Optometric Education Consultants

## Pharmaceutical Update 2022

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Nashville – Music City Fall Classic 2022
Optometric Education Consultants

Sunday, October 23, 2022

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## 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

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## 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

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## 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


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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

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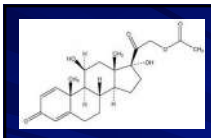
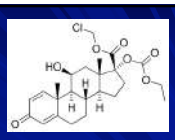
## Steroids
### Ketones versus Esters

- 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

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## 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

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## 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

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## 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%

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## 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

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## 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

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## 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

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## 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

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## 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

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## 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

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## 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

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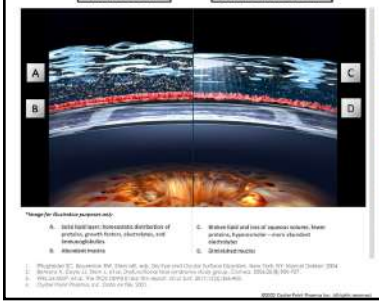
## Normal and Dysfunctional Tear Film*




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

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## 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

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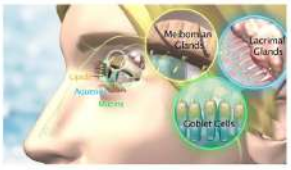
## Parasympathetic Nervous System Controls Tear Film Homeostasis

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]**

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## 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


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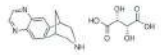
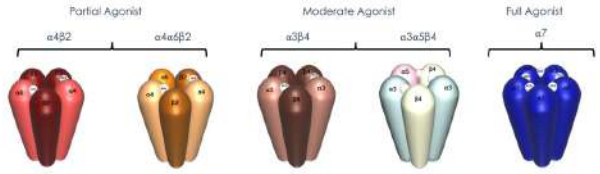
## Varenicline Tartrate



- 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

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## 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

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## Pharmaceutical Update?

Regener-Eyes Ophthalmic Solution

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## 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**

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## 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.

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## 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.

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## 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]

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## 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]

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## 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]

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## 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]

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## 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]

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## 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]

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## 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]

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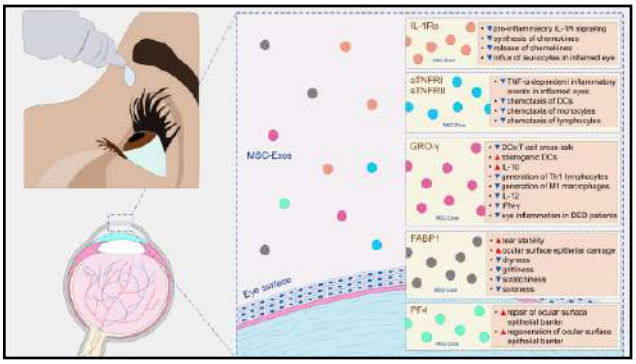


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## Meibomian gland dysfunction (MGD)/meibomian gland regeneration (MGR)

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.

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## 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]

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## 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]

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## 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.

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## 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)

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## Glaucoma

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## 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

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## 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

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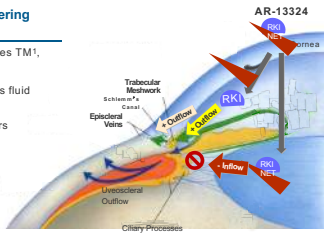
## Rhopressa (ROCK-NET Inhibitor) Triple-Action

**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]




1. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. *Clin Ophthal* 2014;8:883–890.
2. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *J Glaucoma* 2015. 24(1):51-4
3. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure (EVP) in Dutch Belted rabbits. *ARVO* 2014. Abstract 2900

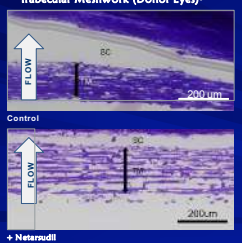
49

## Rhopressa™ 0.02% (netarsudil)

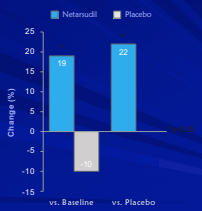
Causes Expansion of TM in Donor Eyes

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

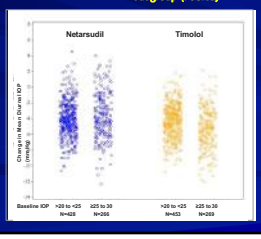
1. Ren R et al. Invest Ophthalmol Vis Sci. 2016;57(14):6197-6209. 2. Sit AJ et al. Presented at AGS 2017.

50

## 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 |

51

## 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 [accessed 2021].

52

## 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

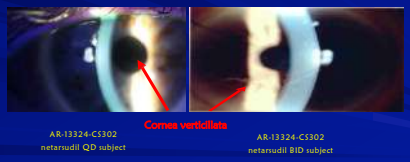
Self-resolving with continued dosing


Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS301, -CS302

53

## 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)




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

54

## 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

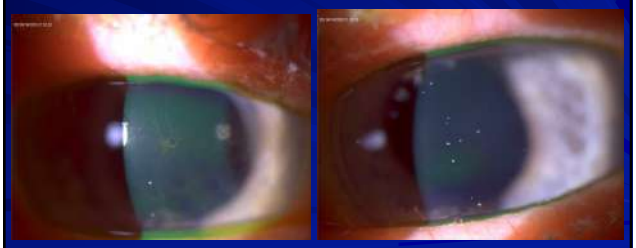
Literature review suggested it is an adaptive response by the body rather than an adverse pathology*

Data on File Based on AR-13324-IPH07
* Raizman MB et al. Surv. Ophthalmol. 2017;62:286-301

55

## My Experience

OD treated OS gtts



56

## Summary of the Most Common Netarsudil Ocular TEAEs

| Conjunctival Hyperemia | Cornea Verticillata | Conjunctival Hemorrhage |
|---|---|---|
| • 54.4% TEAE<br>• Severity did not increased with continued dosing<br>• Sporadic | • 20.9% TEAE<br>• Asymptomatic<br>• 7.4% experienced reduced visual acuity<br>• Not clear to a directly associated<br>• All resolved after 13 weeks of D/C | • 17.2% TEAE<br>• Mild in severity and transient<br>• Self-resolving with continued dosing |

57

## 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

58

## Honeycomb Epithelial Edema Associated With Rho Kinase Inhibition Graft Patient

Thank you! Joe Shovlin, OD, FAAO

59

## 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

60

## 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

61

## 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 Keratoplasty [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

62

## 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

63

## 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

64

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## 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

65

## April 19, 2022


Screenshot from Pharmacompass

66

## Pictures Taken February 21, 2022

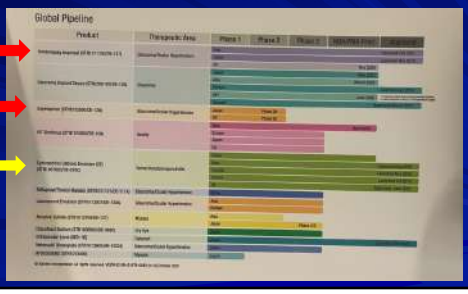
67

## 2-2-2022


Screenshot from Carlisle Medical

68

## What is Coming?

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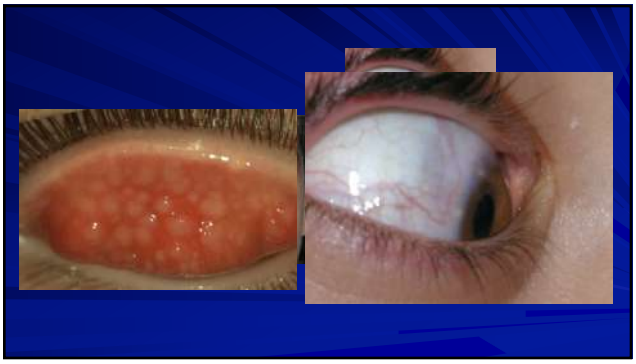

70

## 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

1. Daull P, et al. *J Pharm Pharmacol.* 2014;66:531-541. 2. Lallemand F, et al. *Mucosal Delivery of Biopharmaceuticals.* New York: Springer Science Business Media; 2013.
3. Lallemand F, et al. *J Drug Deliv.* 2012;2012:604204. 4. Baudouin C, et al. *Eur Ophthal Rev.* 2015;9:121-127.

71

## 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

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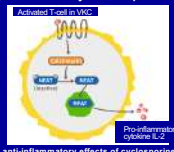
## Verkazia® Proposed Mechanism of Action

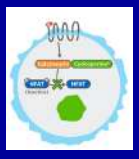
Verkazia® (cyclosporine) ophthalmic emulsion 0.1% is a calcineurin inhibitor, an immunomodulatory agent that interrupts inflammation and allergic responses.

**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

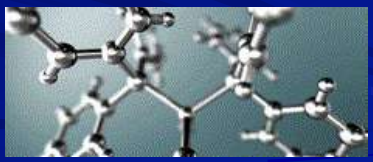
**Cyclosporine inhibits calcineurin and blocks pro-inflammatory cytokines**



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.

73

## Adrenergic Alpha Receptor Agonists



74

## 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

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## 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

76

## 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

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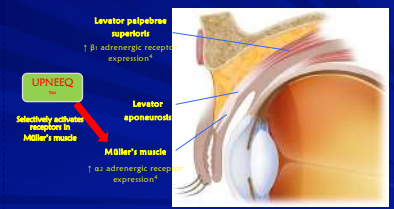
## UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

- 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

78

## 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




**References: 1.** Hamm H, Wahlab 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):1248-1252. **3.** Hendee LO, Snyder C. Over-the-counter ocular decongestants in the United State – mechanism of action and clinical utility for management of ocular redness. *Clin Optom*. 2020;12:95-105. **4.** Esmaeli-Gutstein B, Hewlett B, Pashby R, Christopher J, Harvey J. Distribution of adrenergic receptor subtypes in the retractor muscles of the upper eyelid. *Ophthalmic Plast Reconstr Surg*. 1998;15(2):92-96.

79

79

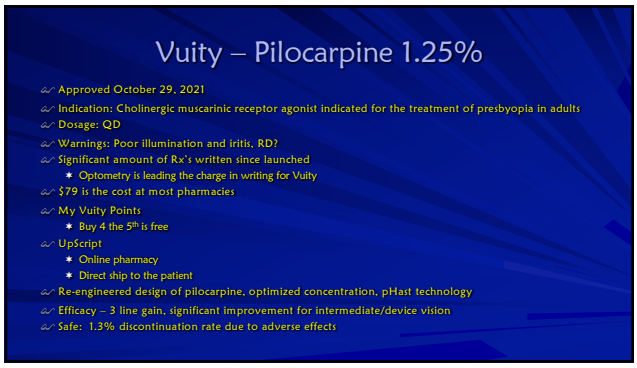
## UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

- 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

80


81


82

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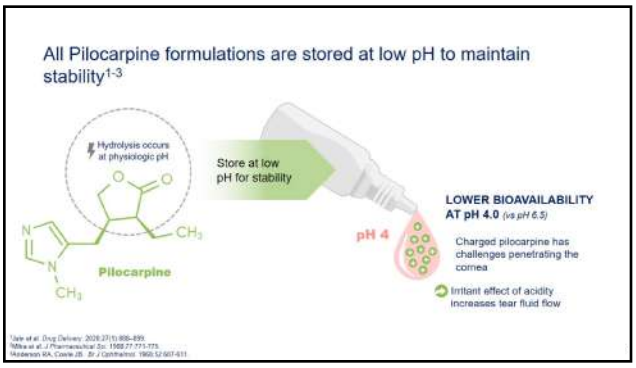


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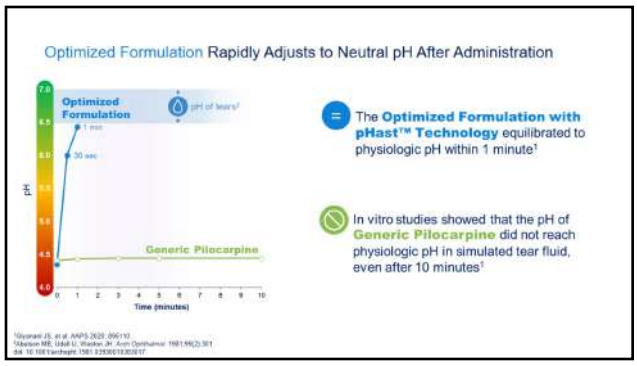


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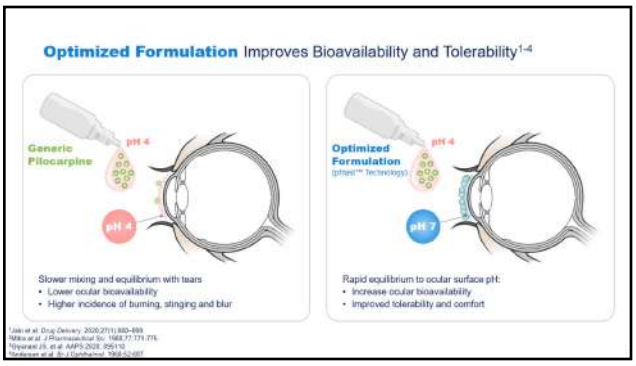


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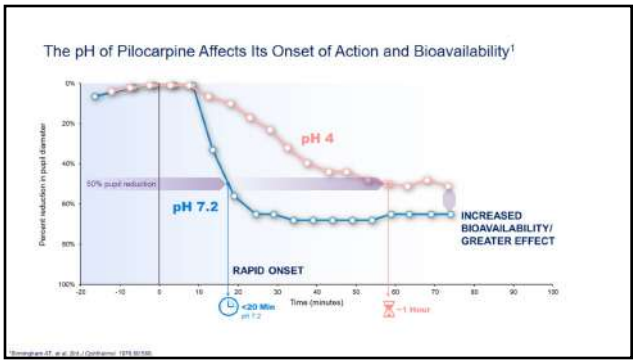


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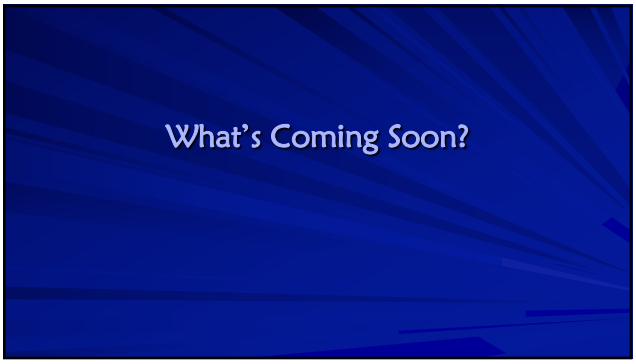


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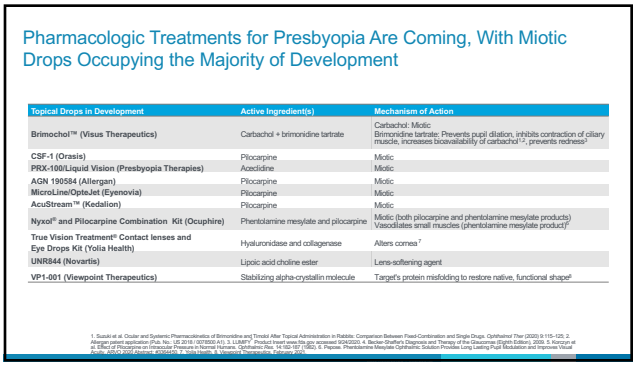


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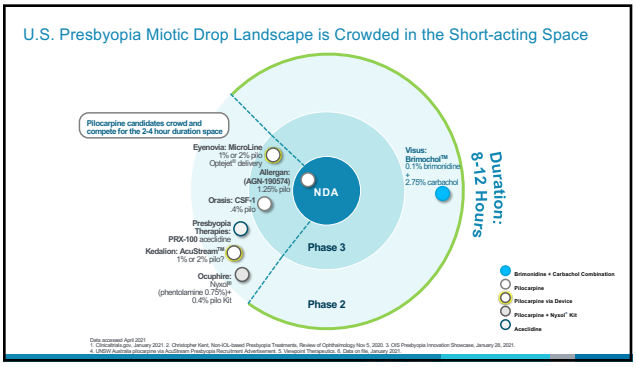


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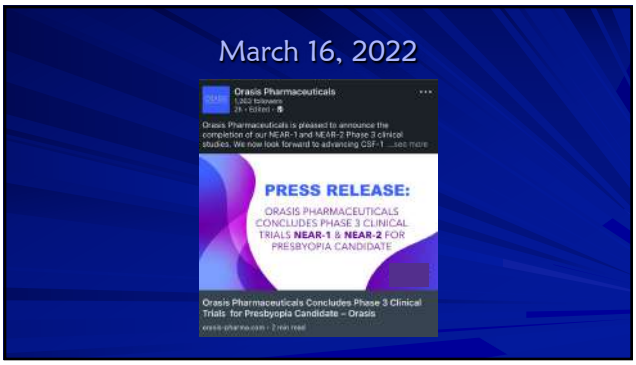
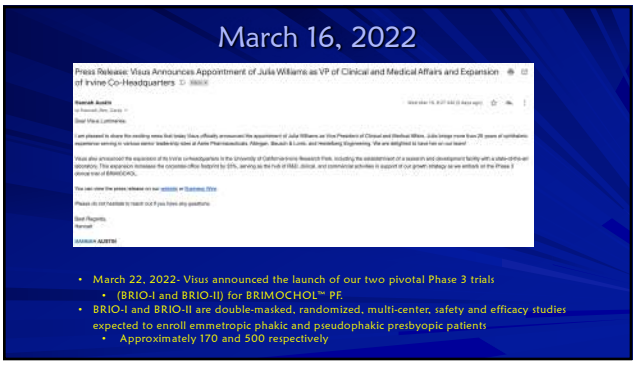



91

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## 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).

93

## Demodex Blepharitis and a New Therapeutic on the Horizon

94

## 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

95

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

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


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

96

## Ocular Biologics

97

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## 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

98

## 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

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## 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

100

## 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%

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## 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

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## 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

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## 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

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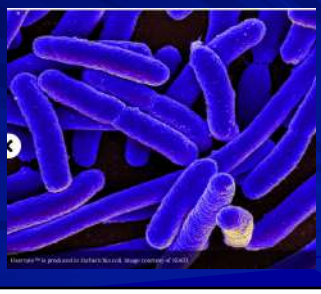
## Escherichia Coli



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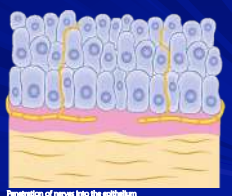
## Pathophysiology of NK[1]

- 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.

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## 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.

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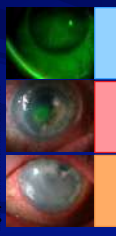
## NK classification



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

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2.

108

## 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[3,4]

**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. Musi S, Colafrancesco V, Sorrelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea.* 2010;29:1161–1168.

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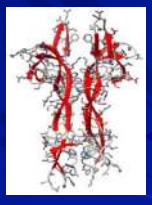
## Active ingredient structurally identical to human nerve growth factor produced in ocular tissues

- 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(18):1909.

110

## 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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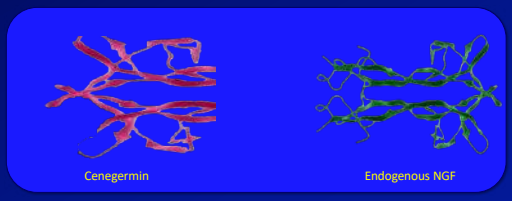
## Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues




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.

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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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## Let's Hear From a Patient


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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-dispensate 33.3%

**Study NGF0214 (N=24 per group)**
U.S patients with NK in one or both eyes
NCT02227147

65.2% Completely healed
Vehicle-dispensate 30.8%

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.
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)

- 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.

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Thyroid Disease
and
Thyroid Eye Disease

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February 25, 2019
"Nothing Else Can Be Done"

119

February 25, 2019
"Nothing Else Can Be Done"

120

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

121

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

122


123


124


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## 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

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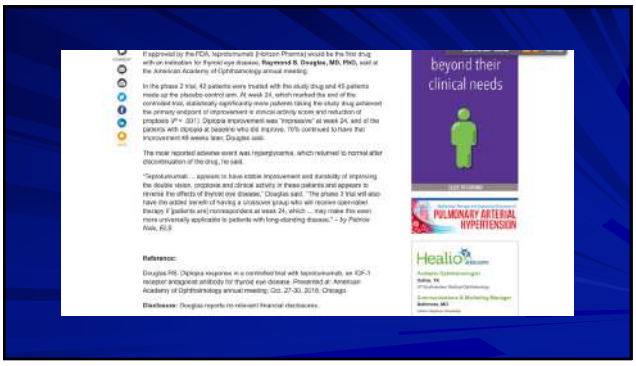


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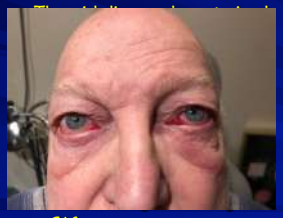
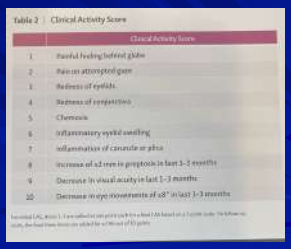
## Clinical Activity Score (CAS)



CAS



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## 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

© Elsevier 2005

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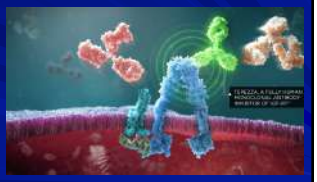
## Teprotumumab-trbw (Tepezza)



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

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## 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 monodonal antibody
        - All the proteins are human – less to no sensitivity – more focused effect
      - Obital fibroblasts to myofibroblast or adipocytes
      - Hyaluronic acid, glycosaminoglycan

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## 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

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## 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

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## 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.

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## 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

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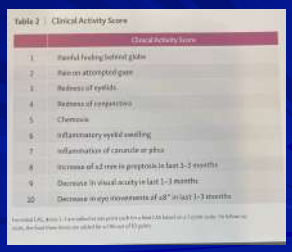
## Tepezza?



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## Teprotumumab-trbw (Tepezza)

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

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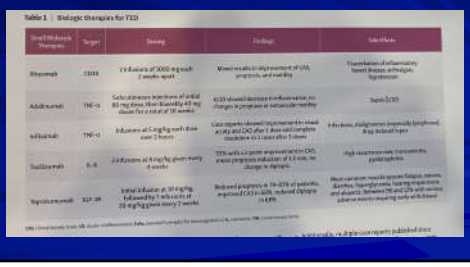
## Biologics Used Off Label for TED



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**Questions? Thank You!**

**Pharmaceutical Update 2022**

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

Sunday, October 23, 2022

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