular surface health.
2. Utilize **objective tests** to quantify the severity of the dry eye disease.
3. Determine the **underlying etiology** - is it aqueous deficient, evaporative, or a combination of both?

Early OSD Detection



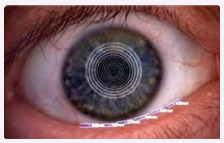
Corneal Staining

Fluorescein or lissamine green dye reveals compromised epithelium.



Gland Dysfunction

Meibography visualizes obstructed glands glands contributing to tear instability. instability.



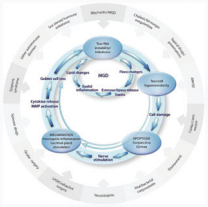
Tear Film Assessment

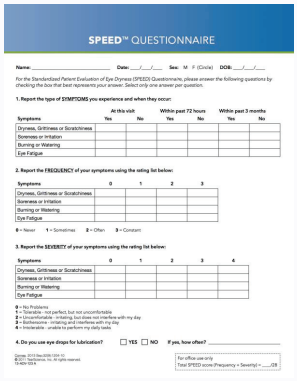
Tear film quality analysis detects early early homeostatic imbalances.

Desiccating Stress

1

- Desiccating stress is a central pathophysiologic mechanism for all forms of dry eye disease (DED)
- Excessive tear film evaporation leads to hyperosmolarity, which causes inflammation and apoptosis, reducing the ability of mucins to lubricate the ocular surface
- Hyperosmolarity also leads to a breakdown of homeostatic control, causing tear film instability
- An osmolarity reading above 308 mOsms/L or an inter-eye difference of >8 mOsm/L are indications of mild osmolarity and loss of homeostasis
- Moderate to severe dry eye is associated with osmolarity readings above 316 mOsm/L





Symptoms

- OSDI or OSDI-6 (Ocular Surface Disease Index-_Allergan_)
- SPEED (Standardized Patient Evaluation of Eye Dryness and Ocular Surface Disease Index-_TearScience_
- DEQ-5 (The Dry Eye Questionnaire-_Chalmers et al_)

Point of care testing

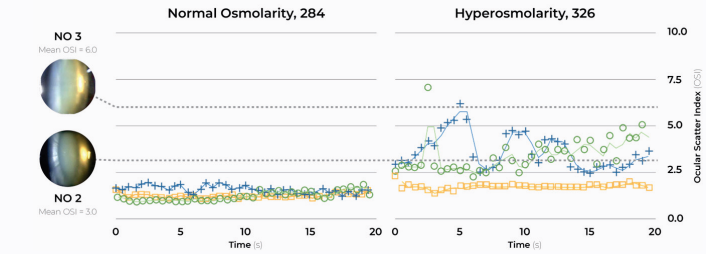
- Tear Osmolarity-This diagnostic tool measures the concentration of tears, or osmolarity. In reviewed literature Osmolarity readings above 308 mOsms/L or an inter-eye difference of >8 mOsm/L are an indication of mild osmolarity and loss of homeostasis.
- MMP-9 (Metalloproteinase-9) is a nonspecific inflammatory marker that can be present in patients who have dry eye disease.

Osmolarity

- **Normal** - Between 280-295 mOsm/L1
- **Hyperosmolar** - Central pathophysiologic mechanism for all forms of DED
- Causes inflammation and apoptosis & reduces the ability of mucins to lubricate
- Leads to a breakdown of homeostatic control causing tear film instability
- 308 mOsm/L is a highly sensitive cut-off point that delineates a normal from a mild/moderate dry eye population. 316 mOsm/L for moderate/severe
- **Inter-eye difference** = Hallmark of DED (>8 mOsms/L between eyes)
- Unstable tear film causes inter-eye differences

1Potvin, Richard et al, *Clinical Ophthalmology* 2015:9 2039–2047

Hyperosmolarity Creates Light Scatter



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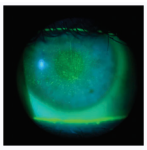
Tear Quantity



- **Tear Meniscus Height**-This information tells us how much tear volume is present. The normal average is 0.2mm.
- **Lissamine Green**-This vital dye stains devitalized cells of the conjunctiva. Symptoms and conjunctival staining characterize Level 1 dry eye disease1. No corneal signs will be present. This dye is a must have otherwise you will miss Level 1 severity and may put off treatment until the patient progresses to Level 2 or 3.
- **NaFl (Sodium Fluoroscein)**-This vital dye stains corneal breaks and devitalized cells of the cornea. Certainly an important indicator in establishing the health of the cornea.
- **Measuring TBUT or Tear Break Up Time** gives important information about how long the tear film stays in place or the stability of the tears.
- **Phenol Red** is a patient preferred Shirmer's test. It measures tear volume in 15 seconds with much less reflex tearing than Shirmer's. Nice to have when an objective measure of tear volume is needed for those truly aqueous deficient patients.

Afferent neural signals[1-3]

Travel from LFU to CNS

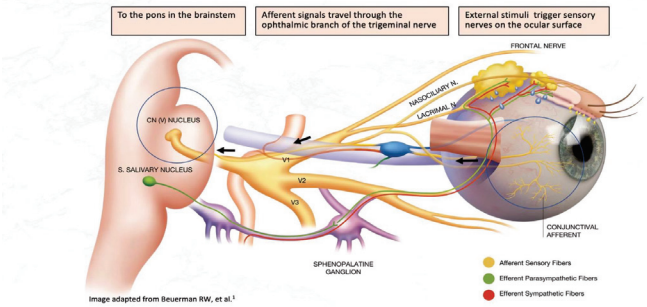
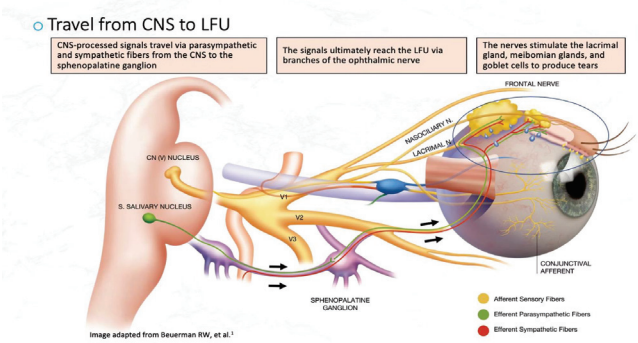


Image adapted from Beuerman RW, et al.[1]

1. Beuerman RW, et al. In: Pflugfelder SC, et al, eds. *Dry Eye and Ocular Surface Disorders*. 2004. 2. Kossler AL, et al. *Ophthal Plast Reconstr Surg*. 2015;31(2):145-151.
3. Dartt DA. *Ocul Surf*. 2004;2(2):76-91.

Efferent neural signals[1-3]

Travel from CNS to LFU



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3. Dartt DA. *Ocul Surf*. 2004;2(2):76-91.

Lid structure and function

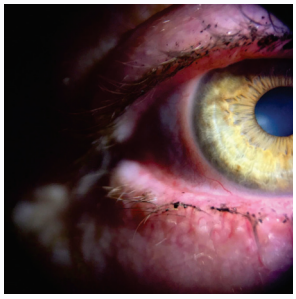
- Lid morphology with the slit-lamp is the basic diagnostic test here.
- Expression of meibomian glands is important to know the quality of meibum and quantity that are functioning. Diagnostic tools: cotton swab, fingertip, or meibomian gland evaluator7.
- Blink rate-Identifying patients that have a partial blink, full blink, and how many times they blink is important to evaluate. Proper blinking facilitates meibomian gland functionanality8.
- Meibography-This diagnostic tool images the integrity of the meibomian glands using infared cameras. This can be a powerful tool to help patients understand how these glands can impact their disease process. Certainly a nice to have when you have adopted all the must have's we've talked about. Several instruments are on the market that offer this with other important diagnostic testing with algorithms like non-invasive tear break up time, tear meniscus, blink rate, corneal topography, and videography.

Normal Eyelid (meibomian) Glands:
Meibomian glands produce the oils needed for a healthy tear film

Gland (oil) Dropout:
MGD occurs when the meibomian glands become blocked. If this blockage is left untreated the glands will drop out entirely.

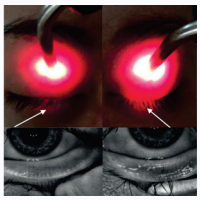
Ocular Rosacea

Ocular rosacea is a chronic inflammatory condition that affects the eyes and eyelids. It is often associated with the skin condition rosacea, which causes redness, flushing, and visible blood vessels on the face. Ocular rosacea can lead to a range of eye-related symptoms, including irritation, dryness, and sensitivity to light.



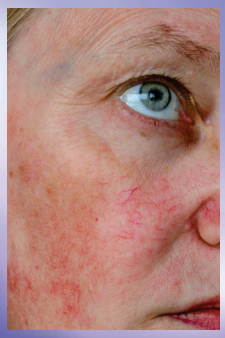
Lid Seal-When do your eyes feel worse?

- Moisture chamber goggles can be used to evaluate the impact of environmental factors on dry eye symptoms.
- Wearing the goggles can help determine if the patient's eyes feel worse in dry, windy, or low-humidity environments.
- This can provide insight into the evaporative component of the patient's dry eye disease and guide treatment recommendations.

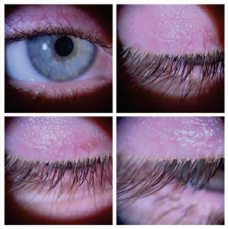


Patient Assessment

Evaluating the patient's symptoms, signs, and diagnostic test results is crucial in determining the underlying cause of dry eye disease and developing an appropriate treatment plan. A comprehensive patient assessment involves a thorough history, clinical examination, and appropriate diagnostic testing.



Eyelid Evolution



1 **Anatomy**

The eyelids play a crucial role in maintaining the health and function of the ocular surface. They are composed of complex structures, including the skin, muscle, connective tissue, and meibomian glands, which work together to protect the eye and facilitate tear film distribution.

2 **Dysfunction**

Disruption of the delicate eyelid anatomy can lead to various pathological conditions, such as meibomian gland dysfunction (MGD), blepharitis, and dry eye disease. These conditions can significantly impact the quality of life for patients, causing discomfort, visual disturbances, and even vision loss if left untreated.

3 **Intervention**

Advancements in eyelid-focused therapies, including thermal pulsation, microblepharoexfoliation, and targeted pharmacological treatments, have revolutionized the management of eyelid-related disorders. These innovative approaches aim to restore the normal function of the eyelids, improving tear film stability and reducing the burden of dry eye disease.

DEMODEX BLEPHARITIS| A PERVASIVE AND DAMAGING EYE DISEASE

1

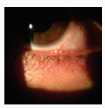
- **Blepharitis is the inflammation of the eyelids** causing irritation and redness
- **69% of blepharitis cases are due to Demodex infestation leading to Demodex blepharitis1-4**
- Demodex mites are implicated in other diseases of the lid and lid margin, including blepharitis and meibomian gland dysfunction2,3
- Demodex mites are associated with acne vulgaris, folliculitis, rosacea, seborrheic dermatitis, perioral and scalp hair loss, and basal cell carcinoma1,3
- **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

CLINICAL MANIFESTATIONS OF DEMODEX BLEPHARITIS

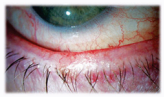
Disorders of Eyelashes

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



Meibomian Gland Dysfunction

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



Lid Margin Inflammation

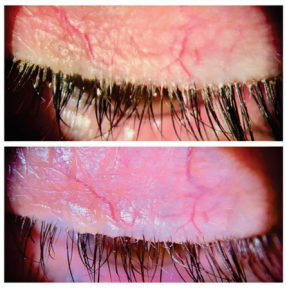
Severe lid margin inflammation can be caused by mechanical blockage and a delayed host immune hypersensitivity reaction

Conjunctival Inflammation

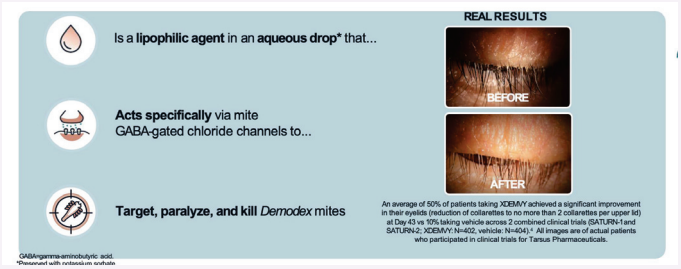
Without proper hygiene, lid margin inflammation may spread over to the conjunctiva producing a condition known as blepharoconjunctivitis

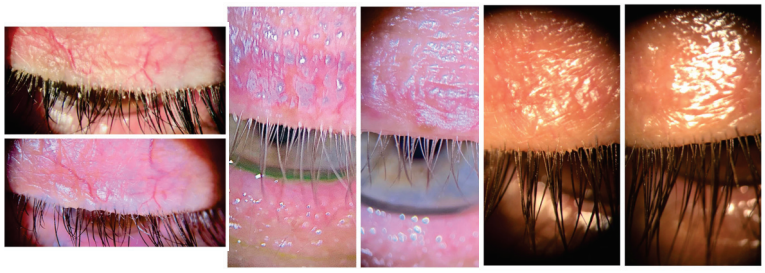
Collarettes Are a Pathognomonic Sign of Demodex Blepharitis

Collarettes, or cylindrical dandruff, are composed of mite waste products and eggs. They are translucent, solidified exudative excretions that form a cylindrical collar cuffing around the base of the eyelash follicle. Collarettes are displaced along the shaft of the lash as it grows, and they are also displaced due to bacterial overgrowth. Collarettes are composed of regurgitated undigested mite waste combined with epithelial cells, keratin, mite eggs, and secreted proteases and lipases that cause irritation. 100% of patients with collarettes have Demodex blepharitis.

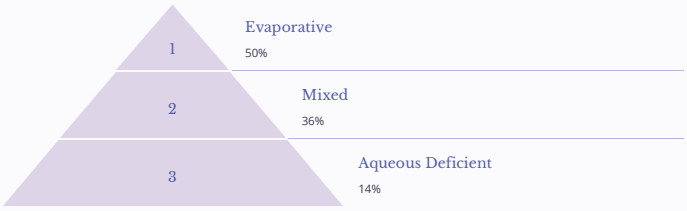


MECHANISM OF ACTION OF TP-03 (Lotilaner Ophthalmic Solution 0.25%)

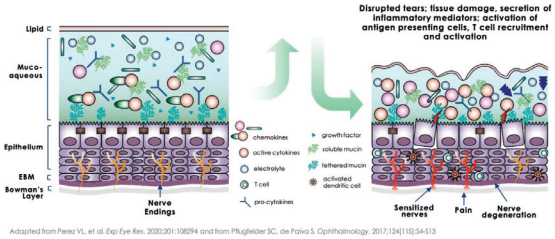




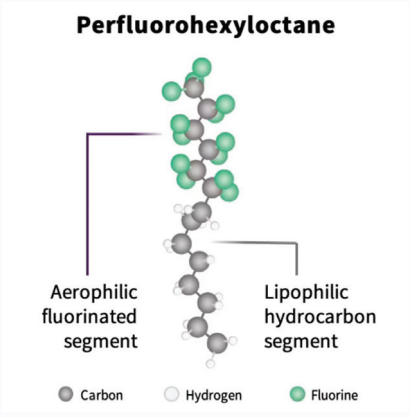
The Majority of DED Has an Evaporative Etiology

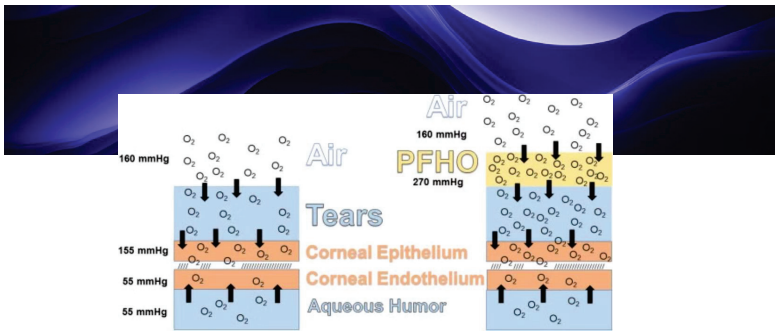


MGD, the major contributor to the evaporative etiology of DED, is present in ≥86% of cases.



Adapted from Perez VL, et al. *Exp Eye Res*. 2020;201:108294 and from Pflugfelder SC, de Paiva S. *Ophthalmology*. 2017;124(1S):S4-S13.





Neal Stolowich, Jason Vittitow, Robert Kissling, Douglas Borchman, Oxygen-Carrying Capacity of Perfluorohexyloctane, a Novel Eye Drop for Dry Eye Disease, Current Therapeutic Research, Volume 98, 2023

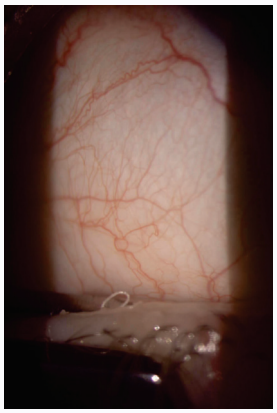
Cyclosporine 1.0% in Perfluorobutylpentane

1

- **Description:** 0.1%cyclosporine is soluble in the EyeSol®excipient perfluorobutylpentane
- **Target indication:** Signs and symptoms of DED
- **Dosing:** BID
- **Mechanisms of action:** PF Topical anti-inflammatory and immunomodulator
- **FDA status:** ESSENCE-1, ESSENCE-2

Interventional Dry Eye

Innovative treatments and technologies are emerging to address the underlying causes of dry eye disease and provide lasting relief for patients.



Sahara- Ayres BD, Bloomenstein MR, Loh J, Chester T, Saenz B, Echegoyen J, Kannarr SR, Perez VL, Rodriguez TC, Dickerson JE Jr. A Randomized, Controlled Trial Comparing Tearcare® and Cyclosporine Ophthalmic Emulsion for the Treatment of Dry Eye Disease (SAHARA). Clin Ophthalmol. 2023 Dec 18;17:3925-3940. doi: 10.2147/OPTH.S442971. PMID: 38143559; PMCID: PMC10741761.

- TearCare treatment is superior to branded Restasis in improving TBUT and multiple measures of meibomian gland function
- Both treatments produce significant improvements in patient reported symptoms
- TearCare administration and therapeutic effect in SAHARA RCT is consistent with "real-world"
- Compliance to branded Restasis in SAHARA RCT was likely atypical of "real-world" patient behavior1 (on average 5.7 bottles over 6 months)
- Results of SAHARA RCT may warrant earlier intervention with TearCare
- Equal third-party patient access to TearCare may be justified

1. Uchino M, Yokoi N, Shimazaki J, Hori Y, Tsubota K, On Behalf Of The Japan Dry Eye Society. Adherence to Eye Drops Usage in Dry Eye Patients and Reasons for Non-Compliance: A Web-Based Survey. J Clin Med. 2022 Jan 12;11(2):367. doi: 10.3390/jcm11020367. PMID: 35054060; PMCID: PMC8779746.

Paradigm Shift

1

- The treatment of dry eye disease is undergoing a paradigm shift, moving away from a one-size-fits-all approach to a more personalized, targeted approach.
- New technologies and therapies are emerging that address the underlying causes of dry eye, rather than just treating the symptoms.
- These innovative solutions are aimed at restoring the natural tear film, reducing inflammation, and improving overall ocular surface health.
- By addressing the root causes of dry eye, these new treatments have the potential to provide long-lasting relief and improve the quality of life for patients.
- As our understanding of the complex pathophysiology of dry eye continues to evolve, the field is poised for even more exciting advancements in the years to come.

Amniotic Membranes

- Available in cryopreserved or dehydrated form, amniotic membranes act as therapeutic bandages, restoring the health of the ocular surface. Patients that have central corneal staining are good candidates and can benefit from the therapeutic benefits of amniotic membranes, whether if their disease has aqueous-deficient or evaporative components.

- It really depends on the patients' disease on how long they wear them, it can be as little as 3 days but typically is 5-7 days.

Artificial Tears

Artificial tears aim to supplement tears to bathe the corneal surface as a means of providing **short-term relief**. They are available in **low-viscosity** and **high-viscosity** gels and ointments.

Ideal patients are already being treated and need a complementary component to their regimen. Both aqueous deficient and evaporative patients are candidates.

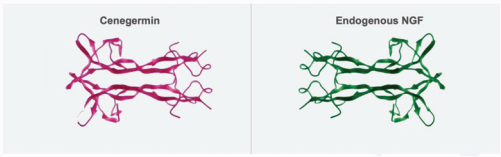
Preservative-free formulations are generally prescribed to preclude the patient from additional discomfort due to the long-term use of artificial tears that contain preservatives that can place the patient at risk for corneal toxicity.

Watch outs are using tears instead of uncovering what is really going on at/with the ocular surface. Don't use tears as a primary therapeutic approach, only use to support the main act of therapy. Recommend specific preservative free drops and carry them in the office, as the artificial tear aisle at the box stores is quite overwhelming for patients.

HA, **Trehalose**, and **Preservative Free** are some examples of artificial tear formulations.

Autologous Serum

- Autologous serum, or the use of a patient's own blood with the red blood cells and clotting factors removed as eye drops, contains many important growth factors and nutrients normally found in healthy tears. Therefore, optometrists prescribe the sterile, preservative-free solution to DED patients.
- These drops are typically reserved for the moderate to severe patient. I usually start with 20% but they can reconstituted to 30% or 40%
- As there are many regulations in place when patients blood is involved it's become harder to obtain this for patients.



Cenegermin-When It's Not Just DED!

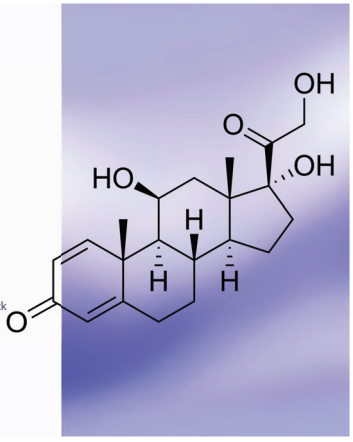
Known commercially as Oxervate (Dompe), this 0.002% topical solution contains a recombinant form of human nerve growth factor, a protein made by the human body, that acts through specific high-affinity and low-affinity nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.

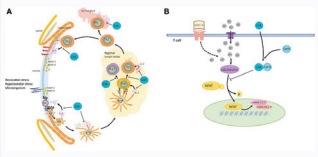
It is prescribed for patients who have neurotrophic keratitis, also known as neurotrophic keratopathy, a rare disease that can progress to corneal scarring and vision loss, and is dosed 6 x day for 8 weeks.

It is exciting to have an option for these patients, as it can be quite visually devastating. Historically it was quite expensive costing as much as 90K, but now can be very affordable.

Topical Corticosteroids

- **Topical corticosteroids quell ocular inflammation.** The ideal patient for this treatment has symptoms of moderate to severe DED and, specifically, associated inflammation that can't be controlled via cyclosporine or lifitegrast alone.
- **Topical steroids can provide symptomatic relief,** but due to long-term side effects, should only be used for short-pulsed duration typically 2-4 weeks with an appointment to always check IOP.





Cyclosporine

Cyclosporine blocks T-cell activation, consequently inhibiting inflammatory cytokine production (selective inhibition of IL-I). Additionally, cyclosporine treatment has been shown to increase goblet cell density in the conjunctiva.

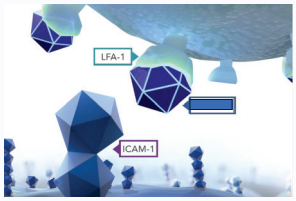
Ideal candidates are those that need a long-term strategy to treat inflammation and can be aqueous deficient or evaporative patients.

The drops begin to work immediately. However, the average life of a T-cell is approximately 90 days so the T-cells that are already activated have to die for full therapeutic target to be met. It is critical to teach patients the why of this drug so that they don't stop the drops on their own before experiencing full therapeutic relief.

Lifitegrast

Lifitegrast is engineered to mimic ICAM-1's binding domain to LFA-1 and is believed to act as a competitive antagonist to block the binding between LFA-1 and ICAM-1, which results in the inhibition of T-cell migration into target tissues. This, in turn, reduces cytokine release and decreases further T-cell recruitment.

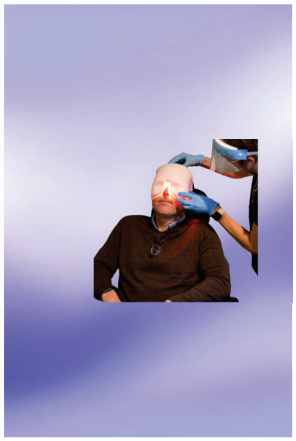
Both patient types, aqueous-deficient or evaporative can benefit. It is FDA approved for dry eye disease symptoms as well as signs.



LLLT or Photobiomodulation

Low-level laser (light) therapy (LLLT) or photobiomodulation is a non-invasive treatment that uses low-intensity light to stimulate, heal, and restore the skin and ocular tissues. According to research, LLLT can be an effective treatment for meibomian gland dysfunction (MGD), a leading cause of dry eye disease.

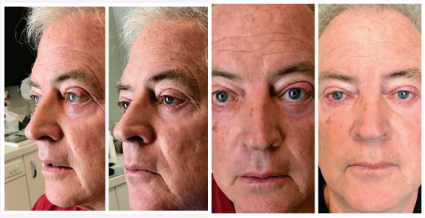
A study published in the *Seminars in Cutaneous Medicine and Surgery* journal in 2013 found that LLLT can have a stimulating, healing, and restoring effect on the skin. Similarly, a study published in the *Investigative Ophthalmology & Visual Science* journal in 2020 demonstrated the potential of LLLT in the treatment of MGD.



Intense Pulsed Light

- Also known as IPL, this treatment of different wavelengths of light targets the small vessels that contribute to inflammatory dry eye and ocular rosacea.
- Ideal DED patients are those who have telangiectasia's, ocular rosacea, or acne rosacea and fall in the Fitzpatrick skin typing I-IV.
- This is an easy in office procedure to perform. Proper use of laser grade corneal shields or adhesives is paramount for patient safety.

Chalazia Treatment- Incision Free, Injection Free, Scar Free Management



In Other Words: MGD is Supported by the BEISTO

Bacteria and Demodex

Meibomian gland dysfunction (MGD) is supported by various factors, including the presence of bacteria and Demodex mites in the meibomian glands.

Enzymes and Biochemistry

Enzymes like lipases, esterases, and transferases, as well as the effects of cytokines on the biochemistry of meibum, including its sphingolipid composition, also play a role in MGD.

Inflammation and Stasis

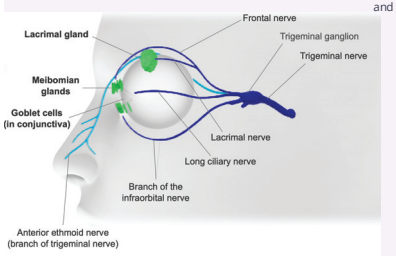
Inflammation and stasis of the meibum, or the slowing down of the natural flow of meibum, are additional factors that contribute to MGD.

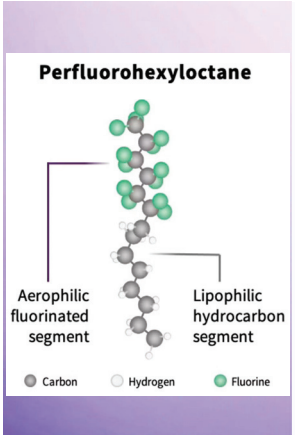
Temperature and Obstruction

An increased melting temperature of the meibum, as well as obstruction and hyperkeratinization of the meibomian glands, are also important aspects of MGD.

Neurostimulation

Neurostimulation results in endogenous tear production, giving patients a way to manage their DED and gain relief immediately. Specifically, the device targets the trigeminal nerve, which controls the lacrimal functional unit (LFU). This is important because the LFU is responsible for the lacrimal gland and accessory glands, as well as goblet cells degranulating and meibomian gland function.





Perfluorohexyloctane

- Mimics natural meibum-lowers surface tension and helps prevent evaporation
- Stays in the tear film for up to 6 hours per PK Rabbit studies
- Yes-AND

Punctal Plugs

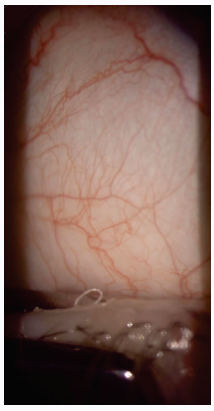
Punctal plugs allow tears to stay in the eye longer instead of draining through the canaliculus into the nasolacrimal system. Truly aqueous deficient patients benefit the most, like patients with Sjogren's. When considering plugs, optometrists should make sure the inflammation has been treated first, as not treating it creates more inflammatory factors present on the front surface of the eye, which can exacerbate DED symptoms.

Scleral Lenses

Scleral lenses contain a sterile water bath that can support the front surface of an eye that has DED and any corneal irregularities. This results in increased comfort for DED patients. Patients that have central corneal staining, with aqueous deficiency or evaporative disease are good candidates. Address any lid disease and hygiene before fitting the lenses for best success, especially those with evaporative disease.

Supplements

- **Make sure to do a through history of all medications, specifically blood thinners, or anti-coagulants as supplements can increase bleeding time.**
- Research reveals that a low level of omega fatty acids in one's body is a risk factor for DED. Further, modifying one's diet, along with omega fatty acid supplementation can complement other DED treatments, according to research.
- Various omega-3 and omega-6 supplements can be of benefit for aqueous-deficient or evaporative patients due to their anti-inflammatory properties.
- **Correct ratio of DHA/EPA**
- **GLA**



Thermal Pulsation/Heat & EXpression

Thermal pulsation employs heat and massage to the lids to help unblock the meibomian glands. This unblocking helps to resume the natural production of lipids needed for a stable tear film. **Patients that have evaporative disease are the best candidates.** The treatment can be helpful in patients that just cannot maintain compliance at home with heat therapy. Think of it like visiting the dental hygienist every 6 months to one year.

Obstruction and Inflammation

Causes of Obstruction

Congenital absence of meibomian glands, microbiological changes, disruption of the lipid layer by topical medications, and structural damage to the glands by cicatricial diseases can all lead to obstruction of the meibomian glands.

Factors Contributing to Inflammation

Omega-3 fatty acid deficiency, hormonal therapy, aging, and contact lens wear can contribute to increased inflammation. Additionally, an increased melting temperature of the meibum and the presence of Demodex mites can also lead to inflammation.

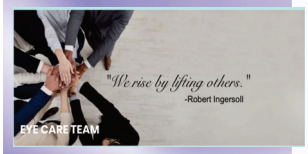
The Interplay

Obstruction and inflammation are closely linked in the development of meibomian gland dysfunction. An effective action plan should address both the underlying causes of obstruction and the associated inflammation to effectively manage this condition.

Diagnosis each disease and treat accordingly:

It is crucial to properly diagnose each patient's specific type of dry eye disease and then tailor the treatment plan accordingly. This comprehensive approach ensures the most effective management of the condition and provides the best possible outcomes for the patient.

- Ocular Rosacea- H10.829
- Demodex Blepharitis-B88.0
- MGD-H02.889-
- Dry Eye H04.123
- K. Sicca H16.233



Team

- Technician
- Ocular Hygenist
- Dry Eye Coordinator

Implementation

The implementation of a comprehensive dry eye management plan requires a collaborative team approach involving various eye care professionals. This ensures a thorough assessment, customized treatment, and ongoing monitoring to address the multifactorial nature of dry eye disease.

Step by Step Approach

1 Ask the right questions

Gather comprehensive information about the patient's medical history, medications, and lifestyle factors that may contribute to dry eye disease.

2 Review Medical history and Medications-Autoimmune or Sleep Apnea

Carefully review the patient's medical history, including any autoimmune conditions or sleep apnea, as these can be associated with dry eye disease.

3 Evaluate Skin Health/Telangiectasias

Examine the patient's skin health, particularly for signs of telangiectasias, which may indicate underlying rosacea or other conditions related to dry eye disease.

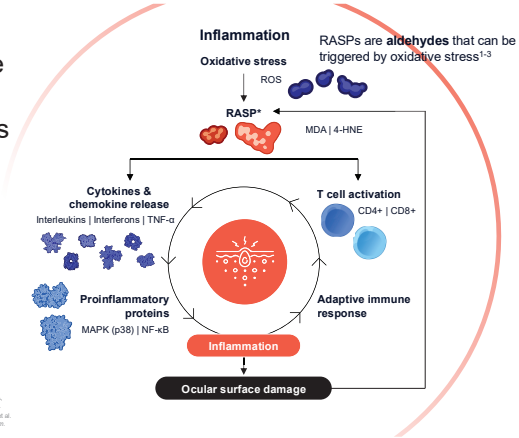
4 Assess Blink reflex, Lid Seal, and Snap Test

Evaluate the patient's blink reflex, lid seal, and perform a snap test to assess the function and integrity of the eyelids and meibomian glands.

Pipeline

The self-perpetuating cycle of inflammation continuously drives chronic DED[1-4]

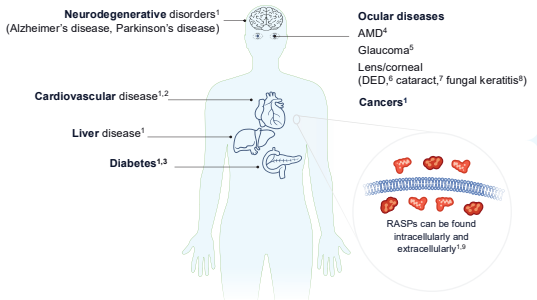
The resulting **inflammation** and **ocular surface damage** are both a **cause and consequence of DED**



*4-HNE and MDA shown as examples of the most commonly studied RASP. 4-HNE, 4-hydroxy-2-nonenal; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; NFkB, nuclear factor-kappa B; TNF, tumor necrosis factor.

1. Periman LM, et al. *J Ocul Pharmacol Ther*. 2020;36(3):137-146; 2. Yu L, et al. *Front Pharmacol*. 2021;12:732887; 3. Ganesalingam K, et al. *Clin Exp Optom*. 2019;102(5):446-454; 4. Bu J, et al. *Antioxidants (Basel)*. 2024;13(4):422.

RASPs play a role in the etiology of many diseases



In part, this may be due to the observed role of RASPs in:

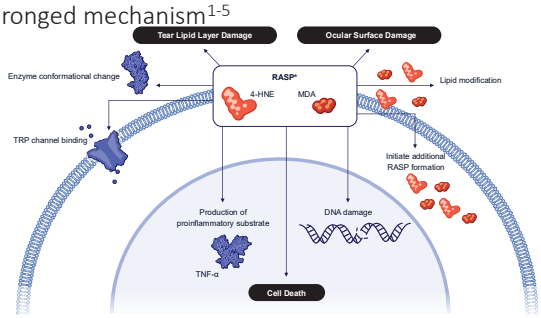
- Nervous system damage[9]
- Vascular issues[10]
- Tear lipid modulation[1,9,10]

AMD, age-related macular degeneration.

1. Ayala A, et al. *Oxid Med Cell Longev*. 2014;2014:360438; 2. Gianazza E, et al. *Redox Biol*. 2019;23:101119; 3. Shanmugam N, et al. *Diabetes*. 2006;57(4):879-888; 4. Abokyi S, et al. *Oxid Med Cell Longev*. 2020;2020:7901070; 5. Pinazo-Duran MD, et al. *Curr Neuropharmacol*. 2018;16(7):903-918; 6. Dogru M, et al. *Invest Ophthalmol Vis Sci*. 2018;59(14):DES163-DES168; 7. Kaur J, et al. *J Clin Diagn Res*. 2012;6(10):1629-1632; 8. Hua X, et al. *Sci Rep*. 2017;7(1):10421; 9. Khan M, et al. *Neural Regen Res*. 2022;17(1):185-193; 10. Hellenthal KEM, et al. *Biomolecules*. 2021;11(10):1401.

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

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



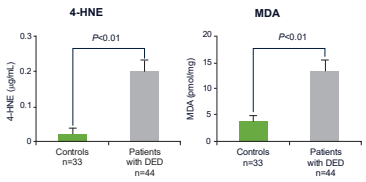
*4-HNE and MDA shown as examples of the most commonly studied RASP. TRP, transient receptor potential.

1. Hellenthal KEM, et al. *Biomolecules*. 2021;11(10):1401; 2. Scarpellini C, et al. *Int J Mol Sci*. 2023;24(1):731; 3. Raghavan S, et al. *J Leukoc Biol*. 2012;92(5):1055-1067; 4. Bu J, et al. *Antioxidants (Basel)*. 2024;13(4):422; 5. Pohl EE, et al. *Molecules*. 2019;24(24):4545.

RASP expression is associated with DED severity and meibomian gland damage

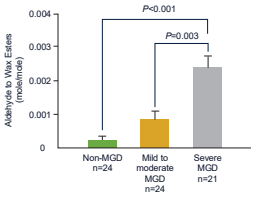
RASPs in tears[1]

RASPs are elevated in tears of individuals with DED vs controls



Meibum lipid composition[2]

Aldehyde* to wax ester ratio increases with MGD severity



*Aldehydes detected using NMR analysis of meibum composition; aldehydes (near 9.8 ppm) were detected in the non-MGD (n=2), mild to moderate MGD (n=7), and severe MGD (n=9) cohorts.
MGD, meibomian gland dysfunction; NMR, nuclear magnetic resonance.

1. Choi W, et al. *Curr Eye Res*. 2016;41:1143-1149; 2. Nagar S, et al. *Invest Ophthalmol Vis Sci*. 2023;64(10):22.

Downstream of RASPs, DED inflammation is modulated by **cytokine release** and **T cell activation**[1-4]

*4-HNE and MDA shown as examples of the most commonly studied RASP.

1. Perriman LM, et al. *J Ocul Pharmacol Ther*. 2020;36(3):137-146; 2. Yu L, et al. *Front Pharmacol*. 2021;12:732887; 3. Ganesalingam K, et al. *Clin Exp Optom*. 2019;102(5):446-454; 4. de Paiva CS, et al. *Mucosal Immunol*. 2022;15(6):1143-1157.

Acoltremon (AR-15512) Ophthalmic Solution 0.003%

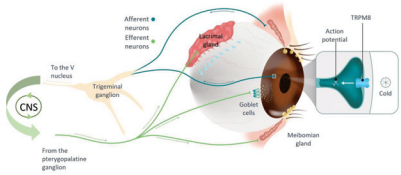
A drug candidate containing acoltremon, a TRPM8 agonist

WHAT IS TRPM8?

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

WHY TRPM8 AS A TARGET FOR DRY EYE?

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



1. Guerrero-Moreno A, Baudouin C, Melik Parsadaniantz S, Réaux-Le Goazigo A. *Front Cell Neurosci*. 2020;14:610342.; 2. McCoy DD, Knowlton WM, McKemy DD. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(6):R1278-R1287. 3. Hirata H and Meng ID. *Invest. Ophthalmol. Vis Sci*. 2010;51(8):3969-3976; 4. Belmonte C, Gallar J. *Invest Ophthalmol Vis Sci*. 2011;52(6):3888-3892. 5. Parra A, Madrid R, Echevarria D, et al. *Nat Med*. 2010;16(12):1396-1399. 6. Quallo T, Vastani N, Horridge E et al. *Nat Commun*. 2015; 6: 7150.

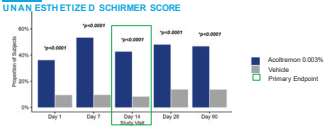
Acoltremon (AR-15512) Ophthalmic Solution 0.003%

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

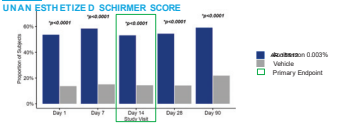
Enrollment	931 dry eye subjects completed COMET-2 and -3 studies
Primary **Unanesthetized Schirmer Test**	• Higher % of subjects with ≥ 10 mm increase in unanesthetized Schirmer Test scores on Day 14 with acoltremon 0.003% (ACO) compared to vehicle • Similar results seen on Day 1 and Day 90 (secondary endpoints)
Key Secondary **SANDE Score**	• Change from baseline in SANDE scores were greater with ACO on Day 28 in COMET-2 (P=0.0138); numerically greater with ACO in COMET-3 (P=0.1321)
Exploratory **Ocular Staining**	• Change from baseline in total corneal and total conjunctival staining were observed at Day 7 through Day 90
Adverse Events	• ACO was well-tolerated, and there were no reported serious ocular adverse events

Primary endpoint met in both phase 3 (COMET) trials

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



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



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

Summary

- Acoltremon 0.003% increased tear production in a large proportion of subjects in both pivotal phase 3 studies[1,2]
  - The primary endpoint, proportion of subjects with a ≥10-mm increase in unanesthetized Schirmer score at day 14, was met in both phase 3 studies, COMET-2 and COMET-3 ($P<0.0001$)
  - Tear production was observed as early as after the first dose and continued through day 90
- The efficacy of acoltremon 0.003% was supported by[1,2]:
  - **DED symptom reduction:** Improvements in global SANDE scores were statistically significantly greater than vehicle scores in COMET-2 and within the pooled analysis and directionally in favor of acoltremon 0.003% in COMET-3
  - **Ocular surface staining:** As exploratory endpoints, reductions in total corneal and total conjunctival staining was observed in both individual studies as well as in the pooled analysis
- Acoltremon 0.003% was well tolerated by subjects over the 90-day duration of both pivotal studies[1,2]
  - The only ocular treatment-emergent adverse event with >2.5% incidence was mild instillation site burning/stinging, which was reported in ≅51% of subjects receiving acoltremon 0.003%
    - In COMET-4, burning/stinging was reported to be transient, with ≈86% of subjects who experienced the sensation reporting a duration of 1 minute or less[3]

1. https://clinicaltrials.gov/study/NCT05285644. Accessed September 24, 2024. 2. https://clinicaltrials.gov/study/NCT05360966.Accessed September 24, 2024.
3. https://clinicaltrials.gov/study/NCT05493111. Accessed September 24, 2024.

TRPM8 as a Potential Therapeutic Target

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

Acoltremon and IVW-1001 are investigational drugs and have not been approved for commercialization.
TRPM8, transient receptor potential melastatin 8.
1. https://clinicaltrials.gov/study/NCT05285644. Accessed March 27, 2024. 2. https://clinicaltrials.gov/study/NCT05385666. Accessed March 27, 2024. 3. Wirta DL, et al. Ocul Surf. 2022;26:166-173. 4. IVW-1001 phase 1/2in subjects with dry eye disease. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT06400459. Accessed July 25, 2024. 5. Liang, BG et al. *Disease. Invest. Ophthalmol. Vis. Sci.* 2024;65(7):5763.

AZR-MD-001 is positioned to be the first and only pharmaceutical therapy to treat meibomian gland dysfunction (MGD) by:

- improving the meibum quality and quantity,
- restoring meibomian gland function, and
- treating evaporative dry eye signs & symptoms.

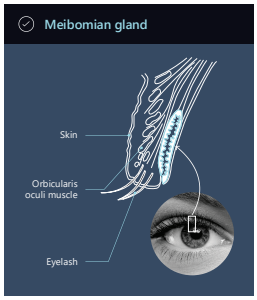
AZR-MD-001 is a keratolytic ointment dosed 2x per week @ bedtime directly to the meibomian glands

Normal meibum is a clear liquid at body temperature

Lubricate the ocular surface during blinking and protect against tear evaporation.[1,2,3]

Meibum consists of a complex mixture of various *Proteins*, lipids, and other components[1]
- More than 90 different ***proteins*** identified in the meibum[5]
- 100s of different species of lipids, most of which are wax and cholesteryl esters[4]
- Indirect immunofluorescence determined keratin proteins expressed in humans meibomian glands in the normal eye[6]

Keratins are helical structural *proteins* present in the meibum



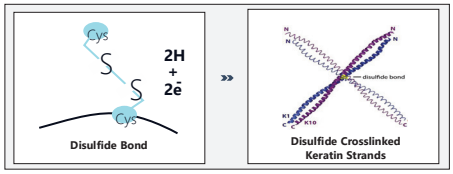
[1]Green-Church KB, et al. Invest Oph Vis Sci. 2011 Mar 30;52(4):1979-93. [2]Blackie CA, et al. Cornea. 2010;29(12):1333-45. [3]Knop E, et al. Invest Ophthalmol Vis Sci. 2011;52(4):1938-78. [4]Butovich IA Prog Retin Eye Res. 28 (6): 483–498 [5]Tsai, PS, et al. Br J Ophthalmol. 90 (3): 372–7. [6]Jester JV, et al. Invest Ophthalmol Vis Sci. 1989;30(5):927-935.

Disulfide Bond Formation
Production of *protein* aggregates

Oxidative stress contributes to the pathology of MGD[1] and the formation of aberrant disulfide bonds

Aberrant disulfide bonds leads to formation of excess keratin aggregates in unwanted locations

Keratin protein release in the absence of crosslinking won't lead to the formation of keratin aggregates

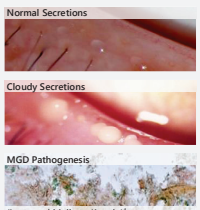


[1]Ibrahim OM, et al. PLoS One. 2014;9(7):e99328.

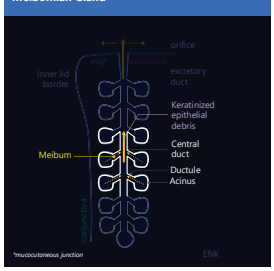
Keratinization may be present in multiple places in the Meibomian gland:

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

Meibum Viscosity



Meibomian Gland



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

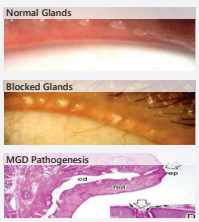
Keratinization may be present in multiple places in the Meibomian gland:

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

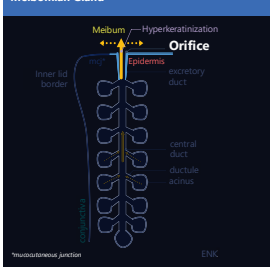
Keratin formation is a natural process
- Keratin is produced and sheds at physiological rates to confer its protective role while not accumulating in excess

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

Gland Orifice



Meibomian Gland



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

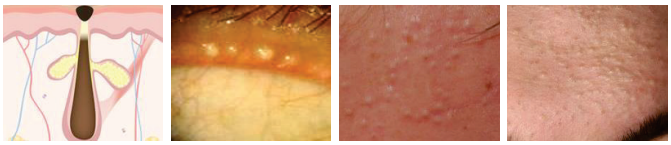
What are keratolytics?
Agents that soften skin through the process of breaking down keratin shed the skin epithelium or horny outer layer

Similar to the lid margin, secretory gland hyperkeratinization plays an important role in various skin disorders

Comedonal lesions in acne are inspissated hair follicles, filled with corneocytes, sebum, and other debris

Keratolytic treatments are used to shed dead corneocytes, loosen the sebum plug, and prevent the formation of inflammatory papules and pustules

Acne – Keratin Plug	Blocked Meibomian Glands	Closed Comedones	Comedonal Acne



Triple Mechanism of Action

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

DECREASE
meibomian gland hyperkeratinization of ducts and orifices
Keratostatic

LOOSEN
meibomian gland blockages
Keratolytic

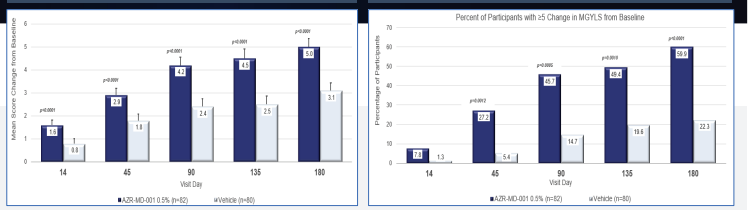
INCREASE
secretion of meibomian gland lipids
Lipogenic

AZR-MD-001 Shows Statistically Significant Improvement in MGYLS Sign

Meibomian Gland Yielding Liquid Secretion (MGYLS) in target population; change from baseline

Number of Open Glands
Statistically Significant Difference from Control

% of Patients with Normal Open Glands
Clinically Significant Difference from Control



AZR-MD-001 (0.5%) show a significant treatment response vs. control for MGYLS

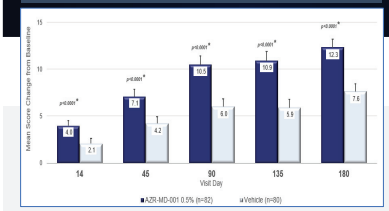
p-values completed using LS mean percentage compared to vehicle at the time points indicated

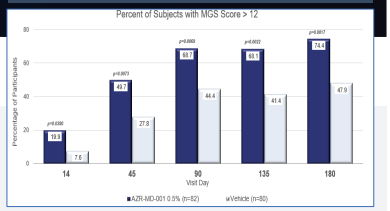
AZR-MD-001 Shows Statistically Significant Improvement in MGS Sign

Meibomian Gland Score (MGS) in target population; change from baseline

Quality of Meibum
Statistically Significant Difference from Control

% of Patients with Normal Meibum
Clinically Significant Difference from Control





AZR-MD-001 (0.5%) show a significant treatment response vs. control for MGS

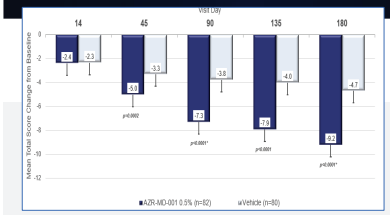
1. Meibomian gland secretion
p-values completed using LS mean difference from baseline at the time points indicated
* p<0.05 change from baseline compared to vehicle

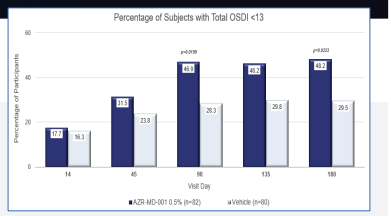
AZR-MD-001 Shows Statistically Significant Improvement in Symptoms for OSDI©

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

Reduction in Symptoms
Statistically Significant Difference from Control

% of Asymptomatic Patients
Clinically Significant Difference from Control





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

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

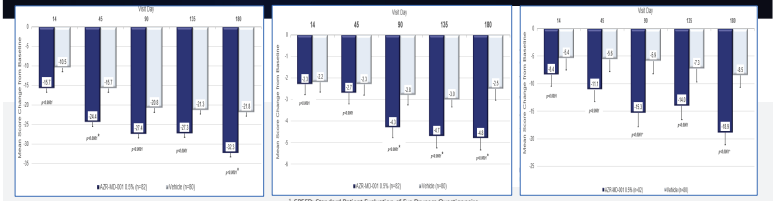
MCID for OSDI: 4.5 – 7.3 for Mild to Moderate Disease*
*Miller KL, et al. Minimal Clinically Important Difference for the Ocular Surface Disease Index. Arch Ophthalmol. 2010;128(1):94-101.

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

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

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

Statistically Significant Decreased Itching
Itching Score Change from Baseline



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

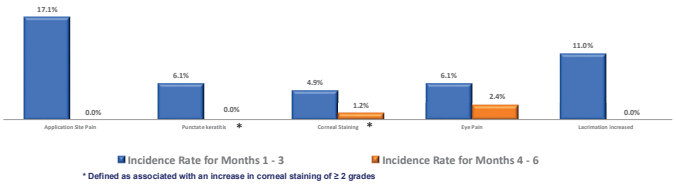
1. SPEED: Standard Patient Evaluation of Eye Dryness Questionnaire
p-values completed using LS mean difference from baseline at the time points indicated
* p<0.05 change from baseline compared to vehicle

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

Reduction of TEAEs (≥5%) Over Time for AZR-MD-001 0.5%

Safety Data Set

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



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

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

AZR-MD-001 Clinical Data Review:

Robust, Consistent Clinical Effect across Multiple Clinically & Commercially Relevant Endpoints

Strong Trial Efficacy

- **U.S. Regulatory requirements achieved**
- 3-mo. Co-Primary Endpoints met statistical significance and clinically meaningful benefit for 0.5% over vehicle[1]
- 6-mo. Further improvement in **all signs and symptoms** with continued use through 6-months
  - Durability of effect strengthens US filling and supports an ex-US regulatory strategy

Restored Gland Function

- **61.7%** of patients had their glands opened to a normal level[2] at 6-mo.
- **75%** of patients had their meibum quality return to normal levels[3] at 6-mo.

Improved Patient Symptoms

- **54.7%** of patients became asymptomatic as measured by Total OSDI© at 6-mo.
- Improved tear stability – Over a 2 second improvement in Tear Break Up Time maintained from Month 3 onward
- **Significantly improved patient symptoms** across multiple patient-reported outcome measures (SPEED, average VAS, Eye Dryness, Eye Discomfort, Ocular Itch)

1. In a single study in ITT population (all randomized patients)
2. MGYLS responder rate; p=0.0005 compared to vehicle at month 3; improvement from baseline of 4.2 glands (p<0.0001)
3. MCS responder rate; p=0.0069 compared to vehicle at month 3; improvement form baseline of 10.5 (p<0.0001)

BeSpoke Vision

Thank You

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