

They May Feel OK, But They Could Have NK

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Financial Disclosures

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Neurotrophic keratitis

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

John Sheppard

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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, Masiero 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>

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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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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 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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Neuropathic Pain Perception

- Itch
- Irritation
- dryness
- grittiness
- burning
- aching
- light sensitivity

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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, Mesmer E, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131.
 2. Mastroianni L, Mazzoni-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017; 231(4):717-24

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Endogenous NGF maintains corneal integrity by three mechanisms

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

SHOWN IN PRECLINICAL MODELS²

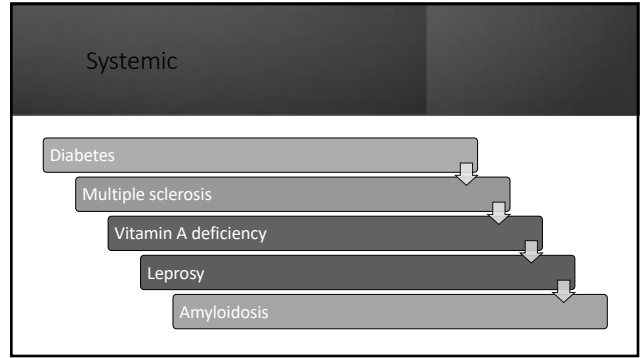
1. Dua H, Said D, Mesmer E, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131.
 2. Dua H, Said D, Mesmer E, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131.

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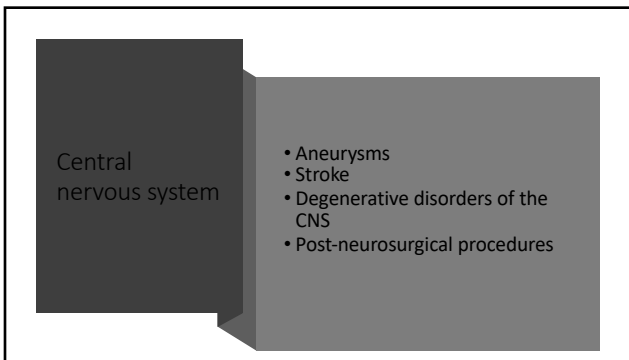
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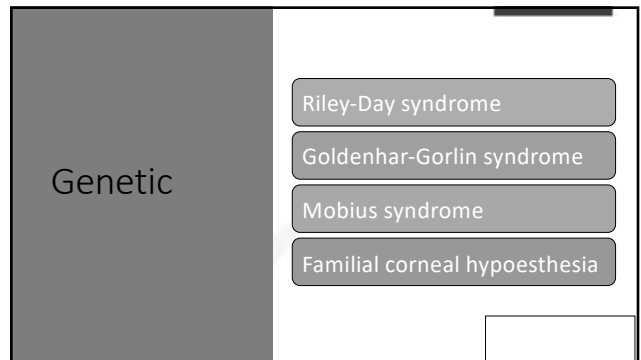
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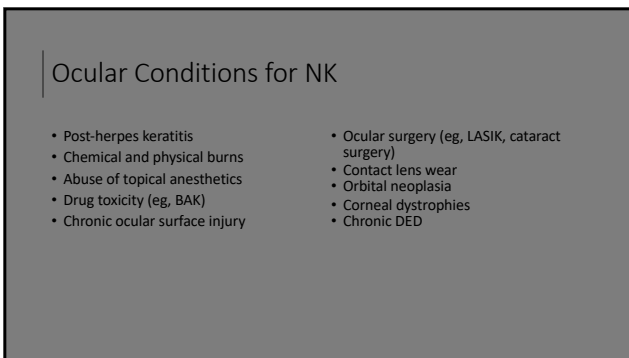
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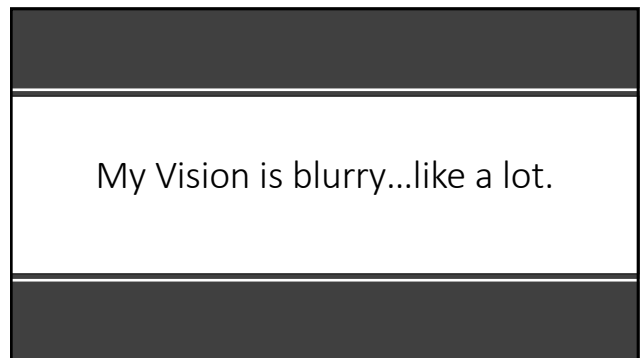
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“Can I do my other eye first?”

- 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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Testing corneal sensitivity IS IMPORTANT TO DIAGNOSING NK

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, Lambase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014;8:571-579.

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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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Mackie Classification

NK is a Degenerative Disease¹

The Mackie Classification Represents One Way to Assess NK Progression²

- Some vision loss can potentially be seen in all stages of NK³
- If untreated, moderate NK progresses to severe disease with associated risks of profound vision loss resulting from scarring and corneal perforation³

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Mackie Classification

STAGE 1
Mild

STAGE 2
Moderate

STAGE 3
Severe

- Improve epithelial quality and transparency
- Avoid epithelial breakdown

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

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

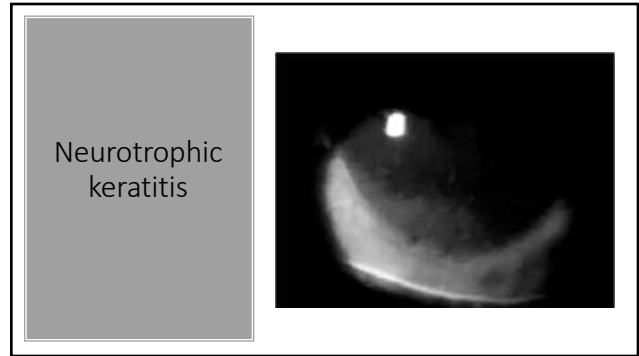
1. Versura P, Giannaccare G, Pellegrini M, Sebastiani S, Campos EC. Neurotrophic keratitis: current challenges and future prospects. Eye Brain. 2018;10:37-45. 2. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. Prog Retin Eye Res. 2018;66:107-131.

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NK Study Group 7 Step Staging

Stage	Clinical Features	Imaging	Stage	Clinical Features	Imaging
0	Altered sensation without keratopathy		Stage 4 (severe)	Persistent or recurrent epithelial defect and stromal scarring without corneal ulceration	
1 (Mild)	Epitheliopathy without stromal haze		Stage 5 (severe)	Persistent or recurrent epithelial defect with corneal ulceration	
2 (Moderate)	Epitheliopathy with stromal haze		Stage 6 (severe)	Corneal perforation	
Stage 3 (severe)	Persistent or recurrent epithelial defects				

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Neurotrophic keratitis

	Early/mild cases (e.g., Stage 1)	Moderate (e.g., Stage 2)	Late/severe cases (e.g., Stage 3)
Discontinue all contact lenses containing topical medications	+	+	+
Medical management			
Topical preservative-free drops	+	+	+
Topical preservative-free gel drops or ointments	+	+	+
Autologous serum drops, human umbilical cord serum, platelet rich plasma	+	+	+
Recombinant human nerve growth factor (prostaglandin)	+	+	+
Prostacyclin topical preservative-free emulsion (including antiangiogenesis)	+	+	+
Matrix metalloproteinase inhibitors	+	+	+
Non-surgical interventions (i.e., office procedures)			
Corneal therapeutic contact lenses	+	+	+
Prose Hyper-seal ocular amniotic membrane	+	+	+
Amniotic occlusion	+	+	+
Symbiont (transcatheter) tissue adhesion	+	+	+
Surgical interventions (i.e., operating room procedures)			
Tarsorrhaphy	+	+	+
Amniotic membrane transplant	+	+	+
Corneal resection	+	+	+

*Treatments rated as potentially optional, depending on the patient's individual circumstances
 †Treatments rated as potentially appropriate, depending on the patient's individual circumstances (not noted in the manuscript)

Dana, R., Farid, 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. Amgen's Myalept takes the top spot while two newcomers enter the GoodRx rankings.

Drug	Company	Price per month (USD)
1. Myalept	Amgen Pharma	71264
2. Revlimid	Horizon Therapeutics	32342
3. Humira	AbbVie	31739
4. Actemra	Horizon Therapeutics	32711
5. Tysabri	Genentech	30939
6. Sildenafil	Takeda	27614
7. Daraprim	Horizon Therapeutics	40009
8. Janskin	Amgen Pharma	46714
9. Xarelto	Bayer	44341
10. Chondral	Horizon	42074

<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 sx, gradually worsening
- Primary symptoms: constant burning, moderate photophobia
- Treated with Restasis, Xiidra, ATs, Warm compresses, plugs, steroids, LipiFlow
- **"NOTHING HELPS!!"**

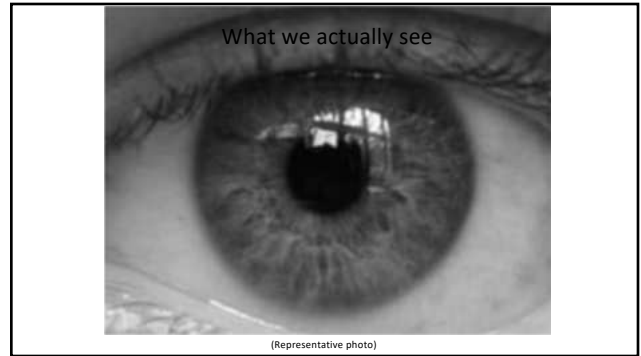
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Signs vs. Symptoms

- 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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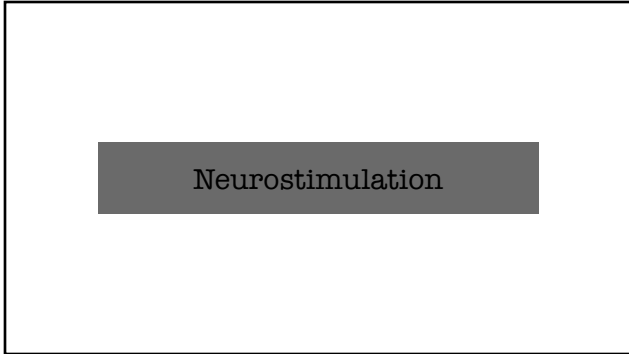
Neuropathic or Neurotrophic

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Treatment: What to Expect for Neuropathic

- **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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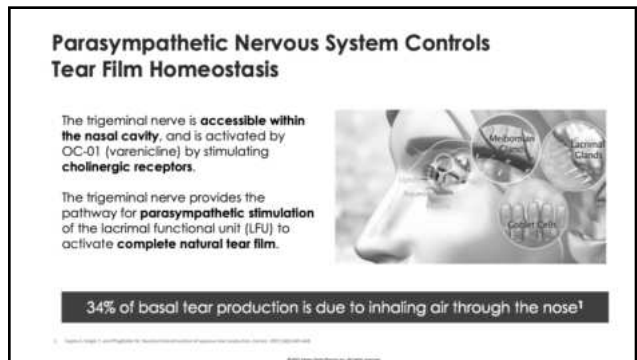
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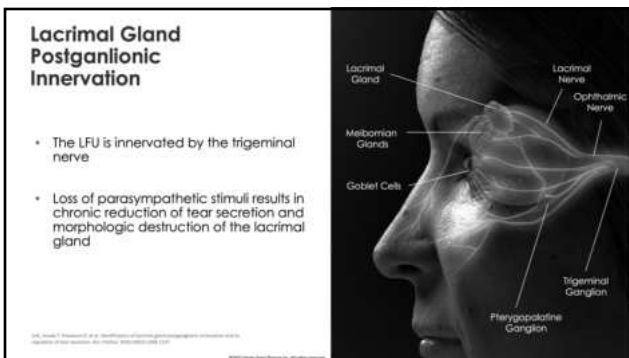
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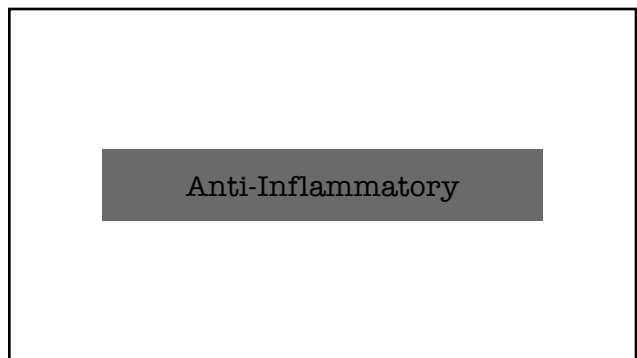
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New Players and Old Friends

- Lotemax SM**
 - (loteprednol etabonate ophthalmic gel) 0.38%
 - tid
- Inveltys**
 - (loteprednol etabonate ophthalmic suspension 1%)
 - bid
- Flarex**
 - (fluorometholone acetate ophthalmic suspension) 0.1%

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Dexamethasone (Ocular Therapeutix)

- dexamethasone ophthalmic insert 0.4% mg
 - Indicated to treat inflammation and pain following cataract surgery
 - Statistically significant level of patients were pain-free on post-op day 8

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Autologous serum tears

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Autologous plasma & nerve regeneration

- Rao (Houston) et al. BIO 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

	Styrene	Control	Experimental	Control	Experimental	Control	Control
Parameter	control	st/1%	control	st/1%	control	control	control
	mean	mean	mean	mean	mean	SD	SD
Styrene	10.0(1.2)	0.0(0.0)	1.2(1.2)	0.1(0.0)	1.7(0.3)	0.0(1.2)	1.0(1.2)
Plasma	10.0(0.0)	0.0(0.0)	0.0	0.0(0.0)	0.0(0.0)	0.0(1.4)	0.1(1.6)
	p=0.002	p=0.000		p=0.000	p=0.000		p=0.000

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

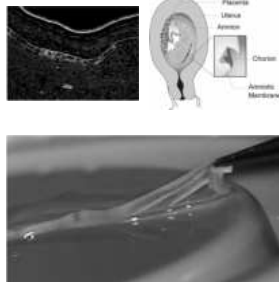
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Amniotic Membrane

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The Amniotic Membrane

- The amniotic membrane is the innermost lining of the placenta (amnion)
- Amniotic membrane shares the same cell origin as the fetus
 - Stem cell behavior
- Structural similarity to all human tissue




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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/mm ² • 3 mo: 18,827 +/- 5453 um/mm ²
Improvement in TBUT	•8.3 +/- 2.5 to 13.9 +/- 2.2
Control group showed no change in all parameters	



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The CRYOTEK™ Method

- Patented and proprietary cryopreservation
- Ensures key active components of the **Extracellular Matrix (ECM)** are retained
- The **only** method that retains both:
 - The integrity of the tissue structure
 - The key active (ECM) components
- Safe and effective
 - Supported by over **300** peer-reviewed articles
 - Over **100,000** implanted
- Bio-Tissue Cryopreserved Amniotic Membrane is the **ONLY** AM granted wound healing indication by the FDA.



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Acellular Amniotic Membrane

ACELLFX


- HCT/P (human cells, tissue, and cellular-based product)
- Nutrient rich
- Collagen III, IV, and V
- Fibronectin
- Laminin
- Proteoglycans
- Thera Pharmaceuticals

Human amniotic membrane sourced from Cesarean donors

Processed without chemicals, cross-linking agents, germicides or antibiotics

Air dried

Sterilized



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Acellular Amniotic Membrane

- Ready to use immediately
 - No thawing
 - No rinsing
- No up/Down orientation
- Flexible membrane with no ring
- Allows for multiple applications
- Convenient storage at room temperature for 5 years
- WOO-WOO




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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 1950s¹
- Cenegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein²

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Recombinant NGF

- Multiple studies support use of NGF to repair damaged nerves
- Cenegermin bkbj (Dome, 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?

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CENEGERMIN CLINICAL TRIALS: Study overview

	NGF0212 (REPARO) (n=156)	NGF0214 (n=48)
Geography	Europe 6 Countries (Italy, Germany, UK, France, Spain, Poland)	USA 11 Clinical Centers
Design	3 treatment arms: (vehicle, cenegermin 10 mcg/mL, cenegermin 20 mcg/mL)	2 treatment arms: (vehicle, cenegermin 20 mcg/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) <small>*Primary analysis was <0.5 mm maximum diameter of fluorescein staining in the lesion area at Week 4.</small>	Week 8 Complete corneal healing (defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area)

1. Bonini S, Lambiasi 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. Plugfelder SC, Nociaro-Gonzalez M, Penz VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: a multicenter randomized vehicle-controlled pivotal trial.

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Study Conclusions

After 8 weeks of treatment, 6 times daily

In most patients across two clinical studies, 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 US

Study NGF0214 (N=24 per group)

US patients with NK in one or both eyes

65.2% completely healed

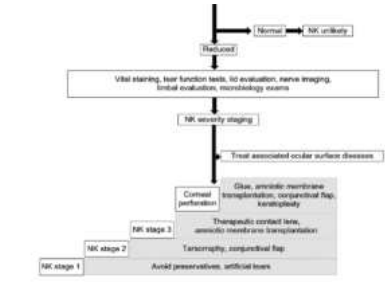
Vehicle response rate 22.7%

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

*Based on REPARO, the study with longest follow-up.

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Treatment Algorithms



The flowchart starts with 'Normal' leading to 'NK unlikely'. 'Reduced' leads to 'Vital staining, tear function tests, ICI evaluation, nerve imaging, clinical evaluation, microbiology screens'. From there, it branches into 'NK severity staging' and 'Treat associated ocular surface disease'. 'NK severity staging' includes 'NK stage 1' (Avoid preservatives, artificial tears), 'NK stage 2' (Tarsorrhaphy, conjunctival flap), and 'NK stage 3' (Therapeutic contact lens, amniotic membrane transplantation). 'Treat associated ocular surface disease' includes 'Gels, amniotic membrane transplantation, conjunctival flap, tarsorrhaphy' and 'Corneal perforation'.

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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 Cenegermin-bkbj ophthalmic solution 0.002% (20 mcg/mL) 	<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 revascularization Sutured AMT

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Thank you