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CLINICAL STUDY PROTOCOL

Title:	An 8-week, multicenter, open label, prospective study with 24 weeks of follow-up to evaluate safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in patients with Stage 1 Neurotrophic Keratitis (NK)
Short Title:	DEFENDO
Study Number:	NGF0120
EudraCT Number/IND:	115892
Study Product:	OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution
Phase of the study:	IV
Protocol Version - Date:	**Version No.0.4–FINAL 04May 2021**
	Amendment 2

STATEMENT OF CONFIDENTIALITY

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ADR	Adverse Drug Reaction
AE	Adverse Event
AMT	Amniotic Membrane Transfer
AT	Artificial Tears
BCDVA	Best Corrected Distance Visual Acuity
BLA	Biologics License Agreement
°C	Degrees Celsius
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DHHS	Department of Health and Human Services
DSUR	Development Safety Update Report
EC	Ethics Committee
e-CRF/CRF	Electronic/Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
°F	Degrees Fahrenheit
FCS	Fluorescein Corneal Staining
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GVHD	Graft Versus Host Disease
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDEEL	Impact of Dry Eye on Everyday Life
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LNGFR	Low-Affinity Nerve Growth Factor Receptor
Log MAR	Logarithm of the Minimum Angle of Resolution
mg/ml	Milligrams per millilitre
MGD	Meibomian Gland Disease
ml	millilitre
mNGF	Murine Nerve Growth Factor
MOP	Manual of Procedures
NEI	National Eye Institute
NGF	Nerve Growth Factor
NGF0212 (REPARO)	Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for

	Neurotrophic Keratitis (REPARO)
NGF0214 (US Trial)	Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy Multicenter Randomized Vehicle-Controlled Pivotal Trial
NK	Neurotrophic Keratitis/Keratopathy
OCP	Ocular Cicatricial Pemphigoid
OCT	Optical Coherence Tomography
PED	Persistent Epithelial Defect
PID	Patient Identification``
PI	Principal Investigator
PK	Punctate keratitis
rhNGF	Recombinant Human Nerve Growth Factor
SAE	Serious Adverse Event
SLE	Slit Lamp Examination
SUSAR	Suspected Unexpected Serious Adverse Reaction
SPK	Superficial punctate keratitis/keratopathy
TEAE	Treat-Emergent Adverse Events
TFBUT	Tear Film Break Up Time
µl	Microliter
µg/ml	Microgram per millilitre

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1. STUDY SYNOPSIS

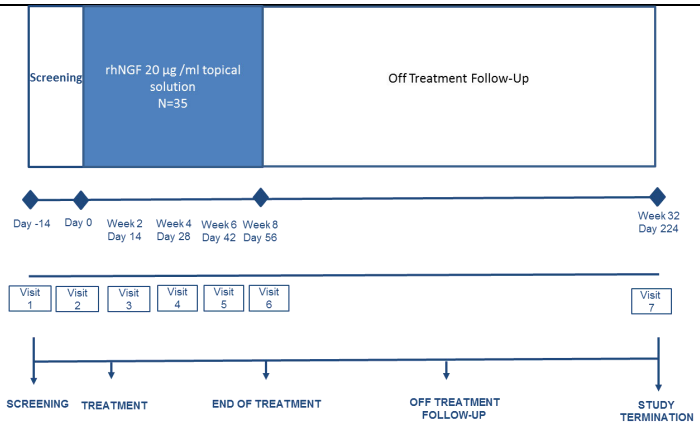
CLINICAL STUDY SYNOPSIS:	
Study Number	NGF0120
Title of Study	An 8-week, multicenter, open label, prospective study with 24 weeks of follow-up to evaluate safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in patients with Stage 1 Neurotrophic Keratitis (NK)
Short Title	DEFENDO
EudraCT N°/IND	115892
Study Centers (Country)	Approximately 5 US study centers
Development Phase	IV
Objectives	**Primary Objective** The primary objective of this study is to evaluate the safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution administered 6 times daily for 8 weeks on the ocular surface, visual function and quality of life in patients with Stage 1 NK. **Secondary Objective** The secondary objective is to evaluate patients who heal at week eight and remain healed (as defined in section 3.3) throughout the follow-up period. In addition, the study aims to evaluate the percentage of subjects that achieve an improvement in corneal sensitivity as measured by the Cochet-Bonnet aesthesiometer at 4 and 8 weeks, and by the last visit week 32. **Exploratory Objectives** The exploratory objectives are to evaluate the change from baseline to weeks 4 & 8 in Schirmer I and the Tear Film Break-Up Time (TFBUT). **Additional Objectives (site specific)** The additional objectives are to evaluate the change from baseline at week 8 and week 24 in confocal microscopy and anterior segment Optical Coherence Tomography (OCT).

Study Design and Methodology	This clinical study will be a multi-center, open label, prospective study of 8 weeks of treatment with 24 weeks of follow-up to evaluate the safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution administered as one drop in the affected eye(s), 6 times per day at 2-hour intervals, for eight weeks in patients with Stage 1 Neurotrophic Keratitis (NK). The study is divided into four phases as follows: 1. **Screening Visit (Day -14):** Procedures for inclusion will be performed at both Visit 1 (Screening) and Visit 2 (Baseline). Commercially available artificial tears (AT) provided by the sponsor will be permitted during the Screening period as needed up to four times a day. 2. **Washout period (from day minus 14 to day 0):** 14 days with no further treatment except commercially available preservative-free artificial tears provided by the sponsor (Note: Xiidra™ and Restasis™ use is disallowed for 14 days prior to Visit 2.) Artificial tears (AT) provided by the sponsor will be permitted up to four times a day and will be tracked via daily diary during washout period. 3. **Treatment:** a. **Treatment (weeks 1-8):** eligible patients will start OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution administered as one drop in the affected eye(s), 6 times per day at 2-hour intervals, for eight weeks. During the treatment period, only study product will be permitted for topical ocular treatment. ***Commercially available preservative free artificial tears (AT) provided by Sponsor are not allowed during the treatment period except as rescue therapy.*** 4. **Follow up (weeks 9-32):** For the 24 weeks post treatment: a. For patients completely healed, no treatment is allowed except for commercially available AT provided by the Sponsor, administration frequency is at the physician's discretion during follow-up based on patients need for

	lubrication. The use of artificial tears will be tracked via a daily dosing diary. b. For patients not completely healed and who don't meet criteria for premature discontinuation, will also be followed up but any topical treatment is allowed at the discretion of the physician. All treatments will be tracked as concomitant medications. No surgical procedures are permitted during the follow-up (i.e. sutured Amniotic Membrane Transfer (AMT), sutured tarsorrhaphy). Permitted items include topical medications and suture less AMT. The study will be a total of 34 weeks in duration: a screening period of 2 weeks, followed by 8 weeks of treatment and a 24-week follow-up period. At the end of the screening period (at Visit 2), patients meeting the entry criteria for this study will be assigned to treatment with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution which will be known as Study Product beginning the morning following Visit 2. Following the completion of the treatment period, patients will be followed up for an additional 24 weeks (for patients healed and non-healed [and not meeting discontinuation criteria] at Week 8) and will be evaluated at the end of the follow-up period. At the investigator's discretion, the subject may be seen for an Unscheduled Visit to evaluate for safety. Patients who prematurely discontinue for whatever reason will not be followed post discontinuation and should have Visit 6 assessments completed. At Visit 1, eligible patients will be instructed to discontinue all topical ophthalmic medications and will only be allowed to use commercially available preservative-free artificial tears provided by the sponsor to be used up to four times per day during the screening period. At the conclusion of the Baseline Visit (Visit 2) eligible patients will be dispensed a 2-week supply of Study Product from the onsite freezer in a sealed bag and will be instructed to self-administer the Study Product one drop six times a day starting on the day **after** Day 0/ Visit 2 through Week 8 of the controlled treatment period.

	A two week supply of study product will additionally be dispensed to the patients during the treatment period at Visits 3, 4 and 5/Weeks 2, 4 and 6. Starting from Visit 2, only the study product will be allowed. Preservative free AT provided by the sponsor ***will not*** be used during the study product treatment period. After the 8 weeks of study product treatment, and during the follow up period, AT should be used only if strictly needed. The use of AT will be tracked in the daily dosing diary. At Visit 6 (End of Treatment), patients will be assessed for corneal healing. **Rescue Therapy:** ***Commercially available preservative free artificial tears (AT) provided by Sponsor are not allowed during the treatment period.*** Per the investigators discretion if the patient requires rescue therapy during the 8-week treatment period then they can receive artificial tears provided by the sponsor up to four times per day. The frequency of rescue therapy must be documented in the patient's diary. **Completely healed patients at week 8** are defined by SPK as Grade ≤1 in the central qualifying zone via FCS (per NEI scale) and no persistent staining in the non-qualifying zones (excluding the superior zone) defined as the absence of pathological staining via corneal photography . Patients who are completely healed at Week 8 will be followed for an additional 24 weeks during the follow-up period. During the 24-week follow-up period (Weeks 9-32) the patients will be followed without any Study Product, however, preservative-free AT (provided by the study sponsor) may be used and documented on the daily diary. If warranted for patient safety, the Investigator may elect to see the subject at an Unscheduled Visit(s) to evaluate the patient. **Patients who are not completely healed at week 8 defined by SPK as Grade 2 via FCS in the central qualifying zone AND who do not meet the criteria for premature discontinuation, will also be followed for an additional 24 weeks during the follow-up period.** During the 24-week follow-up period (Weeks 9-32) the patients will be followed and may be treated at the physician's discretion (retreatment

	with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution is not permitted). Any concomitant treatment must be documented on concomitant medication log. If warranted for patient safety, the Investigator may elect to see the subject at an Unscheduled Visit(s) to evaluate the patient. **Patients who meet the definition of Deterioration or No Improvement in the study eye at week 8 and during the follow up period**, will be discontinued from the study and treated as appropriate at the discretion of the investigator. Deterioration or No Improvement is defined by any of the following: • In the Study Eye, the FCS is unchanged (Grade=3) from baseline in the qualifying NEI zone. • At the PIs discretion in the study eye if any of the non-qualifying zones progress from baseline. • decrease in BCDVA by >10 ETDRS letters from baseline. • progression in staining to a lesion/PED or corneal melting or perforation. • onset of infection (viral, fungal, bacterial) • Require an ocular surgical procedure, including the need for a corneal transplant. *Note: If there is a deterioration in the non-study eye, the Investigator may discontinue treatment in that eye and initiate alternative treatment at their discretion in the non-study eye but continue following the study eye per protocol.* All patients will attend the following clinic visits in the following sequence: • Screening (Visit 1/Day -14) • Baseline and First Study Product Pick-Up (Visit 2/Day 0) • Product Pick-Up (Visit 3/Week 2) • Treatment Assessment and Study Product Pick-Up (Visit 4/Week 4) • Product Pick-Up (Visit 5/Week 6) • End of 8-week Treatment (Visit 6/Week 8) • Follow-Up and Final Study Visit (Visit 7/Week 32)

Study Visits	
Number of Patients	35 evaluable patients (those patients completing 8 weeks of Oxervate™)
Diagnosis and Main Criteria for Inclusion/Exclusion	**Inclusion Criteria:** To be eligible for inclusion into this study, each patient must fulfil the following inclusion criteria: 1. Male or female aged ≥ 18 years. 2. Patients with Stage 1 NK defined by the Mackie criteria (Appendix 4) 3. Patients with Stage 1 NK characterized by all the following: a. superficial punctate keratopathy (SPK) as shown by fluorescein corneal staining (FCS) equal to a grade 3 within the central zone using the National Eye Institute (NEI) scale (Appendix 4). **AND** b. evidence of decreased corneal sensitivity (≤ 4 cm using the Cochet-Bonnet aesthesiometer) in the central qualifying zone. 4. No improvement in NEI zone score between the Screening Visit (Visit 1) and Treatment Visit (Visit 2) for the qualifying zone determined at Visit 2. 5. Have a best corrected distance visual acuity (BCDVA), using corrective lenses if necessary, in the study eye of at least +1.0 Log MAR (Snellen ≤20/200) if the clinician attributes the vision loss to the epithelium and the loss is not related to the macula in the affected eye(s).

	6. The same eye (eligible eye/study eye) fulfills all the above criteria on the day of Screening (Visit 1) and again on Visit 2. 7. Patients with punctal occlusion or punctal plugs inserted prior to the study are eligible for enrollment provided that the punctal occlusion is maintained during the study period. If a punctal plug falls out during the study, it must be reinserted within 7 days. 8. Patients who are at high risk of progression or have a history of Stage 2 or Stage 3 NK per the Mackie classification. 9. Patients who have only one functional eye can be included if they meet all the criteria above and per the investigator's discretion are proper candidates to designate the one functional eye as the study eye. 10. Only patients who satisfy all Informed Consent requirements may be included in the study. The subject and/or his/her legal representative has read, signed, and dated the IRB approved Informed Consent document before any study-related procedures are performed. 11. Patients must have the ability and willingness to comply with study procedures. **Exclusion Criteria:** 1. In the opinion of the Investigator, there is evidence of an active ocular infection (bacterial, viral, protozoal) in either eye. 2. Use of non-diagnostic (e.g., topical drops used for clinical testing/evaluations) medications that can induce corneal toxicity between Visit 1 and Visit 2. 3. In the opinion of the investigator, have current or history of conditions that may confound the study data including but not limited to Ocular Cicatricial Pemphigoid (OCP), Graft Versus Host Disease (GVHD), neuromyelitis optica, uncontrolled dry eye, and Steven Johnson's syndrome. 4. History of severe systemic allergy or severe ocular allergy (including seasonal conjunctivitis expected during the subject's participation in the trial) or chronic conjunctivitis and/or keratitis other than dry eye disease.

	5. Intraocular inflammation defined as Tyndall score >0. 6. Patients with severe vision loss with no potential for visual improvement in the study eye, in the opinion of the investigator, or if the subject is deemed legally blind. 7. Patients with active severe blepharitis and/or severe meibomian gland disease who in the opinion of the investigator will require routine treatment during the study or have required routine treatment within 2 weeks of the study treatment visit (Visit 2). (This includes the use of doxycycline within 2 weeks prior to the treatment visit (Visit 2) for active MGD.) 8. History of any ocular surgery (including eyelid surgery and cataract surgery) within the three months before study treatment (Visit 2) and for Lasik or refractive surgical procedures within 3 months before study treatment (Visit 2). (An exception to the preceding statement is allowed if, in the opinion of the investigator, the ocular surgery is deemed the cause of the NK.) 9. Ocular surgery or elective ocular surgery expected during participation in the trial. 10. Prior surgical procedure(s) for the treatment of NK including but not limited to tarsorrhaphy, conjunctival flap, the exception is for amniotic membrane transplantation. Enrollment of patients previously treated with amniotic membrane transplantation is allowed two weeks after the membrane has fully disappeared within the area with removal of any sutures or two weeks from removal of the Prokera ring before study treatment visit (Visit 2). 11. Treatment with Botox (botulinum toxin) injections in the study eye, used to induce pharmacologic blepharoptosis within 60 days prior study treatment visit (Visit 2). 12. Anticipated need to use therapeutic contact lenses or contact lens wear for refractive correction during the study treatment period in the Study Eye. 13. Patients with unstable medical condition that may confound the study data in the opinion of the investigator including but not limited to diabetes, thyroid disease, autoimmune disease, Parkinson's disease, and Multiple Sclerosis. Stable conditions

	managed with oral or injectable medications can be included, if per the investigator's discretion the patient is not anticipated to have flare ups that could affect the ocular surface. 14. Patients with eyelid abnormality that may alter eyelid function including but not limited to Blepharospasm, Cerebrovascular accident, entropion, ectropion, floppy lid syndrome. 15. Use of glaucoma drops within 14 days prior to study treatment visit (Visit 2) and for the duration of the study. Patients can use oral Diamox during the study to control IOP. 16. Pregnant or lactating at study entry or who are planning a pregnancy. 17. Premenopausal female not using a medically acceptable form of birth control (abstinence, oral contraception, intrauterine device, surgically sterilized). 18. History of drug addiction or alcohol abuse documented within the past 5 years. 19. Participation in a clinical trial with a new active substance 14 days prior to study treatment visit (Visit 2). Per the investigator's evaluation that the participation in another clinical trial for an ocular surface product does not have residual effects on the ocular surface beyond 14 days prior to treatment that could confound the data by having an effect on staining. 20. Participation in another clinical trial study at the same time as the present study. 21. Participation in a Neurotrophic Keratitis study during the past 60 days prior to study treatment visit (Visit 2). 22. Are an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same. 23. Prior failure with treatment for Stage 1, 2 or 3 NK with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution. Failure defined as non-responder or lack of efficacy.

Study Product, Dosage and Mode of Administration	• OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution: in a multiple-dose vial • 6 times/day • Topical Drop
Duration of Treatment	8 weeks
Reference product, Dosage and Mode of Administration	NA
Efficacy Endpoints	**1.** Percentage of patients who experience epithelial healing at 4 and 8 weeks. (Epithelial healing is defined as Grade 1 or absence of staining (Grade 0) in a previously qualifying zone.) **2.** Percentage of patients who remain healed (as defined in #1 above) throughout the follow-up period. **3.** Schirmer I change from baseline to weeks 4 & 8 **4.** TFBUT change from baseline to weeks 4 & 8 **5.** Percentage of patients that achieve an improvement in corneal sensitivity in the NEI zone used to qualify in the study eye as measured by the Cochet-Bonnet aesthesiometer at 4 and 8 weeks, and at the last visit (week 32). **6.** Mean change in BCDVA from baseline to Week 8. **7.** Percentage of patients that achieve a 15- letter gain in BCDVA at 4 and 8 weeks. **8.** Quality of life questionnaires change from baseline at week 8 and week 32 a. IDEEL b. EQ-5D-5L.
Exploratory Efficacy Endpoints	**1.** Frequency of preservative free artificial tears use (n° drops/day) during the follow up period. **At selected sites:** The following may be evaluated as part of a post-hoc analysis: **2.** Change from baseline structural nerve regeneration (density, length, nerve density, tortuosity) per confocal microscopy. **3.** Change from baseline in epithelial thickness per anterior segment OCT.

Safety Measures	Adverse Event Monitoring
Statistical Methods	**Subject Characteristics and Disposition:** For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Baseline demographic and background variables will be summarized. The number of patients who enroll in the study and the number and percentage of patients who complete the study will be presented. The frequency and percentage of patients who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will also be summarized. **Analysis of efficacy variables:** Analyses for responder outcomes will include percentage of response and exact 95% confidence intervals. Analyses of change from baseline and continuous outcomes will include mean and associated asymptotic 95% confidence intervals. No formal hypothesis test will be conducted. **Analysis of safety variables:** Adverse events (AEs) will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and will be summarized overall. AEs will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.

2. SCHEDULE OF EVALUATIONS

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Day (-14)	Day 0 (±2)	Day 14 (-2)	Day 28 (-2)	Day 42 (-2)	Day 56 (-4)	Day 224 (±7)
	Week -2		Week 2	Week 4	Week 6	Week 8	Week 32
Procedures	**Screening**	**Baseline**	**Product Pick-Up**	**Treatment Follow-Up**	**Product Pick-Up**	**End of Treatment**	**Follow-up/ End of Study**
ICF/HIPAA	X						
Demographics, Systemic and Ocular Medical History	X						
Collect date of Stage 1 NK initial diagnosis	X						
Pregnancy Test	X	X				X	
Record AEs	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
IDEEL		X		X		X	X
EQ-5D-5L		X		X		X	X
BCDVA	X	X		X		X	X
External Ocular Examination	X	X		X		X	X
Slit Lamp Examination	X	X		X		X	X
Corneal Photography Without Fluorescein	X	X		X		X	X
TFBUT		X		X		X	X
FCS (NEI Scale)	X	X		X		X	X
Corneal Photography with Fluorescein	X	X		X		X	X
Corneal Sensitivity Testing	X	X		X		X	X
Schirmer Test (w/o Anesthesia)		X		X		X	X
IOP	X	X				X	X
Anterior Segment OCT (selected sites)		X				X	X
Confocal microscopy (selected sites)		X				X	X
Inclusion/Exclusion Criteria	X	X					
Assigned to Treatment		X					
Product Dispensation		X	X	X	X		
Collect Used/Unused Study Product			X	X	X	X	
AT Dispensation	X	-				X	
Dispense Daily Dosing Diary	X	X	X	X	X	X	
Evaluate Daily Dosing Diary			X	X	X	X	
Evaluate AT Use- in patient daily diary		X					X

2.1. BACKGROUND INFORMATION

Neurotrophic keratitis (NK), also known as neurotrophic keratopathy, is a rare degenerative corneal disease caused by an impairment of corneal nerve innervation leading to a decrease or absence in corneal sensation. The cornea is an avascular tissue that is provided with the richest innervation of all body tissues via the trigeminal nerve. Corneal hypoesthesia or anesthesia and decreased reflex tearing

resulting from impaired corneal innervation can lead to a corneal epitheliopathy with a subsequent breakdown of the corneal epithelium, leading to potential visual impairment. Abnormal corneal sensation and epithelial defects with a poor tendency for spontaneous healing are the primary clinical manifestations of NK, which increase the risk for corneal complications associated with vision loss such as a persistent epithelial defect (PED), ulceration, melting, perforation and infectious keratitis. Neurotrophic keratitis has been divided into three stages according to the Mackie classification scheme and treatment recommendations are based on the severity of the corneal involvement.[1]

Based on the Mackie scale, Stage 1 NK is defined by the presence of an epithelial dystrophy or punctate keratopathy accompanied by corneal hypoesthesia. Stage 1 NK requires discontinuation of all topical medications and the administration of preservative-free artificial tears. While some Stage 1 NK patients may heal many do progress to Stage 2 NK. Based on the Mackie scale, Stage 2 NK is defined by the presence of a persistent epithelial defect (PED). The goal of treatment in Stage 2 is to avoid progression of the disease to a corneal ulcer. The same therapeutic approaches as in Stage 1 are used in patients with stage 2 often accompanied by the addition of patching or therapeutic contact lenses and the use of prophylactic antibiotics to prevent the risk of corneal infection. Based on the Mackie scale, Stage 3 NK is defined by the presence of a corneal ulcer, which may progress to corneal melting and perforation. When a corneal ulcer develops, therapy is aimed at promoting corneal healing and preventing corneal melting or perforation. Surgical procedures at this stage (tarsorrhaphy, flap procedures and amniotic membrane transplantation) can preserve or restore ocular integrity but at the expense of cosmetic appearance and visual function.[2, 3] As of today, the only FDA approved pharmacologic therapy for the treatment of NK is OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution, a recombinant human nerve growth factor (rhNGF).[4, 5]

Nerve growth factor (NGF) is a polypeptide essential for the survival and growth of sympathetic and sensory neurons, and for differentiation of neurons in the central nervous system. It binds with at least two classes of receptors: high-affinity tropomyosin receptor kinase A (TrkA), a transmembrane tyrosine kinase, and low-affinity NGF receptor (LNGFR), also known as p75 neurotrophin receptor (p75NTR).[6, 7]

NGF and its receptors TrkA and p75 are expressed in the anterior segment of the eye (iris, ciliary body, lens, cornea, and conjunctiva), and NGF is released in the aqueous humor. Several pieces of experimental evidence suggest that NGF affects all tissues of the anterior ocular segments, playing a crucial role in the physiopathology of several anterior ocular segment diseases.[8, 9]

OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution is a recombinant human nerve growth factor approved by the FDA in August 2018 and it is indicated for the treatment of neurotrophic keratitis. Relevant pre-clinical, toxicological and clinical data are summarized below and can be found in the Package Insert (Appendix 3).[4]

2.2. RELEVANT NON-CLINICAL PHARMACOLOGY

Both in vitro and in vivo data illustrate the biological activity of NGF in terms of neuronal growth and differentiation, as well as in prevention of apoptosis of retinal ganglion cells. Cultured corneal/limbal

cells of rabbit respond well to the proliferation stimulus induced by adding rhNGF or mNGF to the culture media.[10-12]

OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution, a recombinant human nerve growth factor, is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis.[4]

Cenegermin-bkbj, the active ingredient of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution, is structurally identical to the human nerve growth factor (NGF) protein made in ocular tissues.

NGF is an endogenous protein involved in the differentiation and maintenance of neurons, which 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. Endogenous NGF is believed to support corneal integrity through 3 mechanisms; corneal innervation, cell proliferation and tear secretion (shown in preclinical models).[1, 2, 8, 13]

2.3. A SUMMARY OF CLINICAL DATA

The safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution, was studied in a total of 151 patients with neurotrophic keratitis in two, eight-week, randomized controlled multi-center, double-masked studies. In the first study conducted in Europe NGF0212 (REPARO), patients were randomized into three different groups. One group received OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution, a second group received 10µg/mL cenegermin, and the third group received vehicle.[14] In the second study conducted in the US NGF0214, patients were randomized into two groups. One group was treated with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution the other group was treated with vehicle.[15] All eye drops in both studies were given six times daily at 2-hour intervals in the affected eye(s) for eight weeks. In the first study, only patients with the disease in one eye were enrolled, while in the second study, patients with the disease in both eyes were treated in both eyes (bilaterally), the worse eye was considered the study eye for efficacy evaluations. Complete corneal healing (defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea at eight weeks) was demonstrated in 72 percent of patients treated with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution compared to 33.3 percent of patients ($p<0.001$) treated with vehicle in the REPARO trial. For the US trial NGF0214, 65.2 percent of patients treated with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution compared to 16.7 percent of patients treated with vehicle had complete corneal healing at week 8.[14, 15]

The data from the two studies were enclosed into the biologics license application (BLA) and the FDA granted the approval for OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution for the treatment of all stages of NK.[4]

2.4. STUDY RATIONALE

This clinical trial has been designed to demonstrate the efficacy and safety of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution given 6 times a day at 2-hour intervals for 8 weeks in patients with Stage 1 NK. Efficacy will be assessed as epithelial healing of Stage 1 NK as measured by corneal fluorescein staining. Further, the study will evaluate the preservation of effect measured by the percentage of treated patients who remain healed at the 32 week follow up.

2.4.1. Alternative treatments

The only FDA approved product for treatment of NK is OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution. Alternative non-surgical treatment options may include therapeutic soft contact lenses, suture-less amniotic membrane, or tarsorrhaphy.

2.4.2. Description of the Study product

OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution: in a multiple-dose vial.

3. OVERALL STUDY DESIGN AND INVESTIGATIONAL PLAN

3.1. STUDY OBJECTIVES

Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution administered 6 times daily for 8 weeks on the ocular surface, visual function and quality of life in patients with Stage 1 NK.

Secondary Objective

The secondary objective is to evaluate patients who heal at week eight and remain healed (as defined in section 3.3) throughout the follow-up period. In addition, the study aims to evaluate the percentage of subjects that achieve an improvement in corneal sensitivity as measured by the Cochet-Bonnet aesthesiometer at 4 and 8 weeks, and by the last visit week 32.

Exploratory Objectives

The exploratory objectives are to evaluate change from baseline to weeks 4 & 8 in Schirmer I and the Tear Film Break-Up Time (TFBUT) change from baseline to weeks 4 & 8.

Additional Objectives (site specific)

Analysis to evaluate the change from baseline at week 8 and week 24 in confocal microscopy and anterior segment OCT.

3.2. STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 5 study centers located in the United States. At each study center, the Principal Investigator (PI) will be responsible for ensuring that the investigation is conducted according to the signed Investigator agreement, the protocol, GCP guidelines, and local regulations.

The PI at each study center will be responsible for the management of the study, which will consist of maintaining the study file and the patient records, corresponding with the IRB/IEC, completing the case report forms (CRFs) and reporting SAEs (or other important AEs as specified in section 8.0) within 24 hours of initial awareness.

The PI is responsible for supervising any individual or party to whom the investigator delegates trial related duties and functions conducted at the trial site. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

3.3. OVERALL STUDY DESIGN

This clinical study will be a multi-center, open label, prospective study of 8 weeks of treatment with 24 weeks of follow-up to evaluate the safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution administered as one drop in the affected eye(s), 6 times per day at 2-hour intervals, for eight weeks in patients with Stage 1 Neurotrophic Keratitis (NK).

The study is divided into four phases as follows:

5. **Screening Visit (Day -14):** Procedures for inclusion will be performed at both Visit 1 (Screening) and Visit 2 (Baseline). Commercially available artificial tears (AT) provided by the sponsor will be permitted during the Screening period as needed up to four times a day.

6. **Washout period (from day minus 14 to day 0):** 14 days with no further treatment except commercially available preservative-free artificial tears provided by the sponsor. (Note: Xiidra™ and Restasis™ use is disallowed for 14 days prior to Visit 2.) Artificial tears (AT) provided by the sponsor will be permitted up to four times a day and will be tracked via daily diary during washout period.

7. **Treatment:**

    a. **Treatment (weeks 1-8):** eligible patients will start OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution administered as one drop in the affected eye(s), 6 times per day at 2-hour intervals, for eight weeks. During the treatment period, only study product will be permitted for topical ocular treatment. ***Commercially available preservative free artificial tears (AT) provided by Sponsor are not allowed during the treatment period.***

8. **Follow up (weeks 9-32):** For the 24 weeks post treatment:
    a. For patients completely healed, no treatment is allowed except for commercially available AT provided by the Sponsor, administered at the physician's discretion. The use of artificial tears will be tracked via a daily dosing diary.
    b. For patients not completely healed and who don't meet criteria for premature discontinuation, will also be followed up but any treatment is allowed at the discretion of the physician. All treatment will be tracked as concomitant medications.

    Rescue Therapy: ***Commercially available preservative free artificial tears (AT) provided by Sponsor are not allowed during the treatment period.*** Per the investigator's discretion if the patient requires rescue therapy during the 8-week treatment period then they can receive artificial tears provided by the sponsor for up to four times per day. The frequency of rescue therapy must be documented in the patient's diary.

The study will be a total of 34 weeks in duration: a screening period of 2 weeks, followed by 8 weeks of treatment and a 24-week follow-up period. At the end of the screening period (at Visit 2), patients meeting the entry criteria for this study will be assigned to treatment with OXERVATE™ 0.002% (20

mcg/mL) cenegermin-bkbj ophthalmic solution which will be known as Study Product beginning the morning following Visit 2.

Following the completion of the treatment period, patients will be followed up for an additional 24 weeks (for patients healed and non-healed [and not meeting d/c criteria] at Week 8) and will be evaluated at the end of the follow-up period. At the investigator's discretion, the subject may be seen for an Unscheduled Visit to evaluate for safety. Patients who prematurely discontinue for whatever reason will not be followed post discontinuation and should have Visit 6 assessments completed.

At Visit 1, eligible patients will be instructed to discontinue all topical ophthalmic medications and will only be allowed to use commercially available preservative free tears provided by the sponsor to be used up to four times per day during the screening period. At the conclusion of the Baseline Visit (Visit 2) eligible patients will be dispensed a 2-week supply of Study Product from the onsite freezer in a sealed bag and will be instructed to self-administer the Study Product one drop six times a day starting on the day **after** Day 0/ Visit 2 through Week 8 of the controlled treatment period according to the dosing schedule shown in Table 1 (Dosing Schedule).

Table 1 Dosing Schedule

TREATMENT	TREATMENT DOSING SCHEDULE*
OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution	Morning (8 AM)
	Mid-morning (10 AM)
	Noon (12 PM)
	Early afternoon (2 PM)
	Mid afternoon (4 PM)
	Late afternoon (6 PM)

* The above is an example. **The timing of instillation can be adjusted if a patient's awakening and/or bedtime differs throughout the 8 weeks**. The patient should try and keep the daily dosing schedule as consistent as possible by trying to schedule sleep and wake times. A daily dosing diary will be maintained by the subject to track compliance for each dose of study product.

A two week supply of study product will additionally be dispensed to the patients during the treatment period at Visits 3, 4 and 5/Weeks 2, 4 and 6.

Starting from Visit 2, only the study product will be allowed. Preservative free AT provided by the sponsor ***will not*** be used during the study product treatment period. After the 8 weeks of Study Product treatment, and during the follow up period, AT should be used only if strictly needed. The use of AT will be tracked in the daily dosing diary.

At Visit 6 (End of Treatment), patients will be assessed for corneal healing.

Completely healed patients at week 8 are defined by SPK as Grade ≤1 in the central qualifying zone via FCS (per NEI scale) and no persistent staining in the non-qualifying zones (excluding the superior zone) defined as the absence of pathological staining via corneal photography. Patients who are completely healed at Week 8 will be followed for an additional 24 weeks during the follow-up period. During the 24-week follow-up period (Weeks 9-32) the patients will be followed without any Study Product, however, preservative-free AT (provided by the study sponsor) may be used documented on the daily diary. If warranted for patient safety, the Investigator may elect to see the subject at an Unscheduled Visit(s) to evaluate the patient.

Patients who are not completely healed at week 8 are defined by SPK as Grade 2 via FCS in the central qualifying zone AND who do not meet the criteria for premature discontinuation, will also be followed for an additional 24 weeks during the follow-up period. During the 24 week follow-up period (Weeks 9-32) the patients will be followed may be treated at the physician's discretion (retreatment with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution is not permitted). Any concomitant treatment must be documented on concomitant medication log. If warranted for patient safety, the Investigator may elect to see the subject at an Unscheduled Visit(s) to evaluate the patient.

Patients who meet the definition of Deterioration or No Improvement in the study eye at week 8 and during the follow up period, will be discontinued from the study and treated as appropriate at the discretion of the investigator.

Deterioration or No Improvement is defined by any of the following:

- In the Study Eye, the FCS is unchanged (Grade=3) from baseline in the qualifying NEI zone.
- At the PIs discretion, in the study eye there is a progression from baseline in the non-qualifying zones
- decrease in BCDVA by >10 ETDRS letters from baseline.
- progression in staining to a PED or corneal melting or perforation
- onset of infection
- Require an ocular surgical procedure, including the need for a corneal transplant.

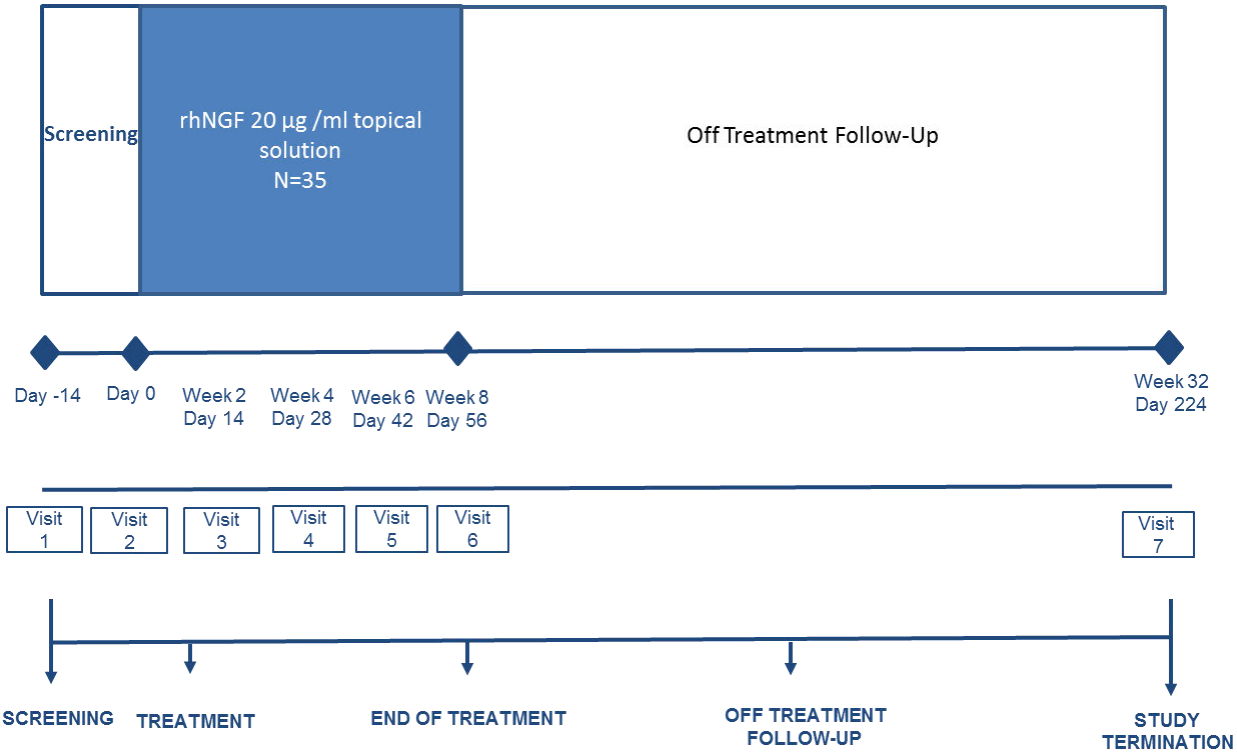
Note: If there is a deterioration in the non-study eye, the Investigator may discontinue treatment in that eye and initiate alternative treatment at their discretion in the non-study eye, but continue following the study eye per protocol.

All patients will attend the following clinic visits in the following sequence:

- Screening (Visit 1/Day -14)
- Baseline and First Study Product Pick-Up (Visit 2/Day 0)
- Product Pick-Up (Visit 3/Week 2)
- Treatment Assessment and Study Product Pick-Up (Visit 4/Week 4)
- Product Pick-Up (Visit 5/Week 6)
- End of 8-week Treatment (Visit 6/Week 8)
- Follow-Up and Final Study Visit (Visit 7/Week 32).

The trial structure for subjects is shown in **Figure 1**

Figure 1 Study Schematic



Any subject who meets the definition of experiencing a deterioration in the study eye, will be discontinued from the study, and followed per the Investigator's discretion.

If there is a deterioration in the non-study eye, the Investigator may discontinue treatment in that eye and initiate alternative treatment at their discretion in the non-study eye, but continue following the study eye per protocol.

3.3.1. Rationale for Selection of dose, and treatment schedule in the study

The dose proposed in this study, OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution (one drop in each eye six times daily for 8 weeks), was tested in the previous NK studies (NGF0212 and NGF0214).

The 20 µg/ml concentration of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution is well sustained by the current manufacturing process and is the commercial formulation currently approved and available in the USA.

The dose and route of administration of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution selected in this study is based on the approved marketed concentration as an eye drop approved for the treatment of NK.

Given the nature of the disease, an eight week treatment period at 6 doses/day is considered sufficient time to produce a reversal of PED in a Stage 2 and Stage 3 (more severe) NK patient population and reaches the maximal response in terms of efficacy as seen in up to 72% (REPARO) of patients who had 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. An established safety profile exists with cenegermin 20 µg /mL having been evaluated in six prior clinical trials. Additionally, toxicology and data showed cenegermin to be well tolerated in animal models with no systemic or ocular toxicity.

Patients with tolerability issues or worsening of symptoms may be discontinued at any time during the study.

4. SELECTION OF STUDY POPULATION

Adult males and females with Stage 1 NK (as defined in the inclusion criteria) will be included. A total of 35 evaluable patients (those patients completing 8 weeks of Oxervate™) are planned to be enrolled.

4.1. INCLUSION CRITERIA

To be eligible for inclusion into this study, each patient must fulfil the following inclusion criteria:

1. Male or female aged ≥ 18 years.
2. Patients with Stage 1 NK defined by the Mackie criteria (Appendix 4)
3. Patients with Stage 1 NK characterized by all the following:
    a. superficial punctate keratopathy (SPK) as shown by fluorescein corneal staining (FCS) equal to a grade 3 within the central zone using the National Eye Institute (NEI) scale (Appendix 4).

        AND

    b. evidence of decreased corneal sensitivity (≤ 4 cm using the Cochet-Bonnet aesthesiometer) in the central qualifying zone of staining.
4. No improvement in NEI zone score between the Screening Visit (Visit 1) and Treatment Visit (Visit 2) for the qualifying zone determined at Visit 2.
5. Have a best corrected distance visual acuity (BCDVA), using corrective lenses if necessary, in the study eye, of at least +1.0 Log MAR (Snellen ≤20/200) if the clinician attributes the vision loss to the epithelium and the loss is not related to the macula in the affected eye(s).
6. The same eye (eligible eye/study eye) fulfills all the above criteria on the day of Screening (Visit 1) and again on Visit 2.
7. Patients with punctal occlusion or punctal plugs inserted prior to the study are eligible for enrollment provided that the punctal occlusion is maintained during the study period. If a punctal plug falls out during the study, it must be reinserted within 7 days.
8. Patients who are at high risk of progression or have a history of Stage 2 or Stage 3 NK per the Mackie classification.
9. Patients who have only one functional eye can be included if they meet all the criteria above and per the investigator's discretion are proper candidates to designate the one functional eye as the study eye.
10. Only patients who satisfy all Informed Consent requirements may be included in the study. The subject and/or his/her legal representative has read, signed, and dated the IRB approved Informed Consent document before any study-related procedures are performed.
11. Patients must have the ability and willingness to comply with study procedures.

4.2. EXCLUSION CRITERIA

Patients who meet any of the following criteria are NOT eligible for inclusion in the study.

1. In the opinion of the Investigator, there is evidence of an active ocular infection (bacterial, viral, protozoal) in either eye.
2. Use of non-diagnostic (e.g., topical drops used for clinical testing/evaluations) medications that can induce corneal toxicity between Visit 1 and Visit 2.
3. In the opinion of the investigator, have current or history of conditions that may confound the study data including but not limited to Ocular Cicatricial Pemphigoid (OCP), Graft Versus Host Disease (GVHD), neuromyelitis optica, uncontrolled dry eye, and Steven Johnson's syndrome.
4. History of severe systemic allergy or severe ocular allergy (including seasonal conjunctivitis expected during the subject's participation in the trial) or chronic conjunctivitis and/or keratitis other than dry eye disease.
5. Intraocular inflammation defined as Tyndall score >0.
6. Patients with severe vision loss with no potential for visual improvement in the study eye in the opinion of the investigator, or if the subject is deemed legally blind.
7. Patients with active severe blepharitis and/or severe meibomian gland disease who in the opinion of the investigator will require routine treatment during the study or have required routine treatment within 2 weeks of the study treatment visit (Visit 2). (This includes the use of doxycycline within 2 weeks prior to the treatment visit (Visit 2) for active MGD.)
8. History of any ocular surgery (including eyelid surgery and cataract surgery) within the three months before study treatment (Visit 2) and for Lasik or refractive surgical procedures within 3 months before study treatment (Visit 2). (An exception to the preceding statement is allowed if, in the opinion of the investigator, the ocular surgery is deemed the cause of the NK).
9. Ocular surgery or elective ocular surgery expected during participation in the trial.
10. Prior surgical procedure(s) for the treatment of NK including but not limited to tarsorrhaphy, conjunctival flap, the exception is for amniotic membrane transplantation. Enrollment of patients previously treated with amniotic membrane transplantation is allowed two weeks after the membrane has fully disappeared within the area with removal of any sutures or two weeks from removal of the Prokera ring before study treatment visit (Visit 2).
11. Treatment with Botox (botulinum toxin) injections in the study eye, used to induce pharmacologic blepharoptosis within 60 days prior study treatment visit (Visit 2).
12. Anticipated need to use therapeutic contact lenses or contact lens wear for refractive correction during the study treatment period in the Study Eye.
13. Patients with unstable medical condition that may confound the study data in the opinion of the investigator including but not limited to diabetes, thyroid disease, autoimmune disease, Parkinson's disease, and Multiple Sclerosis. Stable conditions managed with oral or injectable medications can be included, if per the investigators discretion the patient is not anticipated to have flare ups that could affect the ocular surface.
14. Patients with eyelid abnormality that may alter eyelid function including but not limited to Blepharospasm, Cerebrovascular accident, entropion, ectropion, floppy lid syndrome.

15. Use of glaucoma drops within 14 days prior to study treatment visit (Visit 2) and for the duration of the study. Patients can use oral Diamox during the study to control IOP.
16. Pregnant or lactating at study entry or who are planning a pregnancy.
17. Premenopausal female not using a medically acceptable form of birth control (abstinence, oral contraception, intrauterine device, surgically sterilized).
18. History of drug addiction or alcohol abuse documented within the past 5 years.
19. Participation in a clinical trial with a new active substance 14 days prior to study treatment visit (Visit 2). Per the investigator's evaluation that the participation in another clinical trial for an ocular surface product does not have residual effects on the ocular surface beyond 14 days prior to treatment that could confound the data by having an effect on staining.
20. Participation in another clinical trial study at the same time as the present study.
21. Participation in a Neurotrophic Keratitis study during the past 60 days prior to study treatment visit (Visit 2).
22. Are an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.
23. Prior failure with treatment for Stage 1, 2 or 3 NK with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution. Failure defined as non-responder or lack of efficacy.

4.3. SELECTION OF STUDY EYE

The study eye is the eye at Visit 2 having Grade 3 FCS per the NEI scale in the central zone and a decreased corneal sensitivity (≤ 4 cm using the Cochet-Bonnet aesthesiometer) in the central zone at both Visit 1 and Visit 2. If both eyes have a qualifying central zone meeting FCS and corneal sensitivity requirements at both Visit 1 and Visit 2, the right eye will be selected as study eye.

Note: If both eyes meet the FCS and corneal sensitivity requirements in the central zone, the subject will be treated bilaterally. If only one eye qualifies, but the contralateral eye has FCS in the central zone ≥2 on NEI scale and the Investigator feels that both eyes would benefit from treatment (i.e. the qualifying eye is abnormal, but does not meet criteria for study) both eyes may be treated with study product. Data will be collected and recorded in the eCRF for both eyes throughout the study.

If there is only one qualifying eye/one study eye, only one eye will be treated; however, both eyes will be evaluated, and data will be collected for both eyes.

4.4. ASSIGNMENT OF SUBJECT NUMBER

Each patient who is screened to participate in this study will be assigned a unique 6-digit PID number (e.g. 001101) consisting of a 3-digit study center number followed by the 3-digit screening number assigned sequentially by each study center.

5. STUDY PRODUCT

5.1. PRESENTATION, STORAGE, PACKAGING AND LABELING OF THE STUDY PRODUCT

5.1.1. Presentation of Study Product

The Study Product will be provided as the commercially available OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution. The patient will receive 1 or 2 biweekly cartons sufficient for two weeks of dosing at Visit 2, Visit 3, Visit 4, and Visit 5. The patients will be provided with enough pipettes and adaptors to be used for the administration of the Study Product. The subject will receive a total of 56 (or 112 for bilateral treatment) OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution vials over the 8-week duration of the study product treatment, 1 OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution vial to be used per day. The patient will pick up Study Product from the Investigator's office and bring back used vial for reconciliation at the subsequent study visit.

[redacted]

5.1.4. Description of Study Product

Study Product is OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution. OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution is a sterile perservative-free ophthamic solution containing 0.002% (20 mcg/mL) of rhNFG drug substance.

Each vial contains 1.0 ml of solution.

[redacted]

Commercially available artificial tears will be supplied to patients in the study by the sponsor. Study sponsor will provide SYSTANE® Preservative-Free Original Lubricant Eye Drops to be used up to four times per day as needed during the screening period, and as needed for rescue therapy and during the follow-up period.

5.2. DOSE, ROUTE AND SCHEDULE OF PRODUCT ADMINISTRATION

Both OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution (study product) and SYSTANE Original® (to be used for the screening and follow-up periods only) are to be used in this study and are for topical ocular usage only.

The Study Product will be dosed one drop (35 µl- .70 µg of cenegermin-bkbj/drop) 6 times a day in the affected eye(s) for 8 weeks of treatment. The timing of instillation should be adjusted if a patient's awakening and/or bedtime differs based on the suggestion above in Table 1 Dosing Schedule. An example of Dosing Instructions is also provided in the Manual of Procedures (MOP).

Instructions for First Dose:
Patients will be instructed to self-administer the study product one drop in the affected eye(s) six times a day at 2 hour intervals starting on the day **after** Visit 2 (Day 0-Baseline and First Study product Pick Up) of the treatment period. On Day 1, the patient will start the first dose following Table 1 Dosing Schedule. ***The patient should not start therapy on the same day as Day 0/Visit 2.***

On the day of Visit 3/Week 2 (For Study Product Pick-Up), the Study Product dosed is to be instilled in the clinic by the patient at approximately 2 hours intervals according to their established daily schedule for self-administration of the study product at home and the Study Product should be taken from the kit which is dispensed at the visit. This to ensure the patient does not miss a dose during the drop off and pick up day.

Systane Original® (commercially available preservative free artificial tears provided by sponsor) will be used only as strictly needed during the Screening and Follow up periods. The use of Systane Original® will be clearly documented in the patient's study dosing diary and in the eCRF.

5.3. ACCOUNTABILITY OF THE STUDY PRODUCT

Upon receipt, the study staff designated by the Investigator will inventory the clinical study products, and complete and sign the Receipt of Study Product documentation. A copy of the form will be maintained in the Investigator's records and the original will be provided to Lexitas.

The designated study staff must keep a complete and accurate accounting of all Study Product used via a Dispensing Log. In no case will the Study Product be used in any unauthorized situation.

At Visits 3, 4, 5 and 6, patients will return the used or unused study boxes/vials to the clinic in the original carton.

All Study Product returned by patients should be inventoried same day of return. Inventory will take place at Visits 3, 4, 5 and 6. These records will be made available to the study monitor for the purpose of accounting for all study products. The study monitor will account for all Study Products. The investigator will maintain all used and unused vials after inventory for the duration of the clinical trial. Upon completion of the trial all used and unused vials will be packaged for return to Dompé once the study monitor has concluded no data from patient inventory reconciliation is missing. Once the study is concluded and all records are reviewed for accuracy the CRO will give the PI permission to package and return all vials to Dompé. Return instructions will be provided to investigators.

It is the Investigator's responsibility to ensure the reconciliation of study medications at the conclusion of the study. Any discrepancies and/or deficiencies in study drug accountability must be recorded along with an explanation in the appropriate accountability log.

Study Product which has been dispensed to a patient and returned unused will not be re-dispensed to a different patient.

Unused Study Product must not be discarded or used for any purpose other than the present study. Any remaining Study Product at the end of the trial will be disposed of as determined by Dompé.

5.3.1. Prior and concomitant medications

As a general rule, no ophthalmic medication other than Study Product and concomitant Study Product (Systane® -artificial tears provided by Sponsor) will be given to the patient from the screening day until all the final study evaluations have been completed. Systane®, provided by the Sponsor, may be used ***during screening and the follow up only.***

All medications (including over-the-counter drugs, systemic medications, herbal products, vitamins, and antacids) should be documented at screening and also taken within 14 days of study treatment Visit 2 and throughout the study will be clearly documented on the Concomitant Medications eCRF page.

Medication entries should be specific to product name (if a combination drug product) and spelled correctly. The dose, unit, frequency, route of administration, start date, discontinuation date, and indication should also be recorded. For medications administered only one time, the frequency column may reflect "once."

Table 3 Medications and Procedures	Minimum Washout Period Prior to Treatment (Visit 2)
Have had incisional ocular surface surgery (e.g., LASIK, refractive, pterygium removal).	90 days
Ocular surgery (including eyelid surgery or cataract surgery)	90 days
Botox (botulinum toxin) injections in the study eye.	60 days
Any Investigational Product for NK	60 days
Any Investigational Product applied to the ocular surface if per the investigators discretion the investigational product does not have residual effects on the ocular surface that can confound the data	14 days
Topical ocular or systemic antibiotics for the treatment of an ocular condition	14 days
Topical cyclosporine (all doses and formulations)	14 days
Lifitegrast	14 days
Glaucoma topical medications (Use of Diamox orally during the study is acceptable)-Investigator should ensure stable IOP before/by Visit 2	14 days
Topical ocular corticosteroids, ocular non-steroidal anti-inflammatory drugs (NSAIDs), and topical dermatologic corticosteroids on the face within 14 days prior to Visit 2 and during study participation	14 days
Topical ocular antihistamine and/or mast cell stabilizers within 14 days prior to Visit 2. Have used topical ocular vasoconstrictors for the purpose of eye whitening within 14 days prior to Visit 2 (phenylephrine used to dilate the eyes is allowed).	14 days
Treatments for blepharitis MGD including but not limited to thermal pulsation (Lipiflow), debridement of lid margin (BlephEx), thermal application (MeiBoFlo, Tear Care), meibomian gland probing or doxycycline.	14 days
All topical ophthalmic gels, ointments or drops that can induce corneal toxicity (diagnostic medications used for clinical testing/evaluations are acceptable).	14 days
Enrollment of patients previously treated with amniotic membrane transplantation is allowed two weeks after the membrane has fully disappeared within the area with removal of any sutures or two weeks from removal of the Prokera ring before study treatment visit (Visit 2).	14 days

6. STUDY PROCEDURE AND ASSESSMENTS

For the detailed description of all the clinical examinations listed below refer to the Manual of Procedures (MOP). See the Schedule of Evaluations in Section 2.0 for the list of procedures by visit in the recommended order. The descriptions of the procedures to be performed at each visit are provided below. If possible, the same investigator should perform the assessments for one subject.

6.1. STUDY VISITS AND EXAMINATIONS AND TREATMENT VISITS

6.1.1. Visit 1 (Day -14): SCREENING

Site staff will conduct the following screening assessments **in the order outlined below**. (Note: Procedures that are not required to be conducted in a specific order will be noted with an *)

1. **Informed Consent/HIPAA:** Explain the purpose and nature of the study, and have the subject or legally authorized representative read, sign, and date the IRB approved informed consent document. Provide a photocopy of the signed document to the subject and place the original signed document in the subject chart.

2. ***Demographics, Ocular and Medical History, Previous and Concomitant Ocular and Systemic Medications and Conditions:** Document demographic information and medical history, including herbal therapies, vitamins, and all over the counter as well as prescription topical and systemic medications. Document etiology of NK and all concomitant ocular diseases and systemic conditions. Patients IOP should be measured at screening and if conversion to oral Diamox is initiated, patient should be deemed to have a stable IOP by Visit 2.

3. ***Pregnancy Test:** Perform a urine pregnancy test on any female of childbearing potential and record the results. If a pregnancy test is not required, indicate as not applicable in the eCRF.

4. ***Adverse Events:** Begin monitoring of AE's.

5. **Ophthalmic Examinations:** The following examination/procedures will be performed on BOTH EYES and in order unless otherwise specified. (The grading scale and detailed description of the examinations/procedures are described in the MOP):

    a. **Best-Corrected Distance Visual Acuity (BCDVA) Vision must be measured at each visit using ETDRS visual acuity chart at 4 meters (13 feet). BCDVA testing should precede the administration of any eye drops to dilate or anesthetize the eye, or any examination requiring contact with the eye. If vision is corrected, the same correction should be used throughout the BCDVA testing.**

    b. **External Ocular Examination Assess the motility of the extraocular muscles and the appearance and function of the eyelids before the instillation of any dilating or anesthetic eye drops.**

c. **Slit Lamp Examination (SLE): SLE will assess eyelids, lashes, conjunctiva, cornea, lens, iris, and anterior chamber. The slit lamp examination must be performed before the instillation of any dilating or anesthetic eye drops or the fluorescein agent.**

d. **Corneal Photo Without Fluorescein: Photos of the cornea of both eyes (Visit 1) and the treated eye(s) (Visit 2, Visit 4, Visit 6, and Visit 7) will be taken after slit lamp examination and before the instillation of fluorescein agent by a slit lamp camera focusing on the epithelial defect and using white, diffuse (homogenous) frontal illumination.**

e. **Instill Fluorescein**

f. **Corneal Fluorescein Staining: Following the instillation of fluorescein in the qualifying eye(s) grade (density) of the SPK will be determined using the NEI (National Eye Institute [NEI]/Industry Workshop 0-15) scale.**

g. **Corneal Photo with Fluorescein: As soon as possible after completing the Corneal Fluorescein Staining, a corneal photo of both eyes (Visit 1) and the treated eye(s) (Visit 2, Visit 4, Visit 6, and Visit 7) using cobalt blue illumination will be taken to document the observed corneal findings.**

h. **Corneal Sensitivity: Corneal Sensitivity will be measured using a Cochet Bonnet aesthesiometer before the instillation of any dilating or anesthetic eye drops. Corneal sensitivity will be assessed in the qualifying NEI zones of each eye. Nonqualifying zones (excluding superior) may be tested if the qualifying NEI zone does not meet the corneal sensitivity inclusion.**

i. **IOP**

6. **Inclusion/Exclusion Criteria Screen the subject for protocol inclusion/exclusion criteria as per Sections 4.1 and 4.2.**

7. **Dispense Systane Original®:** Instruct patient to use only as strictly needed and up to 4 times per day during screening period; additionally, instruct the patient to return Systane® bottle (s) at Visit 2

8. ***Dispense Study dosing diary (for Systane use)**

6.1.2. Visit 2 (Day 0 ± 2 days): BASELINE

Patients will enter the single-arm open-label phase of the study if they continue to meet eligibility criteria at Visit 2/Baseline.

1. **IDEEL (Impact of Dry Eye on Everyday Life):** This questionnaire will be assessed by the patient using a self-administered format. This questionnaire is designed to assess health-related

quality of life in patients with visual impairments by representing the patient perspective on the impact of vision problems on functioning.

2. **EQ-5D-5L:** This self-administered questionnaire will be completed by the patient before any ophthalmic examination is performed at a given study visit. The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal.

3. ***Concomitant Ocular and Systemic Medications Update:** Record any change from Screening/Visit 1 in concurrent ocular or non-ocular medications including information on all concomitant and previous medications used within the past 14 days before Visit 2.

4. ***Record AE's**

5. ***Pregnancy Test:** Perform a urine pregnancy test on any female of childbearing potential and record the results. If a pregnancy test is not required, indicate as not applicable in the eCRF.

6. **Ophthalmic Examinations:** following examination/procedures will be performed on BOTH EYES unless otherwise specified:

    a. **BCDVA**

    b. **External Ocular Examination**

    c. **Slit Lamp Examination**

    d. **Corneal Photo Without Fluorescein**

    e. **Instill Fluorescein**

    f. **Tear Film Break-Up Time (TFBUT)**

    g. **Corneal Fluorescein Staining: Using NEI scale (0 to 3 is used for each of the five areas per cornea).**

    h. **Corneal Photo with Fluorescein**

    i. **Wait 10 minutes before performing Schirmer Test**

    j. **Corneal Sensitivity**

    k. **Schirmer Test Without Anesthesia (Schirmer I)**

    l. **IOP**

    m. **Anterior Segment OCT (selected sites)**

n. **Confocal microscopy (selected sites)**

7. **Inclusion/Exclusion: Patients must continue to meet the Screening/Enrollment Criteria. At the end of the Baseline Visit (Day 0), it will be determined if the subject qualifies for continued participation and treatment in the study.**

8. **Study Product Dispensing:** Eligible patients will be supplied with a biweekly kit of Study product sufficient for 2 weeks of treatment per visit.

9. ***Dispense Daily Study Dosing Diary**

10. **Collect used/unused AT and collect/review AT dosing diary**

11. ***Instructions to Subject:** Instruct the subject to initiate dosing the study eye or ***bilaterally*** (if applicable) the following day and to return to the clinic for Visit 3/Week 2 Visit in 2 weeks (14 days). Further instruct the subject to return to the clinic with the Daily Study Dosing Diary and all the empty used/unused daily kit of Study product in the original carton box. Also, remind subject that Systane®, nor any other topical ocular medications), are allowed during study product treatment period.

6.1.3. Visit 3 (Day 14/Week 2 - 2 days) STUDY PRODUCT PICK-UP VISIT

1. ***Concomitant Ocular and Systemic Medications Update**

2. ***Record AE's**

3. ***Collect Used/Unused Study Product, Daily Dosing Diary, and Inventory**

4. ***Study Product Dispensing:** Patients will be supplied with a biweekly kit of Study product sufficient for 2 weeks of treatment.

5. ***Dispense Daily Study Dosing Diary**

6.1.4. Visit 4 (Day 28/Week 4 -2 days): TREATMENT VISIT

1. **IDEEL**

2. **EQ-5D-5L**

3. ***Concomitant Ocular and Systemic Medications Update**

4. ***Record AE's**

5. **Ophthalmic Examinations:** The following examinations/procedures will be performed on BOTH EYES unless otherwise specified:

    a. **BCDVA**

b. **External Ocular Examination**

c. **Slit Lamp Examination**

d. **Corneal Photo Without Fluorescein**

e. **Instill Fluorescein**

f. **TFBUT**

g. **Corneal Fluorescein Staining**

h. **Corneal Photo with Fluorescein**

i. **Wait 10 minutes before performing Schirmer Test**

j. **Corneal Sensitivity**

k. **Schirmer Test Without Anesthesia (Schirmer I)**

6. ***Collect used Study product and Daily Study Dosing Diary**

7. ***Study Product Dispensing: Patients will be supplied with a new biweekly kit of Study product sufficient for 2 weeks of treatment.**

8. ***Dispense Daily Study Dosing Diary**

9. **Instructions to Patient:** Instruct the patient to return to the clinic for Visit 5/Week 6 Study product Pick-Up visit in two weeks. Further instruct the patient to return to the clinic with the Daily Study Dosing Diary and all the empty used/unused daily kit of Study Product in original carton box.

6.1.5. Visit 5 (Day 42/Week 6 - 2 days): STUDY PRODUCT PICK-UP VISIT

1. *** Concomitant Ocular and Systemic Medications Update**

2. ***Record AE's**

3. ***Collect Used/Unused Study Product, Daily Study Dosing Diary, and Inventory**

4. ***Study Product Dispensing:** Patients will be supplied with a biweekly kits of Study product sufficient for 2 weeks of treatment.

5. ***Dispense Daily Study Dosing Diary**

6. ***Instructions to Subject:** Instruct the patient to return to the clinic for Visit 6/Week 8 End of Treatment visit in two weeks. Further instruct the patient to return to the clinic with the Daily Study Dosing Diary and all the empty used/unused daily kit of Study Product in the original

carton. ***Patients should be instructed to try and complete therapy before last treatment appointment, so at time of end of treatment evaluation the patient should have completed the six times a day dosing on Day 56/Week 8 for Visit 6.*** This will require PIs and their staff to try and schedule the last visit at the end of the day, so the patient has sufficient time to complete 6 doses on the day of Visit 6.

6.1.6. Visit 6 (Day 56/Week 8 - 4 days): END OF TREATMENT OR PREMATURE DISCONTINUATION VISIT

1. **IDEEL**
2. **EQ-5D-5L**
3. ***Pregnancy Test for women of childbearing potential:** Perform a urine pregnancy test and record the results.
4. ***Concomitant Ocular and Systemic Medications Update**
5. ***Record AE's**
6. **Ophthalmic Examinations:** The following examination/procedures will be performed on BOTH EYES unless otherwise specified:
    a. **BCDVA**
    b. **External Ocular Examination**
    c. **Slit Lamp Examination**
    d. **Corneal Photo Without Fluorescein**
    e. **Instill Fluorescein**
    f. **TFBUT**
    g. **Corneal Fluorescein Staining**
    h. **Corneal Photo with Fluorescein**
    i. **Wait 10 minutes before performing Schirmer Test**
    j. **Corneal Sensitivity**
    k. **Schirmer Test Without Anesthesia (Schirmer I)**
    l. **IOP**
    m. **Anterior Segment OCT (selected sites)**

n. **Confocal Microscopy (selected sites)**

7. **Collect used Study Product and Subject Dosing Diary**
8. **Dispense Daily Study Dosing Diary**
9. **Dispense Systane®**

6.1.7. Visit 7 (Day 224/Week 32 ±7 days): FOLLOW-UP/FINAL STUDY VISIT

1. **IDEEL**
2. **EQ-5D-5L**
3. ***Concomitant Ocular and Systemic Medications Update**
4. ***Record AE's**
5. **Ophthalmic Examinations**. The following examination/procedures will be performed on BOTH EYES unless otherwise specified:

   a. **BCDVA**

   b. **External Ocular Examination**

   c. **Slit Lamp Examination**

   d. **Corneal Photo Without Fluorescein**

   e. **Instill Fluorescein**

   f. **TFBUT**

   g. **Corneal Fluorescein Staining**

   h. **Corneal Photo with Fluorescein**

   i. **Wait 10 minutes before performing Schirmer Test**

   j. **Corneal Sensitivity**

   k. **Schirmer Test Without Anesthesia (Schirmer I)**

   l. **IOP**

   m. **Anterior Segment OCT (selected sites)**

   n. **Confocal Microscopy (selected sites)**

6. ***Collect Daily Study Dosing Diary**

7. **Patient will be discharged from the study**

6.2. EARLY WITHDRAWAL FROM STUDY

A premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study protocol procedures. Patients can be prematurely discontinued from the study for one of the following reasons:

- Progression from Stage 1 to Stage 2 or Stage 3 NK, or corneal melting/perforation
- At the PI discretion patient is considered to be a non-responder (no improvement from baseline).
- In the qualifying/Study Eye, the FCS is unchanged (Grade=3) from baseline after 8 weeks of treatment in the qualifying NEI zone or there is an increase in FCS ≥1 within a non-qualifying NEI zone in the same eye.
- Decrease in BCDVA by >10 ETDRS letters
- Onset of infection (bacterial or viral)
- Protocol violation, including lack of compliance defined as <80% of doses taken based on diary documentation between treatment clinic visits.
- Withdrawal of consent
- Lost to follow-up during the treatment period (Every effort must be made to contact the patient; a registered letter must be sent)
- Study terminated by the Sponsor
- Other reasons, such as administrative reasons or pregnancy
- Development of AE or unacceptable toxicity per the investigator's discretion, precluding further therapy with the study drug.
- Severe protocol violations, such as an incorrect treatment administration, or a concomitant use of not permitted medications. Before removal, these cases should first be discussed with Dompé.

The reasons for premature discontinuation from the study will be reflected on the Study Termination Record of the CRF. For patients who prematurely discontinue, Visit 6 procedures will be completed, and these patients will be considered off study and will no longer be followed.

For patients that discontinue prematurely, the investigator should refer patients for further treatment as appropriate.

Replacement Procedures

Patients in this study who prematurely discontinue before completion of 8 weeks of treatment with Oxervate™ will be replaced. Patients prematurely discontinuing during follow up treatment will not be replaced.

6.3. END OF STUDY

For this trial, the End of Study is defined as the date of the last visit of the last subject.

7. ENDPOINTS

7.1. STUDY ENDPOINTS

7.1.1. Efficacy endpoints

1. Percentage of patients who experience epithelial healing at 4 and 8 weeks. (Epithelial healing is defined as Grade 1 or absence of staining (Grade 0) in a previously qualifying zone.)
2. Percentage of patients who remain healed (as defined in #1 above) throughout the follow-up period.
3. Schirmer I change from baseline to weeks 4 & 8
4. TFBUT change from baseline to weeks 4 & 8
5. Percentage of patients that achieve an improvement in corneal sensitivity in the NEI zone used to qualify in the study eye as measured by the Cochet-Bonnet aesthesiometer at 4 and 8 weeks, and at the last visit (week 32).
6. Quality of life questionnaires change from baseline at week 8 and week 32
7. IDEEL
8. EQ-5D-5L
9. Mean change in BCDVA from baseline to Week 8.
10. Percentage of patients that achieve a 15- letter gain in BCDVA at 4 and 8 weeks.

7.1.2. Exploratory Efficacy Endpoints

1. Frequency of preservative free artificial tears use (n° drops/day) during the follow up period.

At selected sites:

The following may be evaluated as part of a post-hoc analysis:

2. Change from baseline structural nerve regeneration (density, length, nerve density, tortuosity) per confocal microscopy.
3. Change from baseline in epithelial thickness per anterior segment OCT.

7.1.3. Safety endpoints

1. Adverse Events (AEs) and Treatment-emergent adverse events (TEAEs), assessed throughout the study

8. EVALUATION OF ADVERSE EVENTS AND SAFETY INFORMATION

8.1. DEFINITIONS

Adverse Event

An **Adverse Event** (**AE**) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the Study Product.

This definition includes an exacerbation of preexisting medical conditions or events, historical conditions not present prior to study treatment, which reappear following study treatment, intercurrent illnesses, hypersensitivity reactions, drug-drug or drug-food interactions, medication errors, overdose (both intentional or unintentional), drug misuse/abuse, false positive laboratory test, or the significant worsening of the disease under investigation.

Adverse Drug Reaction

An **Adverse Drug Reaction (ADR)** is defined as an adverse experience which is reasonably likely to have been caused by the drug. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a pharmaceutical product and an occurrence is suspected. Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases, and relevant history.

Adverse drug reactions may arise from use of the Study Product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse, and medication errors, occupational exposure.

The Investigator carefully assesses relationship between event and Study drug using the information below.

Arguments that may suggest a reasonable causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative etiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to the drug
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished)

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

• No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)

• Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

• Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned)

• Disappearance of the event even though the study drug treatment continues or remains unchanged.

Adverse events are to be considered unrelated if the relationship to the study drug as described in the table in section [8.3.2] is none or unlikely; whereas any AE reported in the study having a possible, probable or highly probable relationship to study drug will be considered as an ADR. [For the purposes of safety reporting, "reasonable possibility" means there are facts (evidence) or arguments to suggest a causal relationship between the drug and the adverse event.]

Adverse Event of Special Interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within the study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

In the present study, the following sight-threatening events will follow into the definition of AESI and will be considered equivalent to a SAE and will be reported following the procedures described below for the reporting of a SAE:

- Adverse Events that caused a decrease in visual acuity of >30 ETDRS letters or > +0.6 LogMAR (compared with the last assessment of visual acuity at the last visit) lasting >1 hour.
- Adverse Events that caused a decrease in visual acuity to the level of Light Perception or worse lasting >1 hour.
- Adverse Events that required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- Adverse Events associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis).
- Adverse Events that, in the opinion of the investigator, required medical intervention to prevent permanent loss of sight.

Serious Adverse Event

A **Serious Adverse Event** (**SAE**) is defined as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization,

  NOTE: In general, hospitalization means that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.

- results in persistent or significant disability/incapacity,

  NOTE: This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- is a congenital anomaly/birth defect,
- is medically significant or important medical condition, i.e. an important medical event that based upon appropriate medical judgment, may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed above.

  An important medical condition is an event that may not result in death, be life-threatening, or require hospitalization but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

Pre-planned hospitalization or hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition are not considered to be SAEs.

These events must be recorded in the AE page of the CRF where a variable will be ticked to indicate that they are not SAEs.

Death shall always be reported as SAE. Cause of death shall always be specified when known.

Any preplanned surgery or procedure should be clearly documented in the site source documents by the medically qualified Investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Dompé.

Dompé considers cancer and abortion (spontaneous or non-spontaneous) as serious adverse events, as well as any suspected transmission via a medicinal product of an infectious agent is considered a serious adverse reaction.

Unexpected Adverse Events

An AE or ADR is considered unexpected if it is not listed in the package insert. An event is unexpected also when it is not listed at the specificity or severity that has been observed and listed in the package insert.

The determination of expectedness shall be made based on the package insert. It is the responsibility of the Sponsor to assess whether an AE is expected or unexpected.

Suspected serious unexpected adverse reaction

A **suspected serious unexpected adverse reaction** (**SUSAR**) is defined as an adverse reaction that is both unexpected (not consistent with the applicable product information) and meets the definition of a Serious Adverse Reaction.

8.2. MONITORING FOR ADVERSE EVENTS

At each visit following study informed consent form signature, after the subject has had the opportunity to spontaneously mention any problems, the Investigator or appropriate designee should inquire about AEs by asking the standard questions:

• "Have you had any health problems since your last study visit?"

• "Have there been any changes in the medicines you take since your last study visit?"

AEs should be reported for any clinically relevant change in concomitant condition(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health. Anticipated day-to-day fluctuations of preexisting conditions that do not represent a clinically significant exacerbation or worsening need not be reported as AEs. Changes in any protocol-specific [ocular or] systemic parameter evaluated during the study are to be reviewed by the Investigator. In addition, the subject's responses to any questionnaire utilized during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

8.3. RECORDING

AEs will be collected and recorded for any untoward event that occurs in a patient from the time he or she signs the ICF for the trial until 24 weeks after the last dose of Study Product. Thus, any untoward medical occurrences or unfavorable and unintended signs, symptoms, or diseases that occur in the pretreatment, treatment, or post treatment period are to be considered AEs and/or SAEs, and consequently recorded and reported as such. Should a non-serious AE become serious, the Investigator will then follow the same reporting procedures as for SAEs.

Each AE will be described by:

- Its duration (start and stop dates)
- Severity
- Its relationship to the study drug; (suspected/unsuspected)
- Action(s) taken
- Outcome

Medical conditions/diseases, or cancer related signs/symptoms present before starting study treatment shall be documented in the medical history section of the CRF; these conditions are considered AEs only if they increase either in frequency or severity once informed consent has been signed.

8.3.1. Follow-Up of patients with Adverse Events

The Investigator is responsible for adequate and safe medical care of patients during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. All AEs should be followed-up to determine outcome of the reaction. The Investigator should follow up the event until resolution or stabilization of the condition. It is the Investigator's responsibility to assure that the patients experiencing AEs receive definite treatment for any AE, if required.

If subject was hospitalized due to a SAE, a copy of the discharge summary is to be forwarded to the Sponsor as soon as it becomes available. In addition, a letter from the Investigator that summarizes the events related to the case as well as results of any relevant laboratory tests also may be requested. Further, depending upon the nature of the SAE, Dompé may request copies of applicable segments of the patient's medical records. In case of death, a copy of the autopsy report, if performed, should also be provided.

The Investigator shall inform the Sponsor with an appropriate written communication, whenever he/she becomes aware of new available information regarding the SAE once the condition is resolved or stabilized and when no more information about the event is expected. Additional information received after the initial SAE has been reported to the Sponsor should be reported as follow-up information following the same procedure and timeline as the initial SAE.

For pharmacovigilance purposes, all SAEs should be followed-up to clarify as completely as possible their nature and/or causality and until all queries have been resolved. All SAEs will be followed up until the events resolve or the events or sequelae stabilize, or it is unlikely that any additional information can be obtained after demonstration of due diligence with follow-up efforts (i.e. subject or Investigator is unable to provide additional information, or the subject is lost to follow up), unless subject has withdrawn his/her consent.

8.3.2. Relationship of AEs to the Study Product

The Investigator will assess the possible relationship between the AE and the investigational medication, according to the criteria in **Table** below:

Relationship of the Adverse Event to the Study Product

None (Intercurrent Event)	An event that is not and cannot be related to the Study Product, e.g. patient is a passenger in a road traffic accident.
Unlikely (remote)	Relationship is not likely e.g. a clinical event including laboratory test abnormality with temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide more plausible explanations
Possible	Relationship may exist, but could have been produced by the patient's condition or treatment or other cause
Probable	Relationship is likely, the AE abates upon discontinuation of Study Product and cannot be due to the patient's condition
Highly Probable	Strong relationship, the event abates upon discontinuation of l Study Product and, if applicable, re-appears upon repeat exposure

8.3.3. Severity of AEs

The Investigator will grade the severity of any AE using the definitions in the **Table** below. For each episode, the highest severity grade attained should be reported.

Severity of the Adverse Event

Mild	Grade 1 - Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2 - Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3 - Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])

8.4. SERIOUS ADVERSE EVENT REPORTING

8.4.1. Reporting Procedure for Investigators to Lexitas Pharma Services, Inc. And Dompé Drug Safety

The Investigator must report all SAEs, regardless of presumed causal relationship, to *Lexitas Pharma Services, Inc.* Pharmacovigilance and to Dompé Drug Safety, by e-mail (preferred) or fax within 24 hours of learning of the event.

SAE reporting should be sent to:

SAE Email address: DompeSafety@lexitas.com

Dompé Drug Safety: USDrugSafety@dompe.com

Dompé Drug Safety: +1 (347) -294-3328

In case of failure of/lack of access to email, or fax, the event should be reported using the SAE hotline telephone number: **844-237-6724**.

If an SAE is reported via telephone, the telephone report should be followed by a written report using a reporting method described above (i.e., completion of paper form).

The investigator should also report information on SAEs that continue after patient has completed his/her participation in the study (whether study completion or withdrawal) unless patient has withdrawn his/her consent.

Information on SAEs will be recorded on the SAE form approved by the Sponsor. Additional follow-up information (e.g., test results, autopsy, and discharge summary) may be requested to supplement the SAE report form and can be attached as de-identified records. Follow-up reports (as many as required) should be completed and e-mailed/faxed following the same procedure and timeline above, marking the SAE form as "follow up Number XX".

Whenever more than one SAE is observed, the Investigator should identify which is the primary serious adverse event, i.e. the most relevant one. In any case, the Investigator is requested to record his/her opinion about the relatedness of the observed event(s) with the investigational medication.

In line with CT3 Detailed Guidance and ICH E2A provisions, although the Investigator does not usually need to actively monitor patients for AEs once the trial has ended, if the Investigator becomes aware of a SAE occurring to a patient after that patient has ended his/her participation in the study (whether study completion or withdrawal), the SAE should be reported by the Investigator to the Dompé/Lexitas Pharmacovigilance. Such "post-study cases" should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether expedited reporting is required.

8.4.2. Conditions that should not be reported as serious adverse events

The conditions listed below, that may require hospitalization of a patient, are not considered to be SAE, and shall not be reported as such, but only need to be recorded in the CRF:

- Hospitalizations planned before entry into the clinical study which is part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition.
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Hospitalization for treatments, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.
- Hospitalization for general care not associated with any deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of SAEs given above and not resulting in hospital admission.

In addition, the following situation shall not be considered SAE:

- Trial end points
- Abnormal lab values or test results that do not induce clinical signs and/or symptoms and require intervention/therapy, i.e. are clinically significant.

8.4.3. Reporting Procedure to IRB/IEC and to Regulatory Authorities

SUSAR shall be reported to the Regulatory Authority (FDA and non-US concerned Authority as applicable) by Dompé as soon as possible and in no event later than:

(*a*) seven calendar days after becoming aware of the information if the event is fatal or life threatening; to be followed by any relevant information within eight days.

(*b*) fifteen calendar days after becoming aware of the information if the event is neither fatal nor life threatening.

Lexitas Pharma Services, Inc shall follow up on safety information and shall report any relevant updated findings as soon as available.

If the results of an investigation show that an adverse drug reaction not initially determined to be reportable is reclassified as reportable, *Dompé* shall report such reaction in a written safety report as soon as possible, but in no event later than 7/15 calendar days after the determination is made.

In addition, each IRB/IEC/Regulatory Authority and Investigator will receive appropriate periodic safety updates as per applicable local requirements and regulations.

In addition to reporting the SAE to Dompé and Lexitas, the Investigator must also comply with the requirements related to the reporting of SAEs to the local IRB which approved the study. The requirements of IRBs vary from one IRB to another; however, as a minimum requirement, the Investigators must promptly report all suspected unexpected serious adverse reactions (SUSAR) to their IRB.

In line with provisions set forth in 21CFR312, Dompé shall notify all participating Investigators in an IND safety report of any suspected adverse reaction that is both serious and unexpected and of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than:

- seven calendar days after becoming aware of the information if the event is fatal or life threatening; to be followed by any relevant information within eight days.

- fifteen calendar days after becoming aware of the information if the event is serious but neither fatal nor life threatening.

The Investigators in turn shall notify their local IRB.

Copies of all correspondence relating to reporting of any SUSARs to the local IRB should be maintained in the Investigator's Files.

Dompé shall also notify FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible after Dompé determines that the information qualifies for reporting, shall notify of:

- any suspected adverse reaction that is both serious and unexpected. Dompé must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event.

- findings from other studies that suggest a significant risk in humans exposed to the drug. Such a finding would result in a safety-related change in the overall conduct of the clinical investigation.

- findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug

- increased rate of occurrence of serious suspected adverse reactions.

8.4.4. Periodical Reporting to Regulatory Authorities

Dompé shall be responsible to prepare and submit annual safety reports (Development Safety Update Report – DSUR) to relevant Regulatory Authorities.

8.5. EXPOSURE TO STUDY PRODUCT DURING PREGNANCY

Women of childbearing potential are not excluded from the study if adequate birth control methods are being utilized. Women of childbearing potential are defined as all women physiologically capable of becoming pregnant. Adequate birth control methods are summarized in the protocol's exclusion criteria. Prior to enrolment in the clinical trial, female patients of childbearing potential and their partners must be advised of the importance of avoiding pregnancy during the entire course of the study treatment and for the 30 days after the study treatment period ends and of the potential risks associated with an unintentional pregnancy. During the trial, female patients are to be instructed to contact the Investigator immediately if they suspect they might be pregnant. In the same way, male patients who become aware that the partner might be pregnant, are to be instructed to contact the Investigator immediately.

The Investigator must report every pregnancy on a Pregnancy Report Form as soon as possible (within 24 hours of learning of the pregnancy) to the same contacts specified in Section 8.4.1., even if no AE has occurred, and follow it to term. If, however, the pregnancy is associated with an SAE (e.g., if the mother is hospitalized for dehydration), in addition to the pregnancy report form, a separate SAE report form must be filed as described in Section 8.4.1. with the appropriate serious criterion (e.g., hospitalization) indicated on the SAE report form.

Any pregnancy leads to the immediate exclusion from the trial. Miscarriage, stillbirth, and any malformation/disease must be reported as a SAE.

The pregnant woman (patient or partner) should be followed for pregnancy outcome through delivery or termination of the pregnancy. In any pregnancy that progresses to term, the infant should be followed until 6 months after birth and any congenital abnormalities/birth defects in the infant should be reported as an SAE.

8.6. ADVERSE EVENTS CAUSING TREATMENT DISCONTINUATION

If a patient is withdrawn from the study as a consequence of an AE, this must be recorded and reasoned in the CRF, and the patient must be followed up until the resolution of the AE or as instructed by the medical monitor.

8.7. OVERDOSE

Cases of overdose (accidental or intentional) should be reported in the eDC. Any overdose which results in a serious adverse event is to be reported to Dompé and Lexitas Pharmacovigilance and Dompé Medical Expert, following the same procedure for SAE, within 24 hours from the Investigator's knowledge of its occurrence. This includes reports related to drug intake through different routes (e.g. ingestion) or with suicidal intentions and consequent drug overdose.
An overdose of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution is defined as the administration of 50% or more additional drops on any given treatment day.

The Investigator shall provide information about symptoms, corrective treatment, and outcome of overdose. The Medical Expert should be contacted to discuss corrective treatment, if necessary.

8.8. UNMASKING

This is a single-arm open-label trial with no provisions for masking Study Product.

9. STATISTICS

A general description of the statistical methods used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1. SAMPLE SIZE

A sample size of 35 evaluable patients (patients completing 8 weeks of Oxervate™) will achieve a lower limit of 95% confidence interval equal to 40% and 54% when the percentage of subjects who experience epithelial healing is 58% (at 4-week) and 72% (at 8-week), respectively.

The sample size calculation was based on previous trial calculations from NGF0212 (REPARO) and NGF0214 (US trial) that showed statistical superiority in complete healing after 8 weeks of treatment with cenegermin, 72% and 65.5% respectively. Assumption for this target, has been proportion of patients achieving complete healing of staining (grade 1 or less on NEI scale) by week 8.

9.2. PATIENT POPULATION

Screened Population

The Screened Population will consist of all patients who attended Screening, signed the ICF, and were assigned a PID number.

Analysis Sets

Full Analysis Set: consist of all patients who receive at least one dose of study drug.

Full Treated Set: consist of all patients who receive all 8 weeks of treatment.

9.3. STATISTICAL METHODOLOGY

9.3.1. Demographic and baseline characteristics

Subject Characteristics and Disposition

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).

Baseline demographic and background variables will be summarized. The number of patients who enroll in the study and the number and percentage of patients who complete the study will be presented. The frequency and percentage of patients who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will also be summarized.

9.3.2. Analysis of efficacy variables

Analyses for responder outcomes will include percentage of response and exact 95% confidence intervals. Analyses of change from baseline and continuous outcomes will include mean and associated asymptotic 95% confidence intervals. No formal hypothesis test will be conducted.

9.3.3. Analysis of safety variables

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and will be summarized overall. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.

9.3.4. Missing data *(mandatory)*

The percentage of missing data at each visit will be reported to assess possible causes of dropout. Details for missing data imputation will be described in the SAP.

9.3.5. Changes to the statistical plan

Any deviations from the original statistical plan will be described in the Clinical Study Report.

10. ETHICAL CONSIDERATIONS

10.1 REGULATORY BODY APPROVAL

Dompé or the CRO or other consultant appointed by Dompé will obtain the necessary approval from the Competent Authorities, as needed, prior to initiation of the study.
The study will not be started until written approval from the relevant Competent Authorities (or no objection within the timeframe set by the local regulation, as applicable) has been received by Dompé.

10.2 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

United States

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Principal Investigator (PI). A copy of the approval letter will be supplied to the sponsor, along with a roster of IRB members or the US Department of Health and Human Services (DHHS) general assurance number. During the course of the study, the PI will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study centers in conformance with Code of Federal Regulations (CFR), Title 21, Part 56.

10.3 ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with the protocol, the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, October 2013) and ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP) and any local regulations.

10.4 PATIENT INFORMATION AND CONSENT

Patients, after being explained the study, will give voluntary and written informed consent before participating in any study-related procedures.

The informed consent statement contains all the elements of informed consent contains all the core elements and mandatory statements as defined in the CFR. Signed copies of the ICF and the HIPAA form (if not included as part of the ICF) will be given to the patient, and both documents will be placed in the PI's study files. A unique patient identification (PID) number will be assigned according to Section 4.4 of the protocol at the time the patient signs the ICF.

10.5 CONFIDENTIALITY

All information obtained during the conduct of the study will be regarded as confidential. An agreement for disclosure will be obtained in writing by the patient and will be included in the ICF. Patient's data collected during the study will be handled in accordance with applicable data protection laws and regulations.

On the CRFs and Daily Study Dosing Diaries, patients will be identified ONLY by the assigned patient number. If patient names are included on copies of documents submitted to Lexitas Pharma Services, Inc., the names will be obliterated or masked, and the assigned patient number added to the document.

10.6 COMPENSATION FOR MEDICINE-INDUCED INJURY AND INDEMNIFICATION

Before the trial formally starts, Dompé will take out a study-specific insurance contract according to national laws for patients/Investigators/Institutions participating in the clinical trial.

In case of questions about medical care, cost for medical care or insurance, patients can talk to their Investigator. Contact details will be given in the Patient Informed Consent Document.

11 DATA HANDLING AND RECORD KEEPING

11.1 CASE REPORT FORMS

All data relating to the study will be recorded on CRFs to be provided by the Lexitas, through the EDC system. The PI is responsible for verifying that all data entries in the CRFs are accurate and correct. The PI must sign the completed CRF before its submission to the sponsor.

11.2 DATA MANAGEMENT

Data collection will involve the use of an EDC system, to which only authorized personnel will have access. In addition to periodic monitoring occurring within the system by Dompé/Lexitas Monitors, programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the study centers and electronically closed by those study centers. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring process) and the originator of the data change (if applicable), as well as the PI's approval of all changes performed on his or her patients' data, will be collected.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidelines for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of CRFs, regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for audit by Dompé; its authorized representatives; and Regulatory Inspection by Regulatory Authority.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary, via an audit trail.

12 STUDY MANAGEMENT

The study will be performed in accordance with the protocol, the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP) and any local regulations.

12.1 MONITORING AND QUALITY ASSURANCE

During the course of the trial a clinical research associate (CRA) will make routine site visits to review protocol compliance, assess Study Product and Study concomitant product accountability, and ensure the trial is being conducted according to the pertinent regulatory requirements. The review of the patients' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the trial monitoring (including medical monitoring) will be outlined in a monitoring plan.

Domestic and foreign regulatory authorities, Clinical Research Organization (CRO) Drug Safety and quality assurance, sponsor and or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out with consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

12.2 ACCESS TO RECORDS

The Investigator will allow designated Dompé representatives, including staff from the appointed CRO, and regulatory/ethics bodies to have direct access to the source documents to verify the data reported in the CRFs. Source documents are the originals of any documents used by the Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the trial.

12.3 AUDIT AND INSPECTION

The study site may be audited by Dompé or inspected by a regulatory agency on one or more occasions The Investigator may be informed in advance of such a visit.

12.4 PROTOCOL AMENDMENTS

Any amendment to this protocol will be provided to the PI in writing by Dompé. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the PI, has been received by Dompé. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/EC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits. Deviating from the protocol is permitted only if necessary for the safety or clinical management of the patients and must immediately be reported to Dompé US.

12.5 DISCONTINUATION OF THE STUDY

Dompé reserves the right to terminate the study in its entirety or at a specific study center at any time on the basis of new information regarding safety or efficacy, or if study progress is unsatisfactory, or for other valid administrative reasons.

12.6 PUBLICATIONS

All data generated in this study will be the property of Dompé. Publication of the results by the PI will be subject to mutual agreement between the PI and Dompé US. Data either complete or preliminary cannot be published by PI without permission from Dompé.

13 REFERENCES

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14 APPENDICES

14.3 APPENDIX 3- OXERVATE™ 0.002% (20 MCG/ML) CENEGERMIN-BKBJ OPHTHALMIC SOLUTION PACKAGE INSERT

PATIENT INFORMATION
OXERVATE (ox'-er-vayt)
(cenegermin-bkbj)
ophthalmic solution,
for topical ophthalmic use

What is OXERVATE?
OXERVATE is a prescription eye drop solution used to treat a condition called neurotrophic keratitis.
OXERVATE is safe and effective in children two years of age and older.

Before you use OXERVATE, tell your doctor about all of your medical conditions, including if you:

- have an infection in your eye. If you get an eye infection **while** using OXERVATE, talk your doctor right away.
- are using any other eye drops.
- wear contact lenses.
- are pregnant or plan to become pregnant. It is not known if OXERVATE will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if OXERVATE passes into your breast milk. Talk to your doctor about the best way to feed your baby if you use OXERVATE.

Tell your doctor about all the medicines you take, including prescription and over-the counter medicines, vitamins, and herbal supplements.

How should I use OXERVATE?

- See the complete Instructions for Use at the end of this Patient Information leaflet for detailed instructions about the right way to use OXERVATE.
- Use OXERVATE exactly as your doctor tells you.
- Use 1 drop of OXERVATE in the affected eye or both eyes if needed, 6 times each day, about 2 hours apart starting in the morning. Continue your treatment for 8 weeks.
- If you use any other eye drops, wait **at least 15 minutes before or after** using OXERVATE. This will help to avoid one eye drop diluting the other eye drop.
- If you also use an eye ointment or gel or an eye drop that is thick, use OXERVATE **first**, and then wait **at least 15 minutes before** using the other eye ointment, gel, or drops.
- If you wear contact lenses in your affected eye or both eyes remove them before using OXERVATE and **wait 15 minutes after** using OXERVATE before reinserting them.
- If you miss a dose of OXERVATE, take your next dose at your scheduled time. **Do not** take an extra dose to make up for a missed dose.
- **Do not** use other eye medicines without talking to your doctor.
- Talk to your doctor first before you stop using OXERVATE.
- If you have any questions about how to use OXERVATE, ask your doctor or pharmacist.

What should I avoid while using OXERVATE?
Your vision may be blurred for a short time after using OXERVATE. If this happens, **wait until your vision clears before you drive or use machines**.

What are the possible side effects of OXERVATE?
The most common side effect of OXERVATE is eye pain, enlarged blood vessels in the white of the eyes (ocular hyperemia), swelling (inflammation) of the eye, and increase of tears (increased lacrimation).

Tell your doctor if you have any side effects that bother you. These are not all the possible side effects of OXERVATE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of OXERVATE.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use OXERVATE for a condition for which it was not prescribed. Do not give OXERVATE to other people, even if they have the same symptoms you have. It may harm them.

Dompé

You can ask your pharmacist or doctor for information about OXERVATE that is written for health professional.

What are the ingredients in OXERVATE?
Active ingredient: cenegermin-bkbj

Inactive ingredients: disodium hydrogen phosphate anhydrous, hydroxypropylmethyl cellulose, L-methionine, mannitol, polyethylene glycol 6000, sodium dihydrogen phosphate dihydrate, trehalose dihydrate, Water for Injection, USP, and hydrochloric acid and/or sodium hydroxide to adjust pH.

Manufactured by:
Dompé farmaceutici S.p.A.
Via Campo di Pile
67100 L'Aquila, Italy
U.S. License No. 2074

Manufactured for: Dompé U.S. Inc.

One Marina Park Drive - Ste. 1410, Boston, MA 02210

For more information, go to www.oxervate.com or call 1-833-366-7387.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised or Issued: October 2019

14.4 APPENDIX 4-FLUORESCEIN STAINING NEI / INDUSTRY WORKSHOP SCALE AND MACKIE CLASSIFICATION

The 5 areas of the cornea will be scored by the investigator according to the following scoring system and the total score will also be calculated. NOTE: The TBUT and the FCS may be performed right eye then left eye or staggered with the TBUT for the left eye being done during the waiting period before completing the FCS for the right eye.
https://www.aao.org/image/neiindustry-grading-system

Area Key: 1=Central, 2=Superior, 3=Temporal, 4=Nasal,5=Inferior

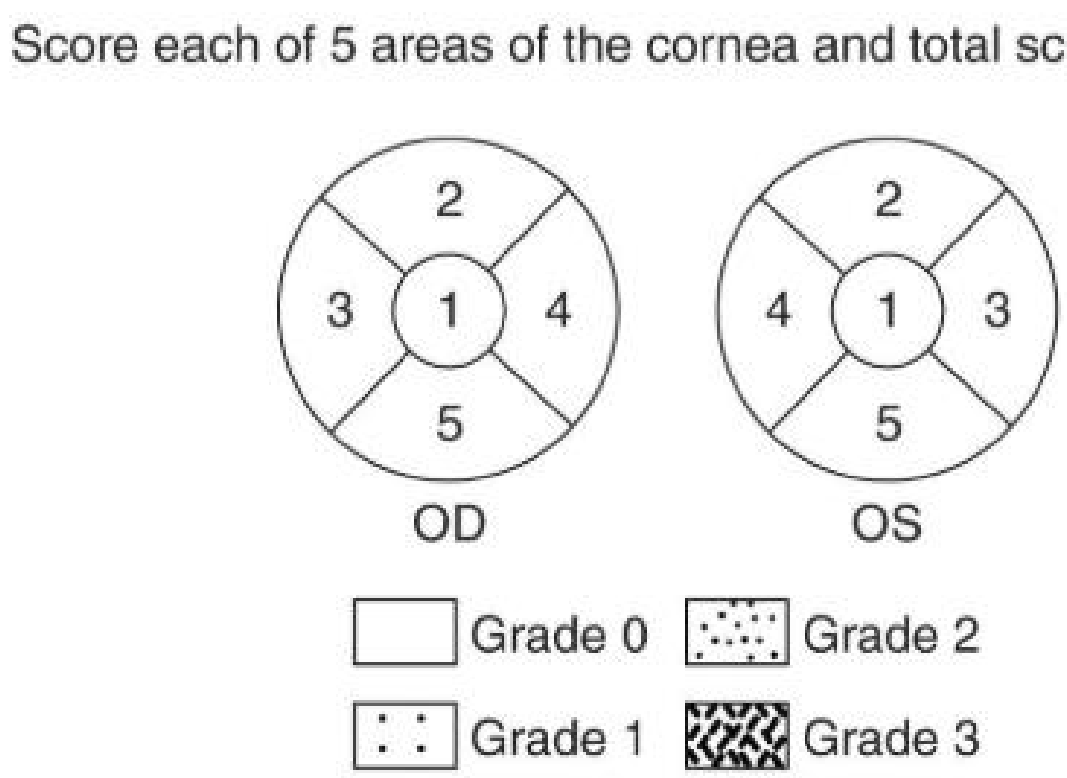

Table 1 – Mackie's Classification[8]

Stage	Clinical findings
I	Corneal epithelial hyperplasia and irregularity Superficial punctate keratopathy Increased viscosity of tear mucus and decreased break-up time
II	Persistent corneal epithelial defect - smooth and rolled edges Descemet's membrane folds and stromal swelling Anterior chamber inflammatory reaction with hypopyon (rare)
III	Corneal ulcer Corneal perforation Corneal stromal melting