New Pharmaceuticals and Their Clinical Applications

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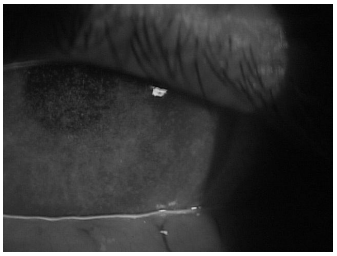
TearClear
TearLab
Teckels
Visant Medical
Visionix
Vital Tears

44 y.o. female patient



- History of HSV OD
- Diabetes for over 10 years with peripheral neuropathy
- Unresponsive to therapy other than amniotic membrane but returns within 3-6 months with recurring symptoms

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

Neurotrophic keratitis (NK) is a result from impaired trigeminal corneal innervation

↓ Lacrimation and blink reflex

↓ Epithelial cell vitality, metabolism, mitosis

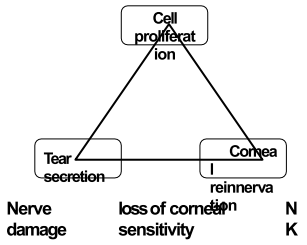
↓ Epithelial trophism and repair

↑ Stromal and intracellular edema

↓ Microvilli

↓ Development of the basal lamina

Endogenous NGF maintains corneal integrity by three mechanisms



Mastropasqua et al. (2017) JCell

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
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s
- Cenegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein

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.

Cenegermin-bkbj: Recombinant human NGF (rhNGF) Proprietary treatment developed by Dompé

~10x more potent than murine NGF based on in vitro studies

Phase I study (74 healthy subjects)

- Favorable safety and tolerability
- No immunogenicity and no significant changes in serum NGF

Safety and pharmacokinetics of escalating doses of human recombinant nerve growth factor eye drops in a double-masked, randomized.Ferrari MP, Mantelli F, Sacchetti M, et al. clinical trial. BioDrugs. 2014;28(3):275e283

Human Nerve Growth Factor

- 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.

Efficacy established as early as week 4

Endpoint of complete corneal healing: **0 mm staining in the lesion area and no persistent staining in the rest of the cornea** (last post-baseline observation carried forward; chi-squared test).

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.

Pool Safety Report

Cenegermin ophthalmic solution 0.002% Dosing and Administration

6

Apply 6 times daily

8

Continue for 8 weeks

Study Conclusions

Up to 72% of patients achieved complete corneal healing;

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

After 8 weeks of treatment, 6 times daily

Study NGF0212

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

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

(REPARO) (N=52 per group)

European patients with NK in one eye

72.0%

Vehicle response rate 33.3%

completely healed

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

65.2%

Vehicle response rate 16.7%

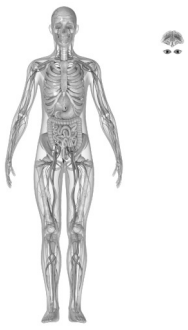
completely healed

Of patients who healed after one 8-week course of treatment…

80%

Remained healed for one year

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.



Etiologies of NK

NK is caused by impairment of trigeminal innervation, and several conditions can lead to this impairment…

OCULAR

SYSTEMIC

CENTRAL NERVOUS SYSTEM

GENETIC

- **Infections** (eg, post-herpes)
- **Ocular surgery** (eg, post-laser vision correction)
- **Contact lens wear**
- Chemical and physical burns
- Abuse of topical anesthetics
- Drug toxicity
- Chronic ocular surface injury

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131.

Etiologies of NK

NK is caused by impairment of trigeminal innervation, and several conditions can lead to this impairment…

OCULAR

SYSTEMIC

CENTRAL NERVOUS SYSTEM

GENETIC

- **Diabetes**
- Multiple sclerosis
- Vitamin A deficiency
- Leprosy
- Amyloidosis

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

Etiologies of NK

NK is caused by impairment of trigeminal innervation, and several conditions can lead to this impairment…

OCULAR

SYSTEMIC

CENTRAL NERVOUS SYSTEM

GENETIC

- **Post-neurosurgical procedures**
- **Stroke**
- Neoplasm
- Aneurysms
- Degenerative disorders of the CNS

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

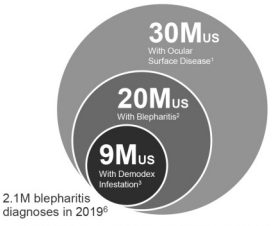
62 y.o. Caucasian Male

- Complains of 'itching eyes' with grittiness
- History of dermatological rosacea
- Has been treated with allergy medication and lid scrubs "but they don't seem to help"
- This is the 5th doctor he has seen

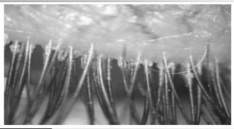
Blepharitis is a Large Unserved Market in Ophthalmology

Demodex Implicated in 45% of Blepharitis Cases[3]

Meta-analysis of 11 studies and 4,741 pts[3]



2.1M blepharitis diagnoses in 2019[6]



Blepharitis Routinely Causes	Eyelids to become red, irritated and itchy, with debris on the eyelashes[1]
Blepharitis Can Lead To	Blurring of vision, missing or misdirected eyelashes, and inflammation of other eye tissue, particularly the cornea[4]
Blepharitis and Surgery	60% of patients preparing to undergo cataract surgery have mild to moderate blepharitis[2]
Contact Lens Drop-out	#1 reason people discontinue contact lens wear is discomfort[5]
Prescription Treatment	None

1. Harmon, Market Scope Dry Eye Analyst Report, 2014; 2. MGD Report IOVS, Special Issue 2011, Vol. 52, N. 4; 3. Zhao - Ophthalmic Epidemiology, 19(2), 95–102, 2012; 4. American Optometric Association; 5. Primary Care Optometry News, February 1997. 6. Symphony Claims Data Analysis. Photo: https://contactlensupdate.com/2015/12/07/managing-demodex-in-clinical-practice/

Demodex is an Underlying Cause of Blepharitis and MGD

2 Species of Mites Contribute to Blepharitis

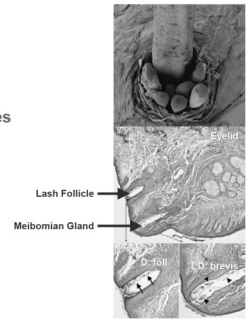
- *Demodex folliculorum*: eyelash follicles
- *Demodex brevis*: meibomian glands in eyelid

***Demodex* Implicated in 45% of Blepharitis Cases**

- Meta-analysis of 11 studies and 4,741 pts[1]

Easily and Rapidly Diagnosed at Slit Lamp

- Cylindrical dandruff, or collarettes, are pathognomonic for *Demodex*[3]



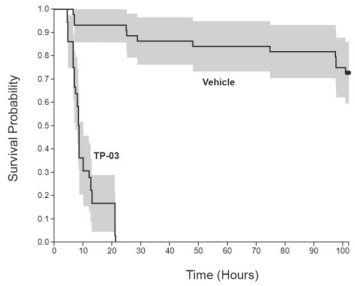
1. Zhao - Ophthalmic Epidemiology, 19(2), 95–102, 2012
2. Schear et al., Ophthal Plast Reconstr Surg, Vol. 32, No. 4, 2016
3. Gao et al., Invst Ophth and Vis Sci, September 2005, Vol. 46, No.

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

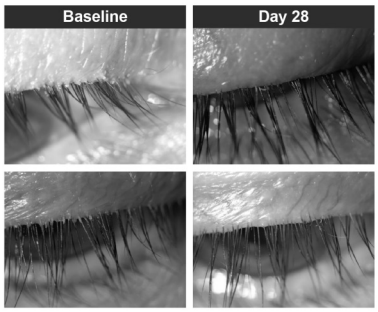
Product Form	Multi-dose eye drop solution bottle, preserved
Indication for Use	Treatment of Demodex Blepharitis
MOA	Paralysis and death of Demodex mites
Diagnosis	Collarettes on slit lamp examination
Dosing	BID for 6 weeks
Efficacy	Collarette cure, mite eradication, other secondary endpoints
Safety	Very clean to-date (mild transient stinging in < 10% of patients)

Mercury Study: TP-03 Works by Killing Mites

Ex-vivo mites extracted from the lashes of blepharitis patients

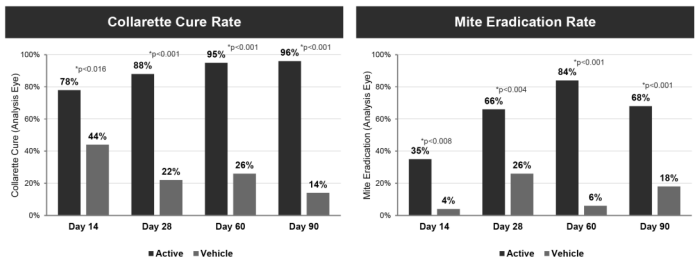


Cure of Collarettes with BID use of TP-03



Jupiter Phase 2b Study: High Collarette Cure Rate and Mite Eradication Rate

FDA-requested primary and secondary endpoints

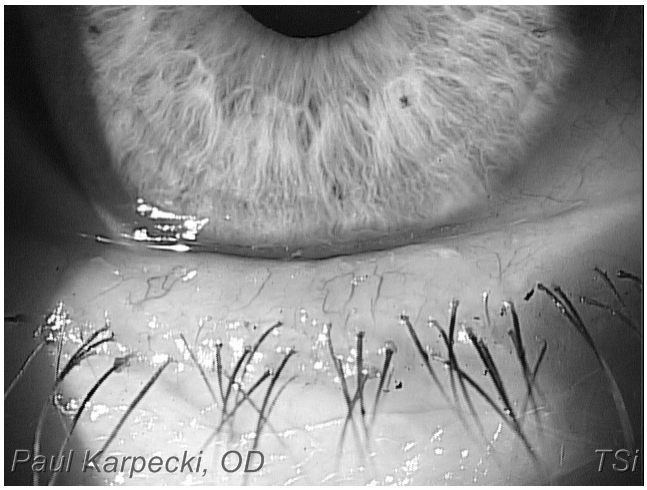


IPL and LLLT

- Intense Pulsed Light Therapy
- Clear association between DED and lid margin inflammatory disease
- Widely accepted as a treatment for dermatological rosacea
- More than 80% of patients with rosacea have MGD
- 20% have ocular signs first

IPL and LLLT

- Telangiectatic vessels and skin erythema release inflammatory mediators
- IPL targets the abnormal erythematous blood vessels
- Affects mitochondrial activity
- Temperature effect on glands?
- Photomodulation affecting cytochrome C or activating fibroblasts and collagen synthesis



IPL/LLLT

1. MGD/EDED
2. DEMODEX
3. Ocular Rosacea
4. CHALAZION
5. HORDEOLUM

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TREATMENT

IT CONSISTS OF A PHASE 1 (WITH A SPECIFIC BLUE LIGHT MASK)
AND A PHASE 2 (WITH THE STANDARD SUPPLIED RED LIGHT MASK)

PHASE 1 – BLUE MASK

Blue light stimulates porphyrins and creates an anti-bacterial action.

PHASE 2 – RED MASK

Red light stimulates ATP by increasing and improving cellular activity, it reduces inflammation and oedema
and works on Meibomian glands.

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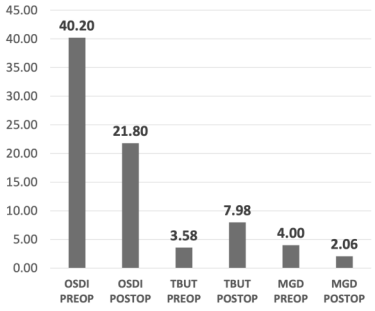
RESULTS



MBE: Blephex

- VIDEOS

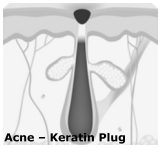
First Keratolytic drug

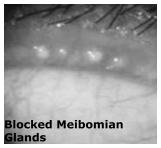
- About to begin phase III trials
- Apply two times per week to lower eyelids
- Maintains effects of debridement or could replace debridement
- Critical to MGD & EDED

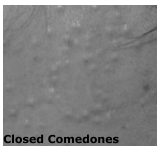
What are keratolytics?

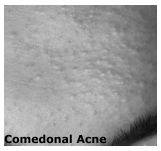
Agents that soften and shed the skin epithelium or horny outer layer of skin through the process of breaking down keratin

- Similar to the lid margin, secretory gland hyperkeratinization plays an important role in various skin disorders
- Comedonal lesions in acne are inspissated hair follicles, filled with corneocytes, sebum, and other debris
- Keratolytic treatments are used to shed dead corneocytes, loosen the sebum plug, and prevent the formation of inflammatory papules and pustules









AZR-MD-001 (selenium sulfide)

Triple MOA for the treatment of MGD

A potent keratolytic, with a unique MoA compared to traditional keratolytic agents, such as urea, AHA and BHA

Keratostatic
Slows down both the rate of keratinocyte proliferation and keratin production[1]

Keratolytic
Softens keratin plug by breaking down disulfide (S-S) bonds, alleviating hyperkeratinization that leads to blockage of Meibomian glands[1]

Lipogenesis
Stimulates lipogenesis to increase the quantity of lipids produced by the Meibomian glands2

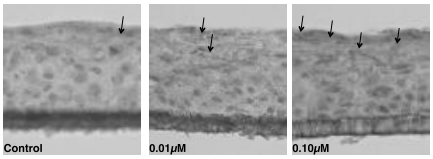
AZR-MD-001 TRIPLE MOA

Decrease meibomian gland hyperkeratinization of ducts and orifices, loosen meibomian gland blockages, and increase secretion of meibomian gland lipids

LIPOGENESIS

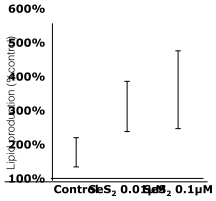
AZR-MD-001 INDUCES LIPOGENESIS AND THUS INCREASES LIPID PRODUCTION IN OIL SECRETING GLANDS

Lipid production was significantly increased
by 282% with 0.01 µM SeS2 and by 348% with 0.1 µM SeS2 ($P < 0.05$)
in a biological model to evaluate the lipogenic effect of selenium sulfide



* Arrows point to lipid staining

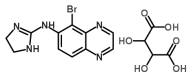
Effect of SeS2 on lipid production
2-h incubation in 3D Human Sebocytes



Eye Whitening

Low dose brimonidine (0.025%)
– Eye whitener
– Low dose alpha adrenergic
– 300% whiter eyes than Visine
– Lasts 6-8 hours
– No rebound hyperemia or tachyphylaxis

Product Profile

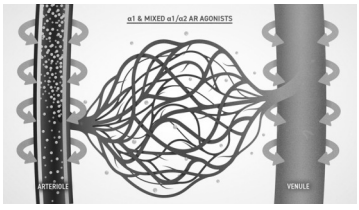


Brimonidine Tartrate

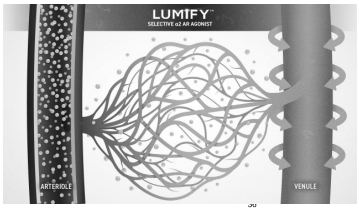
- **Description:** Brimonidine Tartrate (0.025%) drop – OTC NDA. Primary Inactive Ingredients - glycerin, borate buffer system, BAK preservative.
- **Target Indication:** Relief of ocular redness due to minor eye irritations.
- **MOA:** Highly selective α2-AR-specific agonist with minimal action at α1-AR, minimizing the side effects of tachyphylaxis and hyperemia associated with currently marketed, first generation ophthalmic vasoconstrictors (naphazoline, tetrahydrozoline, phenylephrine and oxymetazoline)
- **Dosing:** Topical solution; instill 1-2 drops in the affected eye(s) up to four times daily
- **Current Stage of Development:** Phase III completed; NDA submitted

Mechanism of Action

- α1-AR or Mixed α1-/α2- Agonist
  - Generalized arteriolar and venular constriction reduces redness
  - Arterial constriction creates relative ischemia

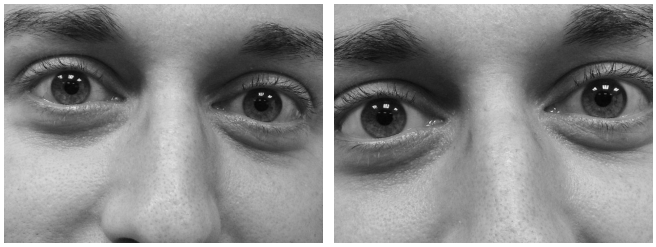


Selective α2- Agonist
- Preferential venular constriction reduces redness
- Normal arterial perfusion allows for reduced potential for ischemia



Phase II – Efficacy in a CAC model

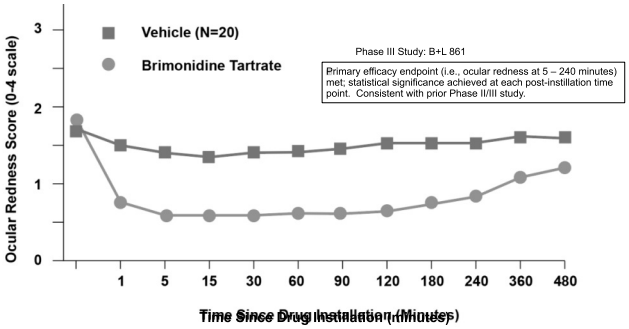
Brimonidine 0.025% in right eye
and oxymetazoline in left eye
(5 minutes post-dose)



Eyes before treatment
(baseline)

Phase III Efficacy – Clinician Redness Score

Significantly greater redness relief beginning 1 minute post-instillation and lasting up to 8 hours, compared to vehicle



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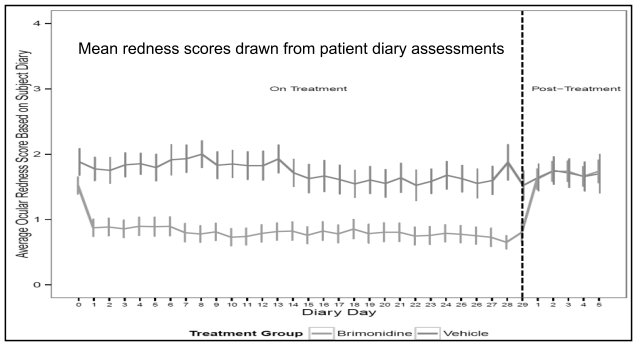
Phase III Efficacy – Patient Diary Assessments

Sustained efficacy across treatment period without tachyphylaxis
No evidence of rebound after cessation of treatment

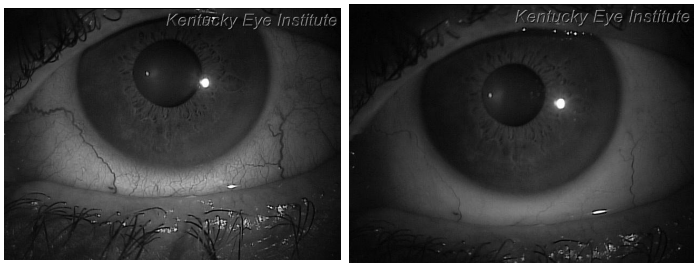


Phase III Safety – Adverse Events

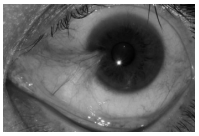
4 subjects reporting at least 1 ocular TEAE, 1 considered related to the study treatment (pain) which was considered mild in severity

Patients Treated with Brimonidine Tartrate (0.025%) N=40	
Adverse Events - Ocular	Events/subjects
All AEs	4 (10%)
TEAEs	4 (10%)
SAEs	0 (0%)
Number of subjects withdrawn due to an AE	0 (0%)

AE = Adverse Event, SAE = Serious Adverse Event; TEAE = Treatment Emergent Adverse Event.
Source: Table 14.3.1.1



Pterygia Cause Discomfort and Impair Visual Function



Pterygium, a common ocular disease, impacts on ocular surface, comfort and significantly impairs visual function.

Prevalence of Pterygia:

- 13 million
- 10 million
- 14 million

References: 1. Hovanesian, J. A. etc., *J. Cataract Refract Surg.*, 2017, 43, 405-419; 2. Rezvan, F. etc., *Surv Ophthalmol.*, 2018, 63, 719-735.

CBT-001 (Nintedanib): Disease Modifying Drug Therapy

Approved oral drug Ofev®:
- Potent multi-kinase inhibitor
- Treats lung cancer and idiopathic pulmonary fibrosis
- Good safety profile

CBT-001 via 505b(2):
- Unique topical formulation
- Decreases pterygium size and reduces hyperemia
- First-in-class, first drug therapy

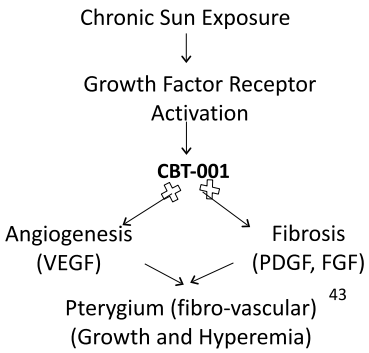
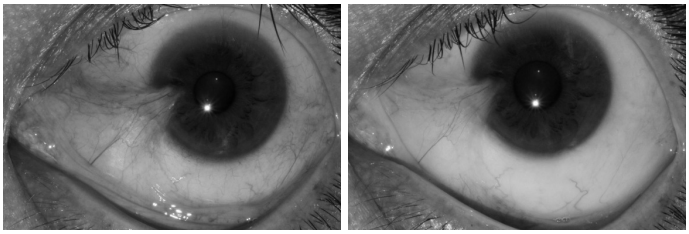
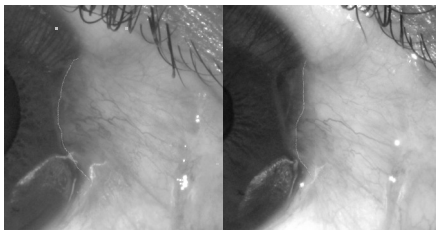


Figure 2. A representative eye treated with CBT-001 showing reduced pterygia vascularity at Week 4.



Day 1 Week 4

CBT-CS101: Phase II Clinical Trial
Pterygium Head Showed Translucent (Regression)

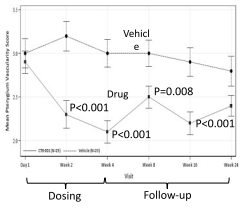


Subject A113, Day 1 Subject A113, Week 4

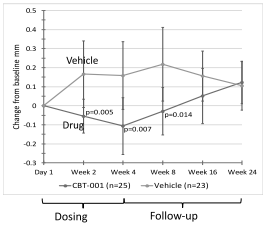
Safety:
- Well tolerated with mostly mild-moderate ocular AEs
- Most common adverse event was mild conjunctival discoloration due to drug color, which was transient and reversible
- No patient withdraw due to AE
- No serious adverse events

Primary and Key Secondary Endpoints Have Shown Significant Improvement During and Post Treatment

Primary Endpoint: Pterygium Vascularity



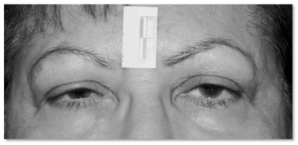
Secondary Endpoint: Cornea Lesion Length



Patients were dosed TID for 4 weeks with 20 weeks follow up.

New Drug Approval

There is a Significant Unmet Need for Non-Surgical Treatment Options for Acquired Blepharoptosis



- **Acquired blepharoptosis** is commonly associated with aging
- **Significant clinical need for effective, non-invasive therapeutic option**
  - Most patients go **untreated** — standard of care is surgery
  - Surgery usually reserved for most severe cases with largest functional impact, involves significant **time**, **cost**, and **risk of complications**[1]
  - <3% of patients with blepharoptosis in U.S. are treated each year

RVL-1201 Phase 3 Clinical Program

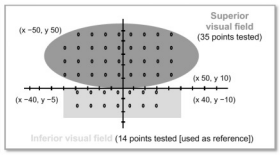
	RVL-1201-201	RVL-1201-202	RVL-1201-203
Enrollment	140	164	234
Design	Randomized, multicenter, double-masked, placebo-controlled	Randomized, multicenter, double-masked, placebo-controlled	Randomized, multicenter, double-masked, placebo-controlled
Duration	6 weeks	6 weeks	12 weeks
Outcomes	▸ Primary efficacy: CFB in number of points seen in top 4 rows of LPFT ▸ Secondary efficacy: CFB in MRD-1 ▸ Safety	▸ Primary efficacy: CFB in number of points seen in top 4 rows of LPFT ▸ Secondary efficacy: CFB in MRD-1 ▸ Safety	Safety

Pivotal Efficacy Study Pivotal Safety Study

Efficacy Endpoints, RVL-1201 Phase 3 Trials

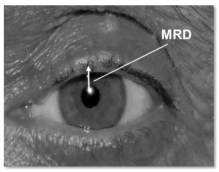
Primary efficacy endpoint

- The LPFT, a customized visual field test designed specifically to assess superior visual field loss due to ptosis,[1] was performed using an HVF analyzer
- 35 points (in the 4 rows at or above 10° from fixation) tested in the superior field
- LPFT score tallied based on the total number of points seen in the top 4 rows

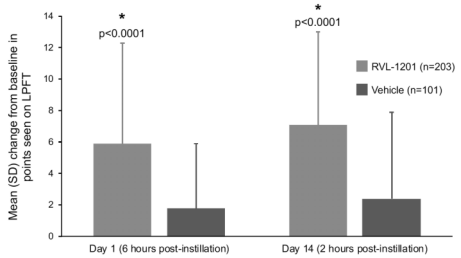


Secondary efficacy endpoint

- MRD-1 is the distance between the center of the pupillary light reflex and the upper eyelid margin with the eye in primary gaze
- Normal MRD-1 is 4-5 mm

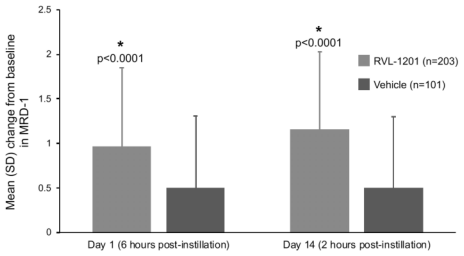


Primary Efficacy Endpoint: Improvement on the LPFT
Combined Efficacy Studies (RVL-1201-201, RVL-1201-202)



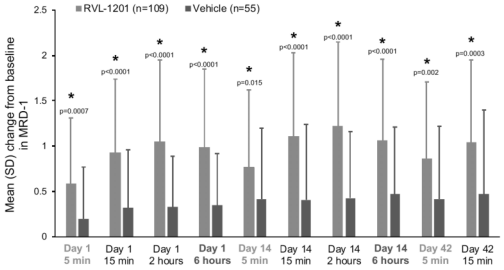
- Increase in points seen on LPFT = **improvement in superior (upper) visual field**

Secondary Efficacy Endpoint: Improvement in MRD-1
Combined Efficacy Studies (RVL-1201-201, RVL-1201-202)



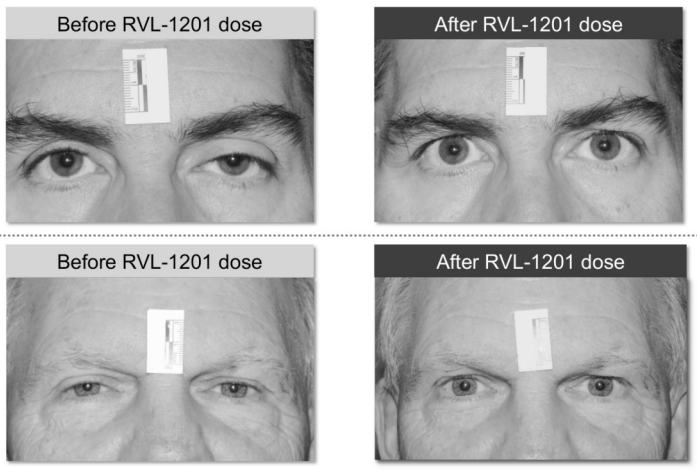
- Increase in MRD-1 = **greater elevation of the upper eyelid**

Secondary Efficacy Endpoint: Improvement in MRD-1



Rapid and sustained effect after application

Significant effect vs. vehicle at **5 minutes** and **6 hours** after drop application



RVL-1201 Safety and Tolerability

Safety

- Overall, treatment-emergent adverse events (AEs) were reported for 31.2% of subjects receiving RVL-1201 and 30.6% of subjects receiving vehicle
  - Most AEs were **mild and did not require treatment**
  - **AEs resulting in treatment discontinuation were uncommon** in subjects receiving RVL-1201 (n=3/94 and n=1/109 subjects in the two 6-week efficacy studies, respectively; n=5/157 subjects in the 12-week safety study)
  - No AE occurred in more than 3.5% of subjects receiving RVL-1201

Tolerability

- Tolerability assessed in 12-wk Ph 3 safety trial
  - 92.0% of subjects rated RVL-1201 as causing **no discomfort**, while 8% rated it as causing **minimal discomfort**

CRANIAL NERVE STIMULATION

TARGETING NUMEROUS DISEASE CONDITIONS

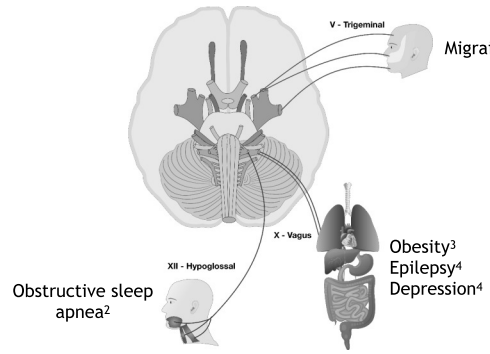


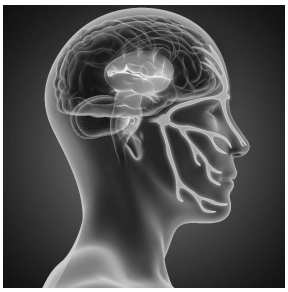
Image adopted from Netters.[5]

1. Zhu and Marmura. *Curr Neurol Neurosci Rep.* 2016; 2. FDA website. Accessed 2016; 3. FDA website. Accessed 2016; 4. FDA website. Accessed 2016.

TRIGEMINAL NERVE (CN V)

BRANCHES AND FUNCTION

- Largest cranial nerve (CN V) with 3 divisions[1,2]
  - Ophthalmic nerve (V1)
  - Maxillary nerve (V2)
  - Mandibular nerve (V3)
- Ophthalmic nerve (V1) comprises 3 branches[1,3]
  - Lacrimal nerve
  - Nasociliary nerve
  - Frontal nerve
- Ophthalmic nerve innervates the lacrimal functional unit (LFU), including[4-6]:
  - Lacrimal gland
  - Meibomian glands
  - Goblet cells



1. Tewfik. Medscape website. Accessed 2016; 2. Morton et al. In: Morton et al, eds. *The Big Picture: Gross Anatomy.* 2011. Accessed 2016; 3. Waxman. In: Waxman SG. eds. *Clinical Neuroanatomy.* 2013. Accessed 2016. 4. Kossler et al. *Ophthal Plast Reconstr Surg.* 2015; 5. Beuerman et al. In: Pflugfelder et al, eds. *Dry Eye and Ocular Surface Disorders.* 2004; 6. Dartt. *Ocul Surf.* 2004.

DISCONTINUED

ITEAR®: A NOVEL NEUROSTIMULATION APPROACH WITH SONIC ENERGY

Drug free, home use, fast onset of action with sustained effect

Handheld, battery powered device with no disposable component

Externally applied

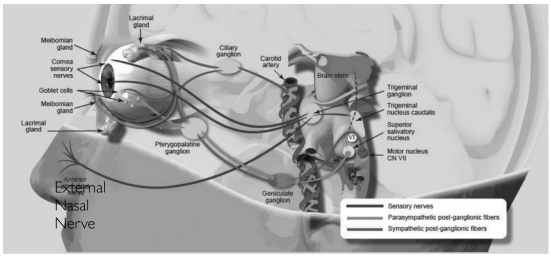
Doctor prescribed, 15s Training

** Investigational Device, Not FDA Cleared

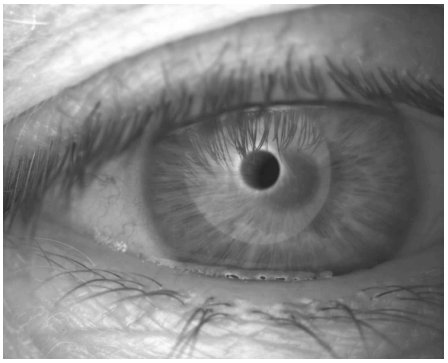
TAKEAWAYS FROM TRIALS

- Array of positive endpoints reflects broad mechanism of action of neuromodulation
- Effective for aqueous tear deficiency and meibomian gland disease
- Acute, sub acute, and chronic benefits to the ocular surface
- Outstanding safety profile
- High value product for dry eye

ACTIVATES CENTRAL REFLEX WHICH RESULTS IN ACTIVATION OF LACRIMAL FUNCTIONAL UNIT



IMMEDIATE TEAR RESPONSE AND MEIBUM SECRETION

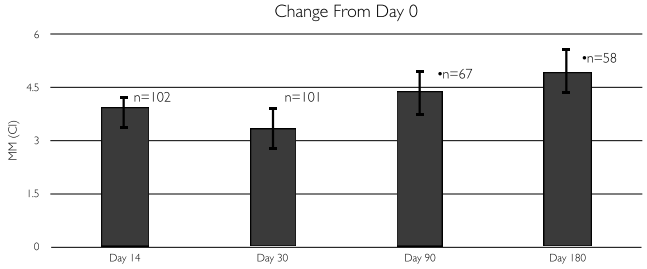


CLP OO2 STUDY

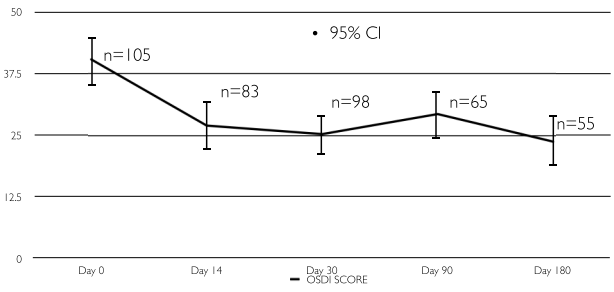
Overview

- **108 subjects 8 sites**
- **30 Day Primary Endpoint (101 subjects)**
- **Option to Continue to 180 days (80 subjects)**
- **Broad demographic and entry criteria**
- **30s per side BID first 30 days, then at least 3x per week**
- **Primary endpoint: Tear Production with Stimulation**
- **Secondary endpoints: Schirmer unstimulated over time, OSDI, Meibomian Gland Expression, Staining, TBUT**

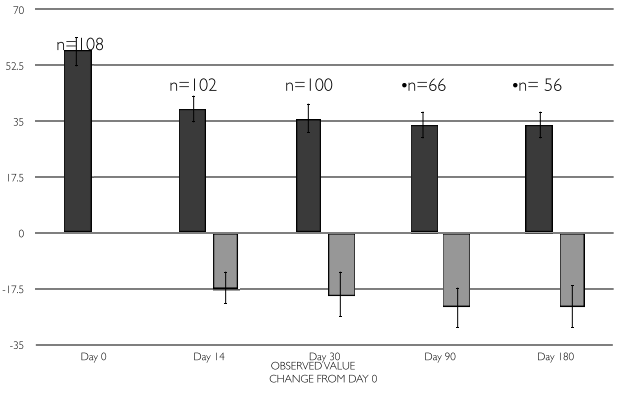
CLP OO2 CHANGE IN PRE-STIMULATION SCHIRMER



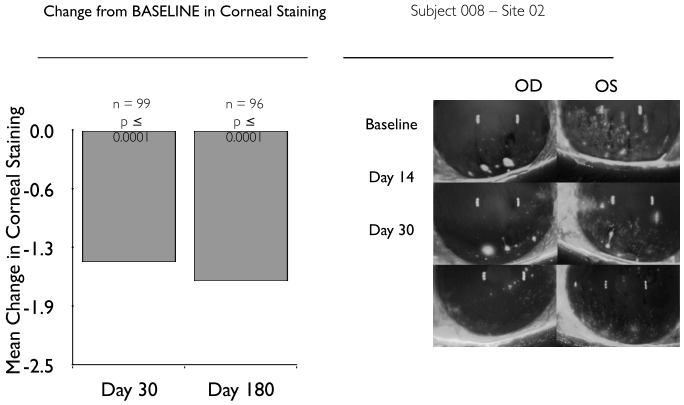
OSDI: ALL SUBJECTS



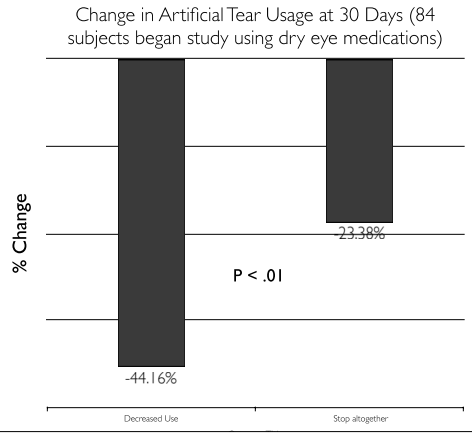
EYE DRYNESS SCORE – VISUAL ANALOGUE SCALE



CORNEAL STAINING



ARTIFICIAL TEAR USAGE



68

ADVERSE EVENTS – TRANSIENT AND MILD

	Relatedness	Impact on Usage	Severity
Headache, sneezing	Related	None	mild
Light Headed, Dizziness	Possibly	None	mild
Stye	Possibly	None	mild
Itching	Possibly	Discontinued	moderate
Temporal Pain	Possibly	Brief Interruption	mild
Nasal Pain	Related	None	mild
Headache	Possibly	None	mild
Dry eye pain	Possibly	None	mild

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Oyster Point Pharma's OC-01/OC-02 for the Treatment of Signs and Symptoms of Dry Eye Disease (DED) Administered Via a Nasal Spray

- OC-01 and OC-02 are being developed to directly address loss of tear film homeostasis in DED and are delivered as a nasal spray.
- Drug candidates bind to nicotinic acetylcholine receptors (nAChRs), which are located on the trigeminal nerve accessible within the nasal cavity, to stimulate tear film production.
- Trigeminal parasympathetic pathway is well characterized with nerves that innervate the lacrimal functional unit (LFU) including cornea, conjunctiva, accessory lacrimal glands, meibomian glands, and goblet cells[1,2,3]

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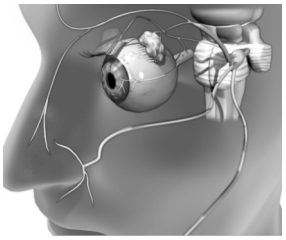
1van der Werf, F. R. A. N. S., Baljet, B., Prins, M. A. A. R. T. E. N., & Otto, J. A. (1996). Innervation of the lacrimal gland in the cynomolgous monkey: a retrograde tracing study. Journal of anatomy, 188(Pt 3), 591.
2LeDoux, M. S., Zhou, Q., Murphy, R. B., Greene, M. L., & Ryan, P. (2001). Parasympathetic innervation of the meibomian glands in rats. Investigative ophthalmology & visual science, 42(11), 2434-2441.
3Dartt, D. A., Mccarthy, D. M., Mercer, H. J., Kessler, T. L., Chung, E. H., & Zieske, J. D. (1995). Localization of nerves adjacent to goblet cells in rat conjunctiva. Current eye research, 14(11), 993-1000.

Trigeminal-Parasympathetic Pathway & DED

- The parasympathetic nervous system (PNS) controls tear film homeostasis
  - 34% of basal tear production is due to inhaled air through the nasal passage[1]
- Efferent parasympathetic nerves innervate the lacrimal functional unit (LFU) including cornea, conjunctiva, accessory lacrimal glands, meibomian glands, and goblet cells[2,3,4]
- Intervention @ the trigeminal-parasympathetic pathway represents a novel approach to producing complete tear film in patients with Dry Eye Disease (DED)



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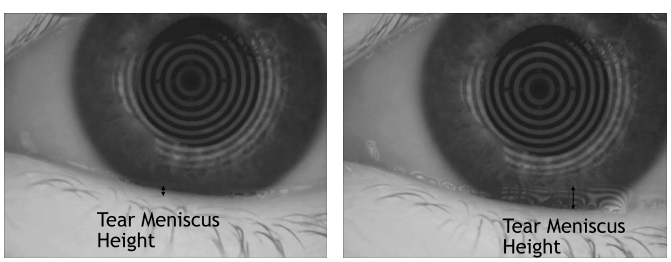
1Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. Cornea. 1997 Nov;16(6):645-8.
2van der Werf, F. R. A. N. S., Baljet, B., Prins, M. A. A. R. T. E. N., & Otto, J. A. (1996). Innervation of the lacrimal gland in the cynomolgous monkey: a retrograde tracing study. Journal of anatomy, 188(Pt 3), 591.
3LeDoux, M. S., Zhou, Q., Murphy, R. B., Greene, M. L., & Ryan, P. (2001). Parasympathetic innervation of the meibomian glands in rats. Investigative ophthalmology & visual science, 42(11), 2434-2441.
4Dartt, D. A., Mccarthy, D. M., Mercer, H. J., Kessler, T. L., Chung, E. H., & Zieske, J. D. (1995). Localization of nerves adjacent to goblet cells in rat conjunctiva. Current eye research, 14(11), 993-1000.

Before and 15 seconds After Administration of OC-02 Nasal Spray



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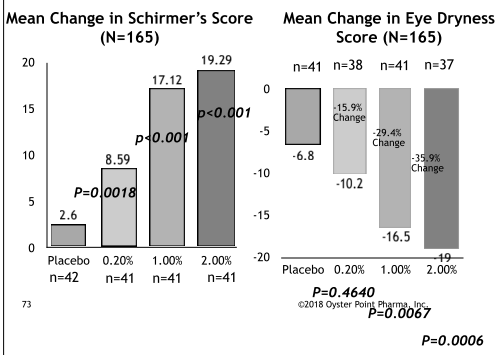
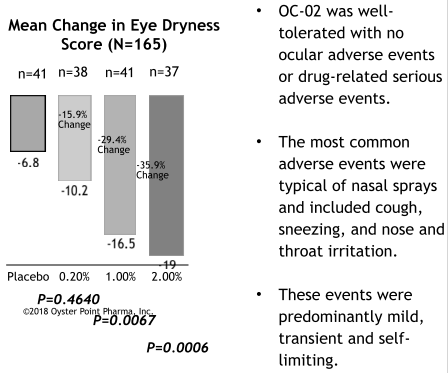
OC-02 Phase 2b Results Demonstrate Significant Improvement in Both Signs and Symptoms of Dry Eye and Clear Dose Response





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- OC-02 was well-tolerated with no ocular adverse events or drug-related serious adverse events.
- The most common adverse events were typical of nasal sprays and included cough, sneezing, and nose and throat irritation.
- These events were predominantly mild, transient and self-limiting.

KLARITY-C

- Compared with Restasis (cyclosporine ophthalmic emulsion) **0.05%**
  - Challenges:
    - Prior authorizations
    - Coupons
    - Call backs
- Klarity-C (Chondroitin sulfate/cyclosporine **0.1%** ophthalmic emulsion PF)

BENEFITS OF CHONDROITIN SULFATE KLARITY BASE

- Enhances patient comfort associated with surgical trauma, contacts, and dry eye
- Provides as a lubricant to the ocular surface[1]
- Contains Chondroitin Sulfate, known to preserve the cornea
- Shown to have anti-inflammatory effects[1,2]

1. Moon W A, Lee H, Shin K C, et al. Short term effects of topical cyclosporine and viscoelastic on the ocular surfaces in patients with dry eye. Korean Journal of Ophthalmology 2007; 21(4):pgs189-194.
2. Llamas-Moreno J F, Baiza-Duran L M, Saucedo-Rodriguez L R, et al. Efficacy and safety of chondroitin sulfate/xanthan gum versus polyethylene glycol/ propylene glycol/hydroxypropyl guar in patients with dry eye. Clinical Ophthalmology 2013; 7:pgs995-999.

Overview of Lotemax SM® Formulation (1 of 2)

A novel formulation of loteprednol etabonate designed to reduce the Lotemax Gel drug concentration (0.38% vs. 0.5%) and dosing frequency (TID vs. QID)

Formulation builds on the heritage and advantages of Lotemax gel 0.5%:

- **Retrometabolically designed corticosteroid[1]**
  - Retains potent anti-inflammatory activity
  - Minimal potential for class AEs
- **Mucoadhesive, non-settling, shear-thinning gel[2,3]**
  - A gel in the bottle; transitions to a liquid upon instillation
  - Transitions to a mucoadhesive liquid on dilution with tears
  - No need to shake (uniform dosing)
  - Non-blurring and comfortable
  - Optimized to stabilize the submicron-sized drug particles

1. Comstock TL, Sheppard JD. *Expert Opin Pharmacother.* 2018;19(4):337-353. **2.** Coffey M, et al. *Clin Ophthalmol.* 2013;7:299-312. **3.** Phillips E, et al. *Invest Ophthalmol Vis Sci.* 2015;56:1525. **4.** Cavet ME et al. *Invest Ophthalmol Vis Sci.* 2015; 56(7):1524.

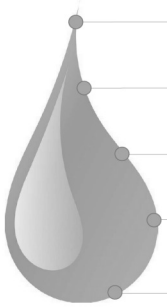
Overview of Lotemax SM® Formulation (2 of 2)

Key new feature:

- **Optimized drug concentration/dosing frequency through reduced drug particle size**
  - Engineered with Submicron Technology
  - Submicron particles increase dissolution and intraocular penetration[1,2]
  - Allows for a simpler dosing regimen (TID) with a reduced concentration of corticosteroid in the formulation[3,4]

1. Phillips E, et al. *Invest Ophthalmol Vis Sci.* 2015;56:1525. **2.** Cavet ME et al. *Invest Ophthalmol Vis Sci.* 2015; 56(7):1524. **3.** Fong R, et al. *J Cataract Ref Surg.* 2018:;44(10):1220-1229. **4.** Vittitow J, et al. *Invest Ophthalmol Vis Sci.* 2018; 59(9):2235.

Lotemax SM® Formulation Attributes



1 Mucoadhesive technology
Polycarbophil imparts formulation with its gel structure and functions as a muco-adhesive enabling LE gel 0.38% to convert from a gel to a viscous fluid upon instillation to the eye prolonging exposure for improved penetration.

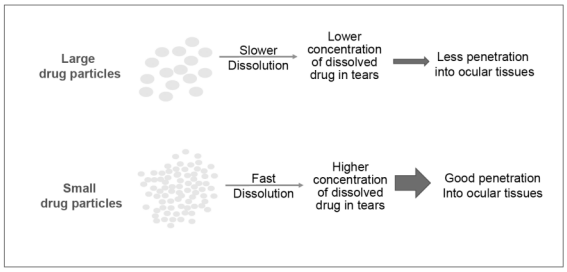
2 Dose uniformity
Shaking the bottle is not required to resuspend the drug, so a consistent concentration of loteprednol etabonate is delivered in every drop of LE gel 0.38%

3 pH of 6.5
This pH close to that of human tears

4 Low preservative with 2 known moisturizers
LE gel 0.38% contains glycerin and propylene glycol, as well as benzalkonium chloride at 0.003% as preservative

5 Submicron particle size
LE drug particles in the submicron particle range allow for optimal ocular penetration into the aqueous humor while reducing the drug concentration

Smaller Drug Particle Size for Faster Dissolution and Improved Ocular Penetration

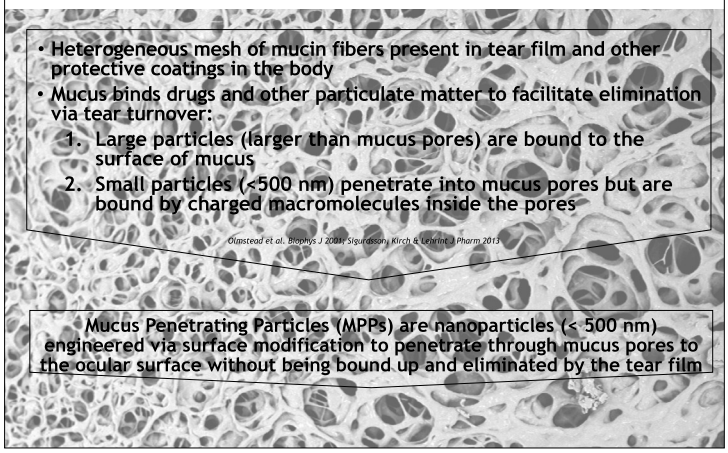


LE particles are ~80% smaller in diameter to facilitate ocular penetration, thus allowing for a decrease in drug concentration and/or dosing frequency

Loteprednol 0.25%: For Dry Eye Flares- October 2020 FDA Approval

- Dry eye is a chronic inflammatory disease with flares that are characterized by acute exacerbations of signs and/or symptoms
- A dry eye flare is a rapid onset, inflammation-driven response to a variety of triggers that typically cannot be adequately managed with the patient's ongoing therapy
- Most dry eye disease patients with or without maintenance dry eye therapy, experience flares and desire rapid relief.
- Regardless of dry eye severity, flares typically occur 4-6 times per year

Mucus – An Innate Defense Mechanism That Can Impair Ocular Drug Delivery

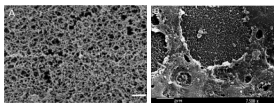


- Heterogeneous mesh of mucin fibers present in tear film and other protective coatings in the body
- Mucus binds drugs and other particulate matter to facilitate elimination via tear turnover:
  1. Large particles (larger than mucus pores) are bound to the surface of mucus
  2. Small particles (<500 nm) penetrate into mucus pores but are bound by charged macromolecules inside the pores

Olanstead et al. Biophys J 2008; Sigurdsson, Kirch & Lehrer. J Pharm 2013

Mucus Penetrating Particles (MPPs) are nanoparticles (< 500 nm) engineered via surface modification to penetrate through mucus pores to the ocular surface without being bound up and eliminated by the tear film

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

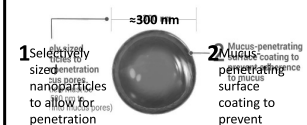


Human airway mucus. Scale bar represents 500 nm.

Microvilli and mucus at the surface of human corneal epithelium.

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

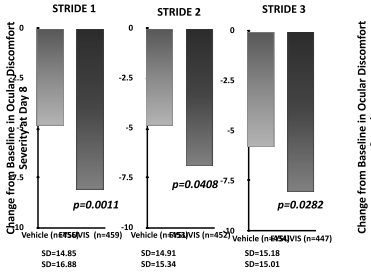
AMPPLIFY® Utilizes Mucus-Penetrating Particles (MPP) With 2 Proprietary Attributes[1-3]



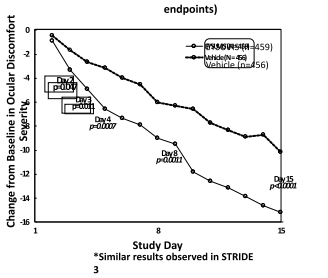
References: 1. Popov A. *J Ocul Pharmcol Ther.* 2020; 36(6): 366-375. **2.** Schopf L, et al. *Ophthalmol Ther.* 2014;3(1-2): 63-72. **3.** Data on file. Kala Pharmaceuticals: Watertown, MA. **4.** Ensign LM, Schneider C, Suk JS, et al. *Adv Mat.* 2012;24(28): 3887-3894.

Rapid Onset of Relief for Ocular Discomfort

Improvements in Day 8 Ocular Discomfort in Phase 3 Trials



Daily Ocular Discomfort Scores from STRIDE 1 (Phase 3) Trial* (Day 4, 8, and 15 pre-specified endpoints)



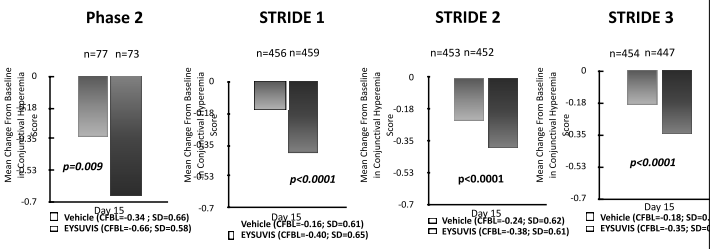
*Similar results observed in STRIDE 3

- Day 8 and 15 were pre-specified efficacy endpoints in STRIDE 1, STRIDE 2 and STRIDE 3
- Day 4, Day 8 and Day 15 were pre-specified efficacy endpoints in STRIDE 1
- p values for the Day 8 and day 15 results in each study are derived comparing the 3 day mean following Day 1 (days 2, 3 and 4) and the 3 day mean prior to Day 8 (Days 5, 6 and 7) and the 3 day mean prior to Day 15 (days 12, 13 and 14) compared to the 3 day mean prior to Day 1 (Baseline)
- The daily ocular discomfort change from baseline data presented in the graph on the right are derived comparing the single day data from each time point to the 3 day mean prior to Day 1 (baseline)

References: 1. Data on file. Kala Pharmaceuticals. Watertown, MA. **2.** Baudouin C et al. Clinical impact of inflammation in dry eye disease: proceedings of the ODISSEY group meeting. *Acta Ophthalmol.* 2018;96(2):111-119. doi:10.1111/aos.13436

Significantly Reduced Conjunctival Hyperemia, a Hallmark Sign of Inflammation[1,2]

Mean Change from Baseline (CFBL) in Conjunctival Hyperemia at Day 15*

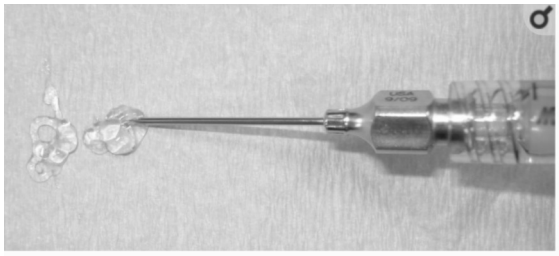


*Change from baseline in Conjunctival Hyperemia at Day 15 was a primary endpoint in STRIDE 1 and STRIDE 2 and a secondary endpoint in the Phase 2 and STRIDE 3 trials.

References: 1. Data on file. Kala Pharmaceuticals. Watertown, MA. **2.** Baudouin C et al. Clinical impact of inflammation in dry eye disease: proceedings of the ODISSEY group meeting. *Acta Ophthalmol.* 2018;96(2):111-119. doi:10.1111/aos.13436

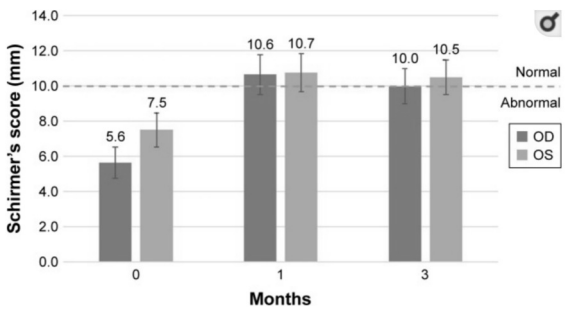
Punctal Occlusion

- May wait on punctal occlusion if have:
  - Allergies
  - Severe MGD
  - Significant blepharitis
  - Inflammatory dry eye?
- Treat those conditions first then plug
- Ideal FIRST treatment option for:
  - Neurotrophic keratopathy
  - Post-LASIK dry eye
  - Lagophthalmos



87

Figure 4



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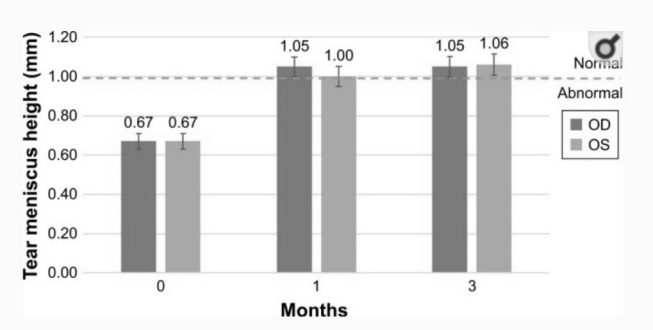

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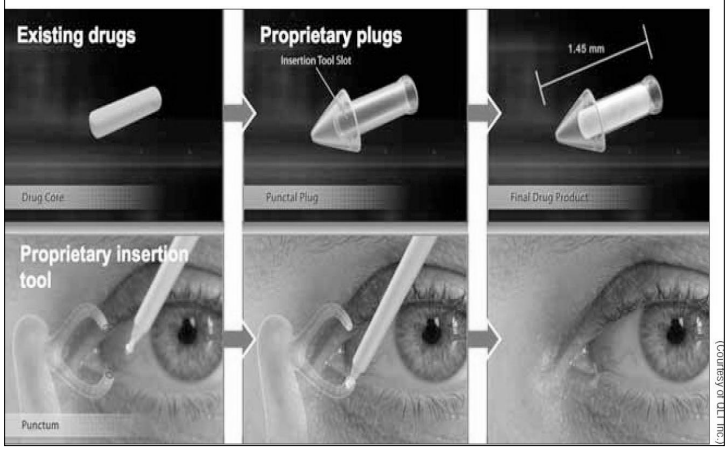
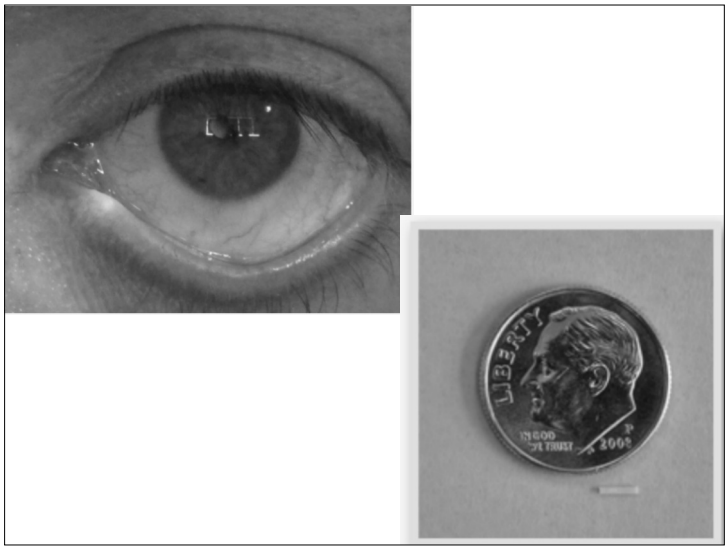
Drug Delivery Advances

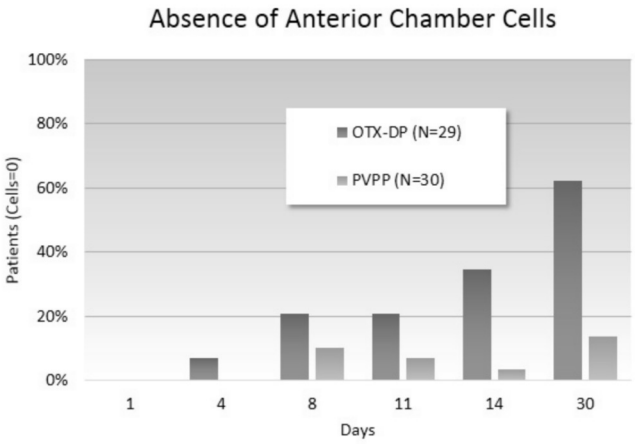


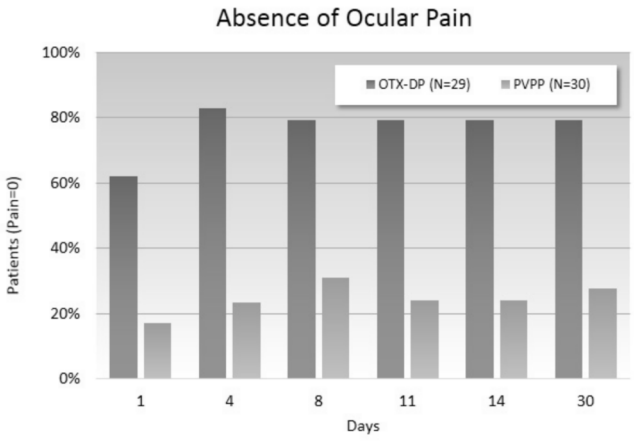
(Courtesy of QLT Inc.)

Punctal Plug Drug Deliver

- Dextenza post cataract
- Dextenza for allergic conjunctivitis
- Sustained release Travoprost
- Dry eye therapy via a punctal plug







Phase III Punctal Plug Drug Deliver

- Evolute
- 94% retention rates in clinical study
- Statistical improvement in inflammation and pain following cataract surgery with only an NSAID within the plug

ACTH Gel Storage and Handling for Administration

ACTH injectable offers flexible dosing for patients and providers

- ACTH (IM or SC) can be given by a caregiver or self-administered, offering patients flexibility to administer it at home or wherever is best for them
  - ACTH Gel is supplied as a 5-mL multi-dose vial (63004-8710-1) containing 80 USP units per mL
  - ACTH Gel should be stored under refrigeration between 2°C and 8°C (36°F-46°F)
    - Is a gel when refrigerated; vials should be warmed to room temperature before using

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Patient Presentation

Patient Demographics (n=91)

- Mean age, 41±14 years (range, 11-78 years)
- Women, n=56 (62%)
- Patients were primarily:
  - Caucasian (n=42; 46%)
  - African American (n=29; 32%)
  - Hispanic/Latino (n=8; 9%)
  - Asian, (n=5 ;5%)
- 69% of patients had 1 or more comorbidities typically associated with uveitis

Uveitis Characteristics (n=91)

- Anatomic presentation
  - Anterior uveitis (n=38; 42%)
  - Intermediate uveitis (n=19; 21%)
  - Posterior uveitis (n=9; 21%)
  - Diffuse uveitis/panuveitis (n=15; 16%)
- Both eyes affected in 59% of cases
- Mean duration of uveitis diagnosis, 3.98 years
- Mean number of acute episodes, 3.5
- Symptom severity
  - Moderate (n=63; 69%)
  - Severe (n=23; 25%)

Observations and Assessments

- ACTH was used for the first time by 83/91 (91%) of patients
- At the time of data collection, Acthar treatment was ongoing at the initial dose in 27 patients (30%), with a mean duration of 16.7 weeks

Physicians' response to:

What is the patient's current status?

- Patients improved, n=76 (84%)
- Patients were same, n= 15 (16%)

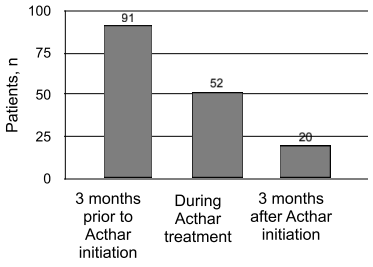
Physician assessment in response to:

Please select the outcomes below that have improved as a result of Acthar treatment

Respondents selected all options that apply	n (%)
Improvements in vision	78 (86)
Improvements in eye pain	25 (27)
Improvements in vitreous haze	24 (26)
Reduction of background medication use	22 (24)
Improvements in vitreous flare	21 (23)
Improvements in macular edema	16 (18)

Additional Observations

Concomitant Medication Use Before, During, and Following the Start of ACTH therapy



Nelson WW, et al. *J Ocul Pharmacol Ther.* 2019 Jan 24. doi: 10.1089/jop.2018.0090. [Epub ahead of print].

- Prior to Acthar initiation, all 91 patients were receiving concomitant medications for uveitis
- Concomitant medications used by ≥20% of patients in the 3 months prior to Acthar initiation included steroid eye drops, oral steroids, intraocular steroids, and nonsteroid eye drops
- The number of patients treated with concomitant medications decreased during Acthar treatment, and during the 3 months following the initiation of Acthar therapy

ACTH Patient Selection: 4 R's

- Recalcitrant (uveitis, keratitis, scleritis etc,)
- Rebound (slow taper recurrence)
- Responders (steroid)
- Reimbursement

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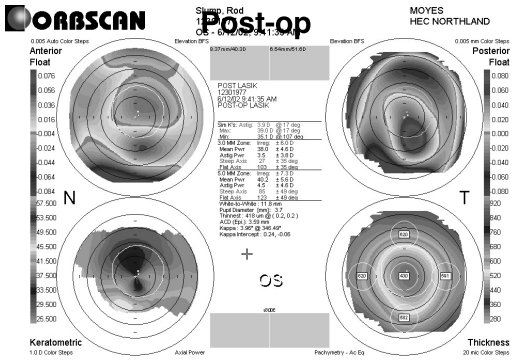
Collagen Cross Linking (CXL) for Keratoconus

Ectasia Diagnosis and Management



Corneal Cross-Linking

- First introduced by Theo Seiler MD
- Involves saturating the cornea with riboflavin (Vit B2)
- Expose cornea to UV light (370 nm) for 30 minutes
- Riboflavin absorbs UV light and produces singlet oxygen
- Causes cross-linking of collagen fibers and extracellular matrix proteins
- To protect the endothelium:
  - Soak cornea for 30 minutes prior
  - Originally required debridement of corneal epithelium
  - Ensure riboflavin has penetrated to the AC

Corneal Cross-Linking

- Riboflavin prevents penetration of uv light
- Older corneas vs. younger corneas and progression of keratoconus
- CXL appears to be the first technology than can halt the progression of ectasia

Corneal Cross-Linking

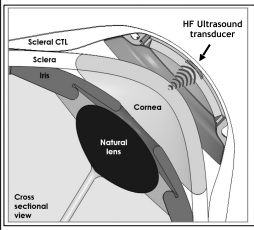
Other potential applications

- Physician sponsored IND for infectious keratitis treatment
  - Ulcers limited to 250 microns
  - May also help with infectious load
- Treatment of corneal edema
  - Cross linking reduces imbibition pressure
  - Internationally it appears to work for 3 mo to 12 mo duration
- Treatment for fluctuating vision post RK

On-Eye Crosslinking: Comfort and Control

Scleral CTL with fiber optic UV delivery

- Eyes open/closed for comfort
- Eliminates motion challenges
- Customized treatment
- Small touchscreen control



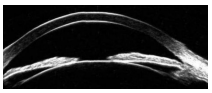
Closed-loop ultrasound elastography feedback control

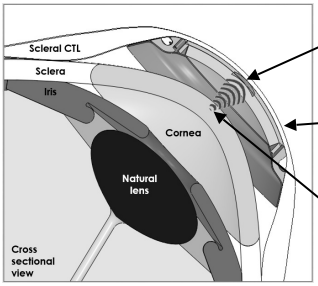
- Accurately measure pre-treatment corneal biomechanics
- CXL induced tissue changes monitored in real time
- UV transparent fluid interface provides acoustic medium and oxygen supply

Ultrasonic Dosimetry (Patents Pending)

Accurate dosing of the UV requires monitoring corneal changes during the treatment

- The cornea is an ideal tissue to query with ultrasound
- Only CXLens' on-eye delivery of UV enables real time ultrasonic dosimetry





- CXLens® UV delivery system design includes a high frequency (HF) ultrasonic transducer within the optical diffuser
- Positional stability of scleral lens enables precise acoustic measurement of ophthalmic structures
- Doppler capability allows assessment of stiffness of corneal membrane

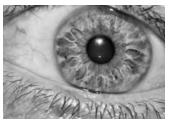
TECLens Approach to Vision Correction

CXLens® - Crosslinking Lens

- CXLens® is single use ultraviolet energy delivery and ultrasound monitoring system built into a scleral contact lens.
- Placed directly on the eye, this next generation CCXL technology enables a multitude of superior capabilities and advantages.

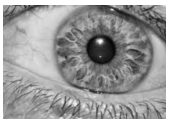
CXLens® Non-Surgical Vision Correction

Myopia
- Crosslink the center of the cornea to stiffen (and thus flatten) the central region



Hyperopia
- Create annular crosslinked region to flatten periphery and steepen center

Astigmatism
- Create a custom 'butterfly' pattern to flatten areas that are aspherically too steep



Proprietary & Confidential

(C)Copyright 2016 TECLens, LLC

Drug Therapy for keratoconus

- IVMED-80
- Phase IIb trials were positive with >1.8D improvement
- Entering phase III clinical studies
- MOA: Upregulates lysyl oxidase (LOX) and induces corneal crosslinking pharmacologically

Presbyopia Correction

- Accommodating IOLs
- Multifocal IOLs
- Corneal Inlay Technology
- Scleral expansion
- Pharmaceutical agents/eye drops

Presbyopia Correction

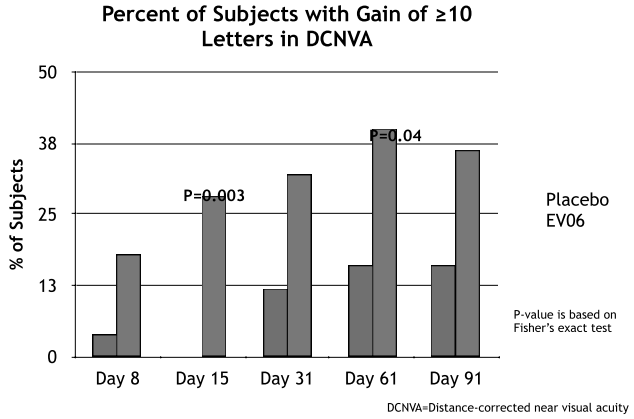
- Accommodating IOLs
- Multifocal IOLs
- Corneal Inlay Technology
- Scleral expansion
- Pharmaceutical agents/eye drops

Elongation Of Focus

[1] Data on File. Tecnis Symfony Green Light Bundle Bench Test DOF2014CT0005. Abbott Medical Optics Inc. 2014

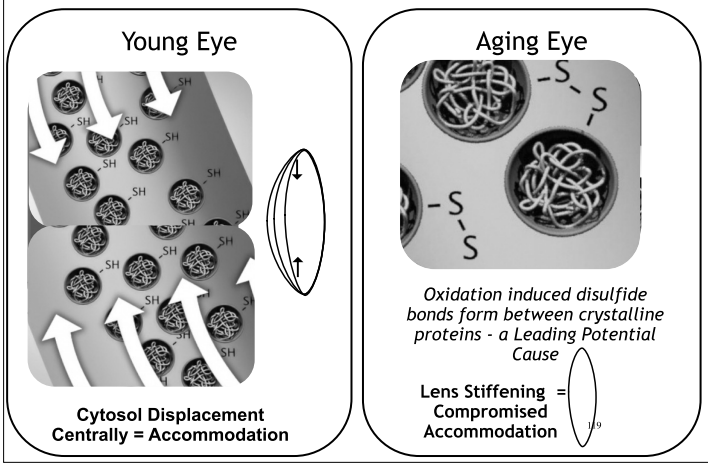
Topical Treatment for Presbyopia

- Pupil Modulation
  - Contains miotics but also proprietary components that allow full 12-14 hours of near and far vision
- Lens softening
  - Contains drops that selectively target and disrupt the disulfide bonds in the lens
  - Total of 3-4 weeks of treatment and permanent results thus far



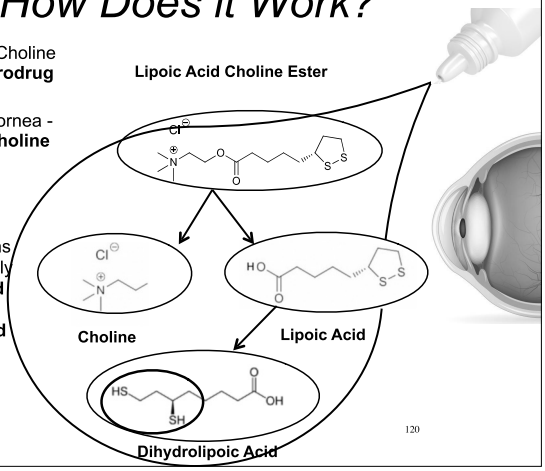
Note: Preliminary analysis based on LOCF in study eye only

How Is Accommodation Lost?



What is EV06?
How Does it Work?

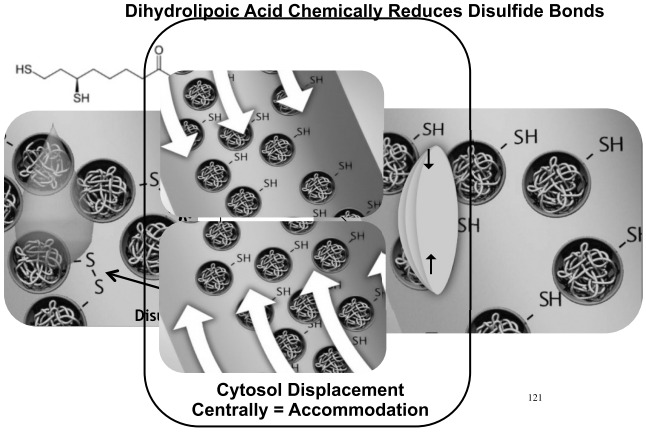
- EV06 (Lipoic Acid Choline Ester, 1.5%) is a **prodrug**
- EV06 penetrates cornea - metabolized into **Choline & Lipoic Acid**, two naturally occurring substances
- Enzymes within lens fiber cells chemically reduce **Lipoic Acid** to active form **Dihydrolipoic Acid**



LENS ELASTICITY IS REGAINED

Dihydrolipoic Acid

Dihydrolipoic Acid Chemically Reduces Disulfide Bonds



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EV06 Safety & Tolerance Results

- No Subjects Discontinued For Adverse Events, Safety Concerns, or Tolerability
- No Sight Related Adverse Events
- Upon Instillation
  - Mean EV06 Comfort Rating 3.0
  - Mean Placebo Comfort Rating 2.7
    - (Scale 0 – 10; "0" = Very Comfortable)
- No Change In Best Corrected Distance Visual Acuity

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EV06 Efficacy Results

- Achieved both Primary Efficacy Results:
  - Improvement in Distance Corrected Near Vision Acuity (DCNVA) in the Study Eye after treatment, which continued throughout the dosing period
  - Higher proportion of subjects with gain of ≥10 letters in DCNVA in the study eye vs. placebo

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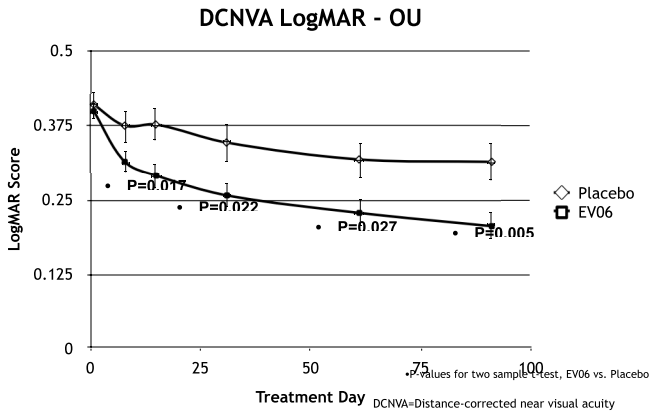
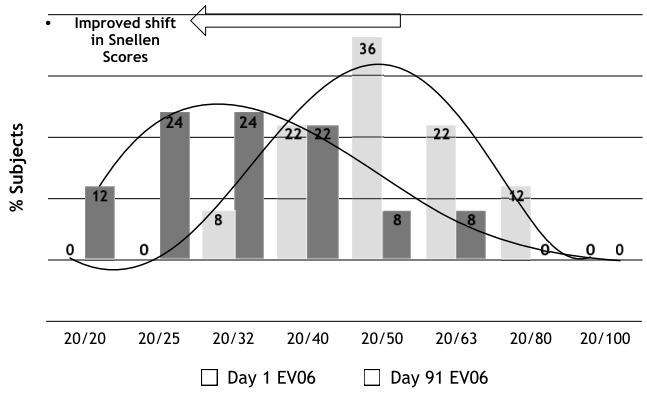
Improvement in Distance Corrected Near Vision Acuity



•P-values for two sample t-test, EV06 vs. Placebo

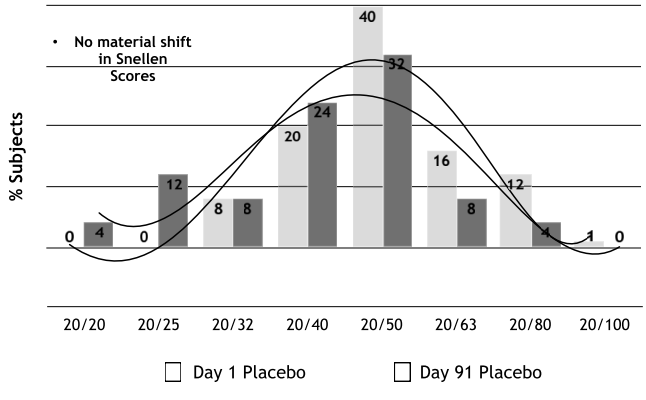
DCNVA=Distance-corrected near visual acuity

• • EV06 DCNVA Snellen score - Day 1 & Day 91



• 125

• • Placebo DCNVA Snellen score - Day 1 & Day 91



• 126

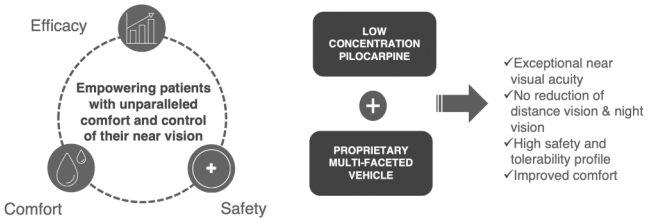
Companies working on Pupil Modulation Therapies for Presbyopia with approvals beginning in 2021

- Allergan (pilo 1.25%)
- Orasis (low dose pilo)
- Eyenovia (pilo 1 or 2 %) with unique 8uL dispenser
- Presbyopia Therapies (acelcedine + tropicamide)
- Visus pharmaceuticals (carbechol + brimonidine)
- Ocuphire (nyxol + low dose pilo)

Future presbyopia drops: miotics

Orasis Pupil Modulation Eye Drop Solution

Demonstrated Efficacy, Safety and Comfort in Phase 2b Studies



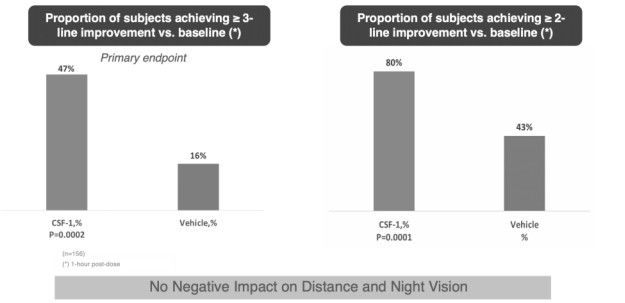
Phase 2b Study Design

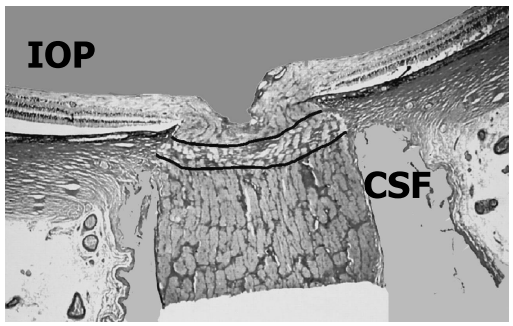
- Parallel-group study (active, vehicle)
- Primary endpoint: 3-line improvement in near visual acuity
- Secondary endpoints: 2-line improvement (near); impact on distance and night vision, various safety and tolerability endpoints

166 subjects

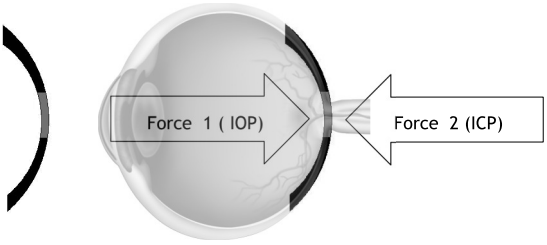
- BID Administration
- Duration – 2 weeks
- Assessments – end of week 1 and end of week 2

Phase 2b demonstrated Efficacy, Safety & Comfort

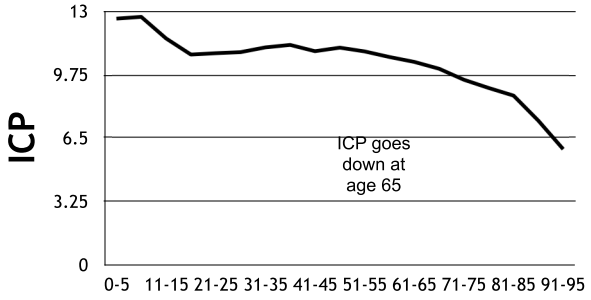




Jonas JB, Berenshtein E, Holbach L.Anatomic relationship between lamina cribrosa, intraocular space, and cerebrospinal fluid space. Invest Ophthalmol Vis Sci. 2003 Dec;44(12):5189-95.

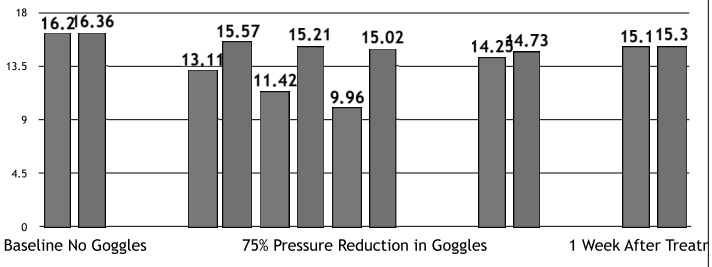


ICP changes with age



Solution?

Intraocular Pressure (mmHg) Reduction With Goggle Compared to Contralateral Control Eye (Consistent Cohort, n=51)

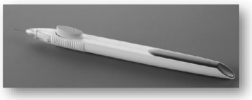


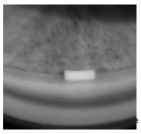
Goggle Eye IOP
Control Eye IOP

Bimatoprost SR

Bimatoprost SR

- A biodegradable bimatoprost sustained-release implant (Bimatoprost SR) addresses the problem of nonadherence in glaucoma
- The implant is placed intracamerally and was designed to deliver a slow release of bimatoprost for IOP lowering over a period of 4–6 months
- Bimatoprost SR is administered using a prefilled, single-use applicator system





2 Weeks Post-injection

- A single intracameral administration of bimatoprost implant 10 µg (Durysta, AbbVie Inc, North Chicago, IL) was approved by the US Food and Drug Administration (FDA) in March 2020 for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT)

Supplied preloaded in a single-use applicator with a 28-gauge needle

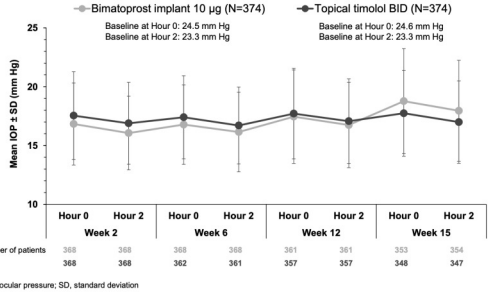
- Who may be candidates for a single administration of bimatoprost implant?
  - Individuals who have difficulty remembering to use eye drops, have difficulty instilling them, or cannot tolerate them
  - Individuals who would like to extend a "drop holiday" before and after selective laser trabeculoplasty (SLT)
  - Individuals with ocular surface problems or whose ocular surface should be spared from drops, such as before ocular surgery

Objective

- To report efficacy and safety outcomes after a single administration of bimatoprost implant 10 µg in patients with OAG and OHT (the currently FDA-approved dose/indication) in phase 1/2 and phase 3 studies

Phase 3 ARTEMIS: Mean IOP Through Week 15 Following a Single 10-µg Implant Administration

- In the pooled phase 3 ARTEMIS 1 and 2 studies, IOP continued to be reduced substantially at Week 15 (last IOP measurement before the second administration), when only 2.1% of implant-treated study eyes had been rescued with topical medication and, therefore, were excluded from the IOP analysis
- The mean (SD) change in IOP from baseline (Hour 0) in implant-treated eyes was −7.0 (3.8) mm Hg at Week 12 and −5.6 (4.1) mm Hg at Week 15



BID, twice daily, IOP, intraocular pressure; SD, standard deviation

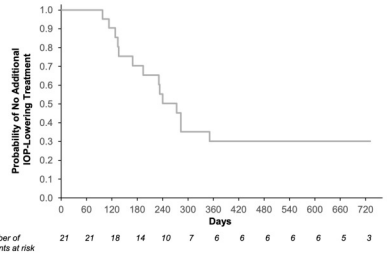
Phase 3 ARTEMIS: Study Eye Adverse Events by Time of Onset or Worsening (Incidence ≥1%)

AE	Number of Patients (%)			
	AE Within 2 Days After Administration		AE >2 Days After Administration	
	Bimatoprost Implant (N=372)	Timolol BID (N=370)	Bimatoprost Implant (N=372)	Timolol BID (N=370)
Any AE	131 (35.2)	93 (25.1)	62 (16.7)	48 (13.0)
Conjunctival hyperemia	66 (17.7)	40 (10.8)	19 (5.1)	11 (3.0)
Eye pain	21 (5.6)	10 (2.7)	2 (0.5)	1 (0.3)
Foreign body sensation	20 (5.4)	9 (2.4)	5 (1.3)	0
Eye irritation	16 (4.3)	16 (4.3)	3 (0.8)	2 (0.5)
Punctate keratitis	13 (3.5)	9 (2.4)	1 (0.3)	3 (0.8)
Vision blurred	13 (3.5)	7 (1.9)	1 (0.3)	1 (0.3)
Photophobia	12 (3.2)	2 (0.5)	3 (0.8)	0
Conjunctival hemorrhage	11 (3.0)	13 (3.5)	0	0
Lacrimation increased	7 (1.9)	9 (2.4)	1 (0.3)	0
Dry eye	5 (1.3)	5 (1.4)	7 (1.9)	4 (1.1)
Iritis	5 (1.3)	0	4 (1.1)	0
Anterior chamber cell	4 (1.1)	0	2 (0.5)	0
Eyelid edema	1 (0.3)	4 (1.1)	0	0
Eyelid erythema	1 (0.3)	4 (1.1)	1 (0.3)	0
IOP increased	0	1 (0.3)	4 (1.1)	4 (1.1)

All study eye AEs reported in ≥1% of patients up to 16 weeks after a single administration of 10-µg bimatoprost implant or sham administration are listed
AE, treatment-emergent adverse event; BID, twice daily; IOP, intraocular pressure

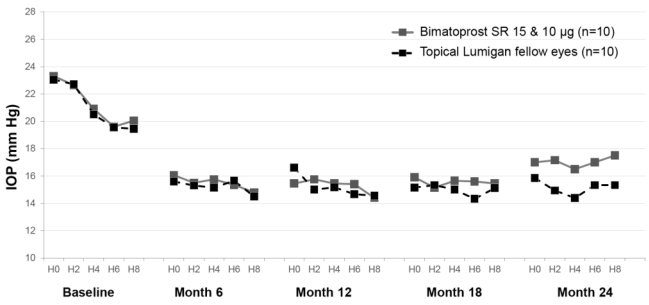
Phase 1/2 APOLLO: Time to Rescue or Retreatment After A Single 10-µg implant (N=21)

- Five of the 21 patients (24%) completed the study without requiring any additional IOP-lowering treatment in the study eye
- In Kaplan-Meier analysis, the median time to use of additional IOP-lowering treatment was 273 days (approximately **9 months**)
- The estimated probability of not needing additional IOP-lowering treatment was **30%** at 1 and 2 years after implant administration



IOP, intraocular pressure

Diurnal IOP after single Bimatoprost SR treatment



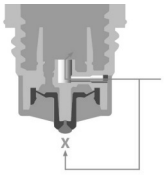
SIMPLE DROPS

- Offers a preservative-free treatment regimen for your patients
- Provides convenience of multiple medications into one combination drop
- May increase patient compliance by reducing the number of drops taken per day
- May reduce costs to your patients with a low monthly cost

PRESERVATIVE-FREE DROPS

All Simple Drops compounded formulations are made preservative-free.

- Products with preservatives may cause adverse reactions such as superficial punctate keratitis, corneal erosion, and conjunctival allergy[4,5]
- Discomfort associated with adverse symptoms can lead to decreased compliance and/or discontinuation of treatment[5]
- Reducing the exposure to preservatives involves reducing the number of drops and/or removing the preservatives completely



4. Inoue, K. Managing adverse effects of glaucoma medications. Clinical Ophthalmology 2014; 8: 903-913.
5. Bagnis, A, Papadia, M, Scotto, R, Traverso, C. Antiglaucoma drugs: The role of preservative-free formulations. Saudi Journal of Ophthalmology 2011; 25(4): 389-394.

GLAUCOMA FORMULATIONS

SIMPLE DROPS COMPOUNDED FORMULATIONS

Topical Offerings	Size
Latanoprost 0.005% PF	7.5mL
Dorzolamide 2% PF	10mL
Dorzolamide 2%/Timolol 0.5%	10mL mL
Timolol 0.5%/Latanoprost 0.005% PF	5mL
Brimonidine 0.15%/Dorzolamide 2% PF	10mL
Timolol 0.5%/Dorzolamide 2%/Latanoprost 0.005% PF	5mL
Timolol 0.5%/Brimonidine 0.15%/Dorzolamide 2% PF	10mL
Timolol 0.5%/Brimonidine 0.15%/Dorzolamide 2%/ Latanoprost 0.005% PF	5mL

MEDICATIONS FOR GLAUCOMA

- **Duo Glaucoma Drop**
  –Latanoprost and timolol
- **Triple Glaucoma Drop**
  –Timolol, bromonidine and dorzolamide
- **Quad Glaucoma Drop**
  –Brimonidine, dorzolamide, latanoprost and timolol

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Gene Therapy & Genomics

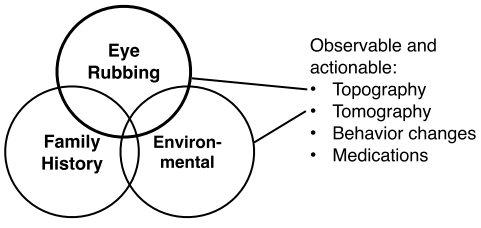
- Generic variants causing most ocular diseases are being discovered
- Examples include glaucoma, dry AMD, Fuchs' and all corneal dystrophies
- Early treatment vs. repair
- Prevention of disease progression (e.g. Avellino Labs)
- Ocular anatomy and architecture are uniquely situated for gene based research

Genetic Testing is here

Why a Genetic Test for Keratoconus?

Don't we already know the etiology?

- Relies on patient memory
- May not be accurate or relevant



Observable and actionable:
- Topography
- Tomography
- Behavior changes
- Medications

There is no one gene responsible for the development of keratoconus but **there is a strong genetic component or link within each group.**[1]

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1. Gordon-Shaag A, et al. BioMed Res Int. Volume 2015, Article ID 795739, 19 pages.

Global Keratoconus Risk 2019

Millions of patients are at risk based on corneal curvature alone

309,000,000
Patients with >46D corneal curvature or >2D cylinder

1,700,000
Between ages 15-30 yrs old

90%
Live in Asia-Pacific Countries
60% in India and China

15

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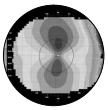
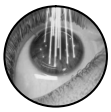
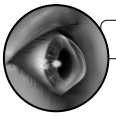
Identifying At Risk Patients

Patients with higher than normal risk for triggering or natural progression of disease

- Patients with >47D cc and/or >2D astigmatism
- Contact Lens and Ortho-K Candidates
- Refractive Surgery Candidates
- Family History of Keratoconus







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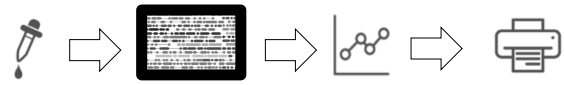
Using Genetic Testing to Identify Patients at Risk



Extraction → Sequencing → Referencing and Variant Risk Scores → Patient Report

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Reading Results

- **98% Accuracy** in detecting targeted genes and variants – Proven in CLIA validation, September 2019
- All variants carry a risk. If it's on the report, some level of risk is identified.
- Negative result = no risk variants found.

KC

Gene	Transcript	cDNA	Zygosity	AA Change	RiskScore†	Relative Risk
[redacted]	NM_000093.4	c.C4135T	Homozygous	p.P1379S	68.45	High Risk
[redacted]	NM_000428.2	c.G2344C	Homozygous	p.E782Q	42.3	Medium Risk
[redacted]	NM_000428.2	c.G2326A	Homozygous	p.V776I	39.23	Low Risk
[redacted]	NM_001127464.1	c.C8260T	Homozygous	p.H2754Y	37.36	Low Risk
[redacted]	NM_001127464.1	c.G8272A	Homozygous	p.E2758K	40.38	Medium Risk

Risk Score Reference Bar:

0 20 40 60 80 100

Very Low Low Medium High Very High

CD

Gene	Transcript	cDNA	Zygosity	AA Change	Reported phenotype
TGFBI	NM_000358.2	c.1631A>G	Homozygous	p.N544S	Corneal dystrophy, lattice intermediate type I/IIIA

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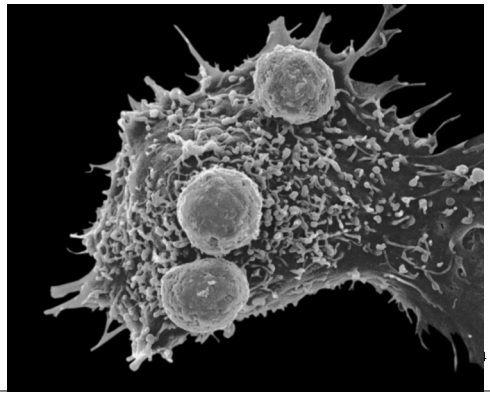
CRISPR Gene Editing and an Adenovirus vector



CRISPR can remove the damaged or faulty genes

Modified Adenovirus can present the proper genetic code to the body for integration

Article | OPEN

Adenoviral vector delivery of RNA-guided CRISPR/Cas9 nuclease complexes induces targeted mutagenesis in a diverse array of human cells

Ignazio Maggio, Maarten Holkers, Jin Liu, Josephine M. Janssen, Xiaoyu Chen & Manuel A. F. V. Gonçalves ✉

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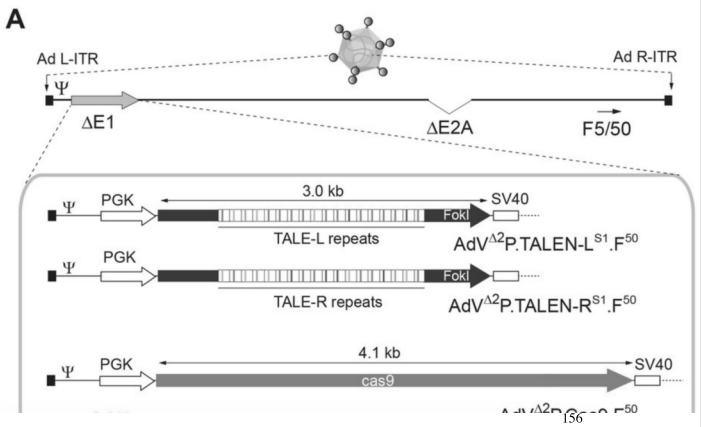
rom: Adenoviral vector delivery of RNA-guided CRISPR/Cas9 nuclease complexes induces targeted mutagenesis diverse array of human cells



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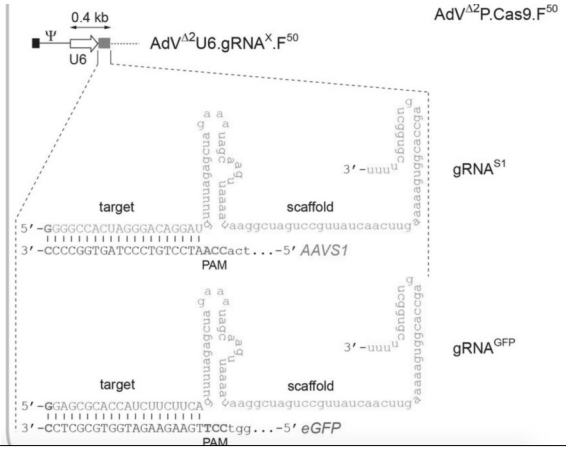
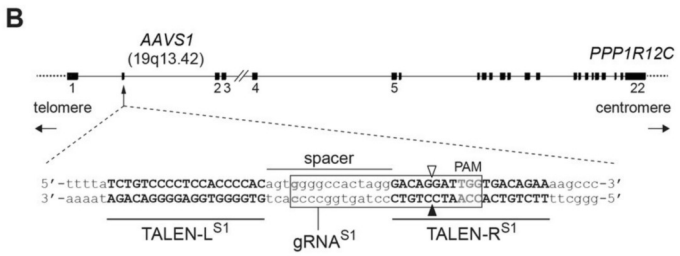
Genetic Treatment for Leber's Optic Neuropathy

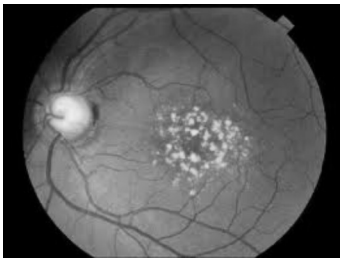


Genetic Treatment for Leber's Optic Neuropathy



AMD Opportunity

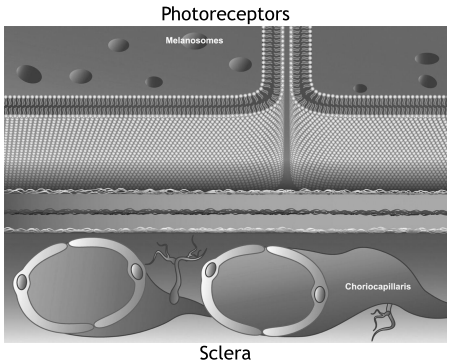
Medical Utility - The AMD Problem



How can the Primary Eye Care Professional identify those at Risk?

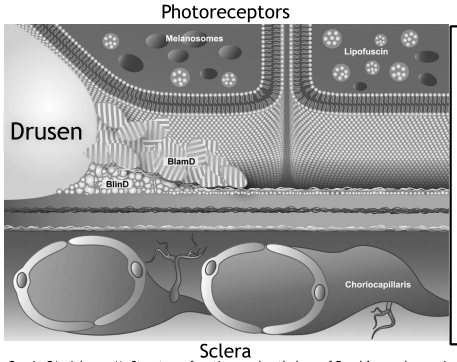
Only 15% to 20% of Early / Intermediate AMD will progress to Advanced disease

Dark Adaptometry



Curcio CA, Johnson M. Structure, function, and pathology of Bruch's membrane. In: Ryan SJ, et al, eds. *Retina, Vol 1, Part 2: Basic Science and Translation to Therapy*. 5th ed. London: Elsevier; 2013:466-481.

Dark Adaptometry



Cholesterol accumulation leads to panmacular deposits (BlinD and BlamD)

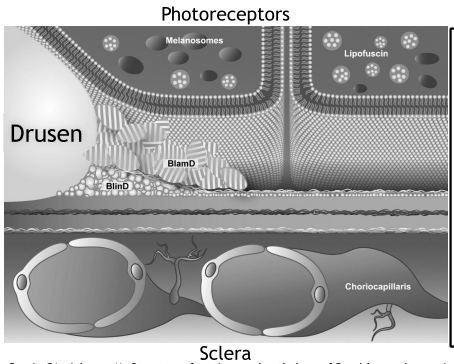
Peaks in these deposits eventually become clinically visible drusen

These extracellular cholesterol deposits affect photoreceptor health by impairing transport, causing inflammation, and predisposing to CNV

In addition, they impair normal transport, including that of vitamin A, across Bruch's membrane

Curcio CA, Johnson M. Structure, function, and pathology of Bruch's membrane. In: Ryan SJ, et al, eds. *Retina, Vol 1, Part 2: Basic Science and Translation to Therapy*. 5th ed. London: Elsevier; 2013:466-481.

Dark Adaptometry



In effect, AMD causes a localized deficiency of vitamin A, and dark adaptation is the best test to measure this change

Curcio CA, Johnson M. Structure, function, and pathology of Bruch's membrane. In: Ryan SJ, et al, eds. *Retina, Vol 1, Part 2: Basic Science and Translation to Therapy*. 5th ed. London: Elsevier; 2013:466-481.

Dark Adaptometry

Dark adaptation is the process of adjusting from day vision to night vision

Easy-to-measure aspect of night vision

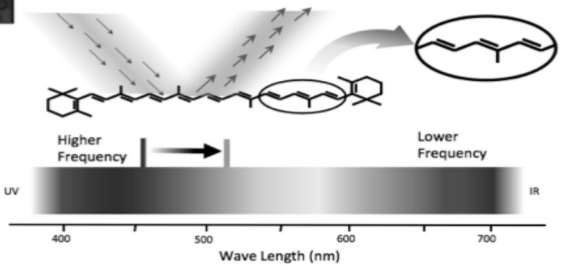
Good for Your Patients, Good for Your Practice

- **CPT Code 92284** for dark adaptation
- $60.03 average national reimbursement
- Monocular testing qualifies for full reimbursement without use of modifier codes
- Co-billable with OCT, imaging and/or visual field
- Multiple ICD-10 codes

Raman Spectroscopy

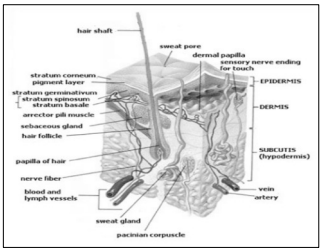
Sir C. V. Raman, Nobel Prize in Physics, 1930

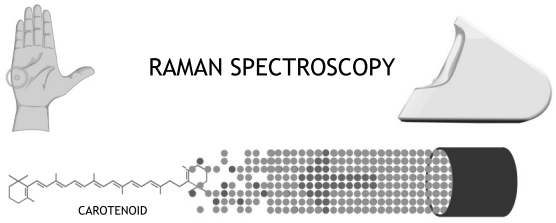
When blue light (at exactly 473 nm) is shined onto carotenoids, the energy of the reflected light is *'shifted'* to green (510 nm) due to a molecular characteristic shared among all carotenoids. This is known as *'Raman shift'*



Skin Carotenoids

- Measured in stratum corneum (0.1 mm) layer of the skin
  - α- and β-Carotenes,
  - Lycopene,
  - Lutein,
  - Zeaxanthin,
  - α-, β-Cryptoxanthin





Resonance Raman spectroscopic evaluation of skin carotenoids as a biomarker of carotenoid status for human studies

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ARTICLE INFO

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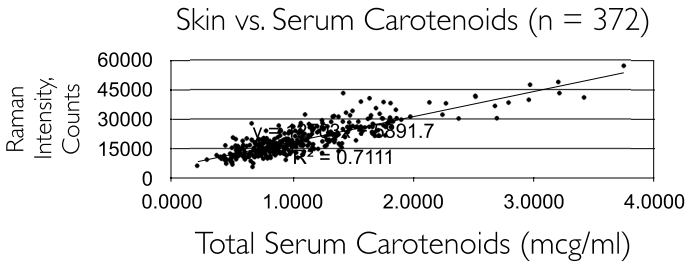
Keywords:
Carotenoids
Skin
Resonance Raman spectroscopy
Beta-carotene
Biomarker

ABSTRACT

Resonance Raman spectroscopy (RRS) is a non-invasive method that has been developed to assess carotenoid status in human tissues including human skin *in vivo*. Skin carotenoid status has been suggested as a promising biomarker for human studies. This manuscript describes research done relevant to the development of this biomarker, including its reproducibility, validity, feasibility for use in field settings, and factors that affect the biomarker such as diet, smoking, and adiposity. Recent studies have evaluated the response of the biomarker to controlled carotenoid interventions, both supplement-based and dietary [e.g., provision of a high-carotenoid fruit and vegetable (F/V)-enriched diet], demonstrating consistent response to intervention. The totality of evidence supports the use of skin carotenoid status as an objective biomarker of F/V intake, although in the cross-sectional setting, diet explains only some of the variation in this biomarker. However, this limitation is also a strength in that skin carotenoids may effectively serve as an integrated biomarker of health, with higher status reflecting greater F/V intake, lack of smoking, and lack of adiposity. Thus, this biomarker holds promise as both a health biomarker and an objective indicator of F/V intake, supporting its further development and utilization for medical and public health purposes.

*Arch Biochem Biophys. PMC 2014 M

Initial Study: Correlation study of skin carotenoids and serum carotenoid levels ; r = 0.84 (p<0.0001)



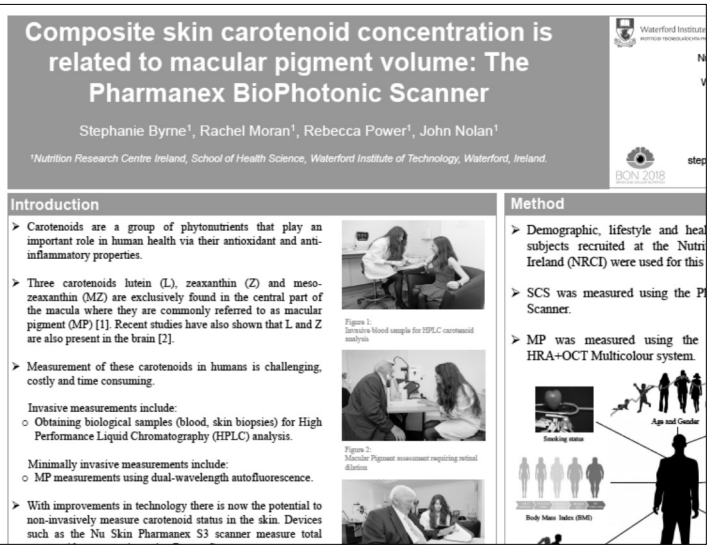
ARVO 2016
RESEARCH: A VISION OF HOPE MAY 1 – 5 | SEATTLE

Interrelationships between Macular, Skin, and Serum Carotenoids Tue, May 03

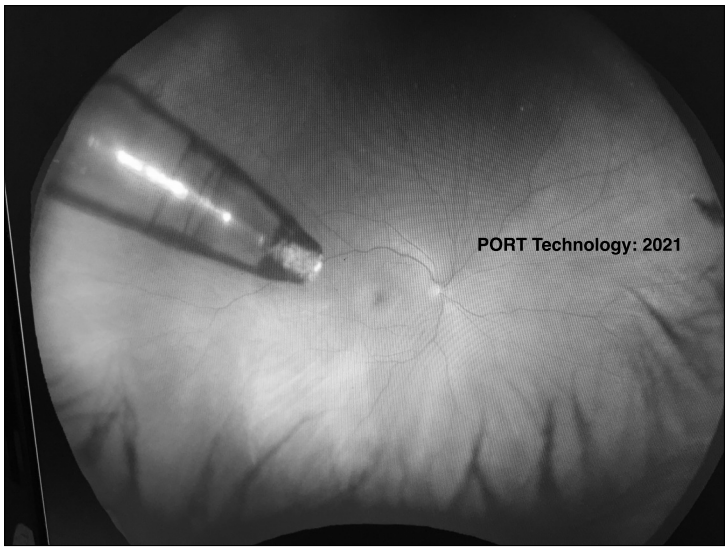
Author Block: *Christopher D. Conrady[1], James E. Bell[1], Brian M. Besch[1], Aruna Gorusupudi[1], Werner Gellermann[1], Kelliann Farnsworth[1], Paul S. Bernstein[1]*
[1] Ophthalmology, University of Utah - Moran Eye Center, Salt Lake City, Utah, United States

Conclusion:

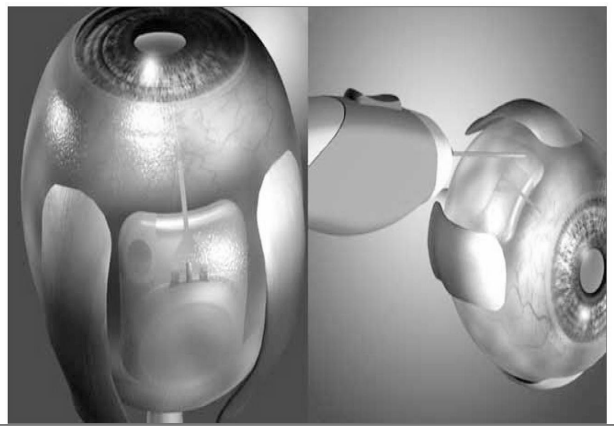
"Skin RRS is a reasonable biomarker of macular carotenoid status that can be readily performed in a wide variety of research, clinical, and non-clinical settings."



- Proven to assist with Bluelight absorption
- Key ingredients include billberry, DHA/EPA, astrazanthin, key carotenoids, vitamin E etc.



Drug Delivery Advances



Adverum Biotechnologies	**ADVM-022**	wAMD	Gene therapy
Alkahest	**AKST4290**	wAMD	Inhibit the negative biological chronokines that increase with age
AsclepiX Therapeutics	**AXT107**	wAMD	A peptide derived from the non-collagenous domain of collagen IV, which inhibits VEGF and activates Tie2
Graybug Vision	**GB-102**	wAMD	Sunitinib malate aimed at reducing intravitreal injections to 2x per year in patients with wet AMD currently managed with anti-VEGF.
Graybug Vision	**GB-103**	wAMD	Formulated to elute sunitinib over a longer duration that may enable once yearly dosing instead of twice yearly dosing
Ophthotech Corp.	**Zimura**	wAMD	inhibit the complement protein C5 preventing inflammasone formation
Outlook Therapeutics	**ONS-5010**	wAMD	Anti-VEGF
REGENXBIO	**RGX-314**	wAMD	One-time subretinal treatment for wAMD that includes the NAV AAV8 vector containing a gene encoding for a monoclonal antibody fragment. The expressed protein is designed to neutralize VEGF activity.
Replenish	**MicroPump Systems**	wAMD, chronic DME or glaucoma	Small, refillable via injection, implantable ocular drug pump. The pump can be programmed to dispense precise nanoliter-sized doses or medication
Aerie pharmaceuticals	**AR-13503**	wAMD, DME	RhoKinase inhibitor implant

Stealth BioTherapeutics	**elamipretide**	dAMD	A peptide compound that penetrates cell membranes, and targets the inner mitochondrial membrane where it binds reversibly to cardiolipin thus normalizing mitochondrial structure and function
Cell Care Therapeutics		Diabetic retinopathy	using stem cell components to harness the patient's immune system to drive the resolution of the inflammatory process and initiates tissue remodeling leading to the stabilization and recovery of retinal neurovascular tissue
Allegro Pharma	**Risuteganib**	DME	Integrin peptide
AsclepiX Therapeutics	**AXT107**	DME	A peptide derived from the non-collagenous domain of collagen IV, which inhibits VEGF and activates Tie2
Oculis	**OCS-01**	DME	Dexamethasone cyclodextrin nanoparticle drops, Glucocorticoid receptor agonists; Immunosuppressants
Oxurion	**THR-149**	DME	PKal Inhibitor
Outlook Therapeutics	**ONS-5010**	DME & BRVO	Anti-VEGF
Oxurion	**THR-687**	DR	Pan RGD integrin antagonist
Oxurion (Thrombogenics)	**THR-317**	DR, DME, MacTel	anti-PIGF

Geographic Atrophy

Allergan/AbbVie	**Brim DS device**	Dry AMD/ Geographic Atrophy	Briminodine alpha adrenergic for neuroprotection
Apellis Pharmaceuticals	**APL-2**	Dry AMD/ Geographic Atrophy	First-in-class treatment targeting C3 (Compliment system)
Galderma	**Oracea**	Geographic Atrophy in AMD	Doxycycline to inhibit MMP
Janssen	**CNTO-2476**	Geographic Atrophy in AMD	AMD cell therapy
Iveric	**Zimura**	Geographic Atrophy in AMD	inhibit the complement protein C5 preventing inflammasone formation

Apellis & Iveric Pharmaceuticals

- New drug in phase III FDA trials for geographic atrophy
- Moderate to early stage disease showing the potential for reversal

What if you could keep preservatives in the bottle and off the eye?

Is BAK required for IOP Reduction? - NO

Perception: BAK plays a role in IOP reduction

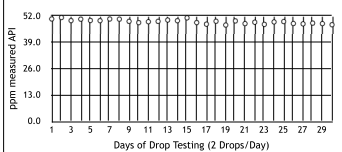
Based on clinical data from nine published studies - Timolol, Dorzolamide/Timolol, Bimatoprost/Timolol, Tafluprost, Travaprost, Latanoprost and Bimatoprost

Efficacy of preservative free product equals the efficacy of BAK-containing products

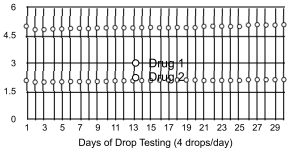
TearClear Glaucoma Drugs:

On target delivery of intended dose through 30-day use (Monotherapy and Combination Drugs)

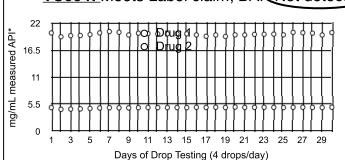
TC002: Meets Label claim; BAK Not detected



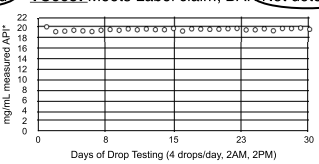
TC003: Meets Label claim; BAK Not detected



TC004: Meets Label claim; BAK Not detected



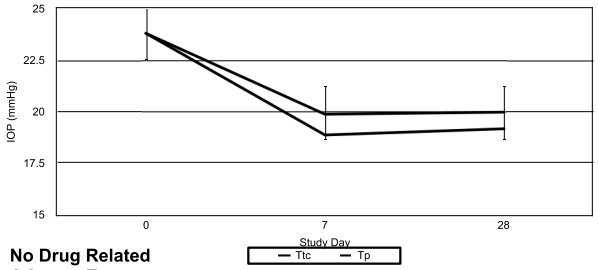
TC005: Meets Label claim; BAK Not detected



Mean values of 6 Bottles

TearClear Timolol OUS Pilot Study

Figure 1. Mean trough intraocular pressure (IOP) at each assessment day



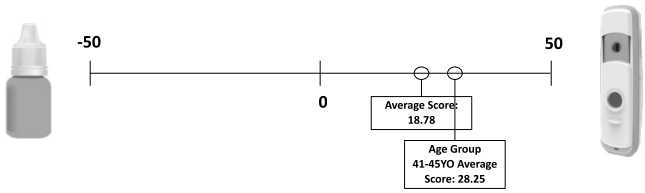
No Drug Related Adverse Events

Customized Materials for Important Indications

TearClear Pipeline

- Glaucoma
  - Beta blockers, prostaglandins, carbonic anhydrase inhibitors, alpha agonists
- Dry Eye
- Allergic Conjunctivitis
- Presbyopia/Myopia
- Post-Op

Respondents Preferred the Optejet® Over the Eyedropper When Asked About Ease of Use, Drug Volume, and User Experience



Adults with presbyopia were asked what medication method they would prefer, based on the Optejet®'s user experience description. Over three quarters of respondents (76%) ranked the Optejet® over the traditional eyedropper. 17 respondents gave the Optejet® a perfect score of 50. In total, over a third (35%) of respondents scored the dispenser a 40 or higher on the -50 to 50 scale.

Allergic Conjunctivitis

Cetirizine

- FDA approval of cetirizine ophthalmic solution 0.24%
- First topical ocular formulation of the antihistamine cetirizine
- First new anti-histamine combo in over a decade

Lastacaft

- True QD drop
- OTC in 2021

Alaway

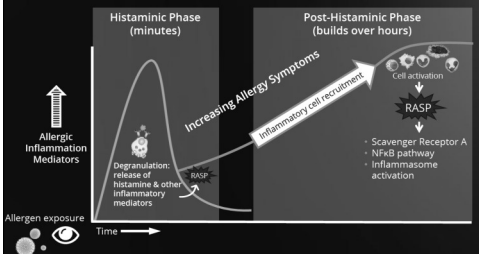
- Preservative-free OTC in 2021

Allergic Conjunctivitis

Reproxalap

- Phase III confirmatory study
- Also being studied for DED
- First new class of medication in AC
- Highly statistically significant data ($p<0.0001$)

Reproxalap's Novel Mechanism of Action Has The Potential to Provide Differentiated Activity Versus Antihistamines



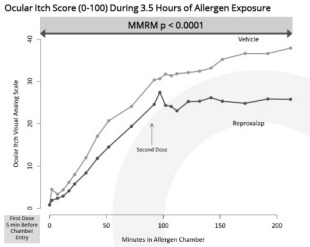
Reproxalap

- Reproxalap irreversibly inhibits RASP, limiting allergic inflammation.
- Reproxalap has the potential to be uniquely effective in post-histaminic allergy, which affects all allergic conjunctivitis patients.

RASP ~ Reactive Aldehyde Species

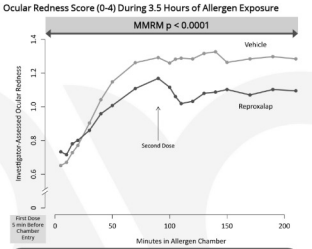
Reproxalap Showed Greater and More Durable Clinical Responses Than Vehicle in Allergen Chamber Clinical Trial

Ocular Itch Score (0-100) During 3.5 Hours of Allergen Exposure



Statistically significant reduction in ocular itch vs. vehicle for more than three hours of exposure to allergen

Ocular Redness Score (0-4) During 3.5 Hours of Allergen Exposure



Statistically significant reduction in ocular redness vs. vehicle for more than three hours of exposure to allergen

The Dry Eye Pipeline

- 20/20 OptimEyes
- AdOM
- Aldeyra
- Aerie
- Alcon
- Allegro
- Allotex
- Allysta
- Aurinia
- AVIZOREX
- Azura
- B+L
- BioLineRx
- Brim
- Cambium
- Cypralis
- Dompe
- Eyedetec
- Genentech
- Hanall Biopharma
- Hovione
- IACTA Pharma
- Lacrisciences
- Novaliq GmbH
- Novartis- Lubricin
- KPI Therapeutics
- LTT Bio-Pharma
- mc2 therapeutics
- MITOTECH
- Nicox
- Oculis
- Oyster Point
- Palatin
- RegeneRx
- Silk Technologies
- Surface Pharmaceuticals
- Tarsus Pharmaceuticals
- TearLab
- Thea Laboratories
- Sylentis
- Visant
- Xigen

THANK YOU!

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