EXPERT INSIGHTS INTO DRY EYE

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Schwartz Laser Eye Center

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DISCLOSURE

- Presenter is on speaker's panel/consultant for:
  - Alcon, Allergan, Azura, B+L, J&J, Kala, Novartis, OcuSoft, Olleyes, Reichert, Eyevance, Sun Pharma, Visus, Tarsus
- President of MRB Eye Consultants
- Past-President of the Optometric Council on Refractive Technology (OCRT)
- Presenter has NO financial interest in any products mentioned..well except:

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STARBUCKS

3

SCREENTIME, ARTIFICIAL TEARS AND BLBCG

4

NEW DRUGS

Anterior Segment

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NEW FDA APPROVED DRUGS

- Eysuvis
  - Kala Pharmaceuticals
- Flarex
  - Eyevance Pharmaceuticals
- Tepeeza
  - Horizon Pharmaceuticals
- Oxervate
  - Dompé

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US PREVALENCE OF DRY EYE DISEASE (DED)

- CONDITION/DISEASE

- Estimated >16 million patients have been diagnosed with DED[1]
- Estimates ~33 million patients suffering from dry eye symptoms[1]
- Almost all adults experience dry eye signs and symptoms
  - DED is often underdiagnosed and undertreated[2]
  - DED is the most common reason for visits to eyecare practitioners (ECPs)[3]
  - ~33% of patients present with complaints about dry eye[1]
- Prevalence is projected to increase due to:
  - Aging population
  - Increased screen time (computers and handheld devices)[1]

REFERENCES: 1. Farrand KF, Fridman M, Stillman IO, Schaumberg DA. Prevalence of Diagnosed Dry Eye Disease in the United States Among Adults Aged 18 Years and Older. Am J Ophthalmol 2017;182:90-8. 2. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification report. Ocul Surf. 2017;15(3):276-283. doi: 10.1016/j.jtos.2017.05.008. 3. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. Clin Ophthalmol. 2009;3:405-12.

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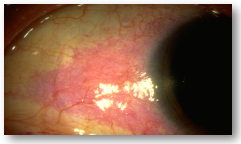
WHAT IS DRY EYE DISEASE & WHY TREAT?

- DEFINITION AND CLASSIFICATION (DEWS II)[1]

Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ***ocular surface inflammation*** *and damage, and neurosensory abnormalities play etiological roles*



Dry eye involves a vicious cycle of ocular surface inflammation that can be self perpetuating and progressive

REFERENCES: 1. TFOS DEWS II Report and Algorithm. Ocul Surf. 2017;15(3):264-449.

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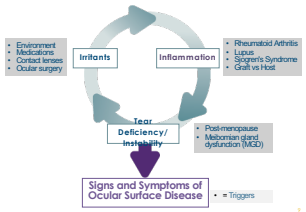
OCULAR SURFACE INFLAMMATION

DRY EYE DISEASE IS A CYCLE OF INFLAMMATION [1,2]

Research has proven that ocular surface inflammation is the core mechanism in the pathogenesis of DED

- No matter where you enter the cycle, the inflammatory cascade continues unless you intervene
- The cycle of ocular surface inflammation can become self-perpetuating and can progressively worsen without intervention



REFERENCES: 1. Wei, Y. The core mechanism of dry eye disease (DED) is inflammation. Eye Contact Lens. 2014;40(4):248-256. 2. Milner, M. Ocular surface inflammation: Vicious cycle of ocular surface disruption. Ophthalmology Times. 2017p.1-2.

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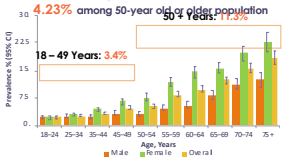
THE GROWING PREVALENCE AND DEMOGRAPHICS OF DRY EYE DISEASE (DED)

- Nearly **38** million US adults have symptoms consistent with dry eye disease[2-4]
- **~17.2 million diagnosed DED patients in the US[4]**
- Aging is one of most common risk factors. Other common risk factors include female gender and post-menopausal estrogen therapy[5]
- **The burden of DED is predicted to escalate in the future, likely because of an aging population and an increasing dependence on multiscreen technologies[1,5,6]**

From 2005–2012 prevalence has increased by[6]

0.5% among 18 to 39-year old population
1.44% among 40 to 49-year old population
4.23% among 50-year old or older population



References: 1. Stapleton F, Alves M, Bunya VY, et al. Ocul Surf. 2017;15:334-365. 2. Paulsen AJ et al. Am J Ophthalmol. 2014;157:799-806. 3. Howden LJ Meyer JA. 2010 Census Briefs. 2011. www.cdc.gov/nchs. 4. Market Scope. 2011 Dry Eye Products Market Report. 5. Bron AJ, de Paiva CS, Chauhan et al. Ocul Surf. 2017;15:438-510. 6. Dana R, Bradley JL, Guerin A, et al. Am J Ophthalmol. 2019;202:47-54.

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EYSUVIS (LOTEPRADNOL ETAOBANTE OPHTHALMIC SUSPENSION) 0.25%

INDICATED FOR THE SHORT TERM (UP TO 2 WEEKS) TREATMENT THE SIGNS AND SYMPTOMS OF DRY EYE DISEASE

Kala Pharmaceuticals

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DRY EYE IS A CHRONIC INFLAMMATORY DISEASE

Inflammation Plays a Key Role in the Pathogenesis and Symptomatology of Dry Eye[1,2]

Most Common Signs/Symptoms in DED[2]

- Conjunctival hyperemia
- Ocular surface staining
- Discomfort/dryness
- Blurry/fluctuating vision
- Eye fatigue

References: 1. Bron AJ et al. Ocul Surf. 2017;15(3):438-510. 2. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017;15(3):276-283. 3. American Academy of Ophthalmology. Dry Eye Syndrome Preferred Practice Pattern. 2018. 4. McDonald M,et al. Ocul Surf. 2016;14(2):144-167.

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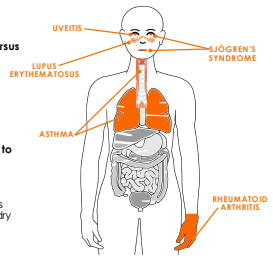
EPISODIC FLARE IS A COMMON FEATURE OF CHRONIC INFLAMMATORY DISEASES SUCH AS DRY EYE

Many chronic inflammatory and autoimmune diseases have episodic exacerbations of signs and symptoms versus consistent continuous disease, often called 'flares'[1]

- Asthma
- Uveitis
- Sjögren's syndrome
- Rheumatoid arthritis
- Lupus erythematosus

Dry eye is a chronic immune disease with periods of dysregulation causing homeostatic imbalance, leading to ocular surface stress[2]

- Contains its own local lymphoid tissues
- Has a diverse microbiome whose composition may be regulated by the antimicrobial and immunomodulatory factors in tears
- Ocular surface inflammation plays a key role in all types of dry eye



References: 1. Rosenblum MD et al. J Clin Invest. 2013;123(4):2228-2233. doi:10.1172/JCI78088. 2. Farid M et al. Ocul Immunol Inflamm. 2016;24(3):337-347. doi:10.3109/09273948.2014.986581.

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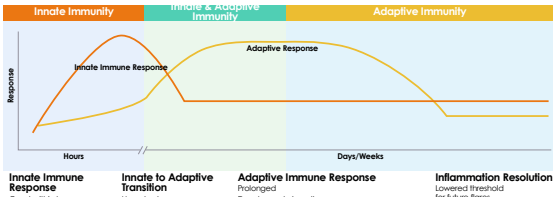
DRY EYE FLARES HAVE RAPID ONSET AND ARE INFLAMMATION-DRIVEN: A POTENTIAL OPPORTUNITY FOR EARLY CORTICOSTEROID TREATMENT INTERVENTION

Acute Dry Eye Flares Involves by Both the Innate and Adaptative Immune Responses[1]



Innate Immune Response
Onset within hours

Innate to Adaptive Transition
Hours to days

Adaptive Immune Response
Prolonged
Days to weeks/months

Inflammation Resolution
Lowered threshold for future flares

Reference: 1. Perez VL, Stern ME, Pflugfelder SC. Inflammatory basis for dry eye disease flares [published online ahead of print, 2020 Oct 8]. Exp Eye Res. 2020;108296.

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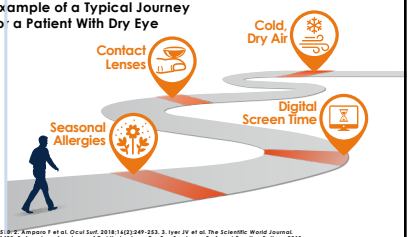
MOST PATIENTS WITH DED SUFFER EPISODIC EXACERBATIONS, DRY EYE FLARES

- Episodic increases in symptoms and signs, or Dry Eye Flares, are rapid-onset, inflammation-driven responses to a variety of triggers that typically cannot be adequately managed with a patient's ongoing maintenance therapy, such as artificial tears and chronic therapies[1-4]
- Triggers may include seasonal allergies, A/C use, digital screen time, air travel, contact lens wear, smoking, diet, medications, and cataract and refractive surgery[5-7]

Example of a Typical Journey for a Patient With Dry Eye



References: 1. Bron AJ et al. Ocul Surf. 2017;15(3):438-510. 2. Amparo F et al. Ocul Surf. 2018;16(2):249-253. 3. Iyer JV et al. The Scientific World Journal. 2012;287875. 4. Kim T et al. Cornea. 2019;38(12):1483-1488. 5. American Academy of Ophthalmology. Dry Eye Syndrome Preferred Practice Pattern. 2018. 6. Walker PM et al. Clin Sci. 2010;291(6):457-472. 7. Tesón M et al. Investig Ophthalmol Vis Sci. 2013;54(3):2093-2099.

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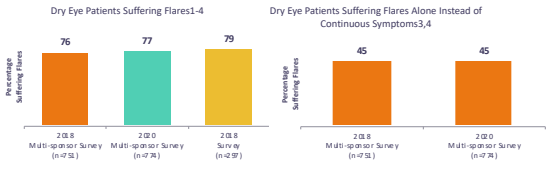
NEARLY 80% OF PATIENTS WITH DRY EYE DISEASE SUFFER FLARES AND ALMOST HALF REPORT HAVING PRIMARILY FLARES INSTEAD OF CONTINUOUS SYMPTOMS



Three Large Studies Have Assessed the Nature of Dry Eye Flare:

- Study of Dry Eye Sufferers conducted by Multi-sponsor Surveys, Inc; trended series[1-3]
  - 2018 study, 15th in series (n=751)[2,3]
  - 2020 study, 16th in series (n=774)[4]
- Survey of Dry Eye Patients conducted in 2018 (n=297)[5]

References: 1. Bazzell RK et al. Presented at: AAO 2019; October 12-15, 2019; San Francisco, CA. 2. Bazzell RK et al. Poster presented at: AAOPT 2019; October 23-27, 2019; Orlando, FL. 3. 2018 Study of Dry Eye Sufferers. Conducted by Multi-sponsor Surveys, Inc. 4. 2020 Study of Dry Eye Sufferers. Conducted by Multi-sponsor Surveys, Inc. 5. Survey of 297 patients commissioned by Kala and performed by a third party.

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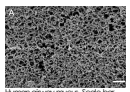
EYSUVIS™ POWERED BY AMPPLIFY® TECHNOLOGY

Mucus Is a Barrier for Topical Ophthalmic Drug Delivery[1]

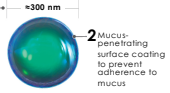


Human airway mucus. Scale bar represents 500 nm.

Microvilli and mucus at the surface of human corneal epithelium.

- Mucins on the tear film form a barrier to particulate matter (e.g., allergens, pathogens, etc.) by trapping them and facilitating their removal from the ocular surface through blinking
- Drug particles in traditional suspensions are also trapped with mucins and are rapidly removed

AMPPLIFY® Utilizes Mucus-Penetrating Particles (MPP) With 2 Proprietary Attributes[1-3]



1 Selectively sized nanoparticles to allow for penetration into mucus pores. (Drug particles less than 500 nm to penetrate into the mucus pores)[1,4]

2 Mucus-penetrating surface coating to prevent adherence to mucus

References: 1. Popov A. J Ocul Pharmacol Ther. 2020; 36(6): 366-375. 2. Schopfl L, et al. Ophthalmol Ther. 2014;3(1-2): 63-72. 3. Data on file. Kala Pharmaceuticals: Watertown, MA. 4. Dolgin LM, Schneider C, Sub JS, et al. Adv Mat. 2017;29(28): 3887-3896.

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FLAREX (FLUOROMETHOLONE ACETATE OPHTHALMIC SUSPENSION) 1%.

EYEVANCE

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HOW TO DESIGN YOUR TREATMENT OF OCULAR SURFACE INFLAMMATION ASSOCIATED WITH DRY EYE DISEASE?

-

FLAREX® is an excellent topical steroid for the treatment of ocular surface inflammation[2]

The efficacy of Pred Forte with the safety of FML*[3]*

REFERENCES: 1. Charters L. Fluorometholone acetate: More benefit than meets the eye. *Ophthalmology Times*. 2019b.
2. FLAREX [package insert]. Fort Worth, TX: Eyevance Pharmaceuticals, LLC; 2019.
3. Leibowitz HM, Hyndiuk RA, Lindsey C, et al. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. *Ann Ophthalmol*. 1984;16(12):1110-1115.
*Trademarks are the property of their respective owners.

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FLAREX® (FLUOROMETHOLONE ACETATE OPHTHALMIC SUSPENSION 0.1%)

TREAT OCULAR SURFACE INFLAMMATION ASSOCIATED WITH DED

- INDICATION[1]
  - Indicated for use in the treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.

FORMULATION[1]
- Fluorometholone **acetate** (a steroid ester)

ACTIVE INGREDIENT
- A topical ophthalmic suspension containing 0.1% fluorometholone acetate
- Formulated at a physiologic pH of 7.3 for comfort

RECOMMENDED DOSING[1]
- Instill 1-2 drops into the conjunctival sac four times daily
- During the initial 24-48 hours, the dosage may be increased to two drops every two hours

REFERENCES: 1. FLAREX [package insert]. Fort Worth, TX: Eyevance Pharmaceuticals, LLC; 2019.

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Horizon

TEPEEZA

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TEPEEZA

TEPEZZA is the first and only FDA-approved Thyroid Eye Disease (TED) treatment

80% of Graves' patients have ocular involvement

15% develop severe visual impairment

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THYROID EYE DISEASE VS GRAVES' DISEASE

	THYROID EYE DISEASE	GRAVES' DISEASE
Area of body affected	Front and back of the eyes	Thyroid (a gland at the base of your neck in front of your windpipe)
What's going on inside the body	Muscle and fat tissue behind the eye become inflamed (red and swollen)	The thyroid becomes overactive, also known as hyperthyroidism
Common symptoms	•Dry, gritty eyes •Sensitivity to light •Eyelid redness and swelling •Itchy eyes •Eye pain, including pain around and behind the eye •Watery, teary eyes •Bulging eyes •Other vision changes	•Fast heartbeat •Irritability •Anxiety •Tiredness •Too much sweating, sensitivity to temperature

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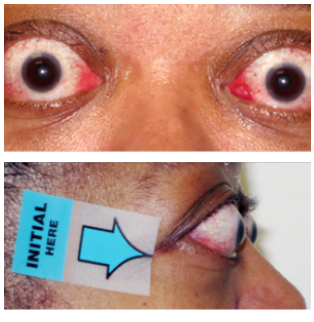
TED

- Clinical Symptoms of TED
  - Dry eye
  - Foreign body sensation
  - Epiphora
  - Photophobia
  - Blurry vision
- Classic symptoms
  - Eyelid retraction (Dalrymple sign)
  - Eyelid lag (von Graefe's sign)



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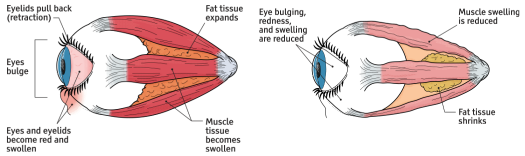
TEPEEZA

- During the progressing (or "active") phase of TED, a special switch called a receptor gets turned on
- Once on, the receptor makes the muscle and fat tissue become swollen, causing symptoms like eye bulging, double vision, pain, and redness
- TEPEZZA is the only medicine that blocks this receptor to treat TED at its source
- By blocking the receptor, TEPEZZA reduces muscle and fat tissue swelling and improves TED symptoms



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TEPEEZA

TEPEZZA is given as 1 (10mg/kg) infusion and then (20mg/kg) every 3 weeks, for a total of 8 infusions.

TEPEZZA treatment should last about 5 months.

Administered in an infusion chair

The first 2 infusions of TEPEZZA will take about 90 minutes each to complete.
The next 6 infusions may be as short as 60 minutes.

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NEUROTROPHIC KERATITIS

Keratoneuralgia

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NEUROTROPHIC KERATITIS

- Corneal innervation is key to treatment
  - SPK to Corneal ulceration
- Keratoneuralgia
  - Intense pain
  - No signs
- Treatment
  - Conventional dry eye treatment
  - Steroids
  - Autologous serum
  - Amniotic membrane
    - Dry vs. Cryo

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MY VISION IS REALLY BAD….

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"CAN I DO MY OTHER EYE FIRST?"

- 72 yo Male
  - Cataracts in both eyes
    - Scheduled for surgery in left eye
    - Starting using drops pre-op
      - "I may have hit my eye with the tip of the drop?"
      - "My vision is way worse now"
    - VaSC
      - 20/200 ph 20/70 OD
      - 20/CF ph 20/200 OS
    - Slex:
      - OD-Corneal Clear, NSC/ASC
      - OS-

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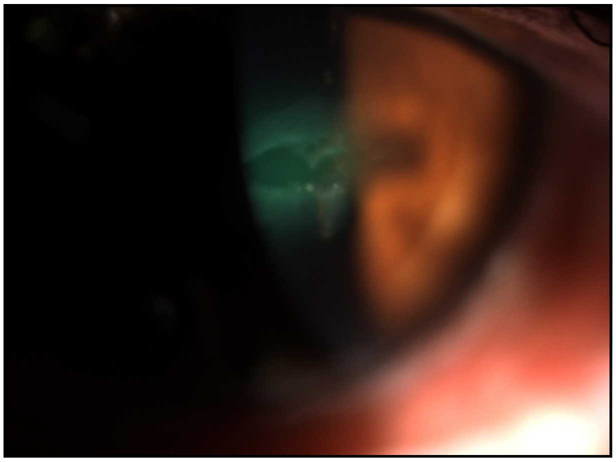

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"IT IS STILL BLURRY…"

Used a BCL, AB

- RTC 1wk
- NO IMPROVEMENT
- BCL-missing…however the patient stated "It feels fine!"
- "Can I do surgery on the other eye?"
  - Cotton-tip sensation:
    - OD-5/10
    - OS- 0/10

Prokera Slim inserted

Rx'd Oxervate

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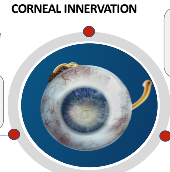
ENDOGENOUS NGF MAINTAINS CORNEAL INTEGRITY BY THREE MECHANISMS

Endogenous Nerve growth factor acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e. p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.[1]

SHOWN IN PRECLINICAL MODELS[1]

CORNEAL INNERVATION

NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves[2,3]



TEAR SECRETION

NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion[1,4]

CELL PROLIFERATION AND DIFFERENTIATION

NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells[1]

1. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017 Apr;232(4):717-724. 2. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res.* 2003 May;76(5):521-42. 3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-9. 4. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea*. 2010;29:1163–1168

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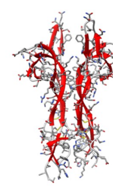
Active ingredient structurally identical to human nerve growth factor produced in ocular tissues



- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons[1]
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s[1]
- Cenegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein[2]

1. Lambiase A, Rama P, Bonini S, Caprioglio G, Aloe L. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. *N Engl J Med* 1998;338:1174-80. 2. Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

- OXERVATE™ is supplied in a weekly carton containing 7 multiple-dose vials*
- A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

- 7 vial adapters
- 42 pipettes
- 42 sterile disinfectant wipes
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra wipes are included as spares

**Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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Study Conclusions

After 8 weeks of treatment, 6 times daily

In the majority of patients across two clinical studies OXERVATE™ (cenegermin ophthalmic solution 0.002%) was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

50 clinical trial sites in Europe and the U.S.

Study NGF0212 (REPARO) (N=52 per group)

European patients with NK in one eye

NCT01756456

72.0% completely healed

Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147

65.2% completely healed

Vehicle response rate 16.7%

Of patients who healed after one 8-week course of treatment… **80%** Remained healed for one year*

*Based on REPARO, the study with longer follow-up

Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing[3]

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343. 2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017. 3. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Dosing and Administration

Instill 1 drop of OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% in the affected eye(s)

2 — Every 2 hours

6 — Apply 6 times daily

8 — Continue for 8 weeks

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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FDA INVESTIGATIVE DRUGS

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NEW NOVEL THERAPEUTICS IN PIPELINE:

- Demodex Blepharitis
  - TP-O3
    - Phase 3 clinical trials starting in 2020/2021
    - Tarsus Pharmaceuticals
- Meibomian Gland Dysfuction
  - AZR-MD-001
    - Phase 3 clinical trials 2021
    - Azura Pharmaceuticals
- Dry Eye
  - OC-01
    - Oyster Point Pharma
    - Phase 3

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DEMODEX

That other Thug!

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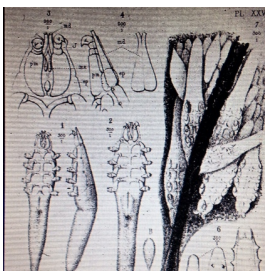

HANDBOOK OF MEDICAL ENTOMOLOGY

Dr. WM. A. RILEY, Professor of Insect Morphology and Parasitology, Cornell University

Dr. O. A. JOHANNSEN, Professor of Biology, Cornell University

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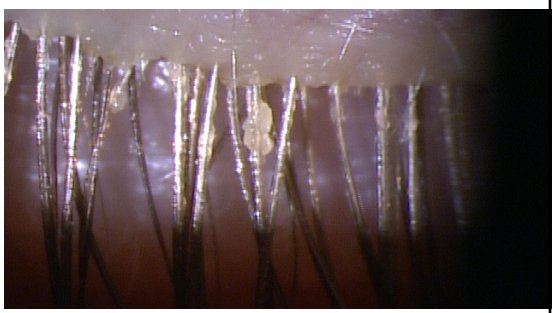

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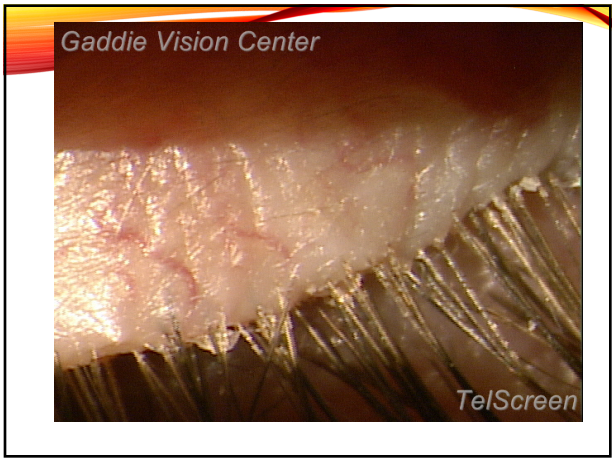

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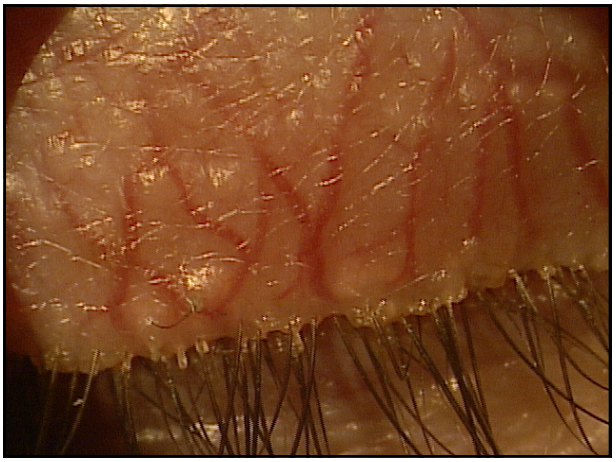

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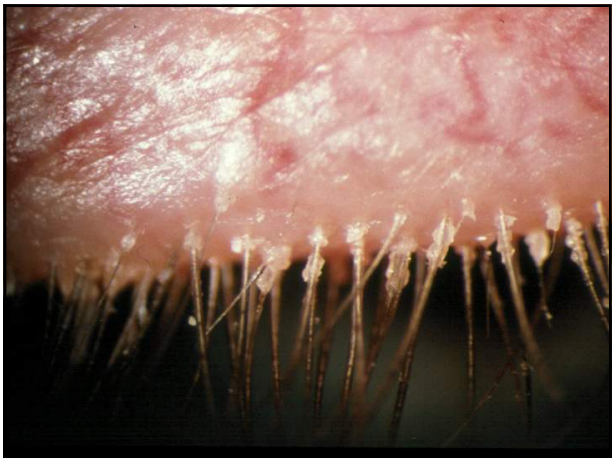


45

46

ROSACEA AND DEMODEX?

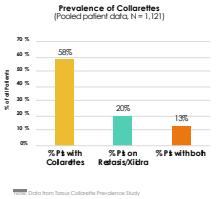
- Rosacea and demodex
  - Meta-analysis of 48 studies
  - 10 different countries
  - 28,527 subjects
  - Rosacea patients 7-8x chance have Demodex

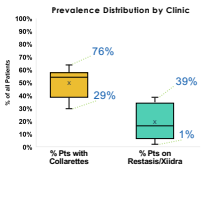
Zhao YE, Wu LP, Peng Y, Cheng H. Retrospective analysis of the association between Demodex infestation and rosacea. Arch Dermatol 2010;146:896Y902.

47

HALF OF ALL PATIENTS ENTERING CLINIC HAVE COLLARETTES

- Since Demodex is newly appreciated as a cause of blepharitis, Tarsus performed the first-ever Demodex blepharitis in-clinic prevalence study
- Methods: EVERY consecutive patient seen by the clinic is evaluated for
  1. Presence of collarettes (the pathognomonic sign and key diagnostic for Demodex blepharitis)
  2. Whether they have an active Rx for dry eye (Restasis® or Xiidra®)
- N = 1,121 consecutive patients, 8 clinics (MDs and ODs, geographically diverse)



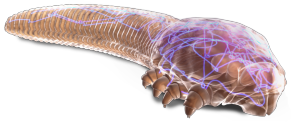


Data from Tarsus Collarette Prevalence Study

48

TP-03 IS A NOVEL THERAPEUTIC DESIGNED TO ERADICATE DEMODEX MITES AND TREAT DEMODEX BLEPHARITIS

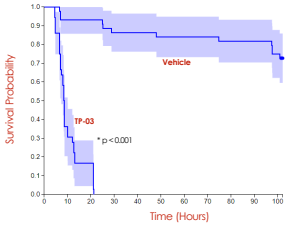
TP-03 is designed to paralyze the mite nervous system through parasite-specific GABA inhibition



49

PHASE 2 STUDY: TP-03 WORKS BY CAUSING MITE DEATH

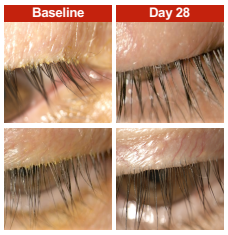
Ex-vivo mites extracted from the lashes of blepharitis patients; 100% of mites dead in < 24 hr



50

TP-03

- Multi-dose eye drop solution bottle, preserved
- Treatment of Demodex blepharitis
- Paralysis and death of Demodex mites
- Collarettes identified in standard eye examination
- BID* for 6 weeks
- 1° collarette cure, 2° mite eradication, 2° redness + collarette cure
- Well-tolerated safety profile



51

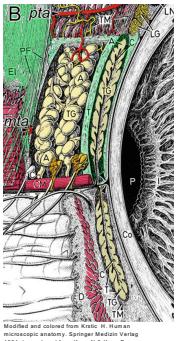
THE MOST COMMON COMPLICATION

Meibomian Gland Dysfunction

52

Meibomian Gland - ANATOMY

- Large sebaceous glands
- No direct contact to hair follicles
- Located in the tarsal plates
  - Upper and lower eye lids



Modified and colored from Kratic H. Human microscopic anatomy. Springer Medizin Verlag 1991, (reproduced from Knop N & Knop E Ophthalmologe 2009; 106:872–883)

53

Meibomian Gland - ANATOMY

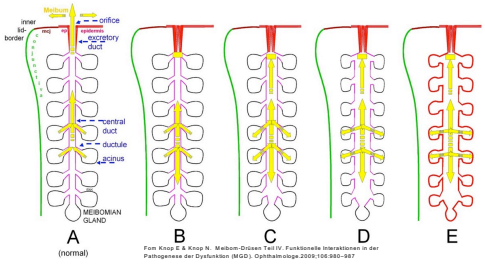
- **Length**
  - Follows the tarsus
- **Number**
  - More in upper lid (30-40)
  - Less in lower lid (20-30)
- **Volume**
  - Higher in upper lid (26µl vs. 13µl)
- Relative functional contribution (upper vs. lower) to the tear film lipid layer is unknown

Modified from Sobotta Atlas der Anatomie des Menschen. Urban & Schwarzenberg Verlag 1982, (reproduced from Knop N & Knop E. Ophthalmologe 2009; 106:872–883)

54

Meibomian Gland – PATHOLOGY

- Obstructive MGD leads to a progressive ductal DILATATION and acinar ATROPHY



55

Prevalence

"MGD is currently thought to be the leading cause of dry eye."
Caroline Blackie
Donald Korb

Blackie, Caroline A., and Donald R. Korb. "MGD: getting to the root cause of dry eye: Review of Optometry 149.6 (2012): 30-37.
Nelson JD, Shimazaki J, Benitez-del-Castillo JM, et al. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1930-7.

56

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57

Prevalence

299 normal
DED patients (M:81 F:218)
10 sites European Union & US

Lemp, Michael A., et al. "Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study." Cornea 31.5 (2012): 472-478.

58

Prevalence

"Overall, **86%** of these qualified DED patients demonstrated signs of MGD."
Michael Lemp

Lemp, Michael A., et al. "Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study." Cornea 31.5 (2012): 472-478.

59

HYPERKERATINIZATION IN MG

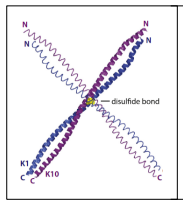
- **Hyperkeratinaztion directly or indirectly leads to physical alterations of both the gland ductal epithelium and secreted meibum resulting in:** [1-5]
  - Decreased meibum
  - Gland atropy
  - Tear film instability
  - Gland atropy
  - Cystic dilation
  - Ductal plugging
- **Hyperkeratinization is a primary cause of obstructive MGD and leads to degenerative gland dilatation and atrophy**[1]

[1]Knop E, et al Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1938-78. [2]Foulks GN, et al Ocul Surf. 2003 Jul;1(3):107-26.
[3]Gutgesell VJ, et al Am J Ophthalmol. 1982;94:383-387. [4]Iron A,et al Ocul Surf. 2004;2:149-165. [5] Knop E. Acta Ophthalmol. 2009;87:2232

60

AZR-MD-001

- Targeting Aberrant Keratin



Keratins are helical structural proteins that make up hair, nails, and skin

Extremely resilient and insoluble

sulfide bond cross-linking hardens structures to give strength and durability

Thermal denaturing
Disulfide bonds are comparatively strong and require considerable thermal energy to break, >144 °C

Chemical denaturing
Readily achieved chemically with a mild disulfide bond disrupting agent, i.e. keratolytic

[1] Bunick, et al. Journal of Investigative Dermatology 2017, Volume 137, 142-150. [2] Istrate et al. Macromol. Biosci. 2009, 9, 805–812

61

AZR-MD-001 (SELENIUM SULFIDE) MOA

- Keratostaic
  - Slows down rate of keratinocyte and keratin production
- Keratolytic
  - Softens keratin plug
  - Breaks down disulphide bonds
- Lipogensis
  - Stimulates lipid production

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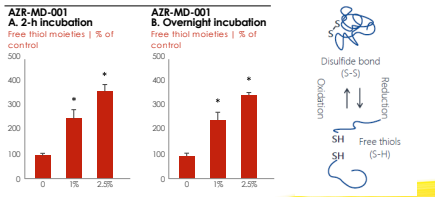
Keratolytic Effect

AZR-MD-001 has keratin softening effect

IN A STUDY EVALUATING THEIN A STUDY EVALUATING THE KERATOLYTIC EFFECT OF AZR-MD-001 IN A HUMAN EX VIVO SKIN MODEL, A STATISTICALLY SIGNIFICANT 2.5- AND 3.5-FOLD INCREASE IN FREE THIOLS, INDICATIVE OF A PROFOUND KERATOLYTIC EFFECT, WAS SEEN AT 1% AND 2.5% AZR-MD-001, RESPECTIVELY, COMPARED TO CONTROL KERATOLYTIC EFFECT OF AZR-MD-001 IN A HUMAN
EX VIVO SKIN MODEL, A STATISTICALLY SIGNIFICANT 2.5- AND 3.5-FOLD INCREASE IN FREE THIOLS, INDICATIVE OF A PROFOUND KERATOLYTIC EFFECT, WAS SEEN AT 1% AND 2.5% AZR-MD-001, RESPECTIVELY, COMPARED TO CONTROL



Data on file, Azura Ophthalmics 2019

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OC-01 PHASE 3

Oyster Point Pharma

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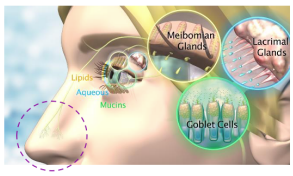
OC-01 NOVEL MOA TO INCREASE NATURAL TEAR FILM

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)



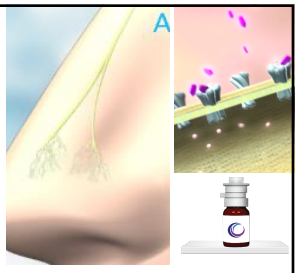
34% of basal tear production is due to inhaling air through the nose[1]

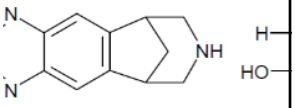
[1]Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. Cornea. 1997;16(6):645-648.

65

OC-01 IS A SELECTIVE NICOTINIC AGONIST

- 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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ONSET-1 & ONSET-2 STUDY DESIGNS

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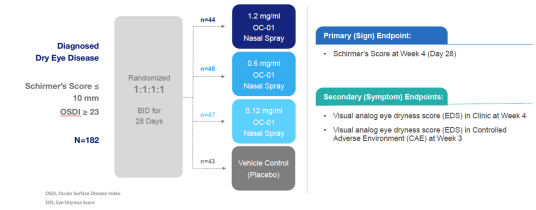
ONSET-1: OC-01 Phase 2b Study Design

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



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ONSET-1: DEMOGRAPHICS[1] AND BASELINE CHARACTERISTICS[2]

		Placebo (n=43)	0.12 mg/ml OC-01 (n=47)	0.6 mg/ml OC-01 (n=48)	1.2 mg/ml OC-01 (n=44)	Total (n=182)
Mean Age at Randomization (years)		64.0 (10.3)	64.2 (12.7)	66.5 (9.4)	67.4 (10.6)	65.5 (10.8)
Age Range (min, max)		32, 89	24, 89	49, 88	22, 84	22, 89
Sex, n (%)	Male	11 (26)	11 (23)	14 (29)	9 (20)	45 (25)
	Female	32 (74)	36 (77)	34 (71)	35 (80)	137 (75)
Race, n (%)	White	40 (93)	42 (89)	39 (81)	36 (82)	157 (86)
	Black or African American	2 (5)	2 (4)	4 (8)	6 (14)	14 (8)
	Asian	1 (2)	3 (6)	4 (8)	0	8 (4)
	American Indian or Alaska Native	0	0	1 (2)	1 (2)	2 (1)
Ethnicity, n (%)	Not Hispanic or Latino	38 (88)	39 (83)	45 (94)	42 (95)	164 (90)
	Hispanic or Latino	5 (12)	8 (17)	3 (6)	2 (5)	18 (10)
Mean Baseline Schirmer's Test (with anesthesia, mm), n (%)		4.5 (2.9)	5.2 (3.1)	4.8 (2.7)	5.5 (3.0)	5.0 (2.9)
Mean Cotton Swab Schirmer's Test (mm), n (%)		25.9 (7.0)	28.2 (7.3)	29.2 (7.8)	29.6 (7.5)	28.3 (7.5)
Mean Baseline Eye Dryness Score (mm), n (%)		65.2 (17.7)	65.6 (20.1)	63.7 (18.4)	53.5 (22.4)	62.1 (20.2)

1. Demographics of ITT-observed Population
2. Baseline Characteristics of Safety Population

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ONSET-2: PHASE 3 STUDY DESIGN

Important Study Design Elements:

- No placebo run-in period utilized as part of the study design
- Broad dry eye patient eligibility criteria
  - Subjects could enter with an Eye Dryness Score from 0-100
  - Main criteria for entry is Schirmer's Score < 10 mm
- National Eye Institute scale used to assess corneal fluorescein staining
  - Scale 0-3 for each of 5 regions: inferior, superior, nasal, temporal, central
  - Entry criteria: A corneal fluorescein staining score of ≥ 2 in at least one corneal region OR have a sum of ≥ 4 for all corneal regions

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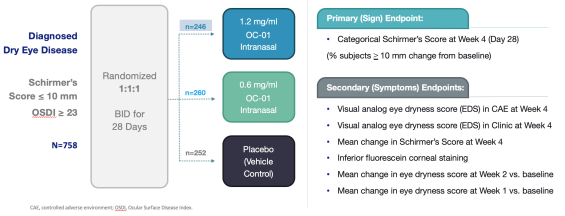
ONSET-2: PHASE 3 STUDY DESIGN

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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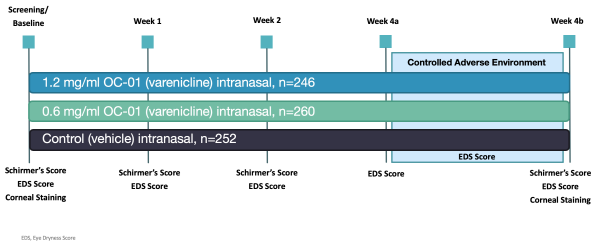
ONSET-2: PHASE 3 STUDY DESIGN



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ONSET-2: DEMOGRAPHICS[1] AND BASELINE CHARACTERISTICS[2]

		Control (n=252)	OC-01 0.6 mg / mL (n=260)	OC-01 1.2 mg / mL (n=246)	Total (n=758)
Mean Age at Randomization (years)		58.4	59.6	58.4	58.8
Age Range (min, max)		23, 95	22, 91	22, 91	22, 95
Sex, n (%)	Male	51 (20.2)	66 (25.4)	65 (26.4)	182 (24.0)
	Female	201 (79.8)	194 (74.6)	181 (73.6)	576 (76.0)
Race, n (%)	White	211 (83.7)	219 (84.2)	200 (81.3)	630 (83.1)
	Black or African American	29 (11.5)	27 (10.4)	35 (14.2)	91 (12.0)
	Asian	5 (2.0)	11 (4.2)	7 (2.8)	23 (3.0)
	American Indian or Alaska Native	6 (2.4)	1 (0.4)	2 (0.8)	9 (1.2)
Ethnicity, n (%)	Not Hispanic or Latino	216 (85.7)	233 (89.6)	209 (85.0)	658 (86.8)
	Hispanic or Latino	36 (14.3)	27 (10.4)	37 (15.0)	100 (13.2)
Mean Baseline Schirmer's Test (with anesthesia, mm)		4.9	5.1	5.4	5.1
Mean Cotton Swab Schirmer's Test (mm)		27.8	27.6	28.1	27.8
Mean Baseline Eye Dryness Score (mm)		58.1	58.5	59.3	58.6

1. Demographics of ITT-observed Population 2. Baseline Characteristics of Safety Population

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EFFICACY DATA

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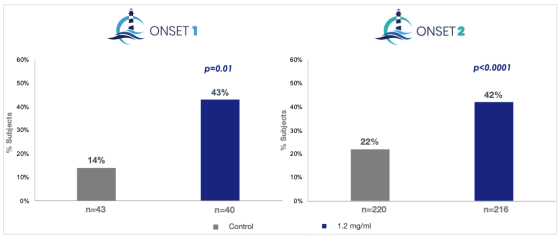
ONSET-1 AND ONSET-2: STATISTICALLY SIGNIFICANT IMPROVEMENT IN SIGNS

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

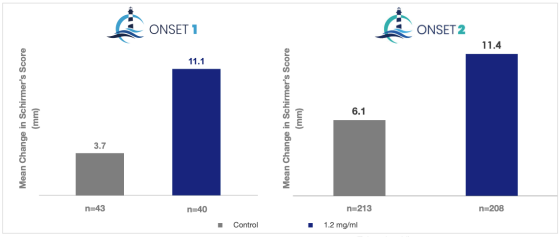


ITT-population
Cochran-Mantel-Haenszel (CMH) test controlling for study site, baseline STS, and baseline EDS
All comparisons made to control group

ITT-population
Cochran-Mantel-Haenszel (CMH) test controlling for study site, baseline STS, and baseline EDS
All comparisons made to control group

75

ONSET-1 AND ONSET-2: STATISTICALLY SIGNIFICANT IMPROVEMENT IN SIGNS



ITT-observed population
ANCOVA calculated using a model with baseline STS, baseline STS with cotton swab stimulation, site ID, and treatment group as covariates
All comparisons made to control group

ITT-observed population
ANCOVA model with treatment, site, baseline STS, and baseline EDS as covariates
All comparisons made to control group
* Nominal p-value

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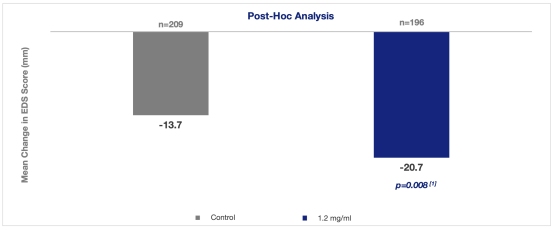
ONSET-2: IMPROVEMENT IN SYMPTOMS IN CAE

Mean Change in Eye Dryness Score After 2 hours in CAE vs. Baseline



[1] Post-Hoc Analysis, nominal p-value
ITT-population (excluding sites 45 and 48), Least Square (LS) means were derived from ANCOVA model with treatment, site, treated in chamber (Y/N), baseline STS, and baseline EDS as covariates
All comparisons made to control group

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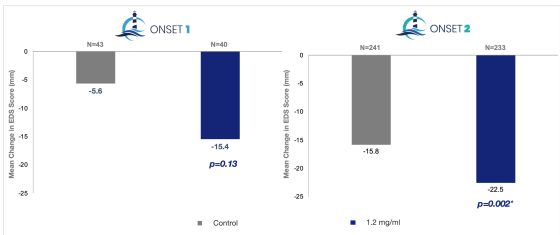
STUDY COMPARISON: STATISTICALLY SIGNIFICANT IMPROVEMENT IN SYMPTOMS

Mean Change in Baseline Eye Dryness Score – Week 4 (ITT-Observed)



ITT-population, ANCOVA model with baseline, site, and treatment group as covariates
All comparisons made to control group

ITT population, Least Square (LS) means were derived from ANCOVA model with treatment, site, baseline STS, and baseline EDS as covariates
Missing data were imputed using last-available data
All comparisons made to control group
* Nominal p-value

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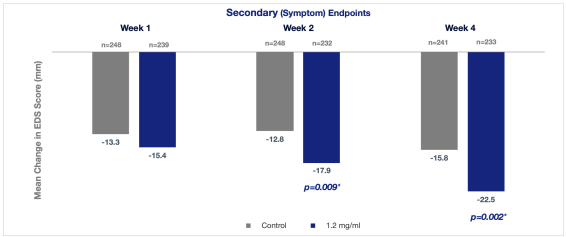
ONSET-2: STATISTICALLY SIGNIFICANT IMPROVEMENT IN SYMPTOMS

Mean Change in Baseline Eye Dryness Score (ITT-Observed)



ITT-population, Least Square (LS) means were derived from ANCOVA model with treatment, site, baseline STS, and baseline EDS as covariates.
All comparisons made to control group.
* Nominal p-value

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SAFETY DATA

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ONSET-2: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS

	Control (n=251) n (%)	1.2 mg/mL (n=245) n (%)
Subjects with any Treatment-Emergent Adverse Events (TEAE)	135 (53.8)	241 (98.4)
Subjects with any Treatment-Related Treatment-Emergent Serious Adverse Events (SAE)	0	0
Subjects with any Ocular TEAE	31 (12.4)	32 (13.1)
Subjects with any TEAEs Leading to Discontinuation[1]	4 (1.6)	8 (3.3)
Related to Study Drug[1]	2 (0.8)	5 (2.0)

Subjects reporting more than 1 event are only counted once at the maximum relationship reported.
A TEAE is defined as an AE that is new or worsened in severity compared to the first dose of study drug.
AE records were cut off at 28-day treatment period.
Safety population
1. ITT population

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ONSET-2: ADVERSE EVENT PROFILE

Treatment-Emergent Adverse Events >5% of Subjects Potentially Related to OC-01

	Control (n=251)	OC-01 1.2 mg / mL (n=245)
Sneeze after any instillation	73 (29.1)	237 (96.7)
Cough after any instillation	5 (2.0)	53 (21.6)
Throat Irritation after any instillation	5 (2.0)	44 (18.0)
Instillation Site Irritation	3 (1.2)	35 (14.3)

- 1 case (0.4%) ocular burning/irritation
- 5 events of dysgeusia (2%)
- No complaints of bad smell

- No serious adverse events related to study drug
- All events mild (99.9%) or moderate (0.1%) in severity. No severe events

Subjects reporting more than 1 event are only counted once at the maximum relationship reported.
A TEAE is defined as an AE that is new or worsened in severity compared to the first dose of study drug
Safety population
AE records were cut off at 28-day treatment period.

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NEW DROPS COMING FOR PRESBYOPIA

- Ophthalmic drops-future
  - Mitotic based
    - constriction of the pupil
    - Increase depth of focus
    - mono-vision based
      - Numerous different formulations
      - Early studies indicate good tolerability
      - Phase III trials almost complete
  - Mitotic and Enhanced Accommodation
    - Bilateral
    - Synergistic drop formulation
  - Lens Restoration drops
    - Anti-oxidant to break down disulfide bonds
    - Increase lens flexibility
    - Binocular

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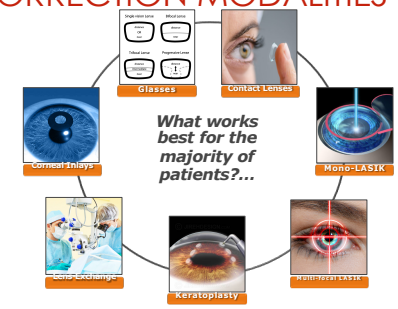
MULTIPLE PRESBYOPIA CORRECTION MODALITIES EXIST



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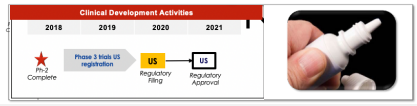
ALLERGAN INTENDS TO LAUNCH THE 1ST PHARMACEUTICAL APPROACH TO PRESBYOPIC NEAR VISION CORRECTION



Description	• ***Topical once-daily drop*** instilled in both (OU) or non-dominant eye • Improves quality of ***near visual acuity for multiple hours post dose*** • ***Fast onset-of-action, reversible, non invasive, well-tolerated*** • ***Addresses un-met needs*** with current options (e.g. reading glasses, contacts, surgery) • AGN-1883* has ***completed successful Ph-2b studies, Ph-3 initiated late 2018***
Benefits	• Provides ***alternative for patients who are dissatisfied*** with current options • ***May delay or prevent need for glasses/lenses*** or refractive surgical intervention • Gives patients ***freedom and independence from reading glasses*** when they want it – ***an alternative but complementary choice***

* Product under investigational use; efficacy and safety have not been established

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OUT WITH OLD AND IN WITH NEW..

- Adapt to new ideas
- Sea Change
  - You can be on the wave
  - Or you can float away….

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Thank you.

THAT'S ALL…

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