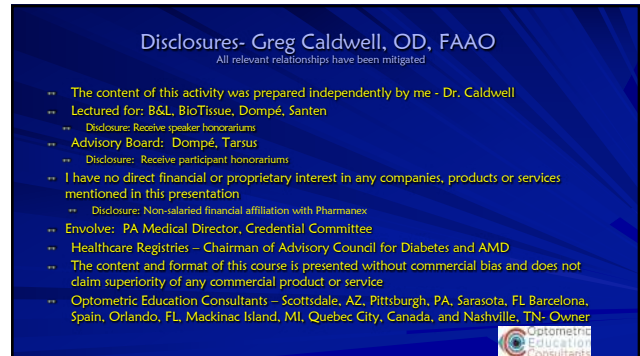


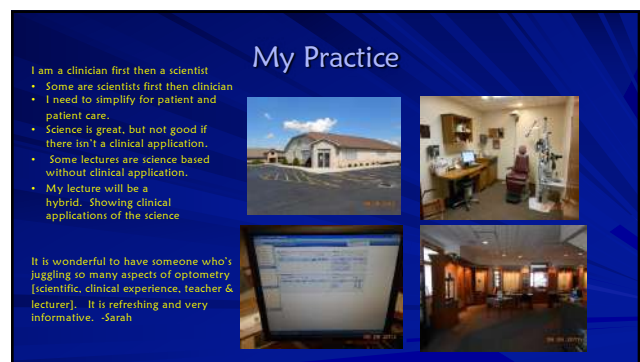
2



3



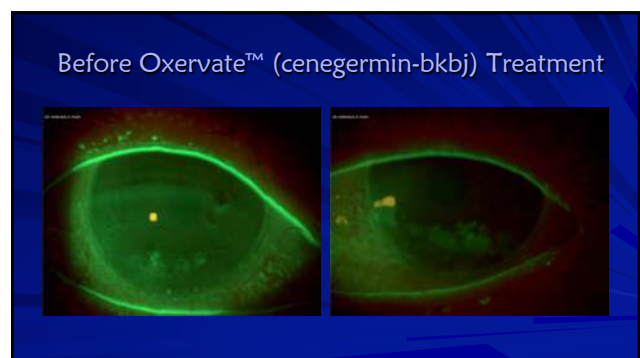
4



5

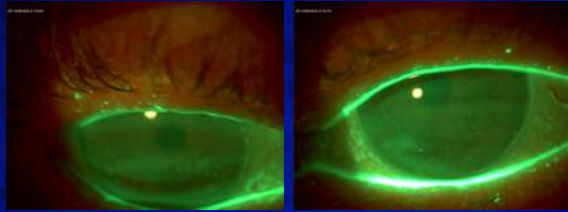


6



7

After Oxervate™ (cenegermin-bkbj) Treatment



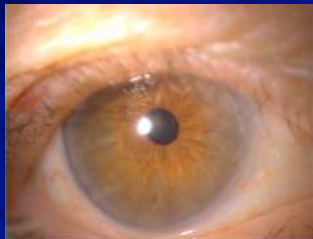
8

Corneal Sensitivity Testing



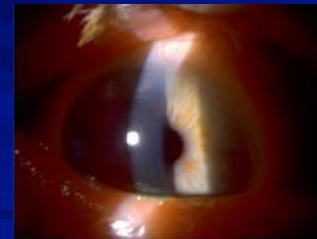
9

Cornea Sensitive Testing – Another Patient



10

Cornea Sensitive Testing – Yet Another Patient



11

Oxervate™ (cenegermin-bkbj)

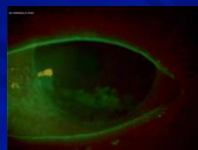
Grading corneal sensitivity: (Cotton Tip)

- * Normal
- * Reduced
- * Absent

- * Reduced in all quadrants and centrally
- * Absent inferior quadrant, reduced everywhere else

Neurotrophic Keratitis: (Staining)

- * Mild – Stage 1
- * Moderate – Stage 2
- * Severe – Stage 3



12

Neurotrophic Keratitis is a Degenerative Disease

The Mackie classification represents one way to assess or grade NK – stage or progression



13



17



Pathophysiology of NK¹

- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production and blink rate due to the reduction of trigeminal reflexes
- Impairment of trigeminal innervation leads to decreased corneal epithelium renewal and healing rate, and ultimately the development of NK

Penetration of nerve into the epithelium

1. Montenegro L, et al. J Cell Pathol. 2017;232:717-24. 2. Miller LJ, et al. Exp Eye Res. 2003;76:521-43.

20

Trigeminal nerve damage leading to NK¹

Impaired corneal trigeminal innervation

Impairment of trophic supply

Impairment of trigeminal reflexes

Corneal epithelial alterations

Impairment of corneal healing

Reduced tear film production & blink rate

Spontaneous corneal epithelial breakdown

Neurotrophic keratitis

Adapted from: 1. Montenegro L, et al. J Cell Pathol. 2017;232:717-24.

21

Etiologies Associated with NK

Ocular <ul style="list-style-type: none"> Herpes (simplex or zoster) infection Other infections e.g. acanthamoeba Chemical or physical burn Abuse of topical anaesthetics Drug toxicity <u>Chronic ocular surface injury or inflammation</u> Ocular surgery Cataract surgery LASIK, PRK PK and DALK Collagen crosslinking for keratoconus Vitrectomy for retinal detachment Photocoagulation for diabetic retinopathy Post-surgical or laser treatment Routine laser for proliferative diabetic retinopathy Contact lenses Orbital neoplasia Corneal dystrophies 	Central nervous system <ul style="list-style-type: none"> Neoplasm Aneurysms Stroke Degenerative CNS disorders Post-neurosurgical procedures <ul style="list-style-type: none"> For acoustic neuroma For trigeminal neuralgia Other surgical injury to trigeminal nerve 	Systemic <ul style="list-style-type: none"> Diabetes mellitus Leprosy Vitamin A deficiency Amyloidosis Multiple sclerosis
---	---	---

Genetic

- Riley-Day syndrome (familial dysautonomia)
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoesthesia

DALK=deep anterior lamellar keratoplasty; LASEK=layer in situ keratomileusis; PK=penetrating keratoplasty; DSK=deep anterior lamellar keratoplasty

1. Dua HS, et al. Prog Retin Eye Res. 2018; doi: 10.1016/j.preteyres.2018.04.003.

22

NK classification

Stage 1: Mild

(Epithelial changes only without epithelial defect): Epithelial irregularity without frank epithelial defect, tear film instability and symptoms (hyper-aesthesia) with reduced or absent sensations in one or more quadrants of the cornea

Stage 2: Moderately

(Epithelial defect without stromal defect): Frank persistent epithelial defect and corneal hypo-aesthesia/ anaesthesia

Stage 3: Severe

(Stromal involvement): Stromal involvement from corneal ulcer to lysis to perforation, with corneal hypo-aesthesia/ anaesthesia

1. Dua HS, et al. Prog Retin Eye Res. 2018; doi: 10.1016/j.preteyres.2018.04.003. [Back ahead of print]. 2. Montenegro L, et al. J Cell Pathol. 2017;232:717-24. 3. Dua HS, et al. J Cell Pathol. 2017;232:717-24.

23

Assessment of Corneal Sensitivity is Essential to Confirm NK diagnosis¹

Ocular symptoms

History

Clinical examination and tests

NK suspected

Test corneal sensitivity

Normal

NK unlikely

Reduced

Further tests required

Corneal sensitivity tests:²

- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

1. Dua HS, et al. Prog Retin Eye Res. 2018; doi: 10.1016/j.preteyres.2018.04.003. [Back ahead of print]. 2. Montenegro L, et al. J Cell Pathol. 2017;232:717-24.

24

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 MODELS¹

CORNEAL INNERVATION

NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion^{1,4}

TEAR SECRETION

NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves^{2,3}

CELL PROLIFERATION AND DIFFERENTIATION

NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells⁵

1. Montenegro L, Wilson-Gordic S, Nader M, Sachdev M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. J Cell Physiol. 2017;161:1033-1043. 2. Montenegro L, Wilson-Gordic S, Nader M, Sachdev M. The corneal nerve structure, content and function. J Cell Physiol. 2017;161:1033-1043. 3. Montenegro L, Wilson-Gordic S, Nader M, Sachdev M. The role of corneal nerves in the pathogenesis of neurotrophic keratitis. Clin Ophthalmol. 2018;12:16-24. 4. Dua HS, et al. J Cell Pathol. 2017;232:717-24. 5. Dua HS, et al. J Cell Pathol. 2017;232:717-24.

25




26

Biologic Drugs

- Biologic therapies include wide range of medical products
 - First-generation biologic therapies
 - Vaccines
 - Blood products
 - Stem cell injections
- Today, when people talk about "biologics" they usually mean the second-generation biologic therapy drugs
 - Humira, Remicade, Enbrel
- Biologic therapies
 - Cannot be made using a simple chemical reaction
 - Mixing ingredients together in a laboratory, the way conventional drugs are made
 - Are made using living organisms

27



Question?

Biologic drugs are:

- Large molecules
- Small molecules
- Nano-particles (super small molecules)
- I don't know, that is why I am here

28

Small Molecule Drugs versus Biologics

- Small molecule drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions
 - Organic chemistry
 - Inorganic chemistry
- Biologics are made by harvesting the substances produced and secreted by constructed cells
 - Genetic engineering – is the closest manufacturing process of a biologic drug

29

Biologic Drugs versus Small Molecule Drugs

- Biologic Drugs**
 - Larger, complex, dynamic structures
 - Diverse populations of molecules
 - Not easily characterized
 - Complicated manufacturing
 - Example: Teprotumumab (Tepvezza)
- Small Molecule Drugs**
 - Synthetic
 - Manufactured using a defined chemical process
 - Smaller and simpler
 - Example: Aspirin


30

Size and Complexity of Biologic Drugs

Size & Complexity – Small Molecule Drugs & Proteins		
	Small Molecule Drug	Large Molecule Drug
Size	Aspirin ~21 atoms	Insulin ~5,800 atoms
Complexity	Bike ~20 lbs	Car ~3,000 lbs
		Business Jet ~30,000 lbs (retired fuel)

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2811111/>

31

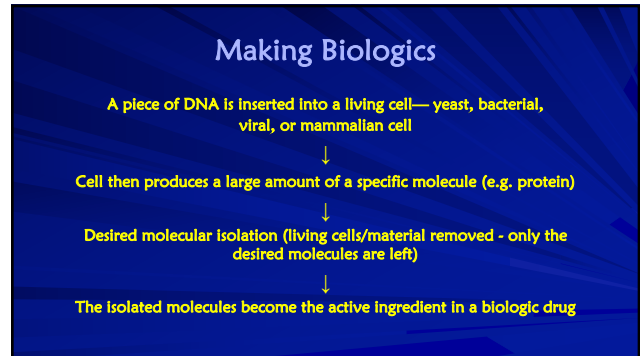


Question?

Biologic drugs are produced by inserting DNA into:

- A. Yeast
- B. Bacteria
- C. Virus
- D. All the above
- E. I don't know, that is why I am here

32

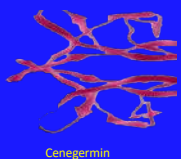
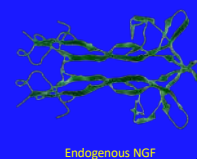


33



34

Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues

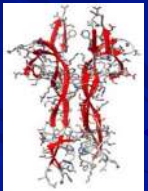
Cenegermin Endogenous NGF

Cenegermin-bkbj, the active ingredient in the FDA-approved OXERVATE™ (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL), is structurally identical to the human NGF protein found in ocular tissues

35

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



1. Lundquist R, Rosen P, Bennett V, Gearing H, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med 1998;339:1373-80. 2. Vardar R. New Drug. Toxicity Data. Submitting Neurotrophic Keratitis. JAMA 2018;320(10):1100

36

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) (0.1% package insert), Boston, MA, Somax U.S., Inc., 2018

37

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)

2 Every 2 hours

6 Apply 6 times daily

8 Continue for 8 weeks

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) (0.5 package insert) Boston, MA: Dompé U.S., Inc.; 2018.

38

Let's Hear From a Patient

April 7, 2020 - After 1 week

April 21, 2020 - After 3 weeks

May 12, 2020 - After 6 weeks

39

Study Conclusions

After 8 weeks of treatment, 6 times daily

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

Study NCF0212 (REPAIR) (N=52 per group)

72.0% Vehicle Healed

Study NCF0214 (N=24 per group)

65.2% Completely Healed

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

*Based on REPAIR, 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 frequent in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

1. Boudé L, Lenthaye A, Bony P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of OXERVATE™ (Cenegermin-bkbj) in Patients with Neurotrophic Keratitis. Ophthalmology. 2018;125:1532-1540. 2. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) (0.5 package insert) Boston, MA: Dompé U.S., Inc.; 2018.

40

OXERVATE™ (cenegermin-bkbj)

- Adverse reactions: very well tolerated
- The most common adverse reaction in clinical trials
 - eye pain, corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears
- Contact lenses (therapeutic or corrective) should be removed before applying cenegermin
 - presence of a contact lens may limit the distribution of cenegermin-bkbj onto the corneal lesion
 - Lenses may be reinserted 15 minutes after administration.

41

Crime and Punishment Match

42

Question and Thank You!

The Non-Healing Cornea Neurotrophic Keratitis

Greg Caldwell, OD, FAAO

Mackinac Island Northern Escape
Optometric Education Consultants
Saturday, August 19, 2023

43