Disruptive Innovations in Ocular Surface Disease

Elizabeth Yeu, MD

Assistant Professor, Eastern Virginia Medical School
Virginia Eye Consultants
Cornea, Cataract, External Disease and Refractive Surgery
Hampton/Norfolk/Suffolk/Virginia Beach, VA

TWIN CITIES OCULAR SURFACE DISEASE SYMPOSIUM

Financial Interests Disclosure

- Alcon: C, R
- Allergan: C
- Aurea Medical: C
- Avedro: C
- Bausch & Lomb/Valeant: C, R
- BioTissue: C, R
- Beaver Visitec : C
- Bruder: C
- EyePoint Pharmaceuticals: C
- iOptics: C, R
- Glaukos: S
- Guidepoint: C
- J & J Vision: C
- LENSAR: C
- Kala Pharmaceuticals: C
- Merck: C
- Mynosys: C
- Novartis: C
- Ocular Science: C, R
- Ocular Therapeutix: C
- Ocusoft: C
- Omeros: C
- Oyster Point Pharmaceuticals: C
- Science Based Health: C
- Shire: C
- Sight Sciences: C
- SightLife Surgical: C
- Sun: C
- TopCon: C, R
- TearLab Corporation: C, R
- TearScience: C
- Zeiss: C

Treatment Strategies in 2019

- Lubricants
  - Tears (emulsions, solutions), gels, ointments, sustained-release formulation
  - Ingredients
    - Hyaluronic acid, Carboxymethylcellulose (CMC), Lipid-based
- Nutrition
  - Oral essential fatty acids
  - Vitamin A ointment

Treatment Strategies in 2019: Lid Margin Disease Management

- Warm compress and lid massage
  - Difficult to maintain adequate temperature; poor compliance
- Lid scrubs
  - Commercial soap scrubs
  - Tea tree oil in *Demodex* mite infestation[1]
- In-office lid margin cleansing and meibomian gland expression for anterior blepharitis and posterior blepharitis
  - Motorized/mechanical devices[2]
  - Thermal and thermal pulsation[3]
  - Intraductal probing[4]
  - Intense pulsed light[5]

1. Gao YY, et al. *Cornea*. 2007;26(2):136-143; 2. Korb DR, Blackie CA. *Cornea*. 2013;32(12):1554-1557;
3. Lane SS, et al. *Cornea*. 2012;31(4):396-404; 4. Maskin SL. *Cornea*. 2010;29(10):1145-1152;
5. Craig JP, et al. *Invest Ophthalmol Vis Sci*. 2015;56(3):1965-1970.

Treatment Strategies in 2019

- Anti-inflammatory agents
  - Topical corticosteroids
  - Topical cyclosporine A emulsion (CSA), 0.05%
  - Topical lifitegrast, 5%
  - Oral tetracyclines or macrolides
  - Topical azithromycin
- Amniotic membrane products: anti-inflammatory and promote wound healing
- Neurostimulation
  - Intranasal neurostimulation device (TrueTear)

Dry Eye Disease is Highly Prevalent with Substantial Unmet Need

~34 Million adults in the U.S. are estimated to have DED, however…

Only 8% of eye doctors state they can adequately treat dry eye patients with current options

Paulsen, et al. Am J Ophthalmol. 2014.

TFOS. What Is DEWS II. Available at http://www.tearfilm.org/dettreports-tfos_dew_ii_report/32_30/eng.

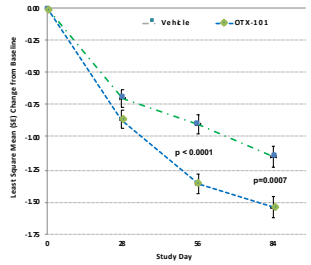
Anti-Inflammatories

- Cyclosporine 0.09% (Cequa)
  - In nanomicellar solution
  - Approved in late 2018
  - Indication to increase tear production for dry eye disease
- Loteprednol 0.25%
  - In mucous-penetrating nanparticle (MPP)
  - Acute treatment of dry eye flares

Cyclosporine 0.09% in nanomicellar solution

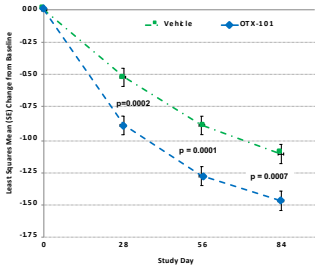
Tear Production				
	OTX-101-2014-001		OTX-101-2016-001	
	CEQUA N = 152	Vehicle N = 152	CEQUA N = 371	Vehicle N = 373
≥ 10-mm increase in tear production (% of eyes) at Day 84	16.8%	8.6%	16.6%	9.2%
Difference (95% CI)	8.2% (1.9%, 14.6%)		7.3% (3.3%, 11.3%)	
p-value versus vehicle	<0.01		<0.01	

Total Conjunctival Staining (Excluding Superior Zones)
Change from Baseline



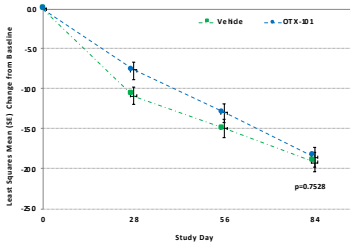
Luchs, J. Scientific Paper ASCRS Annual Meeting 2018.

Total Corneal Fluorescein Staining
Change from Baseline



Luchs, J. Scientific Paper ASCRS Annual Meeting 2018.

Global Symptom Score (SANDE)
Change from Baseline



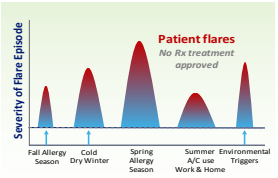
Luchs, J. Scientific Paper ASCRS Annual Meeting 2018.

Loteprednol 0.25% in MPP for Dry Eye Flares

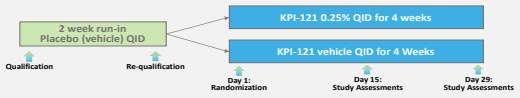
- Loteprednol etabonate 0.25% in the AMPPLIFY™ nanosuspension is ~300 nm
  - Traditional loteprednol etabonate (LE) suspension 6,000 nm
  - Current LE concentrations 0.5% (Lotemax) and 0.2% (Alrex)
- In FDA Phase 3 clinical trials

The Reality of Dry Eye Disease

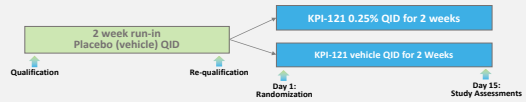
- DED is a chronic condition with episodic flares
- A dry eye flare is a rapid-onset inflammation-driven response to external stimuli or environmental insult
  - Seasonal or perennial allergies
  - Weather, humidity, travel
  - Stress, change in sleep pattern, poor diet
  - Change in systemic medications or health
  - Ocular surgery
- Most dry eye disease patients with or without maintenance dry eye therapy, experience flares
- Regardless of dry eye severity, flares typically occur 4-6 times per year.



One Phase 2 and Two Phase 3 Dry Eye Clinical Trials Completed

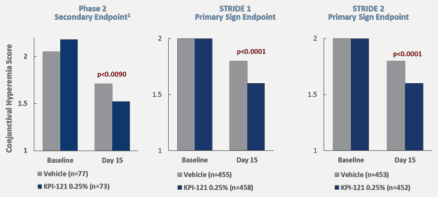


C-002 (Phase 2)



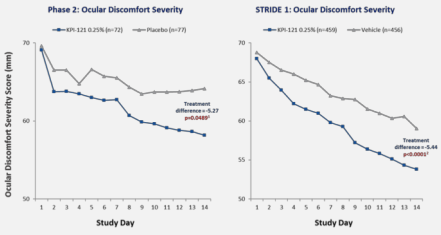
C-006 & C-007 (Phase 3)
STRIDE 1 & STRIDE 2

Statistical Significance for Conjunctival Hyperemia in all 3 Trials



Results for Conjunctival Hyperemia at Day15 Across Trials

Similar Treatment Benefit Seen in Phase 2 and STRIDE 1



[1]Using statistical analysis defined in STRIDE 1/2 Statistical Analysis Plan (comparison of 3 day means)
[2]Using pre-specified statistical analysis as per Statistical Analysis Plan (comparison of 3 day means)

Totality of Data Demonstrates Efficacy for Signs and Symptoms of DED

KPI-121 0.25% Results and Key Findings				
		Phase II	STRIDE 1	STRIDE 2
SIGN	Variable	Conjunctival Hyperemia (CH)	Conjunctival Hyperemia (CH)	Conjunctival Hyperemia (CH)
	P	0.0090	<0.0001	<0.0001
SYMPTOM	Variable	Ocular Discomfort Severity (ODS)[1]	Ocular Discomfort Severity (ODS)	Ocular Discomfort Severity (ODS)
	P	0.0489**	<0.0001	0.1289

Primary Endpoints with statistical significance
Secondary Endpoint of the Phase II Trial; **Using the STRIDE 1/2 statistical analysis plan

KPI-121 0.25% Demonstrated Similar IOP Profile to Placebo in Both Trials

Mean IOP

STRIDE 1

	KPI-121 0.25% Mean (SD) in mmHg (n=459)	Vehicle Mean (SD) in mmHg (n=456)
Day 1	14.9 (2.57)	15.3 (2.52)
Day 15	15.1 (2.67)	14.9 (2.68)

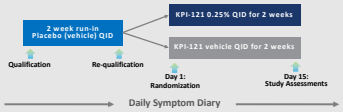
STRIDE 2

	KPI-121 0.25% Mean (SD) in mmHg (n=453)	Vehicle Mean (SD) in mmHg (n=452)
Day 1	14.9 (2.53)	14.9 (2.48)
Day 15	15.0 (2.65)	14.6 (2.41)

Number of Patients with IOP Increase > 5 mmHg Leading to IOP ≥ 21 mmHg

STRIDE 1		STRIDE 2		COMBINED	
KPI-121 0.25%	Vehicle	KPI-121 0.25%	Vehicle	KPI-121 0.25%	Vehicle
2/455 (0.4%)	2/453 (0.4%)	5/448 (1.1%)	0/448 (0.0%)	7/903 (0.8%)	2/901 (0.2%)

STRIDE 3 Design Focus on Symptom Endpoints

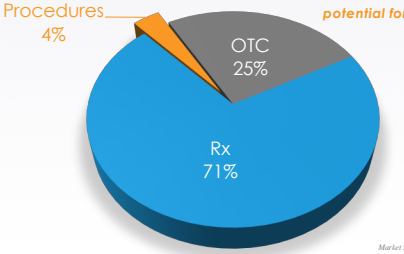


Key Aspects of STRIDE 3 Study Design:

- Similar design to STRIDE 1 and 2
- Specific modifications made to inclusion/exclusion criteria to address key factors which are expected to improve the probability of success
- Independent primary endpoints of Day 15 Ocular Discomfort in ITT population and severe subgroup
  - Achieving either endpoint should satisfy symptom requirement
- Study ongoing and topline results anticipated in Q4 2019

Procedures Currently Represent 4% of all US Dry Eye Revenue

Revenue for Dry Eye Products by Segment



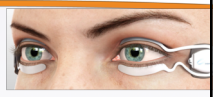
"Newer dry eye procedures offer the most significant potential for market growth."
– Market Scope

Market Scope 2017 Dry Eye Products Report

TearCare

Personalized Open Eye Experience

For those who suffer from dry eye disease, TearCare® is the most personalized procedure that offers a savvy approach



- Natural-blink design

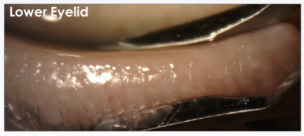
- Ultra-precise meibomian gland clearance
- Patented smart system

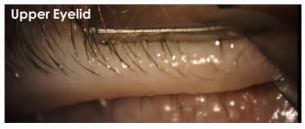
TearCare

For the application of localized heat when the current medical community recommends the application of a warm compress to the eyelids. Such applications would include Meibomian Gland Dysfunction (MGD), Dry Eye, or Blepharitis

TearCare® During Thermal Delivery and Clearing

SIGHT SCIENCES





Pilot Data Review

TearCare® Pilot Study
Initial 6-month data published in Clinical Ophthalmology, April 2018

Purpose:

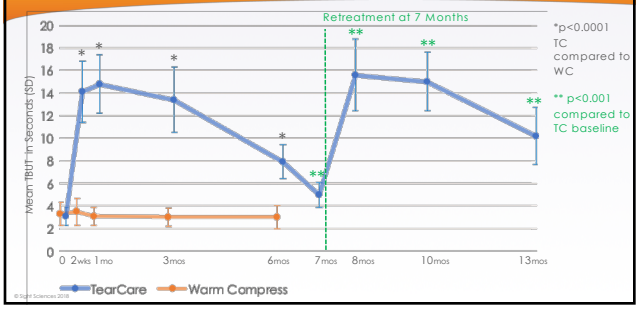
- Preliminary Assessment of the Long-Term Safety & Effectiveness of the TearCare® System in the Treatment of the Signs & Symptoms of Dry Eye Disease
- Assess Re-Treatment at 6 months
- Gather data to help design pivotal study

Study Details:

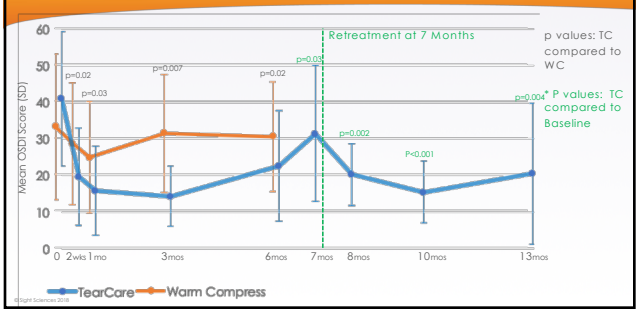
- Single Center: David Badawi, MD
- Prospective, randomized, controlled trial
- 24 Subjects followed for 6 months
  - 12 TearCare subjects
  - 12 Warm Compress subjects (5 minutes daily for 1 month)
- All 12 original TearCare subjects were re-treated at 7 months and followed for another 6 months (13 months total) *(re-treatment results not yet published)*

24

Pilot Data: Tear Breakup Time



Pilot Data: OSDI



iLux® In-Office MGD Treatment

Handheld iLux® device

- Magnifier allows the user to **view the eyelid margin**
- **Warms** the eyelid tissue within a therapeutic target range to melt the meibum blocking the orifices, then **applies compression** to express the melted meibum through the orifices
- Amount of heat and pressure is under **direct control of the user**

iLux® Smart Tip

- Sterile, **single-patient-use** disposable tip
- **Inner and outer pads** are covered with a soft, biocompatible silicone material
- Contains **precision temperature sensors** that continually monitor inner and outer eyelid temperature and ensure therapeutic heat levels during treatment

Treatment with iLux® is Intuitive for Doctors and Their Technicians to Perform

See It
View the blocked Meibomian glands through the magnifying lens

Heat It
Slide the heater control switch forward to activate the LED lights, applying localized heat to melt the blockages

Treat It
Use the compression control button to gently compress the eyelid and clear the blocked Meibomian glands

Personalize It
Select only the areas that need treatment and perform up to four targeted treatments per eye. Monitor treatment time and temperature on the display, and view expressed meibum through the magnifying lens

iLux®: Intuitive, In-Office MGD Treatment

iLux® Device Delivers Efficacy and Showed Non-Inferiority of MGD Treatment Relative To LipiFlow^[1]

- **Study Objective**: To compare the changes in Meibomian gland function and evaporative dry eye (EDE) symptoms after treatment with iLux® and LipiFlow^
- **Study Design:** This was a randomized, open-label, multisite clinical trial that enrolled 142 subjects from 8 study sites. Subjects were randomized for bilateral treatment in a 1:1 ratio between the iLux® treatment group and the LipiFlow^ group. Primary and secondary efficacy endpoints were assessed at baseline and 2 and 4 weeks post-treatment

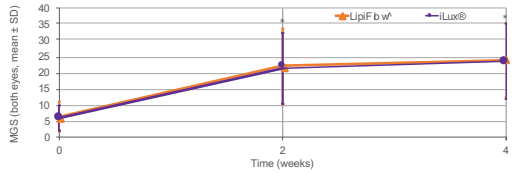
- **Primary Effectiveness Endpoints:** Meibomian Gland Score (MGS) and Tear Breakup Time (TBUT), as well as **secondary endpoint** of Ocular Surface Disease Index (OSDI) symptom scores
- **Results: iLux® was non-inferior** relative to LipiFlow^ with respect to MGS, TBUT, and OSDI, at all assessed timepoints

^ LipiFlow is a trademark of Johnson & Johnson Vision Care, Inc.

Reference: 1. Harden DR, Schanzlin JD, Dishler JG, et al. Comparison of a Handheld Infrared Heating and Compression Device for Treatment of Meibomian Gland Dysfunction to a Thermal Pulsation Device. Presented at the Annual Meeting of the American Society of Cataract and Refractive Surgery (ASCRS); April 13-17, 2018; Washington, D.C.

Meibomian Gland Score (MGS) Significantly Improved From Baseline at Week 2 and Week 4 After Treatment With iLux®

Meibomian Gland Score (MGS)[1]



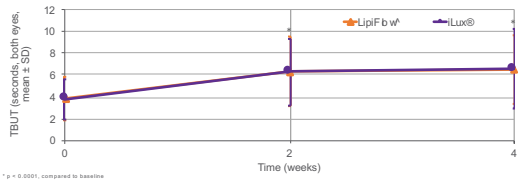
* p < 0.0001, compared to baseline

^ LipiFlow is a trademark of Johnson & Johnson Vision Care, Inc.

Reference: 1. Harden DR, Schanzlin JD, Dishler JG, et al. Comparison of a Handheld Infrared Heating and Compression Device for Treatment of Meibomian Gland Dysfunction to a Thermal Pulsation Device. Presented at the Annual Meeting of the American Society of Cataract and Refractive Surgery (ASCRS); April 13-17, 2018; Washington, D.C.

Tear Breakup Time (TBUT) Significantly Improved From Baseline at Week 2 and Week 4 After Treatment With iLux®

Tear breakup time (TBUT)[1]



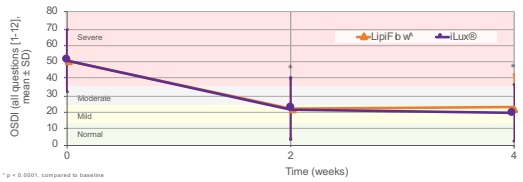
* p < 0.0001, compared to baseline

^ LipiFlow is a trademark of Johnson & Johnson Vision Care, Inc.

Reference: 1. Harden DR, Schanzlin JD, Dishler JG, et al. Comparison of a Handheld Infrared Heating and Compression Device for Treatment of Meibomian Gland Dysfunction to a Thermal Pulsation Device. Presented at the Annual Meeting of the American Society of Cataract and Refractive Surgery (ASCRS); April 13-17, 2018; Washington, D.C.

Ocular Surface Disease Index (OSDI) Significantly Improved From Baseline at Week 2 and Week 4 After Treatment With iLux®

Ocular Surface Disease Index (OSDI)[1]



* p < 0.0001, compared to baseline

^ LipiFlow is a trademark of Johnson & Johnson Vision Care, Inc.

Reference: 1. Harden DR, Schanzlin JD, Dishler JG, et al. Comparison of a Handheld Infrared Heating and Compression Device for Treatment of Meibomian Gland Dysfunction to a Thermal Pulsation Device. Presented at the Annual Meeting of the American Society of Cataract and Refractive Surgery (ASCRS); April 13-17, 2018; Washington, D.C.

iLux® Does Not Cause Excessive Heating of the Eye

- An open-label safety study of iLux® found **no sign of excessive heating** of the cornea, outer eyelid, or surrounding surface[1]*
- Standard optometric assessments of the cornea and subjects' vision demonstrated **no corneal damage and minimal impact on vision**[1]*

Comparison of pre- and post-heating temperature readings (n=30 eyes)[1]*

Tissue Site	Pre-heating temperature (°C)	Post-heating temperature (°C)	Change in temperature (°C)
Corneal	Maximum: 36.9 Mean: 36.0 ± 0.6	Maximum: 38.8 Mean: 37.7 ± 0.5	+1.8
Outer eyelid	Maximum: 37.4 Mean 36.5 ± 0.5	Maximum: 40.6 Mean: 38.5 ± 0.8	+3.2
Surrounding surface	Maximum: 37.6 Mean: 36.8 ± 0.5	Maximum: 39.7 Mean: 38.2 ± 0.7	+2.1

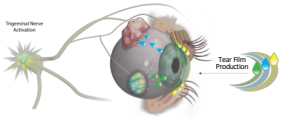
* Heating performed in the medial-nasal and medial-temporal zones in the upper and lower eyelids of each eye for 90 seconds in each zone

Reference: 1. Harden DR, Karpecki PM, Owen J. Safety parameters of a handheld infrared heating and compression device for management of Meibomian gland dysfunction. Presented at the ASCRS-ASOA Annual Meeting, April 13-17, 2018. Washington, D.C.

Neurostimulation and DED

The Parasympathetic Nervous System (PNS) Is a Critical Regulator of the Lacrimal Functional Unit (LFU) and a Healthy Tear Film

The **parasympathetic nervous system** regulates the Lacrimal Functional Unit (LFU) and Tear Film Production via the Trigeminal Nerve **accessible within the nose**



[1] Gupta A, Heigle T, Pflugfelder SC. Nasolacrimal stimulation of aqueous tear production. *Cornea*. 1997 Nov;16(6):645–8.
[2] van der Werf, F. R. A. N. S., Buijel, 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.
[3] LeDoux, M. S., Zhou, D., Murphy, R. B., Greene, M. L., & Ryan, P. (2001). Parasympathetic innervation of the meibomian glands in rats. *Investigative ophthalmology & visual science*, *42*(11), 2636-2641.
[4] Dartt, 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.

Dry Eye Disease is characterized by tear film dysfunction, yet there is a gap between anti-inflammatories and options that directly increase tear film production and address the need for rapidity in symptom reduction

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]

Ivan 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.
Zoukhri, M. S., Zhou, Q., Murphy, A. A., Greene, W. L., & Ryan, P. (2001). Parasympathetic innervation of the meibomian glands in rats. Investigative ophthalmology & visual science, 42(12), 2838-2845.
Barrett, D. A., Mccarthy, D. M., Mercer, H. J., Kessler, T. L., Chung, E. H., & Zenke, J. D. (1995). Localization of nerves adjacent to goblet cells in rat conjunctiva. Current eye research, 14(11), 993-1000.

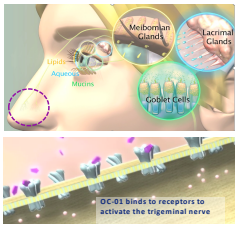
Oyster Point is Developing a Disruptive Approach to Treating Dry Eye Disease Based on Neuroscience and Role of the LFU

Ideal Compound | **Novel Mechanism of Action**

The trigeminal nerve is **accessible within the nasal cavity** and can be activated by stimulating **Nicotinic acetylcholine receptors** (nAChR)

OC-01 nAChR Agonist with Unique Receptor Activation Profile

- Nasal Spray Solution
- Multi Dose Preservative Free
- 50µl volume (Standard is 120µl)
- BID Dosing
- 30 Day Supply

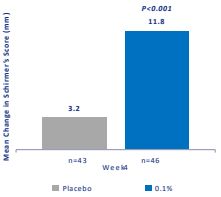


OC-01 Demonstrated Statistically Significant Improvement in Signs and Symptoms of Dry Eye Disease (DED)

ONSET

Mean Change from Baseline in Schirmer's Score – Week 4

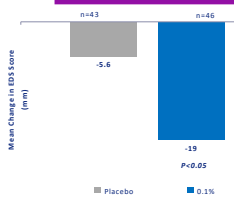
Primary Sign Endpoint



Mean Change from Baseline in Eye Dryness Score (EDS) – Week 4

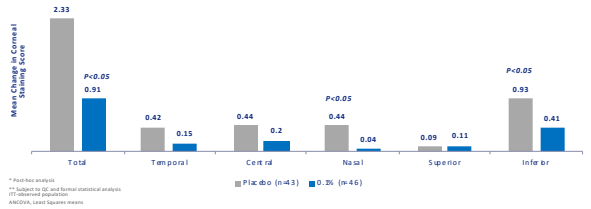
Secondary Symptom Endpoint

Note: The CAE was *not* used for this measurement.

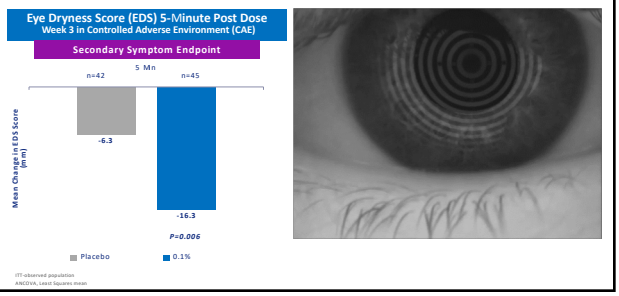


ITT-observed population
ANCOVA, least Squares means

OC-01 Demonstrated Significant Difference from Placebo in Mean Change in Corneal Staining in Total, Nasal and Inferior Regions



OC-01 Is the Only Dry Eye Therapeutic to Demonstrate Immediate and Statistically Significant Improvement in Symptoms of DED



OC-01 is Well Tolerated with Zero Ocular Side Effects

Adverse Events Potentially Related to OC-01 >5% of subjects

Occurred at least once after any installation	OC-01 (0.1%) (n=48)	Placebo (n=43)
Sneeze	38 (79)	0
Cough	6 (13)	0
Throat irritation	7 (15)	0
Instillation site irritation	8 (17)	0
Pharynx dysaesthesia	4 (8)	0

- All events transient and self-limiting immediately following administration
- All events mild (94%) or moderate (4%) in severity. No severe events.
- **No ocular adverse events**; Side effects consistent with that of any nasal spray (sneeze, cough, irritation)

On Track for Initiating Phase 3 in 2019

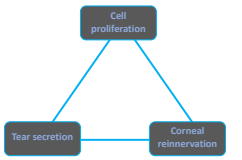
Neurotrophic Keratitis

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

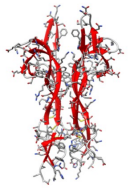
Endogenous NGF maintains corneal integrity by three mechanisms



Nerve damage ⇨ loss of corneal sensitivity ⇨ NK

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

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

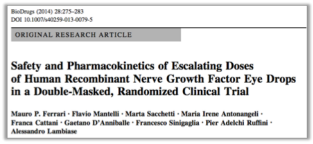
Lambiase A, Rama P, Bonini S, Caprioglio G, Aloe L. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. *N Engl J Med* 1998;338:1174-80.

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


BioDrugs (2014) 28:275–283
DOI 10.1007/s40259-013-0079-5

ORIGINAL RESEARCH ARTICLE

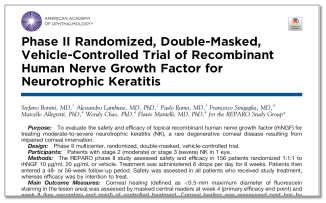
Safety and Pharmacokinetics of Escalating Doses of Human Recombinant Nerve Growth Factor Eye Drops in a Double-Masked, Randomized Clinical Trial

Mauro P. Ferrari · Flavio Mantelli · Marta Sacchetti · Maria Irene Antonangeli · Franca Cattani · Gaetano D'Anniballe · Francesco Sinigaglia · Pier Adelchi Ruffini · Alessandro Lambiase

Resulting product: A more potent, patient-compatible 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

OXERVATE™ (cenegermin-bkbj 20 mcg/ml) was approved by FDA in August 2018


AMERICAN ACADEMY OF OPHTHALMOLOGY

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

Stefano Bonini, MD,[1] Alessandro Lambiase, MD, PhD,[1] Paolo Rama, MD,[1] Francesco Sinigaglia, MD,[2] Marcello Allegretti, PhD,[3] Wendy Chao, PhD,[4] Flavia Manzella, MD, PhD,[4] for the REPARO Study Group[4]

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

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

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

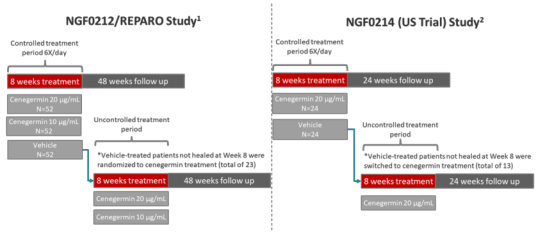
Methods: The REPARO phase II study assessed safety and efficacy in 156 patients randomized 1:1:1 to rhNGF, 10 μg/mL, 20 μg/mL or vehicle. Treatment was administered 6 drops per day for 8 weeks. Patients then entered a 48- or 56-week follow-up period. Safety was assessed in all patients who received study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

Main Outcome Measures: Corneal healing (defined as <0.5-mm maximum diameter of fluorescein staining in the lesion area) was assessed by masked central readers at week 4 (primary efficacy end point) and week 8 (key secondary end point of controlled treatment). Corneal healing was reassessed post hoc to

- 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.

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Pivotal Trials Study Design



The primary efficacy endpoint, which was determined by a central reading center, was "complete corneal healing" defined as 0 mm staining in the lesion area and no persistent staining in the rest of the cornea

1. Bonini S, Lambiase A, Rama P *et al*. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.
2. Chao W, J. BOC, R. D *et al*. Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE); 10–13 June, 2017; Barcelona, Spain. 2017.

Study Criteria

Main inclusion criteria

- Adult NK patients with stage 2 or 3 NK
  - Unilateral NK only in NGF0212/REPARO
  - Unilateral or bilateral NK permitted in NGF0214
- Evidence of decreased corneal sensitivity (<40mm by Cochet-Bonnet aesthesiometer) within the area of the PED or corneal ulcer and outside of the area of the defect, in at least 1 corneal quadrant
- Refractory to ≥1 nonsurgical tx
- No improvement in in 2 weeks prior to enrollment

Main exclusion criteria

- Infection, inflammation, other ocular disease requiring topical tx
  - Glaucoma patients were switched to systemic meds during the study
- Severe blepharitis or MGD
- Prior surgical tx for NK
  - Exception for AMT performed > 6 weeks prior or membrane disappeared > 2 prior
- Stromal involvement in posterior third, corneal melting, or perforation in study eye

1- ClinicalTrials.gov identifier: NCT01756456
2- ClinicalTrials.gov identifier: NCT02227147

Stage 2 and Stage 3 NK patients enrolled

NGF0212/REPARO Study[1,3]

	OXERVATE™ (n=52)	Vehicle (n=52)
Primary NK diagnosis, no. (%)		
Stage 2 (moderate)	27 (51.9)	28 (53.8)
Stage 3 (severe)	25 (48.1)	24 (46.2)
Underlying cause, no. (%)		
Herpetic eye disease	11 (21.2)	18 (34.6)
Neurosurgical procedure	8 (15.3)	7 (13.4)
Ocular surgery or procedure	5 (9.6)	7 (13.4)
Dry eye disease	6 (11.5)	5 (9.6)
Ocular surface injury/inflammation	5 (9.6)	5 (9.6)
Other	5 (9.6)	3 (5.8)
Topical medication (glaucoma)	1 (1.9)	1 (1/9)
Stroke	2 (3.8)	0
Unknown origin	1 (1.9)	0
Systemic medication	0	0

NGF0214 (US Trial) Study[2,3]

	OXERVATE™ (n=24)	Vehicle (n=24)
Primary NK diagnosis, no. (%)		
Stage 2 (moderate)	15 (62.5)	18 (75.0)
Stage 3 (severe)	9 (37.5)	6 (25.0)
Underlying cause, no. (%)		
Herpetic eye disease	9 (37.5)	8 (33.3)
Neurosurgical procedure	1 (4.2)	5 (20.8)
Ocular surgery or procedure	3 (12.5)	4 (16.7)
Dry eye disease	3 (12.5)	3 (12.5)
Ocular surface injury/inflammation	2 (8.3)	1 (4.2)
Other	2 (8.3)	1 (4.2)
Topical medication (glaucoma)	1 (4.2)	1 (4.2)
Stroke	0	1 (4.2)
Unknown origin	2 (8.3)	0
Systemic medication	1 (4.2)	0

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.
2. Chao W, J. BBC, 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 (ESO); 10-13 June, 2017; Barcelona, Spain. 2017.
3. Drug Approval package. OXERVATE (Cenegermin-bkbj) Accessdata.fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761060Orig1s000SumR.pdf. Published 2018. Accessed November 13, 2018

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002%

Dosing and Administration

2 — Every 2 hours instill 1 drop of OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% in the affected eye(s)

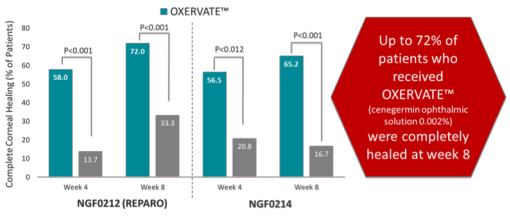
6 — Apply 6 times daily

8 — Continue for 8 weeks

OXERVATE Prescribing Information, 2018.

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).



Up to 72% of patients who received OXERVATE™ (cenegermin ophthalmic solution 0.002%) were completely healed at week 8

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

- No serious adverse reaction related to the treatment occurred in any clinical trials
- The majority of adverse reactions were mild and transient ocular reactions that did not require treatment discontinuation or any corrective treatment

16%

The most common adverse reaction was **eye pain** following instillation, which was reported in approximately 16% of patients.

12/75= 16%
7/23=30.4% (US trial)
5/52= 9.6% (REPARO)

1-10%

Other adverse reactions occurring in 1%-10% of patients taking OXERVATE and more frequently than in the vehicle-treated patients included **corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation**, and **tearing.**

Source: Data on file, pooled analysis of NGF0212/REPARO and NGF0214

Oxervate is neither systemically absorbed, nor immunogenic

- In Phase I (NGF0112) in healthy patients at doses up to 180 µg/ml , serum concentrations of NGF did not differ from basal levels.
- In Phase I/II (NGF0212/REPARO) in NK patients, NGF serum levels were below the lower level of quantification in almost all patients (detectable serum NGF levels likely reflected known inter- and intra-individual fluctuations independent of study treatment).
- No systemic immunogenicity was detected in any clinical studies. With no (or negligible) systemic exposure, off-target pharmacological activity or toxicity are unlikely.
- The hydrophilic rhNGF solution has a very low residence time in the eye (quickly removed with the tear flow).

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343
2. Mauro P. Ferrari et al. Safety and Pharmacokinetics of Escalating Doses of Human Recombinant Nerve Growth Factor Eye Drops in a Double-Masked, Randomized Clinical Trial. BioDrugs (2014) 28:275–283

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

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

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

Study NGF0212 (REPARO) (N=52 per group)

European patients with NK in one eye

NCT01756456

72.0% completely healed

Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147

65.2% completely healed

Vehicle response rate 16.7%

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

80% Remained healed for one year*

*Based on REPARO, the study with longer follow-up

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 (ESO) 10–13 June, 2017, Barcelona, Spain. 2017.