Ocular Pharmacology Updates

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Disclosures - Walter O. Whitley, OD, MBA, FAAO has received consulting fees, honorarium or research funding from:

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Prescribing Considerations

- Indications
- Brand vs. generics
- Does the insurance cover prescriptions?
- Costs of medications
- Compliance
- Patient assistance

TRICARE

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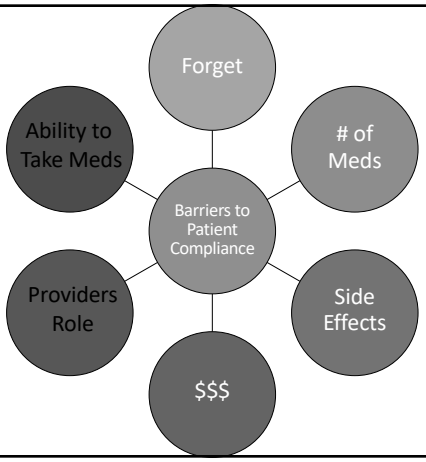

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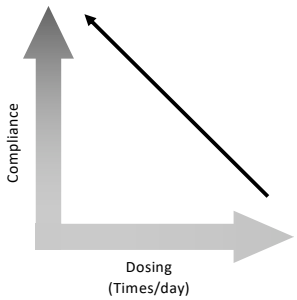
Patient Compliance and Dosing



- Literature review of 76 studies show
  - Compliance increases with decreased dosage regimen and complexity[1]
  - 79% compliance with QD regimen vs 51% for QID regimens (p=0.001)[1]
  - Simpler, less-frequent dosing results in better compliance in a variety of therapeutic classes[1]

1. Claxton et al. *Clinical Therapeutics.* 2001; 23:1296-1310.

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Prescription Considerations

- Review medical history
  - Renal function
  - Liver function
- Review current medications
- Side effect vs. true allergies
- Pregnant or nursing
- Rx for children

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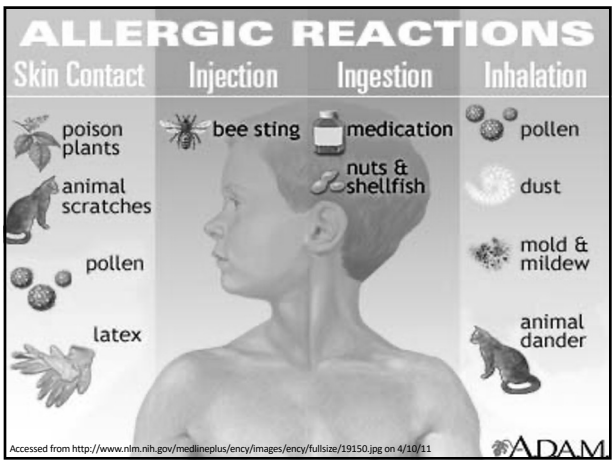

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Prescribing for Women

- Certain meds are OK in pregnancy
- Breast feeding
- Consult OB-GYN if necessary

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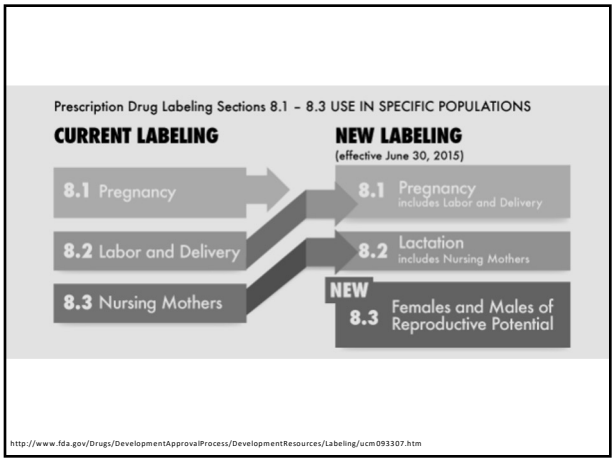

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So What Can Be Used During Pregnancy?

- Antibiotics
  - Amoxicillin
  - Amoxicillin/clavulanate
  - Azithromycin
  - Erythromycin
- Antivirals
  - Acyclovir
  - Valacyclovir
- Anti-inflammatory
  - Prednisone
- Analgesics
  - Acetaminophen
  - Ibuprofen
  - Tylenol #3
  - Vicodin
- Allergy
  - Diphenhydramine
  - Loratadine

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What About Topical Medications During Pregnancy?

- Category B
  - Antibiotics – tobramycin
  - Allergy – alcaftadine
  - Glaucoma - brimonidine
- Category C
  - Allergy - olopatadine
  - Anti-inflammatory – steroids, cyclosporine
  - Anti-viral – ganciclovir, trifluridine

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Prescribing Considerations for Kids

1. Know the age -**12**
2. Know the weight – **88lbs**
3. Look up the dosage
   - mg/kg/day
4. Be good at math
   - Or call the pharmacist
5. Avoid
   - Tetracyclines
   - Fluoroquinolones

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Artificial Tear Supplements

- Improve comfort
- Reduce irritation and friction
- Improve ocular surface
- Store in the fridge

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Poor Brady☹

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Prevalence of Allergy

- A nationwide survey found that more than half (54.6%) of all U.S. citizens test positive to one or more allergens.[1]
- Allergic diseases affect as many as 40 to 50 million Americans.[2]
- Greater than 70% of patients with systemic allergy may manifest ocular symptoms.[3]

[1] Arbes SJ et al. Prevalences of positive skin test responses to 10 common allergens in the U.S. population: Results from the Third National Health and Nutrition Examination Survey. J Allergy Clin Immunol. 2005; 116:377-383.
[2] Airborne allergens: Something in the air. National Institute of Allergy and Infectious Diseases. NIH Publication No. 03-7045. 2003.
[3] Kowalski CH, Belcey L. Evidence-based study design in ocular allergy trials. Curr Opin Allergy Clin Immunol. 2008;8(5):484-8.

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Allergic Conjunctivitis

- Seasonal / perennial allergic conjunctivitis
- Giant papillary conjunctivitis
- Atopic keratoconjunctivitis
- Vernal keratoconjunctivitis

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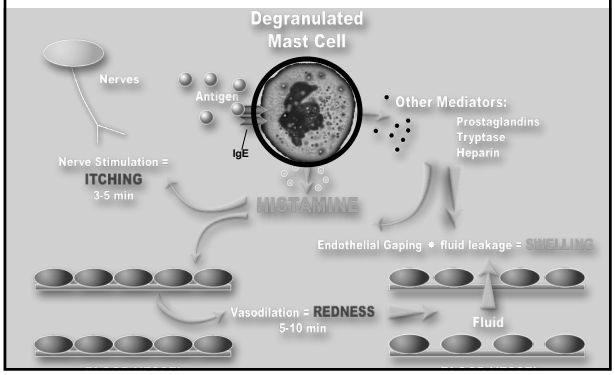
Allergic Cascade



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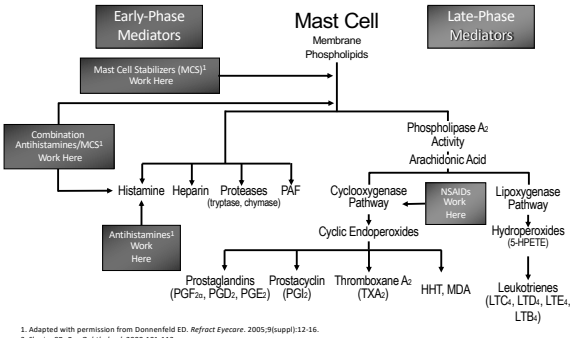
Most Prescription Treatment Options Have a Limited Effect on the Inflammatory Cascade



1. Adapted with permission from Donnenfeld ED. *Refract Eyecare*. 2005;9(suppl):12-16.
2. Sionim CB. *Rev Ophthalmol*. 2000:101-112.

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Graded Pharmacotherapy

Stepwise Treatment Strategies for Allergic Conjunctivitis	
Mild	Avoidance, cold compresses, tears, over-the-counter medications
	Topical antihistamines/mast cell stabilizers
	Oral antiallergics (allergists may already have patients on orals; may exacerbate the ocular condition while improving the nasal condition) Montelukast
Moderate	+ Mast cell stabilizers (treats allergy before mediator is released)
	+ Combination antihistamine/mast cell stabilizers
	+ Topical corticosteroids (most beneficial for severe outbreaks)
Severe	Topical corticosteroids (short course; fluorometholone/dexamethasone/loteprednol/prednisolone)
	Topical immunomodulating agents (tacrolimus, cyclosporine)
	Oral steroids

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ANTIGEN SKIN TESTING

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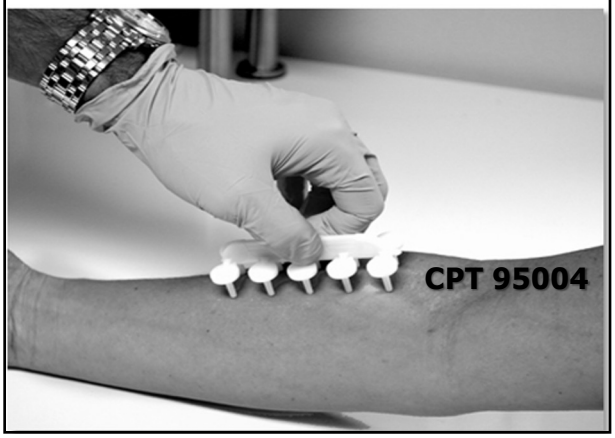

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Montelukast Sodium aka Singulair

- Leukotriene receptor antagonist
- Indications:
  - Prophylaxis and chronic treatment for asthma
  - Acute prevention of exercise-induced brochoconstriction
  - Relief of symptoms of allergic rhinitis
- 10 mg tablet qd
- Side effects
  - Behavior or mood changes, URI, fever, headache, sore throat, cough, stomach pain, diarrhea, ear ache or ear infection, flu, runny nose, and sinus infection

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12 Patient Allergy Tips

- Never rub your eyes
- Wash your hands
- Use allergy free pillows
- Stay indoors
- Use drops for eyes, sprays for nose
- Avoid "get the red" out vasoconstrictors
- Chill your drops
- Use cool compresses
- Apply allergy drops proactively
- Pets out of the house or bedroom
- Know and avoid your personal antigens
- Try Montelukast: no sedation, no drying

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Vernal Keratoconjunctivitis

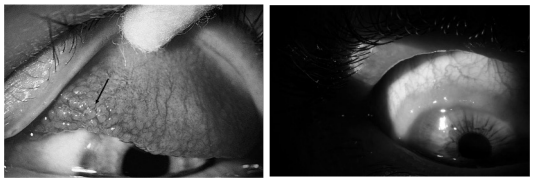

Photo accessed from https://www.merckmanuals.com/en-pr/professional/multimedia/image/vernal-conjunctivitis on 12/20/22.
Photo accessed from https://morancore.utah.edu/basic-ophthalmology-review/conjunctivitis/ on 12/20/22

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Vernal Keratoconjunctivitis

- Seasonally recurring, bilateral, and severe form of allergic inflammation affecting the ocular surface
- Uncommon
- Boys living in warm, dry, subtropical climates
- Can cause severe damage to the ocular surface, leading to corneal scarring and vision loss if not treated properly
- Symptoms: Redness, tearing, mucous discharge, itching, photophobia
- Signs: Horner-Trantas dots, shield ulcers, upper tarsal giant papillae

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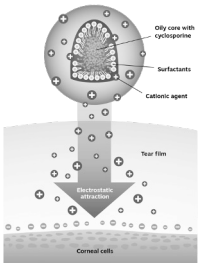
Cyclosporine ophthalmic emulsion 0.1%

- Verkazia® (Santen) is a calcineurin inhibitor immunosuppressant indicated for the treatment of vernal keratoconjunctivitis in children and adults
- Dosage: QID
- Cationic charged nanosized droplets



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Clinical Data

- Two randomized, multicenter, double-masked, vehicle controlled, clinical trials
- VEKTIS – patients with severe VKC were randomized to four times a daily of Verkazia 1mg/mL or two times a day of Verkazia 1mg/mL and vehicle group for the first 4 months (Period 1)
- NOVATIVE – patients with moderate to severe VKC were randomized to QID of Verkazia 1mg/mL or QID of cyclosporine ophthalmic emulsion 0.5mg/mL and vehicle group for the first month (Period 1).
- In both studies, patients randomized to the vehicle group were switched to Verkazia (QID or BID) from Month 4 to Month 12 in VEKTIS study and to cyclosporine 0.5mg/mL QID or 1 mg/mL from Month 1 to month 4 in NOVATIVE study (Period 2)

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Clinical Data

- Verkazia demonstrated improvements in inflammation of the cornea (keratitis score) and ocular itching.
- AE >5%
  - Eye pain 12%
  - Eye pruritus (8%)

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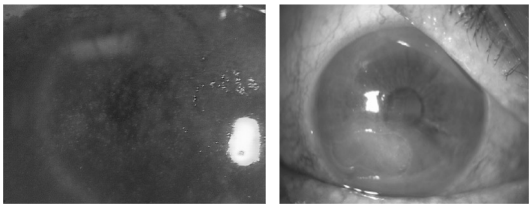

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Case Example

- The 84 year old, AA female presents for 3-4 month DES check (no touch) and MMP-9 testing. Pt has a h/o DES and POAG mild OU. Pt states OS>OD has some itching. Pt states she has only been using her cyclosporine 0.05% and AT's. She never picked up fluoromethalone drops and is not using AT's ointment or a heat mask.

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Ocular Hx:
- Dry eye syndrome – 10+ yrs
- Herpes stromal keratitis OS
  - Inactive – Last episode 2020
- Anterior scleritis OS
  - Inactive
- POAG - Mild OU
- Pterygium sx OU
- Phaco / istent OU
- Previous treatments
  - Amniotic membrane OS (2019, 2020)
  - Punctal cautery (2011) OU
  - PGA OU

Med Hx:
- NIDDM 15 yrs
- Osteoarthritis
- Hypothyroid
- Seasonal allergies
- Meds:
  - Ceterizine
  - Lactulose
  - Levothyroxone

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Clinical Exam

- Lids / Lashes – Clear and good position
- Conjunctiva – tr injection OU
- Cornea
  - OD 2+ Inf SPK
  - OS Dense SPK, 1+ K edema
- A/C – Deep and Quiet
- PCIOL OU
- IOP – 11 mmHg OU
- K Sensitivity – OD Normal OS Reduced

Anything else we should add???

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Do you test for K sensitivity?

If so, how?

Central vs. S/I/N/T/C??

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Corneal Sensation

- Greatest in the central cornea (elderly patients – more sensitive in the periphery)
- Drops rapidly as distance increases from the limbus
- Falls with increasing age
- Is not affected by iris color
- More sensitive in the temporal limbus than the inferior limbus
- Reduction has been reported in diabetes type 1 and type 2

Faulkner WJ, Varley GA. Corneal diagnostic techniques. In: Krachmer JH, Mannis MJ, Holland EJ, eds. Cornea. 2nd ed. Vol. 1 Philadelphia: Elsevier/Mosby; 2005:229-235. External Disease and Cornea, Section 8. Basic and Clinical Science Course, AAO, 2010.

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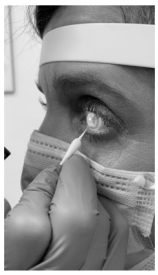
Corneal Sensitivity Testing



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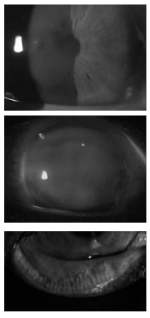
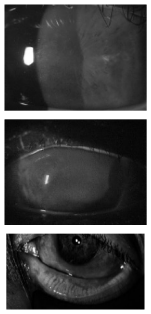
OD



OS



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Neurotrophic Keratitis: Classification

Mackie classification

- Stage I is characterized by hyperplasia and/or irregularity of the epithelium, evolving to punctate keratopathy, corneal edema, neovascularization, stromal scarring.
- Stage II is defined by a recurrent or persistent epithelial defects or a PED without stromal thinning.
- Stage III: stromal involvement leads to corneal ulcer, melting and perforation

Mackie IA. Neuroparalytic keratitis. Current Ocular Therapy. Philadelphia, PA: WB Saunders; 1995:452-4.

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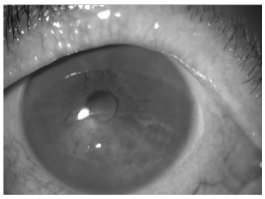

Stage 1
Rose bengal staining of the inferior palpebral conjunctiva
Decreased TBUT
Increased mucous viscosity
Punctate corneal epithelial fluorescein staining (resembles dry eye)

Mackie IA. In: Fraunfelder F, Roy FH, Meyer SM, eds. Current Ocular Therapy. WB Saunders; 1995.

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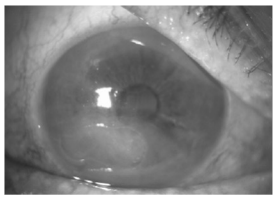

Stage 2
Epithelial defect • Typically oval in shape • In central/inferior cornea • Surrounded by a rim of loose epithelium • Edges may become smooth and rolled
Stromal swelling with folds in the Descemet membrane
Anterior chamber inflammatory reaction may be present

Mackie IA. In: Fraunfelder F, Roy FH, Meyer SM, eds. Current Ocular Therapy. WB Saunders; 1995.

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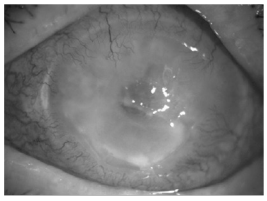

Stage 3
• Corneal ulcer
• Stromal lysis/melting
• Perforation

Mackie IA. In: Fraunfelder F, Roy FH, Meyer SM, eds. Current Ocular Therapy. WB Saunders; 1995.

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Endogenous nerve growth factor (NGF) and its role in NK:

Impaired trigeminal corneal innervation

- ↓ Lacrimation and blink reflex
- ↓ Epithelial cell vitality, metabolism, mitosis
- ↓ Epithelial trophism and repair
- ↑ Stromal and intracellular edema
- ↓ Microvilli
- ↓ Development of the basal lamina

Mastropasqua et al. (2017) J Cell Physiol 232:717-24

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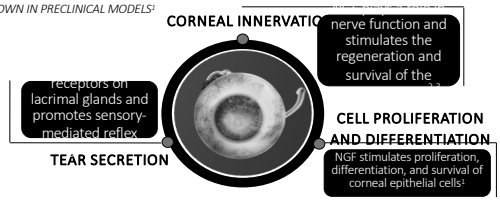
Endogenous NGF Maintains Corneal Integrity By Three Mechanisms

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

SHOWN IN PRECLINICAL MODELS[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, Colaffrancesco V, Sorrenti E, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Gland: of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea.* 2016;29:1163–1168.

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Severity-Based Therapy	Stage	Therapy
	1	• Preservative-free artificial tears formulations • Punctal occlusion • Hydrogel contact lens (consider large diameter) • Recombinant human NGF (rhNGF, cenegermin) • Serum/plasma/platelet rich plasma
	2	Supportive therapies plus: • rhNGF • Scleral lens (± serum/plasma) • Amniotic membrane • Botulinum induced ptosis, Tarsorrhaphy
	3	• rhNGF • Keratoplasty + scleral lens, tarsorrhaphy, neurotization

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579. Sheha H, Tighe S, Hashem O, Hayashida Y. Update on cenegermin eye drops in the treatment of neurotrophic keratitis. *Clin Ophthalmol.* 2019;13:1973-1980. Published Oct 7, 2019.

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Serum/Plasma Therapy

- Serum/plasma have reported efficacy as primary or adjunct therapy
- Reported success of serum alone (20-50% concentration) ranges from 71 to 100% within 90 days (Guadilla et al. Arch Soc Esp Offalmol 2013; Jeng and Dupps Cornea 2009; Pflugfelder *AJO* 2006)
- Umbilical cord serum may be more effective and has higher concentrations of substance P and NGF than peripheral blood serum (Yoon KC et al. *Ophthalmology* 2007)
- Epithelial defect healed in 97.4% of stage 2-3 NK after 11 weeks of plasma rich in growth factors (PRGF) (Sanchez-Avila RM et al. *Int Ophthalmol* 2018)
- Serum can be used safely in combination with SiH CL. No inflammation or CL deposits were observed (Choi JA *ECL* 2011)

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Amniotic Membrane

- Randomized clinical trial reported healing of refractory neurotrophic ulcers with conventional therapy (lubrication plus BCL or tarsorrhaphy) or amniotic membrane transplant (AMT). Healing rates were similar in the 2 groups: 67% with conventional therapy and 73% with AMT (Khokhar S et al. Cornea 2005)
- AMT was also equivalent to autologous serum (AS) in healing neurotropic ulcers: 70% for AS and 73% for AMT (Turkoglu E et al. Semin Ophthalmol 2014)
- Multilayer AMT recommended for deep ulcers and Descemetoceles (Kruse F et al. Ophthalmology 1999)

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Scleral Lens

- Use of fluid filled scleral contact lenses for treatment of NK initially reported decades ago (Romero-Rangel et al. *AJO* 2000)
- Non-healing corneal epithelial defects with BCL healed without recurrence in all 9 eyes treated with PROSE scleral lens (Ling J et al. *Am J Ophthalmol* 2013)
- Overnight wear (with close monitoring) may accelerate healing (Lim P et al. *AJO* 2013)

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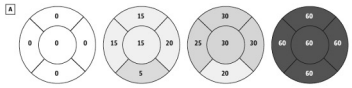
Corneal Neurotization

- Corneal sensitivity restored after sural nerve grafts (Elbaz et al. *JAMA Ophthalmol* 2014)
- Free sural nerve graft was coapted end-to-side with supratrochlear nerve and the distal portion of the nerve was separated into fascicles that were distributed around the limbus
- Corneal sensitivity, measured pre- and post-op with the Cochet-Bonnet esthesiometer, returned to normal after 5 months



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Treatment

- Continue:
  - Cyclosporine 0.05% BID OU
  - Heat Mask
- Stop
  - Oral ceterizine
- Order
  - Cenegermin 20 mcg/mL – Patient to call once meds come in to review meds / demo proper usage
  - Ceterizine ophth sol BID OU
- Follow Up
  - 3-4 months glaucoma / Dilate OCT - G

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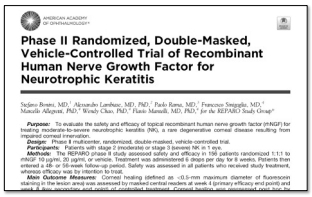
cenegermin-bkbj 20 mcg/ml was approved by FDA in August 2018



Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

Stefano Bonini, MD,[1] Alessandro Lambiase, MD, PhD,[1] Paolo Rama, MD,[1] Francesco Sinagaglia, MD,[1] Marcello Allegretti, PhD,[2] Wendy Chao, PhD,[2] Flavio Mantelli, MD, PhD,[2] *for the* REPARO Study Group[2]

Purpose: To evaluate the safety and efficacy of topical recombinant human nerve growth factor (rhNGF) for healing moderate-to-severe neurotrophic keratitis (NK), a rare degenerative corneal disease resulting from impaired corneal innervation.

Design: Multicenter, randomized, double-masked, vehicle-controlled trial.

Participants: Patients with stage 2 (moderate) or stage 3 (severe) NK in 1 eye.

Methods: The REPARO phase II study assessed safety and efficacy in 156 patients randomized 1:1:1 to rhNGF 10 μg/ml, 20 μg/ml, or vehicle. Treatment was administered 6 drops per day for 8 weeks. Patients then entered a 48- or 56-week follow-up period. Safety was assessed in all patients who received study treatment, whereas efficacy was by intention to treat.

Main Outcome Measures: Corneal healing (defined as ≤0.5-mm maximum diameter of fluorescein staining in the lesion area) was assessed by masked central readers at week 4 (primary efficacy end point) and

- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older
- Available for ordering since January 2019
- Developed by Dompé pharmaceuticals, available through specialty pharmacy

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.

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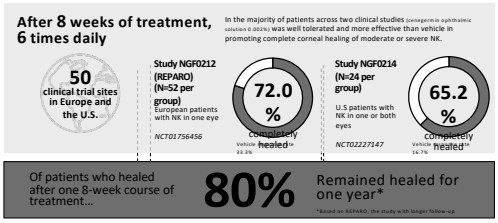
Study Conclusions

Up to 72% of patients achieved complete corneal healing;

80% of healed patients were recurrence free after 1 year*



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1. Bonini S, Lambiase A, Rama P *et al. Ophthalmology* 2018;125:1332-1343.
2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017.

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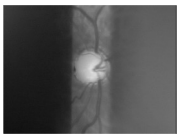
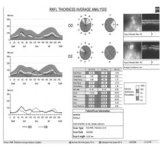
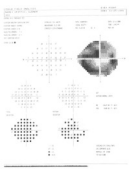
What about Glaucoma??







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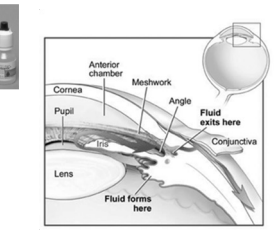
Glaucoma: Medications



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Second Line

- Another med?
  - Alpha agonist
  - Beta blocker
  - Carbonic Anhydrase inhibitor?
- Laser Treatment?
- Minimally invasive glaucoma surgery?
- Tube vs. Trab?

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Preservative Free Latanoprost Ophthalmic Solution 0.005%

- 12/15/22 FDA Approved
- Iyuzeh (latanoprost ophthalmic solution) 0.005% for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.
- In randomized, controlled clinical trials, Iyuzeh lowered IOP by 3-8 mmHg versus 4-8 mmHg by Xalatan (latanoprost ophthalmic solution) 0.005%, which is preserved with BAK.
  - Mean baseline IOP 19-24mHG
- Does not need to be refrigerated

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Omidenepag isopropyl ophthalmic solution 0.002%

- Indicated for the reduction of elevated IOP in patients with primary open-angle glaucoma or ocular hypertension
- FDA Approved 9/22/22
- Selective non-prostaglandin, prostanoid EP2 receptor agonist which increases aqueous humor drainage through the conventional (or trabecular) and uveoscleral outflow pathways

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Omidenepag Isopropyl Versus Latanoprost in Primary Open-Angle Glaucoma and Ocular Hypertension: The Phase 3 AYAME Study

Abstract

Purpose: To evaluate the efficacy and safety of omidenepag isopropyl (OMDI), a selective, non-prostaglandin, prostanoid EP2 receptor agonist, in Japanese patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT).

Design: Phase III, randomized, investigator-masked, active-controlled, parallel-group, noninferiority study (ClinicalTrials.gov NCT02623738).

Methods: After a washout period of 1–4 weeks, eligible patients were randomized (1:1) to OMDI 0.002% or latanoprost 0.005% once daily for 4 weeks. Intraocular pressure (IOP) was measured at 9:00 AM, 1:00 PM, and 5:00 PM at weeks 1, 2, and 4. The primary endpoint was the change from baseline in mean diurnal IOP at week 4. The noninferiority margin for OMDI versus latanoprost was 1.5 mm Hg. Adverse events (AEs) were recorded.

Results: Of the 190 patients randomized, 189 had at least 1 post-baseline IOP measurement. At baseline, patients who received OMDI or latanoprost had a mean ± SD diurnal IOP of 23.78 ± 1.73 mm Hg and 23.40 ± 1.51 mm Hg, respectively. At week 4, least-squares mean ± SE reduction in IOP from baseline with OMDI [−5.93 ± 0.23 mm Hg) was noninferior to that of latanoprost (−6.56 ± 0.22 mm Hg; 95% confidence interval between groups: 0.01–1.26). The most frequently reported treatment-related ocular AEs (OMDI vs latanoprost) were conjunctival hyperemia (23/94 patients [24.5%] vs 10/96 patients [10.4%]), corneal thickening (11/94 patients [11.7%] vs 1/96 patients [1.0%]), and punctate keratitis (0/94 patients vs 5/96 patients [5.2%]). No serious AEs were observed in either group, and there were no discontinuations related to the study drug.

Conclusions: OMDI 0.002% was noninferior to latanoprost 0.005% in reducing IOP in patients with OHT or POAG and was well tolerated.

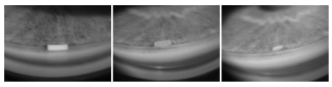
Aihara M, Lu F, Kawata H, Iwata A, Odani-Kawabata N, Shams NK. Omidenepag Isopropyl Versus Latanoprost in Primary Open-Angle Glaucoma and Ocular Hypertension: The Phase 3 AYAME Study. *Am J Ophthalmol*. 2020 Dec;220:53-63. doi: 10.1016/j.ajo.2020.06.003. Epub 2020 Jun 10. Erratum in: *Am J Ophthalmol*. 2021 Nov;231:211. PMID: 32533949.

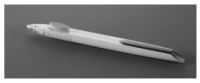
56

Bimatoprost SR (Allergan)

(10-microgram bimatoprost sustained-release implant)

- Biodegradable bimatoprost sustained-release implant
- FDA-approved and indicated to reduce IOP in patients with open angle glaucoma or OHT
- Single intracameral administration
- Demonstrated IOP reductions (hour 0) of 4.9–7.0 mmHg through week 15





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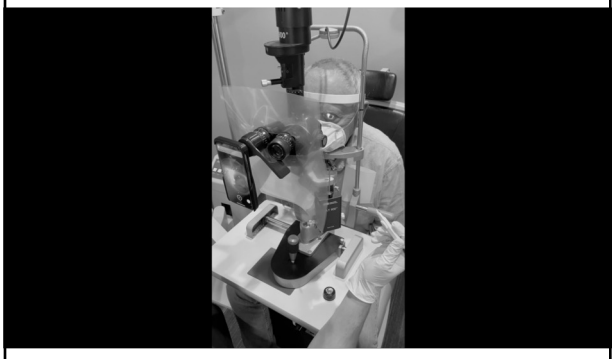
Single Administration of Intracameral Bimatoprost Implant 10 µg in Patients with Open-Angle Glaucoma or Ocular Hypertension

- In the phase 1/2 study (*n* = 21), median time to use of additional IOP-lowering treatment (Kaplan–Meier analysis) was 273 days (approximately 9 months)
- 5 of 21 enrolled patients (23.8%) required no additional IOP-lowering treatment up to 24 months after single administration.
- In each study, after a single implant administration there were no reports of corneal edema, corneal endothelial cell loss, or corneal touch, and no patients had 20% or greater loss in corneal endothelial cell density.

Medeiros FA, Sheybani A, Shah MM, Rivas M, Bai Z, Werts E, Ahmed IIK, Craven ER. Single Administration of Intracameral Bimatoprost Implant 10 µg in Patients with Open-Angle Glaucoma or Ocular Hypertension. Ophthalmol Ther. 2022 Aug;11(4):1517-1537.

58



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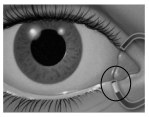
Punctal Plug Delivery Systems

Ocular Therapeutix

- Sustained-release travoprost in an intracanalicular depot composed of polyethylene glycol hydrogel and drug-containing microparticles
  - Drug elutes over 90 day period
  - In Phase 3 Clinical Trials

Mati Therapeutics

- Two formulations have been taken into clinical trials
  - Latanoprost and travoprost for glaucoma
  - Olopatadine for allergy relief



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Travoprost Intracanalicular Insert

(Ocular Therapeutix)

Phase III randomized, double-blind, placebo-controlled clinical trial

Reduction in IOP

	2 Week		6 Week		12 Week	
Diurnal Time Points	mm Hg		mmHg		mmHg	
	OTX-TP	Vehicle	OTX-TP	Vehicle	OTX-TP	Vehicle
8:00 AM	-5.72	-3.88	-4.81	-4.01	-3.91	-3.52
10:00 AM	-4.92	-3.16	-4.03	-3.23	-3.34	-2.63
4:00 PM	-5.22	-3.18	-4.16	-3.14	3.27	-2.60
n=334 OTX-TP	n=211 Vehicle					

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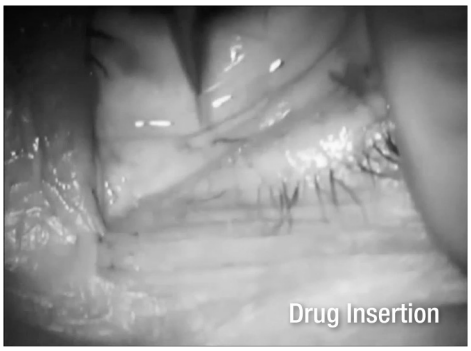

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Latanoprost-Eluting Contact Lens

Attractive option secondary to large residence time in the eye.

63

Latanoprost-Eluting Contact Lens

Comfort of Lens

Patient Compliance

Vision with Lens

Dry Eye/Ocular Surface Disease

Replacement Schedule

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Preclinical Trial and Results

CL_{HI} (149g latanoprost) CL_{LO} (97g latanoprost)

VS

Topical latanoprost

~ 1 week

Ciolino JB, Ross AE, Tulsan R, et al. Latanoprost-eluting contact lenses in glaucomatous monkeys. Ophthalmology 2016; 123:2085 – 2092.

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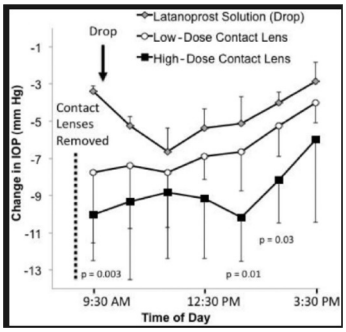
Preclinical Trial and Results



Ciolino JB, Ross AE, Tulsan R, et al. Latanoprost-eluting contact lenses in glaucomatous monkeys. Ophthalmology 2016; 123:2085 – 2092.

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Ocular Surface Disease Pipeline

- MGD
  - AZR-MD-001 (selenium sulfide)
  - NOV03 (100% perfluorohexyloctane)
  - AXR-270
- Dry eye
  - Reproxalap, 0.25%
  - Cyclosporine, 0.1%/perfluorobutylpentane
  - OTX CSI (cyclosporine intracanalicular insert)
  - RGN-279
  - AR-15512
- Blepharitis
  - TP-03 (lotilaner)

ClinicalTrials.gov. Accessed October 18, 2022. https://clinicaltrials.gov
Spiegle L. *Review of Ophthalmology*. February 10, 2022. Accessed October 18, 2022. https://www.reviewofophthalmology.com/article/a-glance-at-the-dryeye-pipeline

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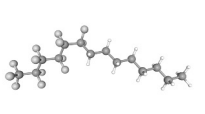
NOV03 Perfluorohexyloctane

- Perfluorohexyloctane
  - Water Free, Preservative Free[1]
  - Long-lasting lubricant[1]
  - Potent inhibitor of evaporation[1]



	Water-Based Technologies	NOV03
Drop size	~25-56 µL[2]	~10 µL[6]
Drug residual time	Brief, 5 -7 min[3]	Long, ~240 min[7]
Spreading	High surface tension hinders spreading[4]	Low surface tension[1,3] Fast-spreading, film-forming properties[1,3,5,6]
Other features	Most contain preservatives[5]	Preservative free.[1] no vision blurring*

1. Tauber J. *Cornea*. 2021;40(9):1132-1140. 2. Lederer CM. *Am J Ophthalmol*. 1986;101(6):691-694 3. Agarwal P. *Pharmaceutics*. 2021;13(2):207 4. Han K. *Chem Cent J*. 2016;10:31. 5. Pucker AD. Over the counter (OTC) artificial tear drops for dry eye syndrome. *Cochrane Database Syst Rev*. 2016;2(2):CD009729. 6. Delicado-Miralles M. *Front Med (Lausanne)*. 2021;8:709712. 7. Kroesser S, et al. Invest Ophthalmol Vis Sci. 2018;59:2414.

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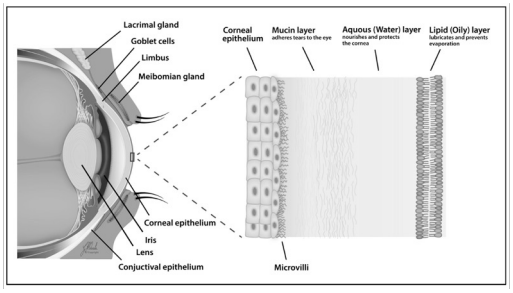
NOV03: Dual Mode of Action



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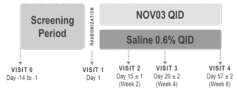
Phase 3 Program: GOBI and MOJAVE

- Multicenter, randomized, double-masked, hypotonic saline (0.6%)-controlled trials in patients with DED associated with MGD
- Patients aged ≥ 18 years old with self-reported history of DED in both eyes
- Patients randomly assigned 1:1 to receive NOV03 or saline 1 drop qid in both eyes for 8 weeks
- Primary outcomes:
  - CFB in tCFS (NEI scale) at day 57
  - CFB in VAS dryness score at day 57
- Secondary outcomes:
  - CFB in dryness score (VAS) at day 15
  - CFB in tCFS (NEI scale) at day 15
  - CFB of VAS burning/stinging at day 57
  - CFB in cCFS at day 57
- Safety outcomes:
  - Ocular and nonocular AEs, BCVA, slitlamp biomicroscopy, IOP, dilated fundoscopy



Tauber J, et al. Paper presented at: 2022 Annual Meeting of the American Society of Cataract and Refractive Surgery; April 22-26, 2022; Washington, DC.
Sheppard JD, et al. *Invest Ophthalmol Vis Sci*. 2022;63(7):1531.

Abbreviations: AE, adverse event; cCFS, central corneal fluorescein staining; CFB, change from baseline; tCFS, total corneal fluorescein staining; VAS, Visual Analogue Scale.

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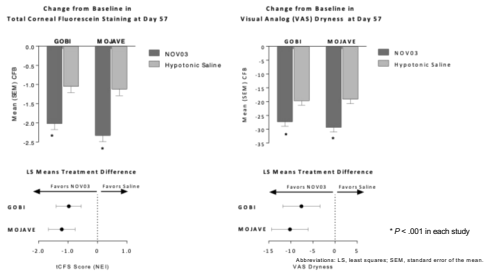
Primary Efficacy: *Both* Sign and Symptom End points Met



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Sheppard JD, et al. *Invest Ophthalmol Vis Sci*. 2022;63(7):1531.

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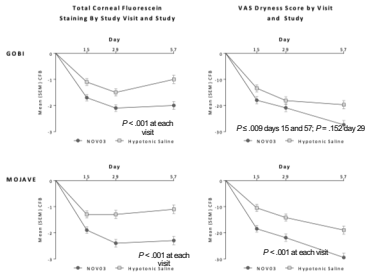
Key Secondary End points: Improvements as early as Day 15



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Sheppard JD, et al. *Invest Ophthalmol Vis Sci*. 2022;63(7):1531.

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NOV03 was well tolerated

GOBI

	Number of Patients (%)	
	NOV03 (n = 303)	SALINE (n = 294)
Patients with ≥ 1 ocular study eye AE	25 (8.3)	15 (5.1)
Most common study eye AEs*		
Blurred vision	9 (3.0)	1 (0.3)

MOJAVE

	Number of Patients (%)	
	NOV03 (n = 311)	SALINE (n = 309)
Patients with ≥ 1 ocular study eye AE	30 (9.6)	30 (9.7)
Most common study eye AEs*		
Blepharitis	5 (1.6)	1 (0.3)
Blurred vision	4 (1.3)	1 (0.3)
Conjunctival hyperemia	4 (1.3)	5 (1.6)
Conjunctival papillae	4 (1.3)	5 (1.6)
Eye discharge	1 (0.3)	3 (1.0)
Eye pain	1 (0.3)	3 (1.0)

* Incidence > 1% in either treatment group

Few patients experienced nonocular AEs
None of the nonocular AEs were considered related to treatment
Other safety assessments were unremarkable (BCVA, biomicroscopy, IOP, fundoscopy)

Tauber J, et al. Paper presented at: 2022 Annual Meeting of the American Society of Cataract and Refractive Surgery; April 22-26, 2022; Washington, DC.
Sheppard JD, et al. *Invest Ophthalmol Vis Sci*. 2022;63(7):1531.

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Phase 3 Program: Conclusions

- Primary and secondary end points met for each study
- Ocular AEs were similar in severity and frequency between treatment groups; nonocular AEs were infrequent and similar between the treatment groups
- If approved, this will be the first product for the treatment of DED to need only two phase 3 studies to demonstrate efficacy on signs and symptoms

Tauber J, et al. Paper presented at: 2022 Annual Meeting of the American Society of Cataract and Refractive Surgery; April 22-26, 2022; Washington, DC.
Sheppard JD, et al. *Invest Ophthalmol Vis Sci*. 2022;63(7):1531.

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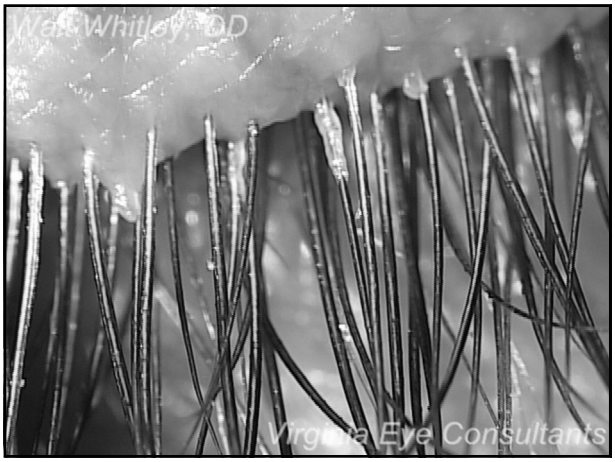

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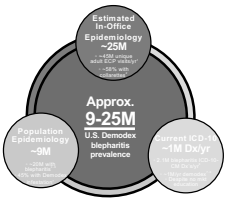
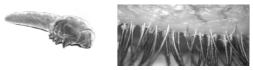
Epidemiology of Demodex Blepharitis





Largely Underdiagnosed, Education Needed	~ 58% of all patients in the eye clinic have collarettes[1] but current impression of only 10-15% of blepharitis cases
Significant head start on Diagnosis	2.1M ICD-10 Blepharitis Dx's/yr[2]
Blepharitis Routinely Causes	Eyelids to become red, irritated and itchy, with debris on the eyelashes[3]
Blepharitis Can Lead To	Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the cornea[4]
Blepharitis and Surgery	Important factor for maximizing surgical outcomes: 67% of cataract patients have Demodex blepharitis[5]
Contact Lens Drop-out	#1 reason people discontinue contact lens wear is discomfort. Studies have shown a direct correlation between Demodex blepharitis and CL intolerance [6,10]
Prescription Treatment	None

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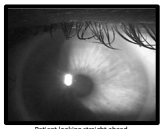
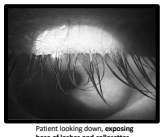


Patient looking straight ahead



Patient looking down, **exposing base of lashes and collarettes**

Images courtesy of Elizabeth Yeu, MD, used with permission.

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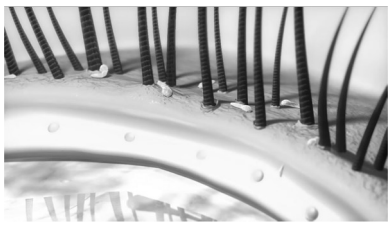
TP-03 (lotilaner ophthalmic solution, 0.25%) is Designed to Eradicate Demodex Mites and Treat Demodex Blepharitis



***Not FDA Approved

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TP-03 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

*BID: Meal is twice per day

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

***Not FDA Approved

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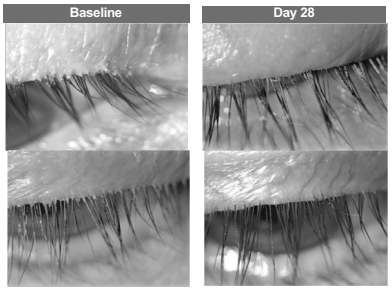
Cure of Collarettes with BID Use of TP-03



***Not FDA Approved

80

Saturn-2 Top Line Results

- Phase 3 randomized, controlled, double-masked trial evaluating the efficacy and safety of TP-03 in patients with *Demodex* blepharitis.
- **Primary endpoint:** Complete collarette cure, defined as 0 to 2 collarettes per lid at day 43, was achieved by 56% of patients on TP-03, compared to 13% on vehicle (p<0.0001).
  - Additionally, 89% of patients achieved a significant, clinically meaningful collarette cure defined by a collarette grade of zero (0) or one (1) at day 43 compared to 33% of those on vehicle (p<0.0001).
- **Secondary endpoints:**
  - **Mite eradication**: Defined as a mite density of zero (0) mites per lash, was achieved by 52% of patients on TP-03 compared to 14% on vehicle (p<0.0001) at day 43.
  - **Complete lid erythema (redness) cure:** 31.1% of patients on TP-03 compared to 9.0% of patients on vehicle (p<0.0001) achieved a complete lid erythema cure at day 43.
  - **Complete composite cure:** 19.2% of patients on TP-03 achieved a complete composite cure, based on achieving both collarette cure and erythema cure, compared to 4.0% on vehicle (p<0.0001) at day 43.

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Saturn-2 Top Line Results

- **Safety Profile:** Consistent with Saturn-1, Saturn-2 trial results demonstrated that TP-03 was well-tolerated with a safety profile similar to the vehicle group.
  - 91% of patients reported that the drop comfort was neutral to very comfortable.
  - There were no serious treatment-related adverse events. The only adverse events occurring at a rate of ≥1% in the TP-03 group were instillation site pain/burning/stinging (7.9%, n=16) and dry eye (1.5%, n=3).

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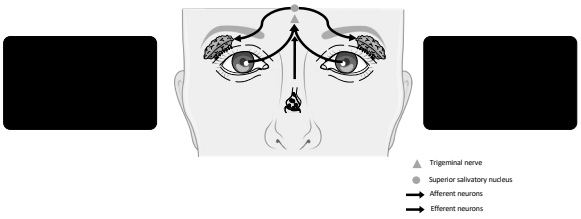
Activating Natural Tear Production via Trigeminal Nerve



1. Green BG. Chem Senses. 2012;37:203-206. 2. Meng ID, Kurose M. Exp Eye Res. 2013;117:79-87. 3. Zhang M, et al. Sig Trans Target Ther. 2020;8:261.

83

Nasal Activation of the Trigeminal Nerve

- Research into nicotinic acetylcholine receptors (nAChR) has demonstrated they are expressed on trigeminal nerve endings and contribute detection of irritants and chemicals[1,2]
- Direct neurostimulation of nAChR-expressing fibers has been shown to increase tear production[3,4]

1. Arredondo J, et al. Chem Senses. 2006;25:63-68. 2. Arends-Nielsen L, et al. Nicotine Tob Res. 2022;24:1849-1860. 3. Wirta O, et al. Cornea. 2022;41:1207-1216. 4. Wirta O, et al. Ophthalmology. 2022;129:370-387.

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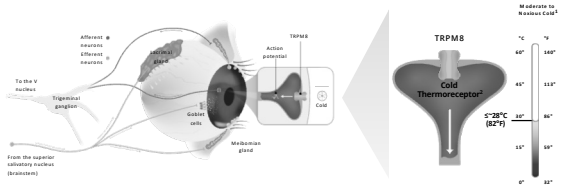
Stimulating TRPM8 for Tear Production



TRPM8 receptors activate trigeminal neural signaling and LFU activity, resulting in the coordinated innervation of the lacrimal gland, goblet cells, and meibomian glands to regulate basal tearing[3-5]

LFU, lacrimal functional unit; TRPM8, transient receptor potential melastatin 8.
1. Ulmsten GU, Wiqvist GB. *ACS Chem Neurosci*. 2013;5:240-247. 2. Belmonte C, et al. *The Ocular Surface*. 2017;15(3):404-437. 3. Dartt DA. *Prog Retin Eye Res*. 2009;28(3):155-177. 4. Ogino MH, Tadi P. Neuroanatomy, trigeminal reflexes. Updated June 5, 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK553641/. Accessed July 25th, 2024. 5. Pflugfelder SC, et al. *Exp Eye Res*. 2020;197:108115.

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TRPM8 as a Potential Therapeutic Target

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

*** PDUFA decision date of April 2, 2025

***Not FDA Approved

Acoltremon and IVW-1001 are investigational drugs and have not been approved for commercialization.
TRPM8, transient receptor potential melastatin 8
1. https://clinicaltrials.gov/study/NCT05285644. Accessed March 27, 2024. 2. https://clinicaltrials.gov/study/NCT05285644. Accessed March 27, 2024. 3. Wirta DL, et al. *Ocul Surf*. 2022;26:166-173. 4. IVW-1001 phase 1/2 in subjects with dry eye disease. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT06400659. Accessed July 25, 2024. 5. Liang, BG et al. *Disease. Invest. Ophthalmol. Vis. Sci.* 2024;65(7):5763.

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Summary: TRPM8 Is a Regulator of Tear Production

Unmet Need
- A novel mechanism to help manage a multifactorial disease[1]

Altered Tear Volume and Composition
- Sustains and perpetuates the DED cycle[1]
- Can be caused by dysfunction in tear-secreting glands or in the neuronal circuits regulating these glands[1]

Neuromodulation
- Leverages the LFU to quickly replenish tear components[2]
- Current option requires nasal delivery[2]

Corneal TRPM8 Receptors
- Regulate tear production by detecting evaporative cooling on the ocular surface[2]
- Being investigated as a target for increasing tear production[3-6]

DED, dry eye disease; LFU, lacrimal functional unit; TRPM8, transient receptor potential melastatin 8
1. Craig JP, et al. *Ocul Surf*. 2017;15(4):802-812. 2. Belmonte C and Gallar J. *Invest Ophthalmol Vis Sci*. 2011;52:2888-2892. 3. Tyrvaya [varenicline solution nasal spray] [prescribing information]. Princeton, NJ: Oyster Point Pharma; 2020. 4. Study Evaluating the Safety and Efficacy of AR-15512 (CONVERT-1). https://clinicaltrials.gov/study/NCT05286644. Accessed March 27, 2024. 5. Study Evaluating the Safety and Efficacy of AR-15512 (CONVERT-2). Accessed March 27, 2024. 6. IVW-1001 phase 1/2 in subjects with dry eye disease. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT06400659. Accessed July 25, 2024

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Reactive Aldehyde Species (RASP)

- Reactive molecules that covalently bind to cellular biomolecules, disrupting their function and activating pro-inflammatory mediators. RASP are formed by a variety of processes, including lipid peroxidation, alcohol oxidation, polyamine and glucose metabolism
- Levels of RASP are generally observed to be elevated in ocular and systemic inflammatory disease, and thus represent therapeutic targets for immune-modulation
- RASP is a pre-cytokine pro-inflammatory mediator that is elevated in the tears of patients with dry eye disease and correlates with dry eye disease symptoms and signs

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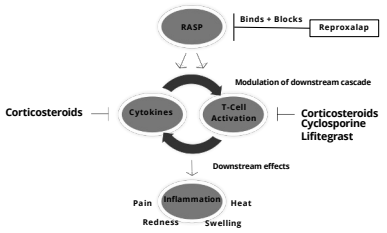
RASP Are Believed to Work at the Top of the Inflammatory Cascade



Sources: Lee SJ et al. HNE-induced 5-LO expression is regulated by NF-kB/ERK and Sp1/p38 MAPK pathways via EGF receptor in murine macrophages. Cardiovasc Res. 2010;88(2):352-9. Chiarpotto E et al. Role of 4-hydroxy-2,3-nonenal in the pathogenesis of fibrosis. Biofactors. 2005;24(3-4):229-34. Natarajan K et al. The advanced lipoxidation end product precursor malondialdehyde induces IL-17E expression and skews lymphocytes to the Th17 subset. Cell Mol Biol Lett. 2015;20(4):647-62. Raghavan S et al. Proinflammatory effects of malondialdehyde in lymphocytes. J Leukoc Biol. 2012;92(5):1053-67. Shanmugam N et al. Proinflammatory effects of advanced lipoxidation end products in monocytes. Diabetes. 2008;57(4):879-88.

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Primary Endpoints Achieved in Phase 3 TRANQUILITY-2 Trial

Aldeyra Therapeutics Achieves Primary Endpoint in Phase 3 TRANQUILITY-2 Trial in Dry Eye Disease and Intends to Submit New Drug Application for Symptoms and Three Sign Endpoints of Dry Eye Disease

June 8, 2022

- *Reproxalap Statistically Superior to Vehicle for Both Prespecified Primary Endpoints of Schirmer Test (p=0.0001) and ≥ 10 mm Schirmer Test Responder Proportions (p<0.0001)*
- *TRANQUILITY-2 Results May Allow for the Most Comprehensive Dry Eye Disease New Drug Application (NDA) Submission to Date*
- *Pending Pre-NDA Meeting with the U.S. Food and Drug Administration (FDA), Clinical Efficacy Trials of Reproxalap Believed to Be Complete*
- *Company to Host Conference Call at 8:00 a.m. ET Today*

LEXINGTON, Mass.--(BUSINESS WIRE)--Jun. 8, 2022-- Aldeyra Therapeutics, Inc. (Nasdaq: ALDX) (Aldeyra) today announced the achievement of the primary endpoint in the Phase 3 TRANQUILITY-2 clinical trial (TRANQUILITY-2) of reproxalap, an investigational new drug candidate, for the treatment of dry eye disease. Reproxalap was statistically superior to vehicle for each of the two prespecified primary endpoints, Schirmer test (p=0.0001) and ≥10 mm

Primary Endpoints:
- Schirmer Test (p=0.0001)
- ≥ 10 mm Schirmer Test responder proportions (p<0.0001)

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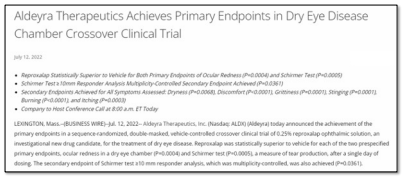
Primary and Secondary Endpoints Achieved in a Well-Controlled Crossover Trial


Aldeyra Therapeutics Achieves Primary Endpoints in Dry Eye Disease Chamber Crossover Clinical Trial

July 12, 2022

- *Reproxalap Statistically Superior to Vehicle for Both Primary Endpoints of Ocular Redness (P=0.0004) and Schirmer Test (P=0.0005)*
- *Schirmer Test ≥ 10mm Responder Analysis Multiplicity-Controlled Secondary Endpoint Achieved (P=0.0361)*
- *Secondary Endpoints Achieved for All Symptoms Assessed: Dryness (P=0.0068), Discomfort (P<0.0001), Grittiness (P<0.0001), Stinging (P=0.0001), Burning (P<0.0001), and Itching (P=0.0003)*
- *Company to Host Conference Call at 8:00 a.m. ET Today*

LEXINGTON, Mass.--(BUSINESS WIRE)--Jul. 12, 2022-- Aldeyra Therapeutics, Inc. (Nasdaq: ALDX) (Aldeyra) today announced the achievement of the primary endpoints in a sequence-randomized, double-masked, vehicle-controlled crossover clinical trial of 0.25% reproxalap ophthalmic solution, an investigational new drug candidate, for the treatment of dry eye disease. Reproxalap was statistically superior to vehicle for each of the two prespecified primary endpoints, ocular redness in a dry eye chamber (P=0.0004) and Schirmer test (P=0.0005), a measure of tear production, after a single day of dosing. The secondary endpoint of Schirmer test ≥10 mm responder analysis, which was multiplicity-controlled, was also achieved (P=0.0361).

Primary Endpoints:
- Schirmer Test (p=0.0005)
- Ocular redness (p=0.0004)

Secondary Endpoints:
- ≥ 10 mm Schirmer Test responder analysis (p=0.0361)
- Dryness (p=0.0068)
- Discomfort (p<0.0001)
- Grittiness (p<0.0001)
- Stinging (p=0.0001)
- Burning (p<0.0001)
- Itching (p=0.0003)

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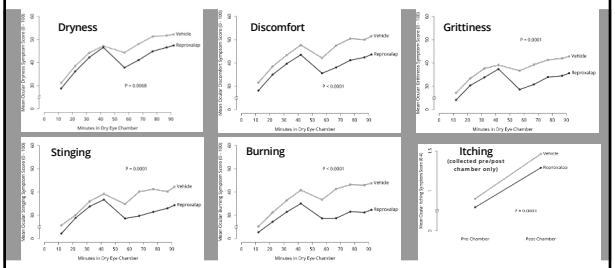
Acute Secondary Symptom Endpoints Achieved in a Dry Eye Disease Crossover Chamber Trial



P values derived from mixed effect model of repeated measures of change from baseline. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

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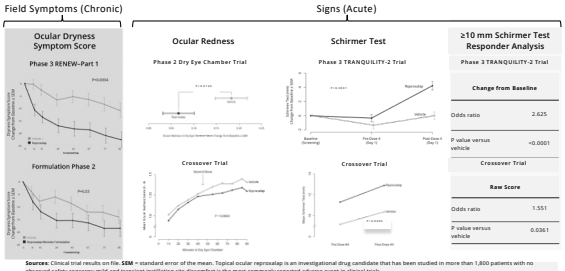
Summary of Reproxalap Data Findings in Dry Eye Disease



Sources: Clinical trial results on file. **SEM** = standard error of the mean. Topical ocular reproxalap is an investigational drug candidate that has been studied in more than 1,800 patients with no observed safety concerns; mild and transient instillation site discomfort is the most commonly reported adverse event in clinical trials.

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EyeSol/Cyclosporine 0.1%

- First-of-a-kind topical treatment of cyclosporine
- Cyclosporine is soluble in the excipient perfluorobutylpentane allowing for its improved bioavailability and better efficacy on the target tissue
- Contains no oils, no surfactants and is preservative-free due to the novel carrier
- Provides additional clinical benefits for patients, such as improved tolerability and decreased visual disturbances
- Each drop 20 µl in size

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EyeSol/Cyclosporine 0.1%

- August 09, 2022 - submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) seeking approval for CyclASol® (cyclosporine ophthalmic solution), a proposed novel treatment for the signs and symptoms of dry eye disease (DED)
- Over 1,000 patients with DED from a Phase 2 dose finding study, the Phase 2b/3 ESSENCE-1 study, the Phase 3 ESSENCE-2 study and its open label extension study.[7,8]

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EyeSol/Cyclosporine 0.1% Clinical Signs

- SS reduction in total corneal fluorescein staining (tCFS) score favoring CyclASol® in both studies at Days 15 and 29.
  - Up to 71.6% of patients responded within four weeks with a clinically meaningful improvement of ≥ 3 grades in total corneal staining. This proportion of responders was significantly higher compared to vehicle-treated patients in both studies. Responders showed also statistically significant improvements in a variety of symptoms compared to non-responders at day 29.
- SS higher percentage of patients with increases of 10 mm from baseline in Schirmer's tear test score at Day 8 and Day 29

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EyeSol/Cyclosporine 0.1% Effect on Tear Production

- Maintenance of effect results from the long-term study CYS-005 confirmed that the effect of CyclASol® was maintained, and even improved for most endpoints, over the 52-week treatment period.
- Safety and Tolerability: Tolerability of CyclASol® was shown by high drop comfort patient ratings in both studies. The most common adverse reaction observed was instillation site reactions, which was reported in 8.1% of patients in the pooled studies. These were in all but one case mild. The only other adverse reaction reported in > 2% of the patients was visual acuity reduced (2.7%).

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Case Of The Red Irritated Swollen Eye

- 50 yo female with 4 week history of redness irritated tearing eyes
- Otherwise healthy hasn't ever seen an eye doctor

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……..or perhaps she has seen 6 other doctors

- 55yo F dx as chronic conjunctivitis with a 3 month history or red eyes and tearing after trials of :
- Artificial tears
- Antibiotic drops
- Steroid drops
- Antibiotic steroid combination drops
- Stopping all drops
- Ointments
- Lid scrubs
- Hot compresses
- Cold compresses
- Luke warm camomile tea and honey compresses
- Acupuncture, acupressure, meditation

if its red consider TED

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Teprotumumab (RV 001)

- An antibody directed against IGF-1, the growth factor pathway associated with the thyroid-hormone receptor
- Teprotumumab is the only medicine to date proven to reduce overall clinical severity and proptosis, and provide a sustained response.[1]
- Can halt progression of active disease and reverse any changes associated with TED, and the effects are long-lasting.

Primary endpoint: 2mm reduction in proptosis
- 82.9% vs. 9.5%

N = 87

1. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med 2017;376:18:1748-61.

100

Other Biologics for TED

- Rituximab
  - Two large, randomized, controlled, concurrent trials were conducted: one in Europe and one in the United States
  - Unfortunately, the results were conflicting, with the European study suggesting a beneficial effect of rituximab[6] and the United States study showing no improvement
- Tocilizumab (Actemra, Genentech)
  - Case reports of improvement in TED
  - Recently completed a randomized, controlled trial, the results of which are pending.

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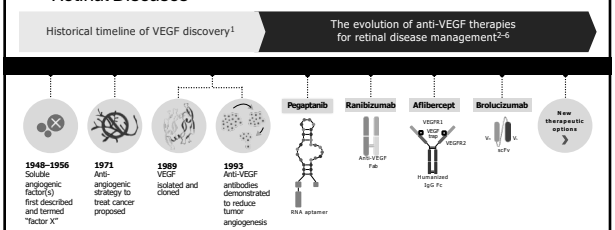
Anti-VEGF Therapies Have Redefined the Care of Patients With Retinal Diseases



Fab = fragment antigen binding; Fc = fragment crystallizable; IgG = immunoglobulin G; scFv = single-chain fragment variable; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; VH = heavy chain variable domain; VL = light chain variable domain.

1. Apte RS, et al. *Cell* 2019;176(6):1248-1264; 2. Sharma A, et al. *Eye (Lond).* 2020;34(4):611-613; 3. Adamis AP, et al. *Eye (Lond).* 2020;34(11):1966-1972; 4. Ranibizumab. Package insert. Genentech; 2006; 5. Aflibercept. Package insert. Regeneron; 2011; 6. Brolucizumab. Package insert. Novartis; 2019.

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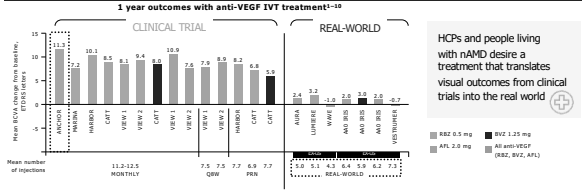
Yet, Visual Acuity Is Not Translated From Clinical Trials to the Real World

Patients with nAMD experience worse visual outcomes in the real world because they receive fewer anti-VEGF injections compared with patients receiving fixed, frequent therapy in randomized clinical trials[1]



HCPs and people living with nAMD desire a treatment that translates visual outcomes from clinical trials into the real world

AFL = aflibercept; BCVA = best-corrected visual acuity; BVZ = bevacizumab; ETDRS = Early Treatment Diabetic Retinopathy Study; HCP = health care professional; IVT = intravitreal; nAMD = neovascular age-related macular degeneration; PRN = as needed; Q8W = every 8 weeks; RBZ = ranibizumab; VEGF = vascular endothelial growth factor.

1. Ciulla TA, et al. *Ophthalmol Retina.* 2020;4(1):19-30; 2. Brown DM, et al. *N Engl J Med.* 2006;355(14):1432-1444; 3. Busbee DM, et al. *Ophthalmology.* 2013;120(5):1046-1056; 4. Heier JS, et al. *Ophthalmology.* 2012;119(12):2537-2548; 5. Martin DF, et al. *N Engl J Med.* 2011;364(20):1897-1908; 6. Rosenfeld PJ, et al. *N Engl J Med.* 2006;355(14):1419-1431; 7. Holz FG, et al. *Br J Ophthalmol.* 2015;99(2):220-226; 8. Cohen SY, et al. *Retina.* 2013;33(3):474-481; 9. Finger RP, et al. *Acta Ophthalmol.* 2013;91(6):540-546; 10. Rao P, et al. *Ophthalmology.* 2018;125(4):522-528; 11. Ciulla TA, et al. *Ophthalmol Retina.* 2018;2(7):645-653.

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Current Standard of Care for nAMD Involves Frequent Injections

Drug	Hallmark Trial	Dose	Key Finding(s)	Safety
Bevacizumab	CATT	1.25 mg Q4W	• Mean BCVA Δ +7.8 letters over 24 months • BCVA and CRT comparable to ranibizumab Q4W	• Higher systemic adverse events with bevacizumab
Ranibizumab	ANCHOR/MARINA	0.5 mg monthly	• Mean BCVA Δ +6.6 to +10 letters over 24 months	• 1.3% - 2.1% endophthalmitis • 6.2% - 10% ocular inflammation ≥1+
Aflibercept	VIEW1/VIEW2	2 mg Q4W or 2 mg Q8W	• Aflibercept noninferior to ranibizumab q4w • Mean BCVA Δ +8.4 to +9.3 letters over 52 weeks • Comparable fluid resolution between groups	• Endophthalmitis in 1% in each group in VIEW1, 0% in VIEW2
Brolucizumab	HAWK/HARRIER	6 mg Q8W or 6 mg Q12W	• Noninferior to aflibercept • Mean BCVA Δ +6.1 to +6.6 letters over 48 weeks • Superior fluid resolution compared to aflibercept	• Endophthalmitis 1% • Inflammation 4% • Rare post-marketing reports of vasculitis

CRT = central retinal thickness; Q4W = every 4 weeks; Q12W = every 12 weeks.

Rosenfeld PJ, et al. *N Engl J Med.* 2006;355(14):1419-1431; Brown DM, et al. *N Engl J Med.* 2006;355(14):1432-1444; Heier JS, et al. *Ophthalmology.* 2012;119(12):2537-2548; Dugel PU, et al. *Ophthalmology.* 2020;127(1):72-84; Brolucizumab. Package Insert. Novartis; 2019; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group; Maguire MG, et al. *Ophthalmology.* 2016;123(8):1751-1761.

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Novel & Pipeline Therapeutic Agents & Treatment Delivery Systems for AMD/DME in Early- or Late-stage Development to Offer Extended Duration of Action via Various Mechanisms or Delivery

- Faricimab
- Aflibercept 8 mg
- KSI-301
- OPT-302
- OCS-01
- THR-149
- UBX1325
- Port delivery system (PDS)
- Gene therapy

AMD = age-related macular degeneration; DME = diabetic macular edema.

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Conclusions

- Exciting times to be an OD!
- More and more innovations are on the way!
- Practice to the highest level of our great profession!!
- wwhitley@cvphealth.com

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