Optometric Education Consultants

Pharmaceutical Update 2022

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Nashville – Music City Fall Classic 2022
Optometric Education Consultants

Sunday, October 23, 2022

Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- The content of this activity was prepared independently by me - Dr. Caldwell
- Lectured for: Alcon, Allergan, Aerie, BioTissue, Kala, Maculogix, Optovue, RVL, Heru
  - Disclosure: Receive speaker honorariums
- Advisory Board: Allergan, Sun, Alcon, Maculogix, Dompe, Visus, Eyenovia
  - Disclosure: Receive participant honorariums
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
  - Disclosure: Non-salaried financial affiliation with Pharmanex
- Envolve: PA Medical Director, Credential Committee
- Healthcare Registries – Chairman of Advisory Council for Diabetes
- The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service
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Course Description

- Every year the FDA approves numerous pharmaceuticals (AKA "Legend Drugs") for the management of diseases in many therapeutic categories
- This course will review recently approved pharmaceuticals that are pertinent to optometric patient care
- This course will review systemic and ocular complications of select pharmaceuticals

Pharmaceutical Resource Matrix

- Commercial/Sales
  - Representatives
    - On label, educational lunches, samples, discount cards, coupons
    - Organizes the promotional dinners
- Medical Affairs- Medical Science Liaison (MSL)
  - OD, MD, PharmD, PhD,…
  - Education, education, education
  - On label or that "off label" question
  - Where the granular discussion occurs
  - No sales
- Clinical Research
  - Company sponsored studies
- Marketing
  - Assists representative on therapeutic usage
  - Consultant, advisory board, promotional speaker
- Market Access
  - Formulary access
    - Commercial and Federal payers

MOA versus MOD

- Mechanism of Action - MOA
- Mechanism of Delivery – MOD

Mechanism of Action (Delivery) – AMPPLIFY Technology

- Mucus is a barrier for topical ophthalmic drug delivery
- AMPPLIFY utilizes two proprietary attributes
  - Nanoparticles to allow penetration into mucus pores
    - Particles smaller than 500 nm
  - Mucus penetrating surface coating
    - Prevents adherence to mucus

eyenovia

Eyenovia Announces Positive Study Results Demonstrating that its Optejet® Delivery Technology Reduces Conjunctival Cell Toxicity from Preserved Ophthalmic Solutions to a Level Comparable with Non-Preserved Solutions

March 15, 2022

Study conducted with Tufts Medical Center represents a breakthrough showing that Microdose Array Print (MAP™) technology can provide similar benefits of non-preserved medications

NEW YORK, March 15, 2022 (GLOBE NEWSWIRE) -- Eyenovia, Inc. (NASDAQ: EYEN), an ophthalmic pharmaceutical technology company developing a pipeline of microdose array print (MAP™) therapeutics, today announced positive results from a research study conducted in collaboration with Dr. Pedram Hamrah, Interim Chairman of Ophthalmology at Tufts Medical Center, which evaluated the ocular surface damage from Latanoprost+Benzalkonium Chloride (BAK) treatment administered via Optejet versus Latanoprost+BAK administered via standard eye drops.

Preservatives in topical ophthalmic drugs administered via standard eye drops help ensure sterility of the product and increase shelf-life. However, patients on chronic topical ophthalmic drug treatments often display long term ocular adverse effects due to toxicity from over-exposure to preservatives.

"Long term use of ophthalmic eye drops with preservatives is a significant clinical concern and therapeutic burden," remarked Professor Robert Weinreb, MD, Chair of Ophthalmology at the University of California, San Diego and member of the Eyenovia Scientific Advisory Board. "For patients with chronic conditions such as glaucoma, this is a major concern when treatment with topical medications can last a lifetime."

Per the study design, conjunctival epithelial cells were exposed to drug by standard drop or Optejet microdose technology. Cell-based assays were then conducted to assess cell viability, cytotoxicity, apoptosis, ROS generation and ATP generation (metabolic activity).

The study found that human conjunctival epithelial cells tolerated Latanoprost+BAK treatment administered via Optejet technology significantly better than Latanoprost+BAK administered via standard drops. Optejet technology had similar results to both latanoprost without BAK and no-treatment controls with respect to all four measures.

Beth Scott, OD, Vice President of Regulatory and Medical Affairs at Eyenovia, commented, "It is well established that BAK preservative in most preserved eye drops causes damage to the ocular surface, including the cornea epithelium, conjunctiva, and neural cells. The current study successfully proved that due to the much smaller volume of drug and preservatives required with the Optejet device, the level of ocular surface damage due to preservative toxicity would be minimal. This study adds to the body of evidence supporting our breakthrough Optejet technology."

About Eyenovia, Inc.

Eyenovia, Inc. (NASDAQ: EYEN) is an ophthalmic pharmaceutical technology company developing a pipeline of microdose array print (MAP™) therapeutics. Eyenovia is currently focused on the late-stage development of microdosed medications for mydriasis, presbyopia and myopia progression. For more information, visit Eyenovia.com.

The Eyenovia Corporate Information slide deck may be found at ir.eyenovia.com/events-and-presentations.

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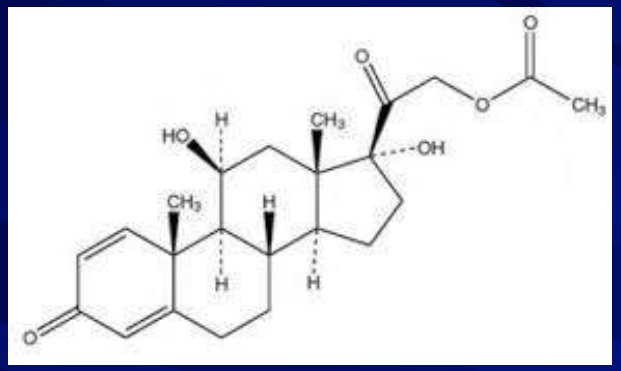
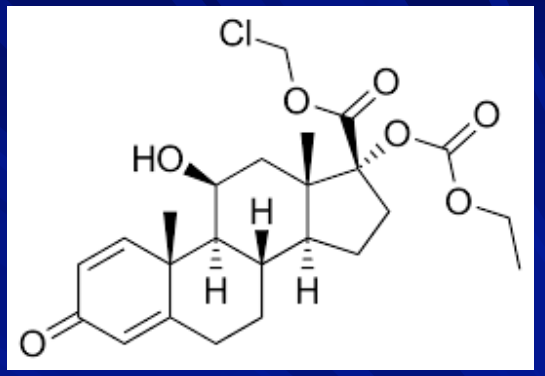
Poll 1

Regarding the various loteprednol etabonate ophthalmic drops?

A. We have enough formulations
B. They are all the same to me
C. Help me with the differences
D. Steroids are steroids they all do the same thing
E. I will place my comment in the chat box



Steroids
Ketones versus Esters



- Prednisolone acetate molecule modified to undergo predictable degradation to inactive metabolites by local esterases
- Corticosteroids, C-20 ketone replaced with a C-20 ester
- C-20 ester steroids are associated with a lower incidence of IOP elevations vs. C-20 ketone steroids
  - IOP and cataracts
- Retrometabolic drug design of loteprednol aims to improve safety while maintaining efficacy

Loteprednol Etabonate Products
Ester Steroids

- Lotemax suspension 0.5%
- Alrex suspension 0.2%
- Lotemax gel 0.5%
- Lotemax SM gel 0.38%
- Inveltys suspension 1.0%
- Eysuvis suspension 0.25%
  - ★ KPI-121

Lotemax SM (loteprednol etabonate) 0.38%

- Indicated for the treatment of post-operative inflammation and pain following ocular surgery
- SubMicron - *Particle size* reduced to facilitate ocular penetration
  - Allowing for a decrease in drug concentration and dosing frequency (TID)
  - Increase intraocular penetration
  - Median particle diameter size reduced 5 to 12.5-fold:
    - LE gel 0.38% = 0.4-0.6 μm
    - Lotemax gel 0.5% = 3-5 μm
  - Potential for a ~10-fold increase in rate of drug dissolution
    - Based on a 10-fold increase in relative surface area with smaller particles

Lotemax SM (loteprednol etabonate) 0.38%

- Increased concentrations demonstrated in ocular tissues
  - Cornea and aqueous humor
  - Following single topical ocular instillation of Lotemax SM 0.38% vs Lotemax gel 0.5% in rabbits
- Compared to Lotemax Gel 0.5%
  - Single topical instillation of Lotemax SM 0.38% were greater in the aqueous humor and cornea
  - Concentrations in the conjunctiva remain the highest out of the ocular tissues, with ample drug to mediate anti-inflammatory effects at the ocular surface
- Formulation advancement while maintaining a low BAK
  - Lowest concentration of BAK, 0.003% among the commercially available corticosteroid ocular drops
    - Inveltys is 0.01%

Lotemax SM (loteprednol etabonate) 0.38%

- Submicron formulation is designed to reduce the Lotemax Gel drug concentration 0.38% vs. 0.5%)
- Dosing frequency TID vs. QID
- Formulation builds on the heritage and advantages of Lotemax gel 0.5%:
- Retrometabolically designed corticosteroid
  - ✶ Retains potent anti-inflammatory activity
  - ✶ Minimal potential for class Aes
- Mucoadhesive, non-settling, shear-thinning gel
  - ✶ A gel in the bottle; transitions to a liquid upon instillation
  - ✶ Becomes mucoadhesive liquid on dilution with tears
  - ✶ No need to shake - uniform dosing
  - ✶ Non-blurring

Inveltys ™ - loteprednol etabonate suspension 1.0%

- Kala Pharmaceuticals
- August 2018
- Now in distribution centers and pharmacies
- Nanoparticle-based Mucus Penetrating Particles (MPP)
  - "Amplified Technology"
  - MOD
  - Allows drug to penetrate through tear mucins
    - Increased penetration into tissues, 3-fold to other loteprednol
- 1.0% post-operative inflammation and pain after ocular surgery
  - Dosage BID
    - First ocular corticosteroid to be BID

Eysuvis - loteprednol etabonate suspension 0.25%

- Kala Pharmaceuticals – KPI-121
  - Approved October 27, 2020
- First prescription therapy – Specifically for the Short-Term treatment of Dry Eye Disease
  - Short term = "up to two weeks"
  - Dry eye flares – dry eye disease characterized by acute exacerbations "flares"
- Contraindications, warnings, and precautions
  - Nothing new to report
  - Delayed healing, IOP, cataracts, infections
- Adverse Reactions
  - The most common was instillation site pain, 5.0% of patients
- Safety and Efficacy based on largest clinical program in DED (n=2871)
  - Stride 1, 2, and 3 studies

Eysuvis - loteprednol etabonate suspension 0.25%

- Dry Eye Flare – characteristics
  - Rapid onset – inflammation driven
  - Response to variety of triggers
  - Not adequately managed with patient's ongoing therapy
  - With or without maintenance therapy
    - DED patients experience flares
      - Desire rapid relief
  - Multiple episodes per year
    - 4-6 times
  - Triggers: seasonal allegies, A/C use, digital screen time, air travel, CL wearing, smoking, diet, medications
- Many chronic inflammatory and autoimmune diseases have episodic exacerbations "flares"
  - Asthma, uveitis, Sjogren's syndrome, rheumatoid arthritis, lupus erythematosus

Eysuvis - loteprednol etabonate suspension 0.25%

- Thoughts on Dry Eye Disease
  - 80% of patients with dry eye disease suffer from flares
    - Patients may not share this at their visit
  - 45% of dry eye patients just have flares instead of continuous symptoms
  - 81% of patients using artificial tears reported flares
  - 17.2 million US patients diagnosed with dry eye disease
    - 75% never tried a prescription therapy
    - 2.9% used steroids for DED
    - 80% patients discontinue their chronic Rx medications by 4 months

Eysuvis - loteprednol etabonate suspension 0.25%

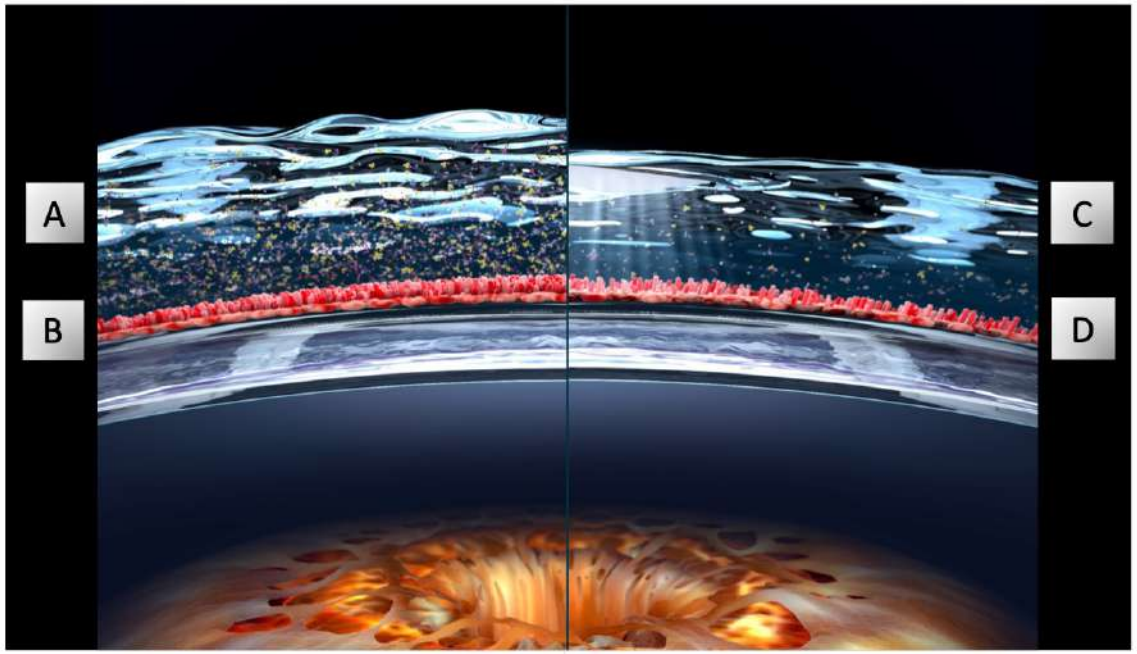
- Mechanism of Action – AMPPLIFY Technology
  - Mucus is a barrier for topical ophthalmic drug delivery
  - AMPPLIFY utilizes two proprietary attributes
    - Nanoparticles to allow penetration into mucus pores
      - Particles smaller than 500 nm
    - Mucus penetrating surface coating
      - Prevents adherence to mucus
  - Allows rapid and enhanced ocular
    - Distribution
    - Penetration

Tyrvaya – varenicline solution 0.03 mg

- October 21, 2021
- Nasal spray
- BID – approximately every 12 hours
- Preservative-free
- 1/33 of dosage of Chantix
  - ★ Depression
  - ★ Smoking cessation

Normal and Dysfunctional Tear Film*

Normal Tear Film[1-3] **Dysfunctional Tear Film**[1-3]



Proteins
- Nerve Growth Factor
- Lysozyme
- Lactoferrin
- Epidermal Growth Factor

Electrolytes
- Sodium
- Chlorine
- Calcium
- Potassium

Mucins
- MUC1
- MUC5AC
- MUC4
- MUC16

Immunoglobulins
- IgG
- IgM
- IgA

Image for illustrative purposes only

A. **Solid lipid layer; homeostatic distribution of proteins, growth factors, electrolytes, and immunoglobulins**

B. **Abundant mucins**

C. **Broken lipid and loss of aqueous volume, fewer proteins, hyperosmolar—more abundant electrolytes**

D. **Diminished mucins**

Natural tears contain a complex mixture of lipids, proteins, mucins and electrolytes.[3]

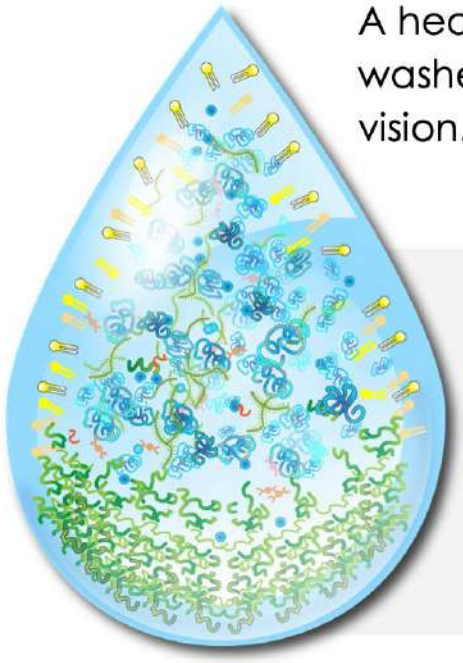
- Over 1,500 proteins
  - Epidermal growth factors
  - Nerve growth factors
  - Transforming growth factor beta (TGF-β)
  - Lysozymes
- 5+ lipid classes
- 20+ mucin classes

1. Pflugfelder SC, Beuerman RW, Stern ME, eds. *Dry Eye and Ocular Surface Disorders*. New York, NY: Marcel Dekker; 2004.
2. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome study group. *Cornea*. 2006;25(8):900-907.
3. Willcox MDP, et al. The TFOS DEWS II tear film report. *Ocul Surf*. 2017;15(3):366-403.
4. Oyster Point Pharma, Inc. Data on file. 2021.

There Is No Substitute for Natural Tear Film

Growth factors, such as nerve growth factor (NGF) and epidermal growth factor (EGF), found in natural human tears, are critical regulators for corneal wound healing.

A healthy tear film lubricates and protects the eyes from injury and infection, washes away foreign particles, and contributes refractive power for clear vision.



TFOS DEWS II tear film report

Natural tears contain a complex mixture of lipids, proteins, mucins, and electrolytes[1,2]

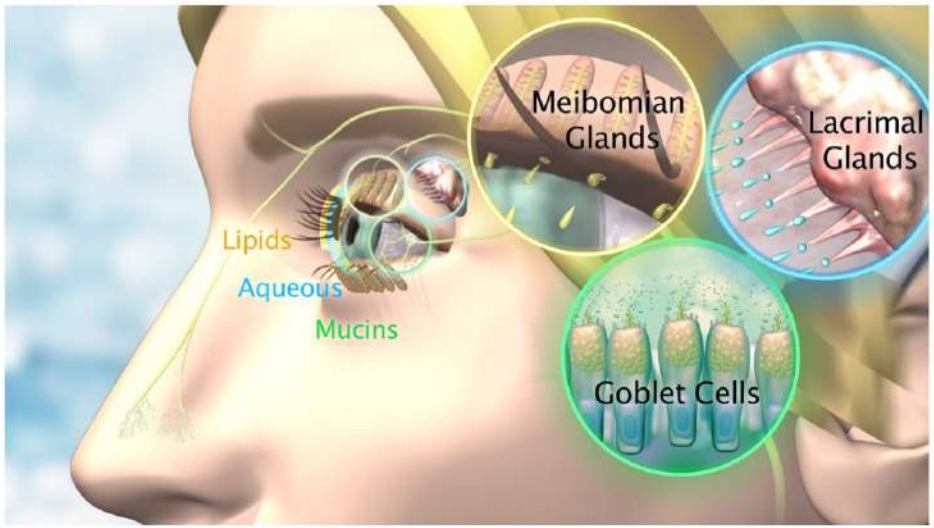
- Over 1,500 proteins
- 5+ lipid classes
- 20+ mucins
- Contains growth factors and has anti-inflammatory and antimicrobial properties

1. Klenkler B, Sheardown H, Jones L. Growth factors in the tear film: role in tissue maintenance, wound healing, and ocular pathology. *Ocul Surf*. 2007;5(3):228-239.
2. Willcox MDP, Argüeso P, Georgiev GA, et al. TFOS DEWS II tear film report. *Ocul Surf*. 2017;15(3):366-403.

Parasympathetic Nervous System Controls Tear Film Homeostasis

The trigeminal nerve is **accessible within the nasal cavity** and is activated by by OC-01 (varenicline solution) nasal spray by activation of **cholinergic receptors.**

The trigeminal nerve provides the pathway for **parasympathetic stimulation** of the lacrimal functional unit (LFU) to activate **complete basal tear film.**

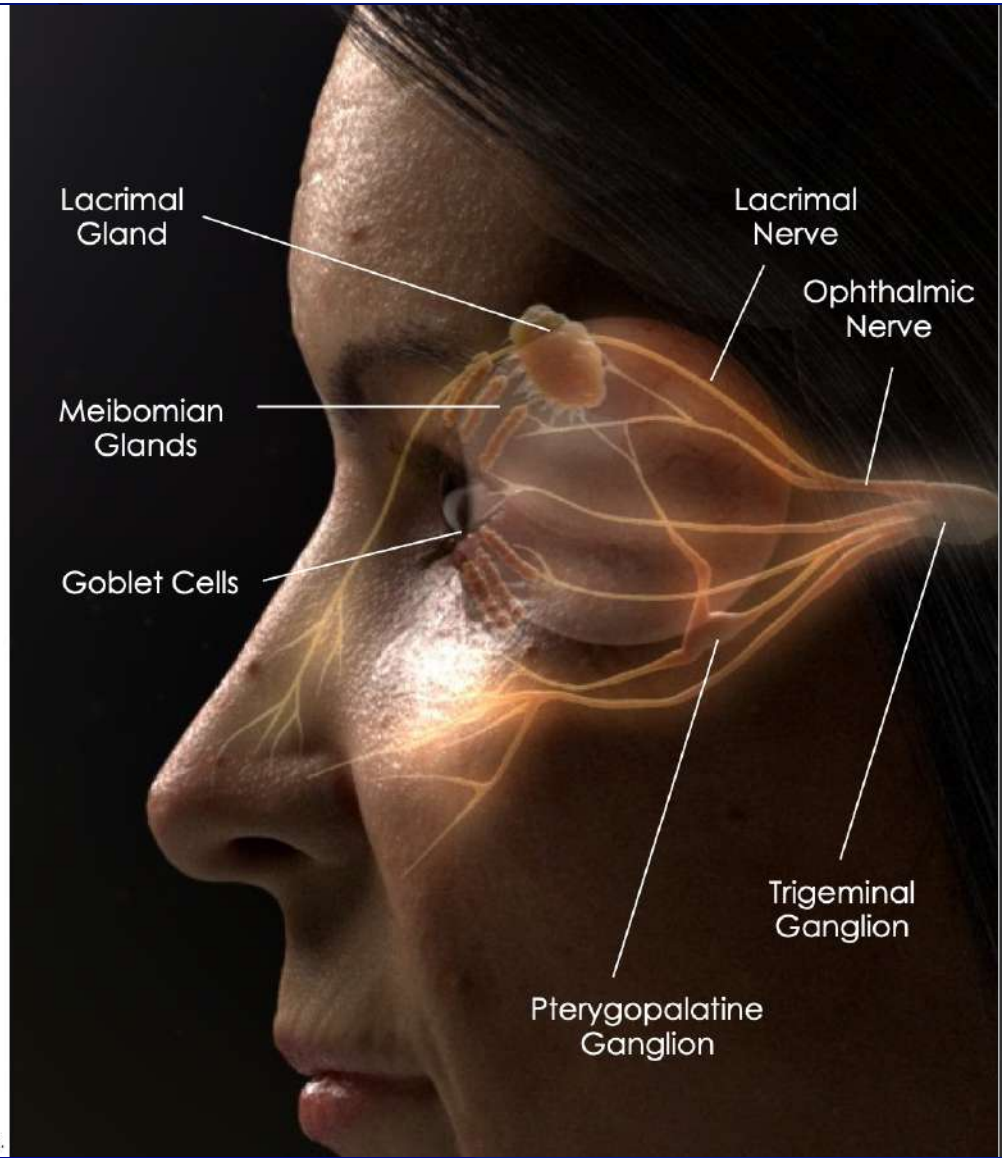


34% of basal tear production is due to inhaling air through the nose[1]

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

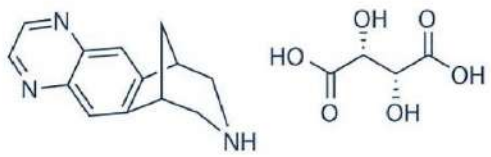
Lacrimal Gland Postganglionic Innervation[1]

- The LFU is innervated by the trigeminal nerve
- Loss of parasympathetic stimuli results in chronic reduction of tear secretion and morphologic destruction of the lacrimal gland

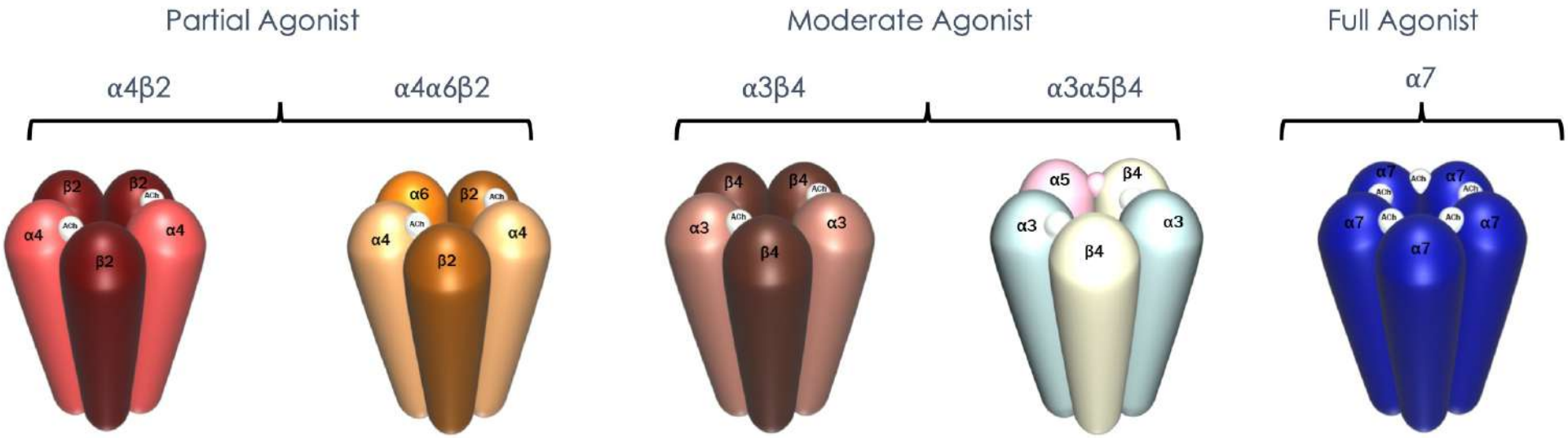


1. Jin K, Imada T, Hisamura R, et al. Identification of lacrimal gland postganglionic innervation and its regulation of tear secretion. *Am J Pathol*. 2020;190(5):1068-1107.

Varenicline Tartrate



- Binds with high affinity and selectivity at α-subunit containing cholinergic receptors located on the trigeminal nerve within the nasal cavity
- Water soluble and diffuses across nasal mucosa quickly



Human Nicotinic Acetylcholine Receptors

OC-01 VNS Highlights[1-4]

- Approved as **TYRVAYA™** (varenicline solution) 0.03 mg October 15, 2021
- Cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease.
- Preservative-free, delivered as a 0.05 mL spray
    - One spray, each nostril, twice daily (approximately 12 hours apart)
    - 0.03 mg concentration | 29 mcg/spray
      0.06 mg concentration | 59 mcg/spray
- Onset of action and sustained outcomes demonstrated in clinical trials, sign outcomes measured at 5 minutes after nasal spray administration
- OC-01 VNS studied in subjects with mild, moderate, and severe dry eye disease as determined by baseline eye dryness score (EDS)
- Most common adverse reaction in clinical trials was sneezing; other adverse reactions reported in >5% of patients include cough, throat irritation, and instillation-site (nose) irritation
- 0.34 ng/mL C_{max} at 2 hours

1. Nau J, Wyatt DJ, Rollema H, Crean CS. A phase I, open-label, randomized, 2-way crossover study to evaluate the relative bioavailability of intranasal and oral varenicline. *Clin Ther*. 2021;43(9):1595-1607. doi:10.1016/j.clinthera.2021.07.020
2. Wirta, D., Torkildsen, G., Boehmer, B., Hollander, D., Bendert, E., Zeng, L., Ackermann, M. and Nau, J., 2021. ONSET-1 Phase 2b Randomized Trial to Evaluate the Safety and Efficacy of OC-01 (Varenicline Solution) Nasal Spray on Signs and Symptoms of Dry Eye Disease. Cornea: December 22, 2021 - Volume - Issue - doi: 10.1097/ICO.0000000000002941
3. Wirta D, Vollmer P, Paauw J, et al. Efficacy and Safety of OC-01 (Varenicline) Nasal Spray on Signs and Symptoms of Dry Eye Disease: the ONSET-2 Phase 3, Randomized Trial [published online ahead of print, 2021 Nov 9]. *Ophthalmology*. 2021;S0161-6420(21)00836-8. doi:10.1016/j.ophtha.2021.11.004
4. Quiroz-Mercado H, Hernandez-Quintela E, Chiu KH, Henry E, Nau JA. A phase II randomized trial to evaluate the long-term (12-week) efficacy and safety of OC-01 (varenicline solution) nasal spray for dry eye disease: The MYSTIC study [published online ahead of print, 2021 Dec 15]. Ocul Surf. 2021;S1542-0124(21)00146-4. doi:10.1016/j.jtos.2021.12.007

Pharmaceutical Update?

Regener-Eyes Ophthalmic Solution

Dosage and Administration

Regener-Eyes® LITE

- Formulated for mild to moderate symptoms
- Instill one to four drops
- One to four times per day in each eye
- Or as recommended by your Eye Care Professional (ECP)
- Each vial can be stored at room temperature

Regener-Eyes® Professional Strength

- Formulated for severe symptoms
- Instill one to four drops
- One to four times per day in each eye
- Or as recommended by your Eye Care Professional (ECP)
- Each vial must be refrigerated

Regener-Eyes

Regener-Eyes® is a first in class, **natural, sterile biologic** ophthalmic solution that is **preservative free.**

Regener-Eyes® Ophthalmic Solution, Professional Strength and LITE contain naturally occurring **cytokines, chemokines and growth factors**

Regener-Eyes®

Generic name - “derived-Multiple Allogeneic Proteins Paracrine Signaling [d-MAPPS]”

Ophthalmic solution that contains a large number of immunoregulatory factors that are capable of penetrating the ocular surface and to efficiently attenuate the detrimental immune response in the eye, promoting repair and regeneration of injured tissue.

Therapeutic Potential for Treatment of DED

Regener-Eyes® efficiently alleviated DED-related symptoms dryness, grittiness, scratchiness, soreness, irritation, burning, watering, foreign body sensation, eye fatigue) and improved functional visual acuity in 131 DED patients, without causing any side effects.

Molecular Mechanisms

Regener-Eyes® is acellular however it contains **proteins** and **cytokines** in addition to the **water, glucose, lactates and electrolytes, and placental-derived biomaterials**

Which produce a large number of bioactive factors (lipids, proteins, enzymes, cytokines, chemokines, immunoregulatory proteins, trophic and growth factors)

As well as microRNAs (miRNAs), which, due to their trophic and antimicrobial properties, support normal fetal growth and offer protection against pathogens and toxins.[10]

Molecular Mechanisms

Regener-Eyes® is a bioengineered biological product derived from human placental-based biomaterials, manufactured under current Good Manufacturing Practices (cGMP), regulated and reviewed by the Food and Drug Administration (FDA).[9]

Regener-Eyes® incorporates Regenerative Processing Plant's (RPP) proprietary patented sterilization process to provide for a safe, sterile product for clinical use.[9]

Regener-Eyes® is enriched with AF-MSC-Exos containing AFMSC derived immunoregulatory, angio-modulatory and trophic factors capable of bypassing biological barriers to efficiently attenuate ongoing inflammation, promoting enhanced tissue repair and regeneration.[8]

Molecular Mechanisms – IL-1Ra

Specifically, Regener-Eyes® contains interleukin 1 receptor antagonist (IL-1Ra), soluble receptors of tumor necrosis factor alpha (sTNFRI, sTNFRII), growth-related oncogene gamma (GRO-γ), fatty acid-binding protein 1 (FABP1) and platelet factor 4 (PF4), which alleviate eye inflammation, support tear stability, and prevent ocular surface epithelial damage, contributing to the enhanced repair and regeneration of ocular surface epithelial barrier in DED patients.[1,9,11–13]

IL-1Ra is a naturally occurring cytokine that acts as an inhibitor of inflammatory cytokine IL-1β that has a crucially important role in the recruitment of circulating leukocytes in inflamed eyes of DED patients.[5–6,12,14]

Molecular Mechanisms – FABP Proteins

Downregulated levels of FABP proteins were noticed in the tears of patients suffering from Sjögren's syndrome and DED.[17]

FABP proteins regulate transepithelial water transport and maintain the epithelial barrier at the ocular surface. [17]

Accordingly, the reduced expression and production of FABP proteins leads to disturbances in the epithelial barrier, causing increased tear evaporation and DED.[17]

Regener-Eyes® contains a high concentration of FABP1 proteins, which are thought to regulate transepithelial water transport, support tear stability, and prevent ocular surface epithelial damage in the eyes of DED patients, resulting in the possible alleviation of dryness, grittiness, scratchiness, and soreness.[1,9,17]

Molecular Mechanisms – PF4

A topical administration of platelet-rich plasma eye drops that contains a large amount of PF4, epithelial growth factors, fibroblast growth factors, and vascular endothelial growth factor successfully treated moderate to severe DED.

Regener-Eyes® contains a high concentration of PF4, which may promote the repair and regeneration of injured epithelial cells on the ocular surface.[1,9,18]

Therefore, the beneficial effects of Regener-Eyes® may be partially explained by the regenerative and protective properties of PF4.[1,9]

Experimental and clinical evidence of Regener-Eyes® - based efficacy in DED treatment

Regener-Eyes® may protect corneal epithelial cells from chemical injury.[12]

While cytoplasm vacuolization and swelling, accompanied by the loss of cell-to-cell contact, were observed in benzalkonium chloride (BAC)-treated human corneal epithelial cells (HCEC) in vitro, these morphological and functional changes were not seen in BAC-treated HCEC that grew in the presence of Regener-Eyes®.[12]

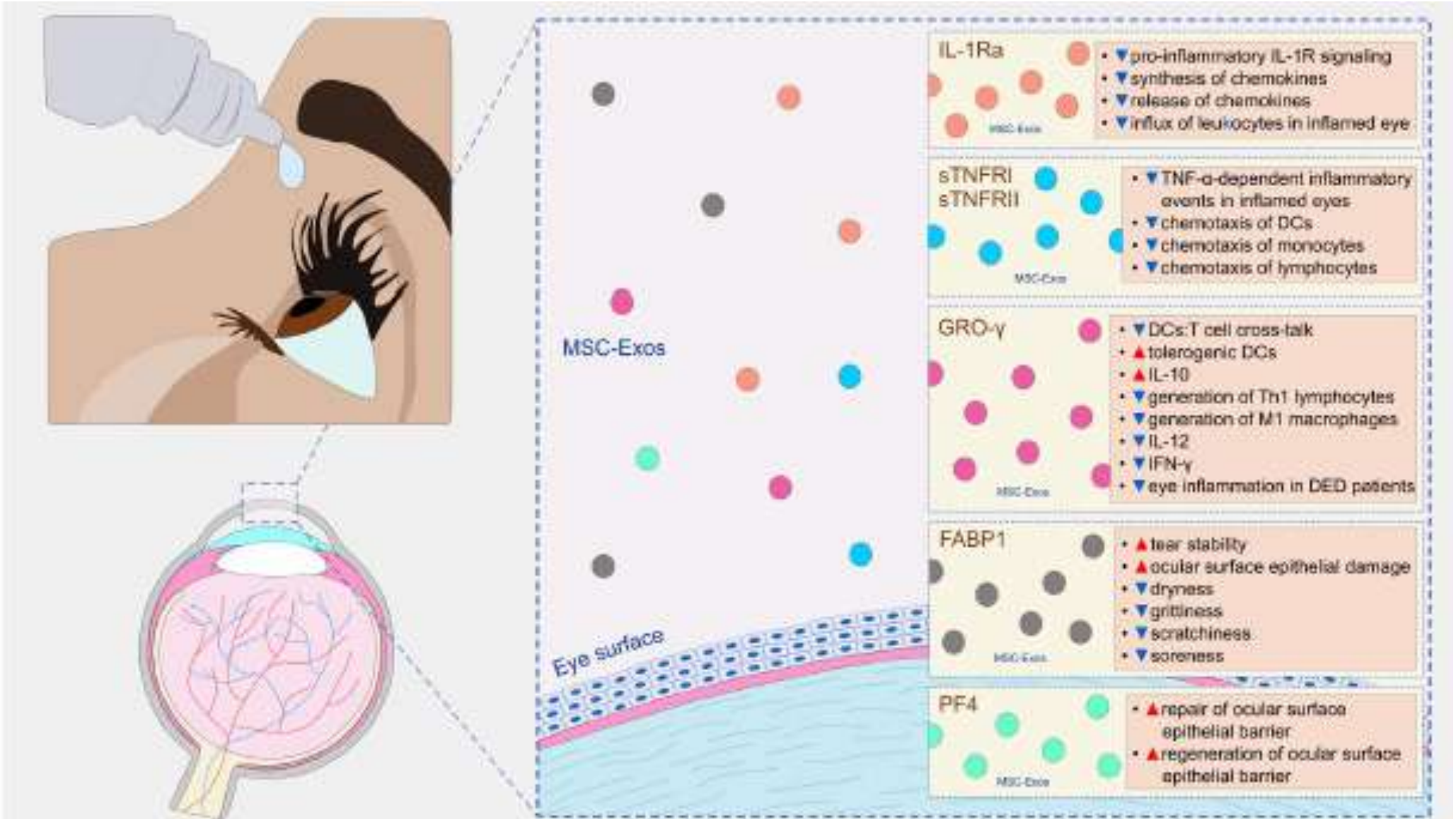
Additionally, Regener-Eyes® significantly improved viability of BAC-injured HCEC while protecting them from BAC-induced chemical injury.[12]

Experimental and clinical evidence of Regener-Eyes® - based efficacy in DED treatment

Regener-Eyes® was shown to help efficiently alleviate ocular discomfort and pain in a study of 131 DED patients (27 males and 104 females with a median age of 62 years [range 19–85]) during a 12-month follow-up period.[12]

Decreases in VAS and SPEED scores in the Regener-Eyes®-treated DED patients were documented 3 months after the administration of Regener-Eyes®, while the highest reduction in VAS and SPEED scores in these patients were observed after 12 months of Regener-Eyes®-based therapy, indicating the increasingly beneficial effects of long-term use in alleviation of ocular symptoms in DED patients.[12]

Importantly, Regener-Eyes® was well tolerated. None of 131 Regener-Eyes®-treated DED patients reported any side effects related to the Regener-Eyes® therapy, suggesting that topical application of Regener-Eyes® is a safe and effective therapeutic approach in DED treatment.[12]


MSC-Exos
Eye surface
IL-1Ra
▼pro-inflammatory IL-1R signaling
▼synthesis of chemokines
▼release of chemokines
▼influx of leukocytes in inflamed eye
sTNFRI
sTNFRII
▼TNF-α-dependent inflammatory events in inflamed eyes
▼chemotaxis of DCs
▼chemotaxis of monocytes
▼chemotaxis of lymphocytes
GRO-γ
▼DCs:T cell cross-talk
▲tolerogenic DCs
▲IL-10
▼generation of Th1 lymphocytes
▼generation of M1 macrophages
▼IL-12
▼IFN-γ
▼eye inflammation in DED patients
FABP1
▲tear stability
▲ocular surface epithelial damage
▼dryness
▼grittiness
▼scratchiness
▼soreness
PF4
▲repair of ocular surface epithelial barrier
▲regeneration of ocular surface epithelial barrier

Meibomian gland dysfunction (MGD)/meibomian gland regeneration (MGR)

Meibomian gland dropout and altered meibum secretion were usually seen in the patients suffering from DED.[19–20]

Both congenital and acquired meibomian gland dysfunction (MGD) results in increased tear film osmolarity and leads to the development of evaporative DED.[19–20]

We recently demonstrated the beneficial effects of Regener-Eyes® in the treatment of MGD-related DED.[13]

In one case report, Regener-Eyes® promoted regeneration of injured meibomian glands and efficiently attenuated DED-related symptoms in a patient suffering from MGD.[13]

Before the topical application of Regener-Eyes®, the meibomian ducts of this MGD patient were dilated, exhibiting enlargement and tortuosity.[13]

The morphology of the meibomian glands was significantly improved after 3 weeks of Regener-Eyes® therapy showing the hypo-illuminescent grape-like clusters.

Meibomian gland dysfunction (MGD)/meibomian gland regeneration (MGR)

The morphology of the meibomian glands was significantly improved after 3 weeks of Regener-Eyes® therapy showing the hypo-illuminescent grape-like clusters.

Similarly, hyper-illuminescent ducts tarsus indicated beneficial effects of Regener-Eyes® in restoration of meibomian gland and ducts morphology.[13]

Additionally, Regener-Eyes® significantly improved DED related symptoms in this MGD patient.[13]

Before topical application of Regener-Eyes®, an MGD patient reported foreign body sensation and pain in the eyes, which were accompanied with grittiness, soreness, irritation, burning, and eye fatigue. Importantly, none of these DED-related symptoms were reported by the MGD patient after 3 weeks of Regener-Eyes® therapy.[13]

Meibomian gland dysfunction (MGD)/meibomian gland regeneration (MGR)

Before topical application of Regener-Eyes®, an MGD patient reported foreign body sensation and pain in the eyes, which were accompanied with grittiness, soreness, irritation, burning, and eye fatigue. Importantly, none of these DED-related symptoms were reported by the MGD patient after 3 weeks of Regener-Eyes® therapy.[13]

Significantly improved tear film breakup time (TBUT) was noticed 3 weeks after Regener-Eyes®-based treatment, indicating restoration of meibomian gland function.[13]

Complications such as ocular pain, persistent bleeding, and infections were not observed during or after the administration of Regener-Eyes®. This MGD patient did not report any adverse effects related to the Regener-Eyes®-based therapy, confirming that Regener-Eyes® is well tolerated and safe for topical application.[13]

Sjögren's Syndrome

Approximately 1 of 10 patients suffering from dry eye has underlying Sjögren's syndrome, an autoimmune disease characterized by immune cell-dependent destruction of lacrimal and salivary glands, ocular discomfort, and visual dysfunction.[21]

Since Sjögren's syndrome-related dry eye is a progressive inflammatory condition, it may lead to corneal perforation, uveitis, scleritis, retinal vasculitis, and optic neuritis. Regener-Eyes® contains immunoregulatory, trophic and neuroprotective factors that could attenuate ongoing inflammation in the eye, promote epithelial cell proliferation, and prevent neural injury.

Accordingly, significantly improved visual acuity, relieved ocular pain and complete healing of corneal epithelial defects were noticed in a Regener-Eyes®-treated patient with Sjögren's syndrome.

Similarly, 4 weeks of Regener-Eyes®-based therapy remarkably improved visual acuity and significantly decreased ocular pain in a 26-year-old female who suffered from severe DED and epithelial basement membrane dystrophy (EBMD) with recurrent corneal erosion syndrome (RCES).

Importantly, no recurrence of RCES symptoms were observed in this Regener-Eyes®-treated patient during a follow-up of 4 months, suggesting beneficial effects of Regener-Eyes® in the repair and regeneration of injured corneal epithelial cells.

Conclusions

Regener-Eyes® drops are a topical therapy for DED; they are a bioengineered biological product. The drops contain a large number of anti-inflammatory and trophic factors that attenuate the detrimental immune response in the eye and protect the epithelial cells of the ocular surface from injury and inflammation.[1,9,12–13,15]

Topical administration of Regener-Eyes® may suppress ongoing ocular inflammation, may improve meibomian gland function, and may enhance the restoration of the ocular surface barrier in DED patients, without causing treatment-related adverse events.[1,13]

Due to its immunosuppressive and regenerative properties, Regener-Eyes® should be considered as a powerful new therapeutic option in the management of DED.

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ACUVUE® Theravision® with Ketotifen

- First and only medication-releasing contact lens for patients who need vision correction and itchy eye relief
- Built-in allergy medication that starts to relieve itchy eyes in minutes
- Providing fast-acting and long-lasting relief
  - Up to 12 hours[5]
- Etafilcon A
- Ketotifen –antihistamine (Zaditor and Alaway)
  - Blocks histamine receptors
  - Stabilizes mast cells
  - Inhibits inflammatory cell accumulation within the eye
- Parameters
  - 8.5 mm base curve/14.2 mm diameter
  - Power Ranges
    - –0.50D to –6.00D (0.25D steps)
    - –6.50D to –12.00D (0.50D steps)

Glaucoma

Optometric Education Consultants

Poll 2

I have used netarsudil (Rhopressa or Rocklatan) in my treatment of glaucoma:

A. Yes
B. No
C. I don't treat glaucoma
D. I will place my comment in the chat box

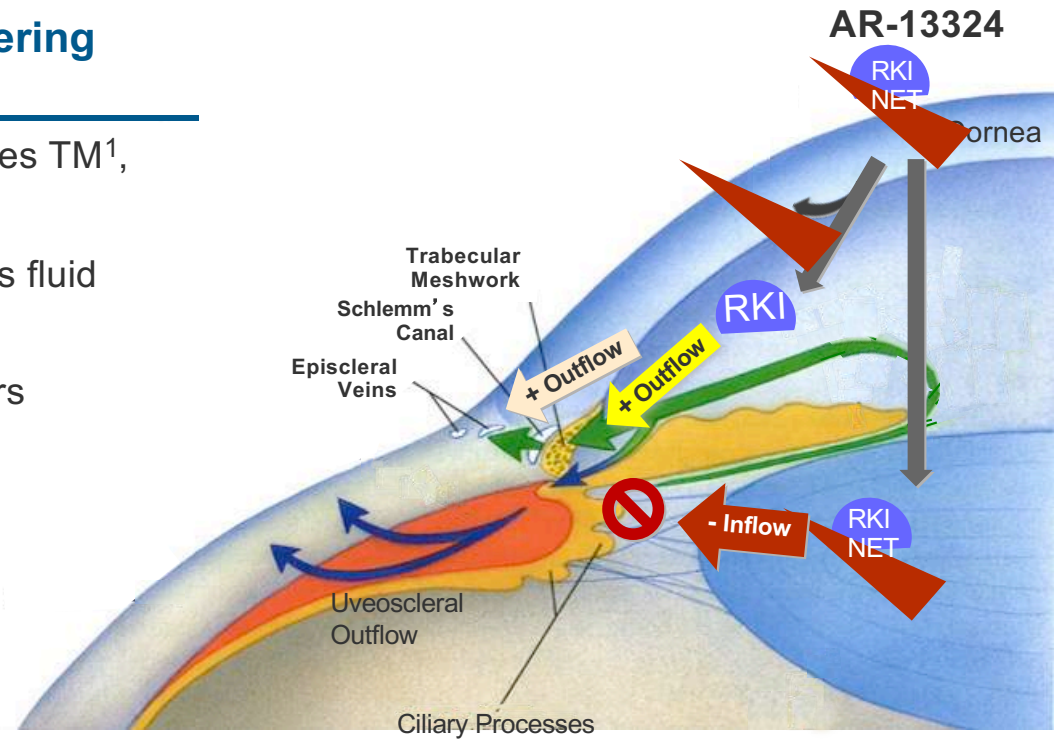
Rhopressa™ 0.02% (netarsudil ophthalmic solution)

- Aerie Pharmaceuticals
  - Approved December 2017
  - Treatment of glaucoma or ocular hypertension
  - Rho kinase inhibitor
    - ROCK-NET Inhibitor
  - Once daily in the evening
    - Twice a day dosing is not well tolerated and is not recommended
  - Side Effects
    - Conjunctival hyperemia
    - Corneal verticillata
    - Conjunctival hemorrhage

Rhopressa (ROCK-NET Inhibitor) Triple-Action

3 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM[1], increases outflow[1,2]
- NET inhibition reduces fluid production[2]
- ROCK inhibition lowers Episcleral Venous Pressure (EVP)[3]



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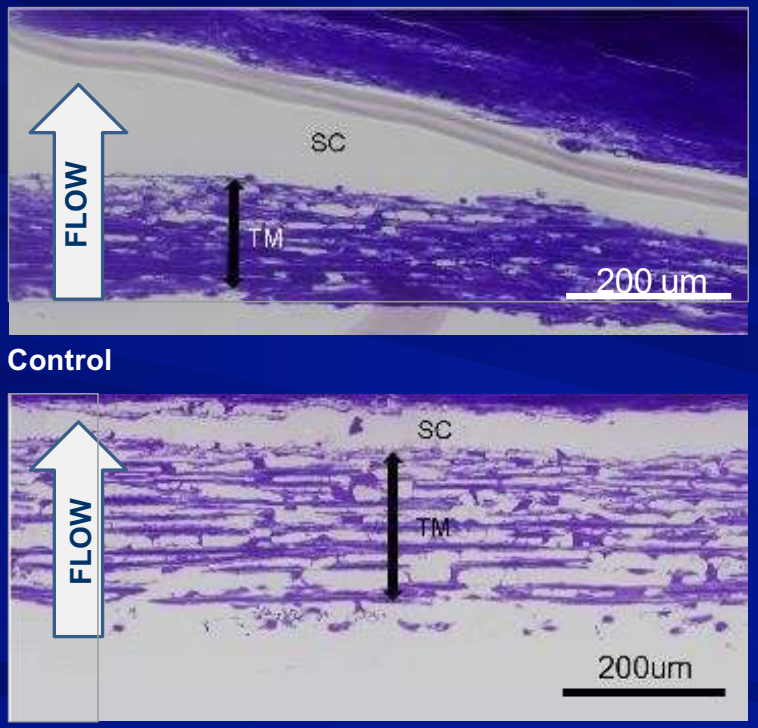
Rhopressa™ 0.02% (netarsudil)

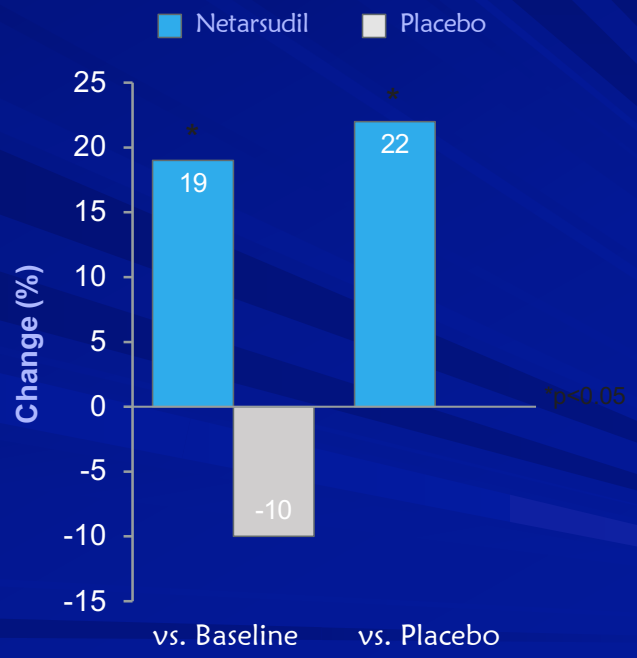
Causes Expansion of TM in Donor Eyes

Increases TM Outflow Facility in Clinic

Trabecular Meshwork (Donor Eyes)[1]



TM Outflow Facility
(Healthy Volunteers)[2]



TM: Trabecular Meshwork; SC: Schlemm's Canal; Control: buffered saline solution; ESV: Episcleral Vein

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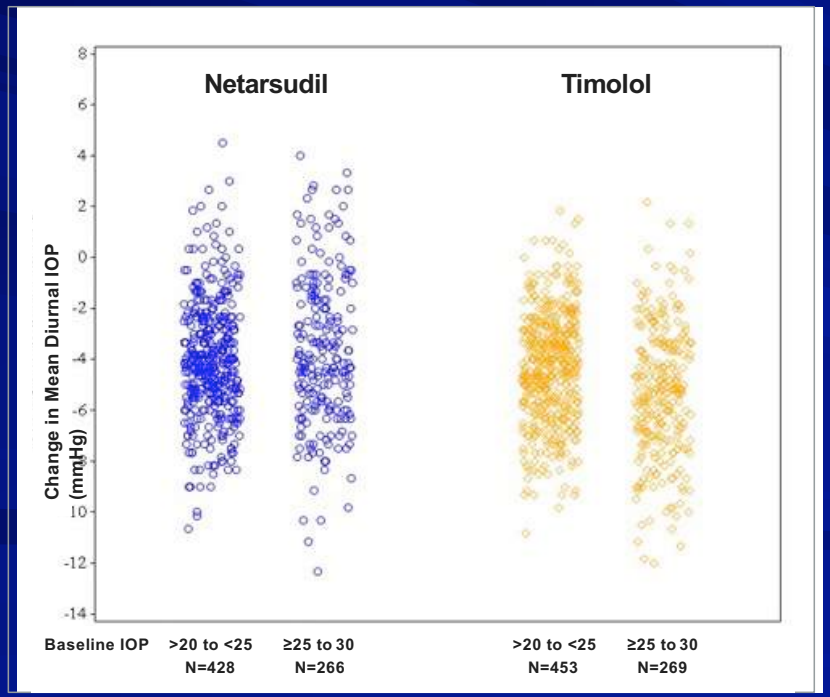
Netarsudil is Similarly Effective at Baseline IOPs <25 mmHg and ≥25 mmHg

Pooled Analysis Rocket 1, Rocket 2, Rocket 4

Day 90: Change from Baseline IOP by Baseline Subgroup (Pooled)



Baseline IOP >20 to <25 mmHg

	Netarsudil QD	Timolol BID
Median	-4.2	-4.3
Mean	-4.1	-4.3
Max	-10.7	-10.8

Baseline IOP ≥25 to <30 mmHg

	Netarsudil QD	Timolol BID
Median	-4.0	-5.3
Mean	-3.7	-5.3
Max	-12.3	-12.0

Rhopressa™ 0.02%

- No labeled contraindications for Rhopressa™
- No clinically relevant effects on vital signs
  - Blood Pressure
    - Changes were generally small and not clinically relevant in both groups
  - Heart Rate
    - Timolol caused statistically significant reduction in the phase 3 studies by an average of 2-3 beats per month

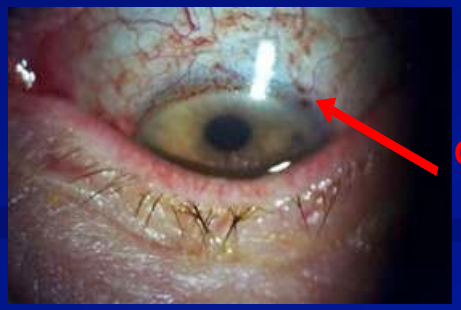
1. RHOPRESSA® (netarsudil ophthalmic solution) 0.02% Prescribing Information. 2. Khouri et al. Association for Research in Vision and Ophthalmology oral presentation 2017 [E-abstract 2461].

Conjunctival Hemorrhage was Sporadic and Severity did not Increase with Continued Dosing

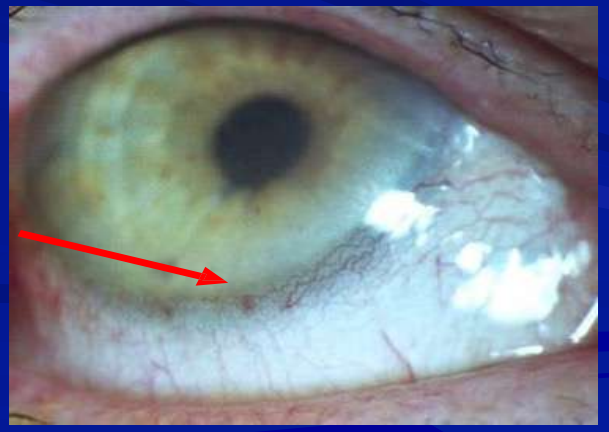
Adverse Events	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
TEAE Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
AE Resulting in Discontinuation	8 (1.0)	0

Majority 92.4% (133/144) of the conjunctival hemorrhage in netarsudil QD group was mild, 6.3% (9/144) was moderate and 1.4% (2/144) was severe

Self-resolving with continued dosing



Conjunctival hemorrhage

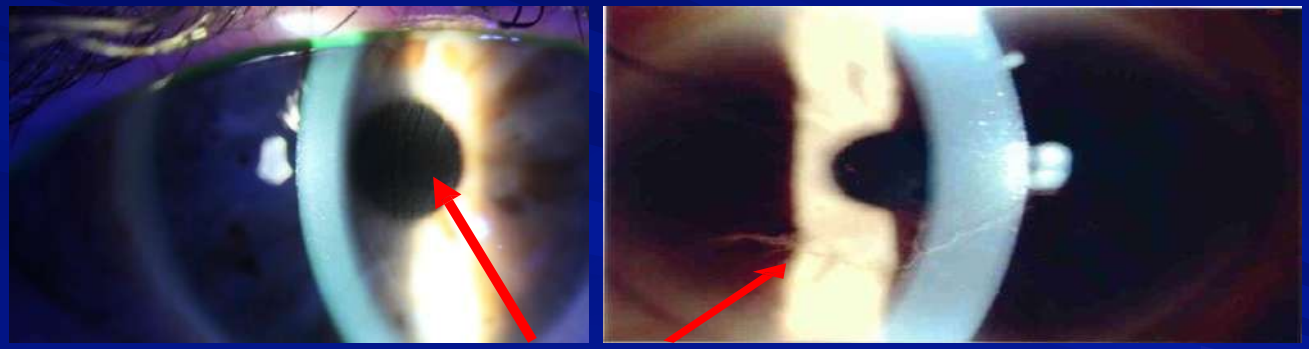


Images were taken from netarsudil subjects

Source: Courtesy of study investigators AR-13324-CS301, -CS302

Cornea Verticillata Observed in Phase 3 Studies

- Cornea verticillata refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium
- Subjects are asymptomatic
- The onset was ~6 to 13 weeks (netarsudil QD)



Cornea verticillata

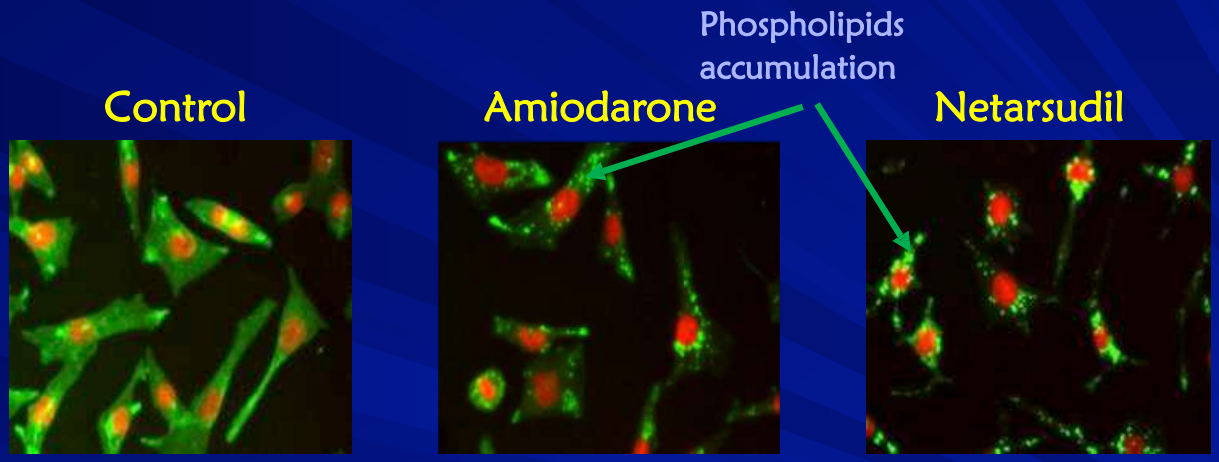
AR-13324-CS302
netarsudil QD subject

AR-13324-CS302
netarsudil BID subject

Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS302

Cornea Verticillata Due to Phospholipidosis

Medications known to cause verticillata: amiodarone, chloroquine, naproxen, phenothiazine, ocular gentamicin and tobramycin*

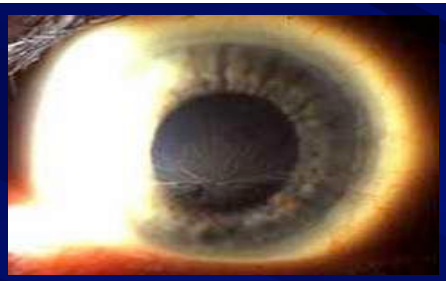


Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes

Literature review suggested it is an adaptive response by the body rather than an adverse pathology*

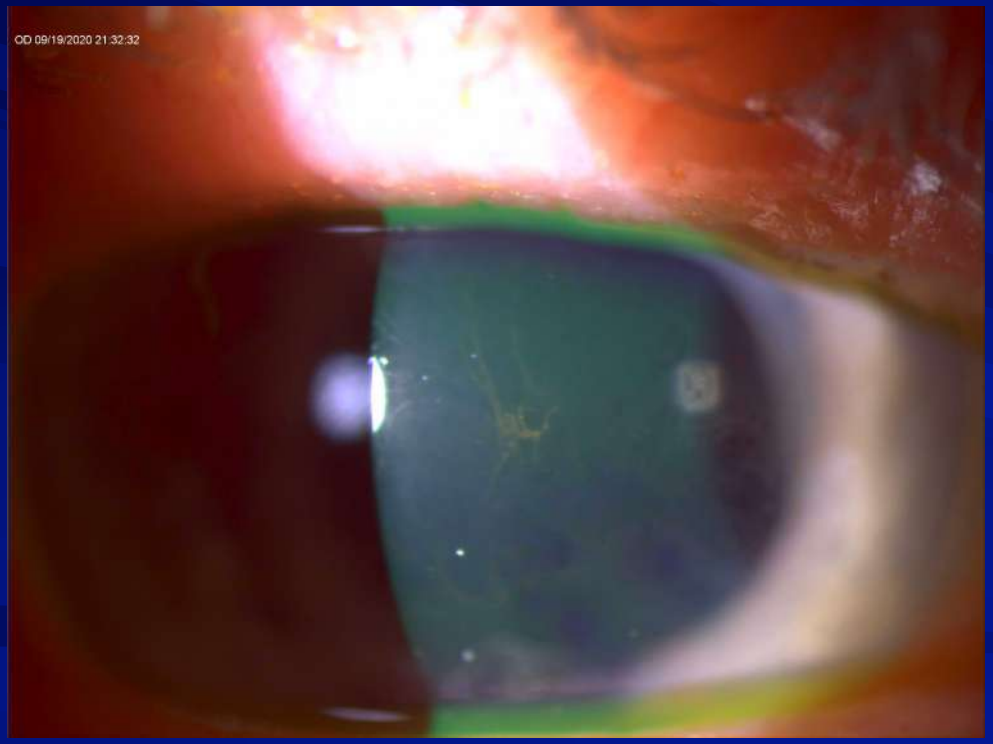
Data on File Based on AR-13324-IPH07

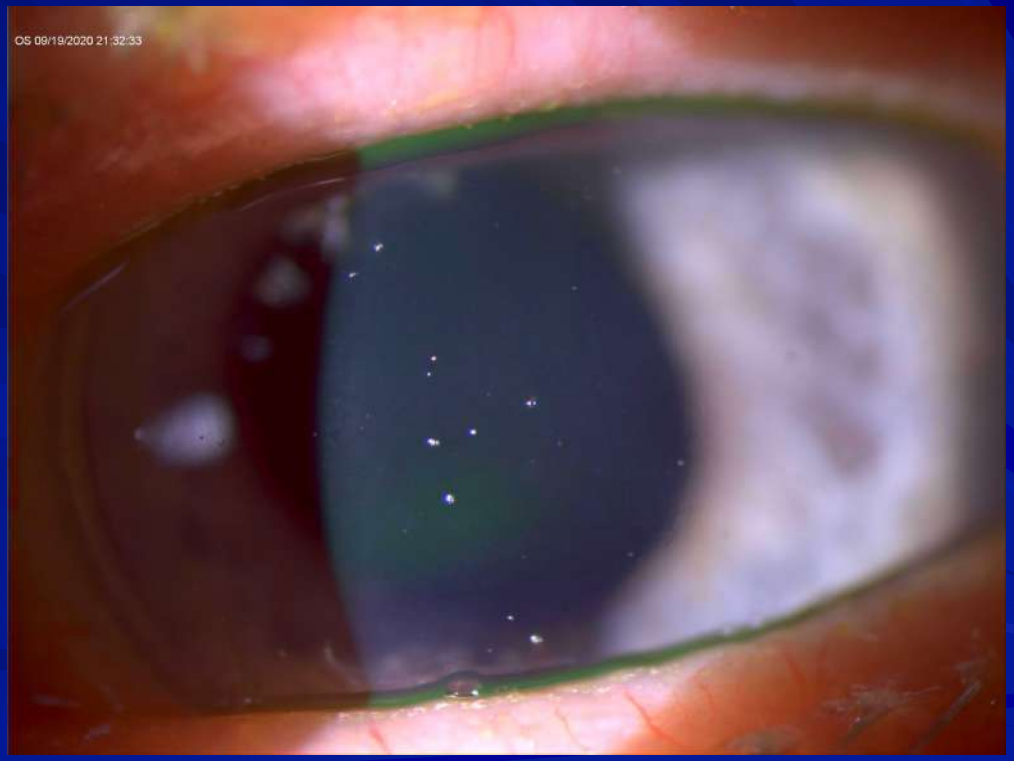
* Raizman MB et al. Surv. Ophthalmol. 2017;62:286-301



My Experience

OD treated OS gtts





Summary of the Most Common Netarsudil Ocular TEAEs

Conjunctival Hyperemia

- 54.4% TEAE
- Severity did not increased with continued dosing
- Sporadic

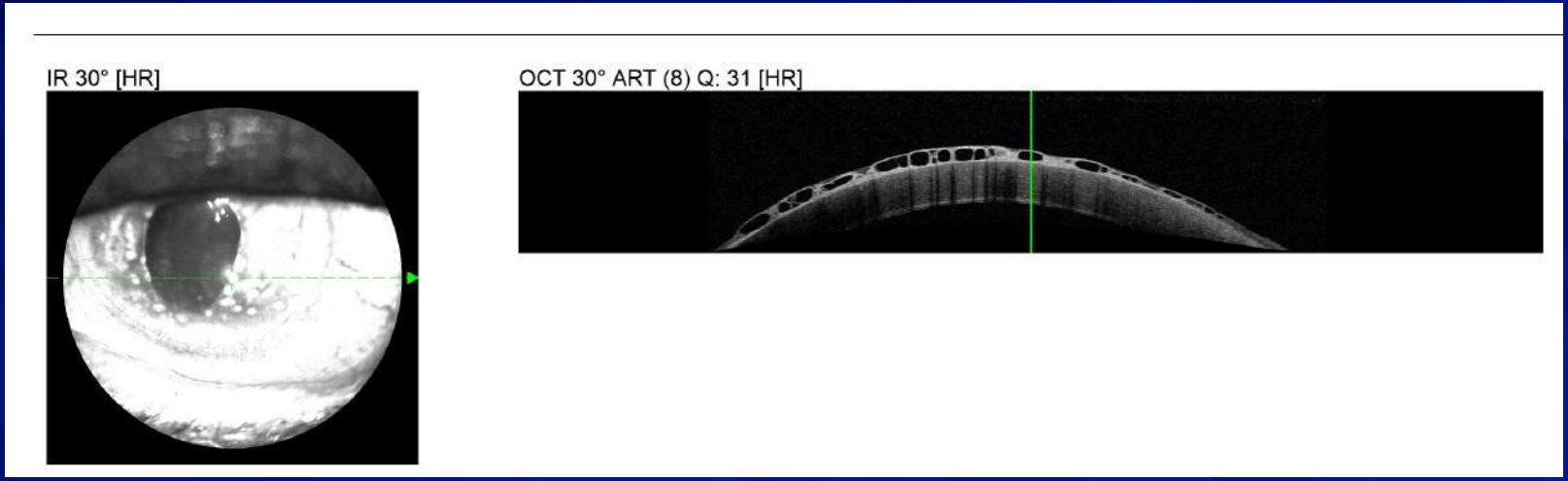
Cornea Verticillata

- 20.9% TEAE
- Asymptomatic
- 7.4% experienced reduced visual acuity
- Not clear to a directly associated
- All resolved after 13 weeks of D/C

Conjunctival Hemorrhage

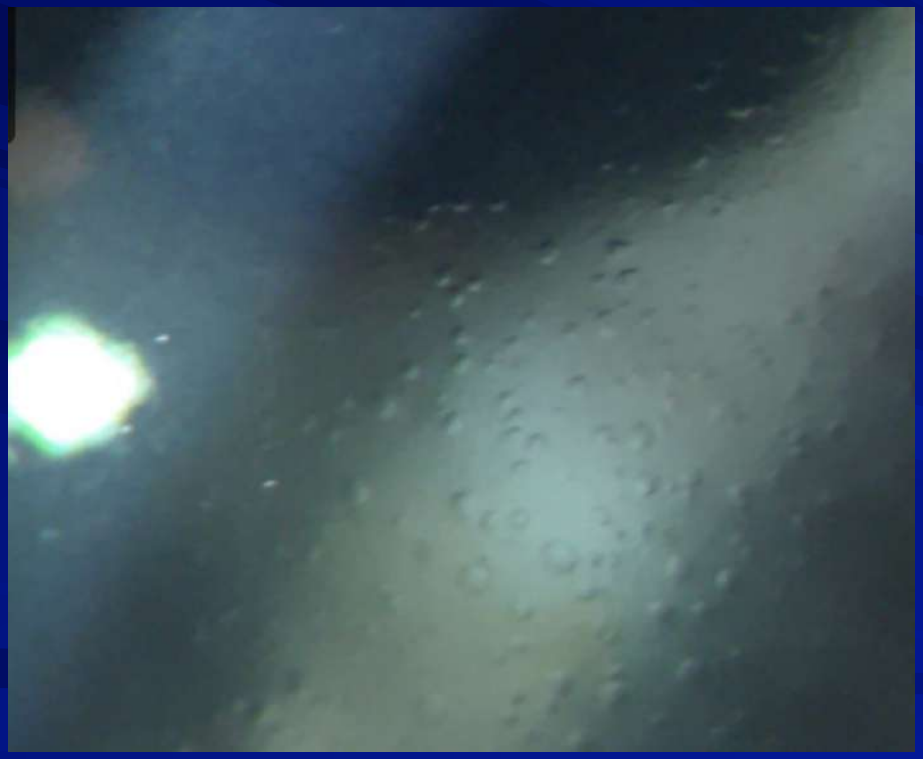
- 17.2% TEAE
- Mild in severity and transient
- Self-resolving with continued dosing

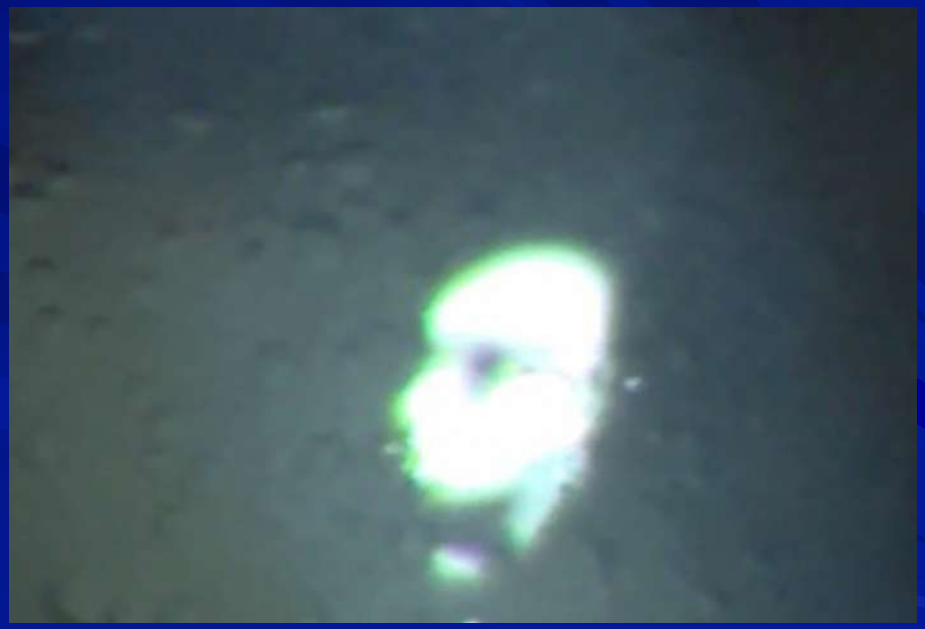
Honeycomb Epithelial Edema Associated With Rho Kinase Inhibition



- Thank you, Charles McBride, O.D., Beaverton, OR (12-23-2020 OGS – Google Groups)
- Sample of Rocklatan yesterday to lower his IOP of 46mmHg
- IOP today was 34
- Didn't measure corneal thickness
- The eye is blind and pretty sure it is neovascular glaucoma
- He's not been seen in three years and recently relocated from Missouri

Honeycomb Epithelial Edema Associated With Rho Kinase Inhibition Graft Patient





Thank you! Joe Shovlin, OD, FAAO

Rocklatan™

(netarsudil/latanoprost ophthalmic solution)
0.02%/0.005%

- Aerie pharmaceuticals
  - ★ March 14, 2019
- Once-daily eye drop
- First PGA combination approved
  - ★ Superiority versus inferiority
- Refrigeration
  - ★ Storage and after opening
    - For now

Vyzulta™ (latanoprostene Bunod) Ophthalmic Solution 0.024%

- Bausch & Lomb
  - previously Vesneo™
- November 2, 2017; approved
- Indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
- Once daily monotherapy
- Dual mechanism of action
  - Uveoscleral pathway to increase aqueous humor outflow
  - Butanediol mononitrate, which releases NO to increase outflow through the trabecular meshwork and Schlemm's canal.
- Ocular adverse events
  - Conjunctival hyperemia, eye irritation, eye pain and instillation site pain
  - Increased pigmentation of the iris and periorbital tissue and growth of eyelashes can occur

Durysta™ (Bimatoprost Implant)

- Allergan
  - Approved May 23, 2020
- Indication: Intracameral administration for the reduction of intraocular pressure in patients with Open Angle Glaucoma or Ocular Hypertension
- Sustained-Release, biodegradable intracameral Implant
- Intracameral implant containing 10 mcg in the drug delivery system
- Contraindications:
  - Active or suspected ocular or periocular infections
  - Corneal endothelial cell dystrophy (e.g. Fuch's Dystrophy)
  - Prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasy [DSAEK])
  - Absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment
  - Hypersensitivity to bimatoprost or any other components of the product

Durysta™ (Bimatoprost Implant)

- Warnings and Precautions
  - ★ Corneal adverse reactions
    - Bimatoprost implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss
  - ★ Iridocorneal angle:
    - Bimatoprost implant should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3)
    - Anatomical obstruction (e.g. scarring) that may prohibit settling in the inferior angle
  - ★ Macular edema
    - Bimatoprost implant should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema
  - ★ Intraocular inflammation
  - ★ Pigmentation
  - ★ Endophthalmitis

Durysta™ (Bimatoprost Implant)

- Dosage and Administration
  - Bimatoprost implant is an ophthalmic drug delivery system for a single intracameral administration of a biodegradable implant
  - Should not be readministered to an eye that received a prior bimatoprost implant
    - On label
- Efficacy
  - Demonstrated in two Phase 3 studies
  - IOP reduction of approximately 5 - 8 mmHg
  - In patients with a mean baseline IOP of 24.5 mmHg

Optometric Education Consultants

Poll 3

Did Combigan go generic?

A. Yes
B. No
C. I don't treat glaucoma
D. I will place my comment in the chat box

April 19, 2022

Screenshot from Pharmacompass

Pictures Taken February 21, 2022

2-2-2022

Screenshot from Carlisle Medical

Generic Release Of Combigan Is Now Available

Released: 02/02/2022

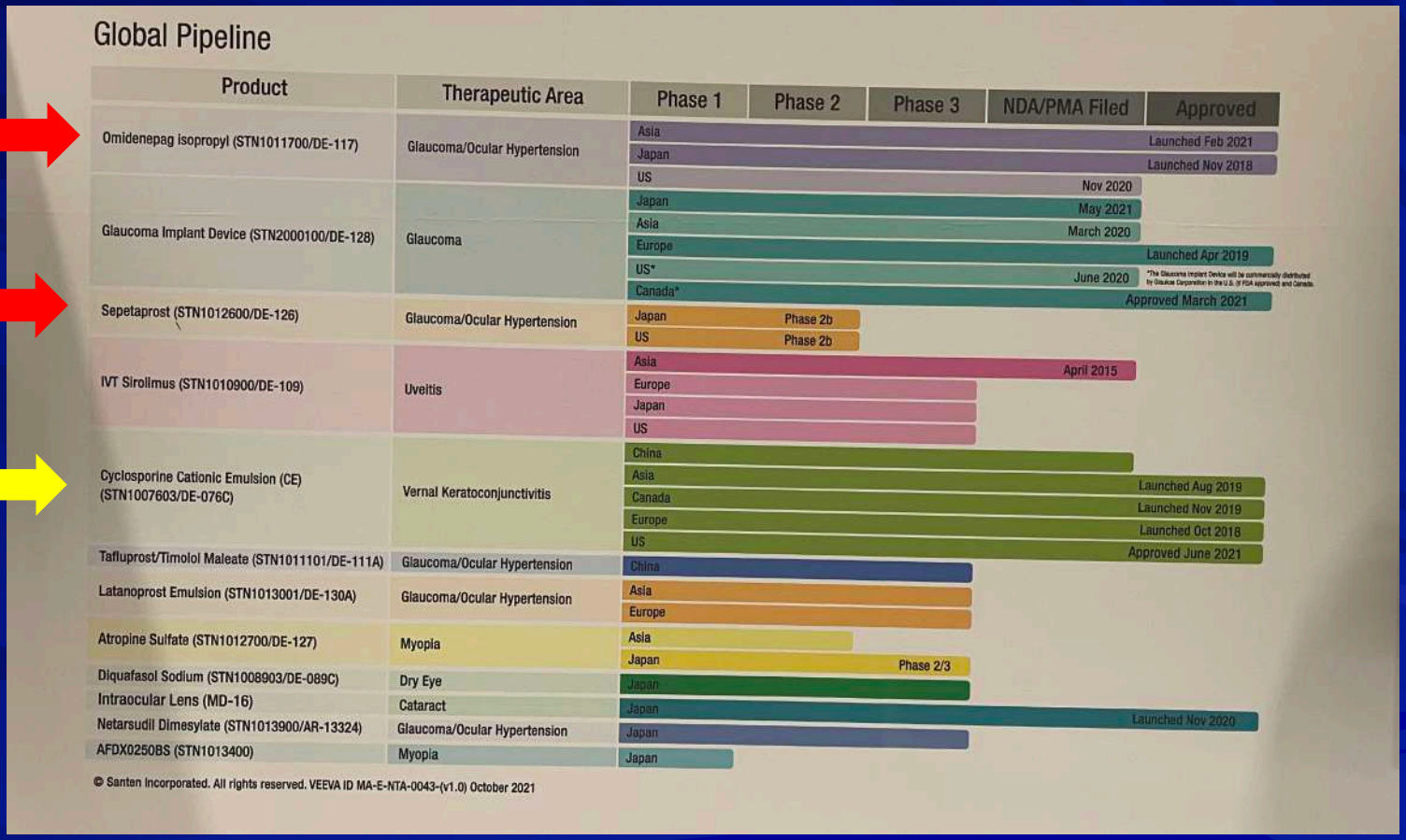
Apotex Corporation has launched the authorized generic version of Combigan® (Brimonidine Timolol OPSO 0.2%/0.5%) in the United States.

Brimonidine Timolol is indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension. Brimonidine Timolol is now available in 5ML, 10ML and 15ML bottles.

Generic prescription drugs approved by the FDA have the same high quality and strength as brand name drugs. Generic prescription drug manufacturing and packaging sites must pass the same quality standards as those of brand name drugs.

If you have any questions or if we may assist you with your pharmacy needs, please contact us at 800-553-1783 or at pharmacy@carlislemedical.com.

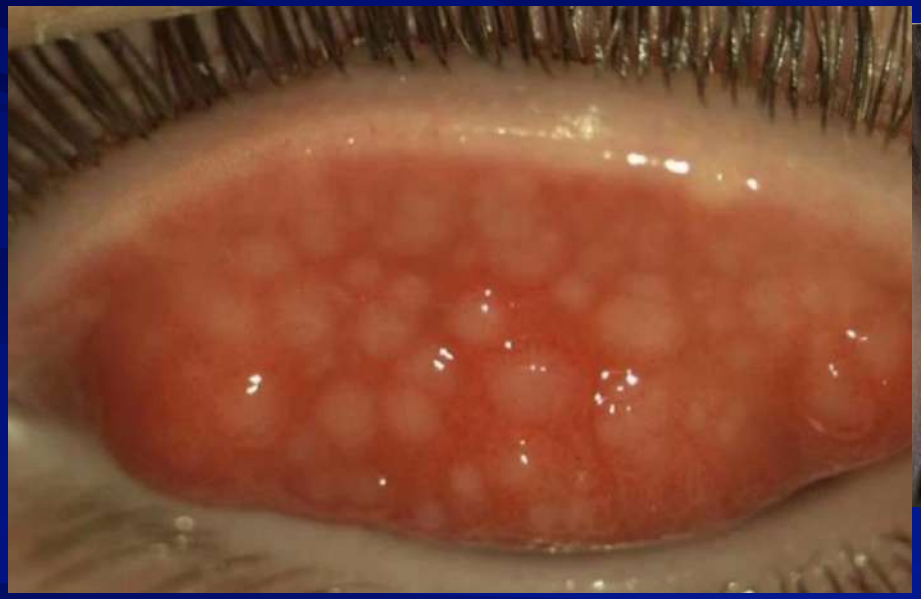
What is Coming?

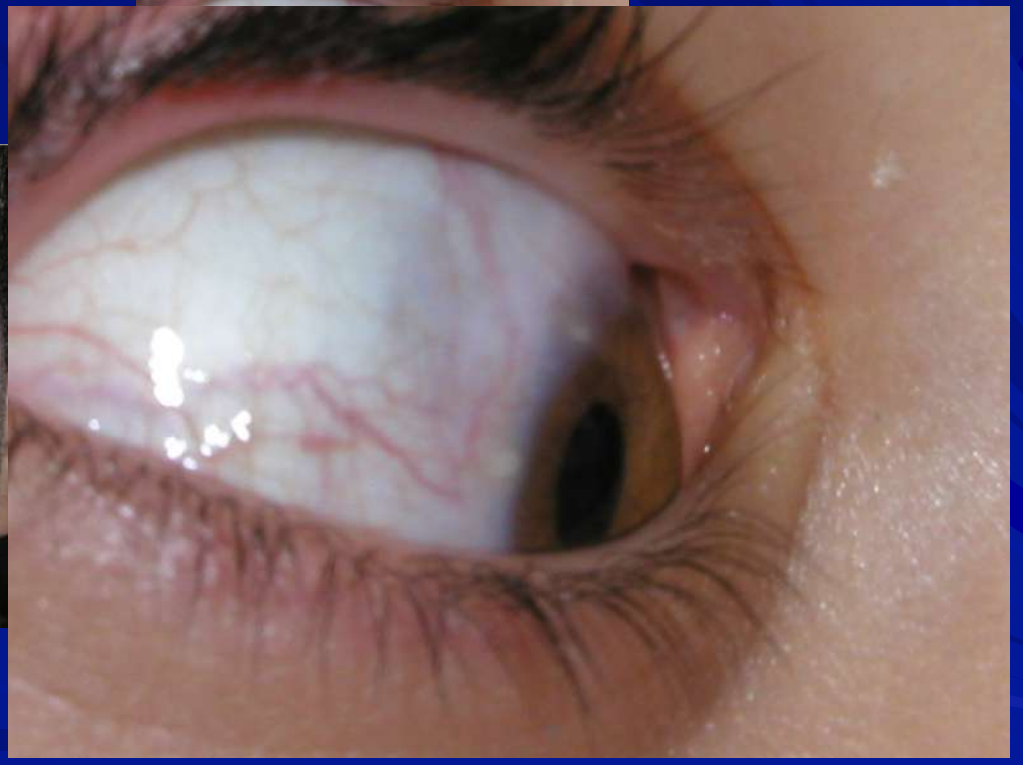


Global Pipeline

Product	Therapeutic Area	Phase 1	Phase 2	Phase 3	NDA/PMA Filed	Approved
Omidenepag isopropyl (STN1011700/DE-117)	Glaucoma/Ocular Hypertension	Asia				Launched Feb 2021
		Japan				Launched Nov 2018
		US			Nov 2020	
Glaucoma Implant Device (STN2000100/DE-128)	Glaucoma	Japan			May 2021	
		Asia			March 2020	
		Europe				Launched Apr 2019
		US*			June 2020	
		Canada*				Approved March 2021
Sepetaprost (STN1012600/DE-126)	Glaucoma/Ocular Hypertension	Japan	Phase 2b			
		US	Phase 2b			
IVT Sirolimus (STN1010900/DE-109)	Uveitis	Asia			April 2015	
		Europe				
		Japan				
		US				
Cyclosporine Cationic Emulsion (CE) (STN1007603/DE-076C)	Vernal Keratoconjunctivitis	China				
		Asia				Launched Aug 2019
		Canada				Launched Nov 2019
		Europe				Launched Oct 2018
		US				Approved June 2021
Tafluprost/Timolol Maleate (STN1011101/DE-111A)	Glaucoma/Ocular Hypertension	China				
Latanoprost Emulsion (STN1013001/DE-130A)	Glaucoma/Ocular Hypertension	Asia				
		Europe				
Atropine Sulfate (STN1012700/DE-127)	Myopia	Asia				
		Japan		Phase 2/3		
Diquafasol Sodium (STN1008903/DE-089C)	Dry Eye	Japan				
Intraocular Lens (MD-16)	Cataract	Japan				Launched Nov 2020
Netarsudil Dimesylate (STN1013900/AR-13324)	Glaucoma/Ocular Hypertension	Japan				
AFDX0250BS (STN1013400)	Myopia	Japan				

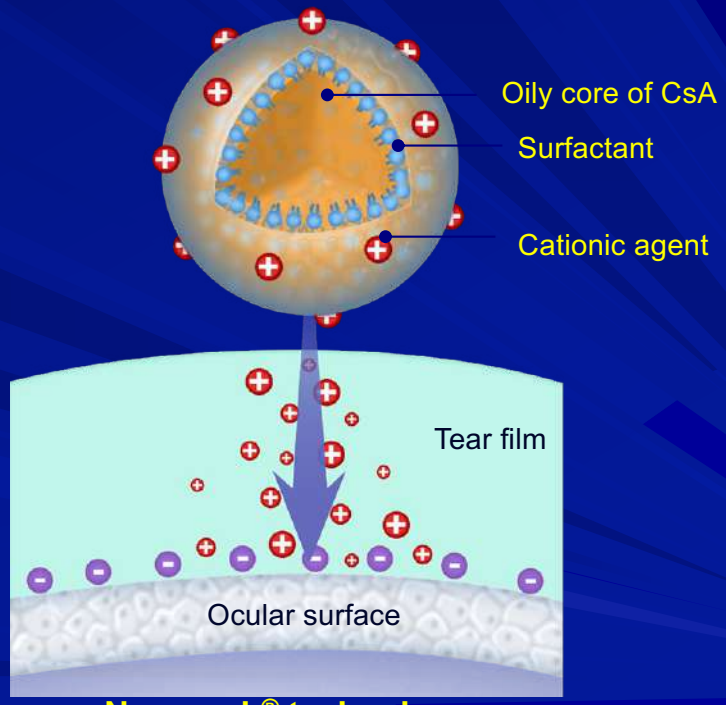
*The Glaucoma Implant Device will be commercially distributed by Glaukos Corporation in the U.S. (if FDA approved) and Canada.





Verkazia – cyclosporine ophthalmic emulsion 0.1%

- Approved June 2021 – Santen
- Coming March/April 2022
- Treatment of Vernal Keratoconjunctivitis (VKC)
- NOVASORB® Technology
- Novasorb® is a positively charged nanoemulsion containing droplets of CsA in an aqueous phase. Each droplet has an oily core which solubilizes the CsA and a coating of surfactants to stabilize the emulsion2
- The positively charged droplets are attracted to the negatively charged cell membranes of the ocular surface structures, which helps Verkazia to spread, increase ocular residence time, and improves its absorption1-3



Novasorb® technology

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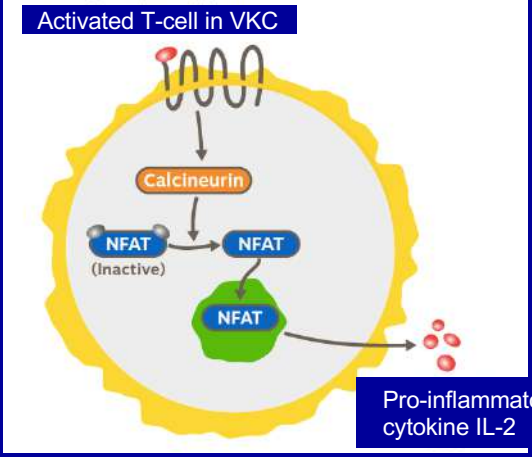
Verkazia – cyclosporine ophthalmic emulsion 0.1%

- Indication: For the treatment of VKC in children and adults
- Dosage and administration
  - One drop administered four times daily (morning, noon, afternoon, and evening) into each affected eye
  - Drops should be milky white
  - Immediately after use, discard the remaining contents from the single-dose vials
  - Treatment can be discontinued after signs and symptoms are resolved and can be reinitiated if there is a recurrence

Verkazia® Proposed Mechanism of Action

Verkazia® contains cyclosporine, an immunomodulatory agent that disrupts inflammation and allergic responses[1]

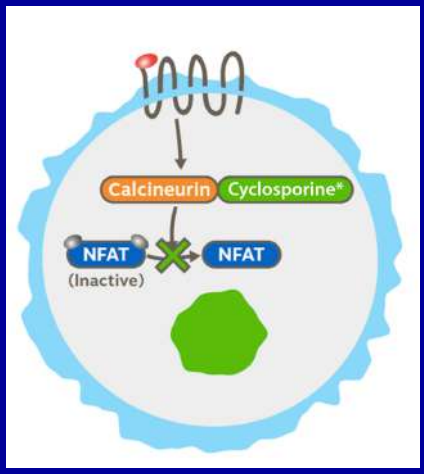
Calcineurin stimulates the pro-inflammatory T-cell response



Additional anti-inflammatory effects of cyclosporine include[2]:

- Inhibition of histamine release from mast cells
- Interfering in the allergy process
- Increased expression of anti-inflammatory cytokines

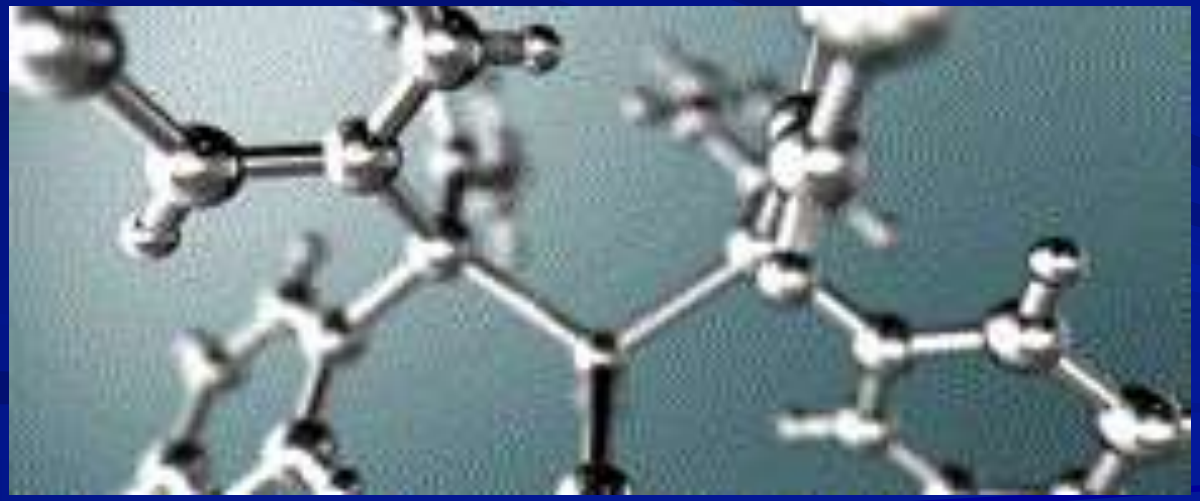
Cyclosporine inhibits calcineurin and blocks pro-inflammatory cytokines



Cyclosporine is bound by the cyclophilin family of proteins within T-cells. IL, interleukin; NFAT, nuclear factor of activated T-cells.

1. Verkazia® (cyclosporine ophthalmic emulsion) 0.1%, for topical ophthalmic use [package insert]. Emeryville, CA: Santen Inc. 2021. 2. Leonardi A. *Ophthalmol Ther.* 2013;2:73-88.

Adrenergic Alpha Receptor Agonists



Adrenergic Alpha Receptor Agonists

- Iopidine 0.5%, 1.0%
  - Apraclonidine
- Alphagan and Alphagan P - 0.2%, 0.15%, and 0.10%
  - Brimonidine tartrate
  - IOP lowering and miosis
- Lumify 0.025%
  - brimonidine tartrate
  - Redness reducer, no pupil response
- Naphcon-A 0,025%
  - Naphazoline hydrochloride 0.025%
  - Acting on alpha-adrenergic receptors in the arterioles of the conjunctiva
- Visine 0.05%
  - Tetrahydrozoline HCl
- Upneeq 0.1%
  - Oxymetazoline hydrochloride
- Oxymetazoline hydrochloride
  - OTC nasal spray
    - 0.05% solution
- OTC eye drops
  - 0.025% solution
- RX topical cream
  - 1% cream
  - Rosacea

Optometric Education Consultants

Poll 4

I have used Upneeq (oxymetazoline HCl) ophthalmic solution 0.1% on my patients:

A. Yes
B. No
C. I will place my comment in the chat box

UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

- Osmotica Pharmaceuticals
  - RVL, Trigen, and Veritical
  - Approved July 9, 2020
- Indicated for the treatment of acquired blepharoptosis in adults
  - Non-surgical treatment for acquired blepharoptosis
- Preservative-free balanced salt solution containing hypromellose
- Warning and Precautions
  - Alpha-adrenergic agonists as a class may impact blood pressure
  - Advise UPNEEQ patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to seek medical care if their condition worsens
  - Use UPNEEQ with caution in patients with cerebral or coronary insufficiency or Sjögren's syndrome
  - UPNEEQ may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma

UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

- Adverse reactions
  - 1-5% of subjects treated with UPNEEQ were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation and headache
- Drug interactions
  - Alpha-adrenergic agonists, as a class, may impact blood pressure.
  - Caution in using drugs such as beta-blockers, anti-hypertensives, and/or cardiac glycosides is advised
  - Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy

Mechanism of Action

- **Oxymetazoline** is a potent, direct-acting α-adrenergic receptor agonist with a **~5:1 affinity for α2:α1 receptors**[1,2,3]
- When applied to the eye, UPNEEQ is thought to stimulate **contraction of Müller's muscle**, raising the upper eyelid

UPNEEQ™

Selectively activates receptors in Müller's muscle

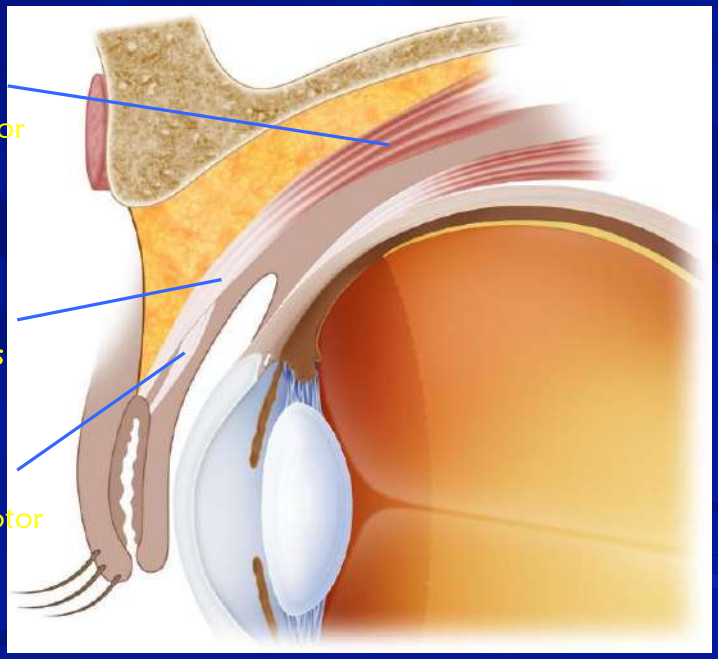
Levator palpebrae superioris

↑ β_1 adrenergic receptor expression[4]

Levator aponeurosis

Müller's muscle

↑ α_2 adrenergic receptor expression[4]



References: 1. Haenisch B, Walstab J, Herberhold S, et al. Alpha-adrenoceptor agonistic activity of oxymetazoline and xylometazoline. *Fundam Clin Pharmacol.* 2010;24(6):729-739. **2.** Sugden D, Anwar N, Klein D. Rat pineal α1-adrenoceptor subtypes: studies using radioligand binding and reverse transcription-polymerase chain reaction analysis. *Br J Pharmacol.* 1996;118(5):1246-1252. **3.** Hosten LO, Snyder C. Over-the-counter ocular decongestants in the United States – mechanisms of action and clinical utility for management of ocular redness. Clin Optom. 2020;12:95-105. **4.** Esmaeli-Gutstein B, Hewlett B, Pashby R, Oestreicher J, Harvey J. Distribution of adrenergic receptor subtypes in the retractor muscles of the upper eyelid. *Ophthalmic Plast Reconstr Surg.* 1999;15(2):92–99.

UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

- Dosing: One drop administered topically to ptotic eye(s), once per day
- Met both primary and secondary efficacy endpoints in phase 3 studies
  - ★ Once-daily resulted in significant improvement
    - Upper visual field
    - Upper eyelid elevation (MRD-1)
  - ★ Upper eyelid elevation was rapid and sustained
    - Significant improvement evident within 5 minutes of instillation in one study
    - Peak effect – 1 hour
    - Lasts – 8 hours

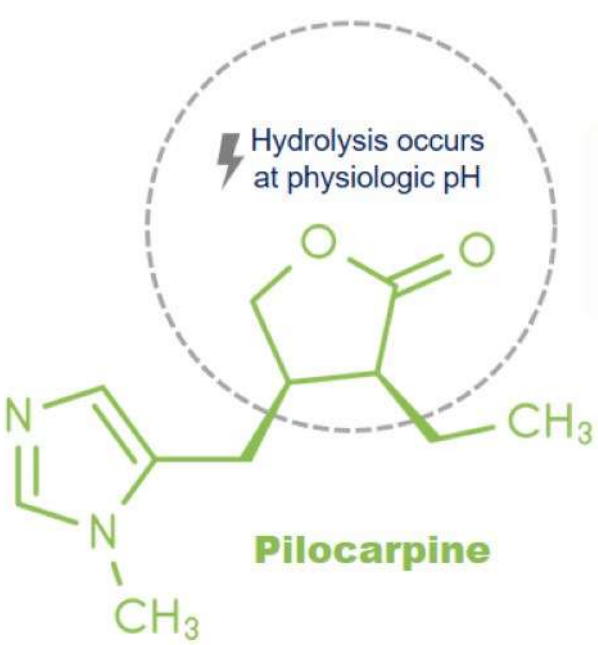
UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

Vuity – Pilocarpine 1.25%

- Approved October 29, 2021
- Indication: Cholinergic muscarinic receptor agonist indicated for the treatment of presbyopia in adults
- Dosage: QD
- Warnings: Poor illumination and iritis, RD?
- Significant amount of Rx's written since launched
  - Optometry is leading the charge in writing for Vuity
- $79 is the cost at most pharmacies
- My Vuity Points
  - Buy 4 the 5th is free
- UpScript
  - Online pharmacy
  - Direct ship to the patient
- Re-engineered design of pilocarpine, optimized concentration, pHast technology
- Efficacy – 3 line gain, significant improvement for intermediate/device vision
- Safe: 1.3% discontinuation rate due to adverse effects

All Pilocarpine formulations are stored at low pH to maintain stability[1-3]



Store at low pH for stability

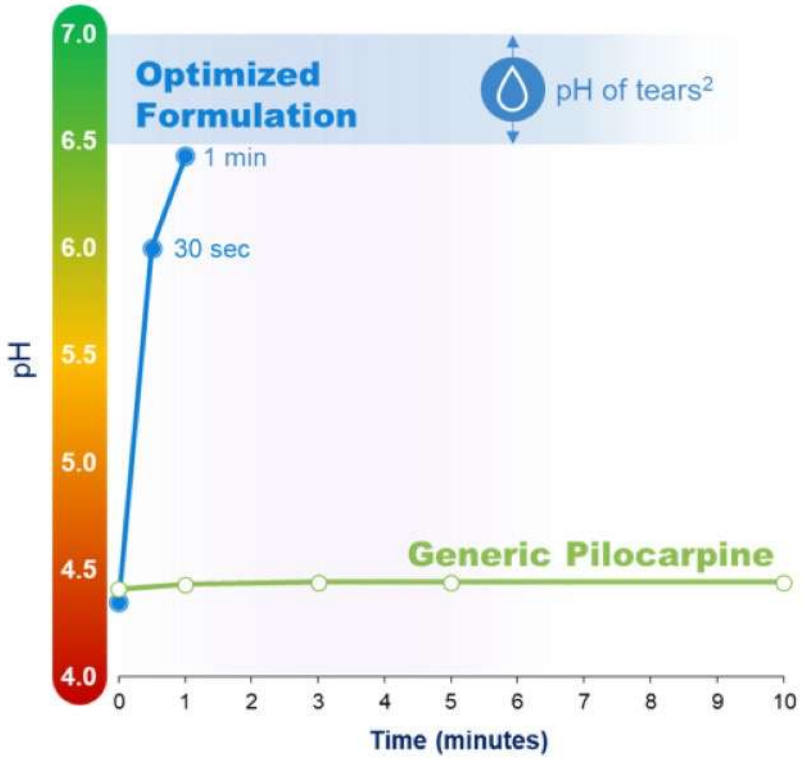
LOWER BIOAVAILABILITY AT pH 4.0 *(vs pH 6.5)*

Charged pilocarpine has challenges penetrating the cornea

Irritant effect of acidity increases tear fluid flow

[1]Jain et al. *Drug Delivery*. 2020;27(1):888–899.
[2]Mitra et al. *J Pharmaceutical Sci*. 1988;77:771-775.
[3]Anderson RA, Cowle JB. *Br J Ophthalmol*. 1968;52:607-611.

Optimized Formulation Rapidly Adjusts to Neutral pH After Administration

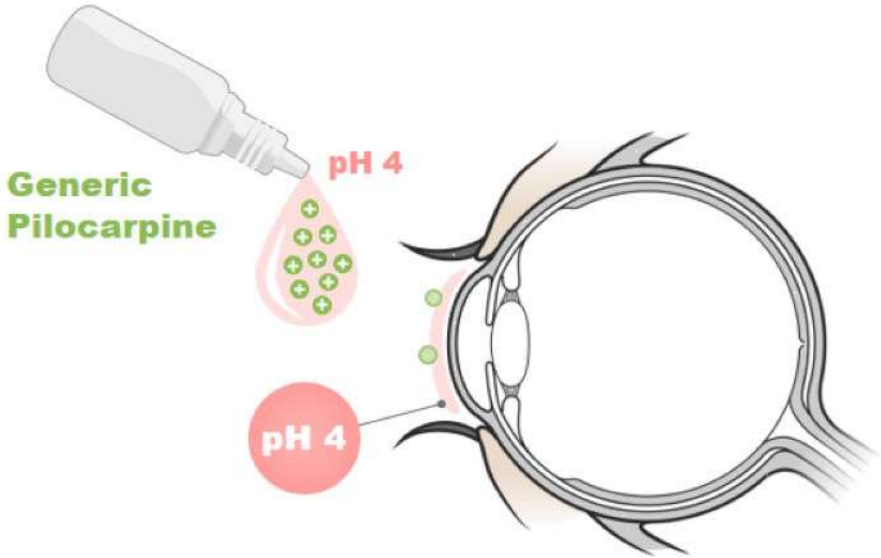


= The **Optimized Formulation with pHast™ Technology** equilibrated to physiologic pH within 1 minute[1]

In vitro studies showed that the pH of **Generic Pilocarpine** did not reach physiologic pH in simulated tear fluid, even after 10 minutes[1]

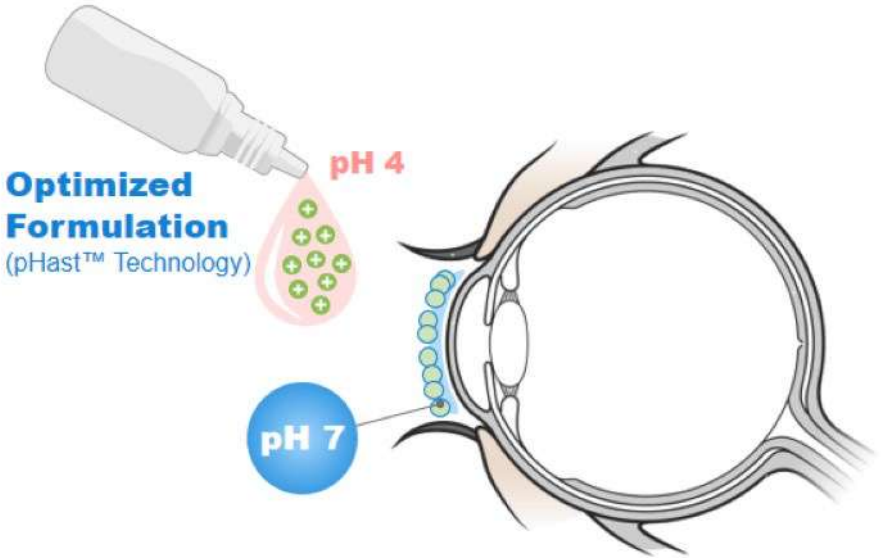
[1]Giyanani JS, et al. AAPS 2020; 895110.
[2]Abelson MB, Udell IJ, Weston JH. *Arch Ophthalmol.* 1981;99(2):301. doi: 10.1001/archopht.1981.03930010303017.

Optimized Formulation Improves Bioavailability and Tolerability[1-4]



Slower mixing and equilibrium with tears

- Lower ocular bioavailability
- Higher incidence of burning, stinging and blur

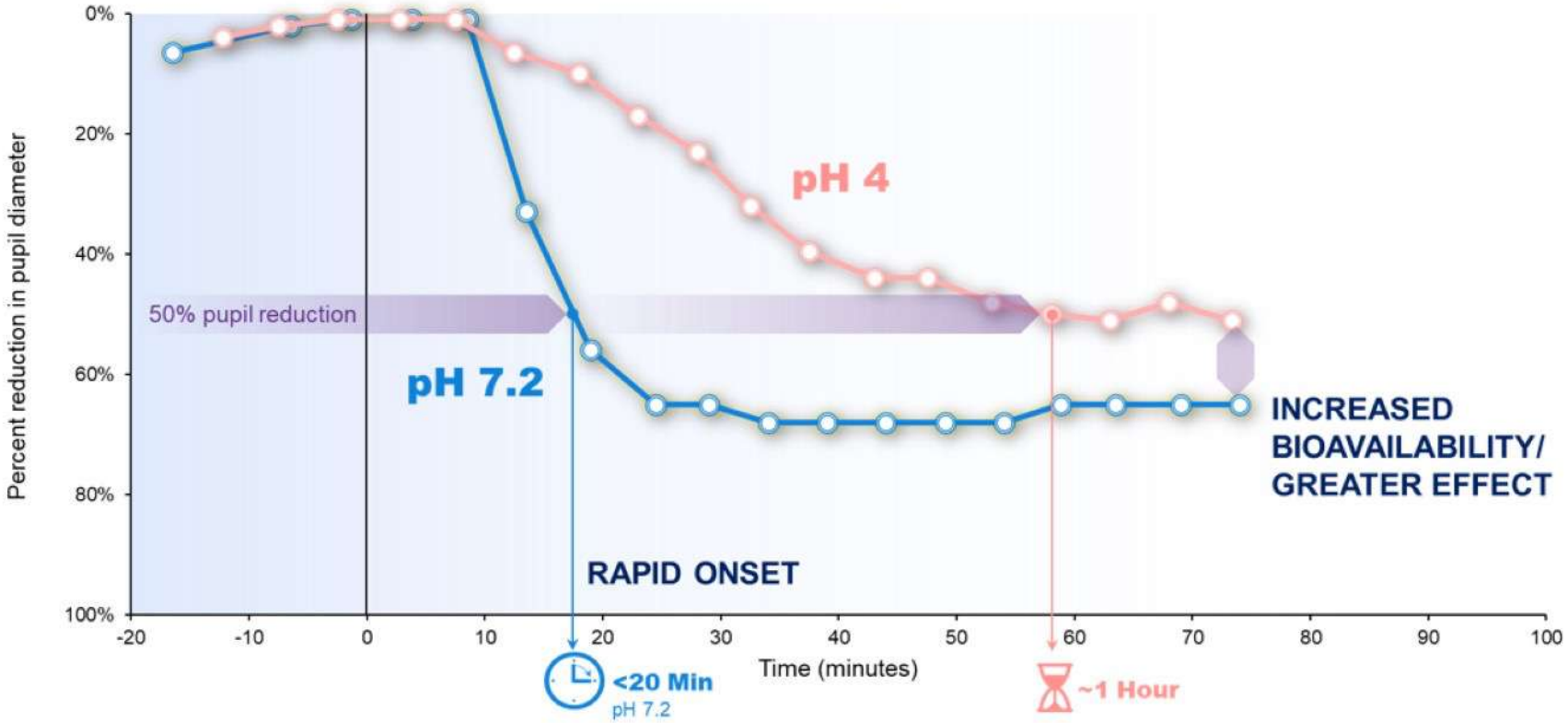


Rapid equilibrium to ocular surface pH:

- Increase ocular bioavailability
- Improved tolerability and comfort

[1]Jain et al. *Drug Delivery*. 2020;27(1):888–899.
[2]Mitra et al. *J Pharmaceutical Sci*. 1988;77:771-775.
[3]Giyanani JS, et al. AAPS 2020; 895110.
[4]Anderson et al. *Br J Ophthalmol*. 1968;52:607.

The pH of Pilocarpine Affects Its Onset of Action and Bioavailability[1]



[1]Birmingham AT, et al. *Brit J Ophthalmol.* 1976;60:568.

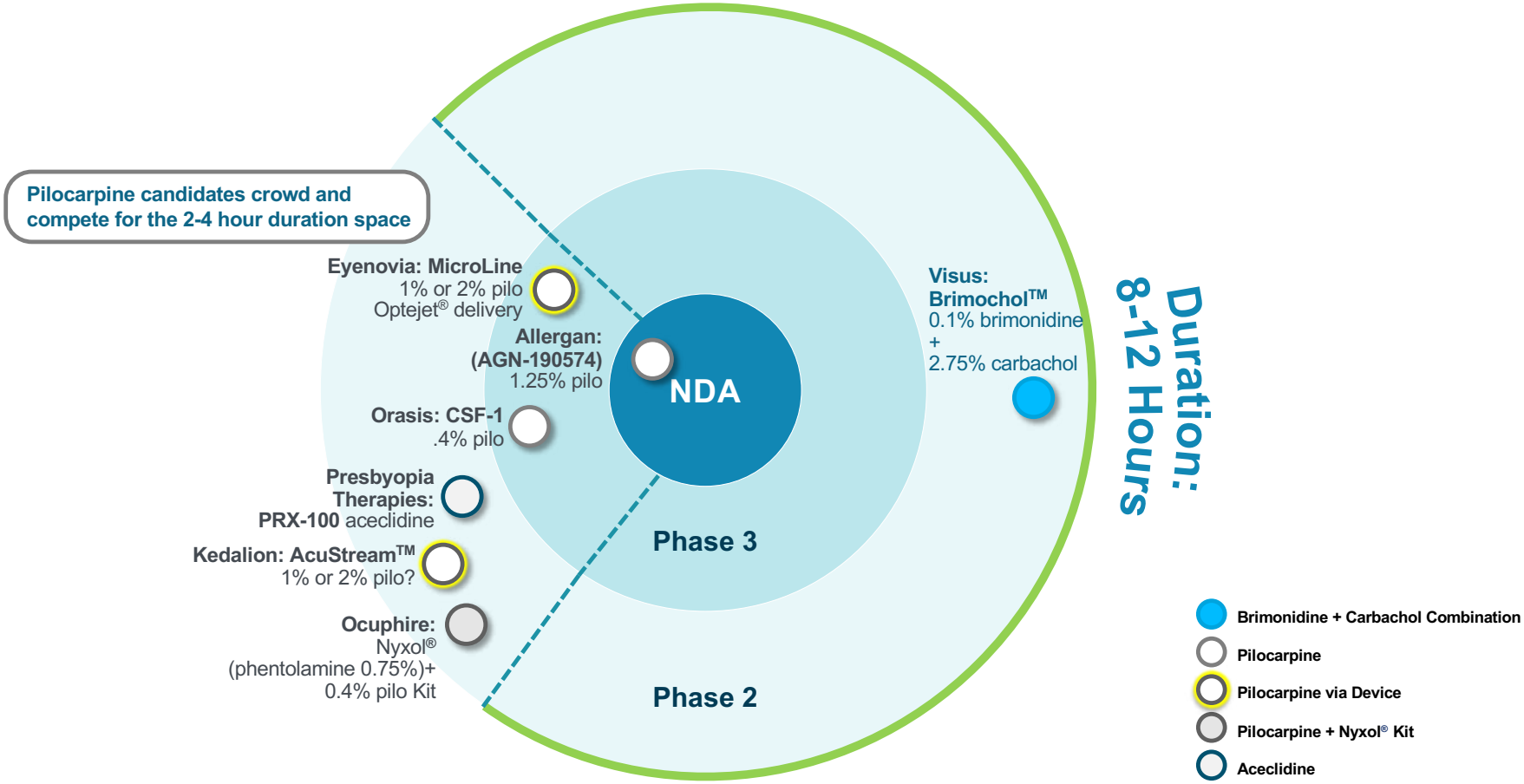
What's Coming Soon?

Pharmacologic Treatments for Presbyopia Are Coming, With Miotic Drops Occupying the Majority of Development

Topical Drops in Development	Active Ingredient(s)	Mechanism of Action
Brimochol™ (Visus Therapeutics)	Carbachol + brimonidine tartrate	Carbachol: Miotic Brimonidine tartrate: Prevents pupil dilation, inhibits contraction of ciliary muscle, increases bioavailability of carbachol[1,2], prevents redness[3]
CSF-1 (Orasis)	Pilocarpine	Miotic
PRX-100/Liquid Vision (Presbyopia Therapies)	Aceclidine	Miotic
AGN 190584 (Allergan)	Pilocarpine	Miotic
MicroLine/OpteJet (Eyenovia)	Pilocarpine	Miotic
AcuStream™ (Kedalion)	Pilocarpine	Miotic
Nyxol® and Pilocarpine Combination Kit (Ocuphire)	Phentolamine mesylate and pilocarpine	Miotic (both pilocarpine and phentolamine mesylate products) Vasodilates small muscles (phentolamine mesylate product)[6]
True Vision Treatment® Contact lenses and Eye Drops Kit (Yolia Health)	Hyaluronidase and collagenase	Alters cornea [7]
UNR844 (Novartis)	Lipoic acid choline ester	Lens-softening agent
VP1-001 (Viewpoint Therapeutics)	Stabilizing alpha-crystallin molecule	Target's protein misfolding to restore native, functional shape[8]

1. Suzuki et al. Ocular and Systemic Pharmacokinetics of Brimonidine and Timolol After Topical Administration in Rabbits: Comparison Between Fixed-Combination and Single Drugs. *Ophthalmol Ther* (2020) 9:115–125; 2. Allergan patent application (Pub. No.: US 2018 / 0078500 A1). 3. LUMIFY® Product Insert www.fda.gov accessed 9/24/2020. 4. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas (Eighth Edition), 2009. 5. Korczyn et al. Effect of Pilocarpine on Intraocular Pressure in Normal Humans. *Ophthalmic Res*. 14:182-187 (1982). 6. Pepose. Phentolamine Mesylate Ophthalmic Solution Provides Long Lasting Pupil Modulation and Improves Visual Acuity, ARVO 2020 Abstract: #3364450. 7. Yolia Health. 8. Viewpoint Therapeutics, February 2021.

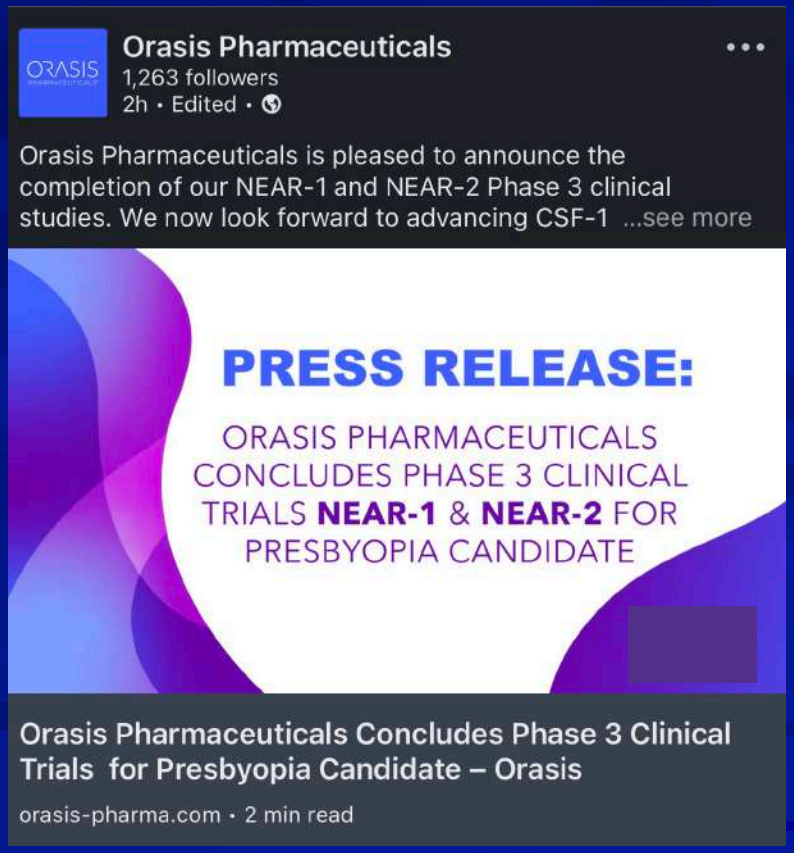
U.S. Presbyopia Miotic Drop Landscape is Crowded in the Short-acting Space



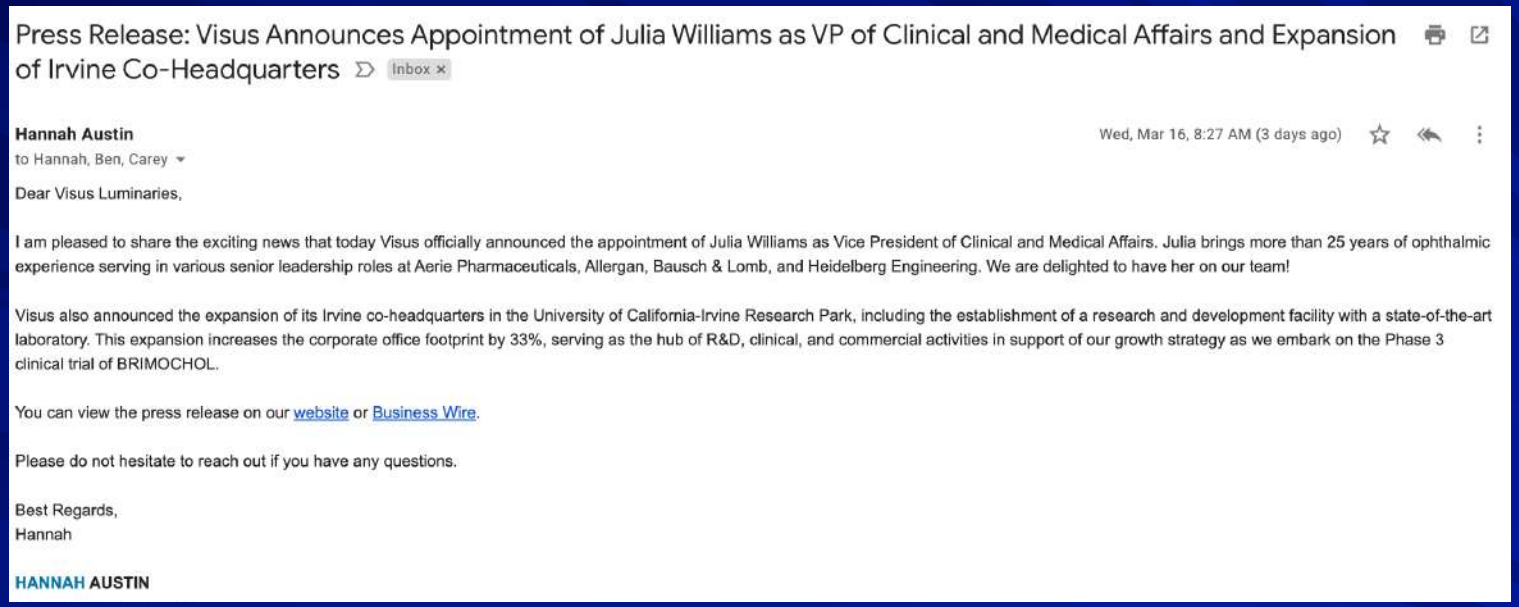
Data accessed April 2021

1. Clinicaltrials.gov, January 2021. 2. Christopher Kent, Non-IOL-based Presbyopia Treatments, Review of Ophthalmology Nov 5, 2020. 3. OIS Presbyopia Innovation Showcase, January 28, 2021.
4. UNSW Australia pilocarpine via AcuStream Presbyopia Recruitment Advertisement. 5. Viewpoint Therapeutics. 6. Data on file, January 2021.

March 16, 2022



March 16, 2022



Press Release: Visus Announces Appointment of Julia Williams as VP of Clinical and Medical Affairs and Expansion of Irvine Co-Headquarters Inbox ×

Hannah Austin
to Hannah, Ben, Carey

Wed, Mar 16, 8:27 AM (3 days ago)

Dear Visus Luminaries,

I am pleased to share the exciting news that today Visus officially announced the appointment of Julia Williams as Vice President of Clinical and Medical Affairs. Julia brings more than 25 years of ophthalmic experience serving in various senior leadership roles at Aerie Pharmaceuticals, Allergan, Bausch & Lomb, and Heidelberg Engineering. We are delighted to have her on our team!

Visus also announced the expansion of its Irvine co-headquarters in the University of California-Irvine Research Park, including the establishment of a research and development facility with a state-of-the-art laboratory. This expansion increases the corporate office footprint by 33%, serving as the hub of R&D, clinical, and commercial activities in support of our growth strategy as we embark on the Phase 3 clinical trial of BRIMOCHOL.

You can view the press release on our website or Business Wire.

Please do not hesitate to reach out if you have any questions.

Best Regards,
Hannah

HANNAH AUSTIN

- March 22, 2022- Visus announced the launch of our two pivotal Phase 3 trials
  - (BRIO-I and BRIO-II) for BRIMOCHOL™ PF.
- BRIO-I and BRIO-II are double-masked, randomized, multi-center, safety and efficacy studies expected to enroll emmetropic phakic and pseudophakic presbyopic patients
  - Approximately 170 and 500 respectively

Two Categories of Presbyopia Drops

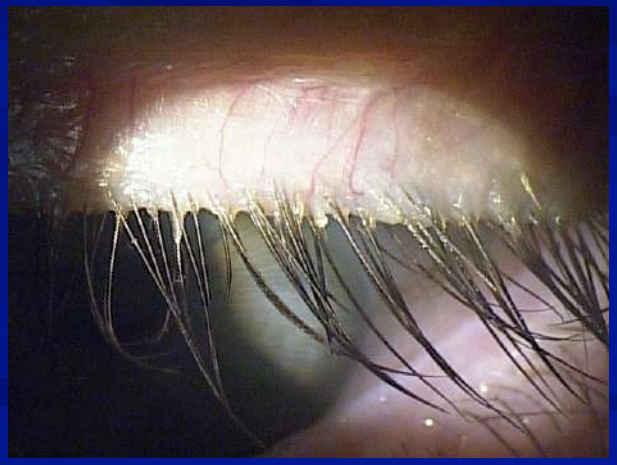
- **Miotic drops** increase depth of field by inducing a pinhole effect
  - Low risk, highly effective and easily reversible compared to surgical alternatives
  - Miotic drops aren't without side effects – headache, brow ache, IOP fluctuations, myopic shift and hyperemia[1,2]
- **Lens softening topical agents** intend to increase ability to accommodate with usage over time

1. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas (Eighth Edition), 2009. 2. Korczyn et al. Effect of Pilocarpine on Intraocular Pressure in Normal Humans. *Ophthalmic Res*. 14:182-187 (1982).

Demodex Blepharitis and a New Therapeutic on the Horizon

Demodex Infestation

- Collarettes are pathognomonic sign of Demodex Infestation
- Collarettes are composed of mite waste products and eggs
  - ★ Regurgitated undigested material combined with epithelial cells, keratin, and mite eggs



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

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

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

Ocular Biologics

Optometric Education Consultants

Poll 5

Which biologic drug has been used in eye care the longest?

A. Oxervate™ cenegermin-bkbj
B. Tepezza™ teprotumumab-trbw
C. Actemra™ tocilizumab
D. Avastin™ bevacizumab
E. I don't know

Treatments for Choroidal Neovascularization (CNV)

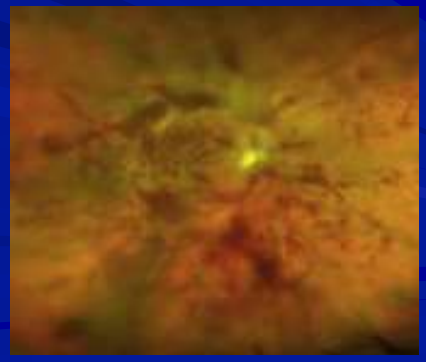
- Where is all started in the eye
- Disorders of the blood vessels in the retina are responsible for some of the most common causes of blindness in the world
  - Retinopathy of prematurity
    - Important cause of blindness in children in middle-income countries
  - Diabetic retinopathy
    - Common cause of blindness in the working-age population of industrialized countries
  - Age-related macular degeneration
    - A common cause of blindness in the world
- These conditions are caused partly by over-production of a protein called vascular endothelial growth factor (VEGF)
- VEGF was discovered in the 1980s and is important in the growth and development of blood vessel in tumor growth
  - 1994 it was proven that retinal hypoxia produces VEGF

Treatments for Choroidal Neovascularization (CNV)

- Current Anti-VEGF treatments
  - Pegaptanib (Macugen)
    - First FDA Approved December 2004
    - RNA aptamer
    - AMD
  - Bevacizumab (Avastin)
    - Humanized full length monoclonal antibody - 2005
    - AMD
  - Ranibizumab (Lucentis)
    - Humanized monoclonal antibody fragment – 2006
    - AMD, DME, DR, RVO
  - Aflibercept (Eylea)
    - Fusion protein – 2011
    - AMD, DME, DR
  - Brolucizumab-dbll (Beovu)
    - Humanized single-chain antibody fragment - 10-8-2019
    - Up to 3 months dosing intervals, most are 4-6 weeks
      - 50% remained 3 months after 1 year

Beovu (brolucizumab)

- Indication: injection is used for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD)
  - Offers a 3-month dosing schedule in the first year of treatment
- Warning issued by the American Society of Retinal Specialists about a series of intraocular inflammation events—some of which led to severe vision loss
- On April 8, 2020, Novartis announced its completion of the review, which included an assessment by an external, independent Safety Review Committee
- Complications: n=1098
  - Intraocular inflammation (IOI) - 4.6% (n=50)
  - IOI + retinal vasculitis – 3.3% (n=36)
  - IOI + retinal vasculitis –retinal (artery) vascular occlusion – 2.1% (n=23)
  - Vision loss of 15 letters or more - <1%



Optometric Education Consultants

Poll 6

Which biologic drug is indicated for the treatment of neurotrophic keratitis?

A. Oxervate™ cenegermin-bkbj
B. Tepezza™ teprotumumab-trbw
C. Actemra™ tocilizumab
D. Avastin™ bevacizumab
E. I don't know

Oxervate™ (cenegermin-bkbj)

- Approved 2018 (August 28, 2018)
- Dompe farmaceutici SpA
- Ophthalmic solution indicated for the treatment of neurotrophic keratitis
- Dosing: Instill 1 drop in affected eye 6 times per day (at 2-hour intervals) for 8 weeks
  - Used as eye drop
    - Not infused or injected
- Storage issues: in the freezer at the pharmacy
  - Patient keeps the individual vials in the fridge – once "actively ready" for use, then it is only stable for 12 hours
- Contraindications
  - None

Optometric Education Consultants

Poll 7

Which living organism is used in the production of Oxervate™ (cenegermin-bkbj)

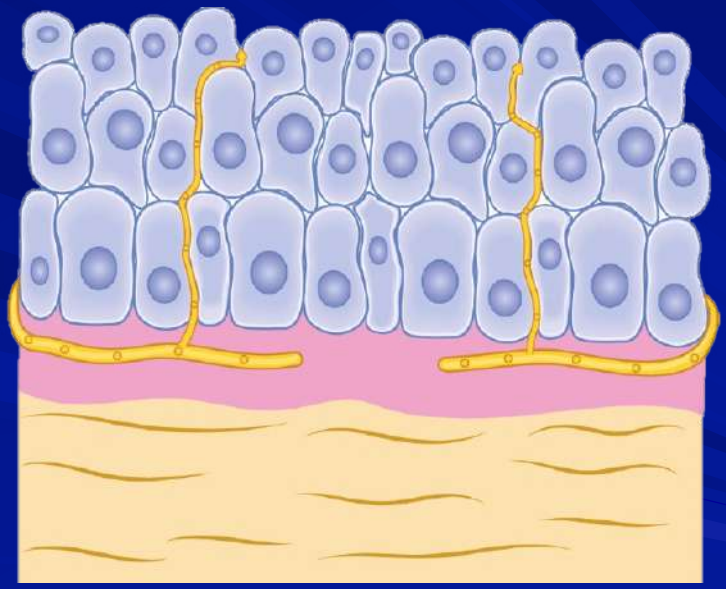
A. Escherichia Coli
B. Chinese Hamster Ovary
C. COVID 19
D. Staphylococcus aureus
E. I don't know

Escherichia Coli

Oxervate™ is produced in Escherichia coli. Image courtesy of NIAID.

Pathophysiology of NK[1]

- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production and blink rate due to the reduction of trigeminal reflexes
- Impairment of trigeminal innervation leads to decreased corneal epithelium renewal and healing rate, and ultimately the development of NK



Penetration of nerves into the epithelium

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42.

Etiologies Associated with NK

Ocular
- Herpes (simplex or zoster) infection
- Other infections e.g acanthamoeba
- Chemical or physical burn
- Abuse of topical anaesthetics
- Drug toxicity
- Chronic ocular surface injury or inflammation
- Ocular surgery
- Cataract surgery
- LASIK, PRK
- PK and DALK
- Collagen crosslinking for keratoconus
- Vitrectomy for retinal detachment
- Photocoagulation for diabetic retinopathy
- Postsurgical or laser treatment
- Routine laser for proliferative diabetic retinopathy
- Contact lenses
- Orbital neoplasia
- Corneal dystrophies

Central nervous system
- Neoplasm
- Aneurysms
- Stroke
- Degenerative CNS disorders
- Post-neurosurgical procedures
  - For acoustic neuroma
  - For trigeminal neuralgia
- Other surgical injury to trigeminal nerve

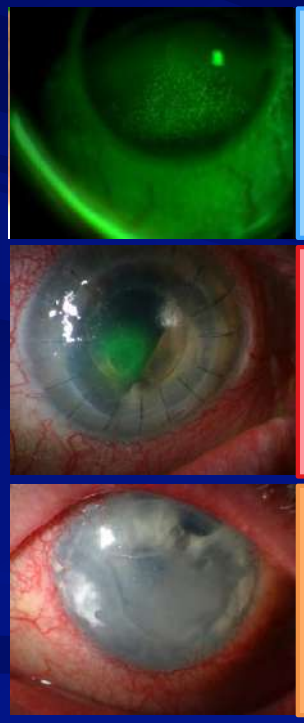
Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

Genetic
- Riley-Day syndrome (familial dysautonomia)
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoaesthesia

DALK=deep anterior lamellar keratoplasty; LASIK=laser in situ keratomileusis; PK=penetrating keratoplasty; PRK=photorefractive keratectomy

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003.

NK classification



Stage 1: Mild

(Epithelial changes only without epithelial defect): Epithelial irregularity without frank epithelial defect, tear film instability and symptoms (hyper-aesthesia) with reduced or absent sensations in one or more quadrants of the cornea

Stage 2: Moderate

(Epithelial defect without stromal defect): Frank persistent epithelial defect and corneal hypo-aesthesia/ anaesthesia

Stage 3: Severe

(Stromal involvement): Stromal involvement from corneal ulcer to lysis to perforation, with corneal hypo-aesthesia/anaesthesia

Images by kind consent of Prof. Messmer and Prof. Dua

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]. 2. 1. Semarero F, et al. Ophthalmologica 2014;231:191–7; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

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]

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

TEAR SECRETION

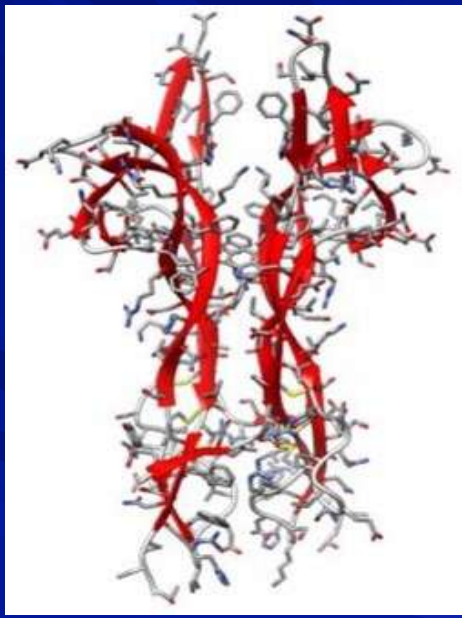
CELL PROLIFERATION AND DIFFERENTIATION

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

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.

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

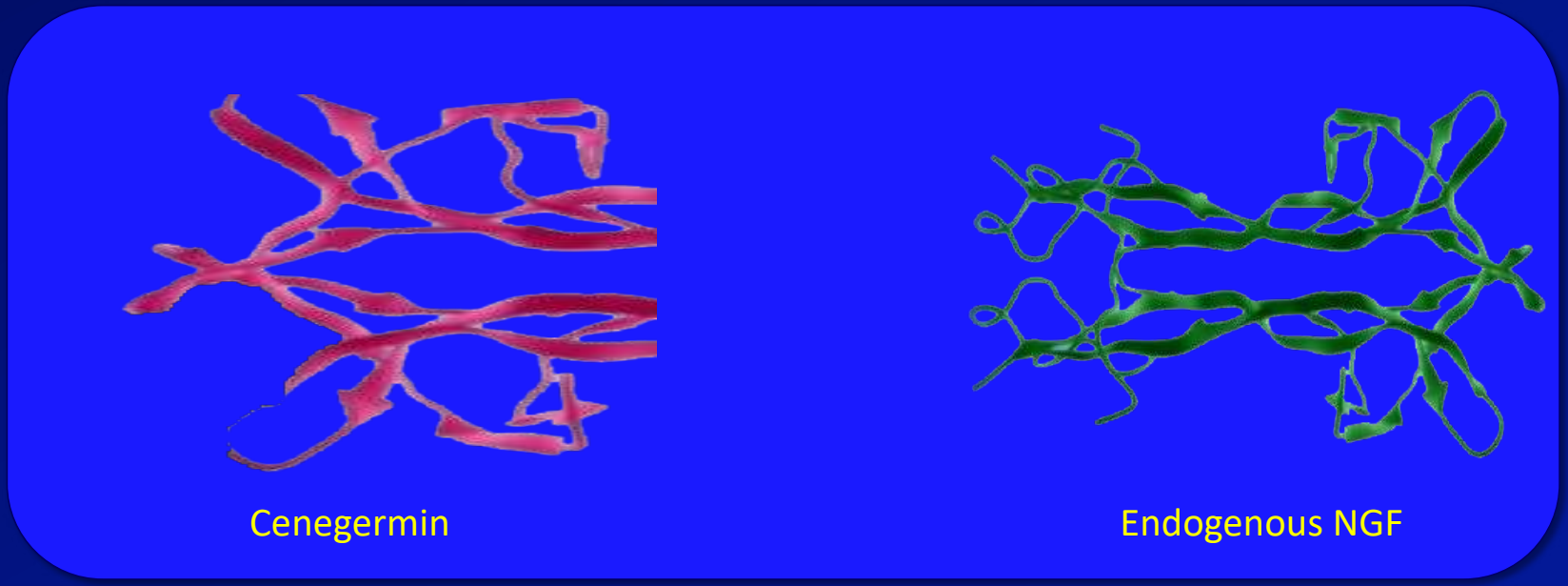
The Delivery System Kit Contains:

- 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.

Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues



Cenegermin-bkbj, the active ingredient in the FDA-approved OXERVATE™ (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL), is structurally identical to the human NGF protein found in ocular tissues

Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

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)

Every 2 hours

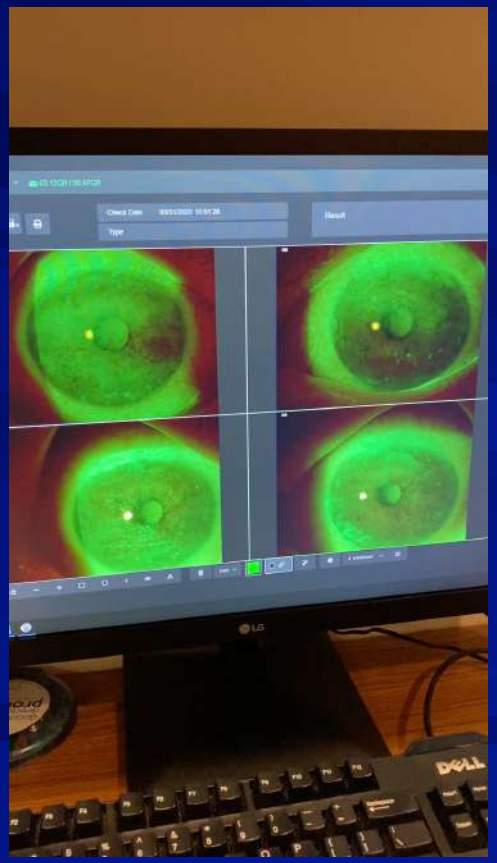
Apply 6 times daily

Continue for 8 weeks

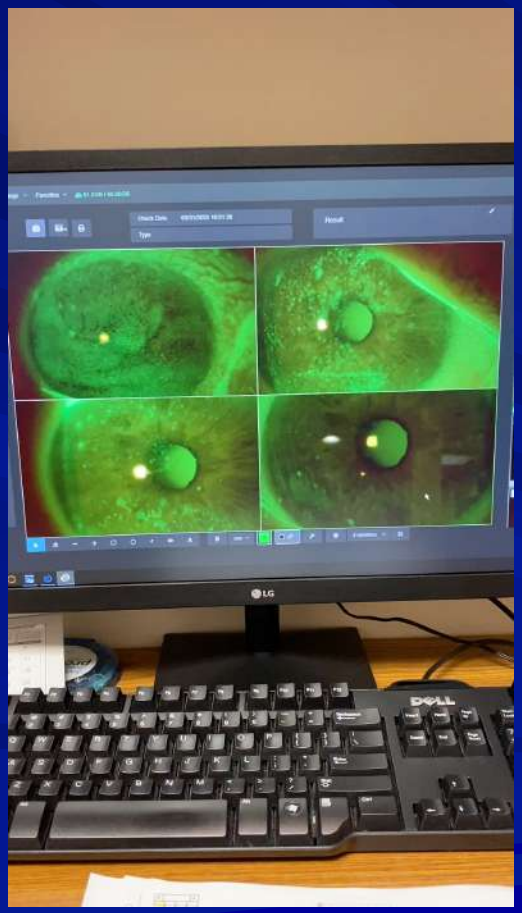
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

Let's Hear From a Patient

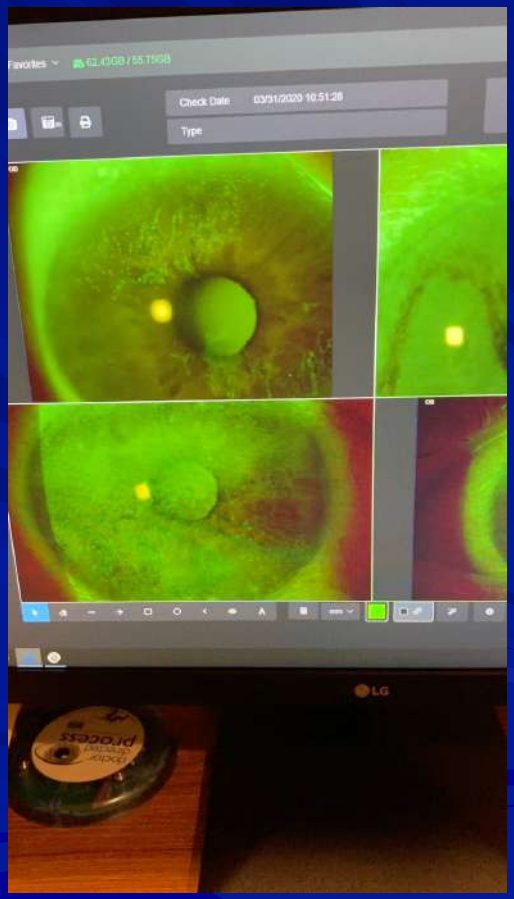
April 7, 2020 - After 1 week



April 21, 2020 - After 3 weeks



May 12, 2020 - After 6 weeks



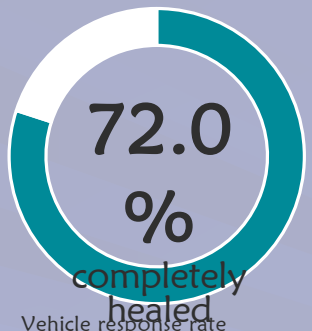
Study Conclusions

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.

Study NGF0212 (REPARO) (N=52 per group)
European patients with NK in one eye

NCT01756456

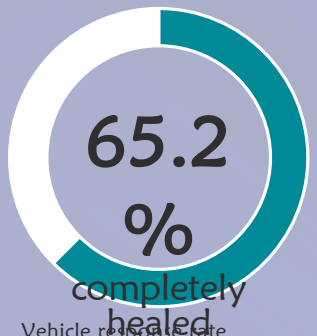


Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147



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

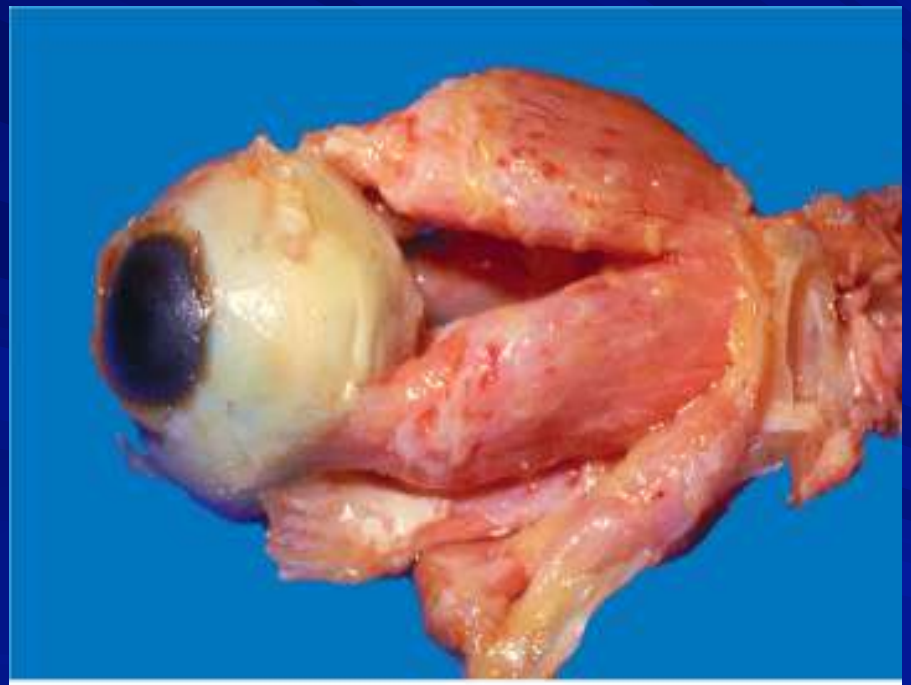
Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation,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

OXERVATE™ (cenegermin-bkbj)

- Adverse reactions: very well tolerated
- The most common adverse reaction in clinical trials
  - eye pain, corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears
- Contact lenses (therapeutic or corrective) should be removed before applying cenegermin
  - presence of a contact lens may limit the distribution of cenegermin-bkbj onto the corneal lesion
  - Lenses may be reinserted 15 minutes after administration.

Thyroid Disease
and
Thyroid Eye Disease



February 25, 2019

"Nothing Else Can Be Done"

February 25, 2019

"Nothing Else Can Be Done"

March 1, 2019 (4 days later)
Oral and Topical Steroids

March 1, 2019 (4 days later)
Oral and Topical Steroids

March 25, 2019

March 25, 2019

April 22, 2019

Optometric Education Consultants

Poll 8

Which biologic drug is indicated for the treatment of thyroid eye disease?

A. Oxervate™ cenegermin-bkbj
B. Tepezza™ teprotumumab-trbw
C. Actemra™ tocilizumab
D. Avastin™ bevacizumab
E. I don't know

MEETING NEWS

Thyroid eye disease therapy shows promise

Primary Care Optometry News, December 2018

CHICAGO — Teprotumumab, an IGF-1 receptor antagonist antibody, demonstrated improvement of double vision in patients with thyroid eye disease, according to a study presented here.

If approved by the FDA, teprotumumab (Horizon Pharma) would be the first drug with an indication for thyroid eye disease, **Raymond S. Douglas, MD, PhD,** said at the American Academy of Ophthalmology annual meeting.

COMMENT

If approved by the FDA, teprotumumab (Horizon Pharma) would be the first drug with an indication for thyroid eye disease, **Raymond S. Douglas, MD, PhD,** said at the American Academy of Ophthalmology annual meeting.

In the phase 2 trial, 42 patients were treated with the study drug and 45 patients made up the placebo control arm. At week 24, which marked the end of the controlled trial, statistically significantly more patients taking the study drug achieved the primary endpoint of improvement in clinical activity score and reduction of proptosis ($P < .001$). Diplopia improvement was "impressive" at week 24, and of the patients with diplopia at baseline who did improve, 70% continued to have that improvement 48 weeks later, Douglas said.

The most reported adverse event was hyperglycemia, which returned to normal after discontinuation of the drug, he said.

"Teprotumumab ... appears to have stable improvement and durability of improving the double vision, proptosis and clinical activity in these patients and appears to reverse the effects of thyroid eye disease," Douglas said. "The phase 3 trial will also have the added benefit of having a crossover group who will receive open-label therapy if [patients are] nonresponders at week 24, which ... may make this even more universally applicable to patients with long-standing disease." – *by Patricia Nale, ELS*

Reference:

Douglas RS. Diplopia response in a controlled trial with teprotumumab, an IGF-1 receptor antagonist antibody for thyroid eye disease. Presented at: American Academy of Ophthalmology annual meeting; Oct. 27-30, 2018; Chicago.

Disclosure: Douglas reports no relevant financial disclosures.

Clinical Activity Score (CAS)

CAS

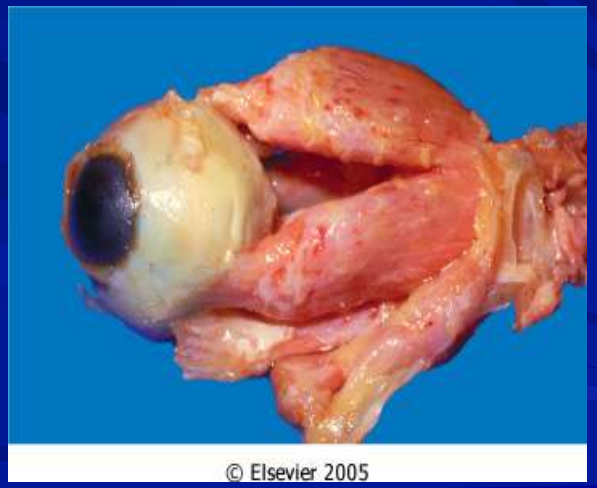
Table 2 | Clinical Activity Score

	Clinical Activity Score
1	Painful feeling behind globe
2	Pain on attempted gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Chemosis
6	Inflammatory eyelid swelling
7	Inflammation of caruncle or plica
8	Increase of ≥2 mm in proptosis in last 1–3 months
9	Decrease in visual acuity in last 1–3 months
10	Decrease in eye movements of ≥8° in last 1–3 months

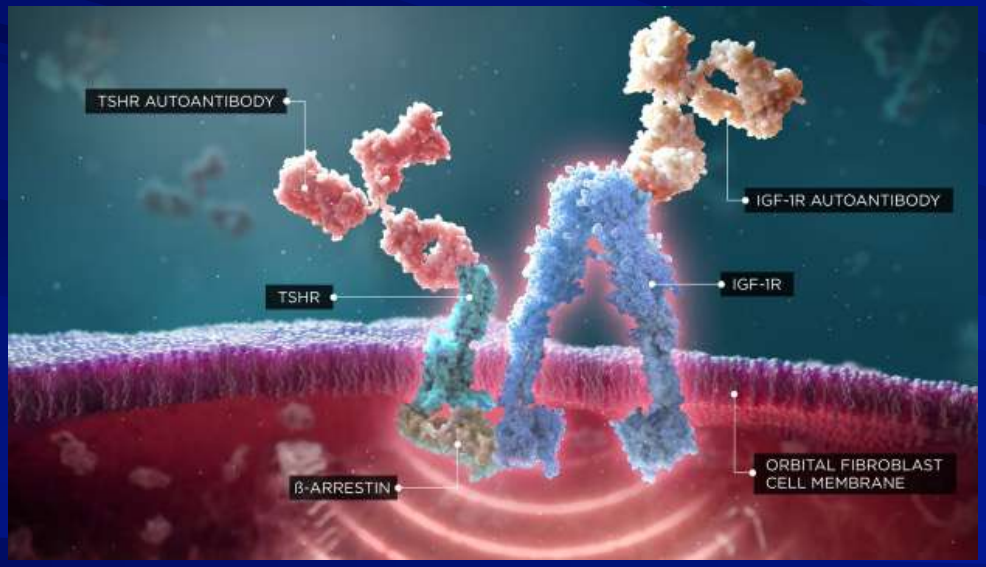
For initial CAS, items 1–7 are tallied at one point each for a final CAS based on a 7-point scale. On follow-up visits, the final three items are added for a CAS out of 10 points

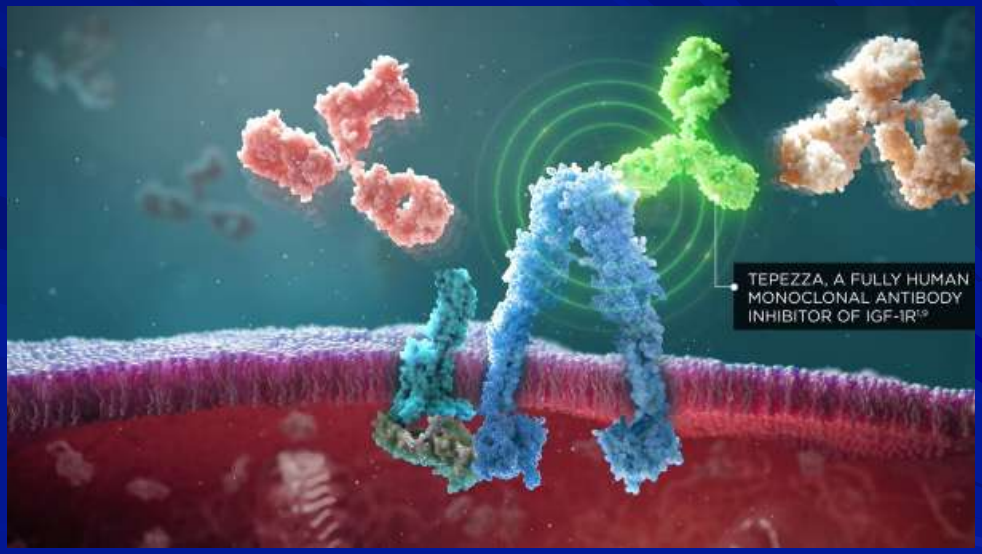
Teprotumumab-trbw (Tepezza)

- Horizon Therapeutics – HQ Dublin, Ireland and US based Chicago
- Biologic pharmaceutical
  - Chinese Hamster Ovary
  - Infusion, 8 total, every 3 weeks
- Thyroid eye disease
  - IGR-1 (Insulin like growth factor 1) and TSH receptors are over expressed
- IGF-1 receptor inhibitor monoclonal antibody
  - On the orbital fibroblasts
    - Inhibiting downstream inflammatory cascade
      - Cytokines, hyaluran, leukotriene
      - Differentiation into adipocytes and myofibroblasts
- Phase 2 and published in New England Journal of Medicine
- Phase 3 completed
  - Published - New England Journal of Medicine
- PDUFA- March 2020, was approved early in 2020



Teprotumumab-trbw (Tepezza)





https://www.tepezza.com/hcp/tepezza-moa/

Immunosuppression?

- Biologics
  - ★ Immunosuppression biologics – suppress the immune system to get the effe3ct
    - Remicade – "1st generation"
      - Chimeric molecule – mouse and human protein, a lot of sensitivity
    - Humira
      - Anti-TNF (RA and Crohn's Disease
      - Fully human protein, less sensitivity
    - Rituxan
      - CD 20 suppressor (B cell suppression)
    - Actively suppress the immune system
  - ★ Immunomodulary
    - Tepezza
      - IGF-1R inhibitor
      - Full humanized monoclonal antibody
        - All the proteins are human – less to no sensitivity – more focused effect
      - Obital fibroblasts to myofibroblast or adipocytes
      - Hyaluronic acid, glycosaminoglycan

Teprotumumab-trbw (Tepezza)

- Optics and Optic-X Studies
  - 8 infusions, every 3 weeks, 24 weeks
  - Optics – acute, less than 9 months of disease
  - Optics X – chronic, 12-16 months disease
- Clinical Activity Score
  - Spontaneous pain, gaze evoked pain, eyelid erythema, chemosis, inflammation
  - Scale of 7, needed 4 to be in the study
- Proptosis
  - Improvement of 2 mm or better
- Diplopia
  - Scale of 0, 1, 2, or 3
- Grave's Ophthalmopathy -Quality of Life Score
  - Scale 0-100

Teprotumumab-trbw (Tepezza)

- Clinical Activity Score (CAS)
  - Spontaneous pain, gaze evoked pain, eyelid erythema, chemosis, inflammation
  - Scale of 7, needed 4 to be in the study
    - 78% improved to 0 or 1, 7% improved 0 or 1 with placebo
- Proptosis
  - Improvement of 2 mm or better
    - 83% had 2 mm or better, 10% with placebo
    - Average was 3.2 mm at week 24
- Diplopia
  - Scale of 0, 1, 2, or 3
    - 68% improved 1 point, 29% with placebo
- Grave's Ophthalmopathy -Quality of Life Score
  - Scale 0-100
    - 17.28 point improved, 1,80 with placebo

Teprotumumab-trbw (Tepezza)

- **Adverse Reactions**
  - **Very well tolerated**

  - The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

Teprotumumab-trbw (Tepezza)

- **Infusion Reactions (mild/moderate):** approximately 4% of patients
  - transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain
  - consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering at a slower infusion rate.

- **Hyperglycemia:** Increased blood glucose or hyperglycemia
  - In clinical trials, 10% of patients experienced hyperglycemia
  - Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with teprotumumab
  - Patients with preexisting diabetes should be euglycemic before beginning treatment

Tepezza?

Table 2 | Clinical Activity Score

	Clinical Activity Score
1	Painful feeling behind globe
2	Pain on attempted gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Chemosis
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For initial CAS, items 1–7 are tallied at one point each for a final CAS based on a 7-point scale. On follow-up visits, the final three items are added for a CAS out of 10 points

Teprotumumab-trbw (Tepezza)

- Infusion center
  - Go to Horizon website
  - Contact Us
  - Type in your question
    - Looking for infusion center

Biologics Used Off Label for TED

Table 1 | **Biologic therapies for TED**

Small Molecule Therapies	Target	Dosing	Findings	Side Effects
Rituximab	CD20	2 infusions of 1000 mg each 2 weeks apart	Mixed results in improvement of CAS, proptosis, and motility	Exacerbation of inflammatory bowel disease, arthralgias, hypotension
Adalimumab	TNF-α	Subcutaneous injections of initial 80 mg dose, then biweekly 40 mg doses for a total of 10 weeks	6/10 showed decrease in inflammation, no changes in proptosis or extraocular motility	Sepsis (1/10)
Infliximab	TNF-α	Infusions at 5 mg/kg each dose over 2 hours	Case reports showed improvement in visual acuity and CAS after 1 dose and complete resolution in 3 cases after 3 doses	Infections, malignancies (especially lymphoma), drug-induced lupus
Tocilizumab	IL-6	3 infusions at 8 mg/kg given every 4 weeks	93% with ≥2-point improvement in CAS, mean proptosis reduction of 1.5 mm, no change in diplopia	High recurrence rate, transaminitis, pyelonephritis
Teprotumumab	IGF-1R	Initial infusion at 10 mg/kg, followed by 7 infusions at 20 mg/kg given every 3 weeks	Reduced proptosis in 79–83% of patients, improved CAS in 69%, reduced diplopia in 68%	Most common: muscle spasms fatigue, nausea, diarrhea, hyperglycemia, hearing impairment, and alopecia. Between 5% and 12% with serious adverse events requiring early withdrawal

CAS, Clinical Activity Score; **CD**, cluster of differentiation; **FcRn**, neonatal Fc receptor for immunoglobulin G; **IL**, interleukin; **TNF**, tumor necrosis factor.

Additionally, multiple case reports published since

Optometric Education Consultants

Questions? Thank You!

Pharmaceutical Update 2022

Greg Caldwell, OD, FAAO
Nashville – Music City Fall Classic 2022
Optometric Education Consultants

Sunday, October 23, 2022