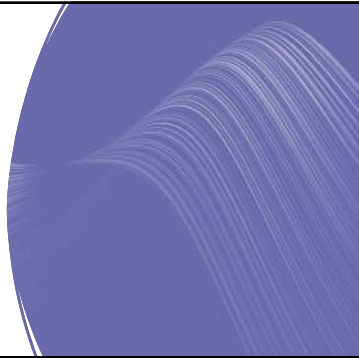


CORNEAL RELATIONSHIP THERAPY: MANAGING THE NEUROTROPHIC KERATITIS

Marc R Bloomenstein OD, FAO
Schwartz Laser Eye Center
Scottsdale, AZ



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Disclosure

- Presenter is on speaker's panel/consultant for:
 - Alcon, Allergan, Azura, B+L, J&J, Novartis, OcuSOFT, Olleyes, Reichert, Sight Sciences, Sun Pharma, Visus, Tarsus, Thea, Bruder, Dompe'
- President of MRB Eye Consultants
- Past-President of the Optometric Council on Refractive Technology (OCRT)
- Presenter has NO financial interest in any products mentioned

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Neurotrophic keratitis

“Some patients look great and feel awful.
Others look terrible and feel great.”
John Sheppard

3

Neurotrophic keratitis

“Stain without pain”


“A key differentiator is the reduction or total loss of corneal sensitivity...caused by damage to the corneal nerve, which leads to breakdown and poor healing of the epithelium.”

Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. J Cell Physiol. 2017;232(4):717-724.
<https://knownk.com/about-nk/#what-is-nk>

4

Nuerotrophic Keratitis

- Classified as a rare disease in the US
- A progressive disease
- Defined by impairment of the trigeminal innervation

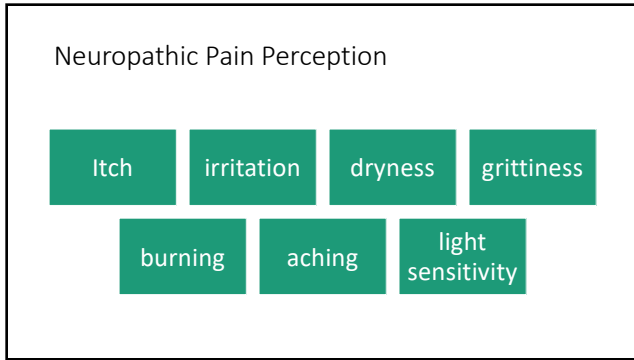


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Corneal Nerves 101

- The cornea is the most powerful pain generator in the body
- 7000 nerve terminals per millimeter square
- Corneal nerves mainly originate
 - Ophthalmic division of the CN V (trigeminal nerve)
 - Branches of the nasociliary branch
 - Branching into two long long ciliary nerves around the limbus
 - Enter radially mid-stromal
- Nociceptive Stimulus
 - Free nerve endings that respond to noxious stimuli
 - Skin, Organ motion, cornea and dental pulp

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Nerve malfunction is the hallmark of NK^{1,2}

Conditions that damage any level of the trigeminal nerve can **disrupt physiological processes** in the ocular surface and lead to NK

Impaired corneal sensitivity leads to diminished protective blink reflexes, abnormal epithelial cell metabolism, and failure to resist the effects of trauma, drying, and infection

1. Dua H, Said D, Messmer E, et al. Neurotrophic keratopathy. Prog Retin Eye Res. 2018;66:107-131.
2. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. J Cell Physiol. 2017;213(4):717-24.

8

Endogenous NGF maintains corneal integrity by three mechanisms

Endogenous Nerve growth factor acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e. p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.³

3. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. J Cell Physiol. 2017;213(4):717-24.

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Several conditions can lead to NK

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- ### Ocular
- Post-herpes keratitis
 - Chemical and physical burns
 - Abuse of topical anesthetics
 - Drug toxicity (eg, BAK)
 - Chronic ocular surface injury
 - Ocular surgery (eg, LASIK, cataract surgery)
 - Contact lens wear
 - Orbital neoplasia
 - Corneal dystrophies
 - Chronic DED

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

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Central nervous system

- Aneurysms
- Stroke
- Degenerative disorders of the CNS
- Postneurosurgical procedures

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Genetic

- Riley-Day syndrome
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoesthesia



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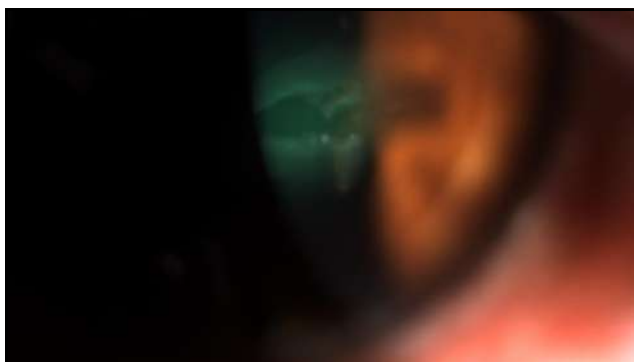
My Vision is blurry...like a lot.

15

"Can I do my other eye first?"

- 72 yo Male
 - Cataracts in both eyes
 - Scheduled for surgery in left eye
 - Starting using drops pre-op
 - "I may have hit my eye with the tip of the drop?"
 - "My vision is way worse now"
 - VaSC
 - 20/200 ph 20/70 OD
 - 20/CF ph 20/200 OS
 - Slex:
 - OD-Corneal Clear, NSC/ASC
 - OS-

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"It is still blurry..."

- Used a BCL, AB
 - RTC 1wk
 - NO IMPROVEMENT
 - BCL-missing...however the patient stated "It feels fine!"
 - "Can I do surgery on the other eye?"
 - Cotton-tip sensation:
 - OD- 5/10
 - OS- 0/10
- Prokera Slim inserted
- Rx'd Oxervate

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Testing corneal sensitivity IS IMPORTANT TO DIAGNOSING NK

QUALITATIVE

COTTON THREAD

- When the cotton thread gently touches the cornea, normal subjects show a blink reaction and can describe the sensation of touch
- Patients with a loss of corneal sensitivity DO NOT react

QUANTITATIVE

COCHET-BONNET AESTHESIOMETER

- Commonly used
- Quantifies corneal sensitivity by a nylon filament of different lengths touching the cornea to elicit a blink or patient response
- Each quadrant of the cornea can be tested separately

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:171-179.

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Mackie Classification

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Mackie Classification

STAGE 1 Mild

- Improve epithelial quality and transparency
- Avoid epithelial breakdown

STAGE 2 Moderate

- Prevent stromal involvement and corneal ulcer formation
- Promote corneal healing

STAGE 3 Severe

- Stop stromal melting
- Prevent perforation that could lead to potential vision loss

L. Versura F, Giannaccare G, Pellegrini M, Sebastiani S, Campos EC. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain*. 2016;18:237-45. Z. Dua HS, Saini SK, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

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Neurotrophic keratitis

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Neurotrophic keratitis

	Early/severe cases (i.e., Stage 1)	Moderate (i.e., Stage 2)	Late/severe cases (i.e., Stage 3)
Discontinue all preservative-containing topical medications	+	+	+
Medical management			
Topical anesthetic free drops	+	+	+
Topical immunosuppressive eye drops or ointments	+	+	+
Autologous serum drops, human umbilical cord serum, plasma-rich plasma	+	+	+
Recombinant human nerve growth factor (recombinant)	+	+	+
Topical platelet-derived growth factor (PDGF)	+	+	+
Topical epidermal growth factor (EGF)	+	+	+
Topical retinoic acid	+	+	+
Topical prostaglandin synthetase inhibitors	+	+	+
Non-surgical interventions (i.e., office procedures)			
Chemical debridement (contact lenses)	+	+	+
Front- or back-surface keratoplasty	+	+	+
Penetrating keratoplasty	+	+	+
Therapeutic keratotomy	+	+	+
Corneal neurotomy	+	+	+

†Treatments listed as potentially optimal, depending on the patient's individual circumstances
‡Treatments listed as potentially appropriate, depending on the patient's individual circumstances (not noted in the manuscript)

Datta, R., Parid, M., Gupta, P.K. et al. Expert consensus on the identification, diagnosis, and treatment of neurotrophic keratopathy. *BMC Ophthalmol* 21, 327 (2021). <https://doi.org/10.1186/s12886-021-02092-1>

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Neurotrophic keratitis

The 20 most expensive pharmacy drugs in the U.S. Amyrt's Myalept takes the top spot while two newcomers enter the GoodRx rankings.

Drug	Company	Price per month (US\$)
1. Myalept	Amyrt Pharma	7159
2. Biocytin	Horizon Therapeutics	5541
3. Biaceticin	EMD Serono	5376
4. Actemra	Horizon Therapeutics	5277
5. Olanzapine	Novartis	4849
6. Taltus	Takeda	4544
7. Darigepan	Vertex Pharmaceuticals	4500
8. Islatravir	Amyrt Pharma	4478
9. Cetryn	Takeda	4441
10. Chondral	Repligen	4157


<https://www.fiercepharma.com/pharma/20-most-expensive-pharmacy-drugs-u-s-2020>

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Monday Morning Patient

Scott Hauswirth, OD

- 71 yo Caucasian female
- 18-month history of dry eye, has seen 8 physicians
- Relatively sudden onset – shortly following uncomplicated cat ex, gradually worsening
- Primary symptoms: constant burning, moderate photophobia
- Treated with Restasis, Xidra, ATs, Warm compresses, plugs, steroids, LipiFlow
- NOTHING HELPS!**



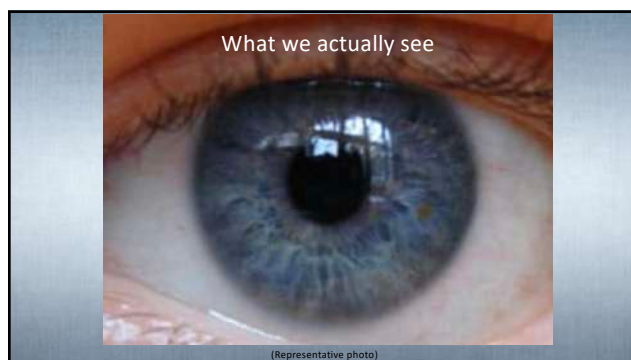
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Signs vs. Symptoms

- There is little correlation between signs and symptoms
- Symptoms may correlate with signs
- Most of us treat according to symptoms

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Treatment Options

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Treatment: What to Expect

- **Mild peripheral** cases difficult to differentiate from typical DE discomfort (continuum)
- **Moderate peripheral** cases respond well to combination of neuroregen + DE therapy
- **Centralized** cases (usually with photophobia) will take several months to respond
 - May require management with systemic medications
 - May require more intervention with pain management

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Neurostimulation

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varenicline solution.03mg
Oyster Point

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There Is No Substitute for Natural Tear Film

Growth factors, such as nerve growth factor (NGF) and epidermal growth factor (EGF), found in natural human tears, are critical regulators for corneal wound healing.
A healthy tear film lubricates and protects the eyes from injury and infection, washes away foreign particles, and contributes refractive power for clear vision.



TFOU DEWS II tear film report

Natural tears contain a complex mixture of lipids, proteins, mucins, and electrolytes^{1,2}

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

1. Daniels R, Sheppard A, Jones L, Sheppard A. The tear film: a complex, multi-layered, and dynamic structure. *Optom*. 2013;94(10):18-24.
2. Sheppard A, Sheppard A, Jones L, Sheppard A. The tear film: a complex, multi-layered, and dynamic structure. *Optom*. 2013;94(10):18-24.

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Parasympathetic Nervous System Controls Tear Film Homeostasis

The trigeminal nerve is **accessible within the nasal cavity**, and is activated by OC-01 (varenicline) by stimulating **cholinergic receptors**.

The trigeminal nerve provides the pathway for **parasympathetic stimulation** of the lacrimal functional unit (LFU) to activate **complete natural tear film**.



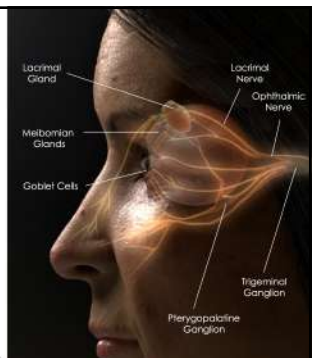
34% of basal tear production is due to inhaling air through the nose¹

1. Gupta A, Singh T, and Phalgunni SC. Neurostimulation of parasympathetic production. *Cornea*. 2017;36(1):149-156.

35

Lacrimal Gland Postganglionic Innervation

- The LFU is innervated by the trigeminal nerve
- Loss of parasympathetic stimuli results in chronic reduction of tear secretion and morphologic destruction of the lacrimal gland



1. Daniels R, Sheppard A, Jones L, Sheppard A. The tear film: a complex, multi-layered, and dynamic structure. *Optom*. 2013;94(10):18-24.

36

NK Treatment Options¹⁻³

Treatments are typically used according to NK stage/severity but are not mutually exclusive of one another. The table is not an exhaustive list of all available treatment options.

Topicals	In-Office Procedures	Surgical Intervention
<ul style="list-style-type: none"> Artificial tears Corticosteroids Autologous serum eye drops Antibiotics Conjunctival epithelial autograft (CEA) 	<ul style="list-style-type: none"> Therapeutic contact lenses Punctal occlusion Non-surgical eyelid closure Multilayer amniotic membrane transplantation (AMT) Tissue adhesives 	<ul style="list-style-type: none"> Tarsorrhaphy Conjunctival flap Corneal transplant Direct neurotization Sutured AMT

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Neuropathic pain & dry eye

“Control / eliminate inflammation and then use your regenerative therapies. The inflammation is what hypersensitizes the nerves in the first place”

Scott Hauswirth, OD

https://www.youtube.com/watch?v=6VZAqNN_JoE

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Neuropathic pain & dry eye

“Don’t prescribe stuff that continues to be an irritant to patients - if they don’t tolerate Restasis/Cequa/Xiidra or whatever don’t continue to push it, find an alternative”

Scott Hauswirth, OD

https://www.youtube.com/watch?v=6VZAqNN_JoE

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Autologous serum tears

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Autologous plasma & nerve regeneration

- Rao (Houston) et al. BJO May 2010
- 11 eyes, 6 pts
- Neurotrophic corneas without active disease
 - Punctate keratopathy / persistent epithelial defects included
- Improvements in aesthesiometry
- Increase in mean CND, CNL, CNW, mean # via confocal
- Complete alleviation in 7, significant improvement in 4

	Pre-treatment	Post-treatment	Significance
Pre-treatment	0.5 (0.2 - 0.8)	1.2 (0.2 - 2.2)	p=0.002
Post-treatment	0.5 (0.2 - 0.8)	1.2 (0.2 - 2.2)	p=0.002

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<https://www.youtube.com/shorts/pFABlYPaWHk>

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<https://www.youtube.com/watch?v=3kmTTHGPQgQ>

1:33

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Amniotic membrane

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Clinical Study
Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease

- CAM vs. conventional DE Tx
- Reduction in VAS
 - 7.1 to 2.2
- Reduction in SPEED
 - 21.8 to 5.9
- Increase in CND/CNL
 - Baseline: 12,241 +/- 5083 um/mm²
 - 3 mo: 18,827 +/- 5453 um/mm²
- Improvement in TBUT
 - 8.3 +/- 2.5 to 13.9 +/- 2.2
- Control group showed no change in all parameters




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Only FDA Approved for NK

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



- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons¹
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s²
- Cenegermin-bkjb, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein³

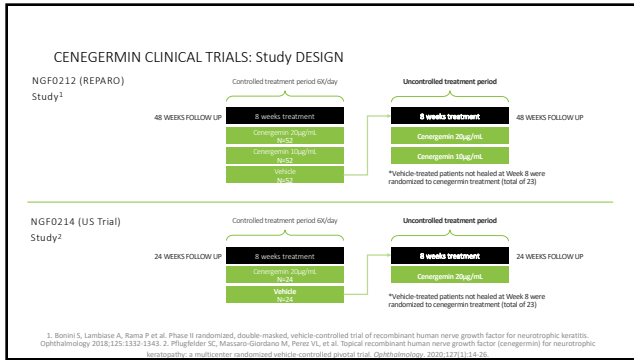
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CENEGERMIN CLINICAL TRIALS: Study overview

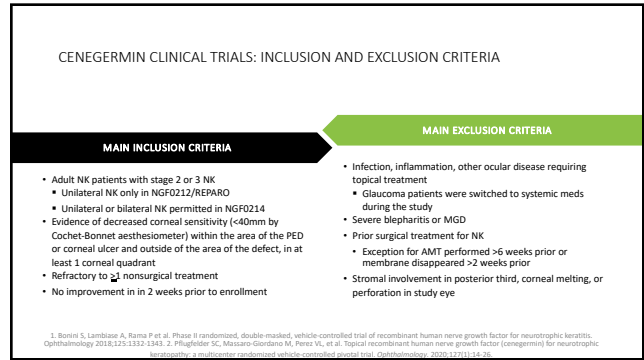
	NGF0212 (REPARO) (n=152)	NGF0214 (n=48)
Geography	Europe 6 Countries (Italy, Germany, UK, France, Spain, Ireland) 32 Clinical Centers	USA 11 Clinical Centers
Design	3 treatment arms: (vehicle, cenegermin 10 mg/mL, cenegermin 20 mg/mL)	2 treatment arms: (vehicle, cenegermin 20 mg/mL)
Vehicle & cenegermin composition	Without antioxidant	With antioxidant (methionine)
Duration of follow up	48 weeks	24 weeks
Uni/bilateral disease	Unilateral	Unilateral and bilateral
Endpoints	Week 8 (Based on a post hoc analysis) Complete corneal healing (defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area) *Primary analysis was <0.5 mm maximum diameter of fluorescein staining in the lesion area at Week 4	Week 8 Complete corneal healing (defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area)

1. Bonini S, Lambase A, Rama F 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. Pflegerfeldt SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: a multicenter randomized vehicle-controlled pivotal trial.

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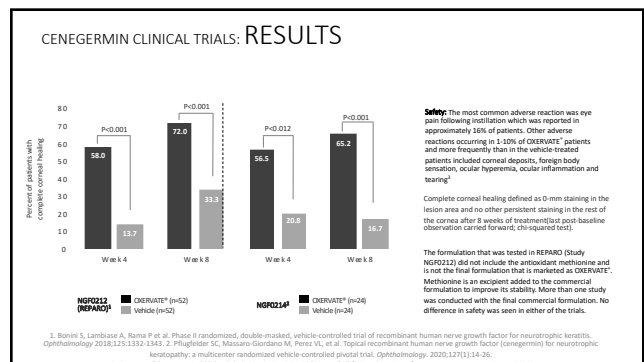
CENEGERMIN CLINICAL TRIALS: BASELINE DEMOGRAPHICS

PRIMARY NK DIAGNOSIS, NO. (%)	NGF0212/REPARO Study ^{1,2}		NGF0214 (US Trial) Study 2,3	
	OXERVATE [®] (n=52)	VEHICLE (n=52)	OXERVATE [®] (n=24)	VEHICLE (n=24)
Stage 2 (moderate)	27 (51.9)	28 (53.8)	15 (62.5)	18 (75.0)
Stage 3 (severe)	25 (48.1)	24 (46.2)	9 (37.5)	6 (25.0)
Underlying cause, no. (%)				
Herpetic eye disease	11 (21.2)	18 (34.6)	9 (37.5)	8 (33.3)
Neurological procedure	8 (15.3)	7 (13.4)	1 (4.2)	5 (20.8)
Ocular surgery or procedure	5 (9.6)	7 (13.4)	3 (12.5)	4 (16.7)
Dry eye disease	6 (11.5)	5 (9.6)	3 (12.5)	3 (12.5)
Ocular surface injury/inflammation	5 (9.6)	5 (9.6)	2 (8.3)	1 (4.2)
Other	5 (9.6)	3 (5.8)	2 (8.3)	1 (4.2)
Topical medication (glaucoma)	1 (1.9)	1 (1.9)	1 (4.2)	1 (4.2)
Stroke	2 (3.8)	0	0	1 (4.2)
Unknown origin	1 (1.9)	0	2 (8.3)	0
Systemic medication	0	0	1 (4.2)	0

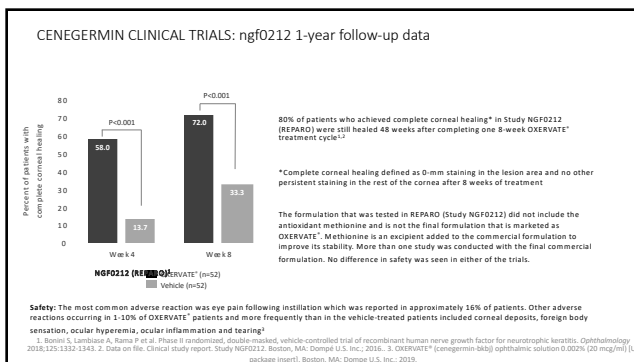
1. Bonini S, Lambiase A, Rama P et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology 2018;125:1332-1343. 2. Pflugfelder SC, Mascaro-Gordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: a multicenter randomized vehicle-controlled pivotal trial. Ophthalmology. 2020;127(1):14-26. 3. Accademia Ioh. Eye. Drug approval packages: OXERVATE (cenegermin-bak). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/1251094Orig1s100000m.pdf

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE[®]. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

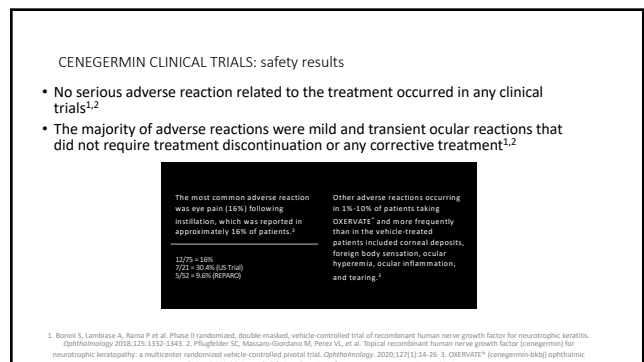
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Study Conclusions

After 8 weeks of treatment, 6 times daily

In most patients across two clinical studies, ceteraximab 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 US

Study NGF0214
(N=24 per group)

US patients with NK
in one or both eyes

NCT02221447

65.2%
completely
healed

Vehicle response rate 28.7%

Of patients who healed after one 8-week course of treatment... **80%** Remained healed for one year


*Based on NGF0214, the study with longer follow-up

1. Mery L, Lumbroso L, Bana P, et al. Phase 3 Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Basic Fibroblast Growth Factor for Neurotrophic Keratitis. *Ophthalmology*. 2018;125(10):1683-1692. doi:10.1016/j.ophtha.2018.03.045. 2. Mery L, et al. Safety and Efficacy of Recombinant Human Basic Fibroblast Growth Factor in Neurotrophic Keratitis: Results of a Phase 3 Randomized, Double-Masked, Vehicle-Controlled Trial. *Invest Ophthalmol Vis Sci*. 2017;58(10):3699-3707. doi:10.1167/iovs.161207. 3. Mery L, et al. Safety and Efficacy of Recombinant Human Basic Fibroblast Growth Factor in Neurotrophic Keratitis: Results of a Phase 3 Randomized, Double-Masked, Vehicle-Controlled Trial. *Invest Ophthalmol Vis Sci*. 2017;58(10):3699-3707. doi:10.1167/iovs.161207.

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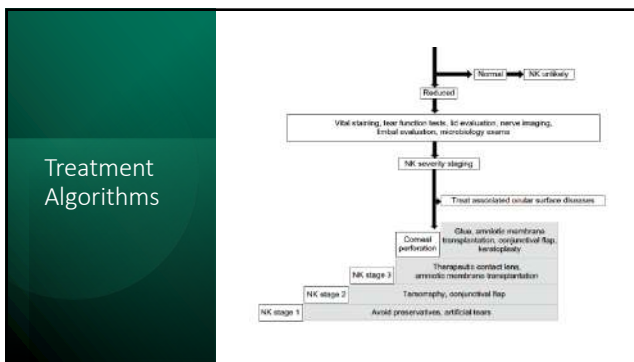
Recombinant NGF

- Multiple studies support use of NGF to repair damaged nerves
- Oxervate (Dompe, Italy)
 - FDA approval December 2018 for neurotrophic keratitis
 - 85,000 x 6 weeks
- NGF also important for epithelial cell turnover & migration¹, LSCN maintenance²
- Could it be used to mitigate pain response?



1) Mery L, et al. *Oxervate*. 2018 Jun 4;4(4):1880-85.
2) Mery L, et al. *Invest Ophthalmol Vis Sci*. 2018 Jun 14;59(12):3699-3707.

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Thank you

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