Optometric Education Consultants

Pharmaceutical Update 2024

Greg Caldwell, OD, FAAO

Optometric Education Consultants

Sunday, March 10, 2024

Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- Lectured for: Alcon, B&L, BioTissue, Dompé
  - Disclosure: Receive speaker honorariums
- Advisory Board: Dompé, ImmunoGen, Iveric
  - 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
- Healthcare Registries – Chairman of Advisory Council for Diabetes and AMD
- The content of this activity was prepared independently by me - Dr. Caldwell
- The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service
- Optometric Education Consultants – Scottsdale, AZ, Pittsburgh, PA, Sarasota, FL , Barcelona, Spain, Orlando, FL, Mackinac Island, MI, Quebec City, Canada, and Nashville, TN- Owner

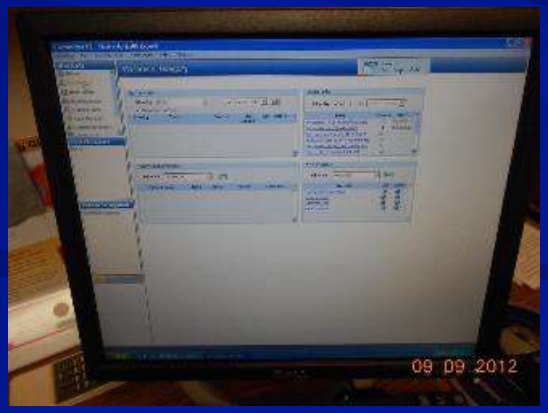
Optometric Education Consultants

My Practice

I am a clinician first then a scientist

- Some are scientists first then clinician
- I need to simplify for patient and patient care.
- Science is great, but not good if there isn't a clinical application.
- Some lectures are science based without clinical application.
- My lecture will be a hybrid. Showing clinical applications of the science

It is wonderful to have someone who's juggling so many aspects of optometry [scientific, clinical experience, teacher & lecturer]. It is refreshing and very informative. -Sarah



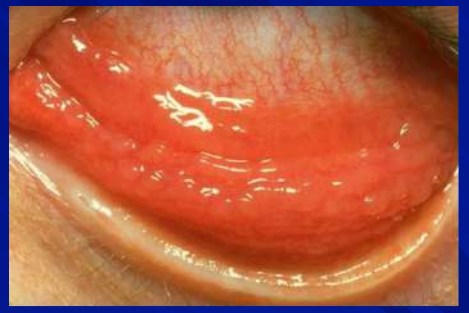
Confidence
Capable
Courage
Commitment

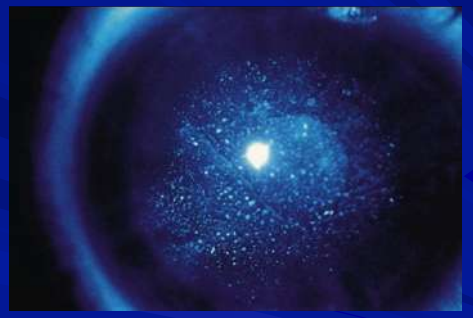
Pharmaceutical Resource Matrix

- 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

If you have a glaucoma practice you have an ocular surface disease practice

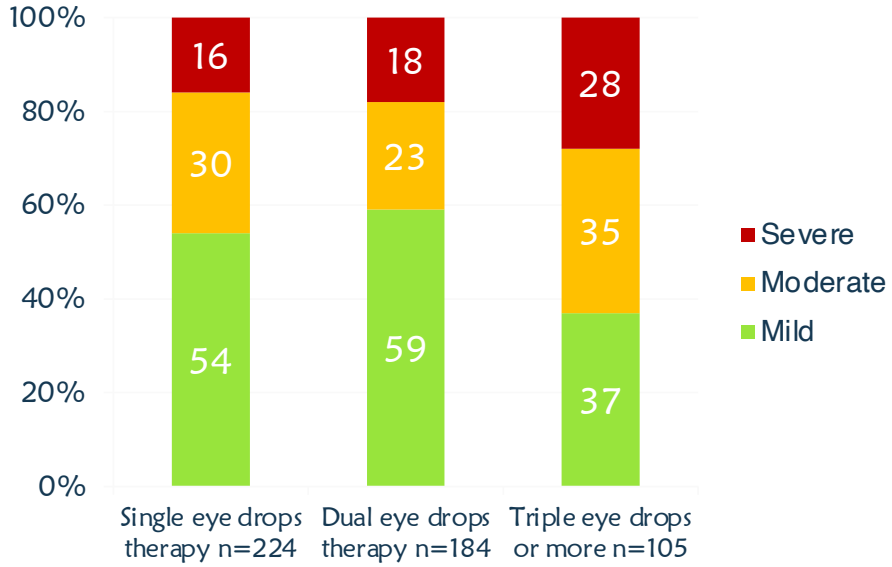
Follicular Conjunctivitis





Superficial Punctuate Keratitis (SPK)

The Relationship Between OSD and Number of Preserved Glaucoma Medications



- This study (n=516) was conducted to determine the prevalence of ocular surface diseases and identify risk factors in a population of patients receiving antiglaucoma eye drops[1].
- This study was conducted in France.

Number of daily eye drops was correlated with the severity of ocular surface disease

1. Baudouin *et al.* Eur. J Ophthalmol 2012; 23(1):47–54

Preservatives in IOP Lowering Medications

BRAND NAME	ACTIVE INGREDIENT	PRESERVATIVE
EYE DROPS WITH BENZALKONIUM CHLORIDE (BAK)		
Iopidine	Apraclonidine 0.5%, 1%	BAK 0.01%
Betoptic S	Betaxolol 0.25%	BAK 0.01%
Betoptic	Betaxolol 0.5%	BAK 0.01%
Lumigan	Bimatoprost 0.01%	BAK 0.02%
Lumigan	Bimatoprost 0.03%	BAK 0.005%
Lumify	Brimonidine 0.025%	BAK 0.01%
Alphagan	Brimonidine 0.2%	BAK 0.005%
Combigan	Brimonidine 0.2%/timolol 0.5%	BAK 0.005%
Azopt	Brinzolamide 1%	BAK 0.01%
Simbrinza	Brinzolamide 1%/brimonidine 0.2%	BAK 0.003%
Trusopt	Dorzolamide 2%	BAK 0.0075%
Cosopt	Dorzolamide 2%/timolol 0.5%	BAK 0.0075%
Xalatan	Latanoprost 0.005%	BAK 0.02%
Rocklatan	Latanoprost 0.005%/netarsudil 0.02%	BAK 0.02%
Vyzulta	Latanoprostene 0.024%	BAK 0.02%
Betagan	Levobunolol 0.25%, 0.5%	BAK 0.004%
Rhopressa	Netarsudil 0.02%	BAK 0.015%
Isopto Carpine	Pilocarpine 1%	BAK 0.01%
Timoptic	Timolol 0.25%, 0.5%	BAK 0.01%

EYE DROPS CONTAINING ALTERNATIVE PRESERVATIVES		
Alphagan P	Brimonidine 0.1%, 0.15%	Purite® (stabilized oxychloro complex) 0.005%
Xelpros	Latanoprost 0.005%	Potassium sorbate
Timoptic-XE	Timolol-XE 0.25%, 0.5%	Benzododecinium bromide 0.012%
Travatan Z	Travoprost 0.004%	sofZia®

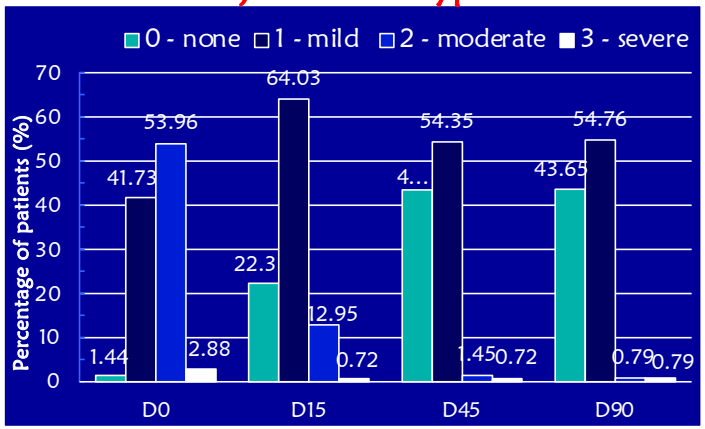
PRESERVATIVE-FREE EYE DROPS		
Cosopt PF	Dorzolamide 2%/timolol 0.5%	Preservative-free
PF Latanoprost	**Latanoprost 0.005%**	**Preservative-free**
Zioptan	Tafluprost 0.0015%	Preservative-free
Timoptic in Ocudose	Timolol 0.25%, 0.5%	Preservative-free

BAK is the most used preservative in topical ophthalmic formulations

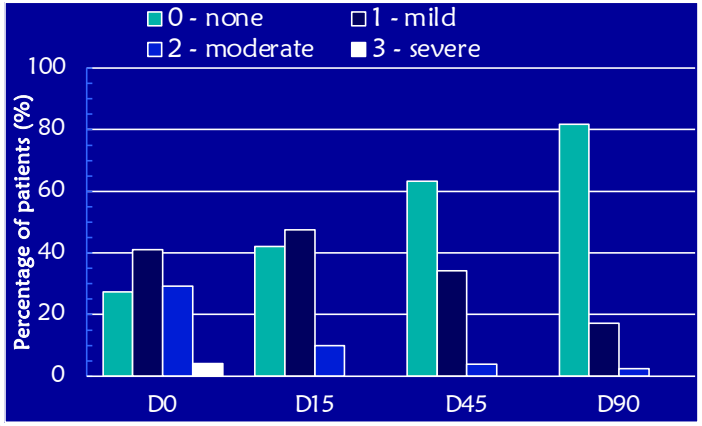
PF-Latanoprost has been approved by the FDA for use in the United States.

The RELIEF study: switching from preserved latanoprost to preservative free latanoprost for 3 months n=140)[1]

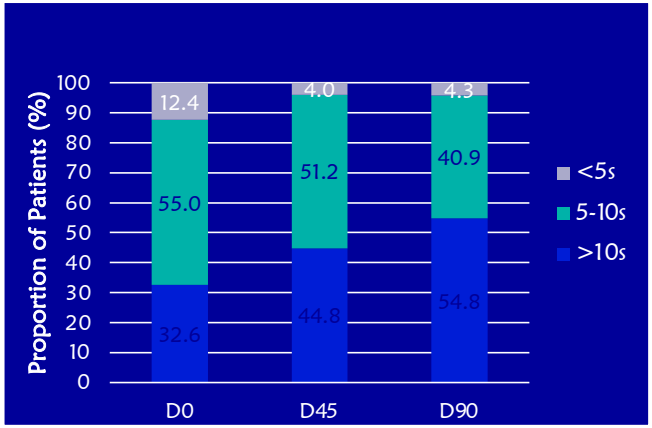
Conjunctival Hyperemia



Blepharitis symptoms



Tear Break-up Time (TBUT)



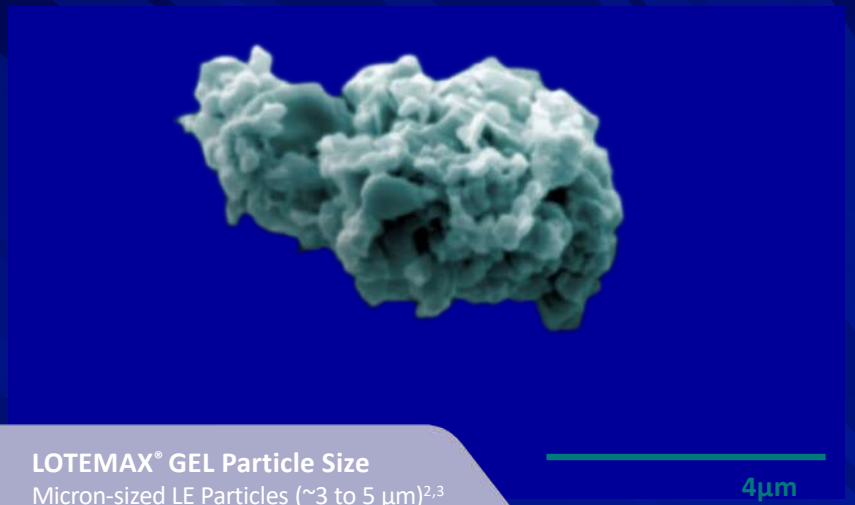
- **Conjunctival hyperemia:** Following the change to PF-latanoprost, there was a progressive decrease in the prevalence of moderate-to-severe conjunctival hyperemia, to 13.7% of patients at D15, 2.2% at D45 and 1.6% at D90 (p<0.0001).
- **Blepharitis:** proportion of patients with no signs of blepharitis increased from 27.3% at D0 to 81.7% after 90 days of PF-latanoprost treatment (p<0.0001).
- **TBUT:** improved compared with baseline (D0), in 23.4% of patients at D45 (p=0.0023) and in 30.7% of patients at D90 (p<0.0001).

*This study was conductted at 8 glaucoma centers in Poland

1. Misiuk-Hojlo M et al., European Journal of Ophthalmology. 2019 Mar;29(2):210-215. doi: 10.1177;

MOA versus MOD

- Mechanism of Action – MOA
  - Rhopressa
  - Miebo
  - Xdemvy
- Mechanism of Delivery – MOD
  - Various loteprednol products
    - Lotemax SM 0.38% and TID
  - Various Cyclosporin products



LOTEMAX® GEL Particle Size
Micron-sized LE Particles (~3 to 5 µm)[2,3]

4µm

LOTEMAX® SM Particle Size
Submicron-sized LE Particles
(~0.4 to 0.6 µm)[2,3]

4µm

Receptors

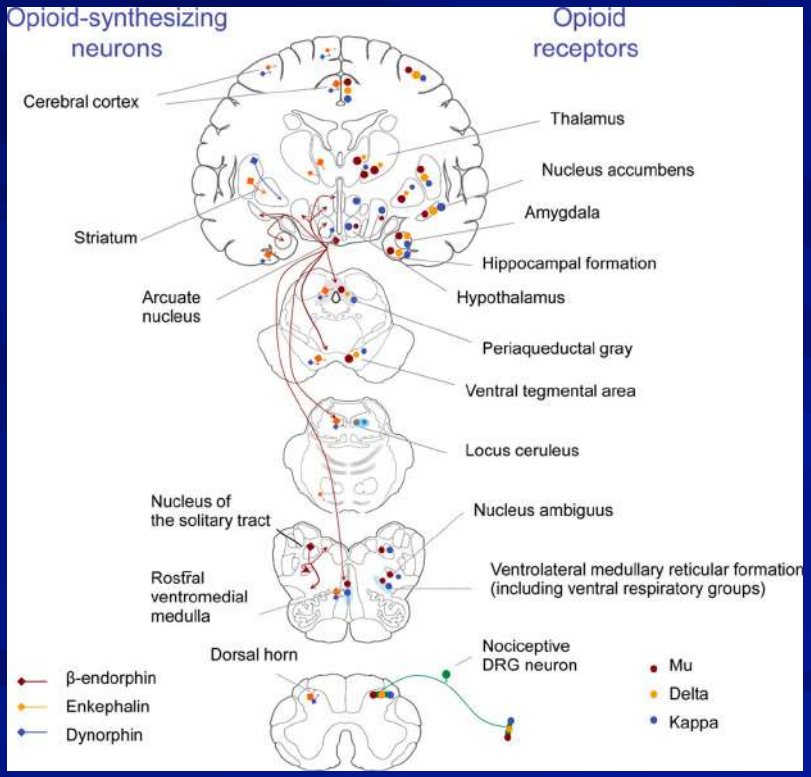
- Opioids relieve pain and induce pain relief by binding to the opioid receptors (mu, kappa, delta) in the brain and spinal cord:
- **Mu, kappa, delta** receptors in other places of the body = ADRs
  - ★ Mu: analgesia, euphoria, miosis, sedation, constipation, respiratory depression, addiction
  - ★ Kappa: analgesia, diuresis, sedation, miosis, dysphoria, psychomimetic effects, respiratory depression, constipation
  - ★ Delta: analgesia

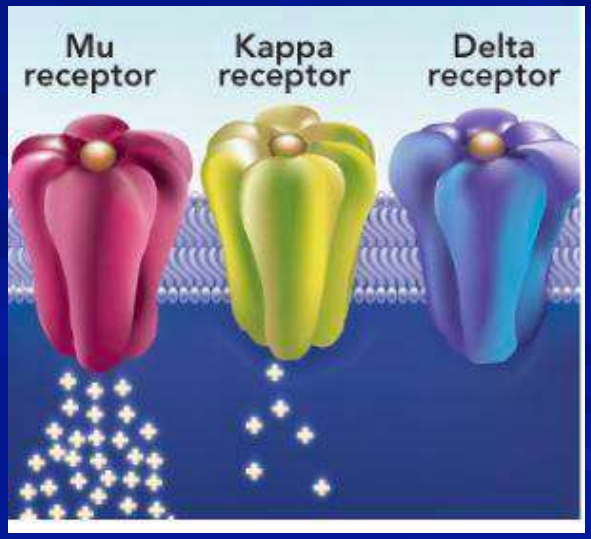
Table 1

OPIOID RECEPTORS	
Opioid Receptor Class	Effects
Mu_1	Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential
Mu_2	Respiratory depression, cardiovascular and gastrointestinal effects, miosis, urinary retention
Delta	Spinal analgesia, cardiovascular depression, decreased brain and myocardial oxygen demand
Kappa	Spinal analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system

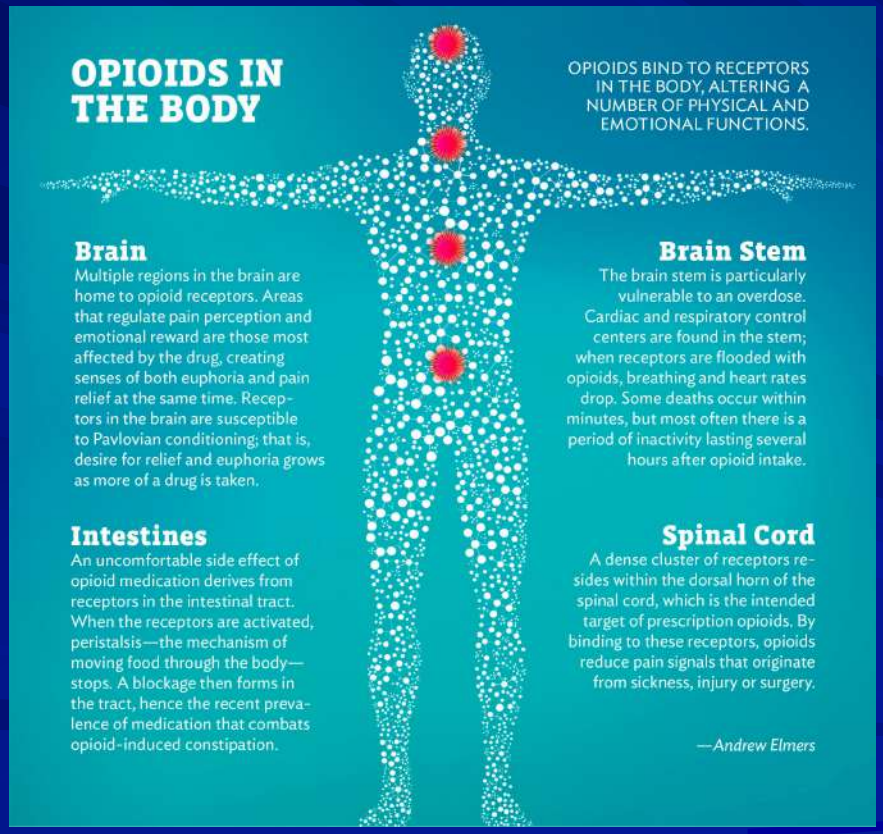
Adapted from references 2 and 3.

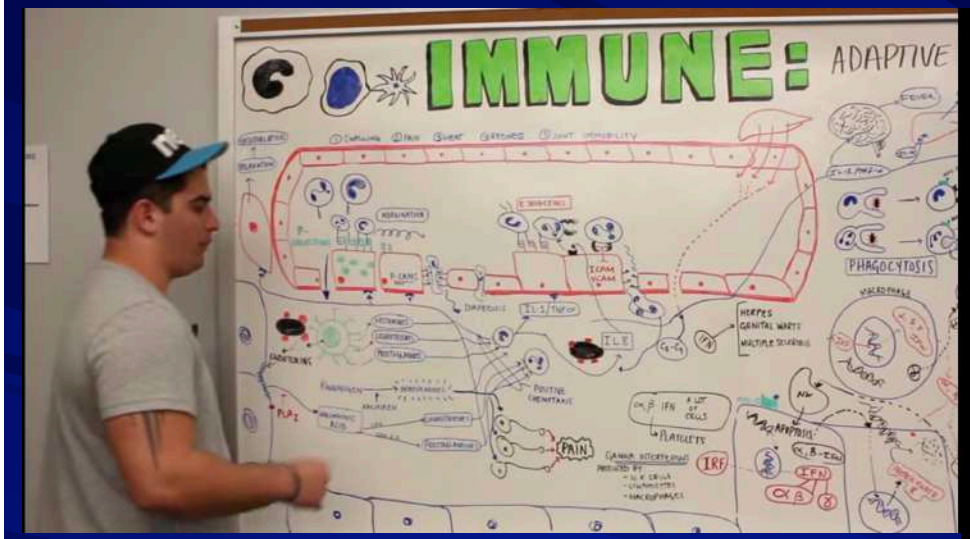
Mu, Delta, and Kappa Receptors

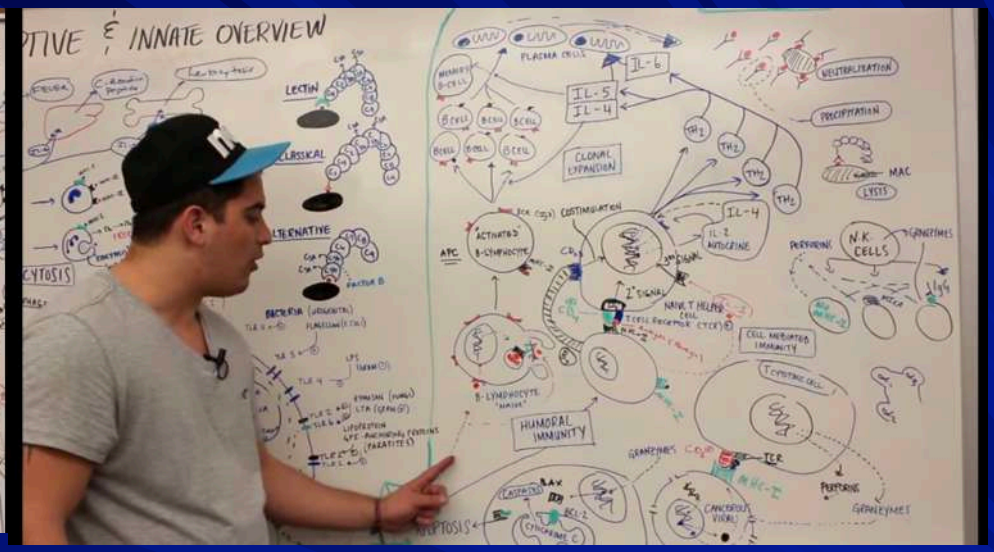


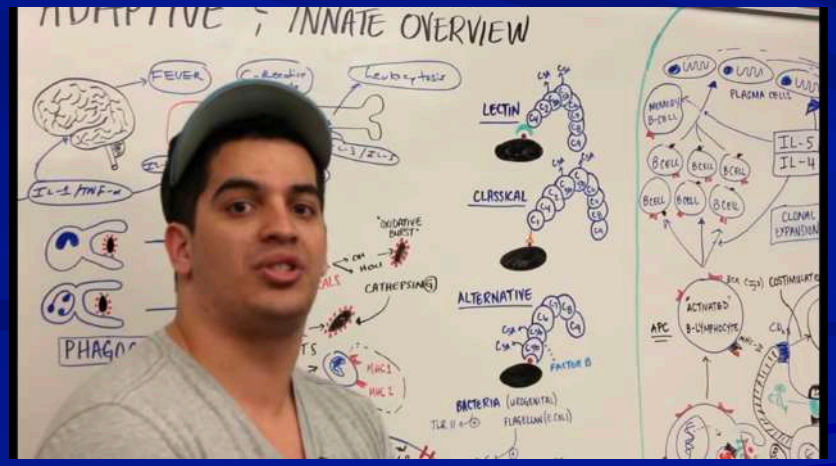


Receptors

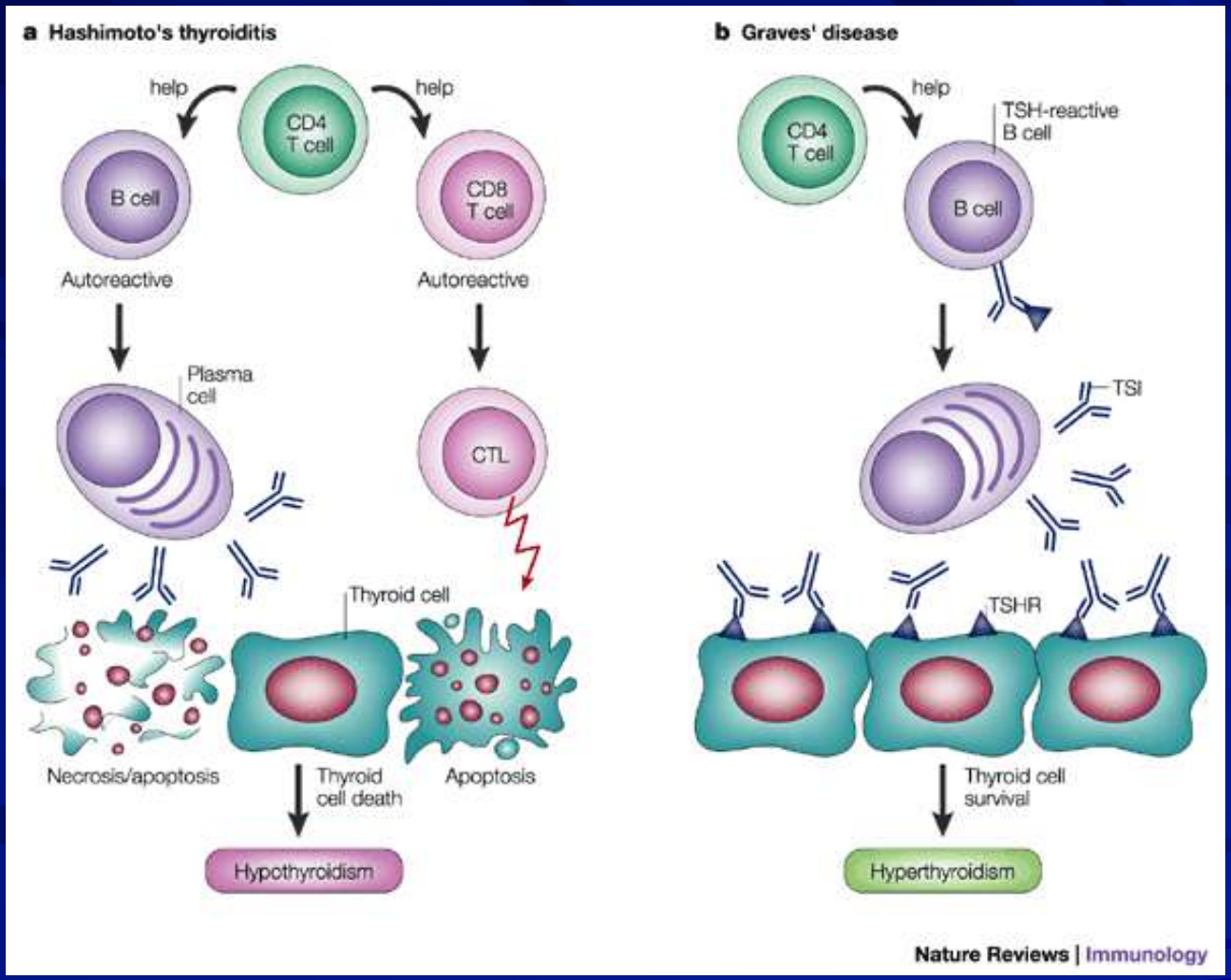

OPIOIDS IN THE BODY
OPIOIDS BIND TO RECEPTORS IN THE BODY, ALTERING A NUMBER OF PHYSICAL AND EMOTIONAL FUNCTIONS.
Brain
Multiple regions in the brain are home to opioid receptors. Areas that regulate pain perception and emotional reward are those most affected by the drug, creating senses of both euphoria and pain relief at the same time. Receptors in the brain are susceptible to Pavlovian conditioning; that is, desire for relief and euphoria grows as more of a drug is taken.
Brain Stem
The brain stem is particularly vulnerable to an overdose. Cardiac and respiratory control centers are found in the stem; when receptors are flooded with opioids, breathing and heart rates drop. Some deaths occur within minutes, but most often there is a period of inactivity lasting several hours after opioid intake.
Intestines
An uncomfortable side effect of opioid medication derives from receptors in the intestinal tract. When the receptors are activated, peristalsis—the mechanism of moving food through the body—stops. A blockage then forms in the tract, hence the recent prevalence of medication that combats opioid-induced constipation.
Spinal Cord
A dense cluster of receptors resides within the dorsal horn of the spinal cord, which is the intended target of prescription opioids. By binding to these receptors, opioids reduce pain signals that originate from sickness, injury or surgery.
—Andrew Elmers







Ninja Nerd Science
YouTube



Published: 01 March 2002

Autoimmune thyroid disease: new models of cell death in autoimmunity

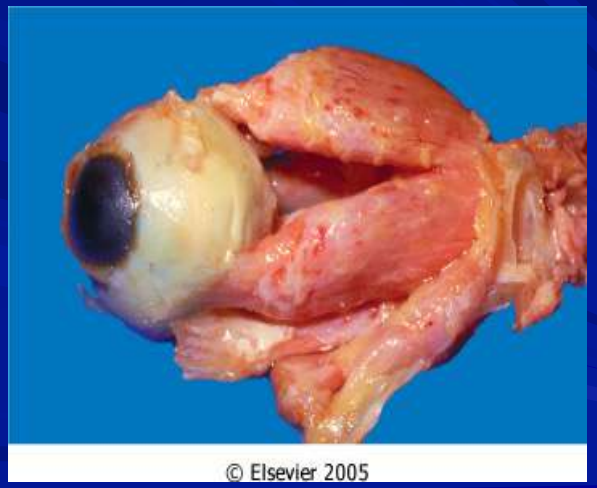
Giorgio Stassi & Ruggero De Maria

Nature Reviews Immunology **2**, 195–204 (2002) | Cite this article

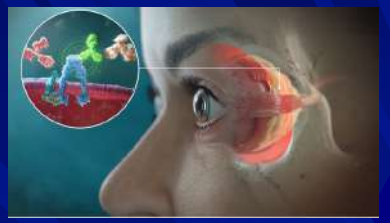
Key Points

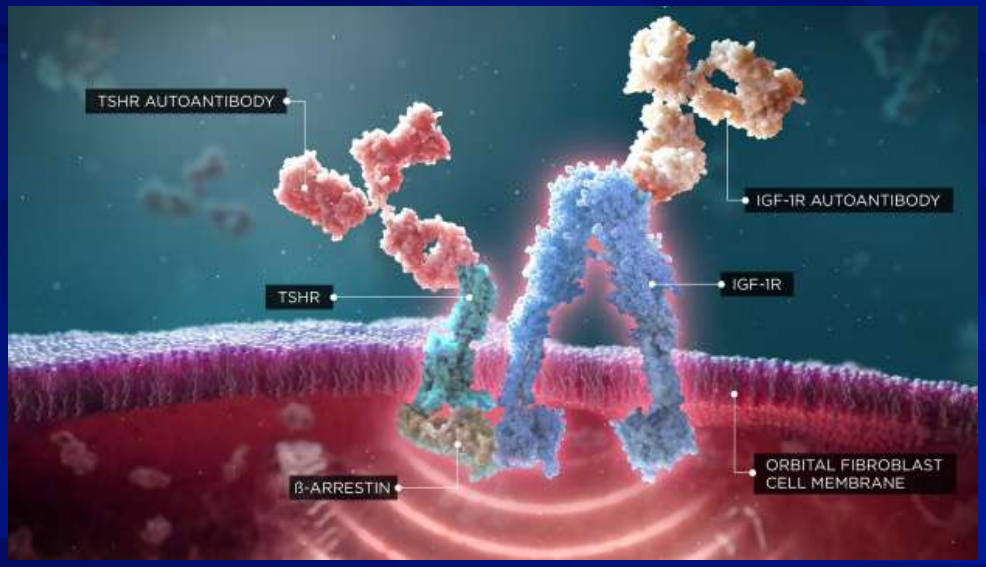
Teprotumumab-trbw (Tepezza)

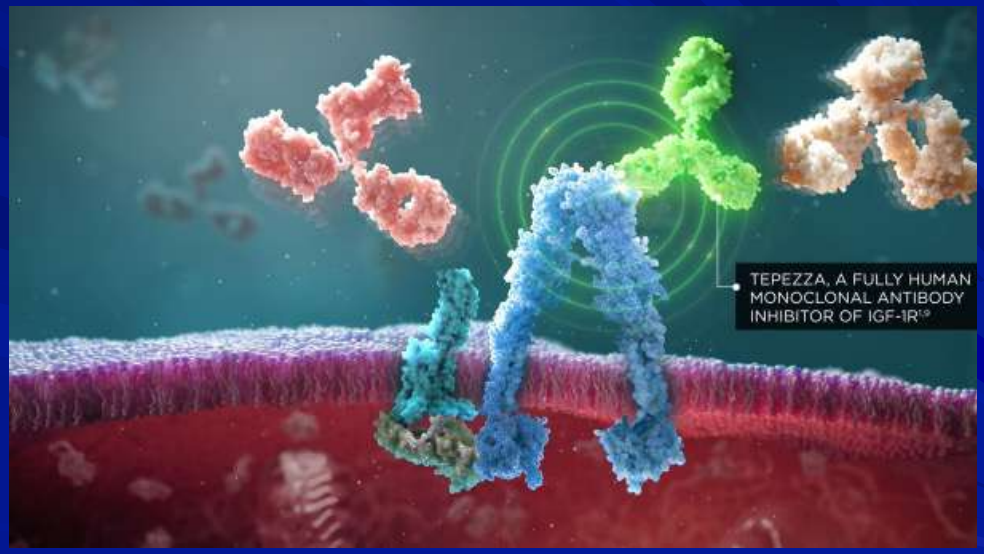
- Horizon Therapeutics – HQ Dublin, Ireland and US based Chicago
- Biologic pharmaceutical
  - Chinese Hamster Ovary
  - Infusion, 8 total, every 3 weeks
- Thyroid eye disease
  - IGR-1 (Insulin like growth factor 1) and TSH receptors are over expressed
- IGF-1 receptor inhibitor monoclonal antibody
  - 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)

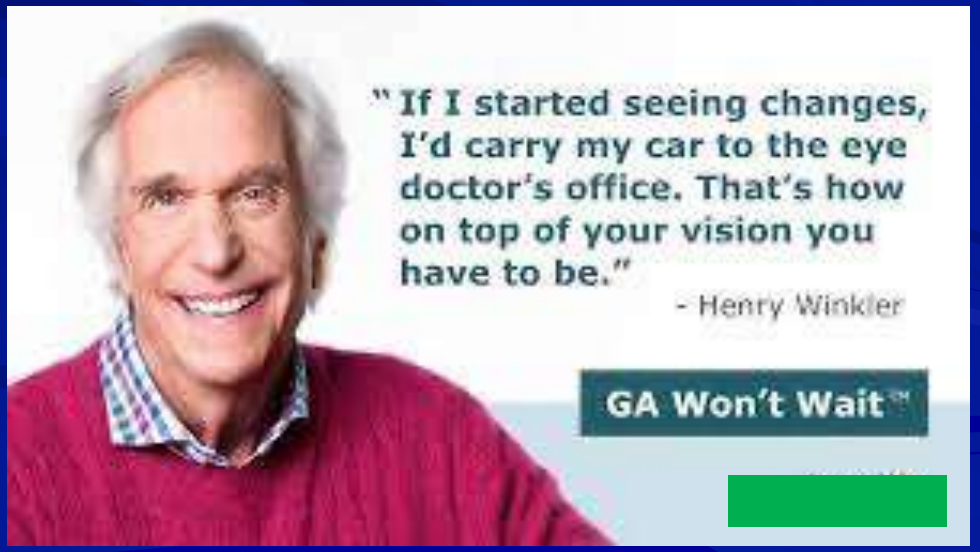






https://www.tepezza.com/hcp/tepezza-moa/


FOX
8
HENRY WINKLER SPREADS AWARENESS OF GEOGRAPHIC ATROPHY, A FORM OF MACULAR DEGENERATION


"If I started seeing changes, I'd carry my car to the eye doctor's office. That's how on top of your vision you have to be."
- Henry Winkler
GA Won't Wait™

visiblegenomics.slingrs.io

2 of 3 PATIENT'S RISK OF ED AMD **LOW**

CONTRIBUTION TO RISK RESULTS

The AMD Lifetime Risk is calculated based upon the patient's genetics, ocular findings, demographic and behavior status. The table below lists the patient's individual factors contributing to their individual risk.

RISK FACTORS

DESCRIPTION OF CONTRIBUTION

PATIENT FACTOR MEASURED	LOWER RISK	MODERATE RISK	HIGHER RISK	PATIENT RESULTS
AMD Grading	0-2 Factors	3 Factors	4 Factors	LOWER
Genetic Markers	Low	Moderate	High	LOWER
Race	Non-White	-	White	HIGHER
Smoking Status	Never	Past	Current	LOWER
BMI Score	<25	25-29	≥30	HIGHER
Gender	Male	-	Female	LOWER
Age (years)	55-64	65-74	≥75	LOWER

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	12/01/2021	0-1235	P-1192

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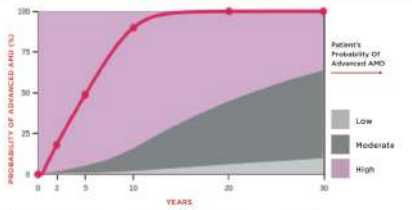
CURRENT AGE **60** RISK OF ADVANCED AMD

PATIENT'S PROBABILITY OF ADVANCED AMD **HIGH**

2 YEARS	18%
5 YEARS	49%
10 YEARS	90%
20 YEARS	100%
30 YEARS	100%



Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	11/24/2021	0-1200	P-1196

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2 of 3 PATIENT'S RISK OF ED AMD **MODERATE**

CONTRIBUTION TO RISK RESULTS

The AMD Lifetime Risk is calculated based upon the patient's genetics, ocular findings, demographic and behavior status. The table below lists the patient's individual factors contributing to their individual risk.

RISK FACTORS

DESCRIPTION OF CONTRIBUTION

PATIENT FACTOR MEASURED	LOWER RISK	MODERATE RISK	HIGHER RISK	PATIENT RESULTS
AMD Grading	0-2 Factors	3 Factors	4 Factors	LOWER
Genetic Markers	Low	Moderate	High	MODERATE
Race	Non-White	-	White	HIGHER
Smoking Status	Never	Past	Current	LOWER
BMI Score	<25	25-29	≥30	LOWER
Gender	Male	-	Female	HIGHER
Age (years)	55-64	65-74	≥75	LOWER

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	11/24/2021	0-1239	P-1195

AMD LIFETIME RISK REPORT
age related macular degeneration

RISK FACTORS

GENETIC CONTRIBUTION

GENE	SNPS	ALLELE	RISK	PATIENT RESULTS
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	rs10490924	GG	Lower Risk (Reference)	X
		GT	Moderate Risk	
		TT	Higher Risk	
CFH (Complement Factor H)	rs1061170	TT	Highly Protective	X
		CT	Moderately Protective	
		CC	Higher Risk (Reference)	
	rs121913059	CC	Lower Risk (Reference)	X
		CT	Moderate Risk	
		TT	Higher Risk	
	rs1410996	AA	Highly Protective	
		GA	Moderately Protective	X
		GG	Higher Risk (Reference)	
C3 (Complement Component 3)	rs2230199	GG	Lower Risk (Reference)	X
		GC	Moderate Risk	
		CC	Higher Risk	

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	[redacted]	[redacted]	[redacted]

AMD PROGRESSION REPORT
age related macular degeneration

RISK FACTORS

DESCRIPTION OF CONTRIBUTION

PATIENT FACTOR MEASURED	LOWER RISK	MODERATE RISK	HIGHER RISK	PATIENT RESULTS
AMD Grading	0-2 Factors	3 Factors	4 Factors	MODERATE
Genetic Markers	Low	Moderate	High	HIGHER
Race	Non-White	-	White	HIGHER
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Gender	Male	-	Female	LOWER
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		CC	Higher Risk (Reference)	
	rs121913059	CC	Lower Risk (Reference)	X
		CT	Moderate Risk	
		TT	Higher Risk	
	rs1410996	AA	Highly Protective	
		GA	Moderately Protective	
		GG	Higher Risk (Reference)	X
C3 (Complement Component 3)	rs2230199	GG	Lower Risk (Reference)	
		GC	Moderate Risk	
		CC	Higher Risk	X

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	11/24/2021	0-1200	P-1196

AMD LIFETIME RISK REPORT
age related macular degeneration

RISK FACTORS

GENETIC CONTRIBUTION

GENE	SNPS	ALLELE	RISK	PATIENT RESULTS
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	rs10490924	GG	Lower Risk (Reference)	
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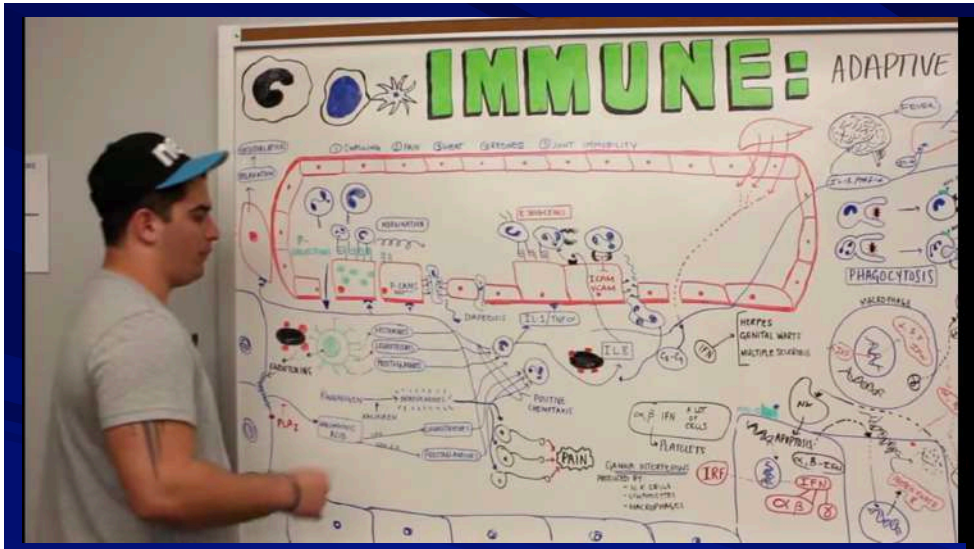
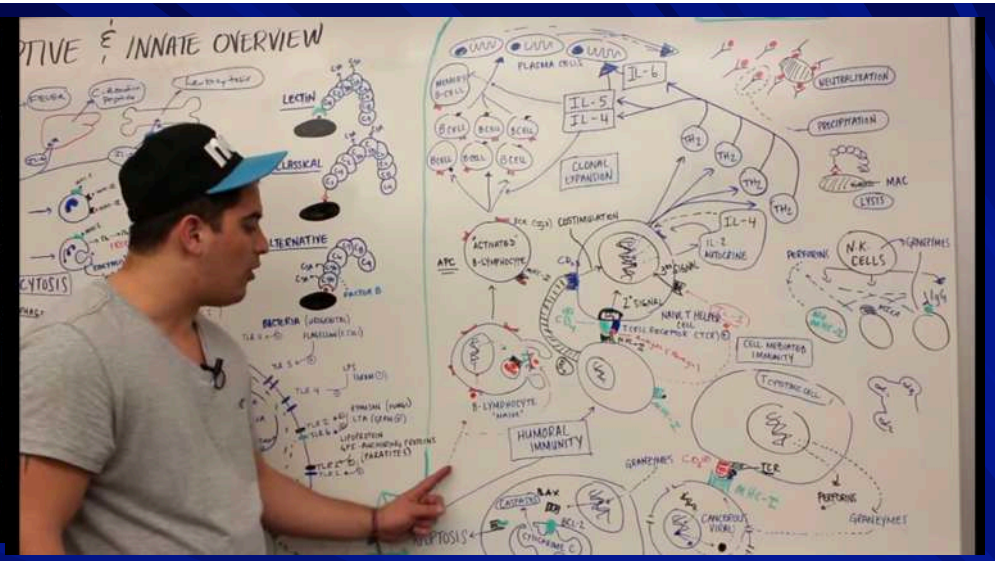
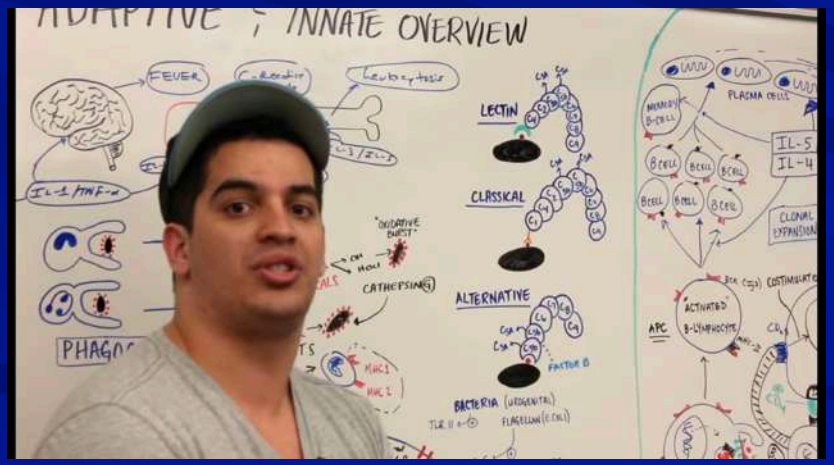
George Miles, M.D., Ph.D.	[redacted]	[redacted]	[redacted]







Ninja Nerd Science
YouTube

Complement factor H in AMD: Bridging genetic associations and pathobiology

Christopher B. Toomey [a, b, 1] ... Catherine Bowes Rickman [a, b]

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https://doi.org/10.1016/j.preteyeres.2017.09.001

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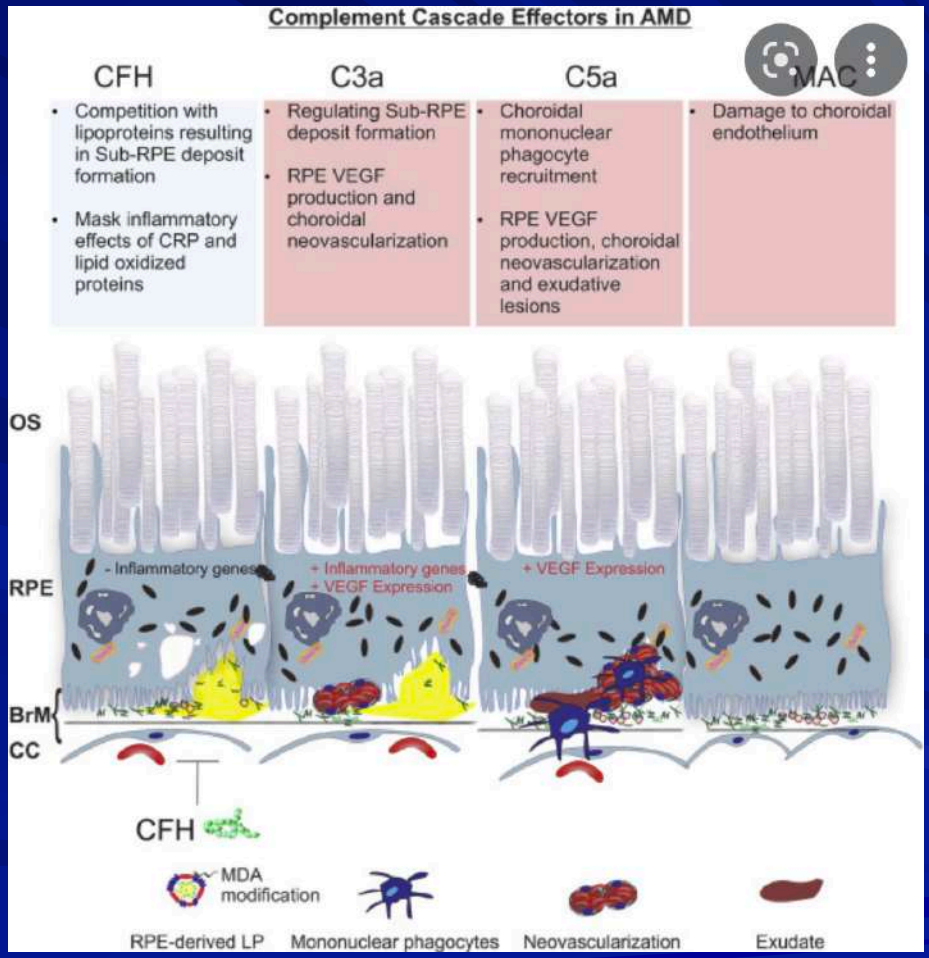
Abstract

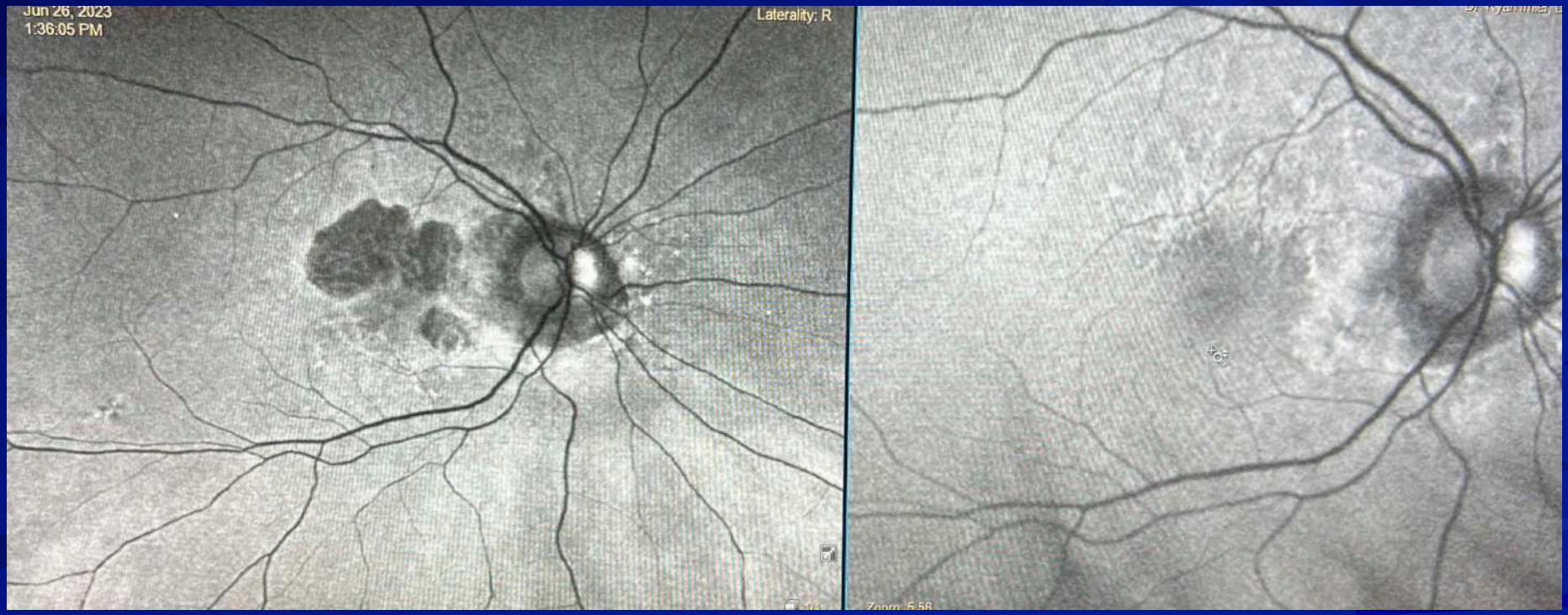
Age-Related Macular Degeneration (AMD) is a complex multifactorial disease characterized in its early stages by lipoprotein accumulations in Bruch's Membrane (BrM), seen on fundoscopic exam as drusen, and in its late forms by neovascularization ("wet") or geographic atrophy of the Retinal Pigmented Epithelial (RPE) cell layer ("dry"). Genetic studies have strongly supported a relationship between the alternative complement cascade, in particular the common H402 variant in Complement Factor H (CFH) and development of AMD. However, the functional significance of the CFH Y402H polymorphism remains elusive. In this

FEEDBACK

sciencedirect.com



Geographic Atrophy

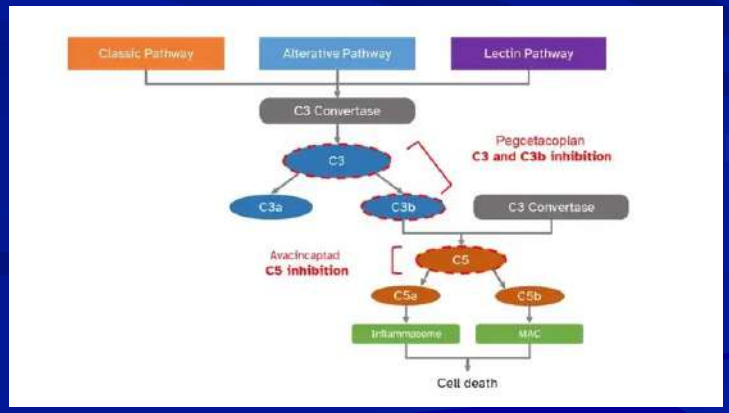


Syfovre (pegcetacoplan injection)

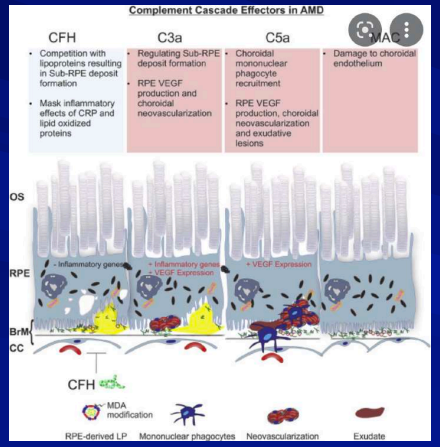
- Apellis Pharmaceuticals
- February 2023 – approved
- Indication: Treatment of geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD)
- Mechanism of action: targeted C3 inhibition therapy
  - Regulating excessive activation of the complement cascade, which could lead to the onset and progression of diseases
- Administered: Intravitreal injection
- Macular degeneration is associated with overaction of the complement system
- C3 activation – inflammation, phagocytosis, cell membrane disruption
- C3 inhibitor is mechanism of action (MOA)
  - Synthetic, peptide-based inhibitor of C3
  - Prevents overactivation

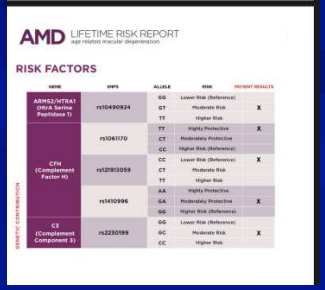
Izervay (avacincaptad pegol intravitreal solution)

- Iveric Bio
- August 2023 – approved
- Indication: treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
- PEGylated RNA aptamer
- Mechanism of action: complement C5 inhibitor formulated to slow GA progression
- Macular degeneration is associated with overaction of the complement system



Inflammatory Lifestyle, Genetics, Epigenetics, and Over Reactive Immune System





Ingredients

Ingredients	Amount	% Daily Value
Serving Size: 1 Packet		
Vitamin A (83% as Beta Carotene (1875 mcg RAE) from *Blakeslea trispora*, and Vitamin A palmitate) (375 mcg RAE)	2250 mcg RAE	250%
Vitamin C (as Calcium Ascorbate)	200 mg	222%
Vitamin D (as Cholecalciferol)	5 mcg (200 IU)	25%
Vitamin E (as D-Alpha-Tocopheryl Acetate, D-Alpha Tocopherol, Tocotrienols)	50.3 mg	335%
Vitamin K (as Phytonadione)	20 mcg	17%
Thiamin (as Thiamine Mononitrate)	3.75 mg	313%
Riboflavin (as Riboflavin)	4.25 mg	327%
Niacin (as Niacinamide)	17.5 mg NE	109%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	500 mcg DFE (300 mcg folic acid)	125%
Vitamin B12 (as Cyanocobalamin)	75 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	50 mcg	33%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30%
Zinc (as Zinc Bisglycinate)	75 mg	68%
Selenium (as L-Selenomethionine, Sodium Selenite)	70 mcg	127%
Copper (as Copper Bisglycinate)	0.5 mg	56%
Manganese (as Manganese Bisglycinate)	1 mg	43%
Chromium (as Chromium Nicotinate Glycinate)	100mcg	286%
Molybdenum (as Molybdenum Bisglycinate)	37.5 mcg	83%
Polyphenol and Flavonoid Blend	97.5 mg	*
Catechins (from *Camellia sinensis* Leaf Extract)	45 mg)	*
Quercetin	25 mg)	*
Grape Seed Extract (min. 95% Polyphenols)	12.5 mg)	*
Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg)	*
Resveratrol (from *Polygonum cuspidatum* root extract)	2.5 mg)	*
Mixed Tocopherols (Gamma, Delta & Beta Tocopherols)	5.3 mg	*
Alpha-Lipoic Acid	15 mg	*
Inositol (as Inositol)	5 mg	*
Carotenoid Blend	2.5 mg	*
Lycopene (as Lycopene)	(2.5 mg)	*
Lutein (from Marigold Flower Extract)	(1 mg)	*
Boron (as Boron Citrate)	1.5 mg	*
Vanadium (as Vanadyl Sulfate)	50 mcg	*

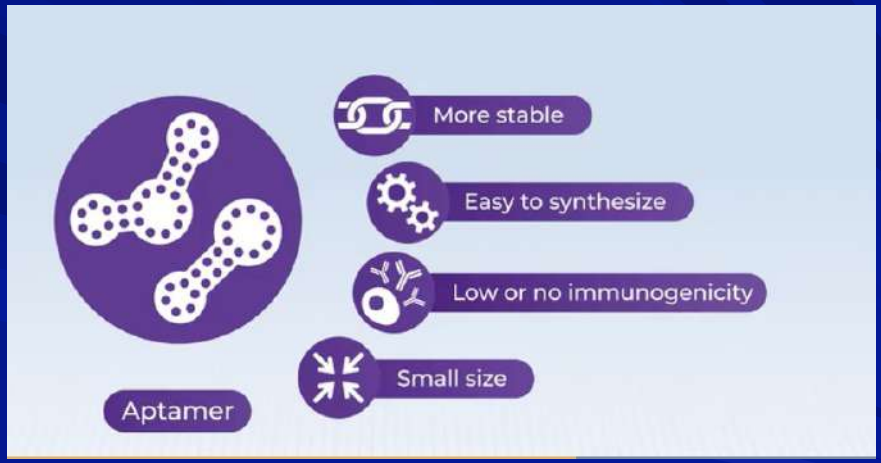
OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Croscarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder).

Evidence Based Medicine

Evidence Informed Risk Adjusted Medicine

Aptamer versus Antibody



Small Molecule Drugs versus Biologics

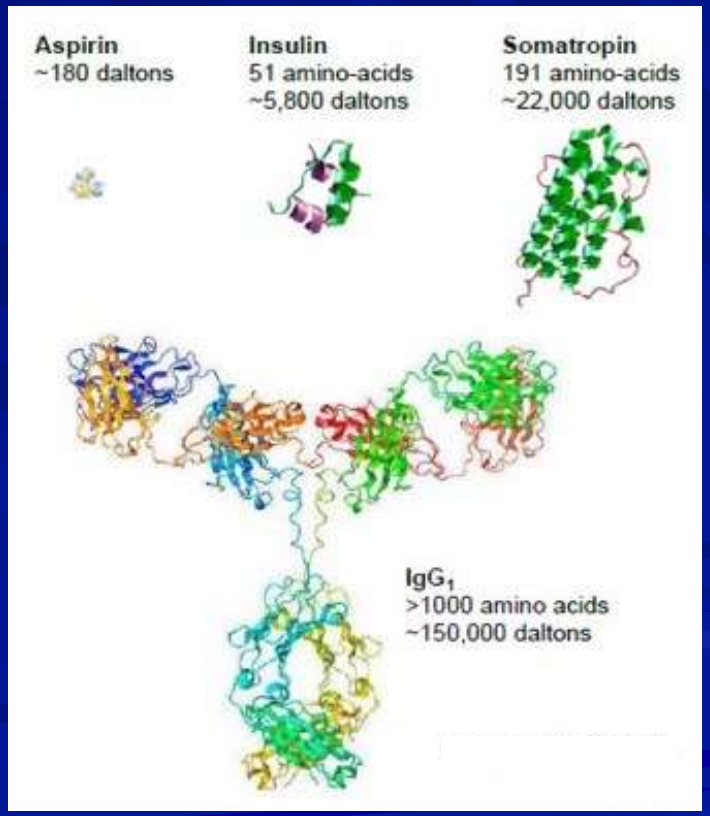
- Small molecule drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions
  - Organic chemistry
  - Inorganic chemistry
- Biologics are made by harvesting the substances produced and secreted by constructed cells
  - Genetic engineering – is the closet manufacturing process of a biologic drug

Size and Complexity of Biologic Drugs

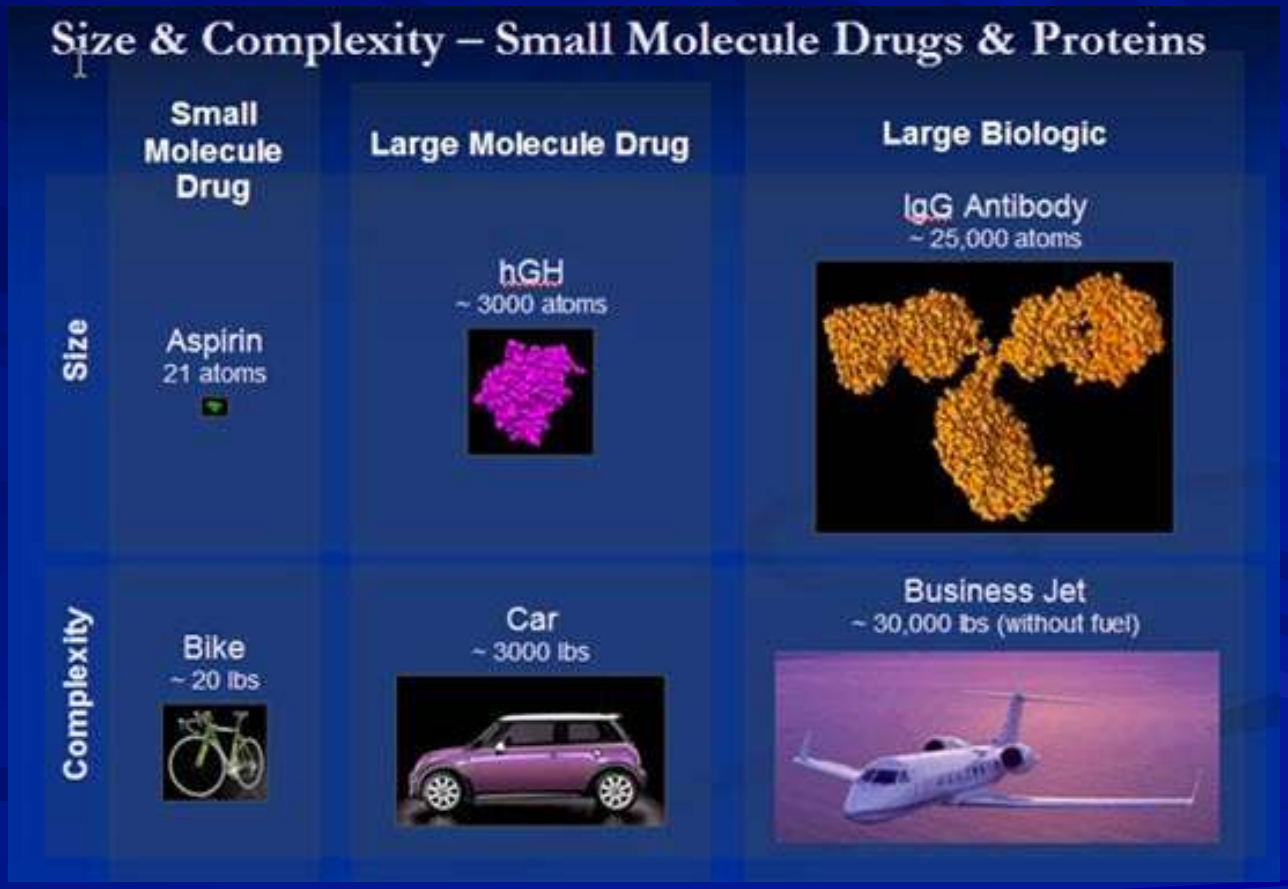
- Small molecule drugs can be taken orally
  - Tend to work in the body within cells
- Biologics are significantly larger in size
  - Typically injected and interact within the body in the bloodstream or on the surfaces of cells, rather than within the cells
- Small molecule drugs
  - Such as aspirin
  - Composed of only 20 to 100 atoms
- Small biologics
  - Such as hormones
  - Composed of 200 to 3000 atoms
- Large biologics
  - Such as antibodies
  - Composed of 5000 to 50,000 atoms

Biologic Drugs versus Small Molecule Drugs

- Biologic Drugs
  - Larger, complex, dynamic structures
  - Diverse populations of molecules
    - Not easily characterized
  - Complicated manufacturing
  - Example: Teprotumumab (Tepezza)
- Small Molecule Drugs
  - Synthetic
  - Manufactured using a defined chemical process
  - Smaller and simpler
  - Example: Aspirin



Size and Complexity of Biologic Drugs



https://www.azbio.org/small-molecules-large-biologics-and-the-biosimilar-debate

Making Biologics

A piece of DNA is inserted into a living cell— yeast, bacterial, viral, or mammalian cell

↓

Cell then produces a large amount of a specific molecule (e.g. protein)

↓

Desired molecular isolation (living cells/material removed - only the desired molecules are left)

↓

The isolated molecules become the active ingredient in a biologic drug

Treatments for Choroidal Neovascularization (CNV)

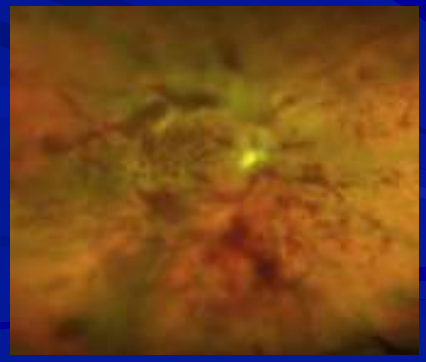
- Where is all started in the eye
- Disorders of the blood vessels in the retina are responsible for some of the most common causes of blindness in the world
  - Retinopathy of prematurity
    - Important cause of blindness in children in middle-income countries
  - Diabetic retinopathy
    - Common 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

Past 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%



Eylea (aflibercept)

- Regeneron Pharmaceuticals, Inc
- Eylea 2 mg versus Eylea HD 8 mg
  - November 18, 2011 – Wet AMD (BLA)
  - July 29, 2014 – Diabetic Macular Edema
  - October 6, 2014 – Macula edema from retinal vein occlusion
  - May 25, 2015 – Diabetic retinopathy
  - August 17, 2018 – New Eylea (sBLA) – wet AMD
  - May 13, 2019 – Diabetic retinopathy (sBLA)
  - February 8, 2023 – ROP
    - Treatment of retinopathy of prematurity (ROP) in preterm infants
    - First pharmacological treatment for ROP in infants

  - Mechanism of action: vascular endothelial growth factor A (VEGF-A) and placental growth factor (PlGF) antagonists that stops the growth of abnormal blood vessels and leakage in the eyes in patients diagnosed with retinal diseases

Biologics License Application (BLA) supplemental Biologics License Application (sBLA)

Eylea (aflibercept)

August 18, 2023 at 6:35 PM EDT

« Back

EYLEA HD (AFLIBERCEPT) INJECTION 8 MG APPROVED BY FDA FOR TREATMENT OF WET AGE-RELATED MACULAR DEGENERATION (WAMD), DIABETIC MACULAR EDEMA (DME) AND DIABETIC RETINOPATHY (DR)

Approval based on the pivotal PULSAR and PHOTON trials in which EYLEA® HD demonstrated clinically equivalent vision gains to EYLEA (aflibercept) Injection 2 mg that were maintained with fewer injections

First and only treatment approved in wAMD and DME for immediate dosing at 8-week and up to 16-week intervals following three initial monthly doses

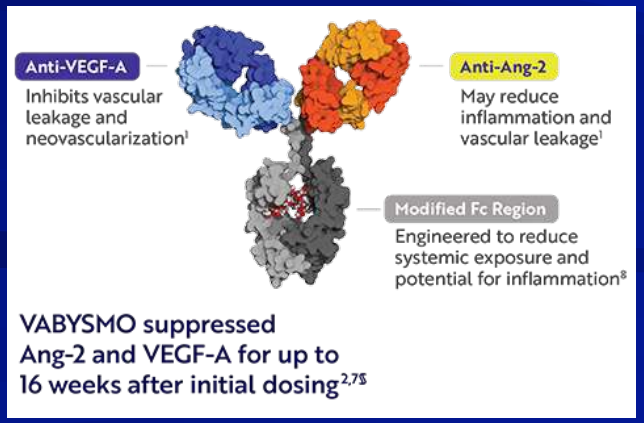
Eylea (aflibercept)

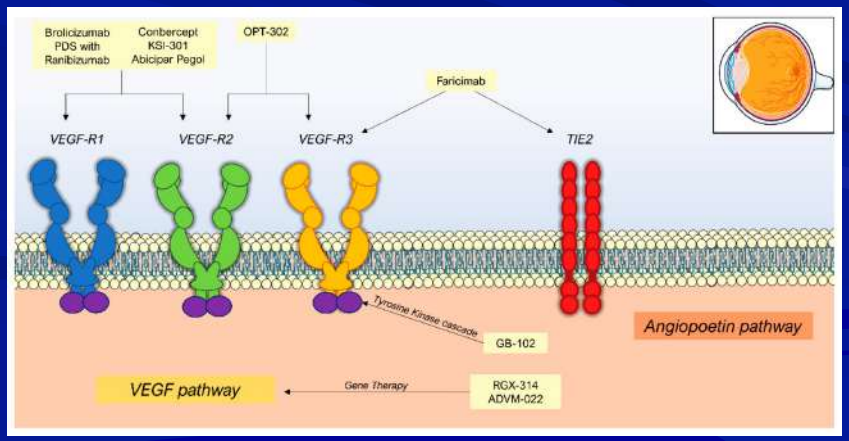
- Now have five approved indications to treat retinal conditions caused by ocular angiogenesis
  - Wet AMD
  - DME
  - Macular edema following retinal vein occlusion (RVO)
  - DR
  - ROP

- Eylea HD 8 mg
  - Wet AMD
  - DME

Vabysmo (faricimab-svoa)

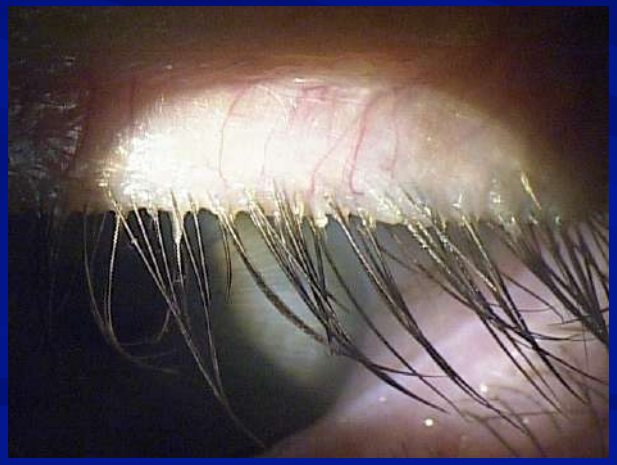
- Genentech
- Indications February 2022
  - ★ Wet age-related macular degeneration (AMD)
  - ★ Diabetic macular edema (DME)
- Indications October 2023
  - ★ Treat macular edema following retinal vein occlusion.
- Mechanism of action: vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor
- Administered: Intravitreal injection
- Extended dosing 1-4 months





Demodex Infestation

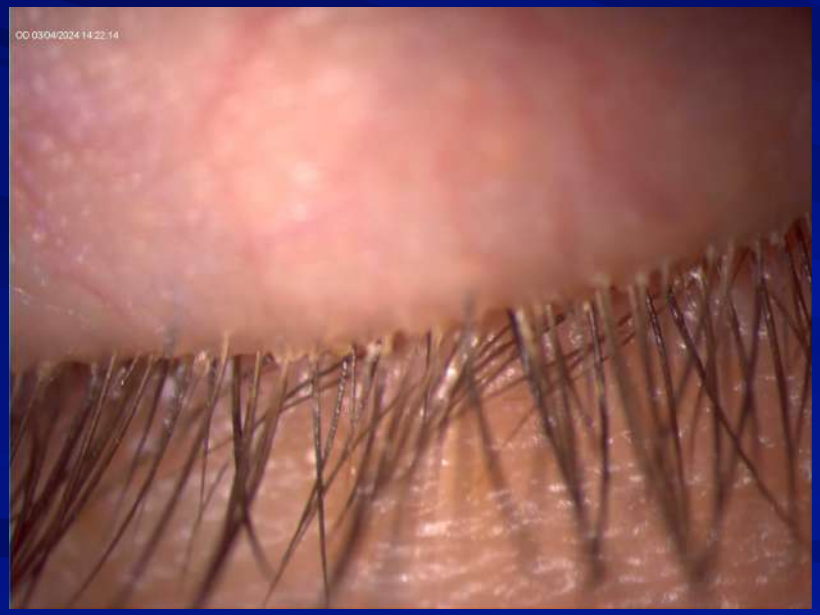
- Collarettes are pathognomonic sign of Demodex Infestation
- Collarettes are composed of mite waste products and eggs
  - ★ Regurgitated undigested material combined with epithelial cells, keratin, and mite eggs

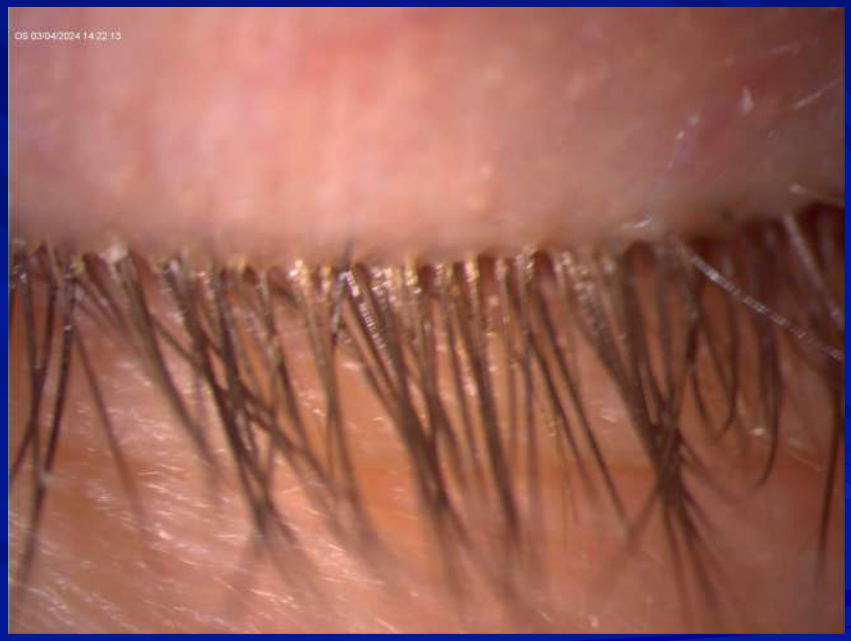


Xdemvy (lotilaner ophthalmic solution) 0.25%

- Tarsus Pharmaceuticals
- Indication: Demodex blepharitis
- Mechanism of action: lotilaner works as an antiparasitic agent to target parasite-specific GABA-Chloride (Cl) channels
  - Located within the nervous system channels of the Demodex mites
- Administration: Drops
- Dosing: 1 gtt BID x 6 weeks

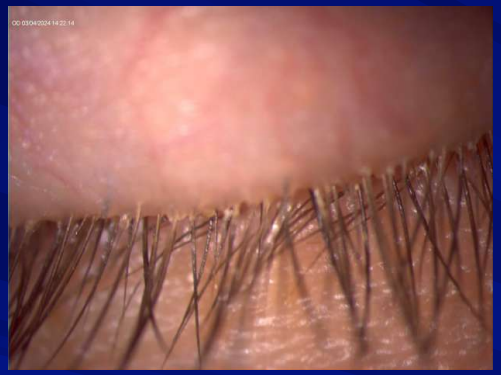
45-Year-Old White Man
Somewhat Symptomatic
October 30, 2023

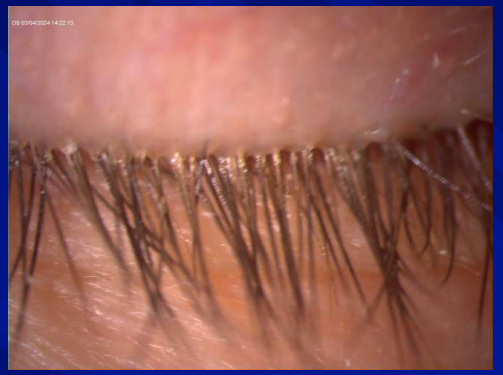


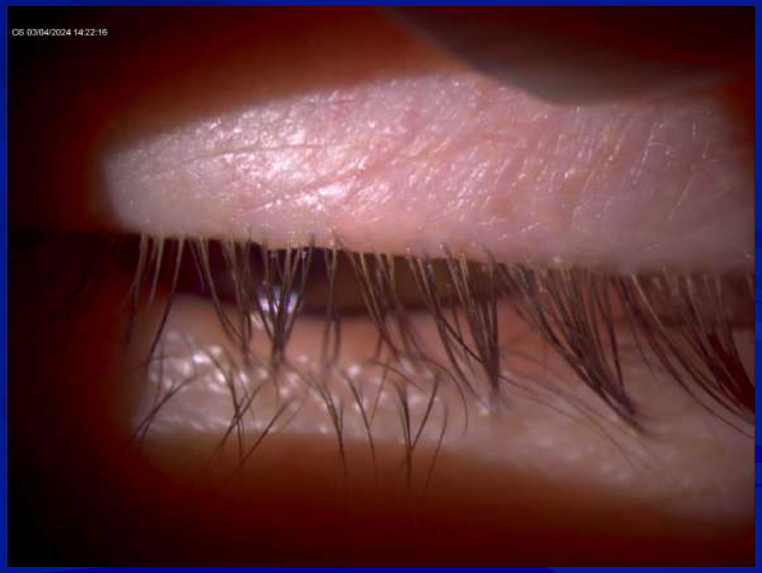


October 30, 2023 - December 4, 2023

5 weeks

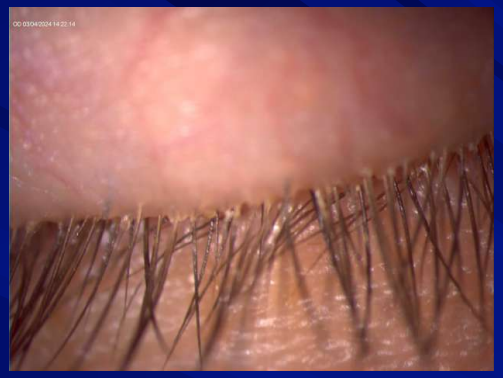


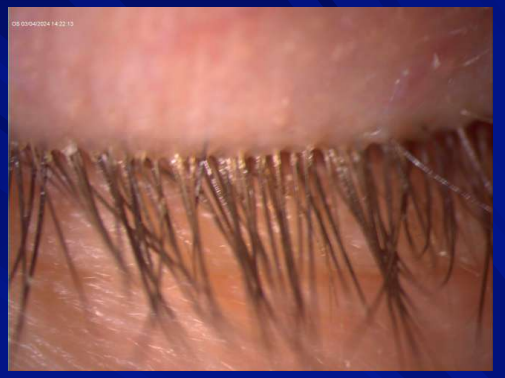




October 30, 2023

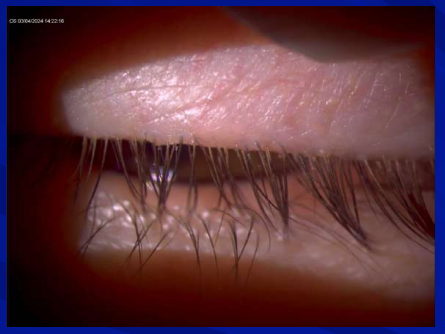
Xdemvy Rx written





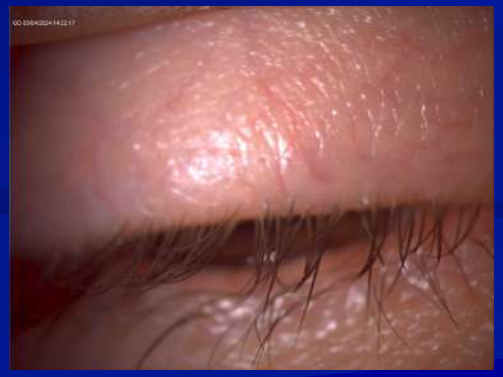
December 4, 2023

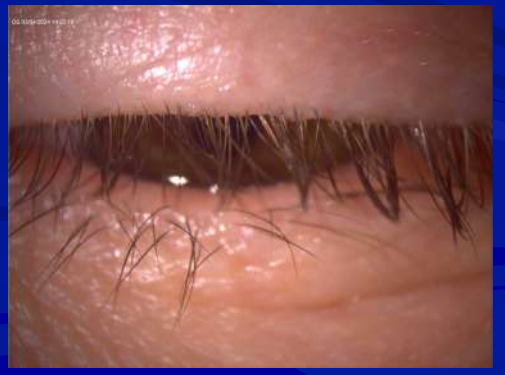
3 weeks treatment



January 9, 2024

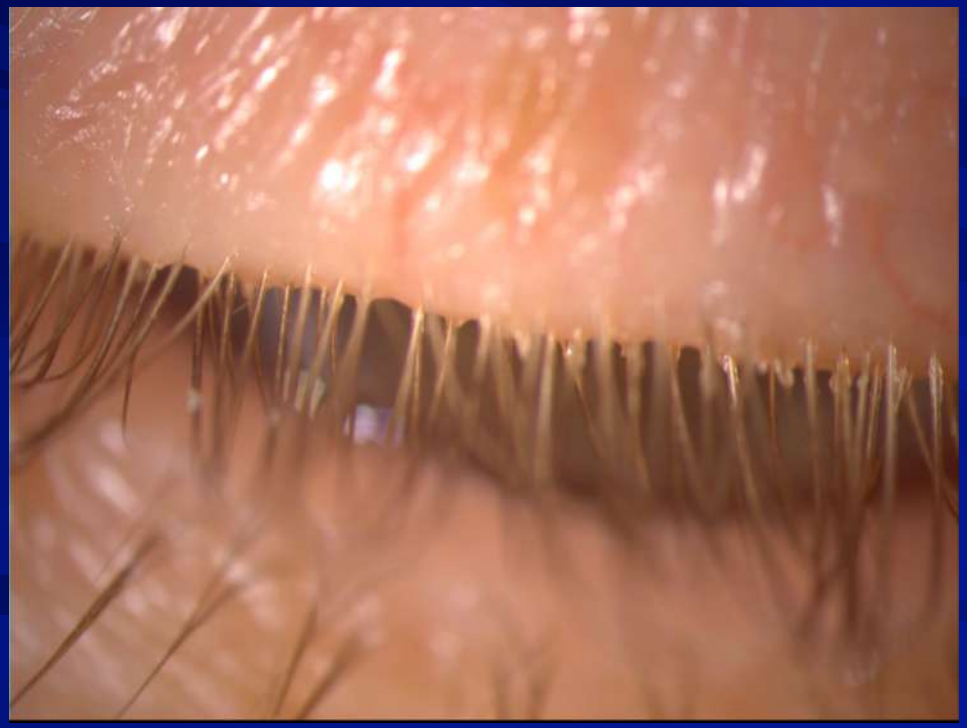
8 weeks since treatment started





Demodex Blepharitis treated with Xdemvy

Neurologist with Itchy Eyes and Eyelids
3 weeks post treatment



Video Examination

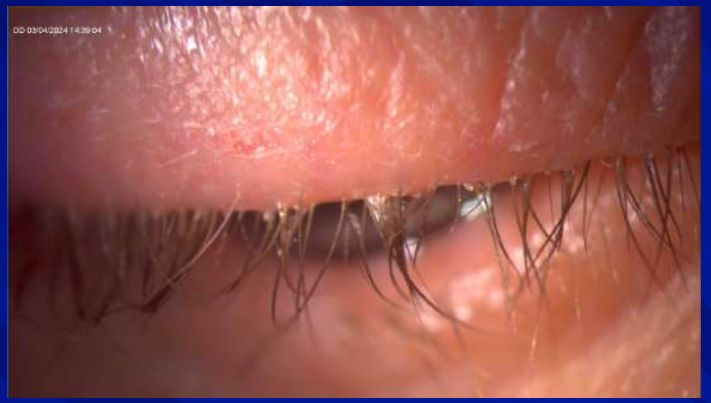
Larry with Itchy and Watery Eyes

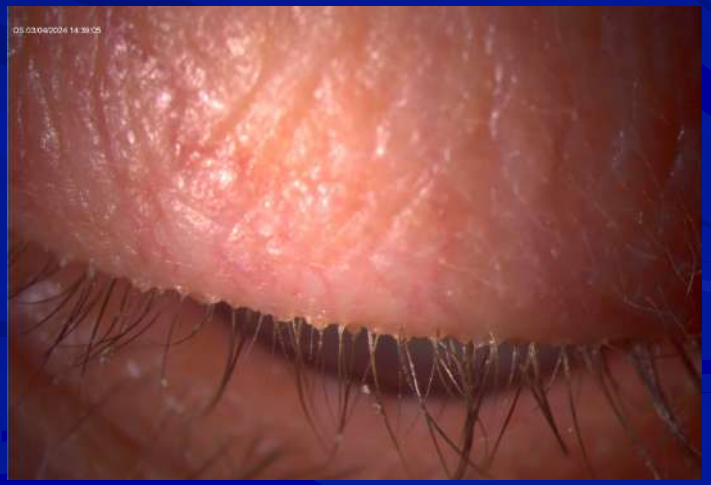
December 18, 2023

- 73 yo Caucasian man – wants 4th opinion on his itchy and watery eyes
- Past ocular treatments – Systane Ultra, Ivizia, Restasis, Xiidra, and "warm soaks"
- History of Pre-DM or DM, HTN, high cholesterol
- Meds: Monjaro, metformin, Farsica, Invokana, Losartan, Zocor, Vit D, glucosamine, and 81 mg ASA

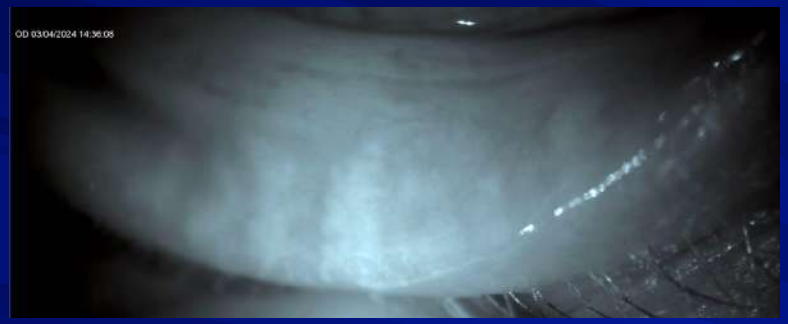
- Hand scanner: 27,000 (Raman Spectroscopy/Pharmanex)

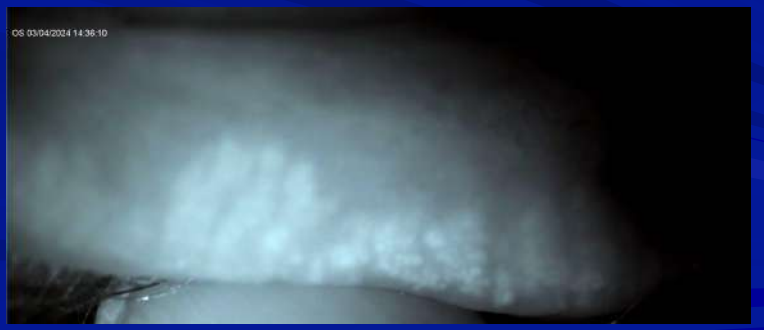
Larry with Itchy and Watery Eyes





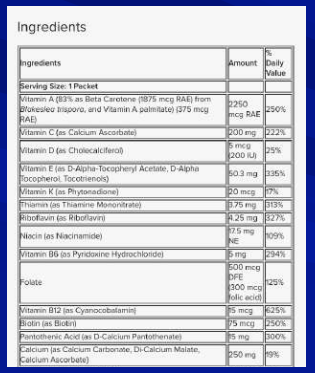
Larry with Itchy and Watery Eyes





Larry with Itchy and Watery Eyes

- Treatment:
  - ★ Lengthy discussion on his complex ocular surface issue
    - Systemic association
    - Environment involvement
    - Lid microbiome dysfunction/dysbiosis
    - Nutritional association
  - ★ Rx Xdemvy
  - ★ Rx LifePak and Marine Omega
  - ★ Continue Ivizia
  - ★ Schedule for IPL



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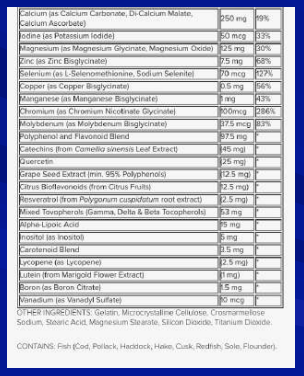
Niacin (as Niacinamide)	17.5 mg NE	109%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	500 mcg DFE (300 mcg folic acid)	125%
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%



Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	50 mcg	33%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30%
Zinc (as Zinc Bisglycinate)	7.5 mg	68%
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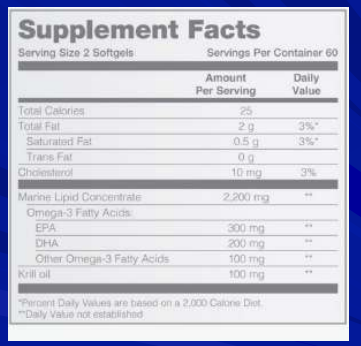
Molybdenum (as Molybdenum Bisglycinate)	37.5 mcg	83%
Polyphenol and Flavonoid Blend	97.5 mg	*
Catechins (from *Camellia sinensis* Leaf Extract)	45 mg	*
Quercetin	25 mg	*
Grape Seed Extract (min. 95% Polyphenols)	12.5 mg	*
Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg	*
Resveratrol (from *Polygonum cuspidatum* root extract)	2.5 mg	*
Mixed Tocopherols (Gamma, Delta & Beta Tocopherols)	5.3 mg	*
Alpha-Lipoic Acid	15 mg	*
Inositol (as Inositol)	5 mg	*
Carotenoid Blend	3.5 mg	*
Lycopene (as Lycopene)	2.5 mg)	*
Lutein (from Marigold Flower Extract)	1 mg)	*
Boron (as Boron Citrate)	1.5 mg	*
Vanadium (as Vanadyl Sulfate)	10 mcg	*

OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Crosmarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder).



Supplement Facts

Serving Size 2 Softgels — Servings Per Container 60

	Amount Per Serving	Daily Value
Total Calories	25	
Total Fat	2 g	3%*
Saturated Fat	0.5 g	3%*
Trans Fat	0 g	
Cholesterol	10 mg	3%
Marine Lipid Concentrate	2,200 mg	**
Omega-3 Fatty Acids:		
EPA	300 mg	**
DHA	200 mg	**
Other Omega-3 Fatty Acids	100 mg	**
Krill oil	100 mg	**

*Percent Daily Values are based on a 2,000 Calorie Diet.
**Daily Value not established

December 18, 2023

Xdemvy Rx written

Importance of looking down

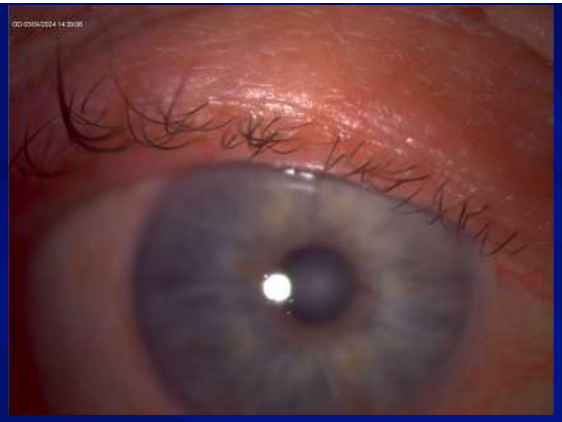
January 22, 2024

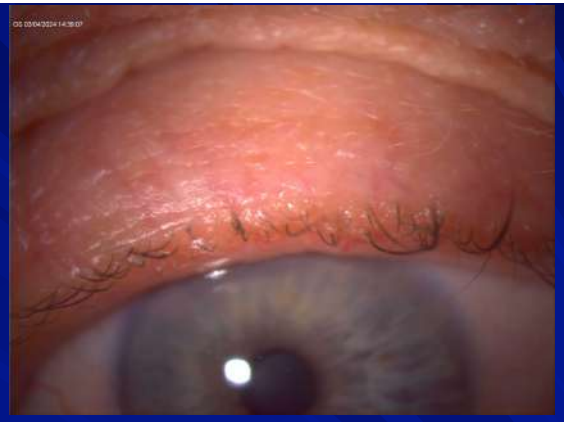
12 days S/P ILP

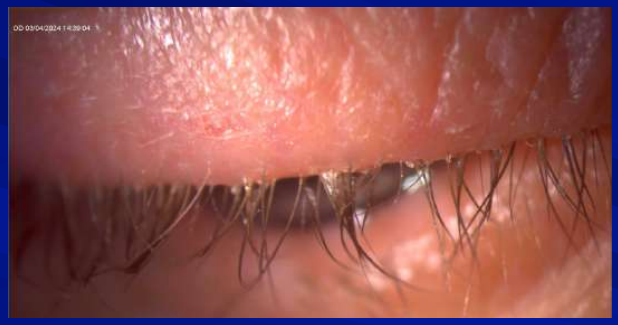
3 weeks Xdemvy treatment

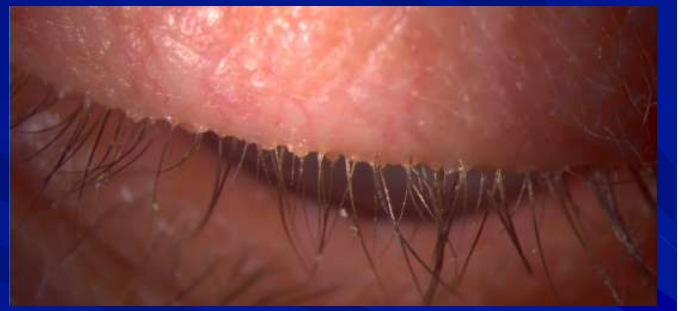
4 weeks on LP and MO

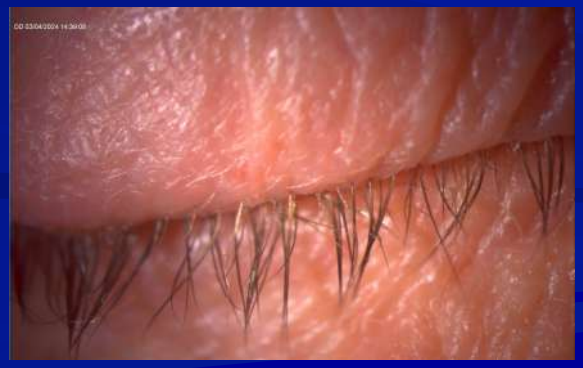
Hand scan: 32,000

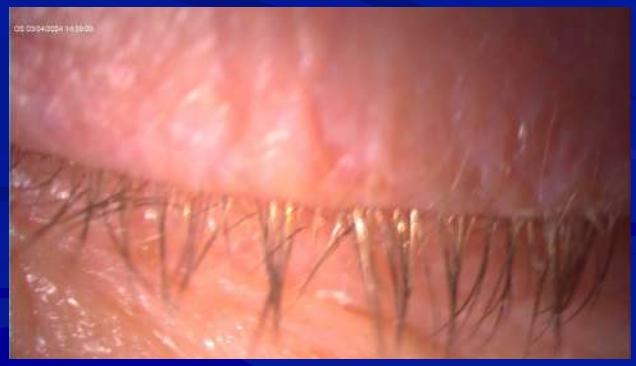






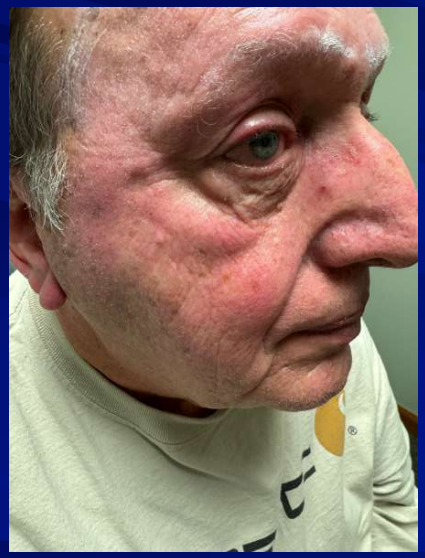






IPL: 1-10-24, 2-7-24, 3-5-2024

Before 1-10-24 Treatment

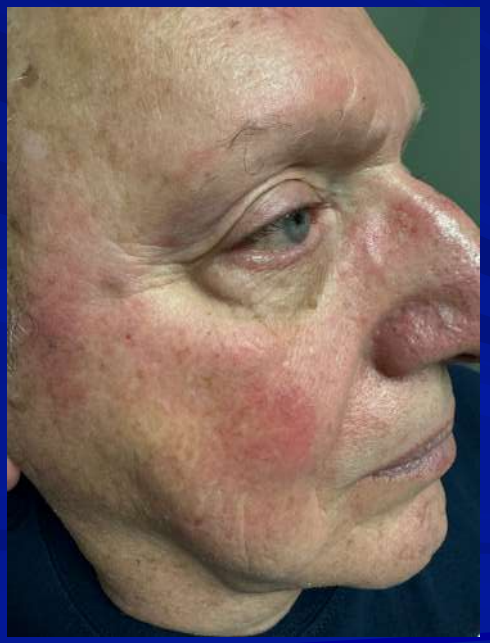


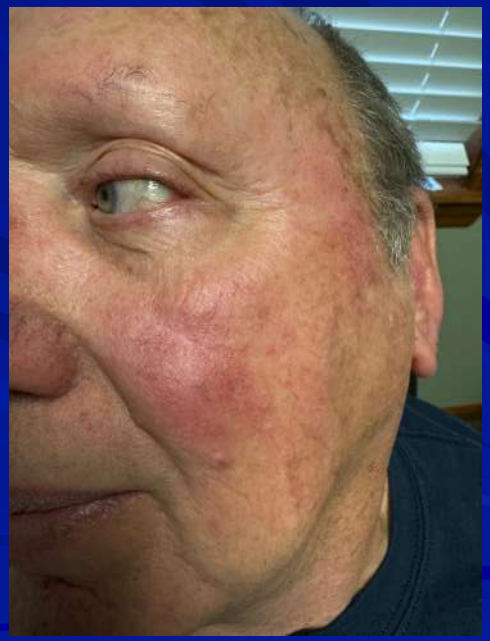
Before 2-7-24 Treatment

IPL: 1-10-24, 2-7-24, 3-5-2024

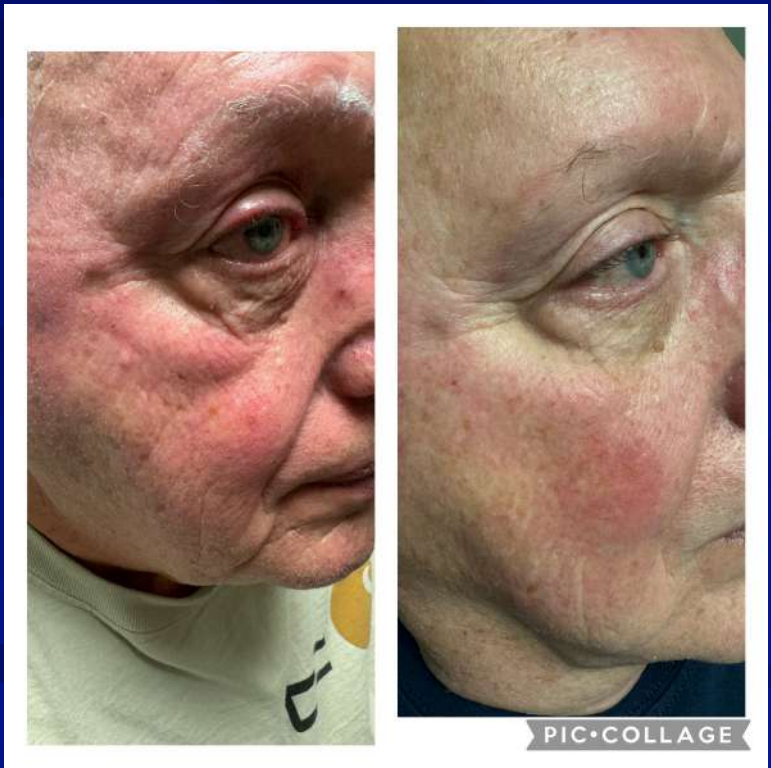
Before 2-7-24 Treatment

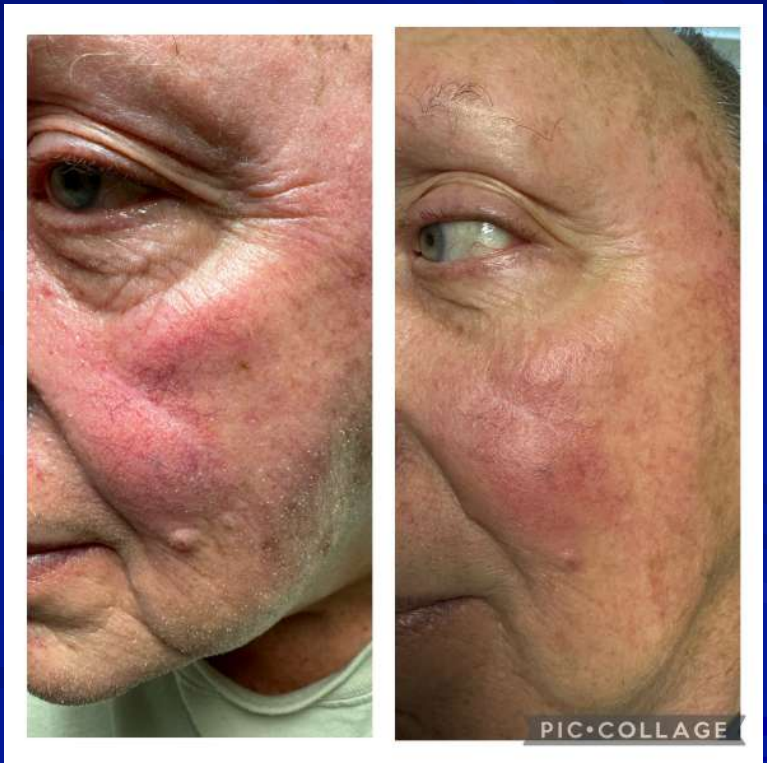
Before 3-5-24 Treatment



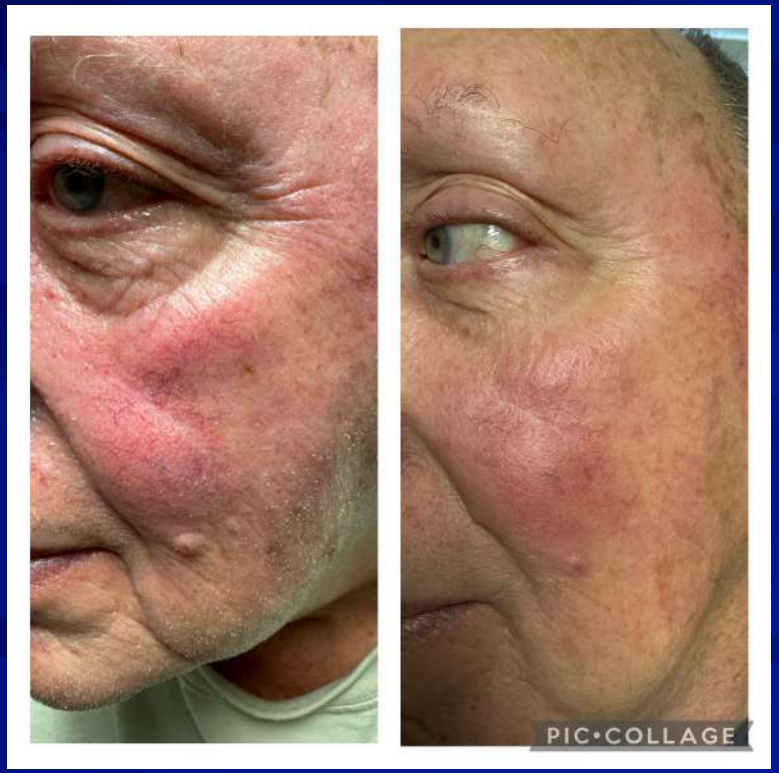


Staff Asks How Is It Going?





Do You Think Nutrition Played a Role?



Ingredients

Ingredients	Amount	% Daily Value
Serving Size: 1 Packet		
Vitamin A (83% as Beta Carotene (1875 mcg RAE) from *Blakeslea trispora*, and Vitamin A palmitate) (375 mcg RAE)	2250 mcg RAE	250%
Vitamin C (as Calcium Ascorbate)	200 mg	222%
Vitamin D (as Cholecalciferol)	5 mcg (200 IU)	25%
Vitamin E (as D-Alpha-Tocopheryl Acetate, D-Alpha Tocopherol, Tocotrienols)	50.3 mg	335%
Vitamin K (as Phytonadione)	20 mcg	17%
Thiamin (as Thiamine Mononitrate)	3.75 mg	313%
Riboflavin (as Riboflavin)	4.25 mg	327%
Niacin (as Niacinamide)	17.5 mg NE	109%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	500 mcg DFE (300 mcg folic acid)	125%
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%

Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	50 mcg	33%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30%
Zinc (as Zinc Bisglycinate)	75 mg	68%
Selenium (as L-Selenomethionine, Sodium Selenite)	70 mcg	127%
Copper (as Copper Bisglycinate)	0.5 mg	56%
Manganese (as Manganese Bisglycinate)	1 mg	43%
Chromium (as Chromium Nicotinate Glycinate)	100mcg	286%
Molybdenum (as Molybdenum Bisglycinate)	37.5 mcg	83%
Polyphenol and Flavonoid Blend	875 mg	†
Catechins (from *Camellia sinensis* Leaf Extract)	145 mg)	†
Quercetin	125 mg)	†
Grape Seed Extract (min. 95% Polyphenols)	112.5 mg)	†
Citrus Bioflavonoids (from Citrus Fruits)	112.5 mg)	†
Resveratrol (from *Polygonum cuspidatum* root extract)	12.5 mg)	†
Mixed Tocopherols (Gamma, Delta & Beta Tocopherols)	53 mg	†
Alpha-Lipoic Acid	75 mg	†
Inositol (as Inositol)	5 mg	†
Carotenoid Blend	2.5 mg	†
Lycopene (as Lycopene)	12.5 mg)	†
Lutein (from Marigold Flower Extract)	1 mg)	†
Boron (as Boron Citrate)	1.5 mg	†
Vanadium (as Vanadyl Sulfate)	10 mcg	†

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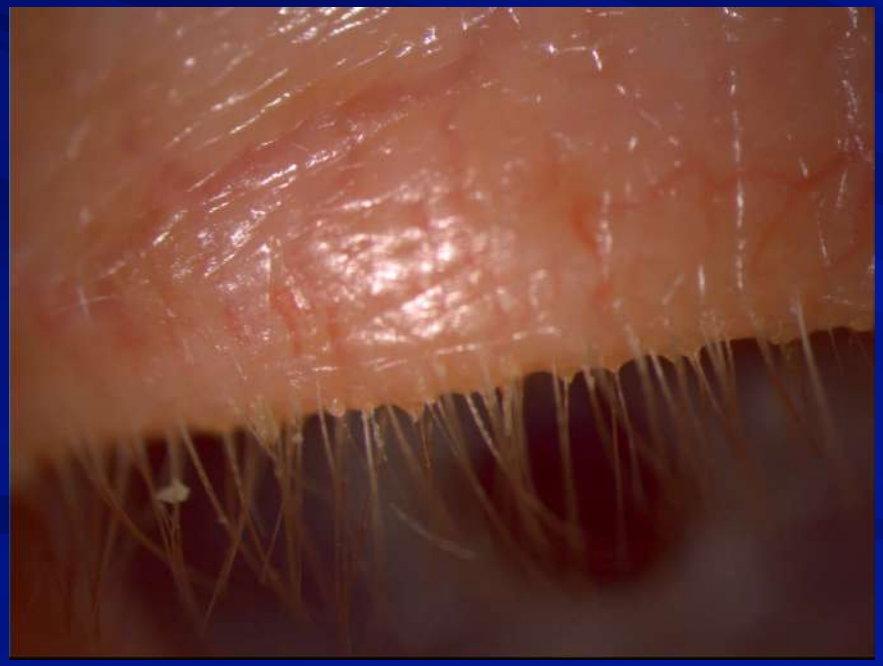
EPA	300 mg	**
DHA	200 mg	**
Other Omega-3 Fatty Acids	100 mg	**
Krill oil	100 mg	**

*Percent Daily Values are based on a 2,000 Calorie Diet.
**Daily Value not established.

Hand Scan: 42,000

59-Year-Old White Man Treated with Xdemvy

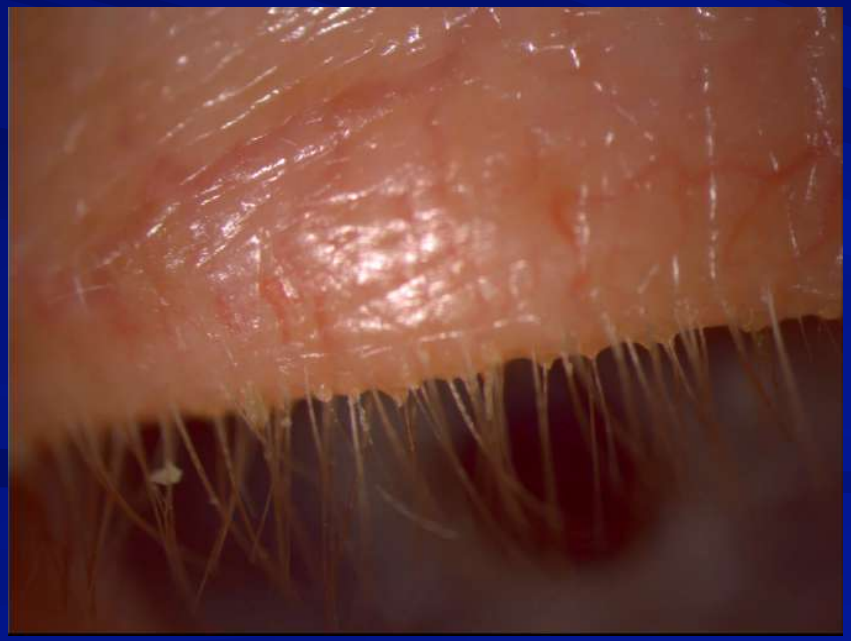
11-28-2023
Video Examination



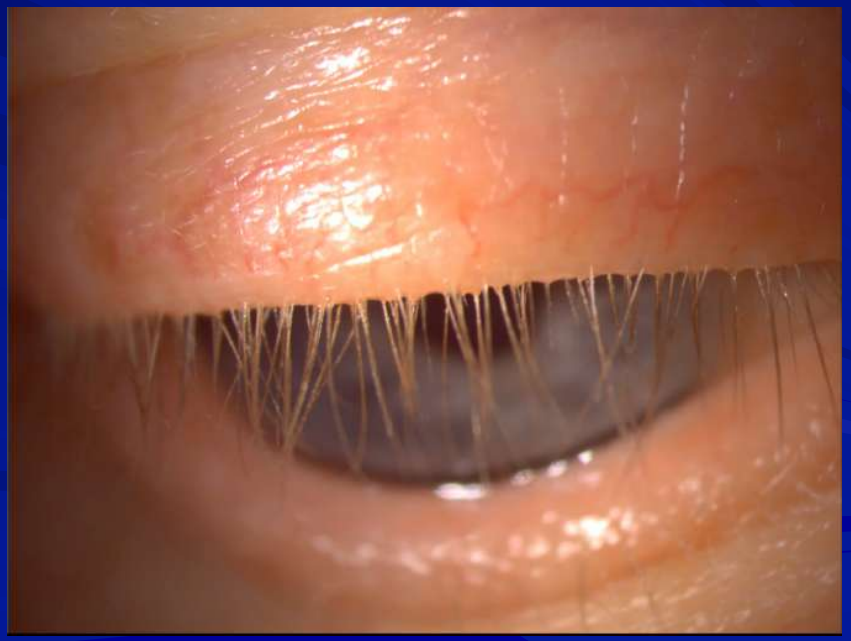
1-2-2024
3 Weeks Xdemvy
Video Examination

44-Year-Old White Woman Treated with Xdemvy

11-28-2023
Video Examination



1-9-2024
3 Weeks Xdemvy
Video Examination



DEMODEX BLEPHARITIS | A PERVASIVE AND DAMAGING EYE DISEASE

- **Blepharitis is the inflammation of the eyelids** causing irritation and redness

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

D. folliculorum

0.3-0.4 mm length
Colonizes the base of the lash follicle[2]

D. brevis

0.1 mm length
Colonizes the meibomian gland[2]

1. Mayo Clinic. Accessed June 28, 2022. https://www.mayoclinic.org/diseases-conditions/blepharitis/symptoms-causes/syc-20370141 **2.** Zhang AC et al. *Ophthalmic Physiol Opt*. 2020;40(4):389-432. **3.** Fromstein SR et al. *Clin Optom (Auckl)*. 2018;10:57-63. **4.** Trattler W et al. *Clin Ophthalmol*. 2022;16:1153-1164. **5.** Litwin D et al. *Iran J Parasitol*. 2017;12(1):12-21.

DEMODEX BLEPHARITIS | MECHANISMS OF DISEASE

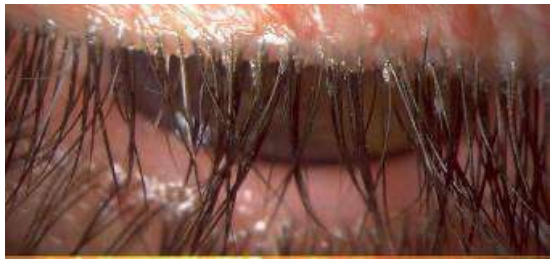


Image courtesy of Laura M. Periman, MD, used with permission.[1]

MECHANICAL

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

BACTERIAL

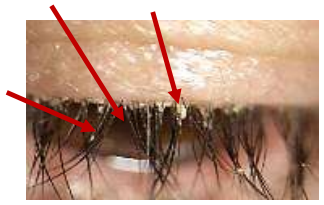
- *Demodex* mites can contribute to blepharitis by carrying bacteria on their exterior surface that may elicit immune responses[3,6-7]

CHEMICAL

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

1. Data on file. Images courtesy of Laura M. Periman, MD; 2022. **2.** Zhang AC et al. *Ophthalmic Physiol Opt.* 2020;40(4):389-432. **3.** Liu J et al. *Curr Opin Allergy Clin Immunol.* 2010;10(5):505-510.
4. Fromstein SR et al. *Clin Optom (Auckl).* 2018;10:57-63. **5.** Gao YY et al. *Invest Ophthalmol Vis Sci.* 2005;46(9):3089-3094. **6.** Zhu M et al. *Front Microbiol.* 2018;9:1719. **7.** Li J et al. *Ophthalmology.* 2010;117(5):870-877.
8. Gao H et al. *Transl Vis Sci Technol.* 2021;10(14):6. **9.** Tarkowski W et al. *Biomed Res Int.* 2015:259109.

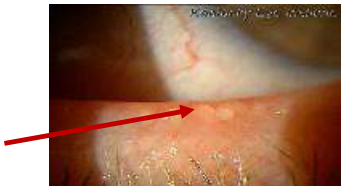
CLINICAL MANIFESTATIONS OF *DEMODEX* BLEPHARITIS



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

Disorders of Eyelashes[1,2]

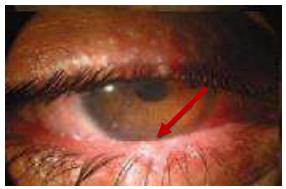
Infestation of the lash follicles can result in collarettes and may lead to malalignment, trichiasis, and madarosis



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

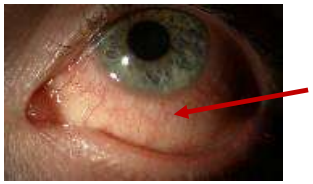
Meibomian Gland Dysfunction[1,2]

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



Lid Margin Inflammation[1,2]

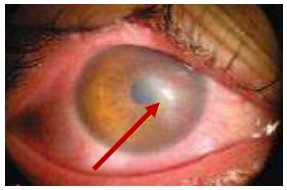
Severe lid margin inflammation can be caused by mechanical blockage and a delayed host immune hypersensitivity reaction



Images courtesy of Elise Kramer, OD, used with permission.

Conjunctival Inflammation[1,2]

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



Corneal Manifestations[1,2]

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

1. Liu J et al. *Curr Opin Allergy Clin Immunol*. 2010;10(5):505-510. **2.** Cheng AM et al. *Curr Opin Ophthalmol*. 2015;26(4):295-300.

THE NEGATIVE BURDEN OF *DEMODEX* BLEPHARITIS IS VERY REAL

80% of patients report negative impact on daily life*

- **Atlas** multicenter, observational study (N=311)
- Evaluated the clinical and patient-reported impact of *Demodex* blepharitis
- Inclusion criteria:
  - At least 1.0 mites per lash
  - >10 collarettes on the upper eye lid
  - At least mild erythema (redness)

Common symptoms that were frequently bothersome*:

55%	46%	23%	21%
Itchy eyes	Dry eyes	Foreign body sensation	Watery eyes

51%
Experienced signs and symptoms ≥4 years

58%
Never diagnosed with blepharitis

33%
Made at least 2, and sometimes >6, visits to a doctor for this condition

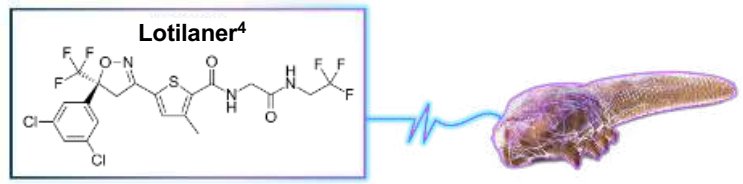
Early identification of *Demodex* blepharitis is critical due to long-term symptoms that have a significant impact on patients

*Per an observational study of adult *Demodex* blepharitis patients from 8 US ophthalmic and optometric centers.
O'Dell L, Dierker DS, Devries DK et al. Psychosocial impact of Demodex blepharitis. Clin Ophthalmol. 2022; 16:2979-2987.

MECHANISM OF ACTION OF Xdemvy (Lotilaner Ophthalmic Solution 0.25%)

Xdemvy - Lotilaner ophthalmic solution 0.25% (Tarsus Pharmaceuticals, Inc.)

- Lotilaner functions as a noncompetitive antagonist of mite and arachnid GABA-gated chloride channels[1,2]
- Directly paralyzes the mite nervous system through parasite-specific GABA inhibition, leading to death[1,2]
- The lipophilic nature of the drop suggests its ability to flow into the oily sebum of the lash follicle where the mites reside[3]



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

Dosing[5]
Twice daily for 6 weeks

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

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

Xdemvy 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

Rinsada

- Biofilm does not stop at the lid
- First in class to remove past the lid margin
  - ★ Bulbar, palpebral conjunctiva & fornix
- Power wash the biofilm - ports of high-pressure irrigation
- **72%** reduction in MMP-9
  - ★ Lasted 12 weeks
- 4.33 improvement on visual analog scale

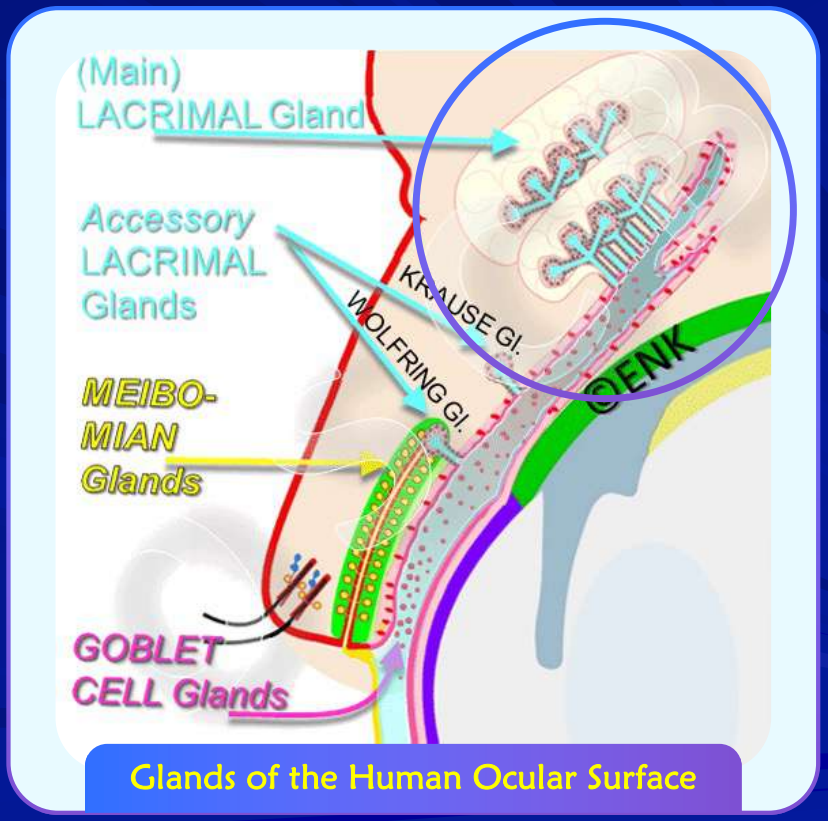
Palpebral conjunctiva & fornix

Not Discussed Anatomical Areas of the Ccular Surface

Conjunctival Fornix

1. Main lacrimal gland ducts
2. Accessory glands of Krause

Aqueous output



Glands of the Human Ocular Surface

Palpebral Conjunctiva & Fornix

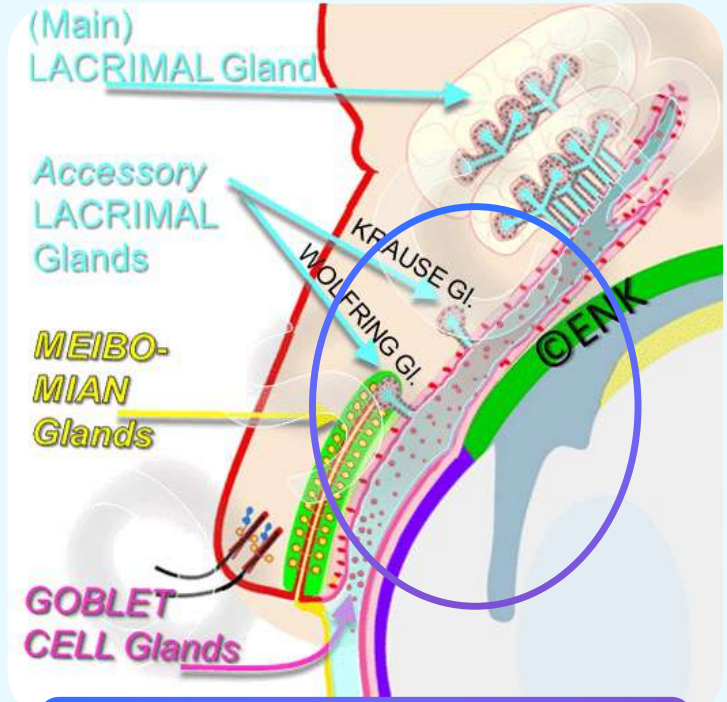
Not Discussed Anatomical Areas of the Ocular Surface

Palpebral Conjunctiva

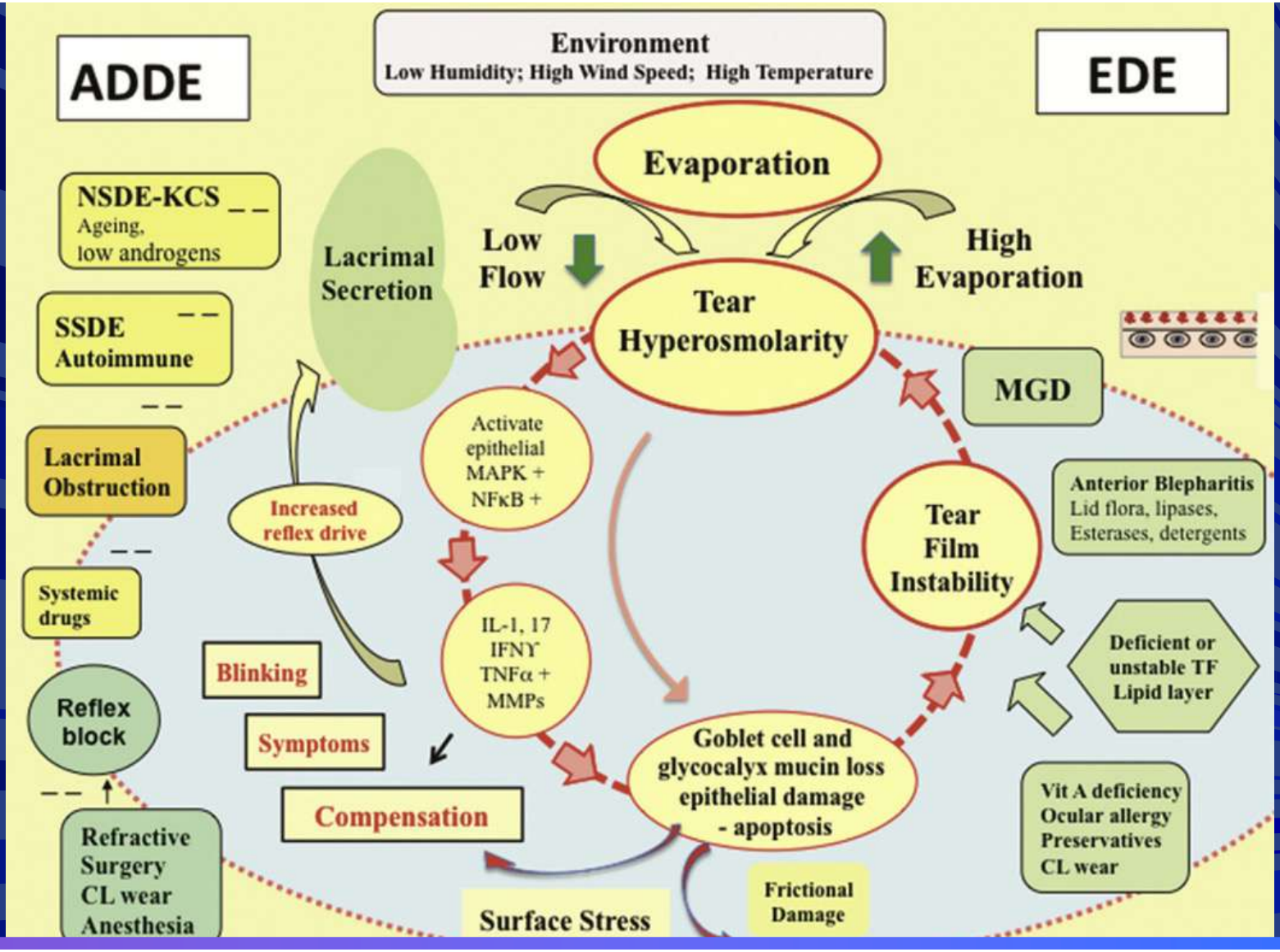
1. Accessory glands of Wolfring
2. Antigen presenting cells
3. NK cells
4. Langerhans Cells
5. Goblet Cells

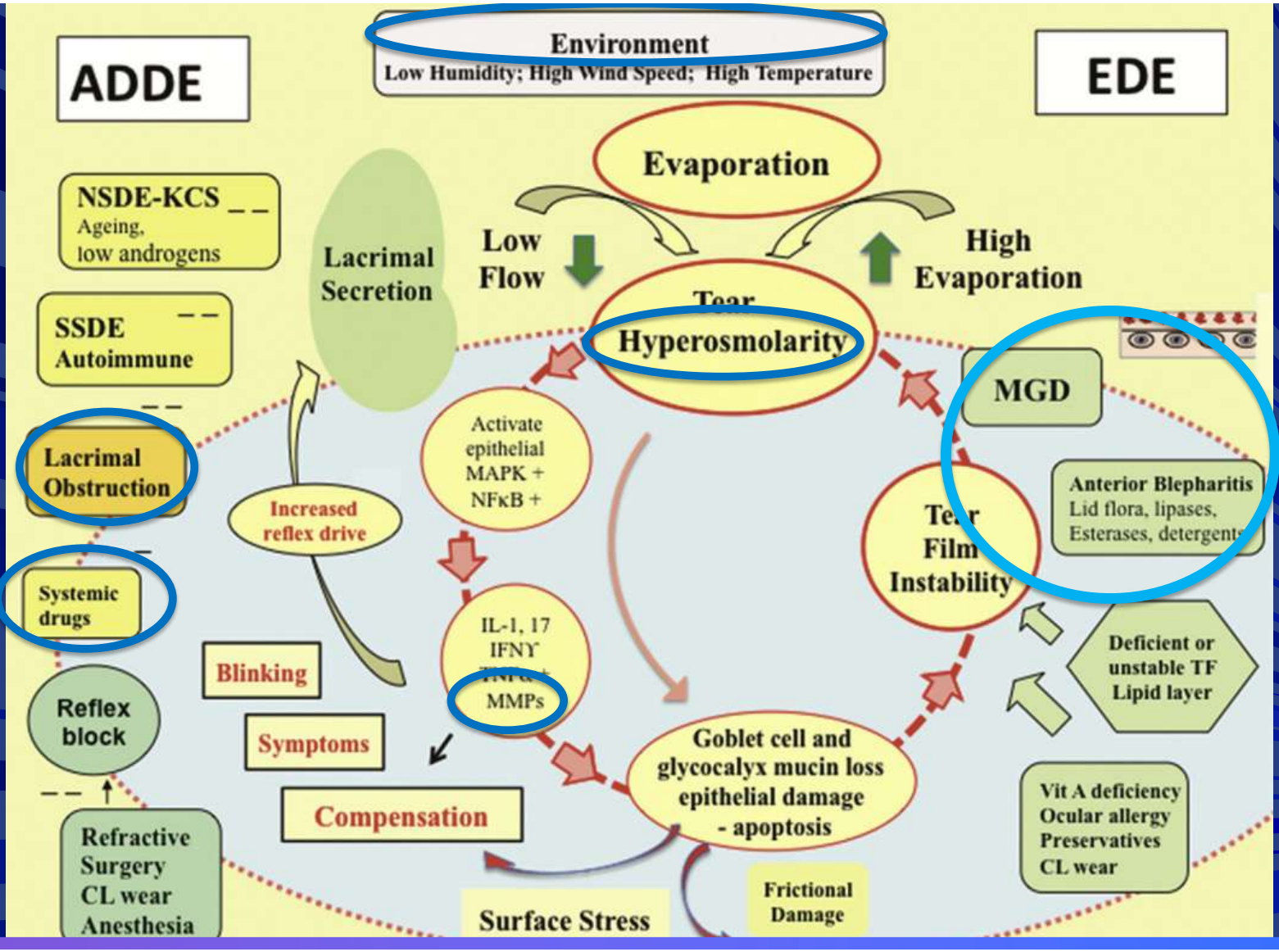
Mediates inflammatory reactions

Aqueous & mucin output



Glands of the Human Ocular Surface


ADDE
Environment
Low Humidity; High Wind Speed; High Temperature
EDE
Evaporation
NSDE-KCS
Ageing,
low androgens
Lacrimal Secretion
Low Flow
High Evaporation
SSDE
Autoimmune
Tear Hyperosmolarity
MGD
Lacrimal Obstruction
Activate epithelial MAPK + NFκB +
Anterior Blepharitis
Lid flora, lipases, Esterases, detergents
Increased reflex drive
Tear Film Instability
Systemic drugs
IL-1, 17
IFNγ
TNFα +
MMPs
Deficient or unstable TF Lipid layer
Blinking
Reflex block
Symptoms
Goblet cell and glycocalyx mucin loss epithelial damage - apoptosis
Vit A deficiency
Ocular allergy
Preservatives
CL wear
Compensation
Refractive Surgery
CL wear
Anesthesia
Frictional Damage
Surface Stress


ADDE
Environment
Low Humidity; High Wind Speed; High Temperature
EDE
Evaporation
NSDE-KCS
Ageing,
low androgens
Lacrimal Secretion
Low Flow
High Evaporation
SSDE
Autoimmune
Tear Hyperosmolarity
MGD
Lacrimal Obstruction
Activate epithelial MAPK + NFκB +
Anterior Blepharitis
Lid flora, lipases, Esterases, detergents
Increased reflex drive
Tear Film Instability
Systemic drugs
IL-1, 17
IFNγ
MMPs
Deficient or unstable TF Lipid layer
Blinking
Reflex block
Symptoms
Goblet cell and glycocalyx mucin loss epithelial damage - apoptosis
Vit A deficiency
Ocular allergy
Preservatives
CL wear
Compensation
Refractive Surgery
CL wear
Anesthesia
Frictional Damage
Surface Stress

Chapter

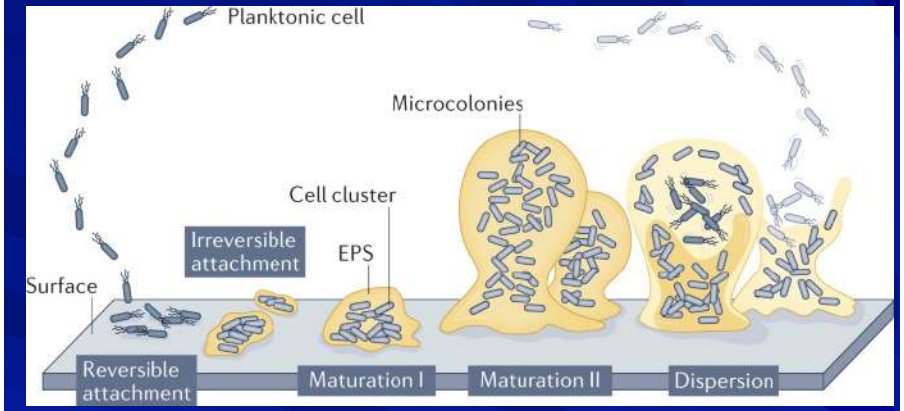
Biofilm Theory for Lid Margin and Dry Eye Disease

Maria Vincent, Jose Quintero, Henry D. Perry and James M. Rynerson

Abstract

Blepharitis and dry eye disease have long been viewed as two distinct diseases with overlapping presentations and separate etiologies. Evaporative dry eye, although frequently associated with aqueous deficiency, is also considered a separate entity. We propose viewing dry eye, both evaporative and insufficiency, as the natural sequelae of chronic blepharitis induced by biofilm. We suggest describing this one chronic disease as dry eye blepharitis syndrome (DEBS). The disease process begins when normal flora bacteria colonize the lid margin beginning shortly after birth. This colonization accompanies the development of a biofilm on the lid margin. As years pass, the biofilm matures, and the increased bacterial population initiates the production of inflammatory virulence factors, such as exotoxins, cytolytic toxins, and super-antigens, which persist on the lid margin for the rest of the patient's life. These virulence factors cause early follicular inflammation and later, meibomian gland dysfunction followed by aqueous insufficiency, and finally, after many decades, loss of the dense collagen in the tarsal plate. We proposed four stages of DEBS, which correlate with the clinical manifestations of folliculitis (anterior blepharitis), meibomitis (meibomian gland dysfunction), lacrimalitis (aqueous deficiency), and lid structure damage evidenced by increased lid laxity resulting in entropion, ectropion, and floppy eyelid syndrome.

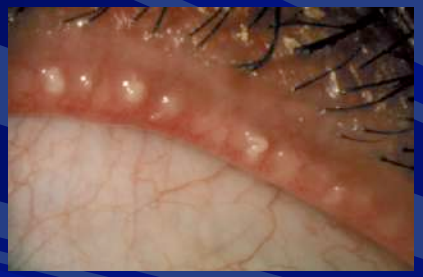
Keywords: biofilm, blepharitis, demodex, dry eye disease, eyelids, meibomian glands, quorum-sensing gene activation, tear film



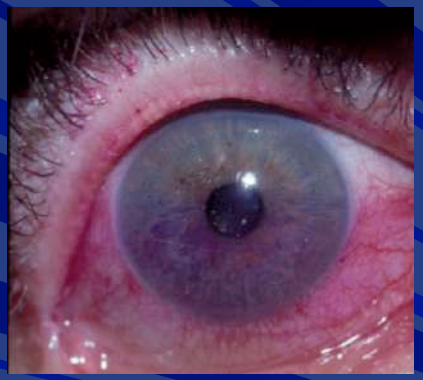
Four Stages of Ocular Biofilms

Blepharitis

MGD



Lacrimalitis



Lid Destruction

1. Vincent, Maria, et al. 'Biofilm Theory for Lid Margin and Dry Eye Disease'. Ocular Surface Diseases - Some Current Date on Tear Film Problem and Keratoconic Diagnosis, IntechOpen, 7 Jan. 2021. Crossref, doi:10.5772/intechopen.89969.

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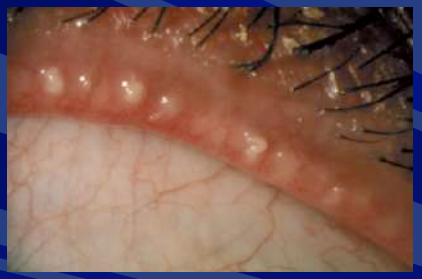
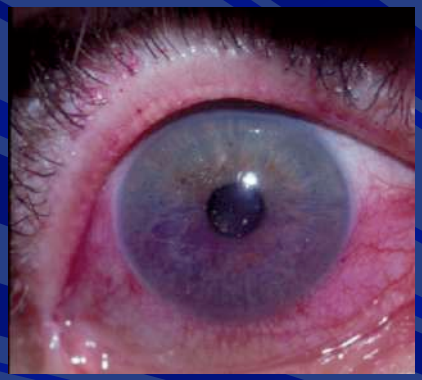


Lacrimalitis



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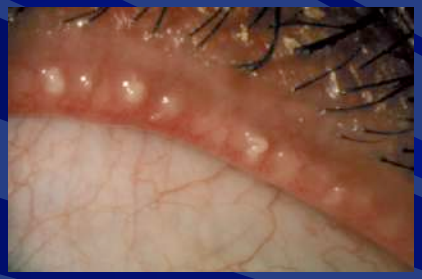
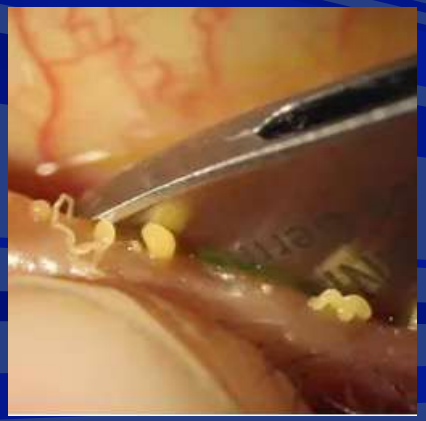
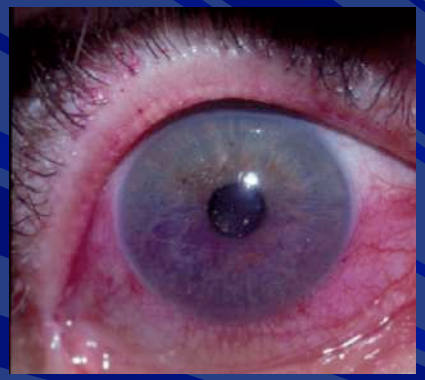




Lacrimalitis



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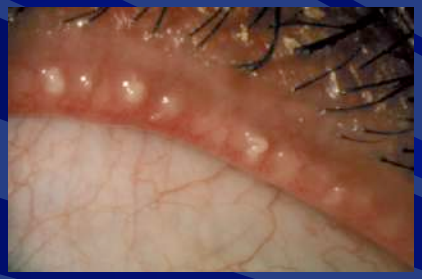
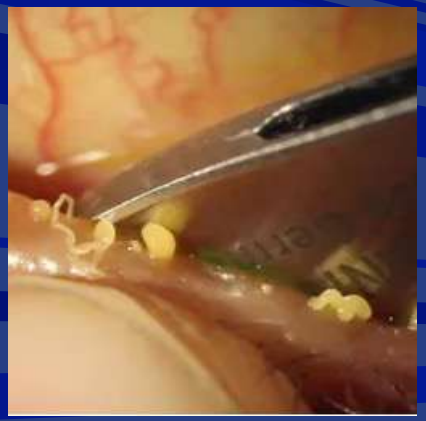
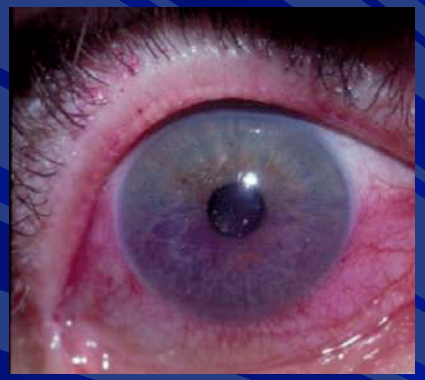




Lacrimalitis



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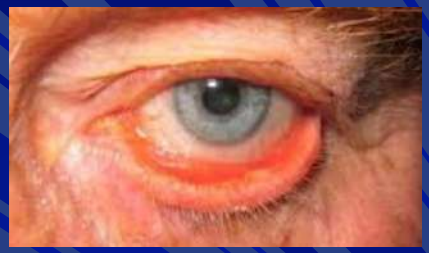
Lid Destruction



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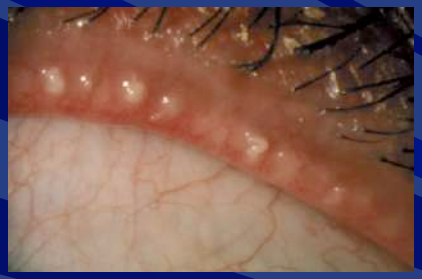
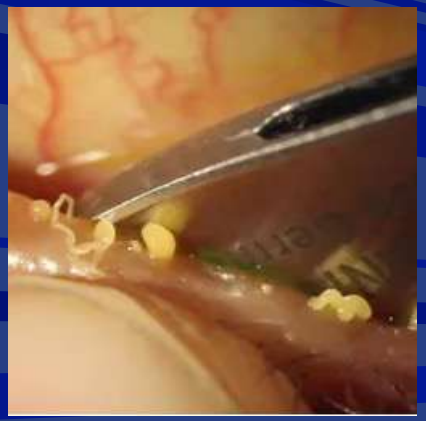
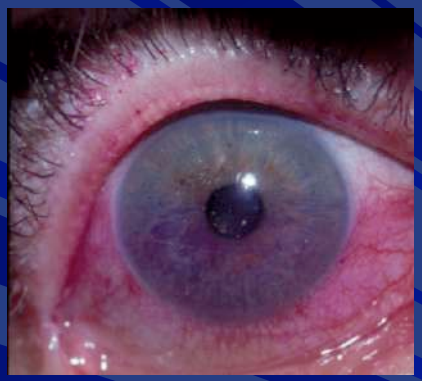
Blepharitis

MGD





Lacrimalitis



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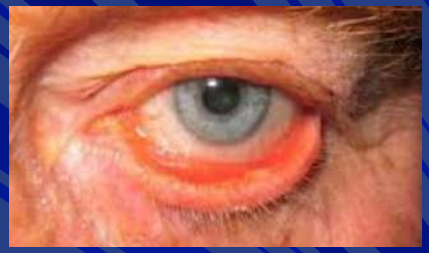
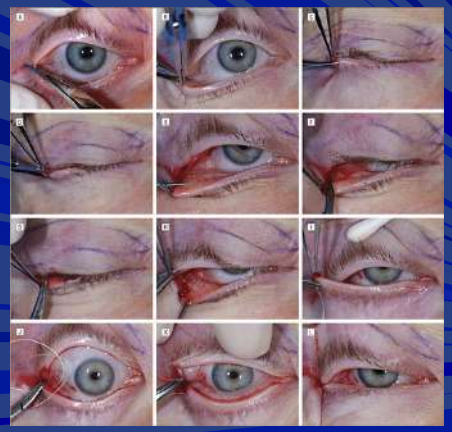
Lid Destruction





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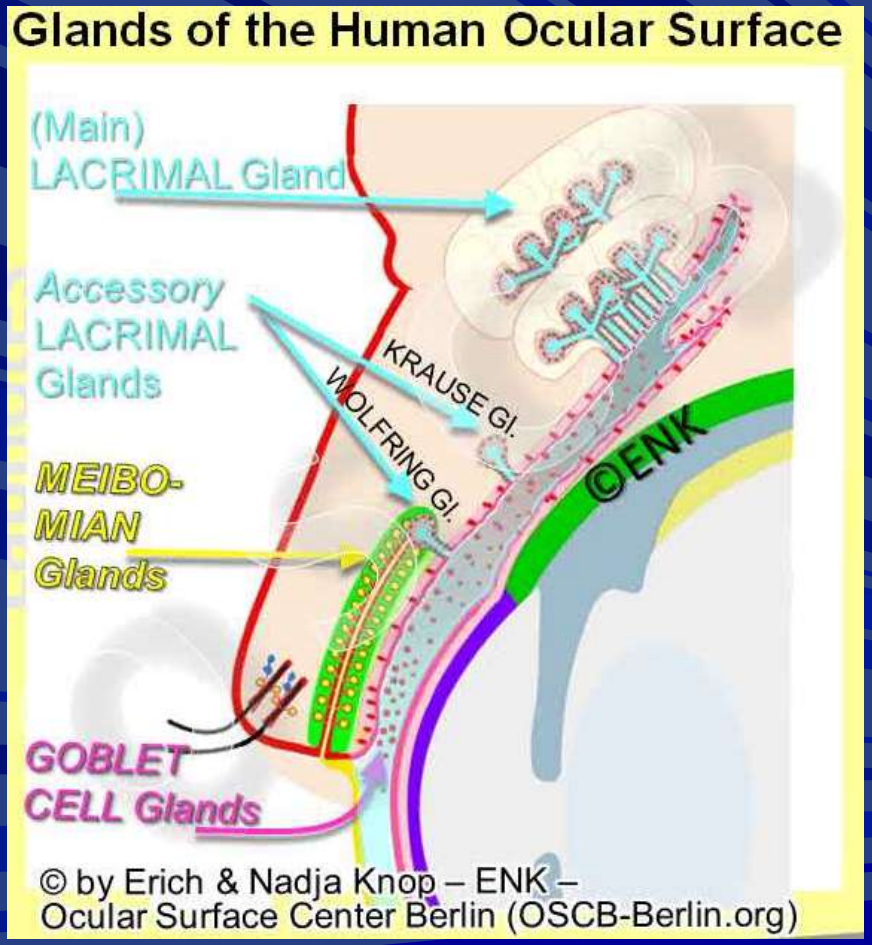
Biofilms Extend Past the Lid Margin into the Palpebral Conjunctiva and Fornix



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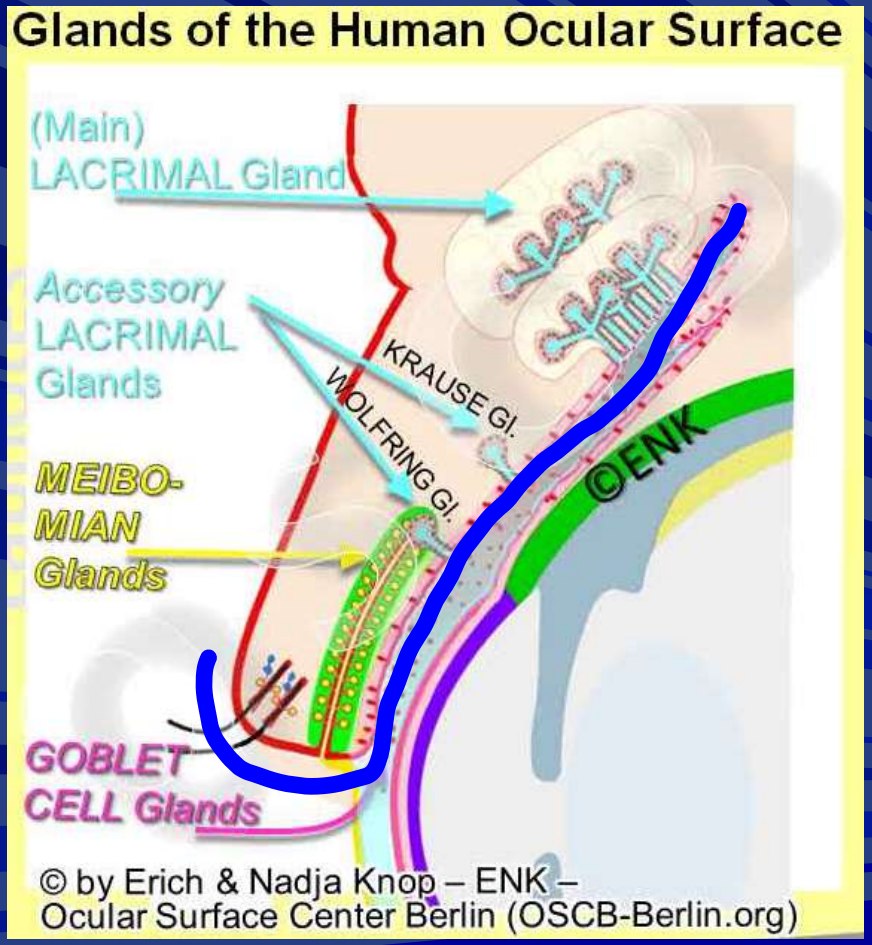
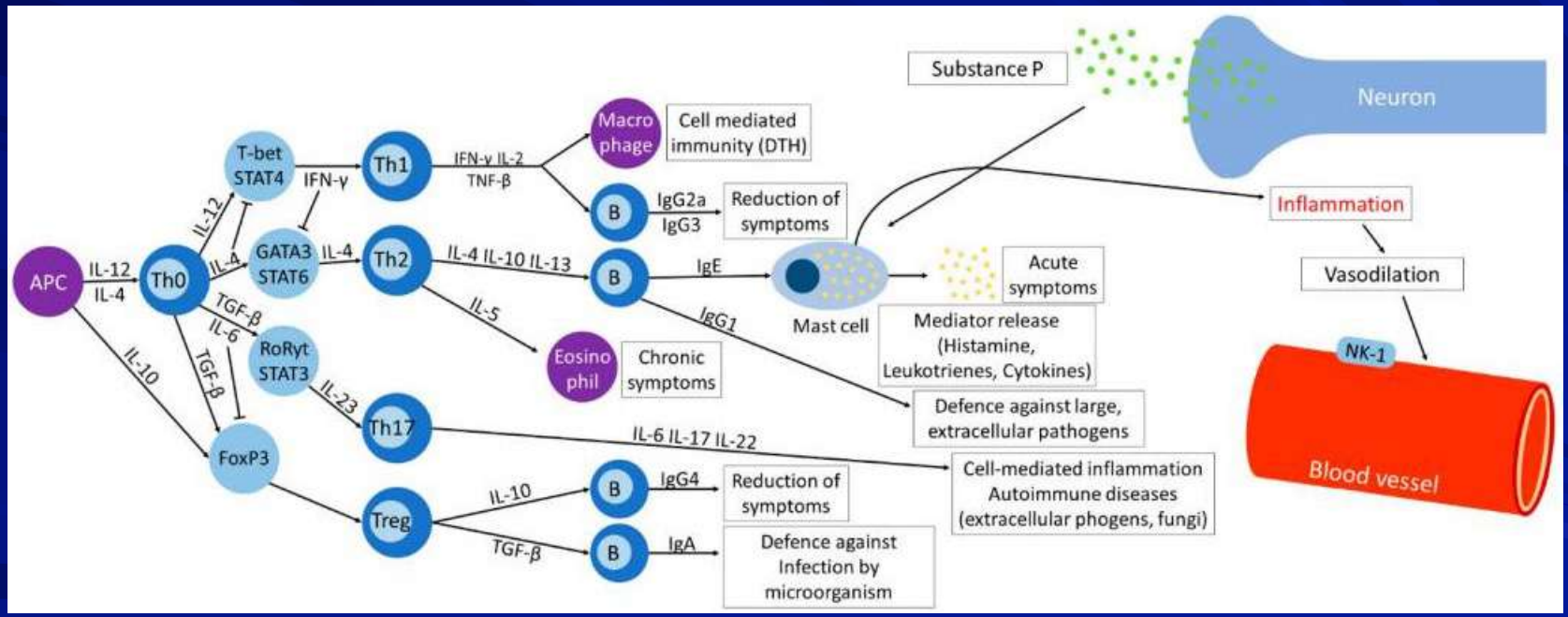


Immune System



Rinsada's Unique Design Targets High Pressure Irrigation at the Palpebral Conjunctiva and Fornix

Biofilms & Demodex Are Not Mutually Exclusive

Demodex attaches onto biofilm infiltrated lashes

Rhee, Michelle K. M.D.; Yeu, Elizabeth M.D.; Barnett, Melissa O.D., FAAO,FSLS, FBCLA; Rapuano, Christopher J. M.D.; Dhaliwal, Deepinder K. M.D.; Nichols, Kelly K. O.D., M.P.H., Ph.D.; Karpecki, Paul O.D.; Mah, Francis S. M.D.; Chan, Arthur Ph.D.; Mun, James Ph.D.; Gaddie, Ian Benjamin O.D.. Demodex Blepharitis: A Comprehensive Review of the Disease, Current Management, and Emerging Therapies. Eye & Contact Lens: Science & Clinical Practice 49(8):p 311-318, August 2023. | DOI: 10.1097/ICL.0000000000001003

Biofilms & Demodex Are Not Mutually Exclusive

REVIEW ARTICLE

OPEN

Demodex Blepharitis: A Comprehensive Review of the Disease, Current Management, and Emerging Therapies

Michelle K. Rhee, M.D., Elizabeth Yeu, M.D., Melissa Barnett, O.D., FAAO,FSLS, FBCLA, Christopher J. Rapuano, M.D., Deepinder K. Dhaliwal, M.D., Kelly K. Nichols, O.D., M.P.H., Ph.D., Paul Karpecki, O.D., Francis S. Mah, M.D., Arthur Chan, Ph.D., James Mun, Ph.D., and Ian Benjamin Gaddie, O.D.

Bacterial Dysbiosis

The relationships among *Demodex* mites and the skin, gut, and ocular microbiota are complex. Historically, anterior blepharitis has often been believed to have a primarily bacterial origin. Eyelashes of patients with blepharitis have significantly higher microbial counts than healthy control subjects.[13] Fu et al.[27] recently reported that *Demodex* infestation may reduce the diversity of the microbiome in the conjunctival sac, thereby destabilizing it.

Bacterial biofilms have been implicated in blepharitis, and it has been proposed that lash deposits in blepharitis may be composed of these biofilms.[28] *Demodex* may also take advantage of the barrier defense "shield" provided by the biofilm to infiltrate the lash follicles and meibomian glands.[29] *Demodex* mites carry concomitant bacteria such as *Streptococcus* and *Staphylococcus* species on their surface, and *Bacillus oleronius* inside their abdomen, producing antigens and inducing an immune response.[17,20–22] In particular, studies have shown a positive correlation between *Staphylococcus epidermidis* and *Demodex* mite density.[30] The mites may act as a vector for other skin and environmental microbes when patients rub their eyes to relieve blepharitis-related itching and discomfort.[30]

Demodex infestation may reduce the diversity of the microbiome in the **conjunctival sac**, therefore destabilizing it

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Miebo (perfluorohexyloctane ophthalmic solution) 100%

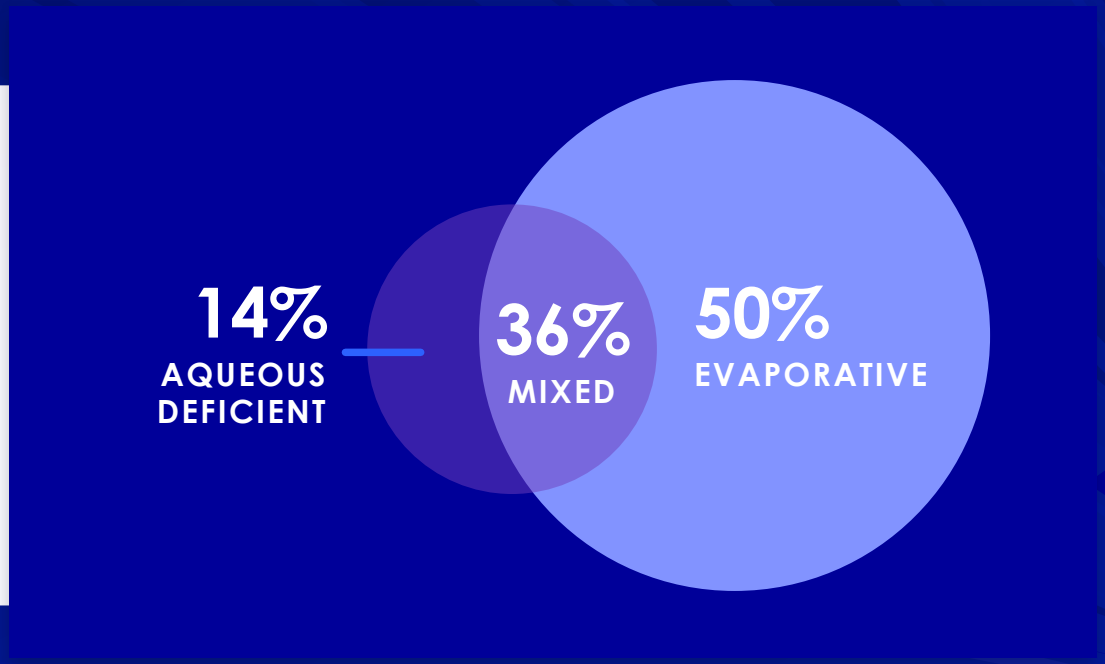
- Bausch & Lomb
- May 2023 – approved
- Indication: treatment of the signs and symptoms of dry eye disease (DED)
- Unique characteristics: water-free, non-steroidal, single-component preservative-free eye drop formulated with 100% perfluorohexyloctane to treat DED
- Mechanism of actions:
  - Spreads rapidly across the ocular surface due to its low surface tension then interacts with the lipophilic portion of the tear film that prevents tear evaporation
  - Can penetrate the meibomian glands, where it interacts with and dissolves altered, viscous meibum in the glands
- Administration: Drops
- Dosing: 1 gtt BID x 6 weeks

Miebo (perfluorohexyloctane ophthalmic solution) 100% Unique Characteristics

- Single-ingredient formulation
- No inactive ingredients
- Water free
- Preservative free
- Mimics key functions of natural meibum
- Forms a monolayer at the air-tear interface = reduced evaporation
- Remains in the tears up to 6 hours
- 11 microliter drop

The Majority of DED Has an Evaporative Etiology

MGD, the major contributor to the evaporative etiology of DED, is present in ≥86% of cases[1-3]

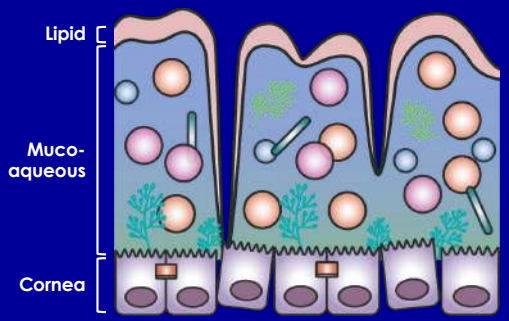


Excessive Evaporation Triggers A Vicious Cycle

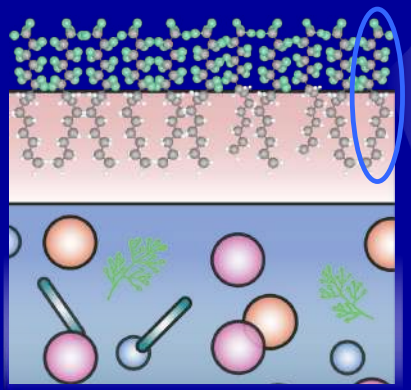
When tear evaporation exceeds supply, loss of homeostasis follows

MIEBO Forms A Monolayer at the Air-liquid Interface

Unstable Tear Film

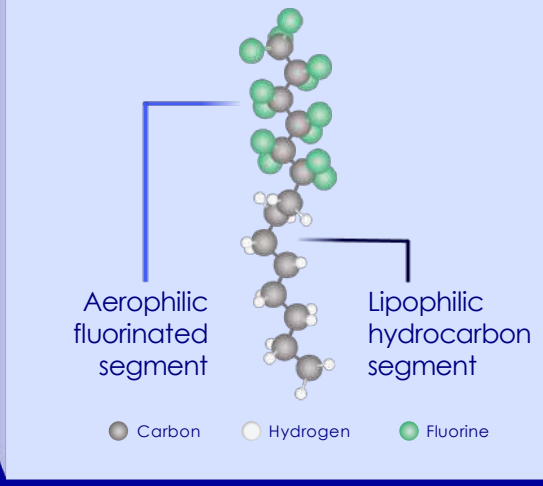


Tear Film with MIEBO



active cytokines chemokines electrolyte chemokines soluble mucin tethered mucin

Perfluorohexyloctane



An Excellent Tolerability Profile

IN 2 PIVOTAL CLINICAL STUDIES OF >1200 PATIENTS (>600 TREATED WITH MIEBO)

Serious ocular AEs

Low rate of discontinuation due to AEs

Low rate of burning or stinging on instillation

There was one ocular AE with an **incidence ≥2%** (blurred vision)

Discontinuation rates for MIEBO were comparable to control (pooled: 0.2% vs 0.5%; GOBI: 0.3% vs 1.0%; MOJAVE: 0% vs 0%) | **Pooled** incidences of instillation site pain, such as burning or stinging, was 0.5% (GOBI: 1.0%; MOJAVE: 0%) | The most common ocular AE was blurred vision, which was mostly mild and transient. Blurred vision (pooled: 2.1%; GOBI: 3.0%; MOJAVE: 1.3%) and conjunctival redness (pooled: 0.8%; GOBI: 0%; MOJAVE: 1.3%) were reported in 1%-3% of individuals

1. Tauber J, et al. *Ophthalmology*. 2023;130(5):516-524. **2.** Sheppard JD, et al. *Am J Ophthalmol*. 2023;252:265-274. **3.** Data on File. Bausch + Lomb Incorporated.
AE, adverse event

MIEBO Offers a Comfortable Experience

In clinical studies, **the majority of patients** rated MIEBO as **COMFORTABLE OR VERY COMFORTABLE** on instillation*

Small drop size (11 μL) means **MIEBO may feel different** from formulations containing water†

There may be **no ocular sensation or blink reflex** upon instillation

Contact lenses should be removed prior to and for at least 30 minutes after the administration of MIEBO.

*Instillation comfort was assessed via questionnaire given approximately 2 minutes after dosing on Day 1 of the GOBI and MOJAVE studies; it was scored on a visual analog scale from 0 to 10 (10 being the most comfortable). Mean pooled comfort score was 8.0 for MIEBO and 8.4 for saline. 81% of patients treated with MIEBO reported a score of 7 or higher.

† Formulations containing water may have a typical drop size of 35 to 50 μL

Vevye (cyclosporine ophthalmic solution) 0.1%

- Harrow – Imprimis
- June 2023 – approval
- Indication: Treatment of the signs and symptoms of dry eye disease (DED)
- Mechanism of action: Calcineurin inhibitor immunosuppressant is meant for topical ophthalmic use
- Vehicle: Perfluorbutylpentane (MOD)
- Unique properties:
  - No pH or osmolarity characteristics
  - Water-free
  - Preservative free
  - Low surface tension – rapid spreading
- Administration: drops
- Dosing: 1 gtt BID
- Drop size: 10 microliters
- Results: Day 29 significantly improved the signs of DED

Nanodropper

- Most eye drops are 30-60 microliters
- Current eyedrop bottles dispense about five times the liquid your eye can absorb
- Up to 80% of every drop is wasted due to overflow onto your cheek
- Drainage by the tear ducts where the medication is absorbed into the rest of your body
- Decades of clinical research has shown that smaller drops are as effective
- Many cases, safer than current drops
- Nanodropper is the only FDA-listed - volume-reducing adaptor for eyedrop bottles
- Twist the Nanodropper onto a compatible bottle

Nanodropper – microliters?

Cequa™ (cyclosporine ophthalmic solution) 0.09%

- Sun Pharmaceuticals, Approved August 2018
- Dosed BID
- Single-use vials
- "New Nanomicellar Ophthalmic Solution for Treatment of Keratoconjunctivitis Sicca"
  - Formulation technology uses micelles
- Gelatinous aggregates of amphipathic molecules
  - Hydrophobic and hydrophilic molecules
  - Ease of entry into conjunctiva and cornea
    - High delivery of cyclosporine A (CsA)

Cequa™ (cyclosporine ophthalmic solution) 0.09%
Indication and Important Safety Information

Indication:

A calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye)

Warnings and Precautions:

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

Use with Contact Lenses: CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution

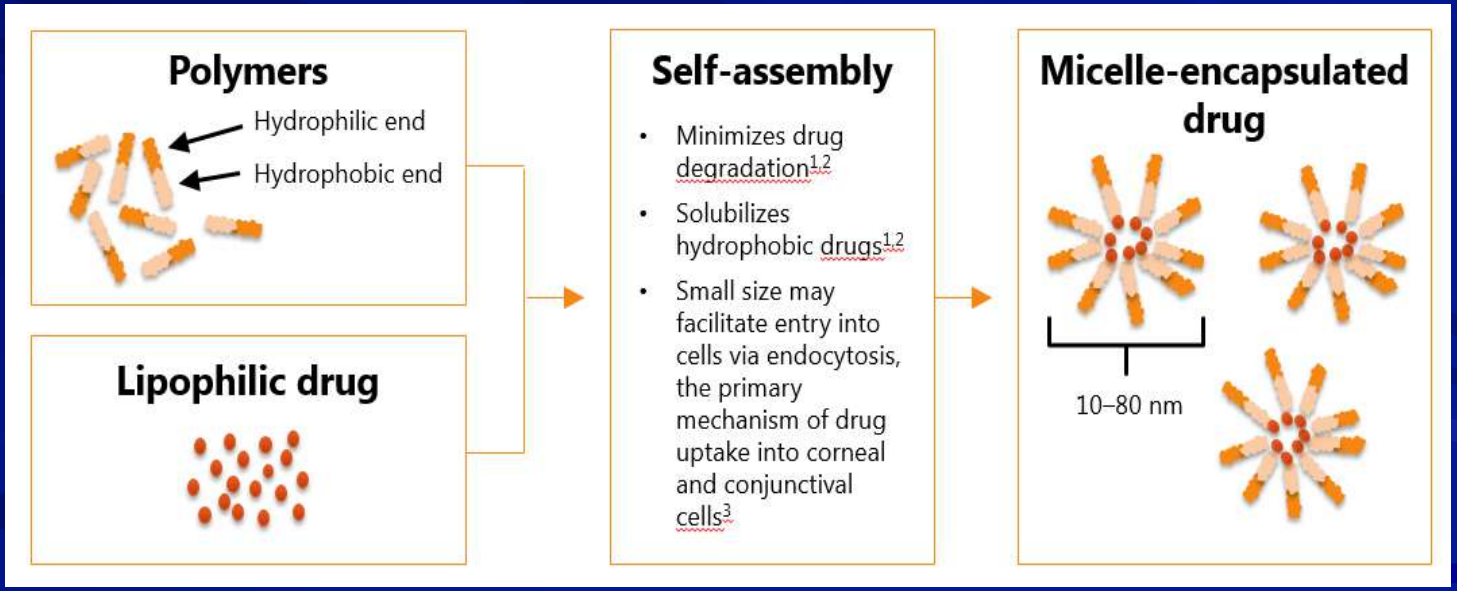
Adverse Reactions:

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%)

Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection

Cequa™ Formulation

- Novel, aqueous, nanomicellar formulation of cyclosporine A 0.09%[1–4]
- Unpreserved, isotonic, neutral pH fluid that is supplied in unit dose vials
- Well tolerated in a 12-week phase 2b/3 study[5]



1. Cholkar K et al. *Recent Pat Nanomed.* 2012;2:82-95 2. Mandal A et al. *J Control Release.* 2017;248:96-116. 3. Vaishya RD et al. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2014;6:422-437. 4. Cholkar K et al. *Transl Vis Sci Technol.* 2015;4:1-16 5. Tauber J, et al. ASCRS 2017 Paper presentation.

Effect of Cequa Cyclosporine Ophthalmic Solution 0.09% in Patients With Dry Eye Disease That Is Inadequately Controlled on Cyclosporine 0.05% Ophthalmic Emulsion
Phase 4 Study Results

- Objective: To evaluate improvement in DED signs and symptoms following use of CsA 0.09% in patients whose DED is inadequately controlled on CsA 0.05%
- A total of 124 patients were included in the ITT population (received ≥1 dose of study drug and had ≥1 postbaseline assessment)
- Mean ± SD patient age was 65.6 ± 11.54 years
- Most enrolled patients were female (109; 87.9%)

CsA 0.09% elicited statistically significant improvement from baseline in total CFS (corneal fluorescein score) score by 4 weeks of treatment

CsA 0.09% elicited statistically significant improvement from baseline in mSANDE (symptoms) score by 4 weeks of treatment

CsA 0.09% elicited statistically significant improvement from baseline in central CFS score by 4 weeks of treatment

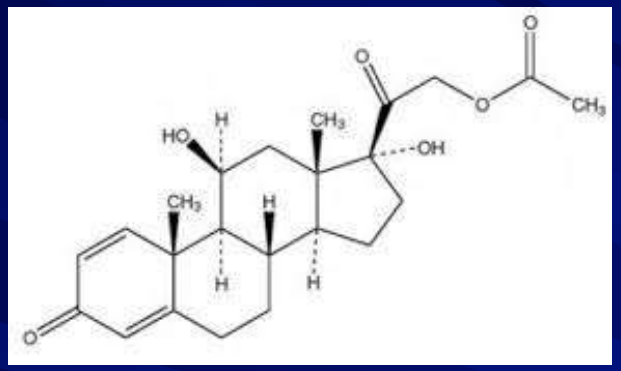
CsA 0.09% elicited statistically significant improvement from baseline in total conjunctival staining score by 4 weeks of treatment

CsA 0.09% elicited statistically significant improvement from baseline in Schirmer's score at Weeks 4 and 12 of treatment

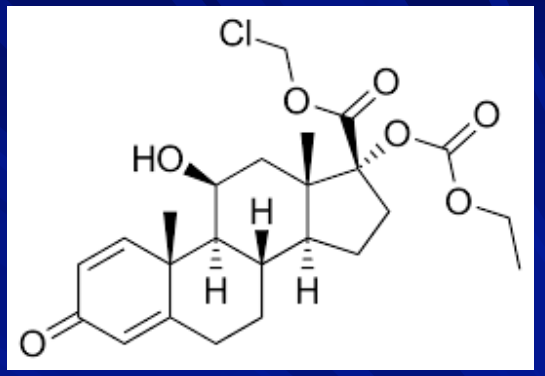
CsA 0.09% elicited statistically significant improvement from baseline in frequency of artificial tear use by 4 weeks of treatment

Effect of Cequa Cyclosporine Ophthalmic Solution 0.09% in Patients With Dry Eye Disease That Is Inadequately Controlled on Cyclosporine 0.05% Ophthalmic Emulsion
Phase 4 Study Results

- CsA 0.09% was generally well tolerated, consistent with its established safety profile
- Overall, 58 patients (43.3%) reported ≥1 TEAE
- Most AEs (73.8%) were mild in severity
- The most common treatment-related AEs were instillation site irritation (12.7%) and instillation site pain (2.2%)
  - All other treatment-related AEs occurred in <2% of patients
- Conclusion
  - Twice-daily administration of CsA 0.09% elicited statistically significant improvement in both total CFS and mSANDE scores in patients whose DED was inadequately controlled on CsA 0.05%
  - Improvements were evident as early as Week 4 and continued to increase in magnitude through Week 12
  - CsA 0.09% was well tolerated in this patient population



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%

Eysuvis- loteprednol etabonate 0.25%

- Kala Pharmaceuticals, now Alcon
- Approved October 27, 2020
- Nanoparticle-based Mucus Penetrating Particles (MPP)
- Dry eye flares
- 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"

Eysuvis - loteprednol etabonate suspension 0.25%

- Mechanism of Action – "AMPPLIFY Technology"
  - Allows drug to penetrate through tear mucins
    - Increased penetration into tissues, 3-fold to original loteprednol
- Nanoparticle-based Mucus Penetrating Particles (MPP)
  - 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

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

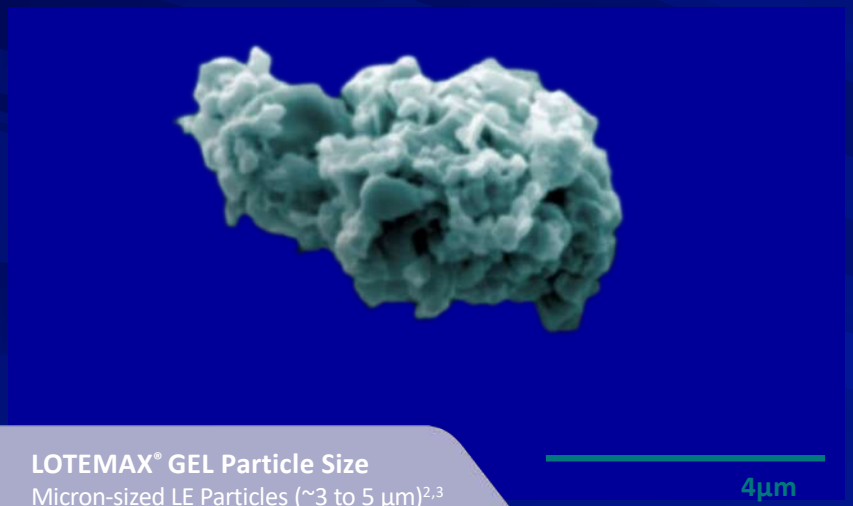
Lotemax SM (loteprednol etabonate) 0.38%

- 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

Submicron Formulation



LOTEMAX® GEL Particle Size
Micron-sized LE Particles (~3 to 5 µm)[2,3]

4µm

LOTEMAX® SM Particle Size
Submicron-sized LE Particles
(~0.4 to 0.6 µm)[2,3]

4µm

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]

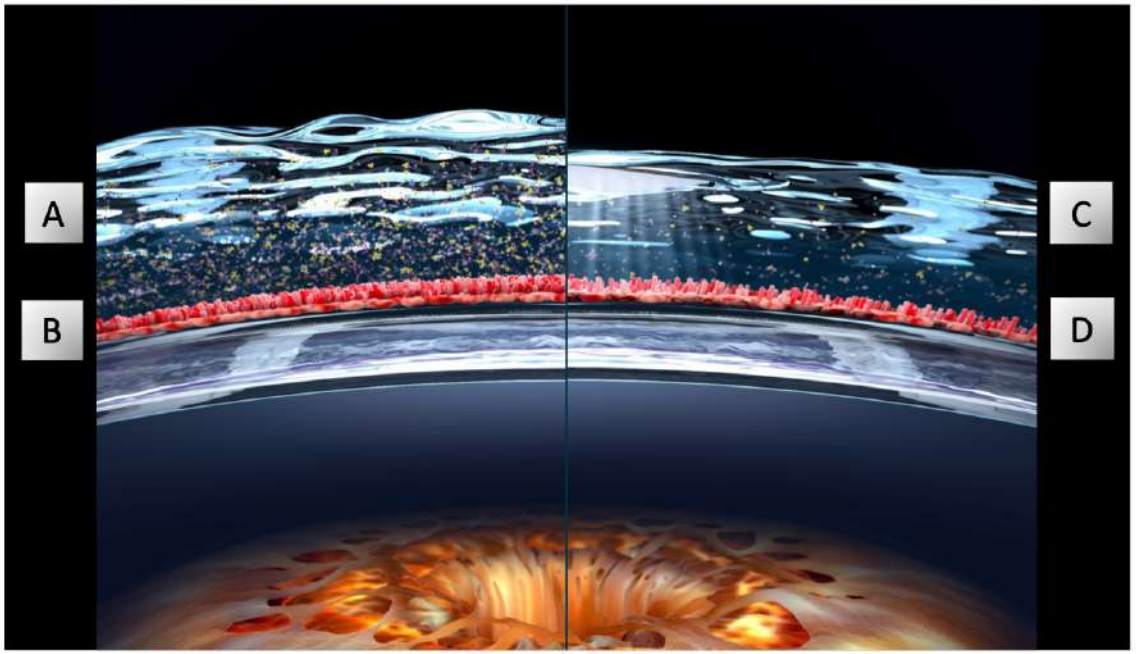


Image for illustrative purposes only

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

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

Electrolytes
- Sodium
- Chlorine
- Calcium
- Potassium

Mucins
- MUC1
- MUC5AC
- MUC4
- MUC16

Immunoglobulins
- IgG
- IgM
- IgA

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

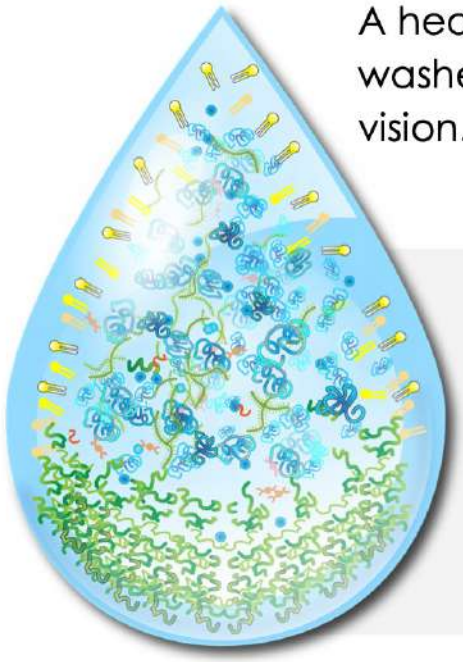
- Over 1,500 proteins
  - Epidermal growth factors
  - Nerve growth factors
  - Transforming growth factor beta (TGF-β)
  - Lysozymes
- 5+ lipid classes
- 20+ mucin classes

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.

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]

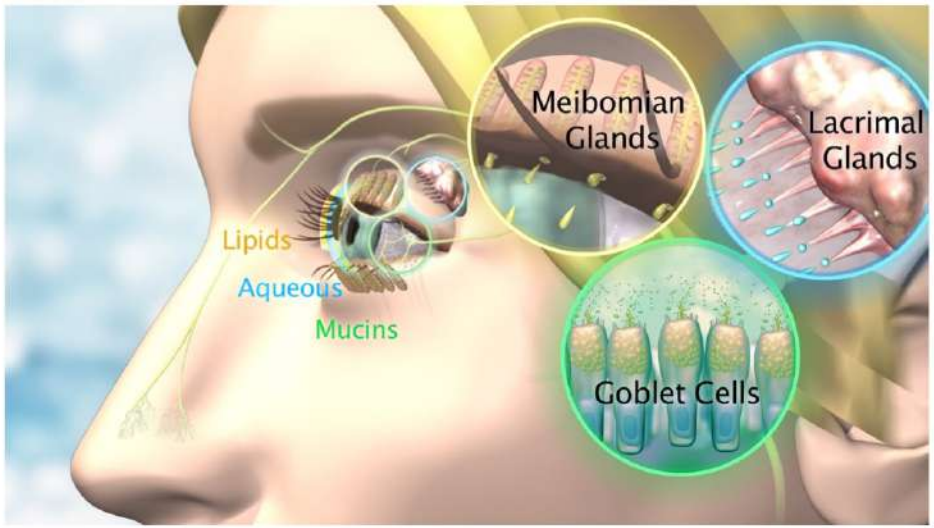
- Over 1,500 proteins
- 5+ lipid classes
- 20+ mucins
- Contains growth factors and has anti-inflammatory and antimicrobial properties

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.**

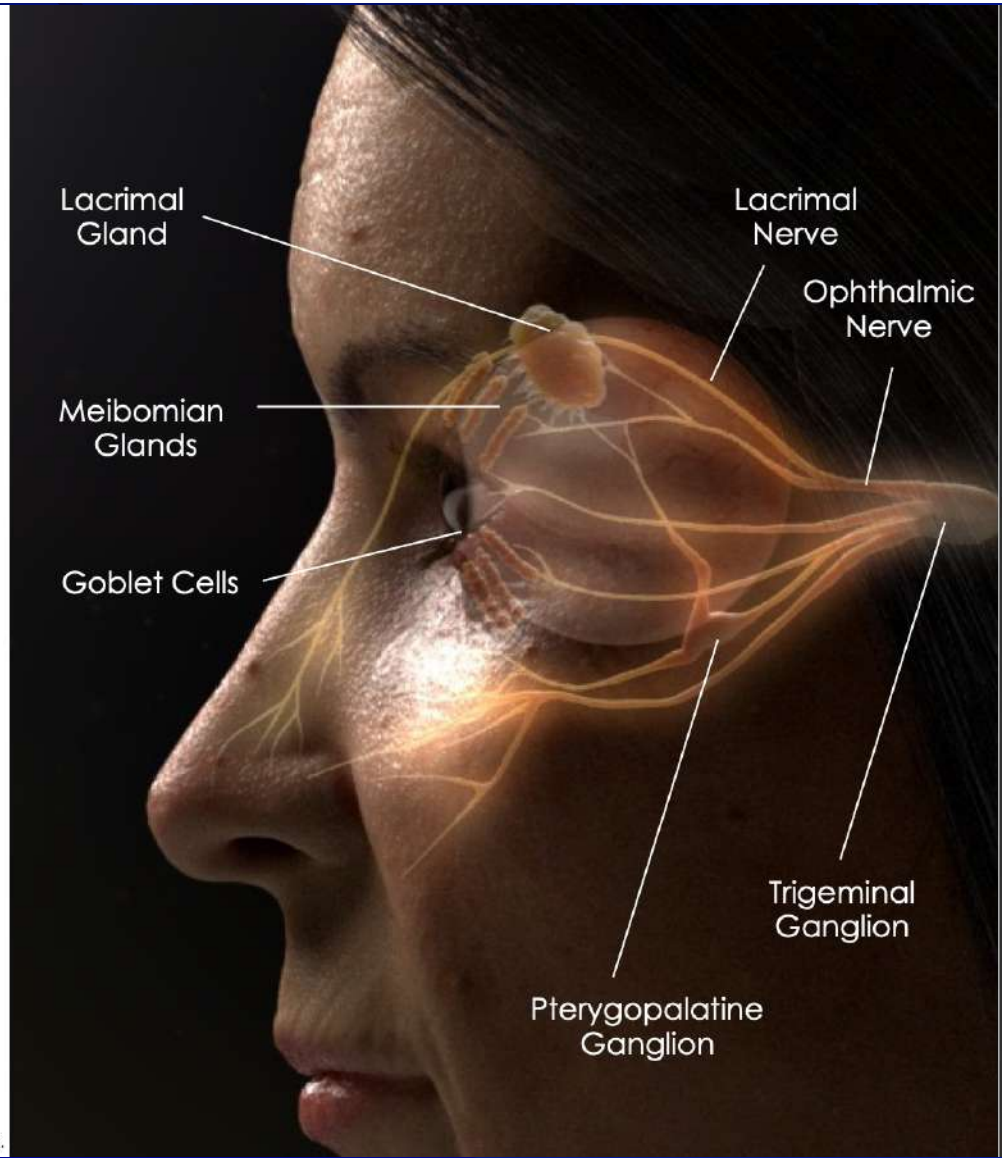


34% of basal tear production is due to inhaling air through the nose[1]

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

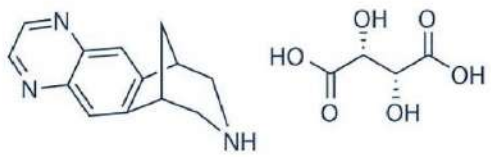
Lacrimal Gland Postganglionic Innervation[1]

- 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

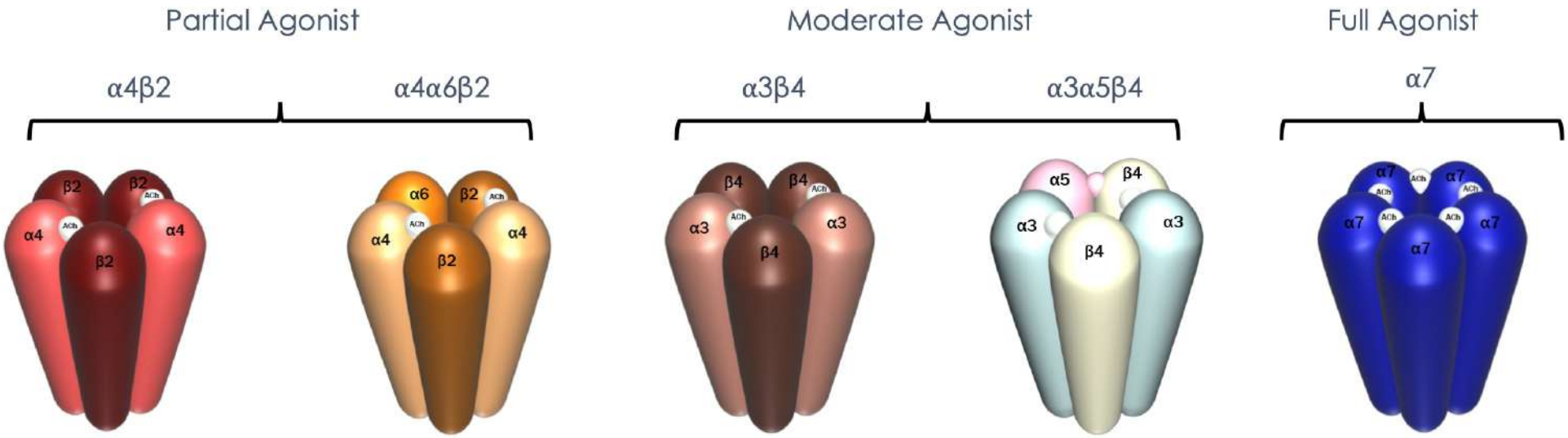


1. Jin K, Imada T, Hisamura R, et al. Identification of lacrimal gland postganglionic innervation and its regulation of tear secretion. *Am J Pathol*. 2020;190(5):1068-1107.

Varenicline Tartrate



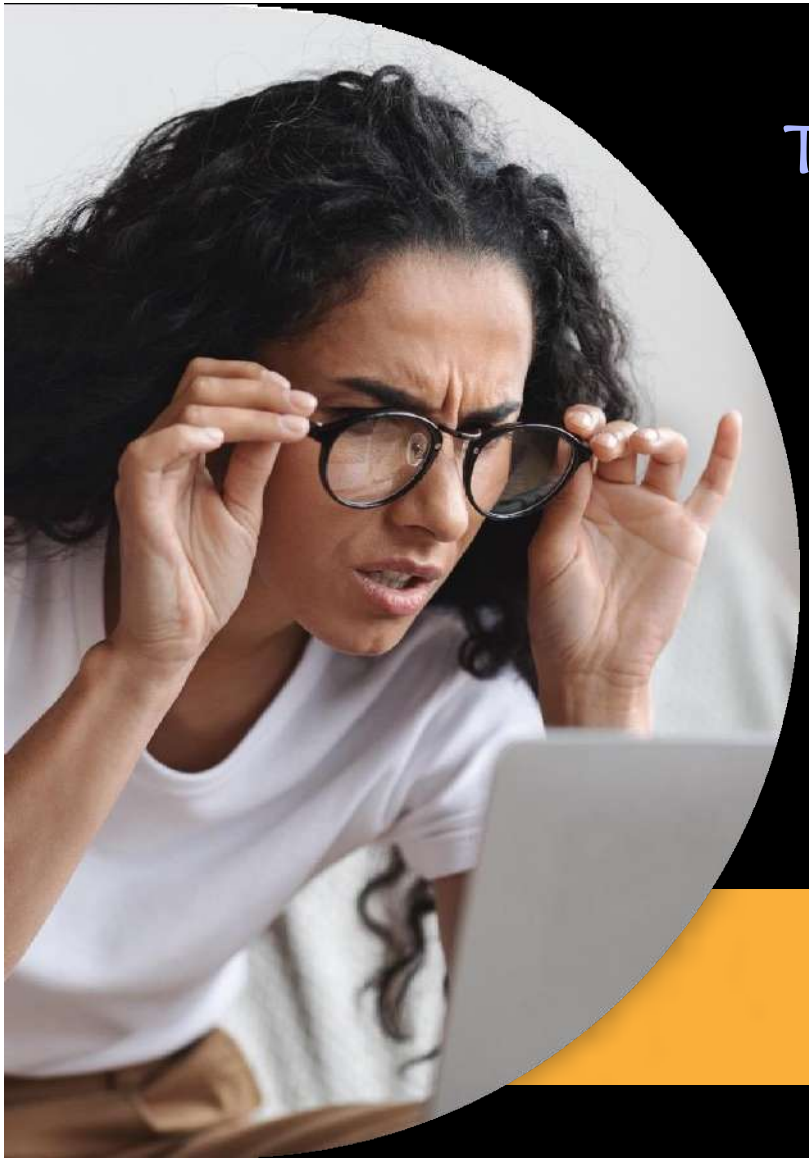
- Binds with high affinity and selectivity at α-subunit containing cholinergic receptors located on the trigeminal nerve within the nasal cavity
- Water soluble and diffuses across nasal mucosa quickly



Tyrvaya – varenicline solution 0.03 mg

- 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



Presbyopia
This Market is Going Away Soon

- Presbyopia, the inevitable loss of near vision
- Research shows adults over 50 lose on average
- 15 lines of near vision per 6 years[1]
- Impacts **128 M** People in the US

Potential **$3B+** Market

Promise of a Once-Daily Eye Drop Solution is Welcomed By All Age Groups

Adapting Early

Seriously Consider
68%

4 – 7 days/wk Usage[1]
80%

45 – 54

Busy Midlife

Seriously Consider
62%

4 – 7 days/wk Usage[1]
79%

55 – 64

Active Aging

Seriously Consider
51%

4 – 7 days/wk Usage[1]
79 %

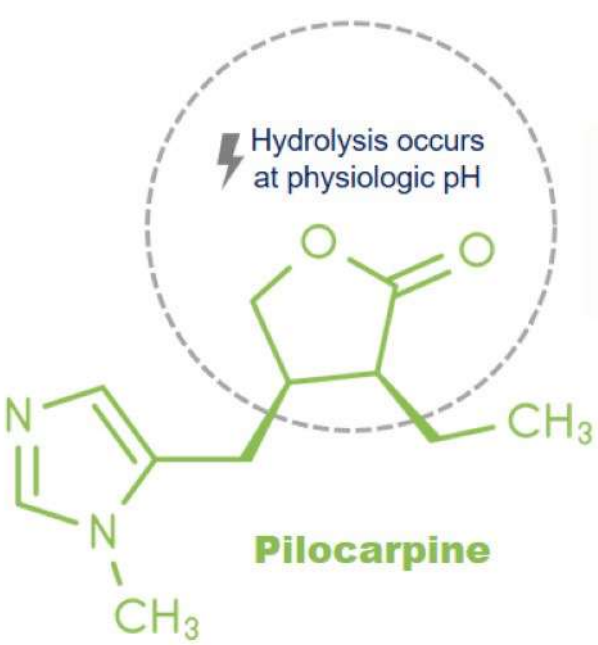
+65

Source: LENZ commissioned survey of 1,358 presbyopes. 1 Percent of those who might or would seriously consider (n=1,293).

Vuity – Pilocarpine 1.25%

- AbbVie (was Allergan)
- Approved October 29, 2021
- Indication: adults with presbyopia
- MOA: Cholinergic muscarinic receptor agonist
- October 2021 - approved as QD dosing
- March 2023 – approved for BID dosing
- Warnings: Poor illumination and iritis, RD?
- Re-engineered design of pilocarpine, optimized concentration, pHast technology

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



Store at low pH for stability

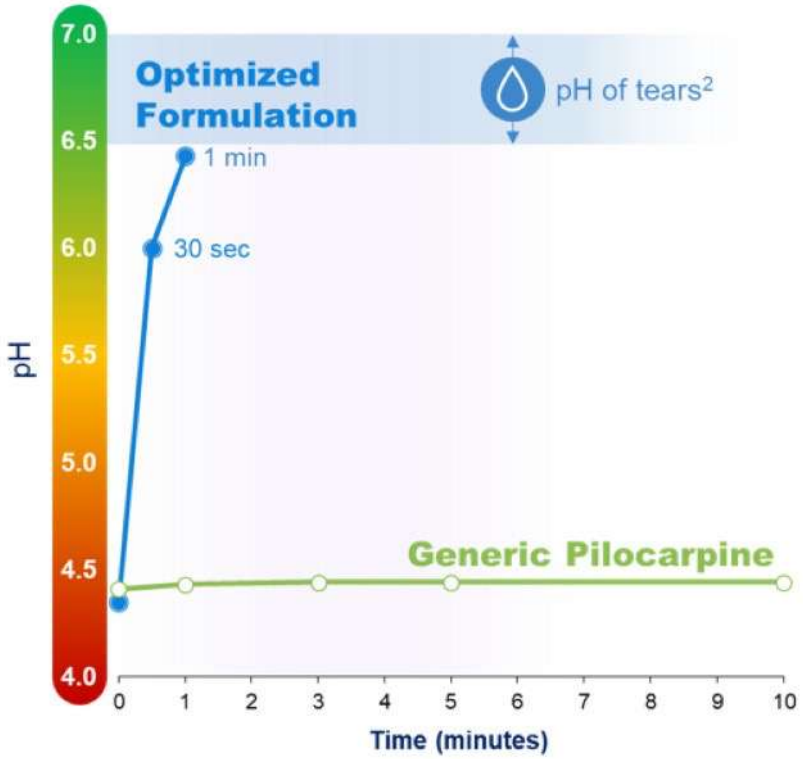
LOWER BIOAVAILABILITY AT pH 4.0 *(vs pH 6.5)*

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

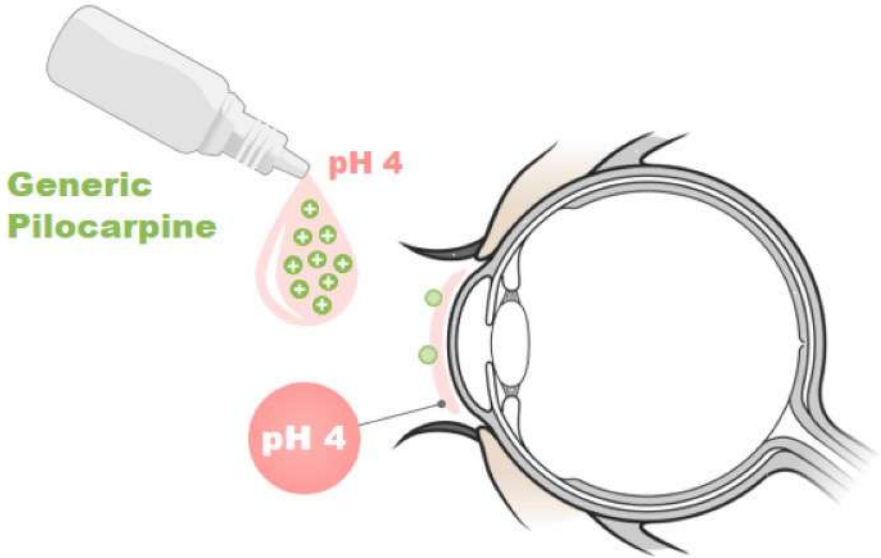


= The **Optimized Formulation with pHast™ Technology** equilibrated to physiologic pH within 1 minute[1]

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

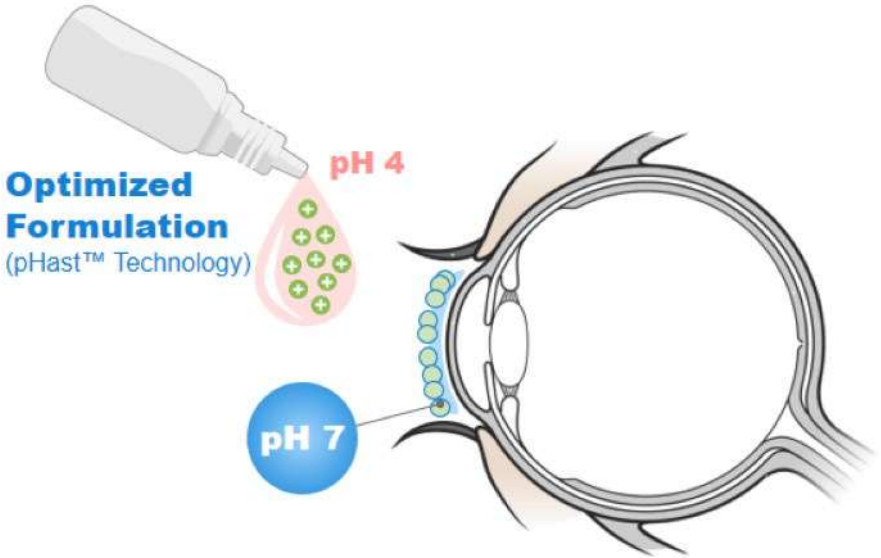
[1]Giyanani JS, et al. AAPS 2020; 895110.
[2]Abelson MB, Udell IJ, Weston JH. *Arch Ophthalmol.* 1981;99(2):301. doi: 10.1001/archopht.1981.03930010303017.

Optimized Formulation Improves Bioavailability and Tolerability[1-4]



Slower mixing and equilibrium with tears

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

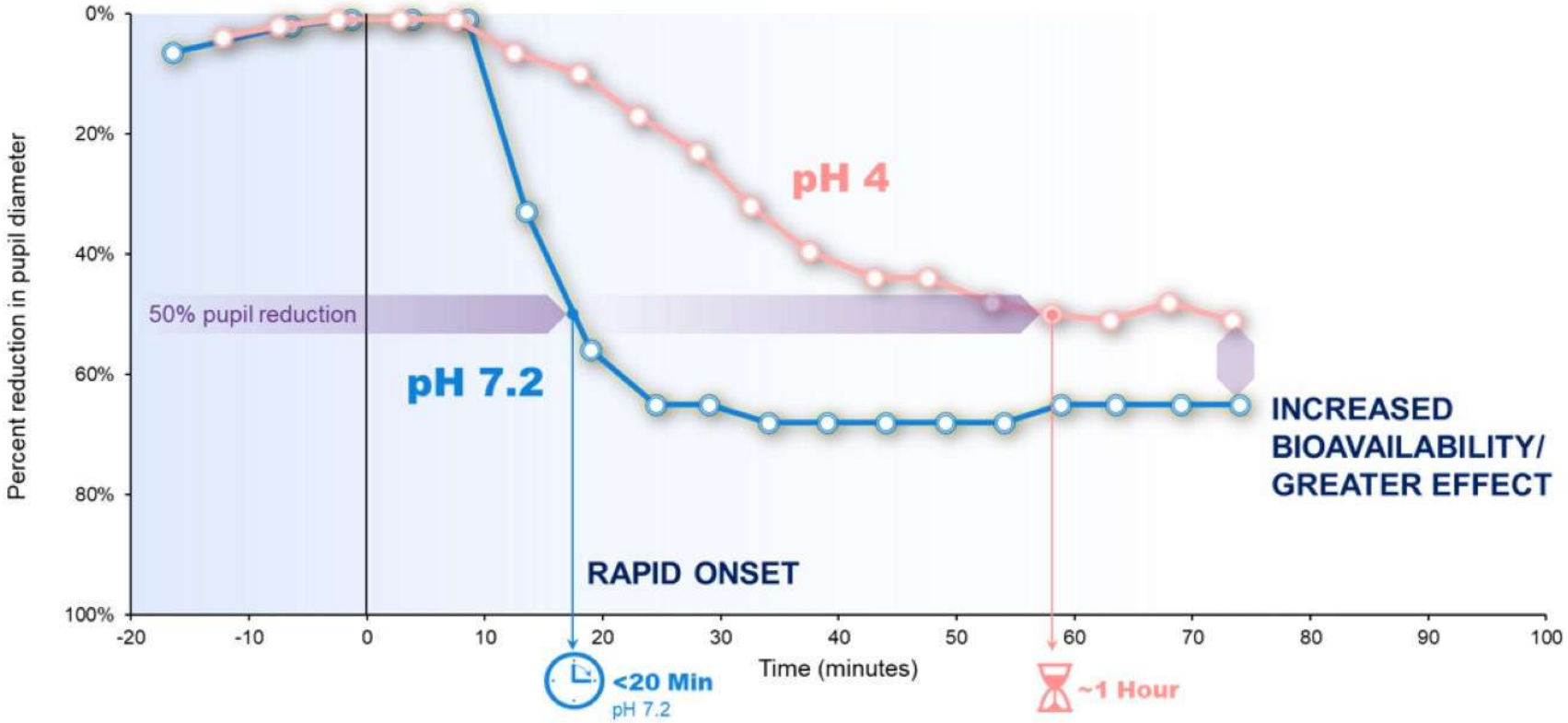


Rapid equilibrium to ocular surface pH:

- 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.

Qlosi (pilocarpine hydrochloride ophthalmic solution) 0.4%

- Orasis Pharmaceuticals
- October 2023 – approval
- Pronounced: CLOH-see
- Indication: Treatment of presbyopia
- Dosing: one drop in each eye can be used daily or as needed
  - Dosing up to twice a day, 2 to 3 hours apart
- Low dose pilocarpine

Aceclidine-Based Eye Drop

- **Lenz – Therapeutics- Late stage** exclusive **aceclidine-based eye drop** with potential of providing **all day** seamless vision for the **vast majority of presbyopes**
- **Not on the market**

Unique MOA Profile	Only miotic shown to achieve pupil sweet spot <2mm w/o myopic shift
Best-in-class clinical data	73% 3-line and 92% 2-line Near Vision improvement at 30min with +10hrs duration
Late Stage	Ongoing Phase 3 trials for LNZ100 and LNZ101
Market Exclusivity	Broad IP protection and NCE status provide strong protection
Proven successful team	Experienced team backed by RA Capital, Alpha Wave Ventures, Versant Ventures, Sectoral Asset Management, Point 72, RTW and others

Mycombi

Tropicamide 1% and Phenylephrine Hydrochloride 2.5% Ophthalmic Spray

- Eyenovia, Inc.
- May 2023 - approval
- Spray
- Indication: For inducing mydriasis
- First-in-class, fixed-dose combo product of tropicamide and phenylephrine
  - Designed to induce mydriasis during in-office diagnostic procedures and conditions that call for short-term pupil dilation

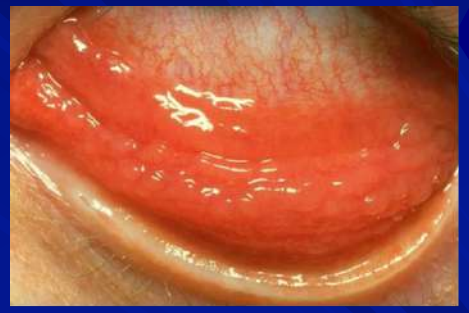
Ryzumvi (phentolamine ophthalmic solution) 0.75%

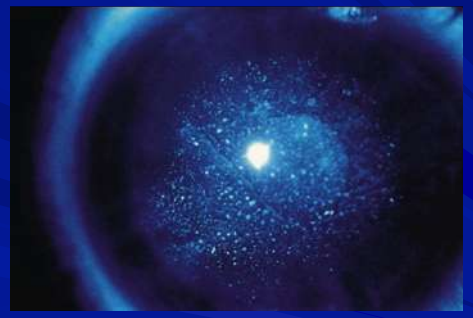
- Viatris
- September 2023 – approval
- Indication: treatment of pharmacologically induced mydriasis produced by adrenergic agonists
- Dosing: 1-2 gtts in the dilated eyes after the exam, 12 years or older
- Dosing: 1 gtt in the dilated eyes after the exam, 3-11 years old
- Mechanism of action: alpha adrenergic blocker, non-selected alpha-1 and alpha-2 adrenergic agonist – iris dilator muscle

- "Rev-Eyes 2.0" - no brow ache and improved redness

If you have a glaucoma practice you have an ocular surface disease practice

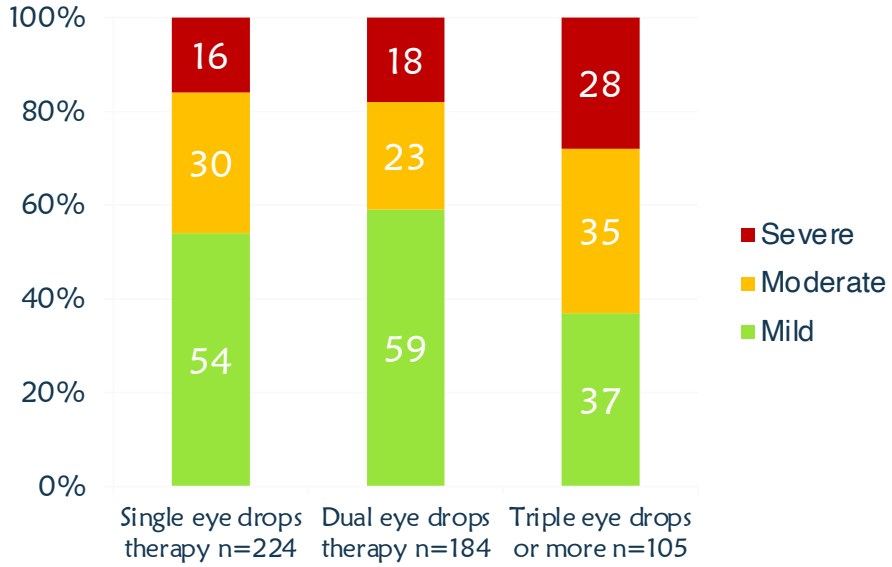
Follicular conjunctivitis





Superficial Punctuate Keratitis (SPK)

The Relationship Between OSD and Number of Preserved Glaucoma Medications

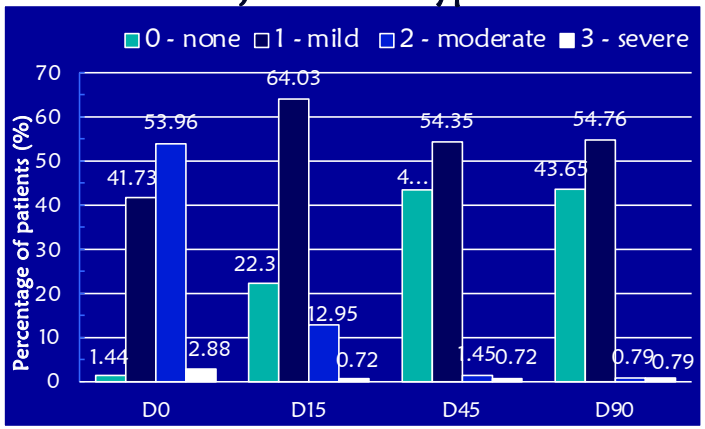


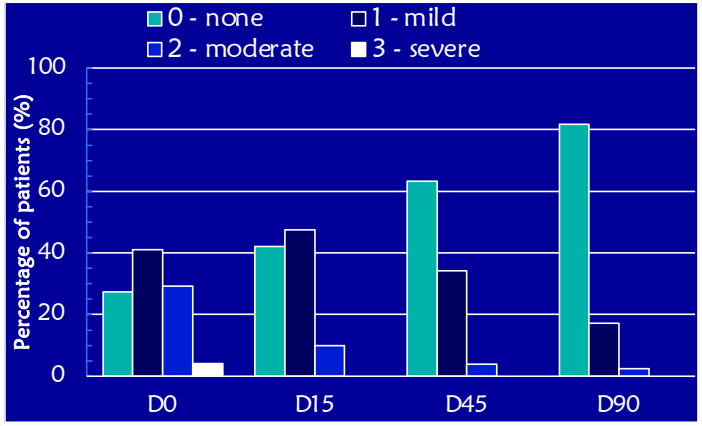
- This study (n=516) was conducted to determine the prevalence of ocular surface diseases and identify risk factors in a population of patients receiving antiglaucoma eye drops[1].
- This study was conducted in France.

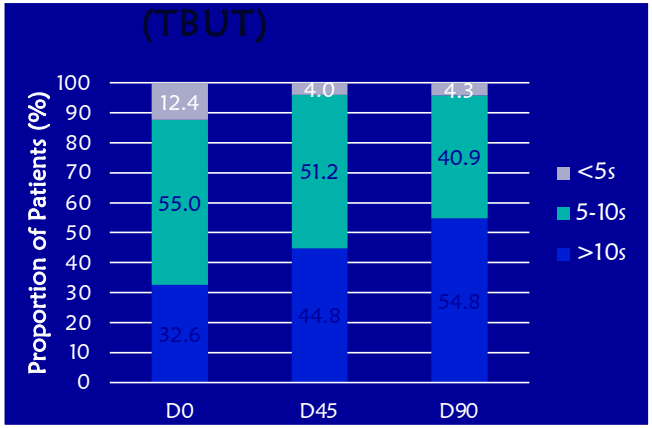
Number of daily eye drops was correlated with the severity of ocular surface disease

1. Baudouin *et al.* Eur. J Ophthalmol 2012; 23(1):47–54

The RELIEF study: switching from preserved latanoprost to preservative free latanoprost for 3 months (n = 140)*[1]







- **Conjunctival hyperemia:** Following the change to PF-latanoprost, there was a progressive decrease in the prevalence of moderate-to-severe conjunctival hyperemia, to 13.7% of patients at D15, 2.2% at D45 and 1.6% at D90 ($p<0.0001$).
- **Blepharitis:** proportion of patients with no signs of blepharitis increased from 27.3% at D0 to 81.7% after 90 days of PF-latanoprost treatment ($p<0.0001$).
- **TBUT:** improved compared with baseline (D0), in 23.4% of patients at D45 ($p=0.0023$) and in 30.7% of patients at D90 ($p<0.0001$).

*This study was conductted at 8 glaucoma centers in Poland

1. Misiuk-Hojlo M et al., European Journal of Ophthalmology. 2019 Mar;29(2):210-215. doi: 10.1177;

Iyuzeh (latanoprost ophthalmic solution) 0.005% Preservative Free

- Thea Pharma Inc
- December 2022 – approval
- Indication: treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT)
- First and only clinically proven formulation of preservative-free latanoprost currently available in the U.S.
- Dosage: single dosage to be placed in the eye(s) once daily in the evening
- Mechanism of action: prostaglandin F2α analogue

Iyuzeh (latanoprost ophthalmic solution) 0.005% Preservative Free

- Launched in Europe as the first preservative-free latanoprost formulation in 2013
- Available in 46 countries including Canada
- PF-Latanoprost formulation approved in the US is the same formulation used in Europe
- Can be stored at room temperature (15C -25C, or 59F - 77F)

Background of Topical Ophthalmic Preservatives

- Preservatives provide important and necessary antimicrobial activity
- Crucial in maintaining sterility and extending the shelf-life of multi-dose formulations of topical ophthalmic medications
- Preservatives are toxic to the ocular surface, particularly in the setting of chronic, prolonged exposure
- As in patients with glaucoma who may have therapeutic regimens that involve multiple eye drops and frequent instillation
- Of all ophthalmic preservatives, benzalkonium chloride (BAK) is the most used and widely studied demonstrating significant ocular surface toxicity
- Although several classes of alternative preservatives have been developed
- All have varying degrees of ocular surface toxicity as well as efficacy profiles

Cytotoxic Effects of BAK on Ocular Tissues

- Can occur at 0.005%, much lower than many of commercially used concentrations of BAK
- Cause tear Film Disruption
  - Acting as a detergent of the lipid layer of the tear film; decreases mucin production
- Induce inflammation and cause damage to
  - Trabecular meshwork
  - Conjunctival tissue and Corneal nerve
  - Goblet cells and decrease its density
- Compromise glaucoma filtration surgery outcomes
  - For each additional BAK-preserved eyedrop, the risk of early surgery failure increased by 21%
- Dose-dependent with cumulative burden of exposure
  - Number of preserved medications, variable BAK concentration in each drop, dosing frequency per day and duration of therapy has been shown to correlate with ocular surface disease prevalence and severity in glaucoma patients and worse quality of life

Preservatives in IOP Lowering Medications

BRAND NAME	ACTIVE INGREDIENT	PRESERVATIVE
EYE DROPS WITH BENZALKONIUM CHLORIDE (BAK)		
Iopidine	Apraclonidine 0.5%, 1%	BAK 0.01%
Betoptic S	Betaxolol 0.25%	BAK 0.01%
Betoptic	Betaxolol 0.5%	BAK 0.01%
Lumigan	Bimatoprost 0.01%	BAK 0.02%
Lumigan	Bimatoprost 0.03%	BAK 0.005%
Lumify	Brimonidine 0.025%	BAK 0.01%
Alphagan	Brimonidine 0.2%	BAK 0.005%
Combigan	Brimonidine 0.2%/timolol 0.5%	BAK 0.005%
Azopt	Brinzolamide 1%	BAK 0.01%
Simbrinza	Brinzolamide 1%/brimonidine 0.2%	BAK 0.003%
Trusopt	Dorzolamide 2%	BAK 0.0075%
Cosopt	Dorzolamide 2%/timolol 0.5%	BAK 0.0075%
Xalatan	Latanoprost 0.005%	BAK 0.02%
Rocklatan	Latanoprost 0.005%/netarsudil 0.02%	BAK 0.02%
Vyzulta	Latanoprostene 0.024%	BAK 0.02%
Betagan	Levobunolol 0.25%, 0.5%	BAK 0.004%
Rhopressa	Netarsudil 0.02%	BAK 0.015%
Isopto Carpine	Pilocarpine 1%	BAK 0.01%
Timoptic	Timolol 0.25%, 0.5%	BAK 0.01%

EYE DROPS CONTAINING ALTERNATIVE PRESERVATIVES		
Alphagan P	Brimonidine 0.1%, 0.15%	Purite® (stabilized oxychloro complex) 0.005%
Xelpros	Latanoprost 0.005%	Potassium sorbate
Timoptic-XE	Timolol-XE 0.25%, 0.5%	Benzododecinium bromide 0.012%
Travatan Z	Travoprost 0.004%	sofZia®

PRESERVATIVE-FREE EYE DROPS		
Cosopt PF	Dorzolamide 2%/timolol 0.5%	Preservative-free
PF Latanoprost	**Latanoprost 0.005%**	**Preservative-free**
Zioptan	Tafluprost 0.0015%	Preservative-free
Timoptic in Ocudose	Timolol 0.25%, 0.5%	Preservative-free

BAK is the most used preservative in topical ophthalmic formulations

PF-Latanoprost has been approved by the FDA for use in the United States.

Alternative Preservatives in Glaucoma Medications

- To reduce the cytotoxicity of BAK, several 'alternative preservatives' have been developed for antiglaucoma medications.
  - Benzododecinium bromide: a quaternary ammonium compound
  - PURITE®: S.O.C (Stabilized Oxychloro Complex)
  - sofZia®: ionic-buffered system (combination of boric acid, zinc, sorbitol, borate and propylene glycol) and functions as an oxidizing preservative
- Although these alternates are considered less toxic than BAK, they still may exert negative impact on ocular surface
  - PURITE (used in Alphagan® P) was shown to induce less corneal and conjunctival inflammatory damage[1].
  - sofZia (used in Travatan Z®): study showed less toxicity compared to BAK[2]

Iyuzeh (latanoprost ophthalmic solution) 0.005% Preservative Free

PF-Latanoprost had a similar IOP lowering efficacy to Xalatan in patients with POAG or OHT. The most common adverse reactions (5% to 35%) were conjunctival hyperemia, eye irritation, eye pruritus, abnormal sensation in eye, foreign body sensation in eyes, vision blurred, and lacrimation increased.

PF-Latanoprost has demonstrated similar IOP lowering efficacy to Xalatan in patients with POAG or OHT with a decade long clinical experience

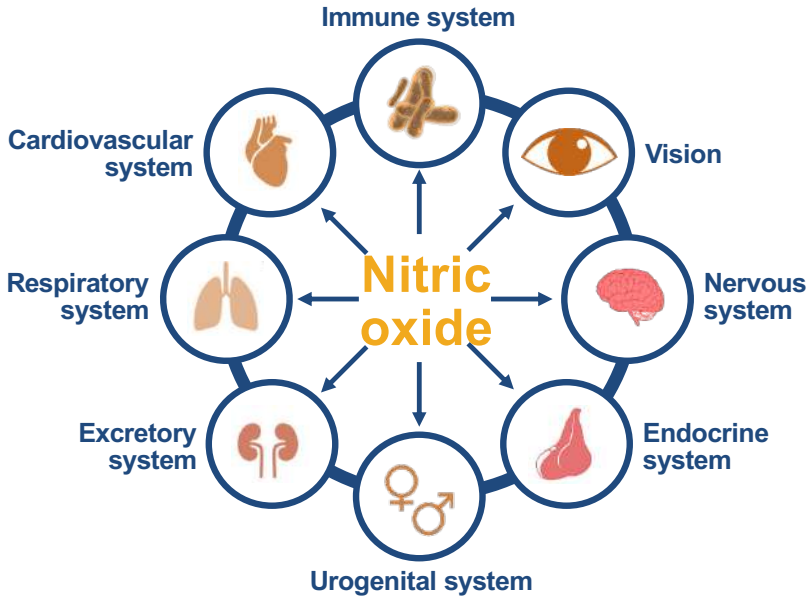
PF Latanoprost has been approved by the FDA, providing US eyecare professionals with another treatment option in their glaucoma treatment armamentarium

Vyzulta™ (latanoprostene Bunod) Ophthalmic Solution 0.024%

- Bausch & Lomb
- November 2, 2017; approved
- Indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
- Only nitric oxide releasing agent that targets both the trabecular meshwork and uveoscleral pathway to reduce IOP
- 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

Nitric Oxide Plays Important Roles Throughout the Body and the Eye

Physiological functions of nitric oxide

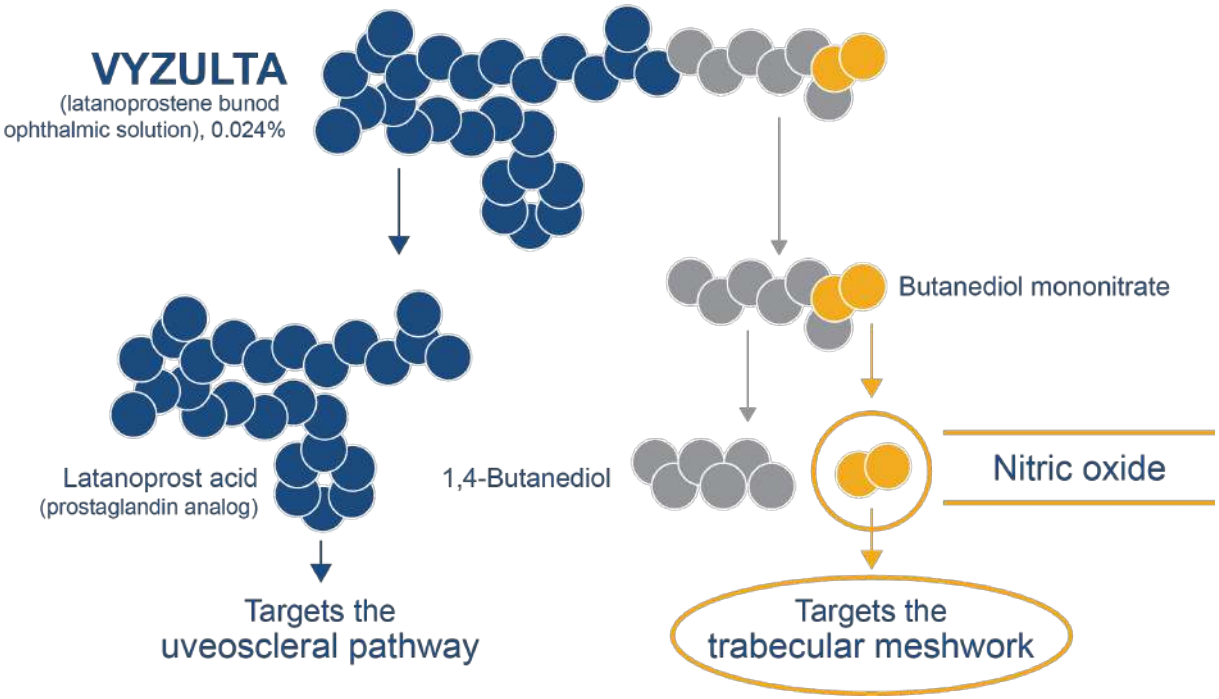


Nitric oxide is a key regulator of numerous physiological functions in the body, including those in the eye

Only VYZULTA® Releases Latanoprost Acid and Nitric Oxide to Reduce IOP

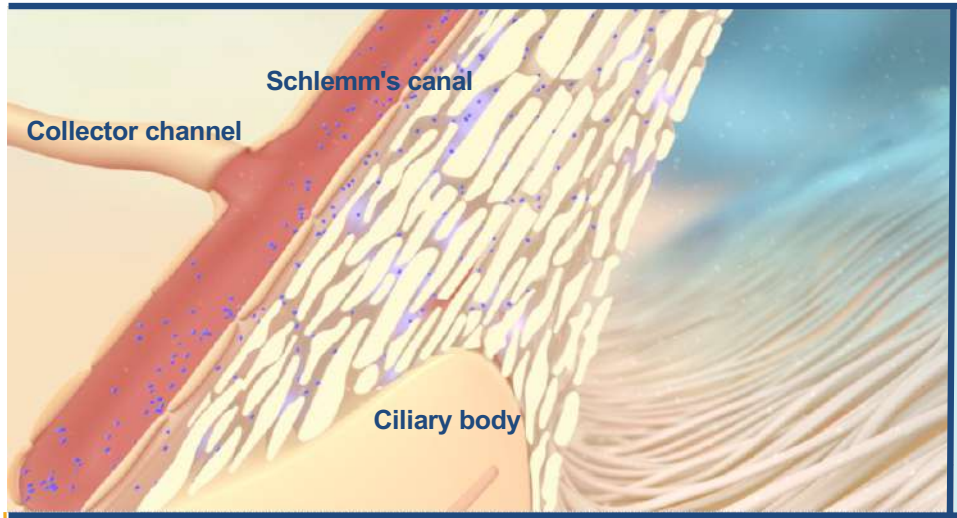
Once metabolized, VYZULTA increases outflow through the

- Uveoscleral pathway
- Trabecular meshwork



Trabecular Meshwork Is the Primary Outflow Pathway in Healthy Eyes, Through Which 60% to 80% of Outflow Occurs

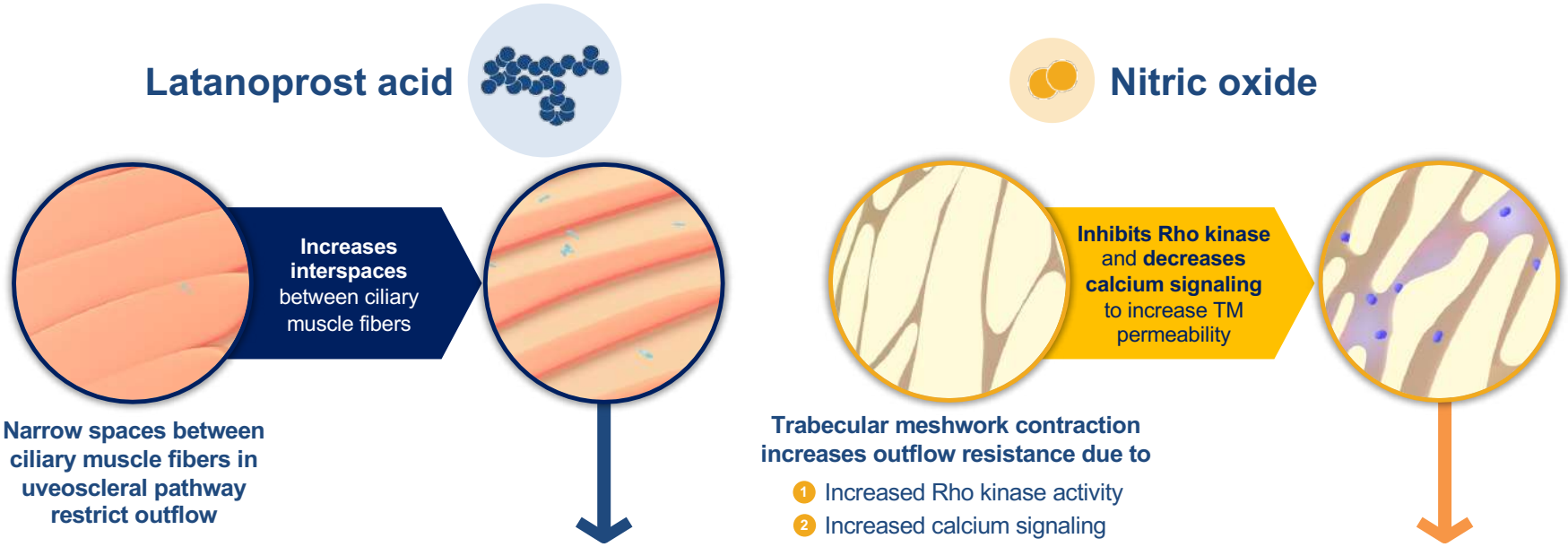
Endogenous nitric oxide regulates aqueous humor outflow by relaxing cells of the TM to lower IOP



- Nitric oxide production is increased in the cells of the Schlemm's canal in response to elevated IOP[2]
- Nitric oxide diffuses to and relaxes the TM to increase outflow and lower IOP[3]

In glaucoma, studies suggest that deficiency in nitric oxide may increase outflow resistance and lead to elevation in IOP

VYZULTA® Delivers Latanoprost Acid and Nitric Oxide to Lower IOP



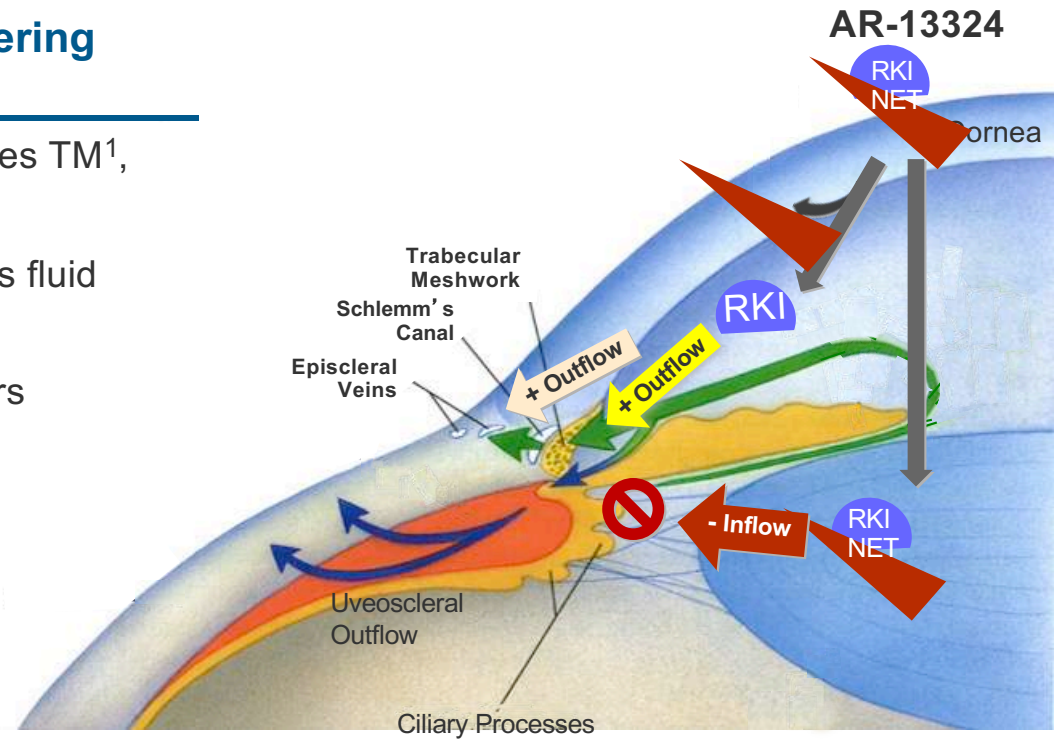
Rhopressa™ 0.02% (netarsudil ophthalmic solution)

- Alcon Pharmaceuticals – was 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]



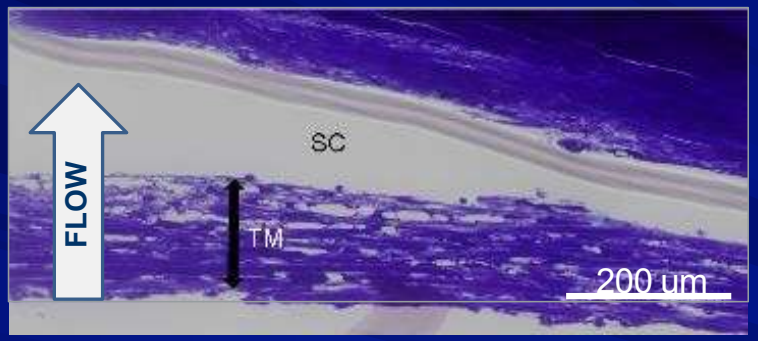
1. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. *Clin Ophthal* 2014;8:883-890.
2. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *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

Rhopressa™ 0.02% (netarsudil)

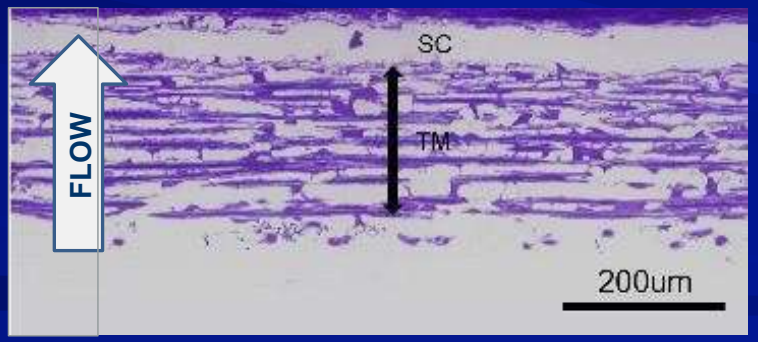
Causes Expansion of TM in Donor Eyes

Increases TM Outflow Facility in Clinic

Trabecular Meshwork (Donor Eyes)[1]

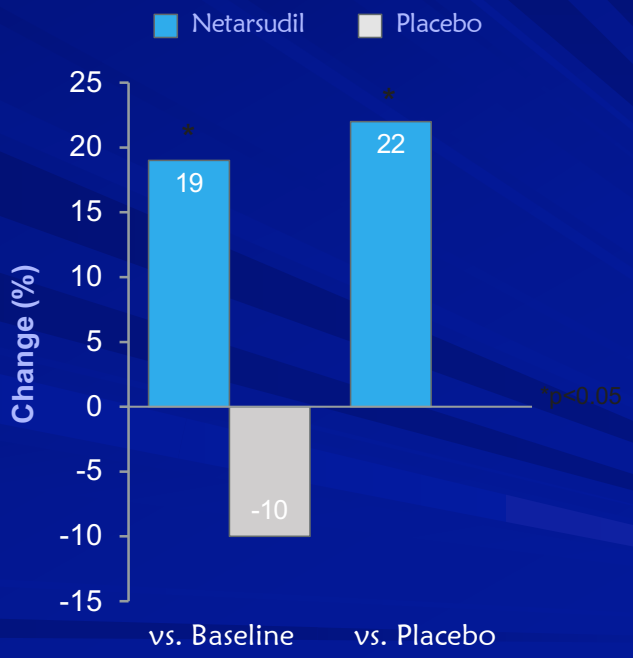


Control



+ Netarsudil

TM Outflow Facility
(Healthy Volunteers)[2]



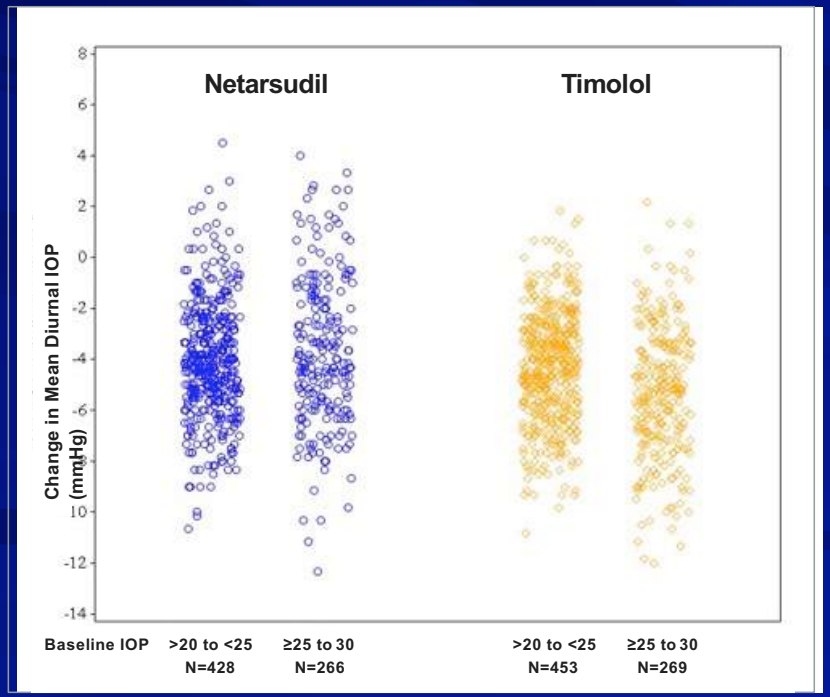
TM: Trabecular Meshwork; SC: Schlemm's Canal; Control: buffered saline solution; ESV: Episcleral Vein

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

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

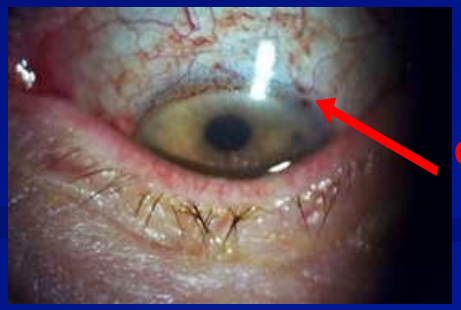
1. RHOPRESSA® (netarsudil ophthalmic solution) 0.02% Prescribing Information. 2. Khouri et al. Association for Research in Vision and Ophthalmology oral presentation 2017 [E-abstract 2461].

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

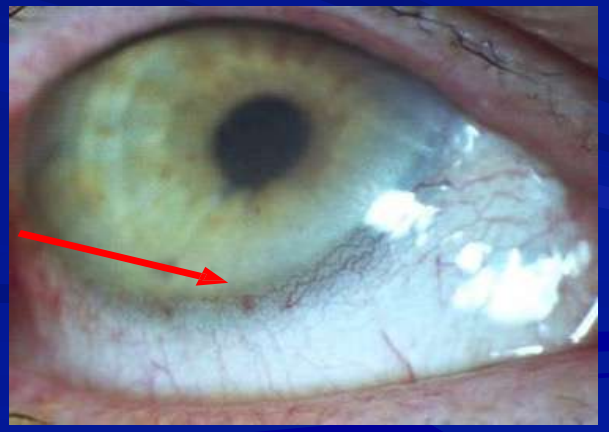
Adverse Events	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
TEAE Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
AE Resulting in Discontinuation	8 (1.0)	0

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

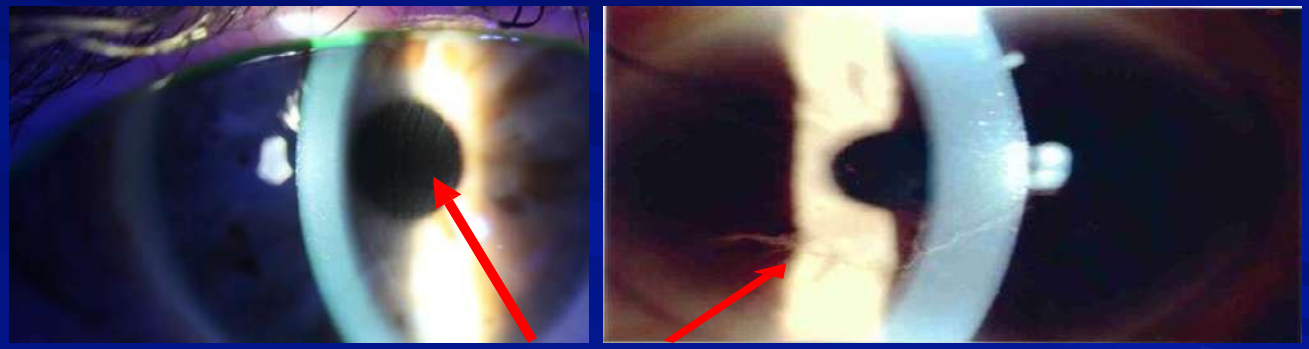


Images were taken from netarsudil subjects

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

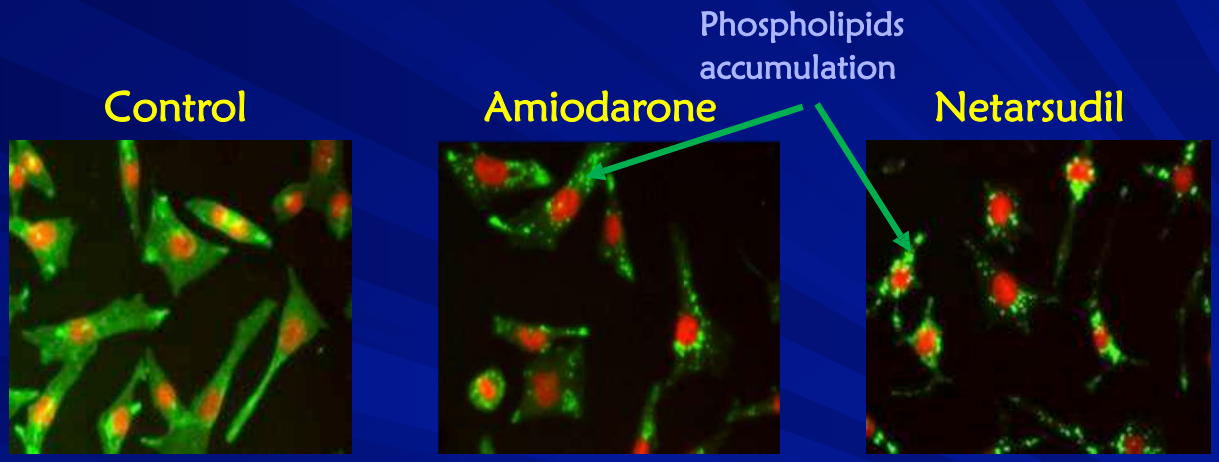
AR-13324-CS302
netarsudil QD subject

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*

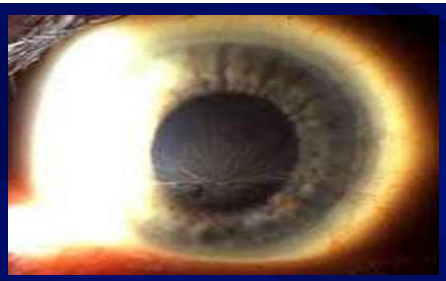


Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes

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

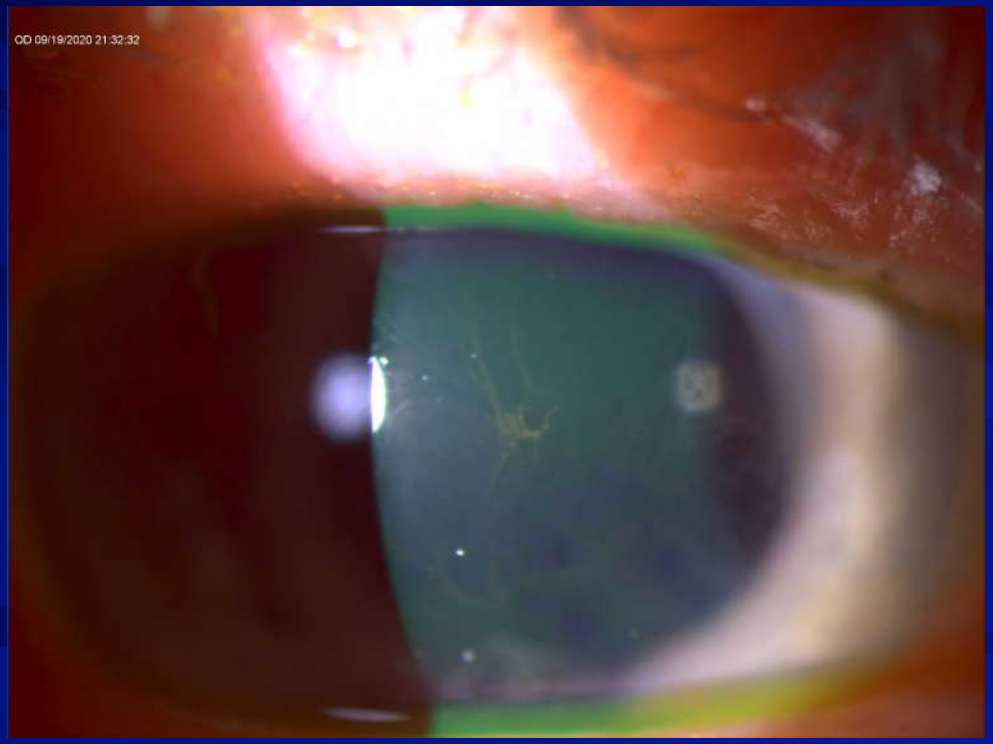
Data on File Based on AR-13324-IPH07

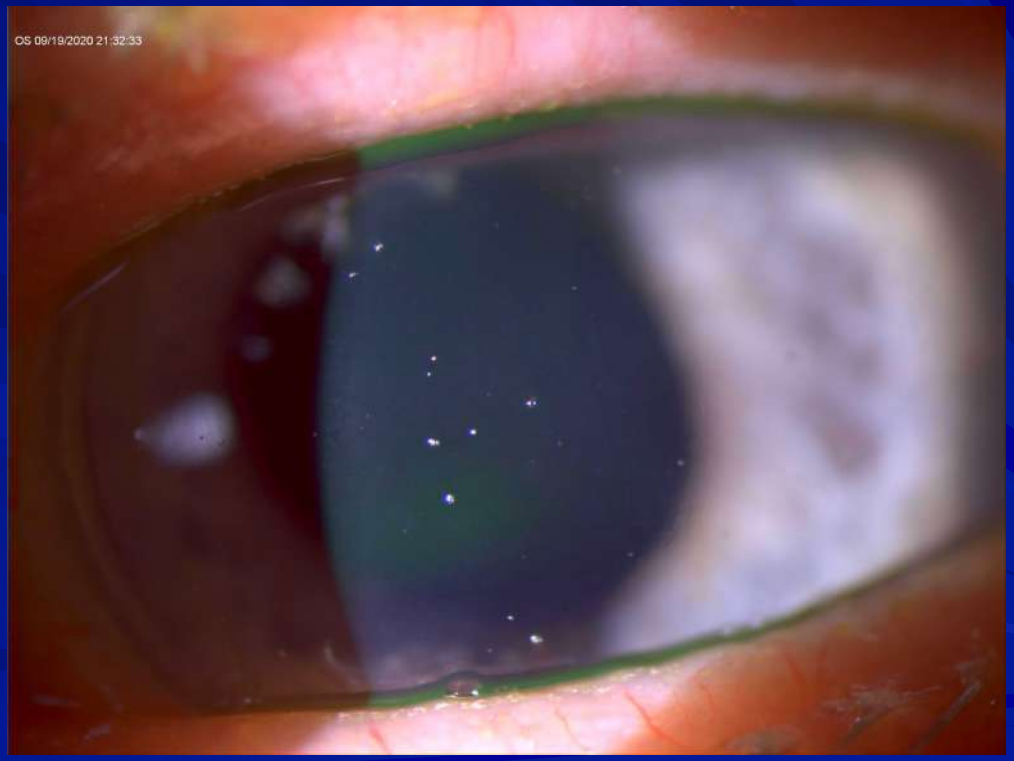
* Raizman MB et al. Surv. Ophthalmol. 2017;62:286-301



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

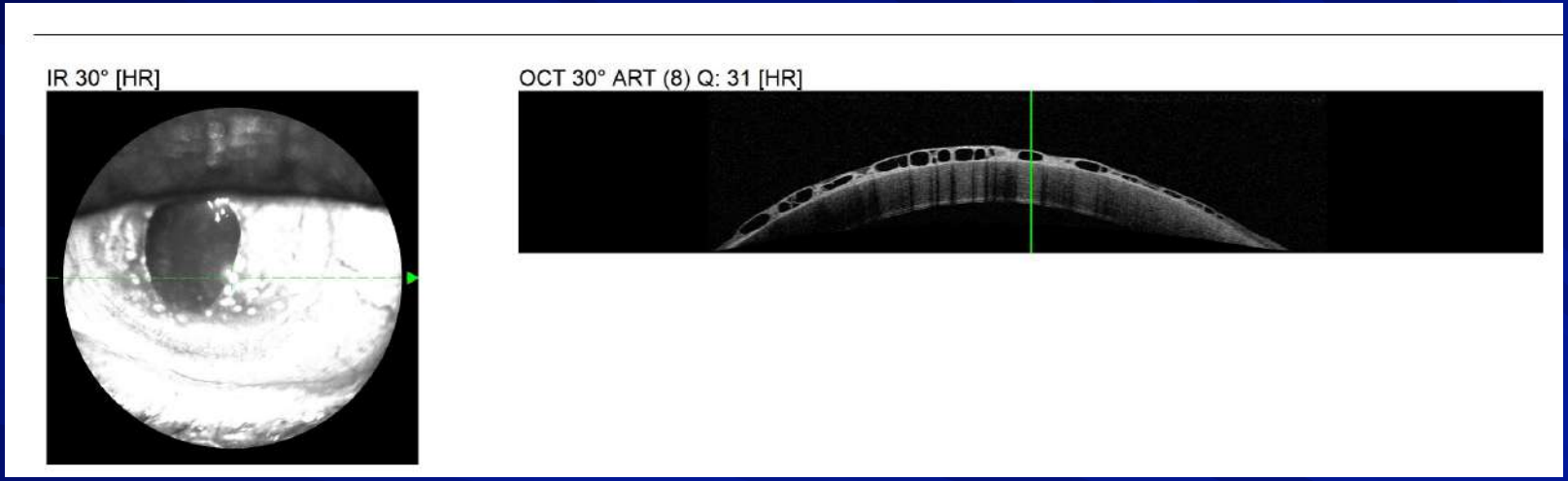
Cornea Verticillata

- 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

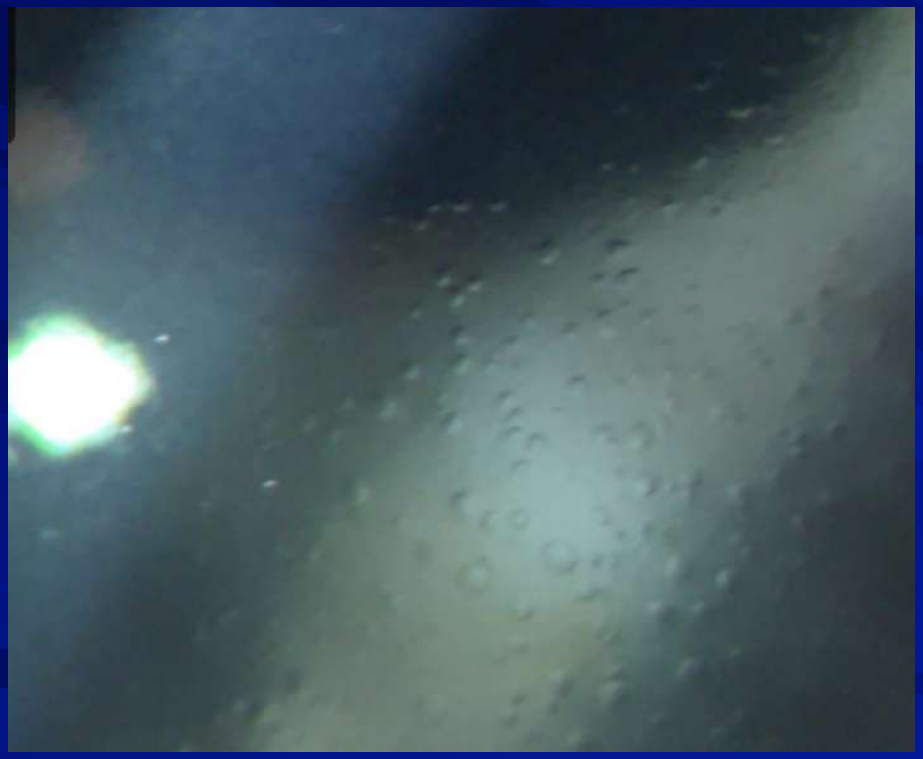
- 17.2% TEAE
- Mild in severity and transient
- Self-resolving with continued dosing

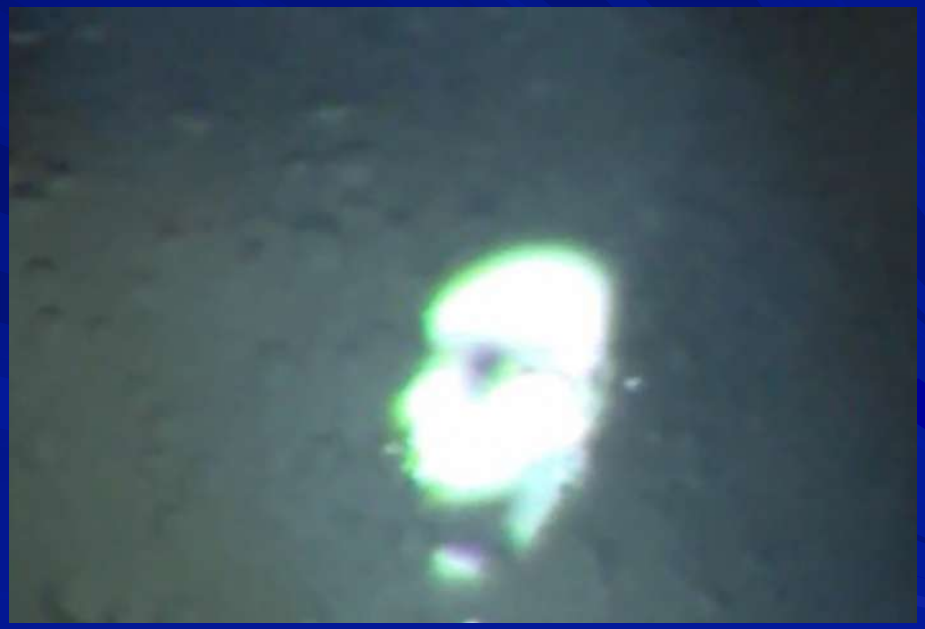
Honeycomb Epithelial Edema Associated With Rho Kinase Inhibition



- 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

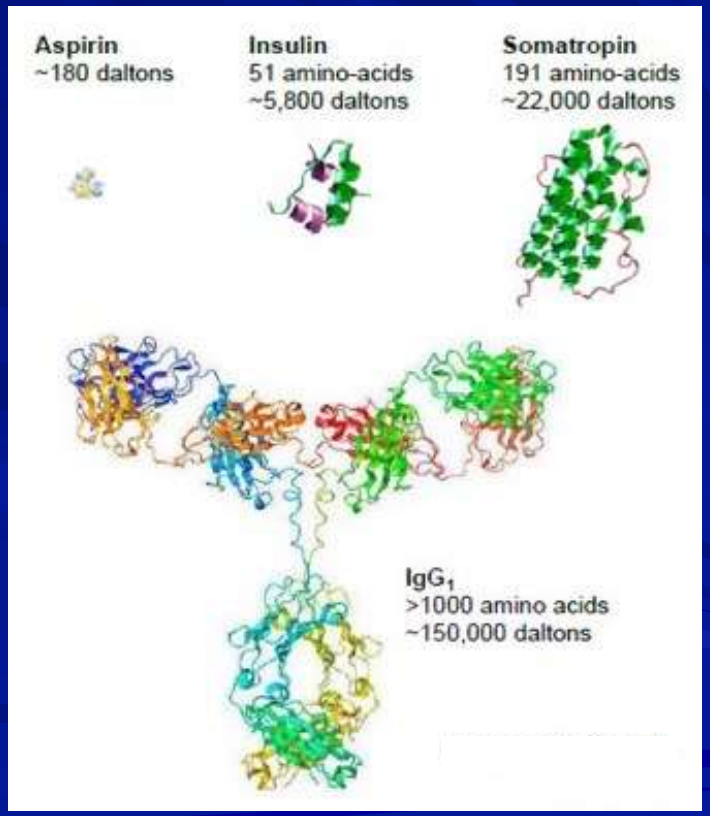
Rocklatan™

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

- Alcon Pharmaceuticals – was Aerie pharmaceuticals
  - March 14, 2019
- Once-daily eye drop
- First PGA combination approved
  - Superiority versus inferiority
- Refrigeration
  - Storage and after opening

Biologic Drugs versus Small Molecule Drugs

- Biologic Drugs
  - Larger, complex, dynamic structures
  - Diverse populations of molecules
    - Not easily characterized
  - Complicated manufacturing
  - Example: Teprotumumab (Tepezza)
- Small Molecule Drugs
  - Synthetic
  - Manufactured using a defined chemical process
  - Smaller and simpler
  - Example: Aspirin



Why Your Patients Are on ELAHERE

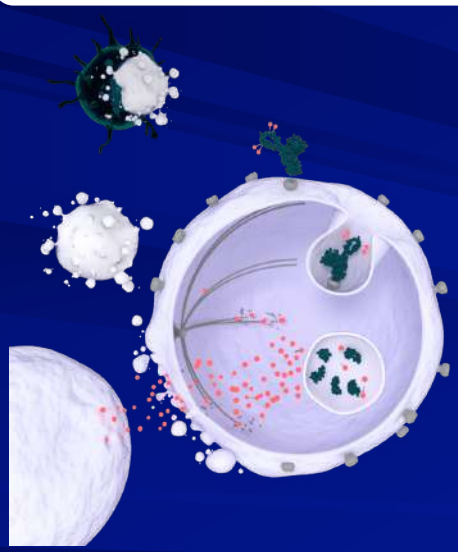
Eye Care Considerations for Patients Treated With ELAHERE

Optometry's role with Elehere - Mirvetuximab Soravtansine gynx (MIRV)

- Antibody-drug conjugate (ADC) comprising an FR-binding antibody, cleavable linker, and maytansinoid DM4 payload
- Primary ocular events with MIRV include corneal disorder, corneal epithelial defect, keratitis, keratopathy, corneal deposits, and punctuate keratitis
- Exam and clear patient for treatment

Elehere - Mirvetuximab Soravtansine

Mirvetuximab soravtansine (MIRV) is the first biomarker-directed agent showing antitumor activity in patients with FRα-positive[a] platinum-resistant ovarian cancer (PROC)[1]



- MIRV is an antibody-drug conjugate (ADC) comprising an FRα-binding antibody, cleavable linker, and maytansinoid DM4 payload[1]
- A phase 3 clinical study, SORAYA, evaluated MIRV in patients with FRα-high PROC who had received 1 to 3 prior therapies, including required bevacizumab[1-3]

Why Your Patients Are on ELAHERE

ELAHERE is a therapy approved to treat certain patients with advanced ovarian cancer

- ELAHERE is indicated for the treatment of adult patients with folate receptor-alpha (FR□) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Who have received one to three prior systemic treatment regimens
- This indication is approved under accelerated approval based on tumor response rate and durability of response

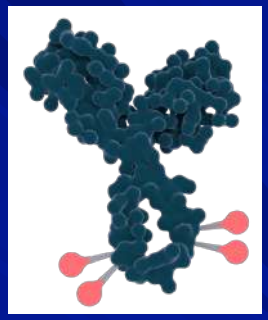
Why Eye Care Is Important for Patients Receiving ELAHERE™

You play a critical role in patient management as ocular adverse events have been observed in patients treated with ELAHERE

BOXED WARNING: OCULAR TOXICITY

- **ELAHERE can cause severe ocular toxicities, including visual impairment, keratopathy, dry eye, photophobia, eye pain, and uveitis.**
- **Conduct an ophthalmic exam including visual acuity and slit lamp exam prior to initiation of ELAHERE, every other cycle for the first 8 cycles, and as clinically indicated.**
- **Administer prophylactic artificial tears and ophthalmic topical steroids.**
- **Withhold ELAHERE for ocular toxicities until improvement and resume at the same or reduced dose.**
- **Discontinue ELAHERE for Grade 4 ocular toxicities.**

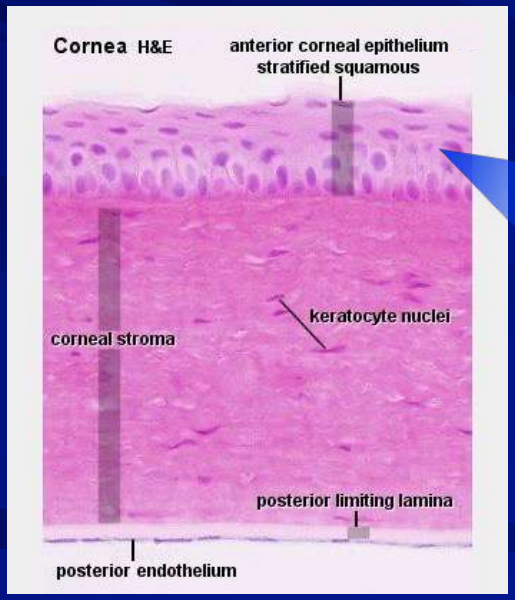
Proposed MOA for Ocular Events Associated With MIRV



- The underlying mechanisms of ocular toxicities remain poorly understood, but it is hypothesized to be an off-target effect on the corneal epithelium due to the lack of FRα receptors in that part of the eye
- Anti-microtubule payloads such as DM4 have been previously associated with resolvable ocular toxicity, such as blurred vision, dry eye, and keratopathy
- One hypothesis for toxicity seen with anti-microtubule payloads is that symptoms arise from a change in curvature of the cornea due to transient alterations in corneal epithelial thickness or corneal biomechanical properties, associated with the presence of microcysts
- Additionally, prolonged retention in circulation associated with MIRV's stable linker may lead to enhance exposure in normal tissues

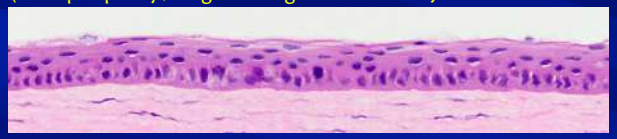
The ocular AE profile of MIRV is a dose-dependent toxicity limited to the corneal epithelium of the eye, with resolvability observed in both non-clinical and human studies

Microscopic Analysis of the Corneal Epithelium

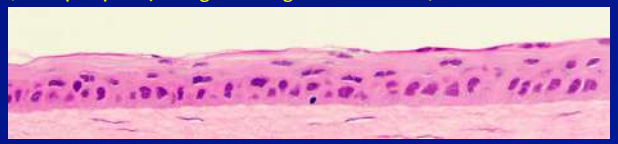


Non-clinical Microscopic Analysis
(Control and MIRV 12-mg/kg Dose)[1]

Control, Left Cornea
(near periphery; original magnification x20)



MIRV 12-mg/kg/dose, Left Cornea
(near periphery; original magnification x20)



Key Observations With MIRV 12-mg/kg Dose

- **Fewer and larger** epithelial cells
- Overall **thinner** epithelial layer
- Basal layer appearing disorganized as **gaps** noted between visible nuclei
- **No visible nuclei** in places across the thickness of the epithelial layer, suggesting no cells other than those of the basal layer were present[1]
- **Lesions only at the periphery** of the cornea

Due to the Possibility of Ocular Adverse Events With ELAHERE Eye Care Is Necessary

Ophthalmic Exams

Preventive Measures

Lubricating Eye Drops

Ophthalmic Topical Steroids

Proactive Management of Ocular Adverse Events

Patients should receive a baseline ophthalmic exam from an ophthalmologist or optometrist prior to treatment initiation and follow-up exams during every other cycle for the first 8 cycles, and as clinically indicated

---

Tell patients to avoid use of contact lenses, unless they are medically necessary

---

Use of preservative-free[a] lubricating eye drops at least 4 times daily and as needed is recommended during treatment with ELAHERE

Use of ophthalmic topical corticosteroids is recommended

- The initial prescription and renewals of any corticosteroid medication should be made only after examination with a slit lamp

Recommended Schedule for Eye Drops

Ophthalmic Topical Corticosteroids

Starting the day before ELAHERE infusion until 3 days after infusion (Days 1–4)

- Advise patients to apply 1 drop in each eye 6 times daily

On Days 5–8

- Advise patients to apply 1 drop in each eye 4 times daily

Lubricating Eye Drops

The use of preservative-free lubricating eye drops is also recommended at least 4 times daily and as needed during treatment. Advise patients to wait at least 10 minutes after administering ophthalmic topical corticosteroids before using lubricating eye drops

What to Look for in the Baseline Ophthalmic Exam

- A baseline ophthalmic examination should include a visual acuity test and slit lamp exam
- Document the patient's current symptoms and visual acuity prior to the initiation of ELAHERE™

Symptom Assessment

Inquire about ocular symptoms (eg, vision impairments, dry eye, photophobia, eye pain), and treat as appropriate

Visual Acuity

Measure best corrected visual acuity at baseline to help understand whether changes have occurred during follow-up exams

Slit Lamp Exam

Assess corneal health (eg, keratopathy, superficial punctate keratitis) is recommended before initiation of treatment with ELAHERE

What to Monitor During Scheduled Follow-up Ophthalmic Exams

Monitor patients every other cycle (~every 6 weeks) for the first 8 cycles (~6 months) of ELAHERE™ for any changes from the baseline ophthalmic exam, and as clinically indicated[1]

Symptom Assessment[1]

- Inquire about any new or worsening ocular symptoms since the most recent ophthalmic exam

Visual Acuity[1]

- Compare against baseline measurement to determine whether best corrected visual acuity has changed

Slit Lamp Exam[1]

- Document any ocular findings, including keratopathy and uveitis

Note: As part of their treatment with ELAHERE, your patient is being prescribed ophthalmic topical steroids that may elevate intraocular pressure

1. ELAHERE. Package Insert. *Refract Surg.* 2021;47(1):53-64. 3. Palacio-Pastrana C, et al. *Clin Ophthalmol.* 2020;14:1581-1589.

Presentation of Keratopathy (Microcyst-like Corneal Epithelial Changes)

- Microcyst-like corneal epithelial changes (MECs) may be identified during ophthalmic slit lamp exams[1]
- MECs can appear in both symptomatic and asymptomatic patients[2]
- Document whether MECs are[3]:
  - Confluent (ie, merging or clumped)
  - Nonconfluent (ie, separated or distinct)

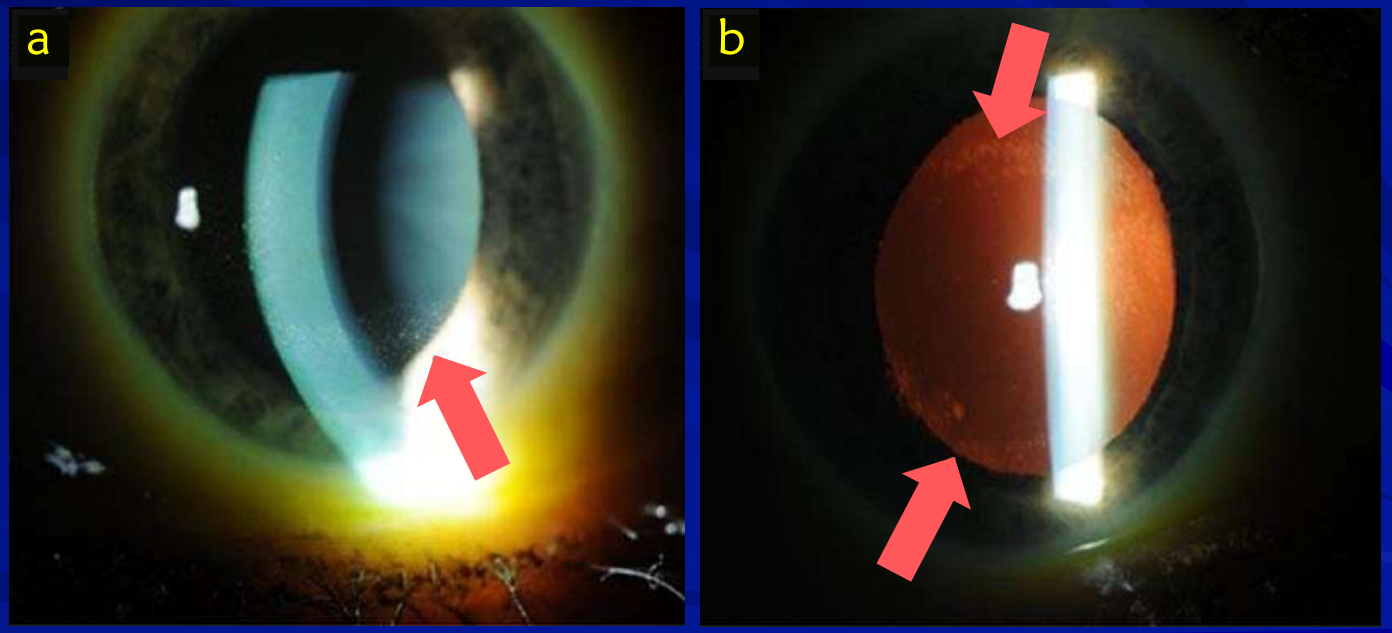


Figure. Arrows denote corneal microcysts observed in a 57-year-old patient 5 weeks after receiving ELAHERE™.[4]

What to Expect With Ocular Events Associated With ELAHERE™

Integrated Safety Analysis of Patients Treated With ELAHERE (N=464)[a]

Timing of Onset

- Median onset to the first ocular adverse event was ~5 weeks (range, 1 day–55.3 weeks)[1]

Impact

- Ocular adverse events of any grade occurred in 61% of patients[1]
  - Grade 1 or 2: >90% of patients
  - Grade 3: 9% of patients
  - Grade 4: 0.2% of patients[b]

Resolution

- No patients had permanent ocular sequelae[2]
- Ocular adverse events led to permanent discontinuation of ELAHERE in 0.6% of patients[1]

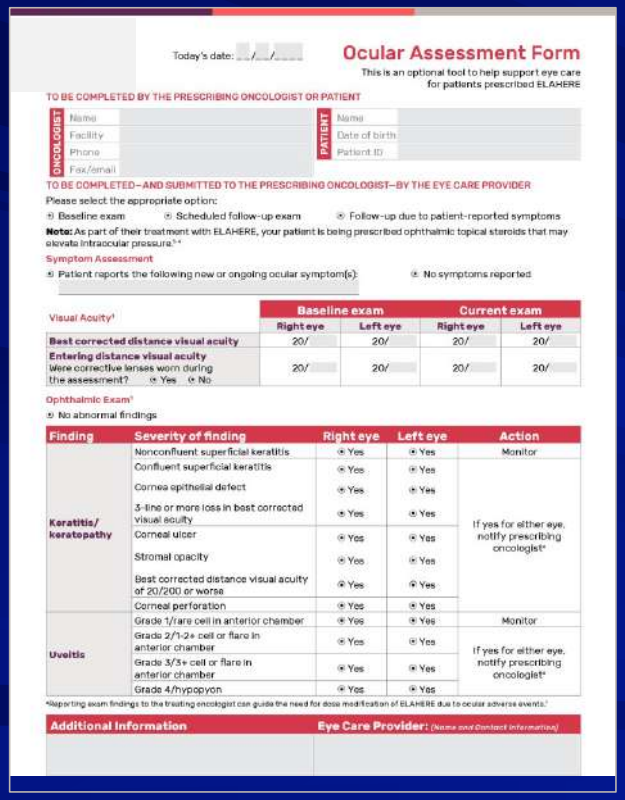
Monitoring Ocular Adverse Events

Ophthalmic Exam Findings Requiring Dose Modifications

Ophthalmic exam finding	Severity of finding	Action
Keratitis/ keratopathy	Nonconfluent superficial keratitis	Monitor
	Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss in best corrected visual acuity	Notify treating oncologist[a]
	Corneal ulcer or stromal opacity or best corrected distance visual acuity of 20/200 or worse	
	Corneal perforation	
Uveitis	Grade 1/rare cell in anterior chamber	Monitor
	Grade 2/1-2+ cell or flare in anterior chamber	Notify treating oncologist[a]
	Grade 3/3+ cell or flare in anterior chamber	
	Grade 4/hypopyon	

Ocular adverse events should be treated by the eye care provider per standard clinical guidelines

Coordinating With the Treating Oncologist



Today's date: __/__/____

Ocular Assessment Form

This is an optional tool to help support eye care for patients prescribed ELAHERE

TO BE COMPLETED BY THE PRESCRIBING ONCOLOGIST OR PATIENT

ONCOLOGIST: Name; Facility; Phone; Fax/email

PATIENT: Name; Date of birth; Patient ID

TO BE COMPLETED – AND SUBMITTED TO THE PRESCRIBING ONCOLOGIST – BY THE EYE CARE PROVIDER

Please select the appropriate option:

○ Baseline exam ○ Scheduled follow-up exam ○ Follow-up due to patient-reported symptoms

Note: As part of their treatment with ELAHERE, your patient is being prescribed ophthalmic topical steroids that may elevate intraocular pressure.[1,2]

Symptom Assessment

○ Patient reports the following new or ongoing ocular symptom(s): ○ No symptoms reported

Visual Acuity[1]	Baseline exam		Current exam	
	Right eye	Left eye	Right eye	Left eye
Best corrected distance visual acuity	20/	20/	20/	20/
Entering distance visual acuity Were corrective lenses worn during the assessment? ○ Yes ○ No	20/	20/	20/	20/

Ophthalmic Exam[1]

○ No abnormal findings

Finding	Severity of finding	Right eye	Left eye	Action
Keratitis/ keratopathy	Nonconfluent superficial keratitis	○ Yes	○ Yes	Monitor
	Confluent superficial keratitis	○ Yes	○ Yes	If yes for either eye, notify prescribing oncologist*
	Cornea epithelial defect	○ Yes	○ Yes	
	3-line or more loss in best corrected visual acuity	○ Yes	○ Yes	
	Corneal ulcer	○ Yes	○ Yes	
	Stromal opacity	○ Yes	○ Yes	
	Best corrected distance visual acuity of 20/200 or worse	○ Yes	○ Yes	
	Corneal perforation	○ Yes	○ Yes	
Uveitis	Grade 1/trace cell in anterior chamber	○ Yes	○ Yes	Monitor
	Grade 2/1-2+ cell or flare in anterior chamber	○ Yes	○ Yes	If yes for either eye, notify prescribing oncologist*
	Grade 3/3+ cell or flare in anterior chamber	○ Yes	○ Yes	
	Grade 4/hypopyon	○ Yes	○ Yes	

*Reporting exam findings to the treating oncologist can guide the need for dose modification of ELAHERE due to ocular adverse events.[1]

Additional Information	Eye Care Provider: *(Name and Contact Information)*

ELAHERE™ Ocular Assessment Form to Guide Ophthalmic Exams and Communicate With Treating Oncologists

- Reporting exam findings to the treating oncologist can guide the need for dose modification due to ocular events
- Dose reductions or modifications may help resolve ocular events
- Ocular adverse events led to permanent discontinuation of ELAHERE in 0.6% of patients

For questions or information about billing and coding, reference the ELAHERE Ocular Billing & Coding Guide

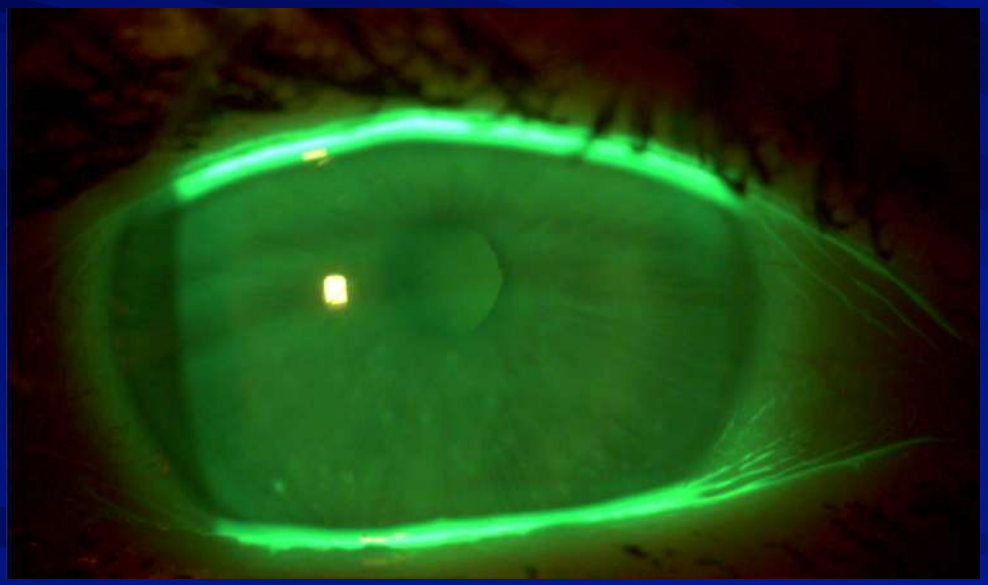
Scan this code to download a copy of the ELAHERE Ocular Assessment Form

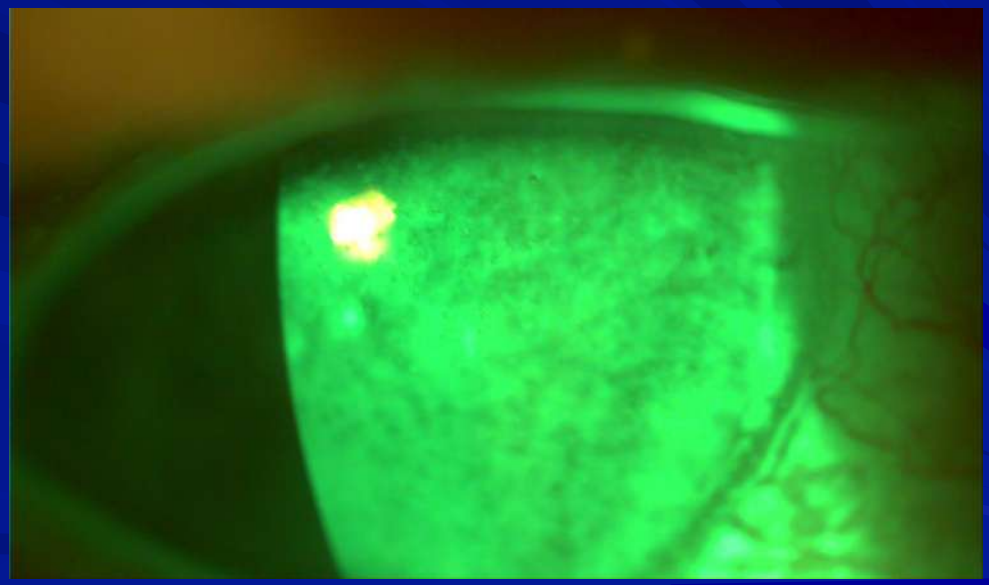
Oxervate™ (cenegermin-bkbj)

- Dompé 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
- 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
- ADRs: eye pain, inflammation, corneal deposits
- Contraindications
  - None

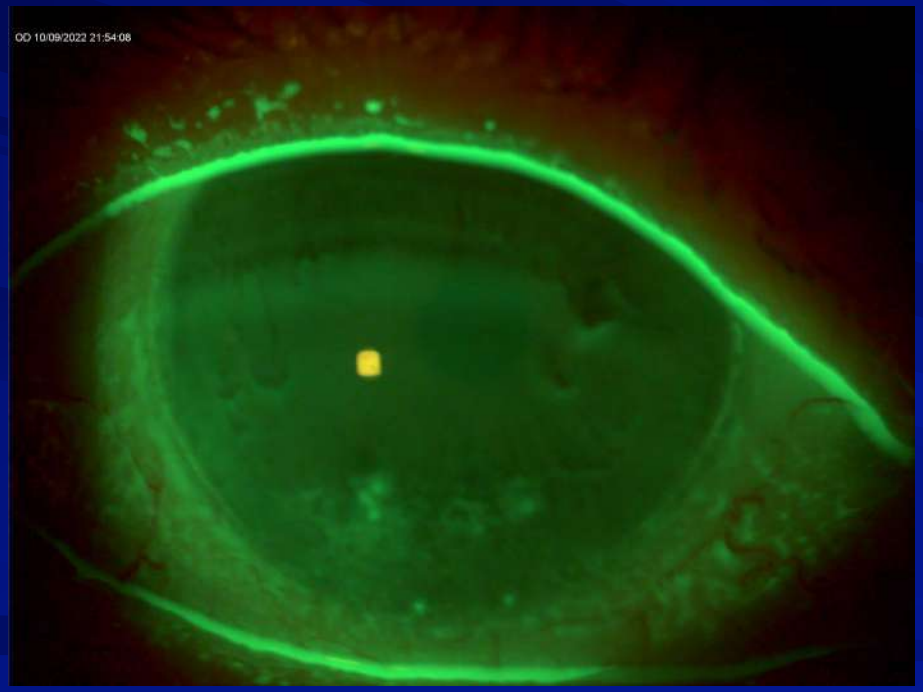
Stain Without Pain!

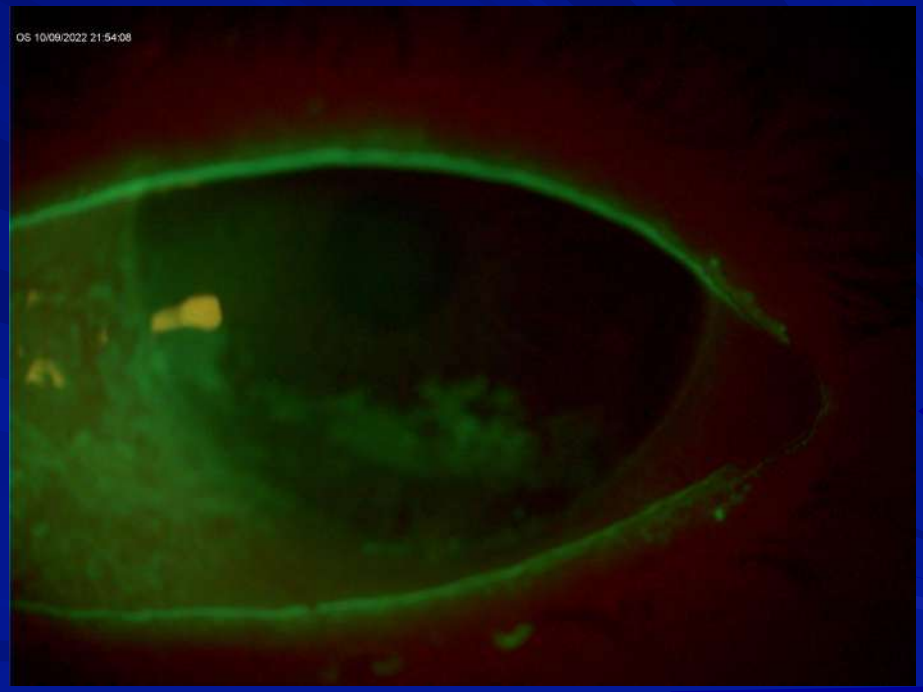
Actually, the OS is More Comfortable – What?



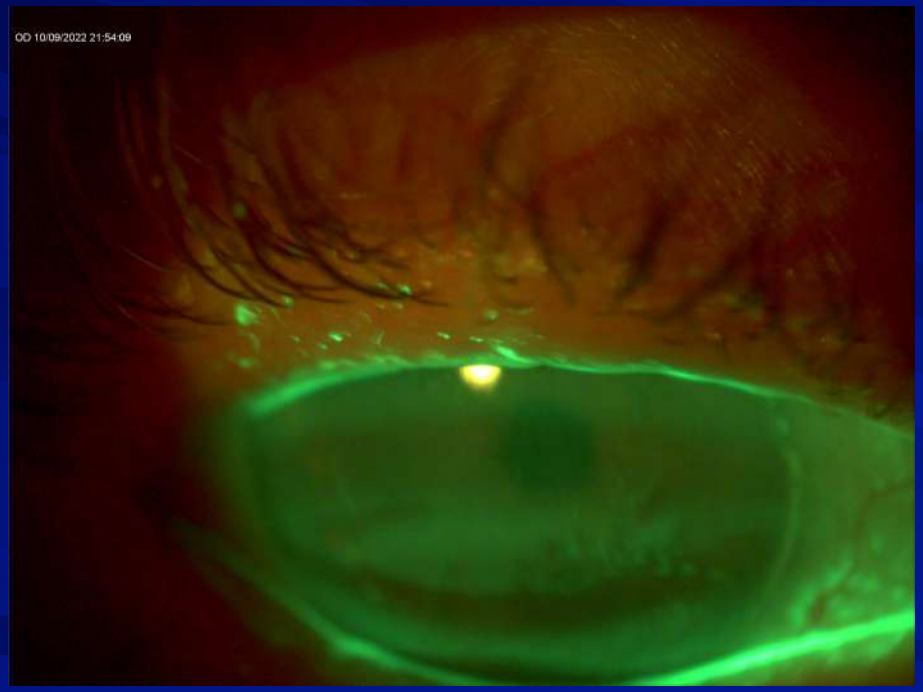


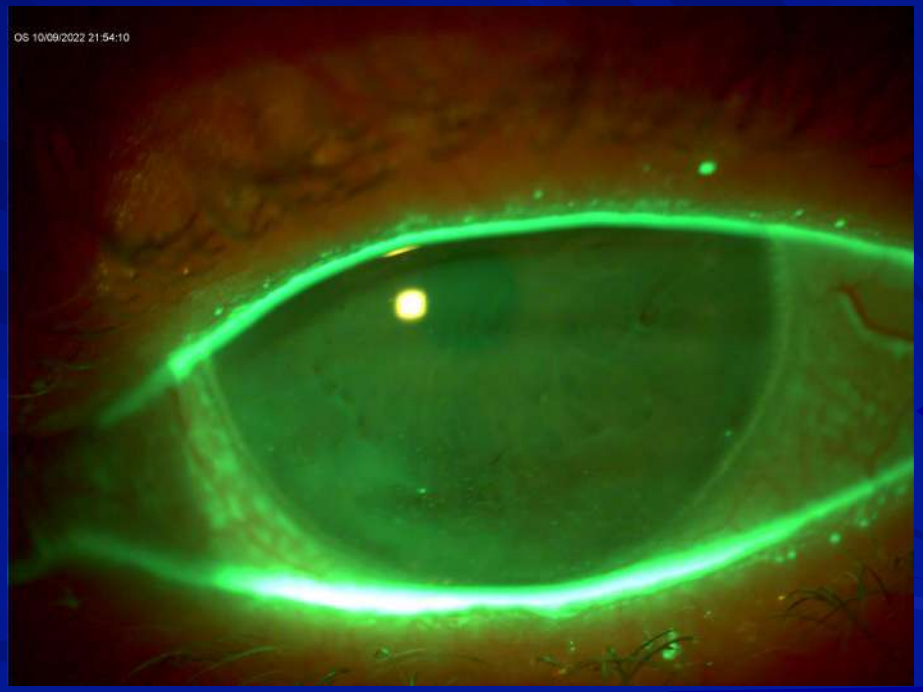
Before Oxervate™ (cenegermin-bkbj) Treatment





After Oxervate™ (cenegermin-bkbj) Treatment





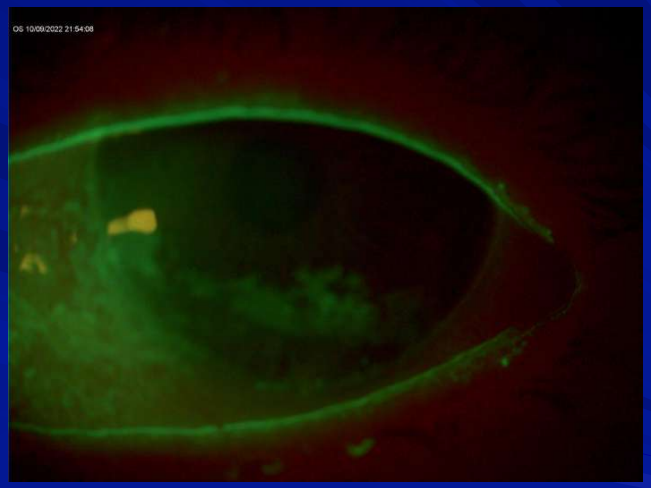
Corneal Sensitivity

Oxervate™ (cenegermin-bkbj)

- Grading corneal sensitivity: (Cotton Tip)
  - Normal
  - Reduced
  - Absent

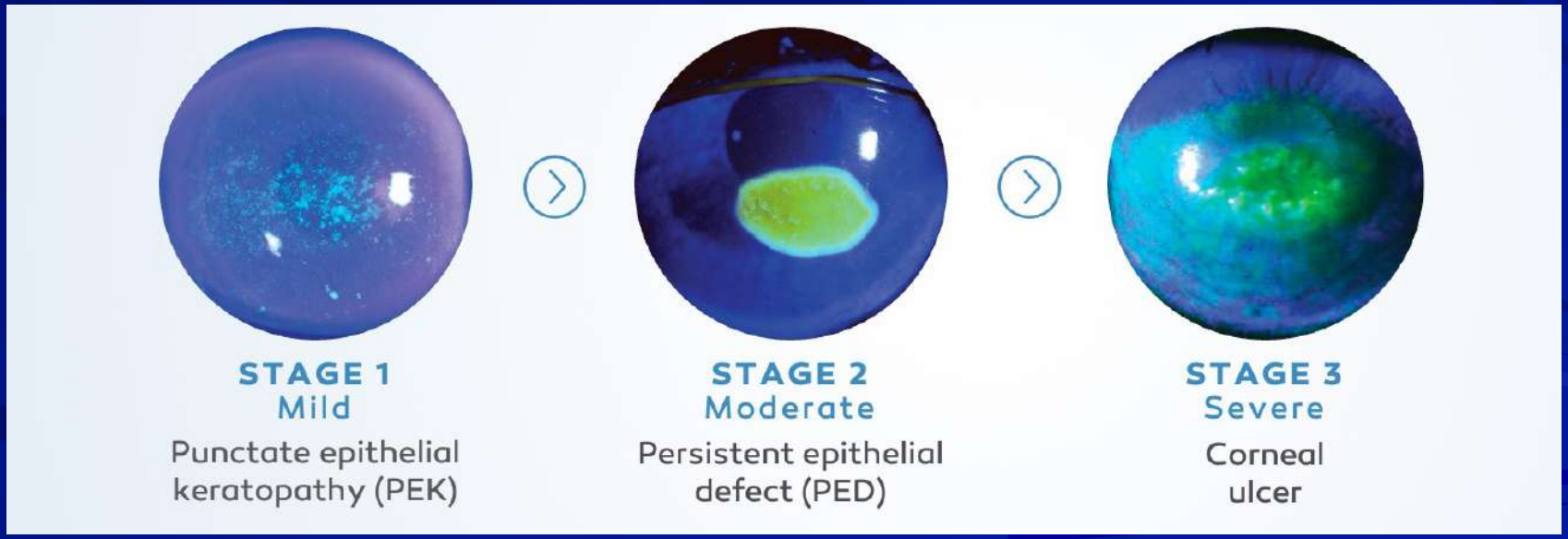
  - Reduced in all quadrants and centrally
  - Absent inferior quadrant, reduced everywhere else

- Neurotrophic Keratitis: (Staining)
  - Mild – Stage 1
  - Moderate – Stage 2
  - Severe – Stage 3



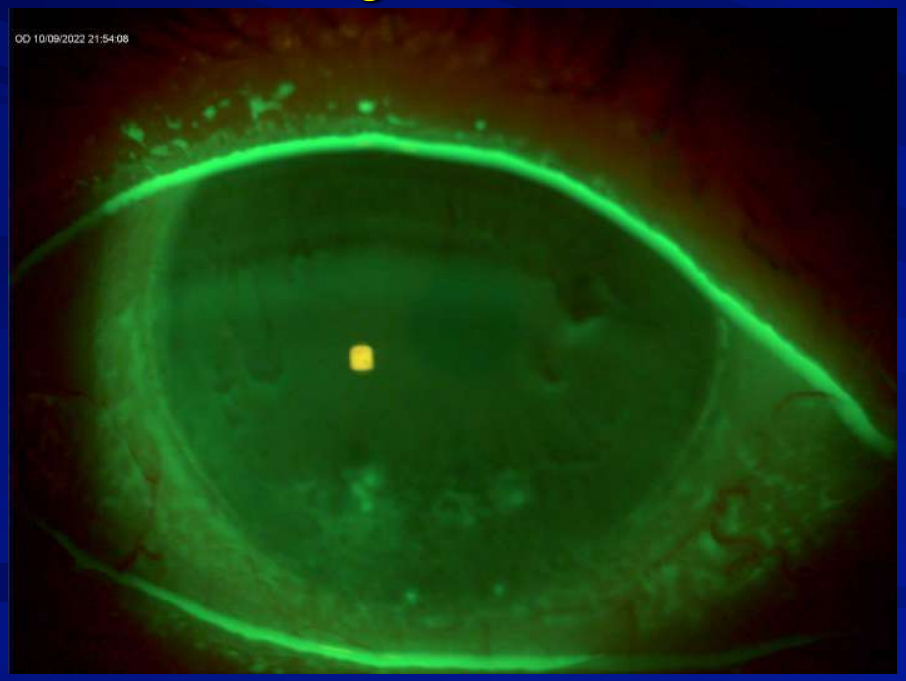
Neurotrophic Keratitis is a Degenerative Disease

- The Mackie classification represents one way to assess or grade NK – stage or progression

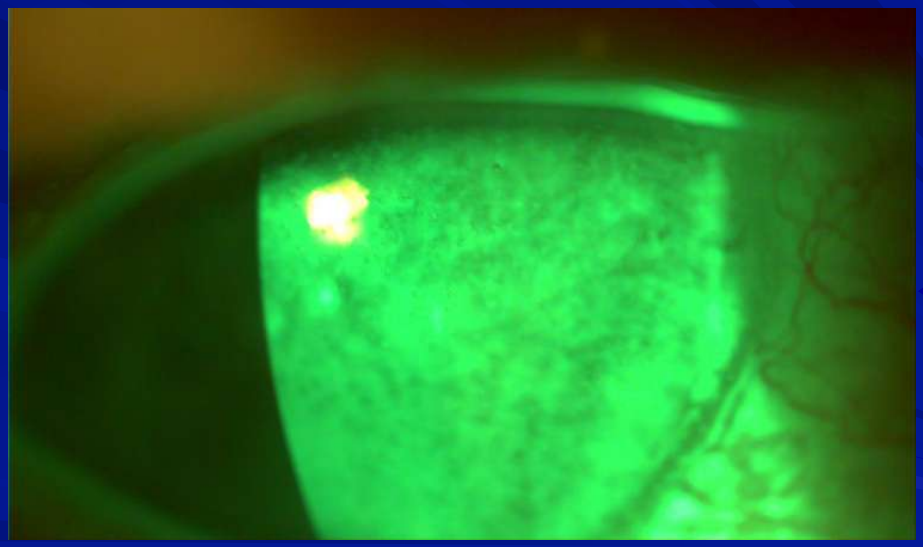


Mackie Classification

Moderate - Stage 2

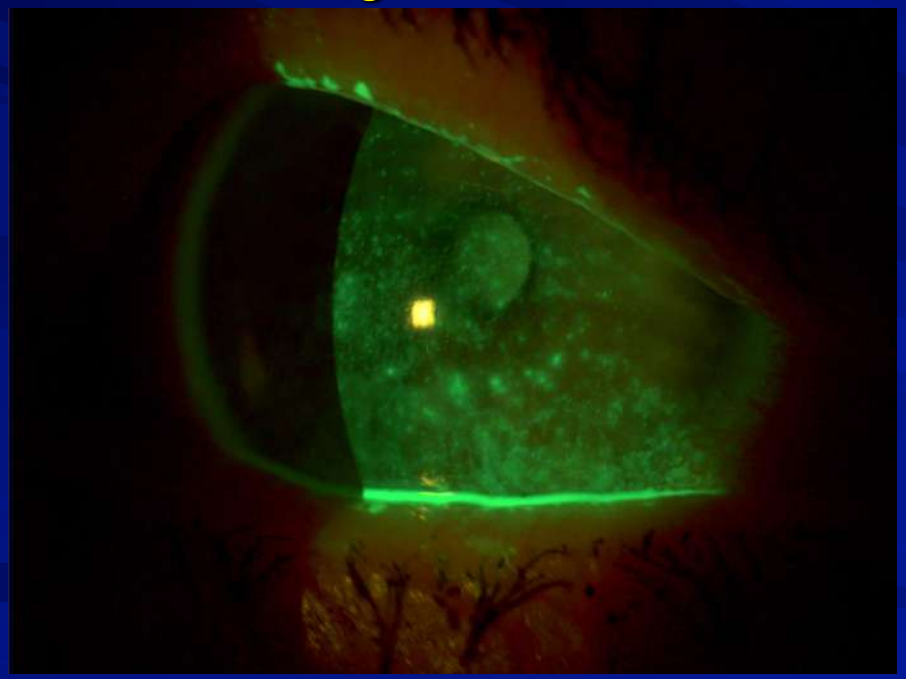


Moderate - Stage 2

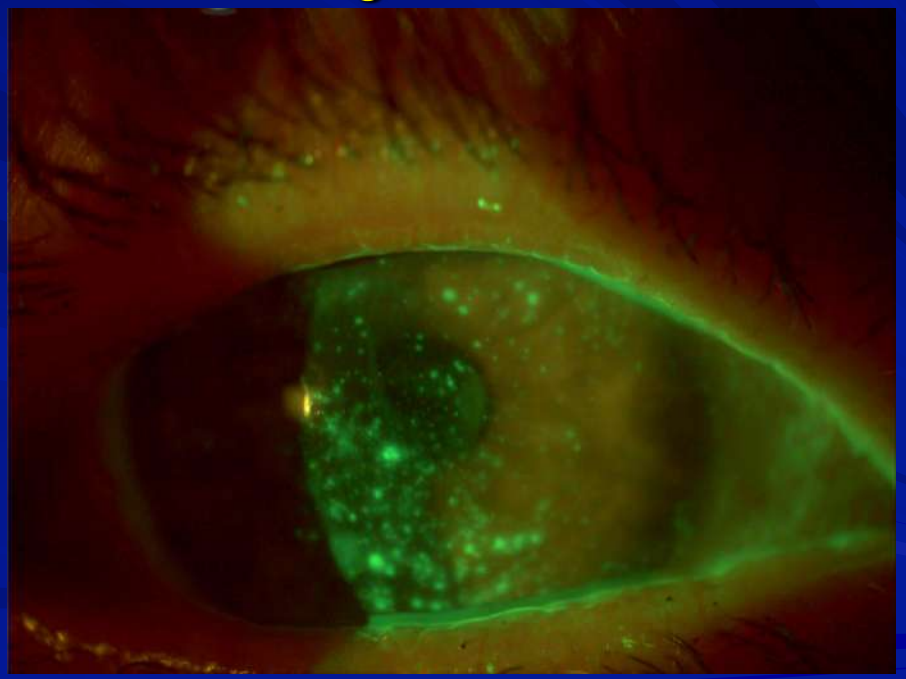


Mackie Classification

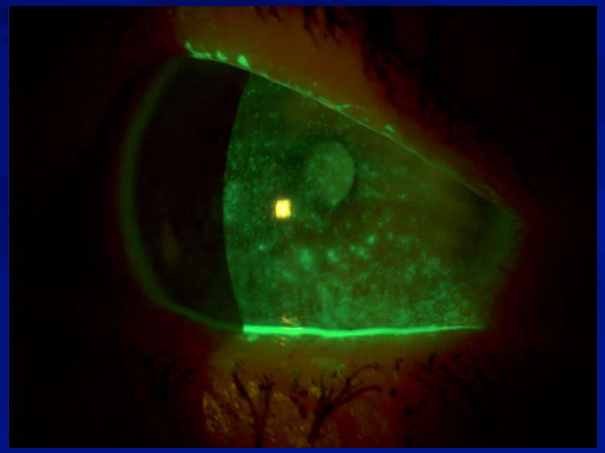
Moderate - Stage 2



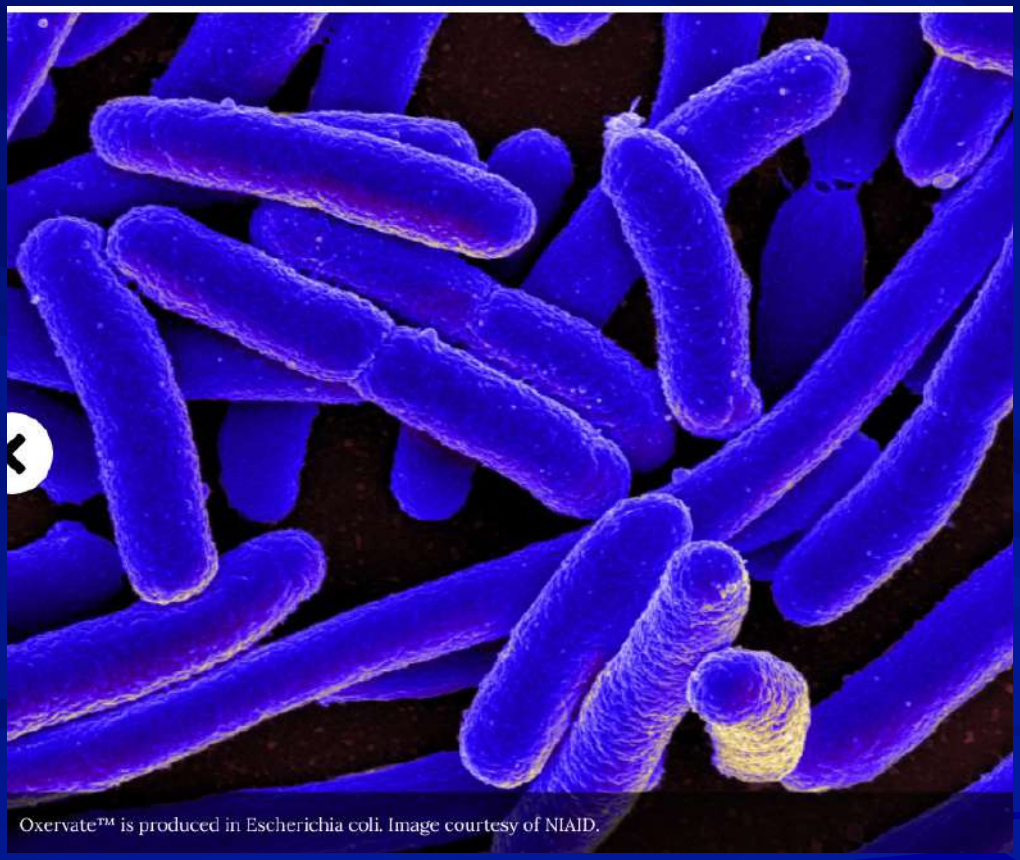
Moderate - Stage 2



Resolved



Escherichia Coli



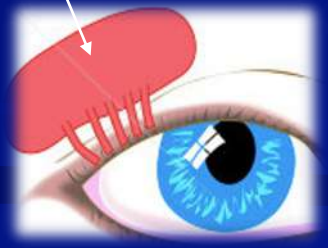
Oxervate™ is produced in Escherichia coli. Image courtesy of NIAID.

Corneal Homeostasis

Interaction between corneal nerves and epithelial cells/keratocytes mediates corneal homeostasis

Corneal nerves stimulate blinking and tear production

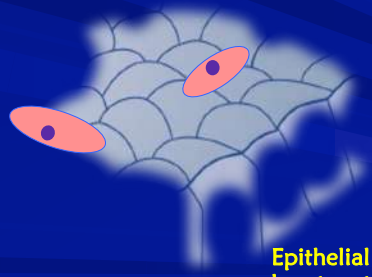
Tear gland



Tear secretion

Tears contain growth factors and nutrients that stimulate epithelial cells

Neurotrophins, neuropeptides and growth factors (e.g., NGF) from epithelial cells and keratocytes mediate nerve fibre survival, differentiation and maturation



Epithelial cells and keratocytes

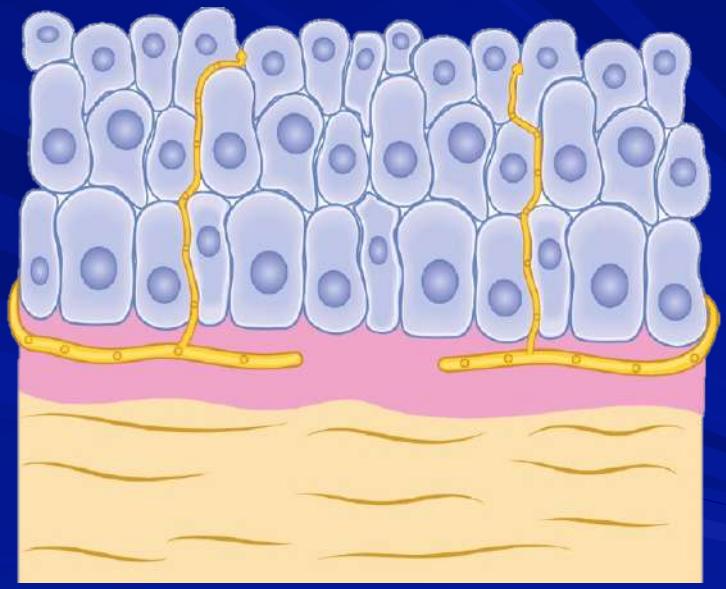
Neuromediators provide trophic support to ocular surface tissues (particularly epithelial cells & keratocytes) that:

- Stimulates wound healing
- Maintains anatomic integrity

Adapted from Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

Pathophysiology of NK[1]

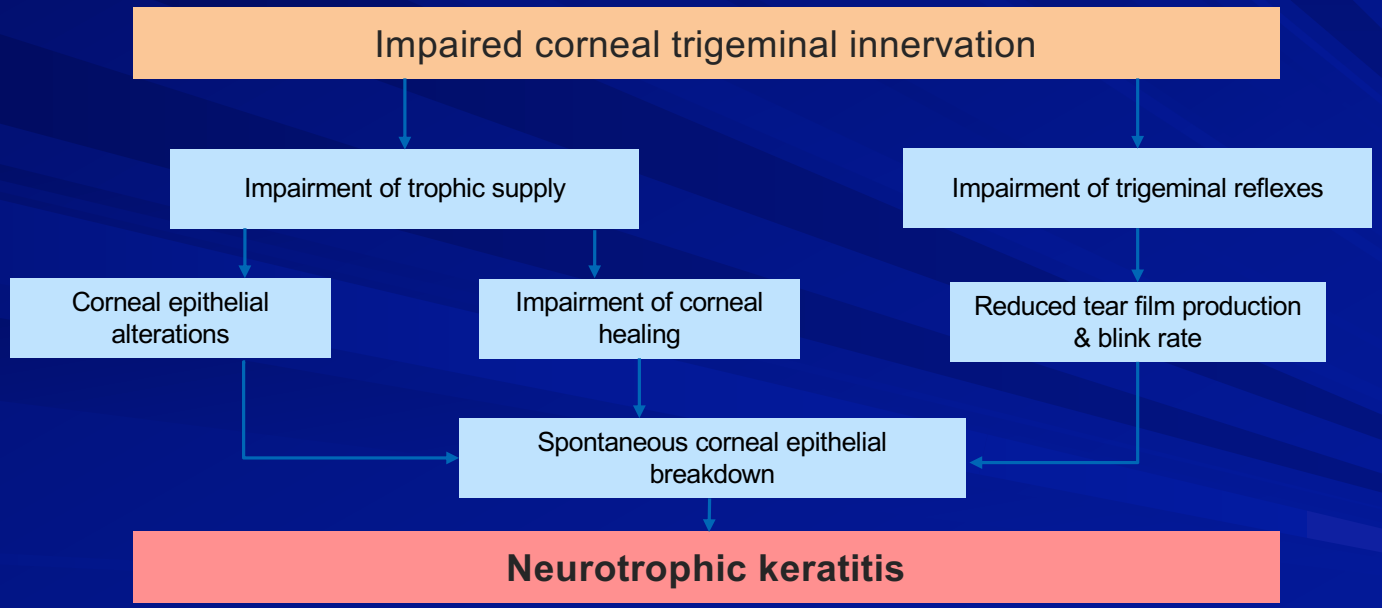
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production 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.

Trigeminal nerve damage leading to NK[1]



Adapted from 1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

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

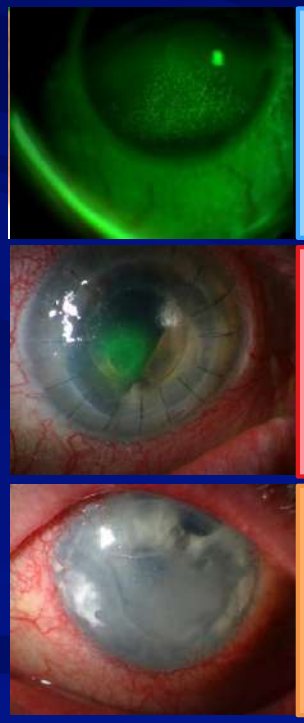
Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

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.

Assessment of Corneal Sensitivity is Essential to Confirm NK diagnosis[1]

Ocular symptoms

History

Clinical examination and tests

NK suspected

Test corneal sensitivity

Normal → NK unlikely

Reduced → Further tests required

Corneal sensitivity tests:[2]

- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

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

TEAR SECRETION

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

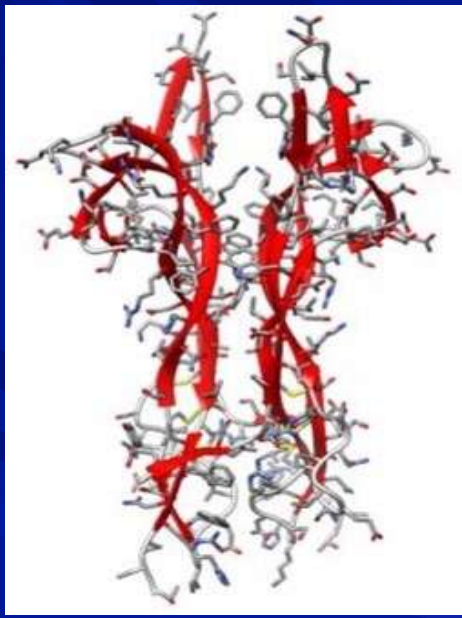
CELL PROLIFERATION AND DIFFERENTIATION

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

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

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

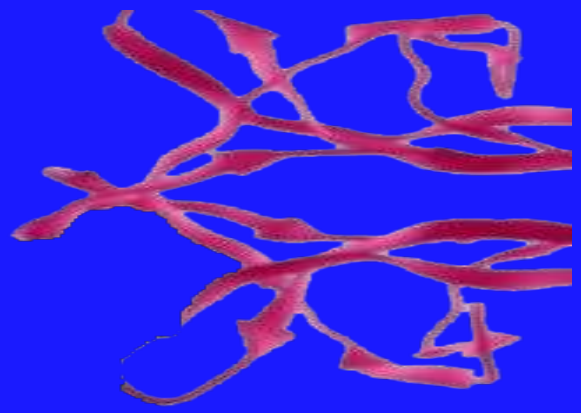
The Delivery System Kit Contains:

- 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

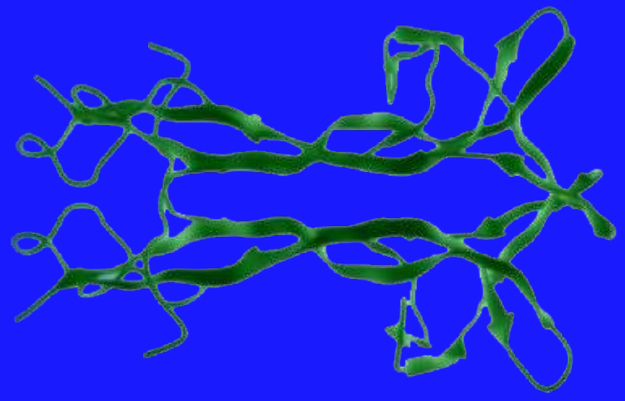
- **Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

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



Endogenous NGF

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

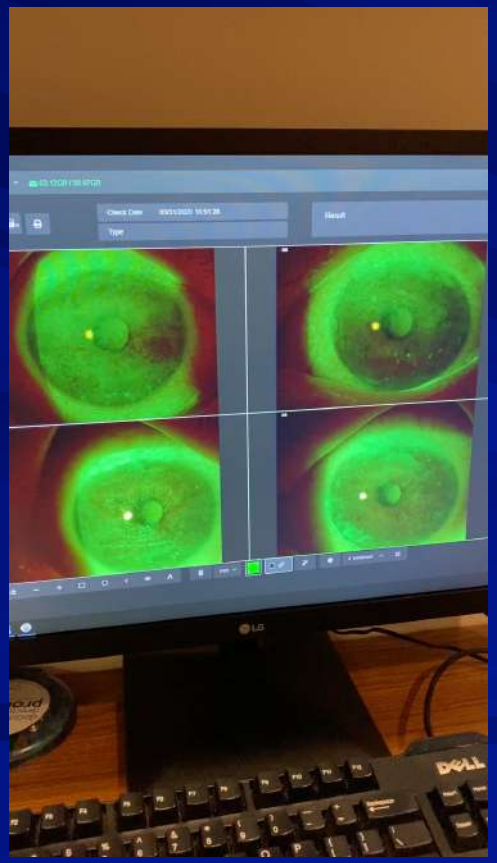
Apply 6 times daily

Continue for 8 weeks

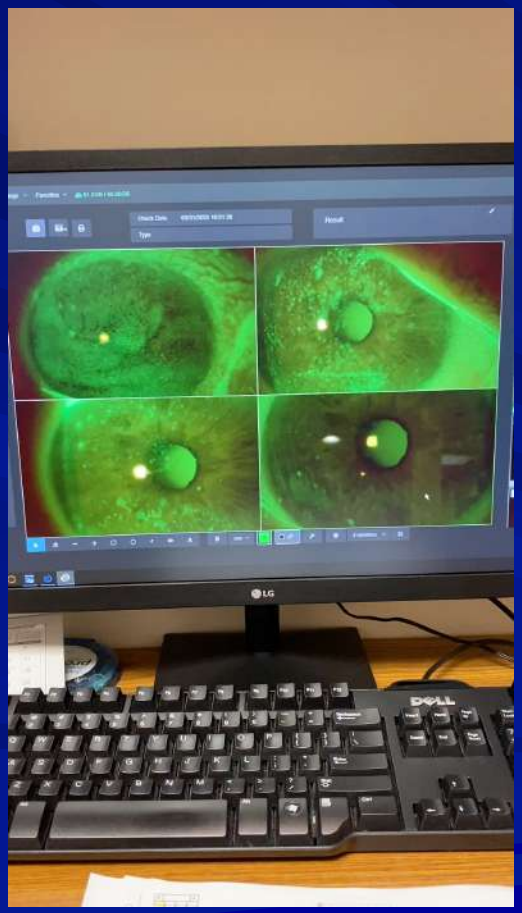
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

Let's Hear From a Patient

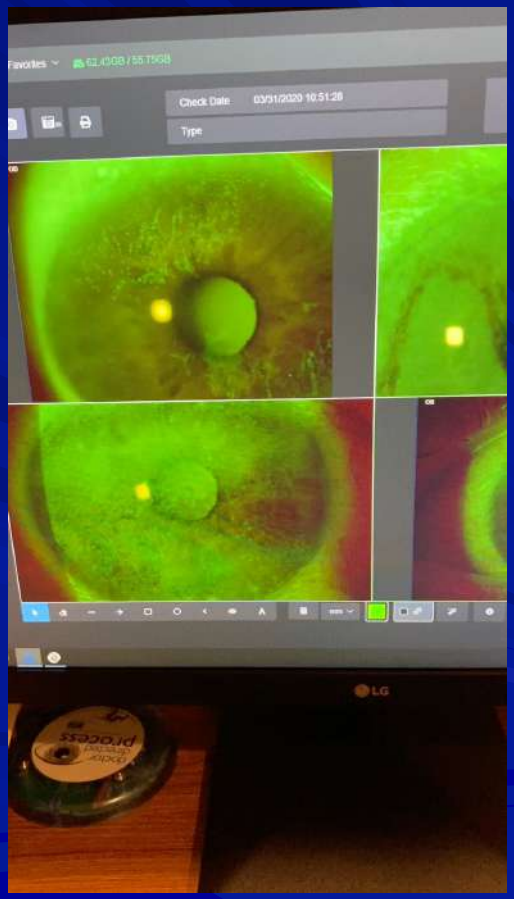
April 7, 2020 - After 1 week



April 21, 2020 - After 3 weeks



May 12, 2020 - After 6 weeks



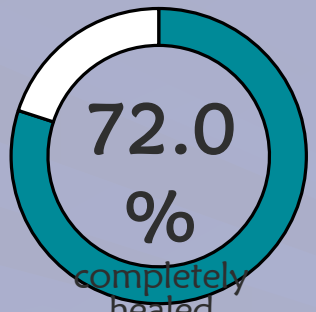
Study Conclusions

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

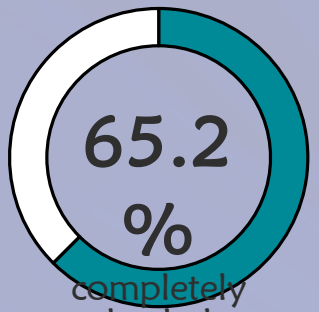


Vehicle response rate 33.3%

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)

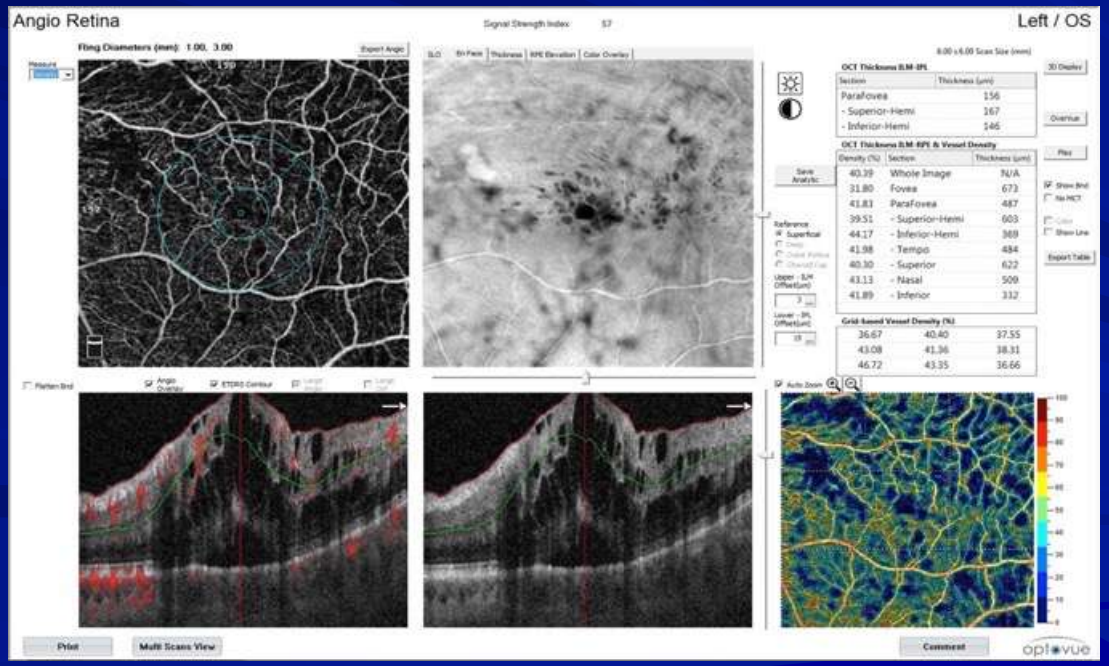
- Adverse reactions: very well tolerated
- The most common adverse reaction in clinical trials
  - eye pain, corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears
- Contact lenses (therapeutic or corrective) should be removed before applying 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.

Humira™ (adalimumab)

- Company: Abbvie
  - Approved July 2016
  - Indication: uveitis
    - Specifically indicated for the treatment of non-infectious intermediate, posterior and panuveitis
  - Mechanism of action: binds to TNF and blocks its action in the body
  - Dosage: subcutaneous injection
    - Recommended dose is 80 mg initial dose
    - Followed by 40 mg every other week starting one week after initial dose
  - The significance of this FDA approval is important! Many insurance companies (ex. Medicare) will not pay for "off-label" uses.

Humira™ (adalimumab)

- Non-infectious intermediate, posterior and panuveitis
  - Reason for reduced acuity?



Humira™ (adalimumab)

- Monitoring parameters:
  - Must place PPD before initiating = if PPD+, then initiation of Humira may convert latent TB to ACTIVE tuberculosis
  - Once Humira is initiated, watch for any signs or symptoms of infection…if the patient has a "cold", "flu", or is taking antibiotics, then Humira dose must be HELD until the patient is healthy.

Hadlima™ (adalimumab-bwwd)

- Biosimilars
  - ★ Hadlima (Adalimumab-bwwd)
    - Biologic agent SIMILAR to Humira
    - What is a "biosimilar"agent?
      - Remember what the FDA say about "biosimilars"

Humira™ (adalimumab)
Hadlima™ (adalimumab-bwwd)

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1):

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative.**

MALIGNANCY (5.2):

- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.**
- **Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.**

Actemra™ (tocilizumab)

INDICATIONS

ACTEMRA is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

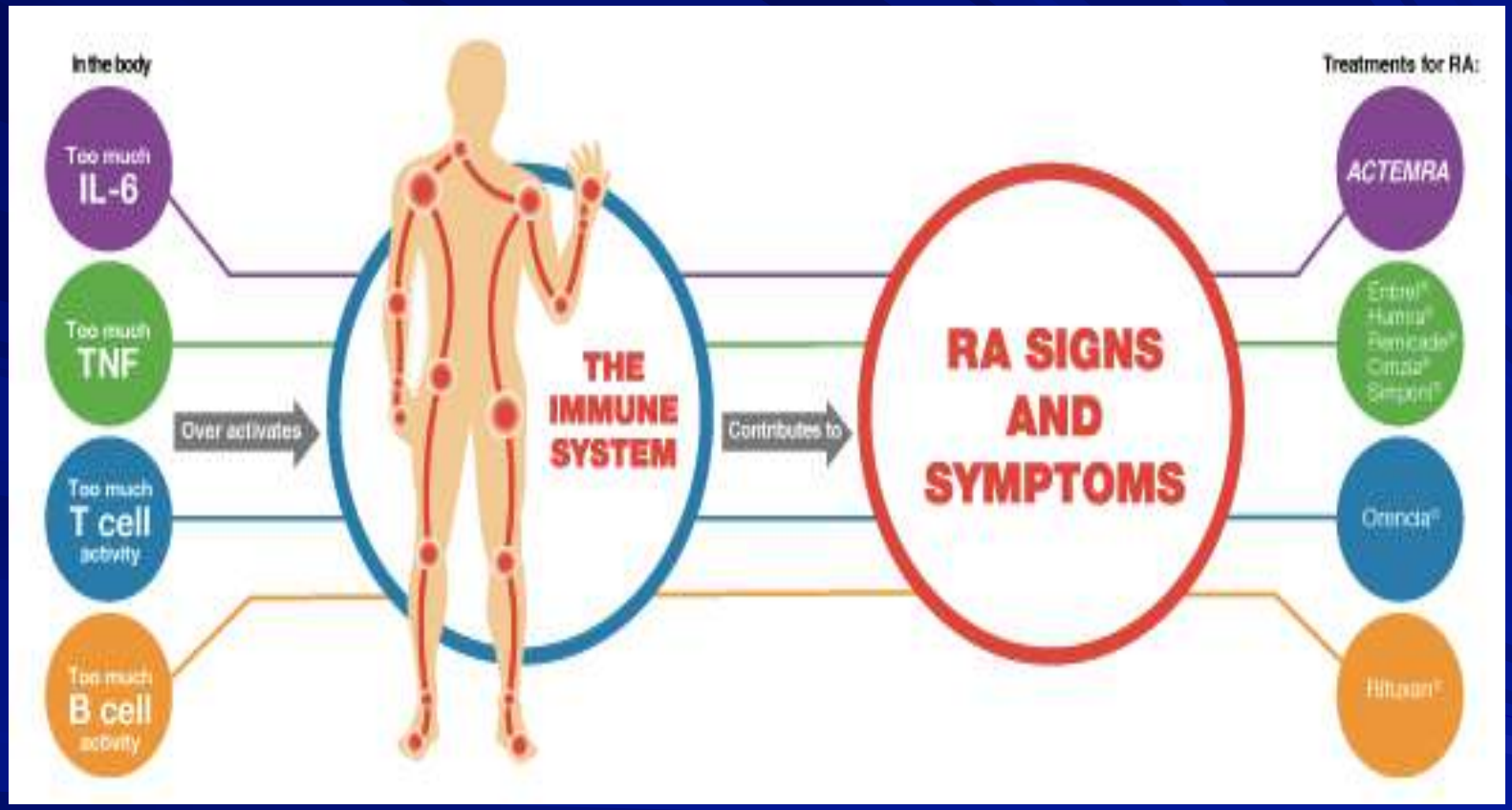
ACTEMRA is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

ACTEMRA is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

ACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

ACTEMRA is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

Let's qualify this statement



From: http://www.actemra.com/actemra/rheumatoid-arthritis/ra.html

Actemra™ (tocilizumab)

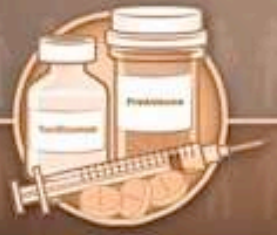
- Actemra™ (tocilizumab)- Genetec
  - First innovative therapy for GCA in more than 50 years
  - Design to speed the development for treatments of serious diseases such as GCA and certain cancers

Actemra™ (tocilizumab)

- Patients were randomized to receive tocilizumab 162 mg weekly injections plus a 6-month and 12-month prednisone-taper compared to controls receiving placebo plus similar steroid taper
- The preliminary results indicate that patients receiving high dose tocilizumab had superior disease remission at 1 year compared to the steroid-only taper
- Further investigation from this study will attempt to identify the lowest therapeutic dose of prednisone that can be used in patients also using tocilizumab, the amount of tocilizumab needed to induce remission, and how long patients stay in remission on this therapy

Tocilizumab

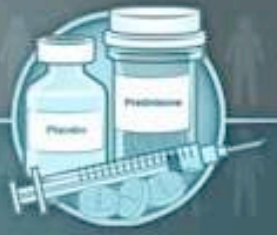
Tocilizumab weekly
+ 26 weeks of
prednisone taper
(N=100)



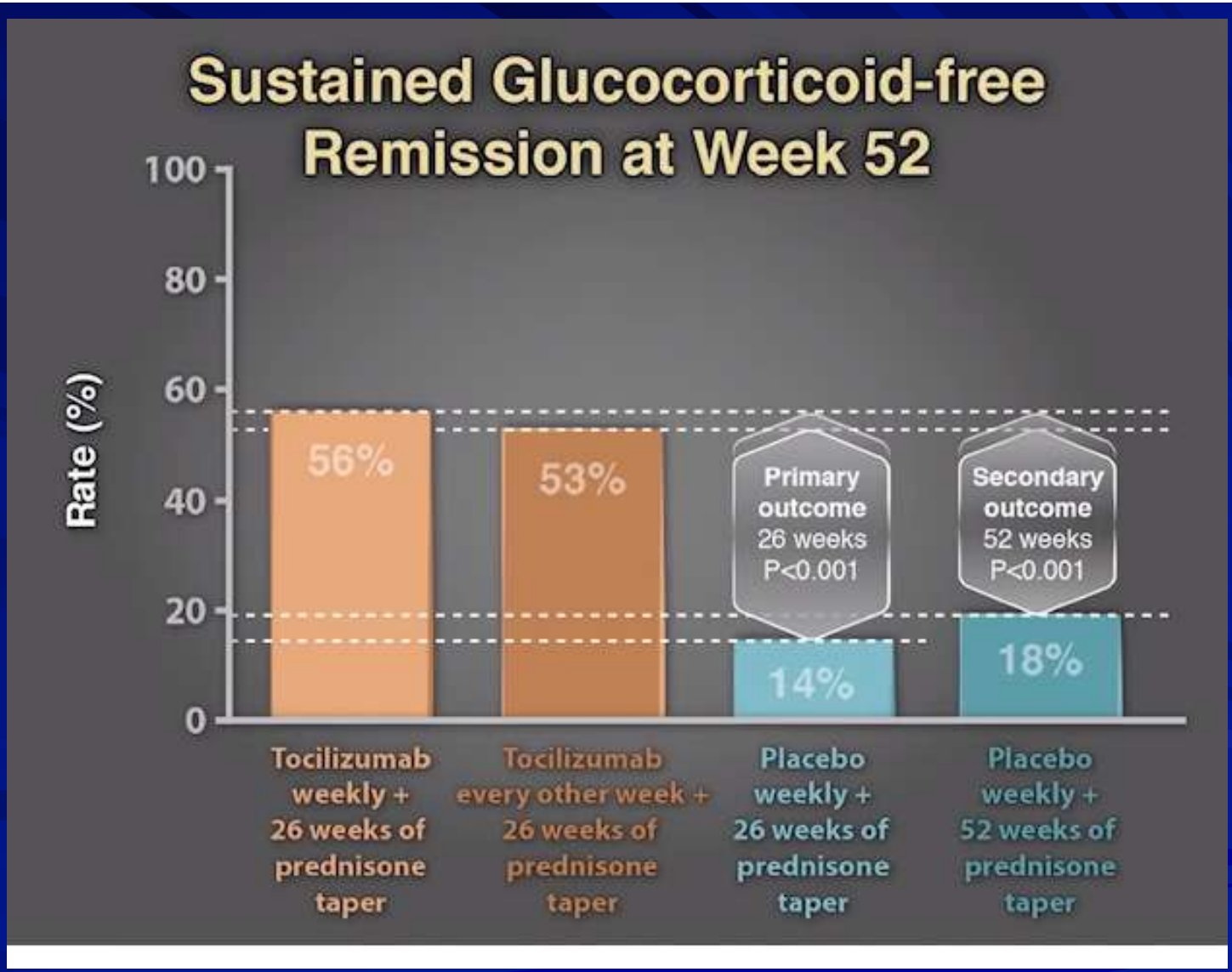
Tocilizumab every other week
+ 26 weeks of prednisone taper
(N=50)

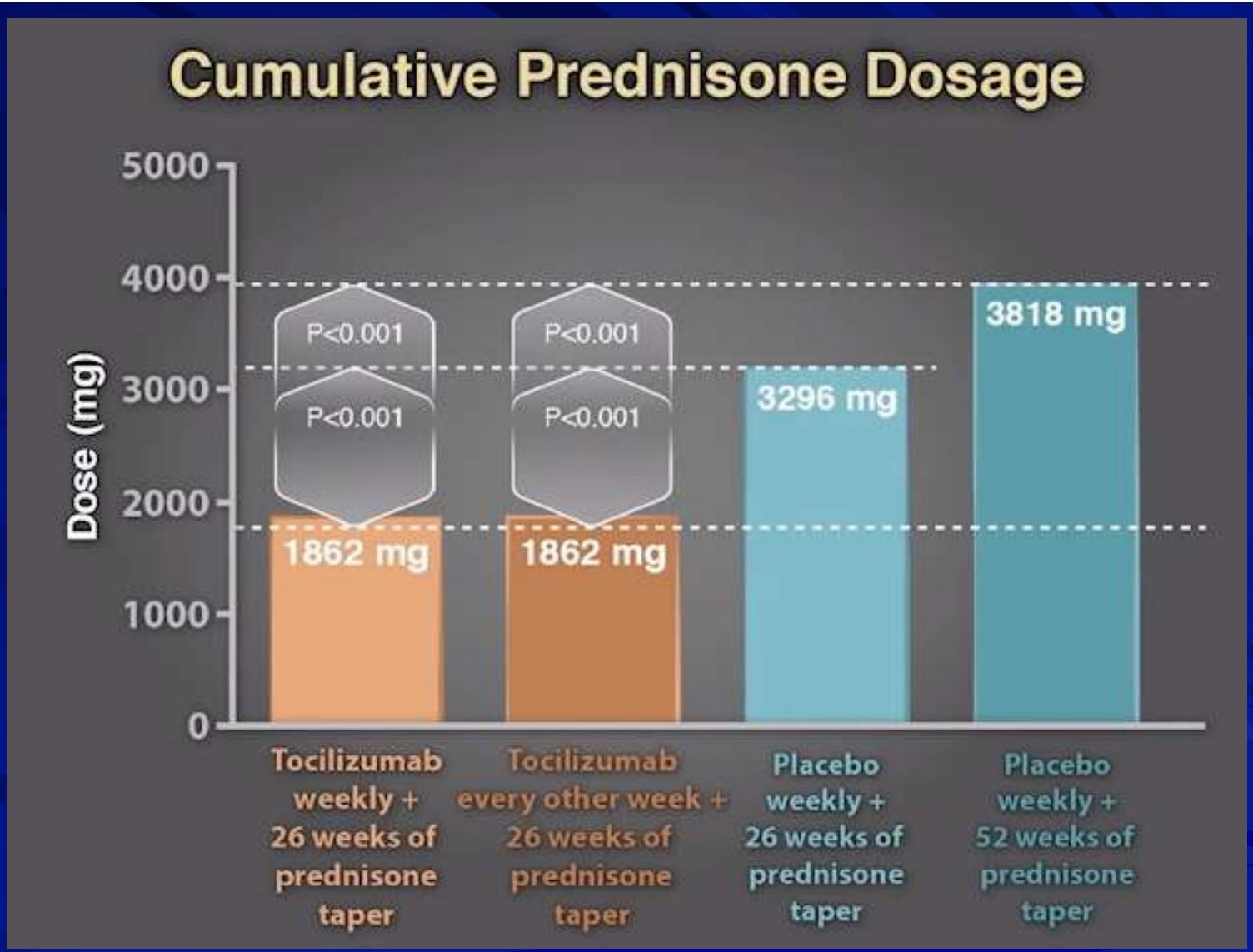
Placebo

Placebo weekly
+ 26 weeks of
prednisone taper
(N=50)



Placebo weekly
+ 52 weeks of
prednisone taper
(N=51)


Sustained Glucocorticoid-free Remission at Week 52
Rate (%)
100
80
60
40
20
0
56%
53%
14%
18%
Primary outcome 26 weeks P<0.001
Secondary outcome 52 weeks P<0.001
Tocilizumab weekly + 26 weeks of prednisone taper
Tocilizumab every other week + 26 weeks of prednisone taper
Placebo weekly + 26 weeks of prednisone taper
Placebo weekly + 52 weeks of prednisone taper


Cumulative Prednisone Dosage
Dose (mg)
5000
4000
3000
2000
1000
0
P<0.001
P<0.001
P<0.001
P<0.001
1862 mg
1862 mg
3296 mg
3818 mg
Tocilizumab weekly + 26 weeks of prednisone taper
Tocilizumab every other week + 26 weeks of prednisone taper
Placebo weekly + 26 weeks of prednisone taper
Placebo weekly + 52 weeks of prednisone taper

Actemra™ (tocilizumab)

- Tocilizumab does ~~not~~ directly treat GCA
  - Reduces steroid load after disease has been adequately treated by steroids and enhances disease remission
- Steroids are main therapy
- Studies are ongoing to see:
  - What is the lowest steroid tapering dose that can be used with tocilizumab
  - Future studies may show tocilizumab as steroid replacement

Tocilizumab (Actemra)

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)**
- **If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA. (5.1)**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

Olumiant™ (baricitinib) and Rinvoq™ (upadacitinib)

- Janus Kinase inhibitors
  - Indicated for the treatment of adult patients with moderate/severe active rheumatoid arthritis
    - Must have failed 1 or more TNF-alpha inhibitors (e.g. Remicade, Humira)
- THE HUB-BUB? It is an orally administered medication, as opposed to MOST of the others that are injectables!
  - Known as "un-jections"

Family Medicine

- Aimovig™ (erenumab-aooe)
- Ajovy ™ (fremanezumab-vfrm)
  - Approved 2018
  - Indicated for the PREVENTIVE treatment of migraine in adult patients
  - Calcitonin gene-related receptor antagonist
    - SQ injection
    - Once per month for either product
    - Once every three months for Ajovy™
- ADRs: constipation, injection site reactions

Erenumab (Aimovig)

5.2 Constipation with Serious Complications

Constipation with serious complications has been reported following the use of AIMOVIG in the postmarketing setting. There were cases that required hospitalization, including cases where surgery was necessary. In a majority of these cases, the onset of constipation was reported after the first dose of AIMOVIG; however, patients have also presented with constipation later on in treatment. AIMOVIG was discontinued in most reported cases of constipation with serious complications. Constipation was one of the most common (up to 3%) adverse reactions reported in clinical studies *[see Adverse Reactions (6.1)]*.

Monitor patients treated with AIMOVIG for severe constipation and manage as clinically appropriate *[see Patient Counseling Information (17)]*. The concurrent use of medications associated with decreased gastrointestinal motility may increase the risk for more severe constipation and the potential for constipation-related complications.

5.3 Hypertension

Development of hypertension and worsening of pre-existing hypertension have been reported following the use of AIMOVIG in the postmarketing setting. Many of the patients had pre-existing hypertension or risk factors for hypertension. There were cases requiring pharmacological treatment and, in some cases, hospitalization. Hypertension may occur at any time during treatment but was most frequently reported within seven days of dose administration. In the majority of the cases, the onset or worsening of hypertension was reported after the first dose. AIMOVIG was discontinued in many of the reported cases.

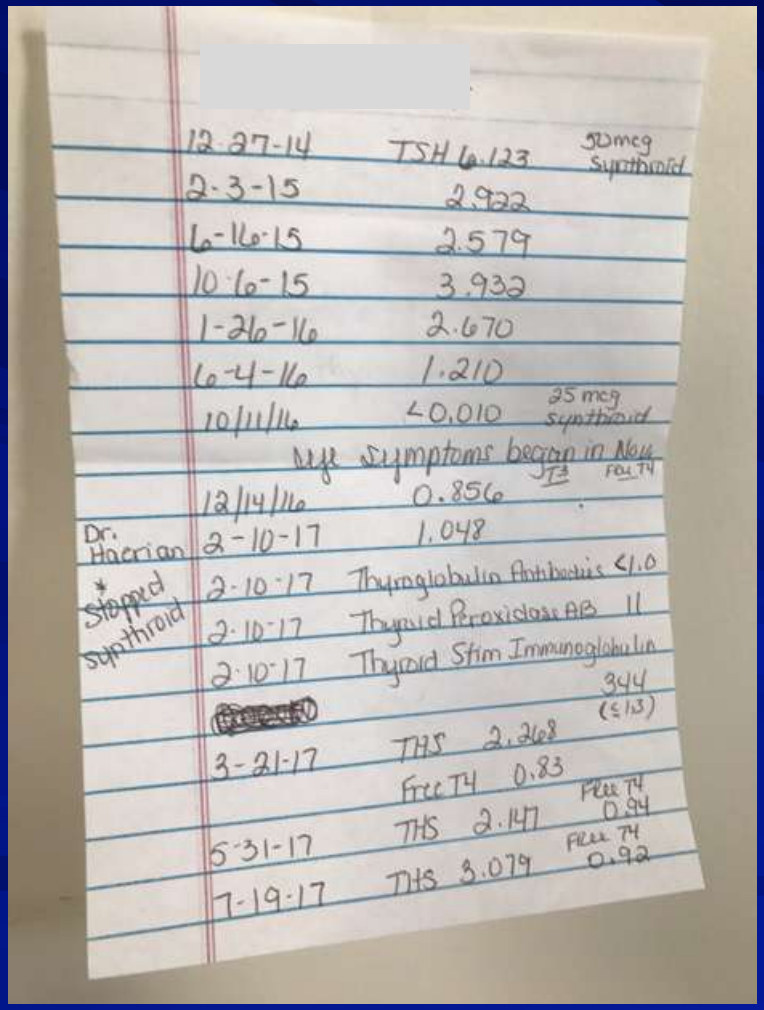
Monitor patients treated with AIMOVIG for new-onset hypertension, or worsening of pre-existing hypertension, and consider whether discontinuation of AIMOVIG is warranted if evaluation fails to establish an alternative etiology.

Antibodies of Thyroid Dysfunction

- TSH Receptor Antibodies
  - Stimulating TSH receptor antibody
    - Thyroid Stimulating Immunoglobulin (TSI)
  - Thyroid blocking antibody (TBAb)
- Thyroid Peroxidase Antibodies (TPOAb)
  - TPO is found in thyroid follicle cells where it converts the thyroid hormone T4 to T3
  - TPOAb contributes to thyroid cellular destruction

- Most autoimmune thyroid dysfunctions have a combination of thyroid antibodies, however depending on which AB is more abundant results in the outcome of the disease

Similar receptors are found in the skin, fat and muscle of the orbit



You're in the Know

Normal Values
Thyroglobulin 20 IU/ml
Peroidase <35 IU/ml
TSI 1.75 IU/ml

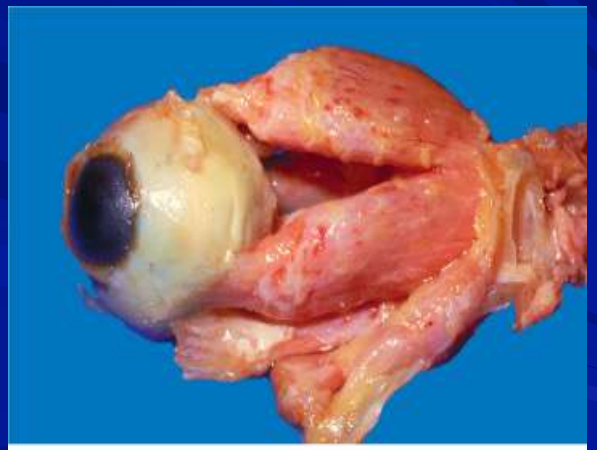
It does work!

Immunosuppression?

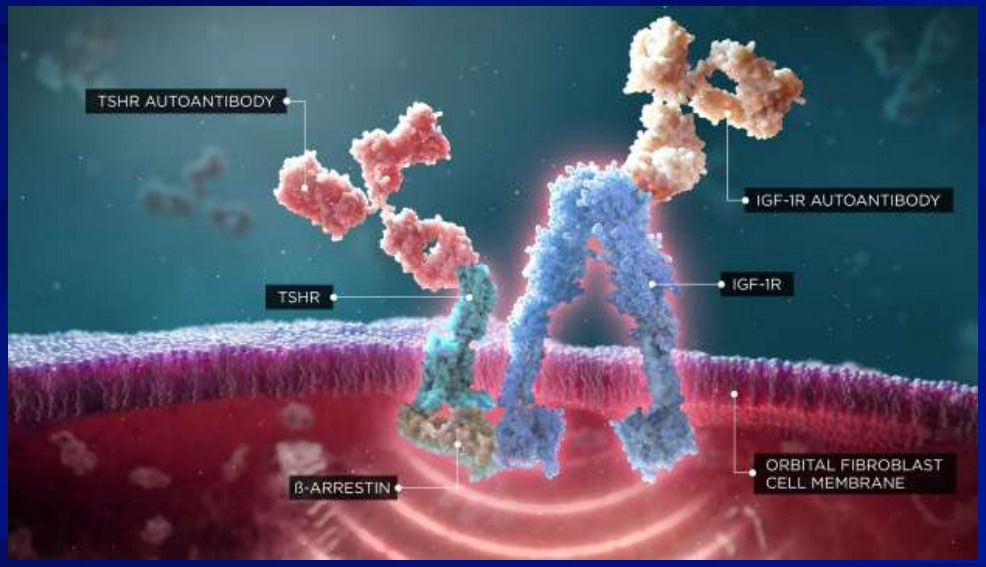
- Biologics
  - Immunosuppression biologics – suppress the immune system to get the effe3ct
    - Remicade – "1st generation"
      - Chimeric molecule – mouse and human protein, a lot of sensitivity
    - Humira
      - Anti-TNF (RA and Crohn's Disease
      - Fully human protein, less sensitivity
    - 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

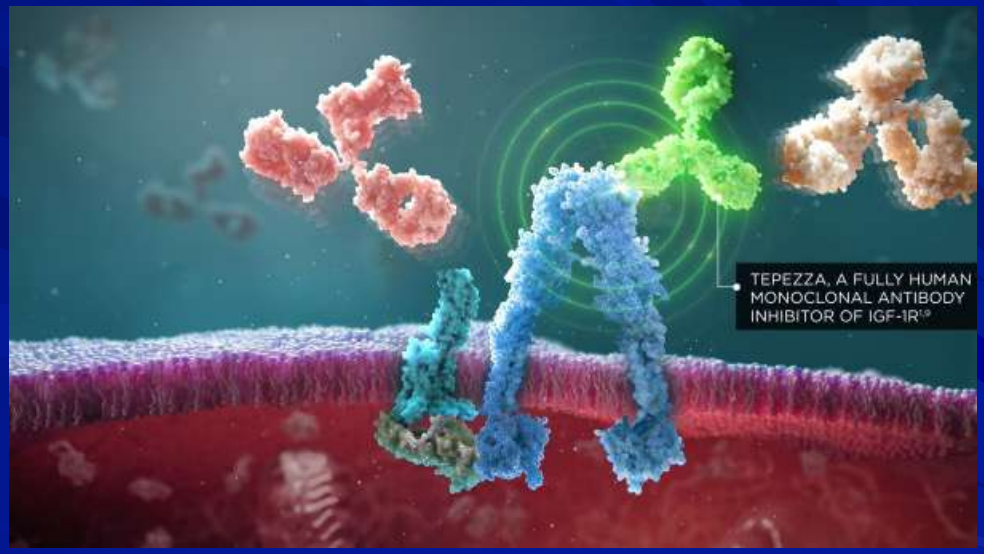
Teprotumumab-trbw (Tepezza)

- 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
  - Not published
- PDUFA- March 2020, was approved early in 2020



Teprotumumab-trbw (Tepezza)





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

Teprotumumab-trbw (Tepezza)

- Clinical Activity Score
  - 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)

- **Infusion Reactions (mild/moderate):** approximately 4% of patients
  - transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain - will occur within 1.5 hours of an infusion
  - For those who have had a previous reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, or corticosteroid and/or administering at a slower infusion rate.

- **Preexisting Inflammatory Bowel Disease:** may cause an exacerbation of preexisting inflammatory bowel disease ("IBD")
  - Monitor patients for flare; may require discontinuation of Teprotumumab (Tepezza)

- **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

Teprotumumab-trbw (Tepezza)

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

Optometric Education Consultants

Pharmaceutical Update 2024

Greg Caldwell, OD, FAAO

Optometric Education Consultants

Sunday, March 10, 2024