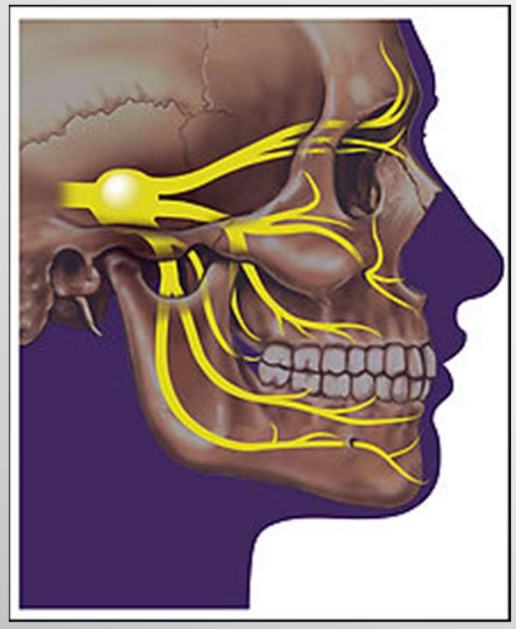
Advances in Neurotrophic Keratopathy

Todd A. Zelczak, OD, FAAO

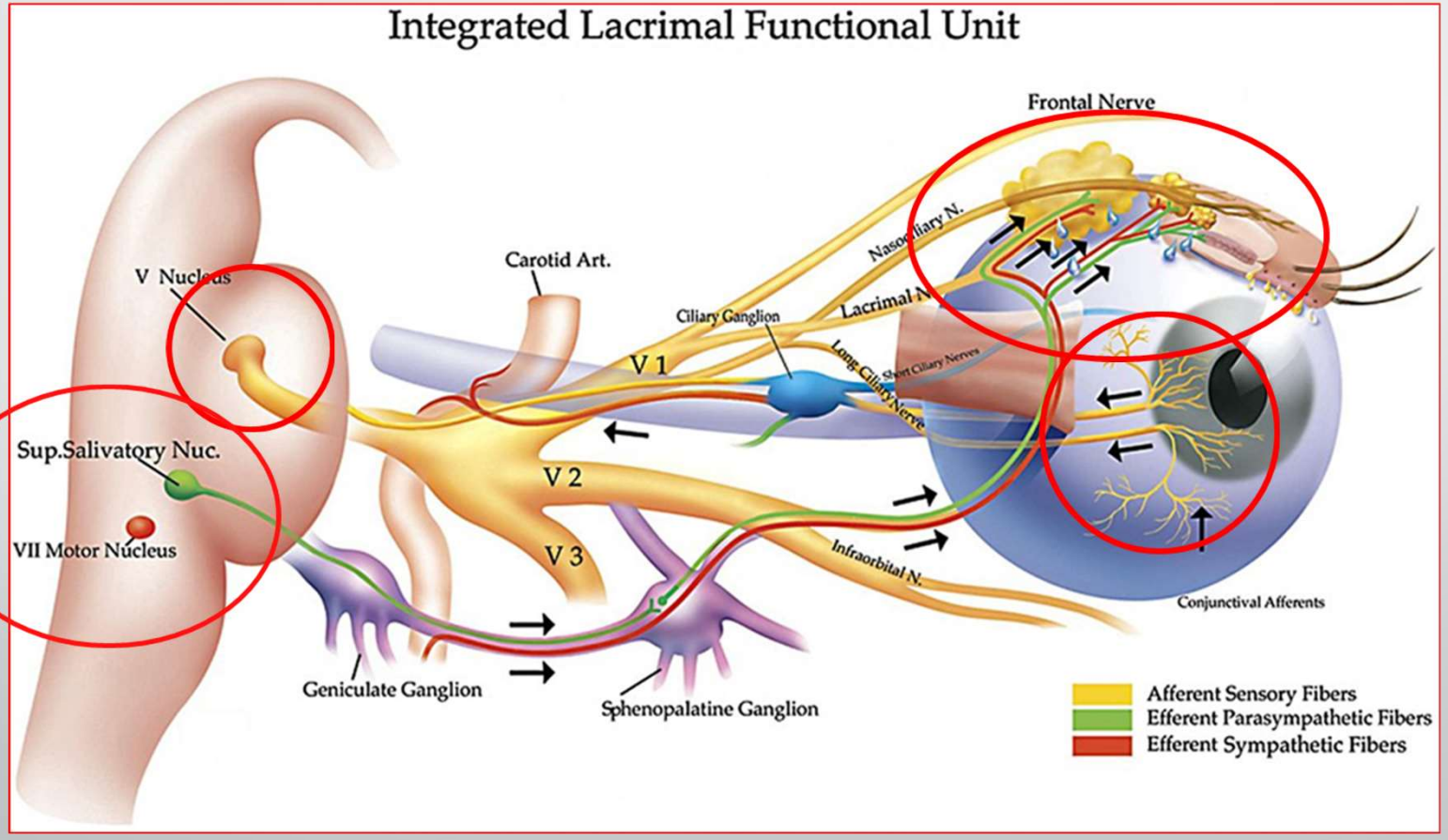
Midwest Optometric Society

Corneal Anatomy

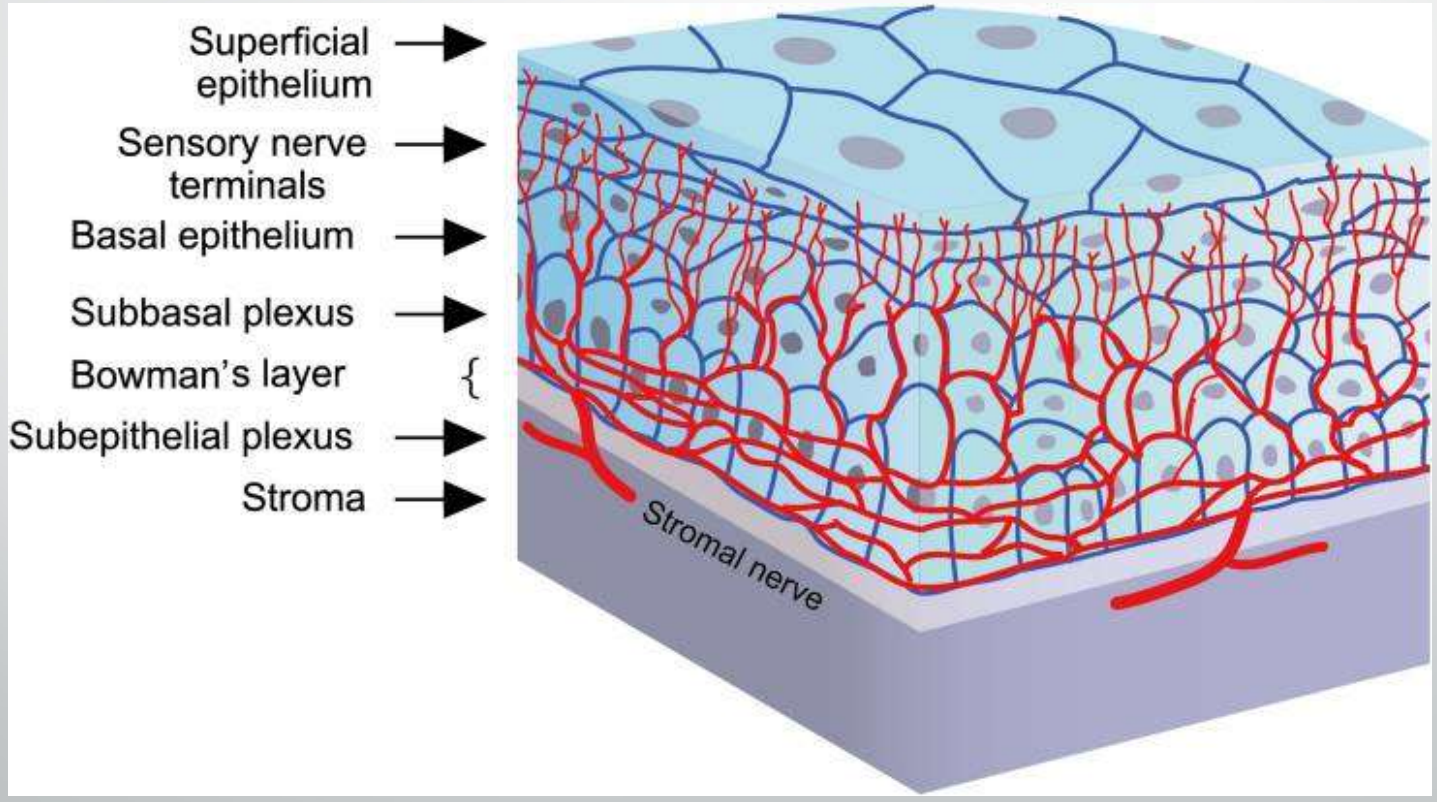


- Most densely innervated tissue in the body
- Ophthalmic branch of trigeminal nerve/autonomic nerves
- Essential for maintaining integrity and clarity of cornea

Corneal Anatomy



Corneal Anatomy



Corneal Maintenance and Healing

Through the release of Trophic Factors

Corneal Nerves

- **Substance P**
- **Calcitonin gene-related peptide**
- Acetylcholine
- Noradrenaline
- Serotonin
- Neuropeptide Y
- Vasointestinal peptide

Corneal Epithelial Cells

- **Nerve growth factor (NGF)**
- Epidermal growth factor
- Ciliary neurotrophic factor
- Glial-cell-derived neurotrophic factor

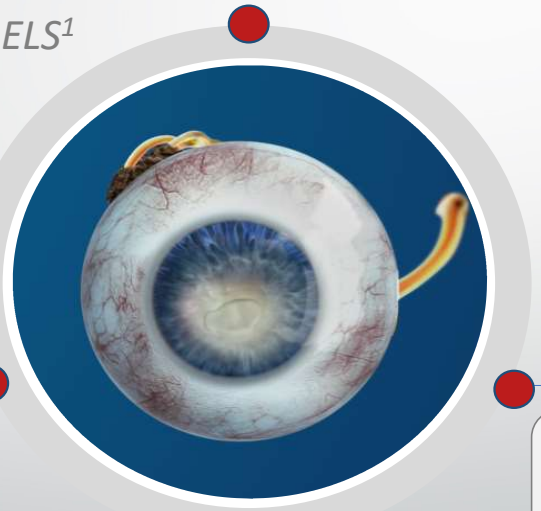
Endogenous NGF maintains corneal integrity by three mechanisms

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]

CORNEAL INNERVATION

SHOWN IN PRECLINICAL MODELS[1]

NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves[2,3]



NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion[1,4]

TEAR SECRETION

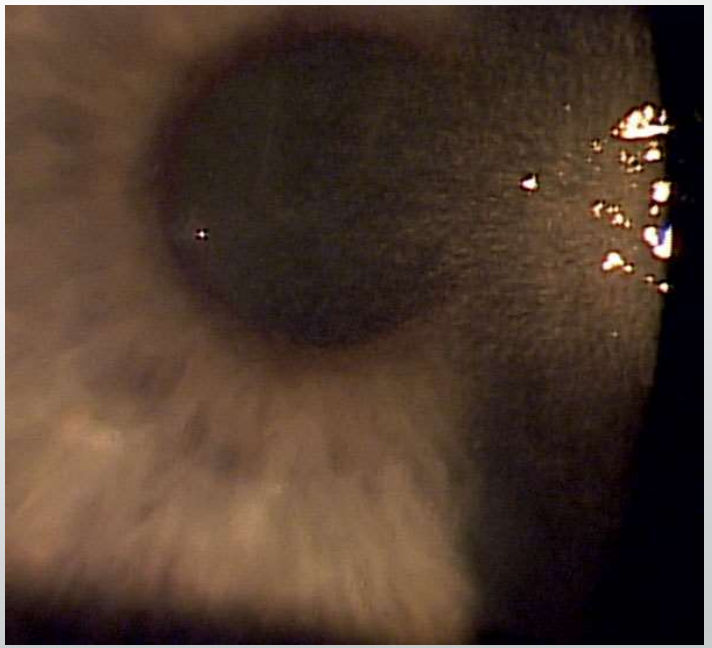
CELL PROLIFERATION AND DIFFERENTIATION

NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells[1]

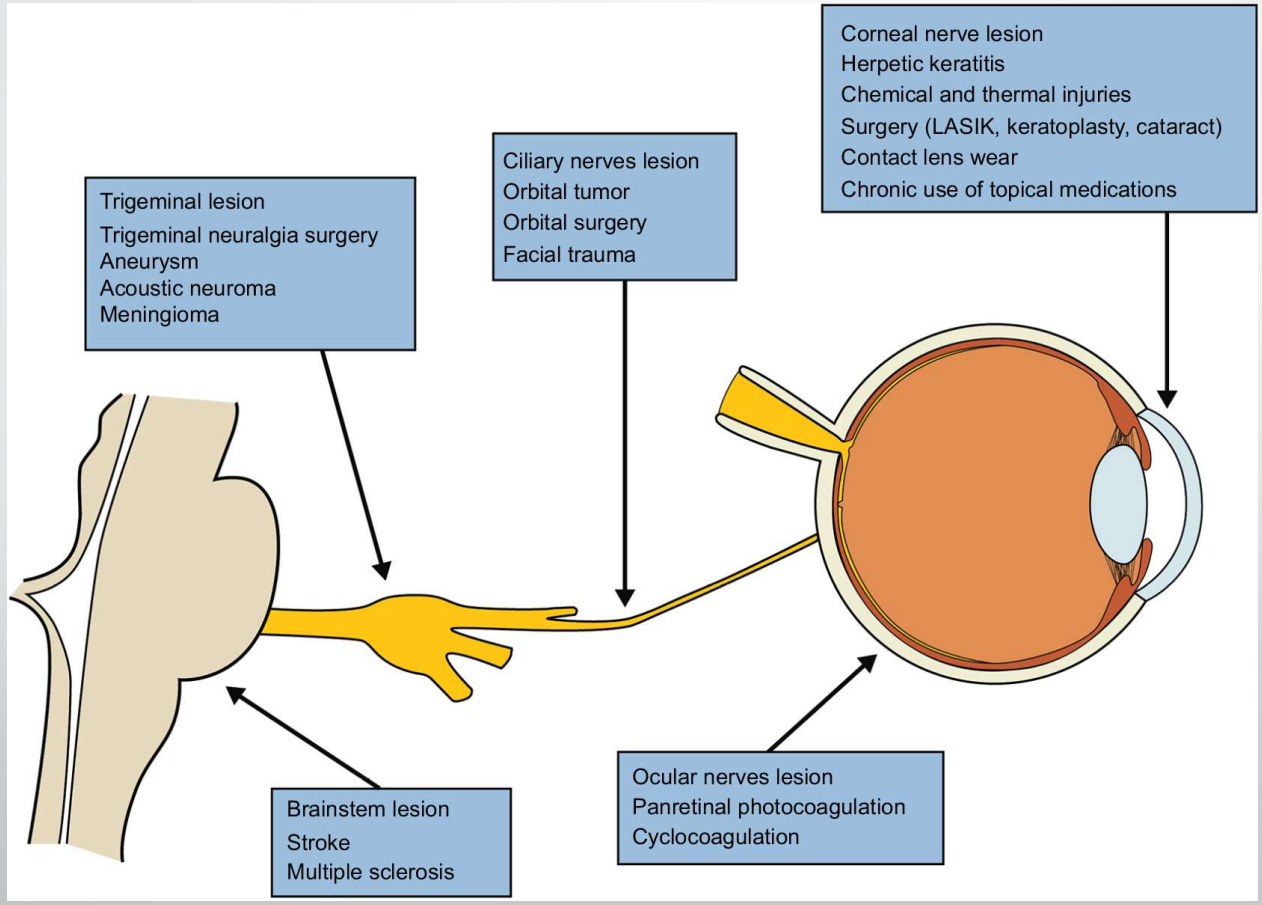
1. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017 Apr;232(4):717-724. 2. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res.* 2003 May;76(5):521-42. 3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-9. 4. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea*. 2010;29:1163–1168

Neurotrophic Keratitis

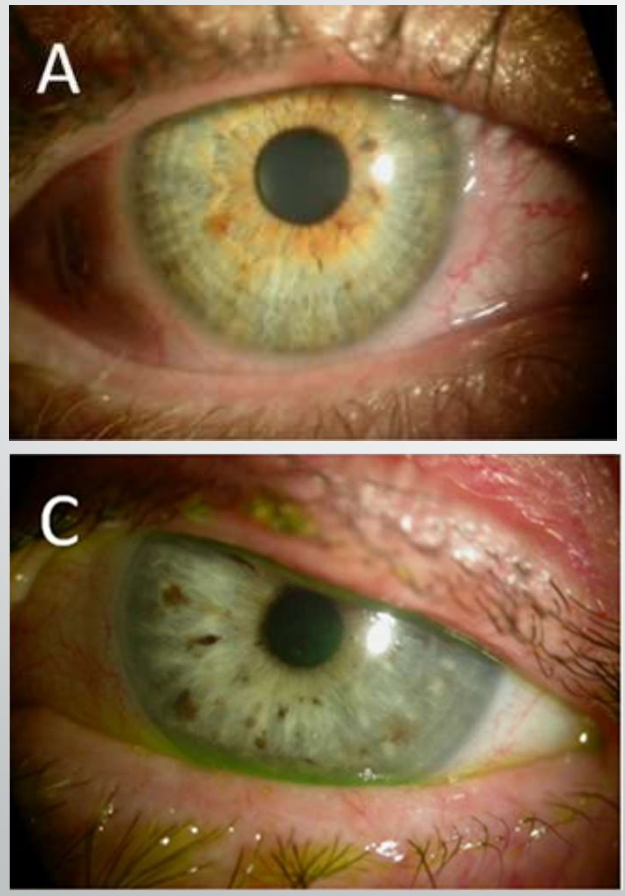
- Rare, degenerative corneal disease
- Damage to trigeminal innervation
- Impaired corneal healing
- Leads to epithelial changes
  - Punctate epithelial keratopathy
  - Persistent epithelial defects
  - Corneal ulceration
  - Corneal Perforation



Causes of Neurotrophic Keratitis

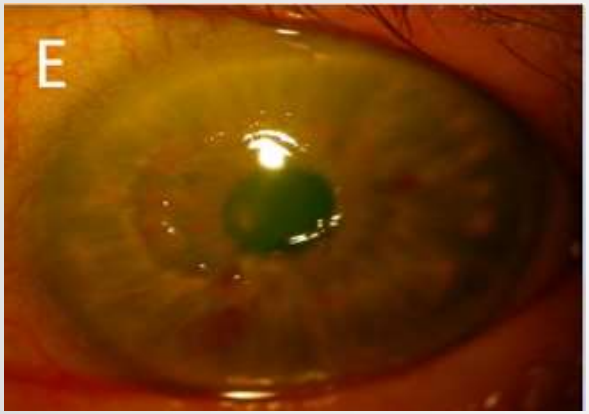


Stages of Neurotrophic Keratopathy



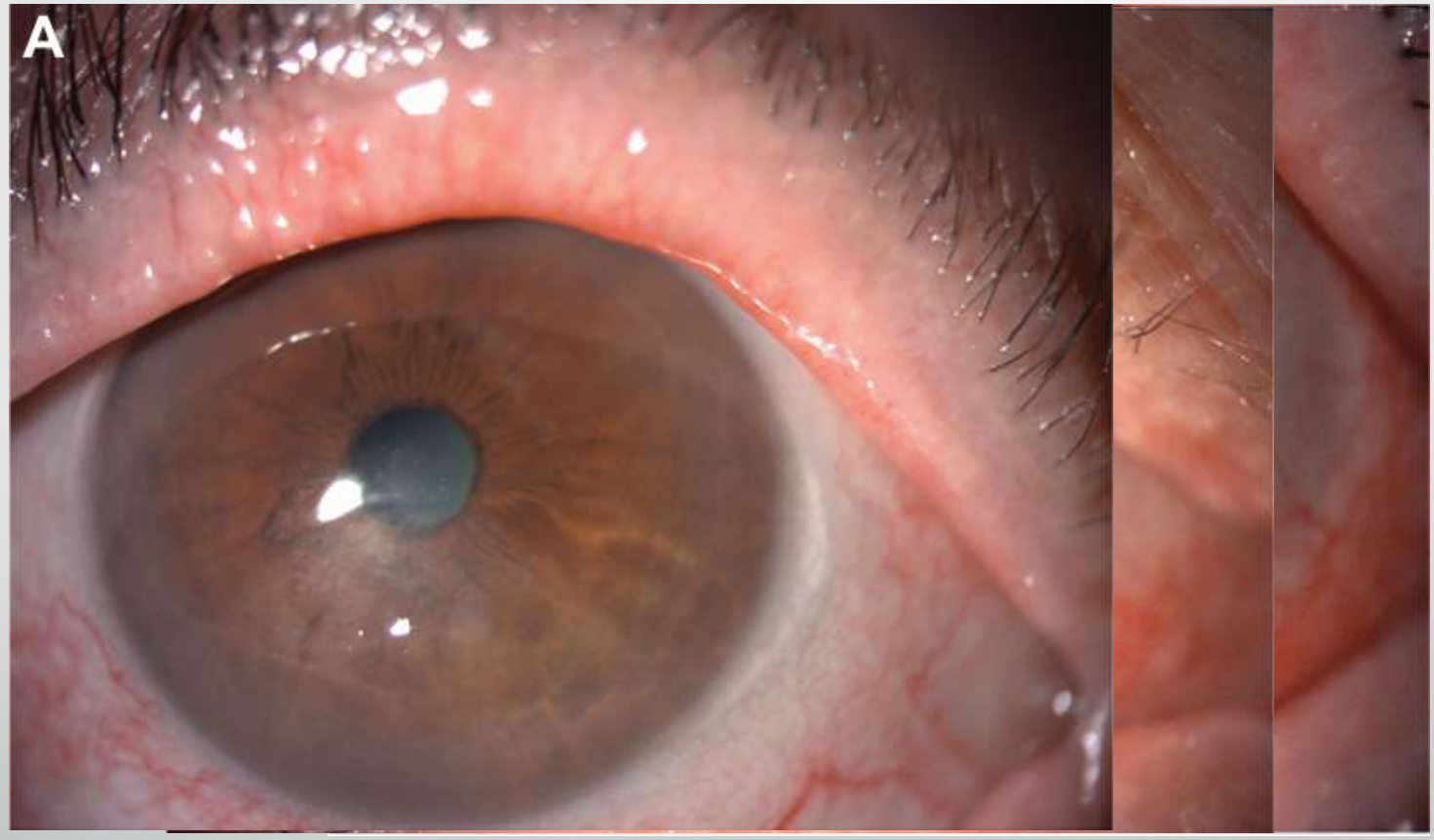
- Impaired Corneal Sensitivity
- Stage 1 - Mild

Stages of Neurotrophic Keratopathy



- Stage 2 – Moderate

- Stage 3 - Severe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Diagnosis of Neurotrophic Keratopathy

- Clinical history

  Identify potentially associated ocular/systemic disease

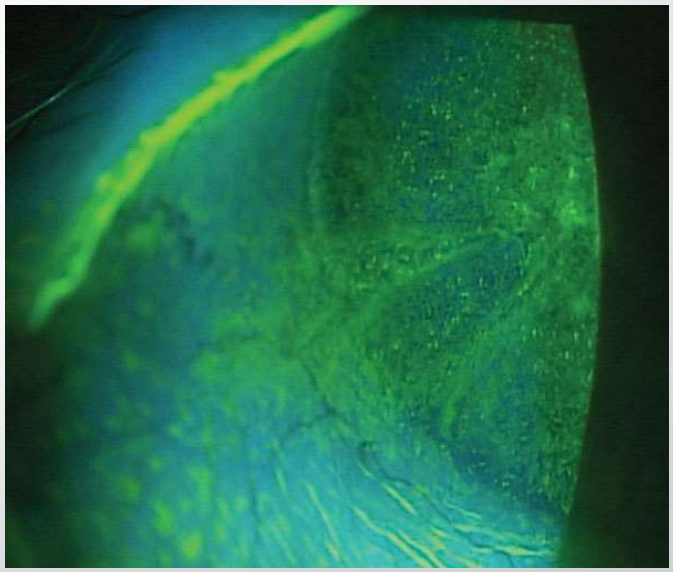
- Clinical examination

  Persistent epithelial defects

  Vital dye staining

  Tear film dynamics (TBUT, Shirmer…)

  Absence of corneal sensitivity



**NK should be always suspected in case of significant discrepancy between ocular signs and symptoms

Management of Neurotrophic Keratopathy

- Based on stage and severity of the disease
  - Medical Management
  - Non-Medical Management
  - Surgical Management
- Objective: Arrest progression and reverse neurotrophic changes

Management of Neurotrophic Keratopathy

Stage 1

- D/C oc/systemic meds associated w ocular toxicity
- PF artificial tears/oints
- Treatment of associated ocular surface diseases(i.e. DED~topical cyclosporine)
- Autogolous serum drops

Stage 2

- More frequent monitoring due to risk of ulcer/melt
- Stage 1 treatment
- Topical antibiotics to prevent infections
- Steroids used w CAUTION
- Therapeutic contact lenses
- Amniotic Membranes

Management of Neurotrophic Keratopathy

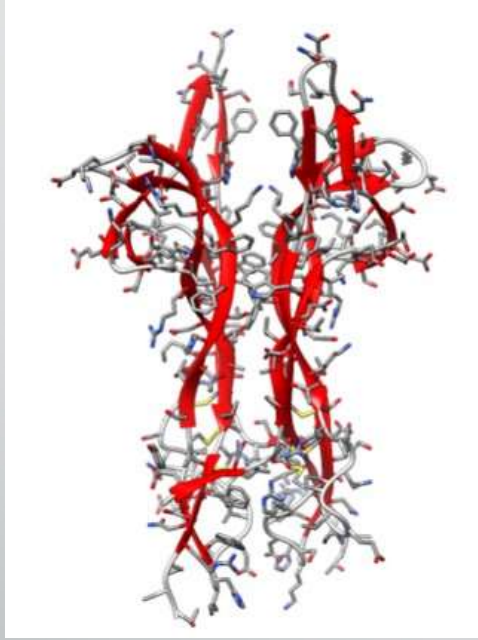
Stage 3

- Unresponsive to Stage 1 and 2 txs
- Amniotic Membrane
- Tarsorrhaphy
- Botulism-induced ptosis
- Conjunctival flap
- Penetrating Keratoplasty

Limitations of Conventional Treatment

- Procedures usually performed late
- Hi risk of corneal scarring and poor vision
- Cosmetic
- Failure to address problem of corneal anesthesia
- Fail to provide permanent cure

Nerve Growth Factor (NGF)



- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons[1]
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950[1]
- NGF is known to support corneal integrity via many mechanisms

1. 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. 2. Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

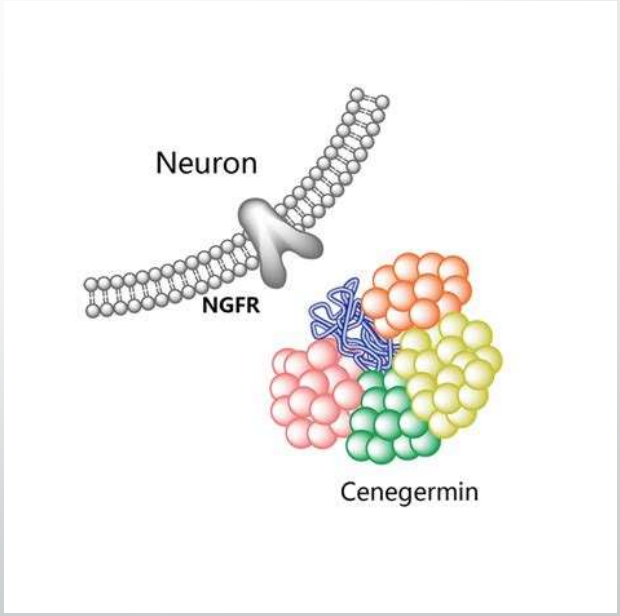
OXERVATE™ (cenegermin-bkbj 20 mcg/ml) was approved by FDA in August 2018

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

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. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

Cenegermin(Oxervate) (rhNGF)

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



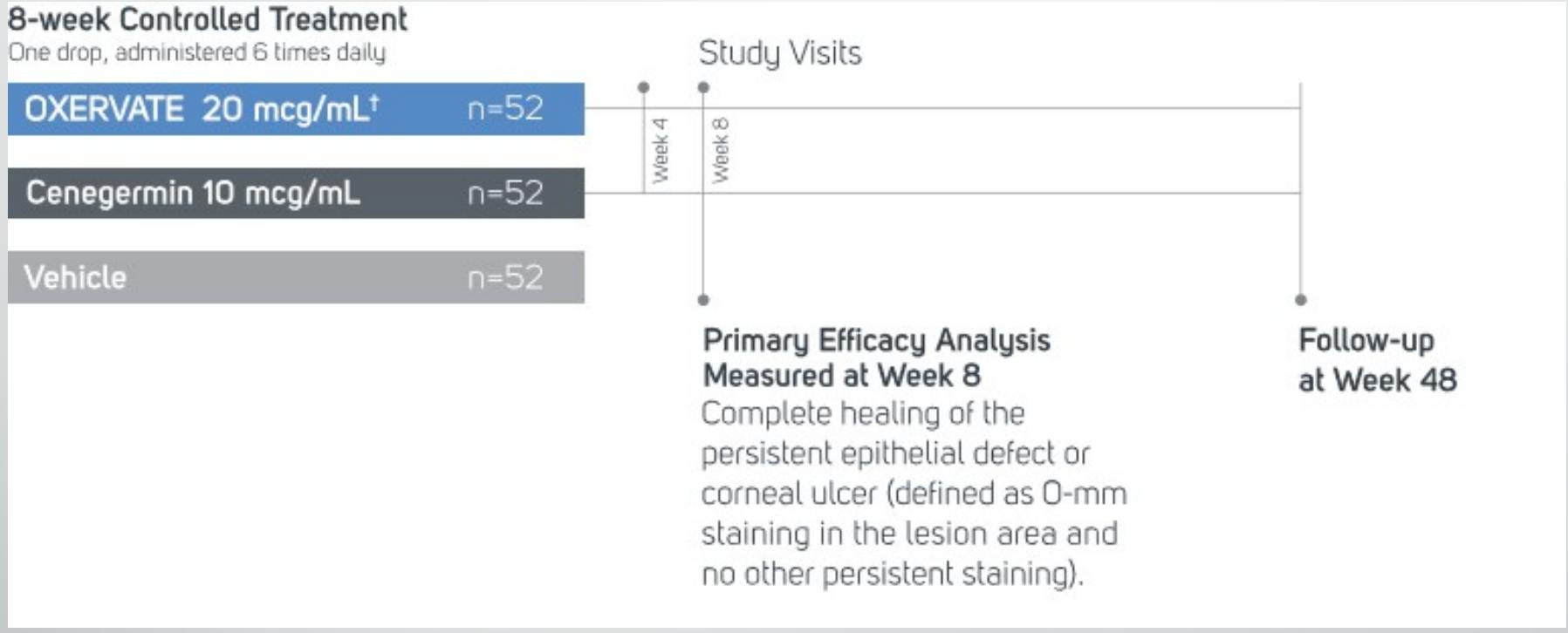
OXERVATE™ (cenegermin-bkbj 20 mcg/ml) was studied in the Largest Combined Population of NK Patients in Controlled Trials

	NGF0212 (REPARO) (n=156)	NGF0214 (n=48)
Geography	Europe 6 Countries (Italy, Germany, UK, France, Spain, Poland) 32 Clinical Centers	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) *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)

FDA approval was based on complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment.

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. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

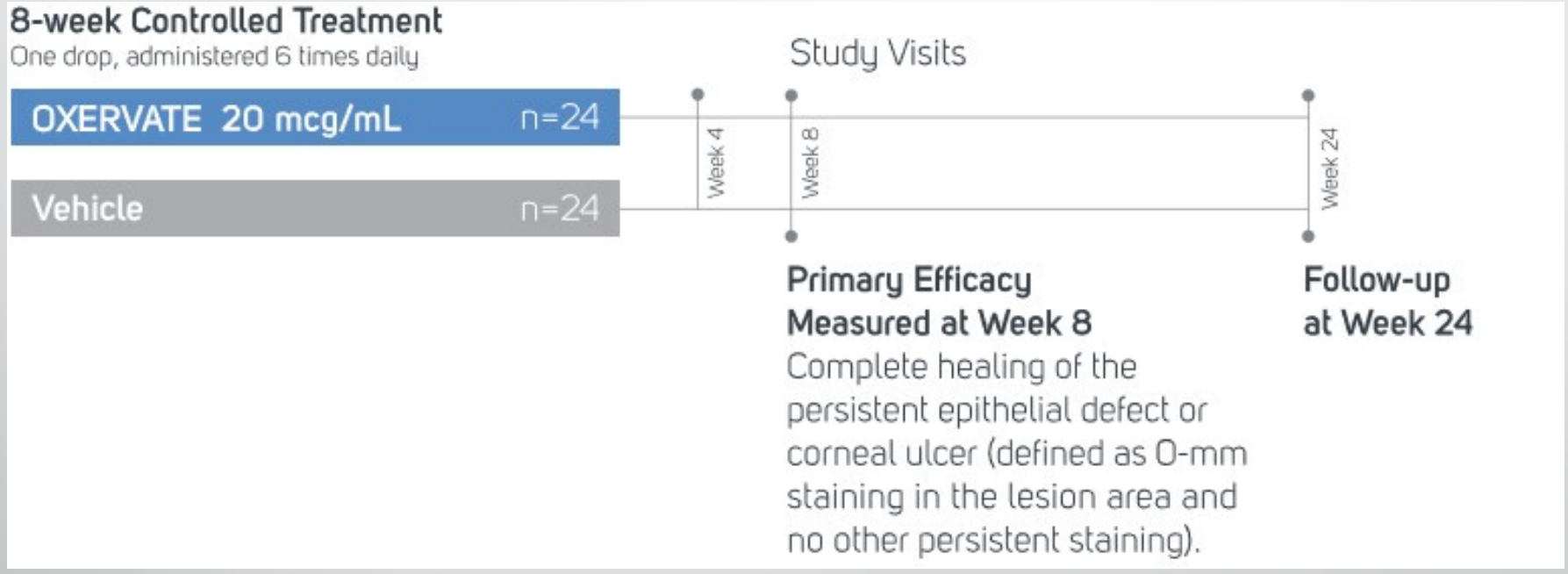
Clinical Trials: Study Design
OXERVATE™ (cenegermin-bkbj 20 mcg/ml)



All patients enrolled had moderate (stage 2) or severe (stage 3) neurotrophic keratitis

*Phase II data only.
†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.

Clinical Trials: Study Design
OXERVATE™ (cenegermin-bkbj 20 mcg/ml)



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Clinical Trials: Study Design

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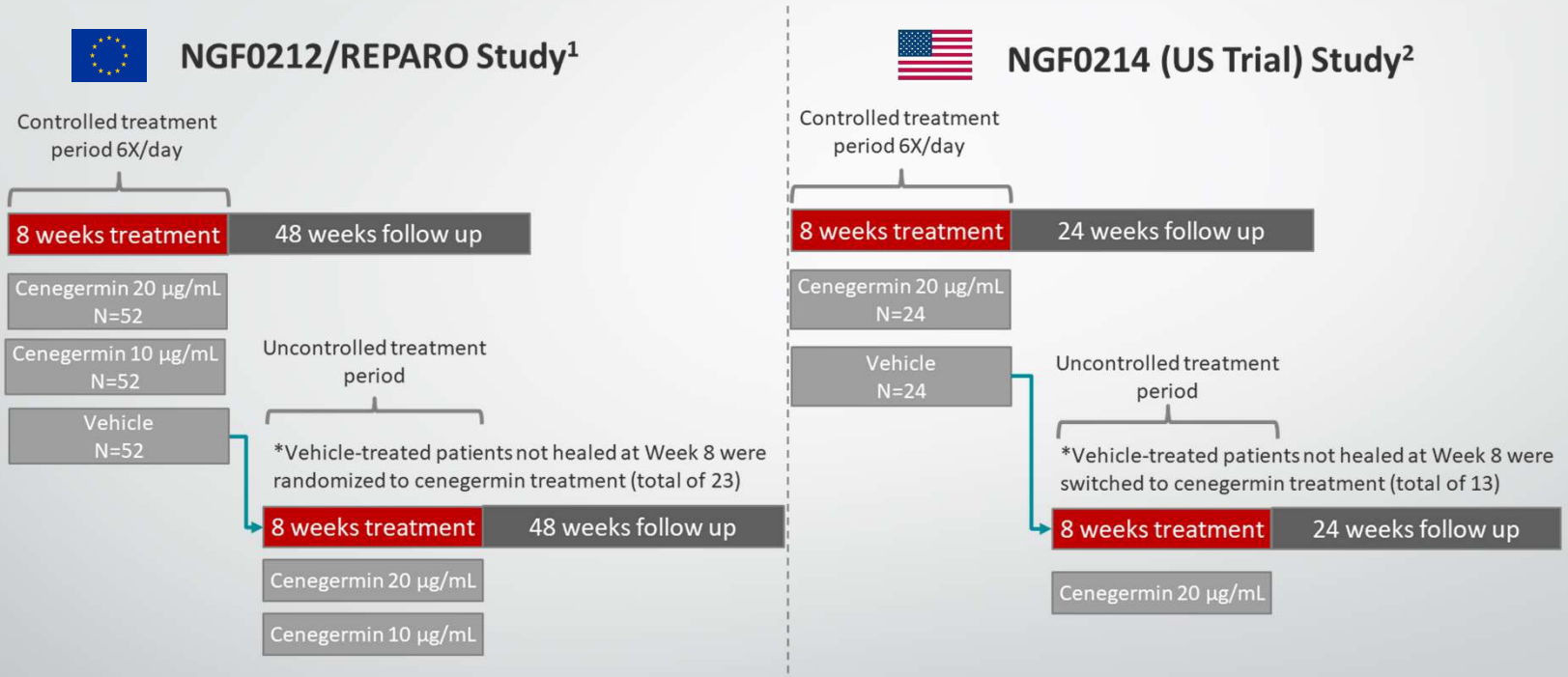

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Clinical Trials: History of NK

OXERVATE™ (cenegermin-bkbj 20 mcg/ml)

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

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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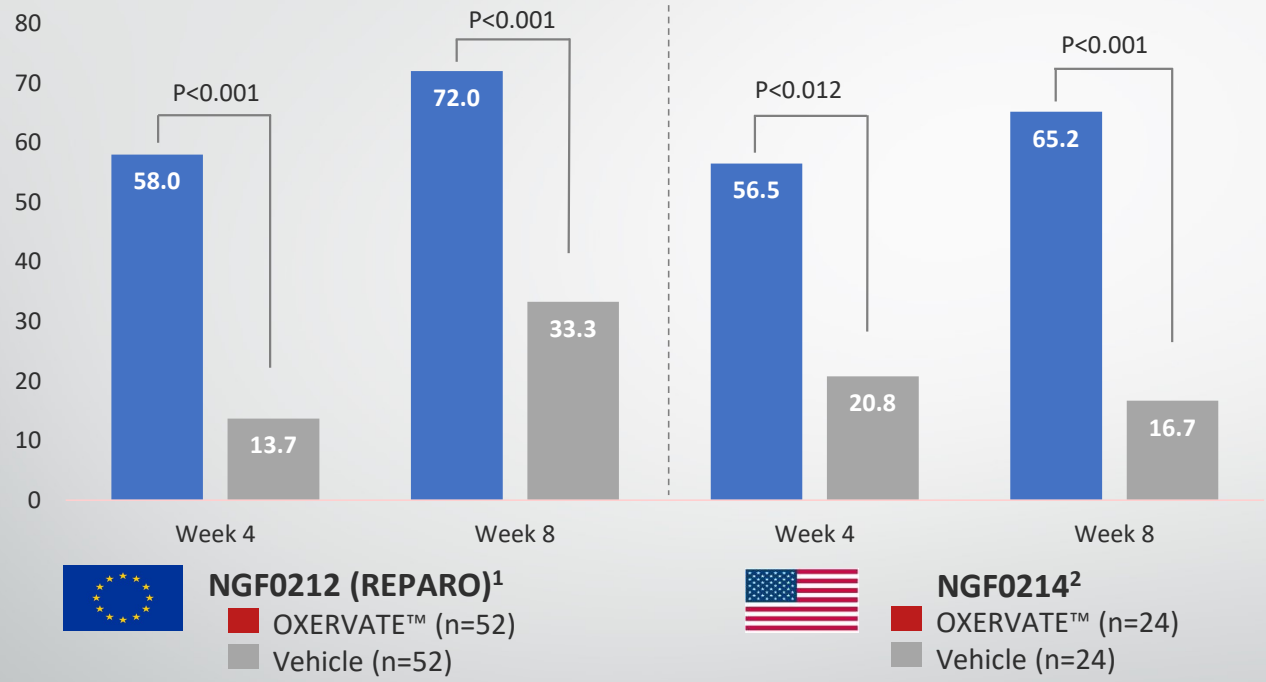
Clinical Trials: Efficacy

OXERVATE™ (cenegermin-bkbj 20 mcg/ml)



Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients
Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing[3]

Complete Corneal Healing* in up to 72% of patients receiving OXERVATE at Week 8

Complete corneal healing defined as 0-mm staining in the lesion area and no other persistent staining in the rest of the cornea after 8 weeks of treatment(last post-baseline observation carried forward; chi-squared test).

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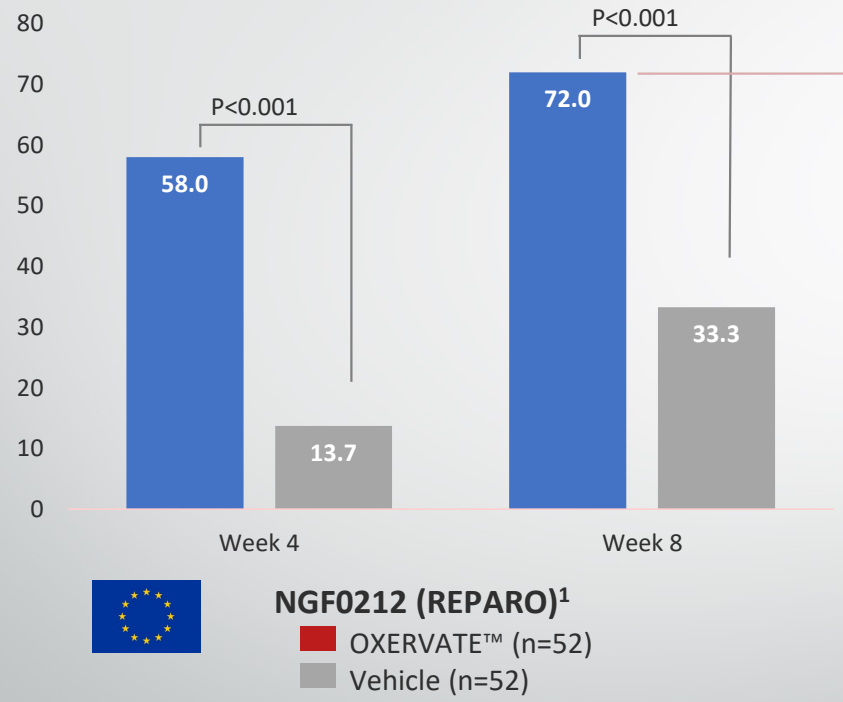
Clinical Trials: Efficacy

OXERVATE™ (cenegermin-bkbj 20 mcg/ml)



80%

of patients who achieved complete corneal healing* in Study NGF0212 (REPARO) were still healed 48 weeks after completing one 8-week OXERVATE™ treatment cycle

*Complete corneal healing defined as 0-mm staining in the lesion area and no other persistent staining in the rest of the cornea after 8 weeks of treatment

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Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing[3]

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Clinical Trials: Pooled Safety Report

OXERVATE™ (cenegermin-bkbj 20 mcg/ml)

- 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

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)

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

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. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% [20 mcg/ml] [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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

After 8 weeks of treatment, 6 times daily

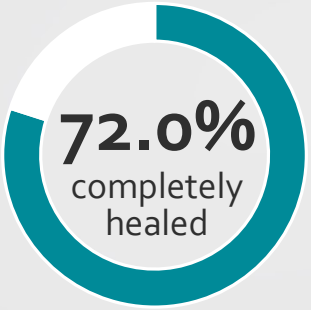
In the majority of patients across two clinical studies OXERVATE™ (cenegermin ophthalmic solution 0.002%) was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

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

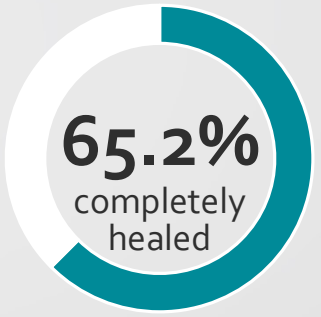


Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147



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

Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing[3]

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

- OXERVATE™ is supplied in a weekly carton containing 7 multiple-dose vials*
- A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

- 7 vial adapters
- 42 pipettes
- 42 sterile disinfectant wipes
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra wipes are included as spares

**Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Dosing and Administration

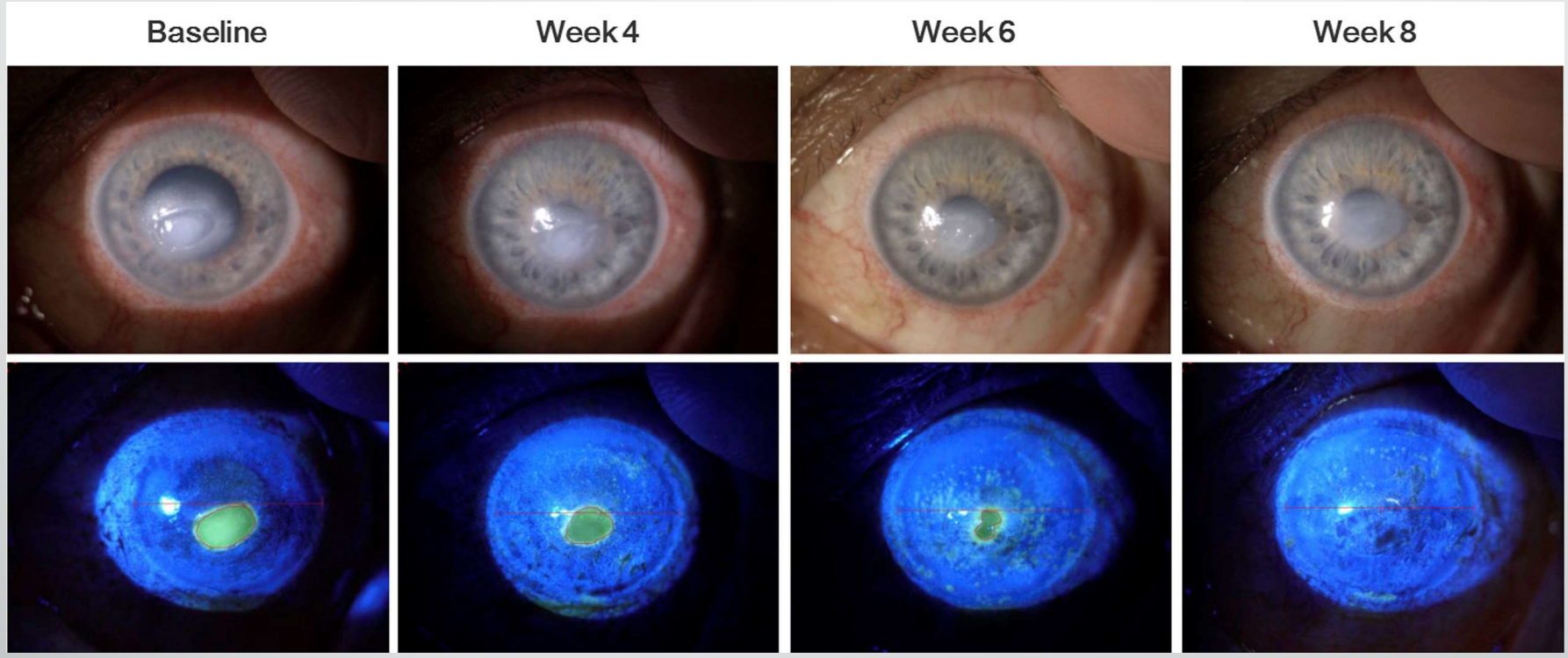
Instill 1 drop of OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% in the affected eye(s)

Every 2 hours

Apply 6 times daily

Continue for 8 weeks

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.



Healing of a neurotrophic corneal ulcer in a patient treated with Oxervate™, viewed under white light (above/top row) and with fluorescein staining under cobalt-blue light (below/bottom row).

Bonini S, Lambiase A, Rama P, Sinigaglia F, Allegretti M, Chao W, Mantelli F, for the REPARO Study Group. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-43.

Summary (Cenegermin)

- NK is underdiagnosed condition, may lead to corneal blindness
- Previous txs for NK palliative and limited to reducing symptoms
- First ever application of human NGF as drug or treatment
- 1st line treatment w stage 2-3 NK
- Demonstrated to be safe and effective in clinical trials