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CLINICAL STUDY PROTOCOL

Title:	A long-term extension study to evaluate the safety and efficacy of OXERVATE 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in patients with Stage 1 Neurotrophic Keratitis who enrolled in the DEFENDO Study
Short Title:	DEFENDO Long-Term Follow-up Study
Study Number:	NGF0122
EudraCT Number/IND:	115892
Study Product:	N/A
Phase of the study:	IV
Protocol Version - Date:	**Version No. 2.0 29Sep2022**

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Table 1 List of Abbreviations and Definitions of Terms

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
CCI	CCI
BCDVA	Best Corrected Distance Visual Acuity
BLA	Biologics License Application
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
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPS2	Global Pharmacovigilance, Safety and Surveillance
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
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
mcg/mL	Microgram per milliliter
mNGF	Murine Nerve Growth Factor
MOP	Manual of Procedures
NGF	Nerve Growth Factor
CCI	

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CCI	
NK	Neurotrophic Keratitis/Keratopathy
CCI	
P75NTR	P75 Neurotrophin Receptor
PED	Persistent Epithelial Defect
PID	Patient Identification
PI	Principal Investigator
rhNGF	Recombinant Human Nerve Growth Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SLE	Slit-Lamp Examination
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFBUT	Tear Film Break Up Time
TrkA	Tropomyosin Receptor Kinase A

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1 STUDY SYNOPSIS

CLINICAL STUDY SYNOPSIS:	
Study Number	NGF0122
Title of Study	A long-term extension study to evaluate the safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in patients with Stage 1 Neurotrophic Keratitis who were enrolled in the DEFENDO Study
Short Title	DEFENDO Long-Term Follow-up Study
EudraCT N°/IND	115892
Study Centers (Country)	4 US Study Centers
Development Phase	IV
Study Objectives	**Primary Objective** The primary objectives are to evaluate the long-term safety and efficacy (healing) of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in Stage 1 Neurotrophic Keratitis (NK) patients who enrolled in the DEFENDO Study. **Secondary Objective** The secondary objectives are to evaluate the long-term efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in terms of Corneal Sensitivity, Schirmer I Test, Tear Film Break Up Time (TFBUT), Best Corrected Distance Visual Acuity (BCDVA), and Quality of Life at 24 and 30 months.

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Design and Methodology	This clinical study will be a multi-center, open label, long-term follow-up study of the patients who were enrolled in the DEFENDO Study who had Stage 1 Neurotrophic Keratitis (NK) who were treated with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution. **The DEFENDO Long-Term Follow-up Study will have follow-up with the patients at month 24 and 30 post-treatment in the DEFENDO Study:** All patients will be evaluated in a real-world setting post the enrollment in the DEFENDO Study through 30 months. Patients will be treated per standard of care as determined by the Investigator CC CCI The original DEFENDO Study duration was for a total of 34 weeks: a screening period of 2 weeks, followed by enrollment in 8 weeks of OXERVATE™ treatment and an Off-Treatment Follow-Up of 6 months. • After completing enrollment in the original DEFENDO Study, patients will be invited to enter the DEFENDO Long-Term Follow-up Study (all standard of care is permitted). Two (2) additional long-term follow-up visits will occur at 24- and 30-months to evaluate long-term clinical outcomes.

	All patients enrolled in the DEFENDO Study who are not meeting exclusion criteria and/or are not lost to follow-up will be eligible for the DEFENDO Long-Term Follow-up Study. During the DEFENDO Long-Term Follow-up Study, the patients may be treated at the physician's discretion. Any concomitant treatment must be documented. If warranted for patient safety, the Investigator may elect to see the patient at an Unscheduled Visit(s) to evaluate the patient.
Number of Patients	Up to 37
Main Criteria for Inclusion/Exclusion	**Inclusion Criteria** - To be eligible for inclusion into this study, each patient must fulfil the following inclusion criteria: 1. Previously enrolled in the DEFENDO Study. 2. Satisfy all Informed Consent requirements. • The patient and/or his/her legal representative has read, signed, and dated the IRB approved Informed Consent document before any study-related procedures are performed. 3. Must have the ability and willingness to comply with study procedures. **Exclusion Criteria** - Patients who meet any of the following criteria are NOT eligible for inclusion in the study: 1. Participating in another study that involves treating the study eye. a. Participation in non-ocular studies is acceptable provided that the treatment is not considered to be confounding with the DEFENDO Long-Term Follow-up Study, in the opinion of the Investigator.
Duration of Treatment	No study treatment will be provided
Reference product, Dosage and Mode of Administration	N/A

Efficacy Endpoints	• Percentage of patients who have corneal epithelial healing at 24 months and 30 months of the long-term follow-up. o Percentage of patients who had corneal epithelial healing at week-8 in the DEFENDO Study, who maintain healing at month 24 and month 30 of the long-term follow-up. o Percentage of patients who did not have corneal epithelial healing at week-8 in the DEFENDO Study who have a healed corneal epithelium at month 24 and month 30 of the long-term follow-up. • Percentage of patients who achieved an improvement in corneal sensitivity at 24 months and 30 months of the long-term follow-up. o Percentage of patients who achieved an improvement in corneal sensitivity at week-8 in the DEFENDO Study who still have improvement in corneal sensitivity at 24 months and 30 months of the long-term follow-up. o Percentage of patients who did not achieve an improvement in corneal sensitivity in the DEFENDO Study who have improvement in corneal sensitivity at 24 months and 30 months of the long-term follow-up. • Change from the Baseline Visit in the DEFENDO Study in Schirmer I scores at 24 months and 30 months of the long-term follow-up. • Change from the Baseline Visit in the DEFENDO Study in TFBUT at 24 months and 30 months of the long-term follow-up. • Change from the Baseline Visit in the DEFENDO Study in BCDVA at 24 months and 30 months of the long-term follow-up.

	• Percentage of patients who achieved a 15-letter improvement in BCDVA at 24 months and 30 months compared to the Baseline Visit and Week 8 of the DEFENDO Study. • Change from the Baseline Visit in the DEFENDO Study in quality of life as measured with the Impact of Dry Eye on Everyday Life (IDEEL) at 24 months and 30 months of the long-term follow-up. • Change from the Baseline Visit in the DEFENDO Study in quality of life as measured with the EQ-5D-5L at 24 months and 30 months of the long-term follow-up. CCI [redacted]
Safety Measures	• Adverse Event Monitoring. • Slit-Lamp Examination results. • External Ocular Examination results.

Statistical Methods	The sample size for this study is not based on hypothesis-testing and power considerations but is determined by the number of patients from the DEFENDO Study who will rollover to the DEFENDO Long-Term Follow-up Study. The DEFENDO Study enrolled a total of 37 patients. The Full Analysis Set (FAS) will consist of all patients who are enrolled (with signed and dated IC) in the DEFENDO Long-Term Follow-up Study. The FAS population will be used for the presenting efficacy and safety results. Appropriate descriptive statistics will be produced according to the nature of the variable. For continuous data, number of observations, mean, standard deviation, median, range (minimum and maximum) and 95% confidence intervals will be presented. For categorical data, frequency distributions and percentages with exact 95% confidence intervals will be presented. Baseline demographic and background variables will be summarized based upon the data originally collected in the DEFENDO Study. The number of patients who enroll in the DEFENDO Long-Term Follow-up Study and the number and percentage of patients who reach 24 months and 30 months of the long-term follow-up will be presented along with the frequency and percentage of patients who withdraw. Efficacy endpoints will be analyzed at each available time point by appropriate inferential tests versus baseline and/or week 8. All tests will be descriptive in nature, no formal hypothesis test will be conducted. 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.

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2 SCHEDULE OF EVALUATIONS

Table 2 Schedule of Evaluations

	Visit 1	Visit 2
	24-27 Months	30-33 Months
Procedures	**24-Month Study Visit**	**30-Month Study Visit / End of Study**
Inclusion/Exclusion Criteria	X	
ICF/HIPAA	X	
Record AEs	X	X
Prior and Concomitant Medications	X	X
IDEEL	X	X
EQ-5D-5L	X	X
BCDVA	X	X
External Ocular Examination	X	X
Slit-Lamp Examination	X	X
Corneal Photography Without Fluorescein	X	X
Instillation of Fluorescein	X	X
TFBUT	X	X
Corneal Photography with Fluorescein	X	X
Corneal Sensitivity Testing	X	X
Schirmer Test (w/o Anesthesia)	X	X
CCI		
CCI		

3 BACKGROUND INFORMATION

The DEFENDO Study was aimed at evaluating the efficacy and safety of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution administered 6 times daily for 8 weeks in patients with Stage 1 neurotrophic keratitis (NK).

The current study is a long-term study evaluating the clinical outcomes of patients at 24 months and 30 months after completion of the DEFENDO Study.

NK, also known as neurotrophic keratopathy/keratitis, 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. NK has been divided into three stages according to the Mackie classification scheme (Appendix 4) and treatment recommendations are based on the severity of 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 (PF-AT). While some Stage 1 NK patients may heal, many cases progress to Stage 2 NK. Based on the Mackie scale, Stage 2 NK is defined by the presence of a PED. The goal of Stage 2 treatment 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 Food and Drug Administration (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 Nerve Growth Factor 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 rhNGF approved by the FDA in August 2018, and it is indicated for the treatment of NK. Relevant pre-clinical, toxicological, and clinical data are summarized below and can be found in the Package Insert (Appendix 3).[4]

3.1 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 Murine Nerve Growth Factor (mNGF) to their culture media. [10-12]

OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution, a rhNGF, is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of NK.[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]

3.2 A SUMMARY OF CLINICAL DATA

The safety, efficacy, and FDA approval of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution, was based upon a total of 151 patients with NK who completed one of two, eight-week, randomized controlled multi-center, double-masked studies. In the first study conducted in Europe, CCI [redacted] patients were randomized into three different groups. One group received OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution, a second group received 10 mcg/mL cenegermin, and the third group received vehicle.[14] In the second study conducted in the US, CCI [redacted] patients were randomized into two groups. One group was treated with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution, and 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, CCI [redacted] 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 these 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]

The phase IV DEFENDO Study involving OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution has since been undertaken to provide additional efficacy and safety information related to OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution. This study enrolled 37 Stage 1 NK patients who were treated with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution 6 times per day at 2-hour intervals for eight weeks. The DEFENDO Study reported 33 probable and 20 possible adverse events (AEs) that were determined to be related to the Study Product; however, only 3 patients discontinued the study because of the AEs they experienced. While these data are still being analyzed, the DEFENDO Long-Term Follow-up Study is a continuation of the DEFENDO Study, which aims to understanding the efficacy and safety OXERVATE™

0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution at 24 and 30 months after the completion of the DEFENDO Study.

3.3 STUDY RATIONALE

This clinical study has been designed as a long-term follow-up study to the DEFENDO Study to understand the long-term clinical outcomes of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in a group of Stage 1 NK patients who complete the DEFENDO Study. The primary objectives are to evaluate the long-term safety and efficacy (healing) of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in Stage 1 NK patients who enrolled in the DEFENDO Study.

3.3.1 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.

3.3.2 Description of the Study Product

No Study Product will be used.

4 OVERALL STUDY DESIGN AND INVESTIGATIONAL PLAN

4.1 STUDY OBJECTIVES

Primary Objective

The primary objectives are to evaluate the long-term safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in Stage 1 NK patients who enrolled in the DEFENDO Study.

Secondary Objective

The secondary objectives are to evaluate the long-term efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in terms of Corneal Sensitivity, Schirmer I Test, Tear Film Break Up Time (TFBUT), Best Corrected Distance Visual Acuity (BCDVA), and Quality of Life at 24 months and 30 months.

CCI [redacted]

CCI [redacted]
CCI [redacted]

CCI [redacted]

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

4.2 STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at 4 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, Good Clinical Practice (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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC), completing the case report forms (CRFs) and reporting Serious Adverse Events (SAE) (or other important Adverse Events (AE) as specified in Section 9.4) within 24 hours of initial awareness.

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

4.3 OVERALL STUDY DESIGN

This clinical study will be a multi-center, open label, long-term follow-up study of the patients who were enrolled in the DEFENDO Study.

The DEFENDO Long-Term Follow-up Study will have follow-up with the patients at months 24-30. All patients will be evaluated in the real-world setting post the 6-month off treatment follow up of the DEFENDO Study through 30 months. Patient will be treated per standard of care as determined by the Investigator and will document topical ophthalmic medications. The original DEFENDO Study duration was a total of 34 weeks: a screening period of 2 weeks, followed by enrollment in 8 weeks of OXERVATE™ treatment and an Off-Treatment Follow-Up of 6 months.

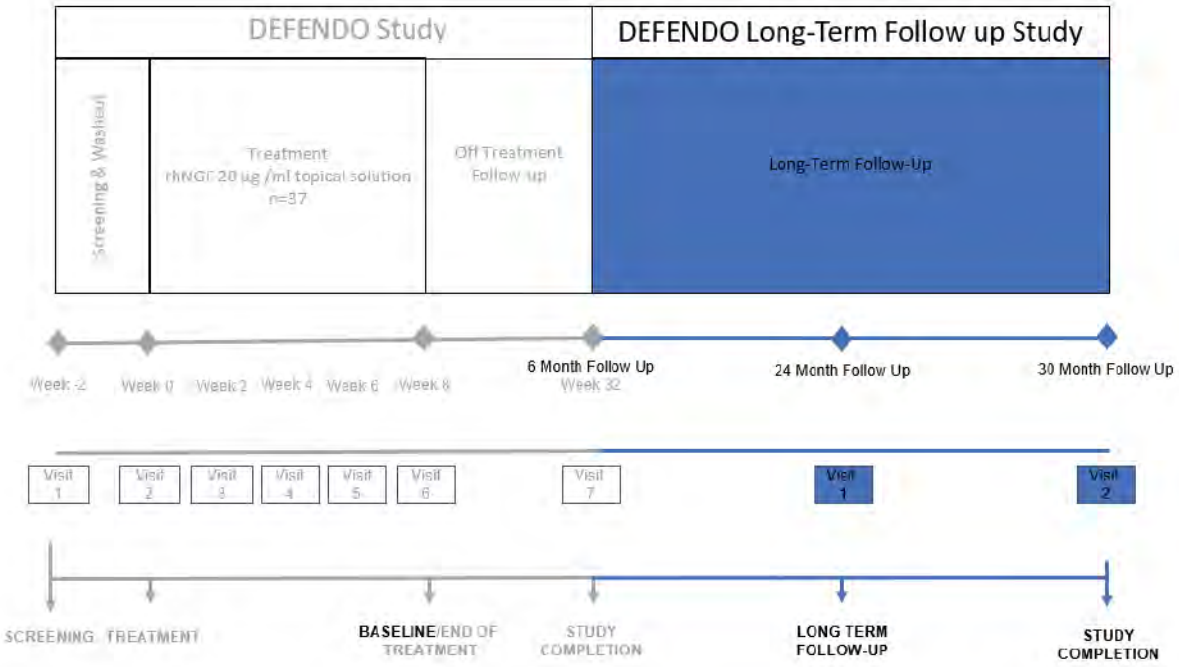
After enrollment in the original DEFENNDO Study, patients will be invited to enter the DEFENDO Long-Term Follow-up Study **(all standard of care is permitted)**. Two (2) additional long-term follow-up visits will occur at 24- and 30-month post-treatment to evaluate long-term clinical outcomes.

All patients enrolled in the DEFENDO Study that are not meeting exclusion criteria and are not lost to follow-up will be eligible for the DEFENDO Long-Term Follow-up Study.

During the DEFENDO Long-Term Follow-up Study, the patients may be treated at the physician's discretion. Any concomitant treatment must be documented. If warranted for patient safety, the Investigator may elect to see the patient at an Unscheduled Visit(s) to evaluate the patient.

Corneal healing will be graded at a Central Reading Center per the Reading Center Charter.

Figure 1 Study Schematic



5 SELECTION OF STUDY POPULATION

Patients who were enrolled in the DEFENDO Study and were not lost to follow up will be enrolled to evaluate the long-term safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in Stage 1 NK patients.

5.1 INCLUSION CRITERIA

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

1. Previously enrolled in the DEFENDO Study.
2. Satisfy all Informed Consent requirements.
    - The patient and/or his/her legal representative has read, signed, and dated the IRB approved Informed Consent document before any study-related procedures are performed.
3. Must have the ability and willingness to comply with study procedures.

5.2 EXCLUSION CRITERIA

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

1. Participating in another study that involves treating the study eye.
    - Participation in non-ocular studies is acceptable provided that the treatment is not considered to be confounding with the DEFENDO Long-Term Follow-up Study, in the opinion of the Investigator.

5.3 ASSIGNMENT OF PATIENT NUMBER

Each patient will maintain the study number they were assigned in the DEFENDO Study.

6 STUDY PRODUCT

6.1 DESCRIPTION OF STUDY PRODUCT

No Study Product will be administered during this study.

6.2 PRIOR AND CONCOMITANT MEDICATIONS

Patient topical medications taken between exiting the DEFENDO Study and enrolling in the DEFENDO Long-Term Follow-up Study will be documented as prior medications.

Patients may be treated according to the standard of care as determined by the Investigator. This may include commercially available OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution. Any treatment history will be documented (including over-the-counter drugs, systemic medications, herbal products, vitamins, and antacids) on the Concomitant Medications electronic CRF (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."

7 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 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 patient.

7.1 STUDY VISITS AND EXAMINATIONS AND TREATMENT VISITS

7.1.1 Visit 1: 24-Month Long-Term Follow-Up

The 24-month long-term follow up is considered from the completion of 8-weeks of treatment. Site staff will conduct the following assessments in the order outlined below:

1. **Inclusion/Exclusion Criteria:** Inclusion/Exclusion criteria will be reviewed, and study eligibility will be determined.
2. **Informed Consent/Health Insurance Portability and Accountability Act (HIPAA):** Explain the purpose and nature of the study and have the patient or legally authorized representative read, sign, and date the IRB approved Informed Consent Form (ICF). Provide a photocopy of the signed document to the patient and place the original signed document in the patient's chart.
3. **Demographics, Medical and Ocular History**: These data from the DEFENDO Study will be carried forward into the current study's electronic data capture (EDC) System; thus, they do not need to be captured separately for this study.
4. **Record AE:** Record any AE since completing the DEFENDO Study in the AE eCRF. Data for AEs that have occurred since the completion of the DEFENDO Study should be obtained from retrospective chart review and / or patient interview. Additional information may be requested via medical records from all applicable healthcare providers, if necessary.
5. **Concomitant and Prior Ocular and Systemic Medications:** Record any concurrent ocular or non-ocular medications including information on all concomitant and previous medications used since completing the DEFENDO Study in the Concomitant Medications eCRF (Section 6.2). Data for topical ocular medications taken since the patient completed the DEFENDO Study should be obtained from retrospective chart review and / or patient interview. Additional information may be requested via medical records from all applicable healthcare providers, if necessary.

6. **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.
7. **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 to provide a simple, generic measure of health for clinical and economic appraisal.
8. **Ophthalmic Examinations:** The following examination/procedures will be performed on BOTH EYES and in the below order. Grading scales and a detailed description of the examinations/procedures are described in the MOP:
    a. **Best-Corrected Distance Visual Acuity (BCDVA):** Vision will be measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart at 4 meters (13 feet) and recorded in Logarithm of the Minimum Angle of Resolution (LogMAR). 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:** The motility of the extraocular muscles and the appearance and function of the eyelids will be evaluated before the instillation of any dilating or anesthetic eye drops.
    c. **Slit-Lamp Examination (SLE):** A SLE will be used to assess eyelids, lashes, conjunctiva, cornea, lens, iris, and anterior chamber. The SLE 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 will be taken after the SLE and before the instillation of fluorescein agent by a slit-lamp camera using white, diffuse (homogenous) frontal illumination.
    e. **Instill Fluorescein**
    f. **Tear Film Break-Up Time (TFBUT)**

g. **Corneal Photography with Fluorescein:** A corneal photo of both eyes 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 one quadrant of each eye.

i. **Schirmer Test without Anesthesia (Schirmer I)**

C CCI [redacted]

C CCI [redacted]

7.1.2 Visit 2: 30-Month Long-Term Follow-Up

The 30-month long-term follow up is considered from the completion of 8-weeks of treatment.

1. **Record AE**
2. **Concomitant and Prior Ocular and Systemic Medications:** The Investigator will conduct a retrospective chart review and patient interview to review all medications since the previous visit.
3. **IDEEL**
4. **EQ-5D-5L**
5. **Ophthalmic Examinations:**
   a. **BCDVA**
   b. **External Ocular Examination**
   c. **SLE**
   d. **Corneal Photo without Fluorescein**
   e. **Instill Fluorescein**
   f. **TFBUT**
   g. **Corneal Photography with Fluorescein**
   h. **Corneal Sensitivity**
   i. **Schirmer Test without Anesthesia (Schirmer I)** CCI [redacted] CCI [redacted]

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6. Patient Discharged from Study

7.2 EARLY WITHDRAWAL FROM STUDY

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

- Withdrawal of consent
- Lost to follow-up (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
- Severe protocol violations. Before removal, these cases should first be discussed with Dompé.

The reasons for premature discontinuation will be reflected on the Study Termination Record of the CRF. For patients who prematurely discontinue, visit 2 procedures will be completed if allowed by the patient, and these patients will be considered off study and will no longer be followed.

Replacement Procedures

Patient replacement will not occur in this study.

7.3 END OF STUDY

For this study, the End of Study is defined as the date of the Last Visit of the Last Patient.

8 ENDPOINTS

8.1 STUDY ENDPOINTS

- Percentage of patients who have corneal epithelial healing at 24 months and 30 months of the long-term follow-up.
    - Percentage of patients who had corneal epithelial healing at week-8 in the DEFENDO Study, who maintain healing at month 24 and month 30 of the long-term follow-up.
    - Percentage of patients who did not have corneal epithelial healing at week-8 in the DEFENDO Study who have a healed corneal epithelium at month 24 and month 30 of the long-term follow-up.
- Percentage of patients who achieved an improvement in corneal sensitivity at 24 months and 30 months of the long-term follow-up.
    - Percentage of patients who achieved an improvement in corneal sensitivity at week-8 in the DEFENDO Study who still have improvement in corneal sensitivity at 24 months and 30 months of the long-term follow-up.
    - Percentage of patients who did not achieve an improvement in corneal sensitivity in the DEFENDO Study who have improvement in corneal sensitivity at 24 months and 30 months of the long-term follow-up.
- Change from the Baseline Visit in the DEFENDO Study in Schirmer I scores at 24 months and 30 months of the long-term follow-up.
- Change from the Baseline Visit in the DEFENDO Study in TFBUT at 24 months and 30 months of the long-term follow-up.
- Change from the Baseline Visit in the DEFENDO Study in BCDVA at 24 months and 30 months of the long-term follow-up.
- Percentage of patients who achieved a 15-letter improvement in BCDVA at 24 months and 30 months compared to the Baseline Visit and Week 8 of the DEFENDO Study.
- Change from the Baseline Visit in the DEFENDO Study in quality of life as measured with the IDEEL at 24 months and 30 months of the long-term follow-up.
- Change from the Baseline Visit in the DEFENDO Study in quality of life as measured with the EQ-5D-5L at 24 months and 30 months of the long-term follow-up.

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8.1.3 Safety Endpoints

- AEs assessed throughout the study.
- Slit-Lamp Examination results.
- External Ocular Examination results.

9 EVALUATION OF ADVERSE EVENTS AND SAFETY INFORMATION

9.1 DEFINITIONS

Adverse Event

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a patient or clinical investigation patient 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 considered related to treatment. This definition includes an exacerbation of preexisting medical conditions or events, historical conditions do not present prior to study treatment in the DEFENDO Study, 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 AE, 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, as applicable, 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 treatment in the DEFENDO Study 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 should carefully evaluate the relationship between the event and previous treatment with OXERVATE or any medicinal product administered at the AE onset. The Investigator should use the following information to help make their decision.

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.

AE are to be considered related or unrelated to the study drug as described in Section 9.3.2. Any AE reported in the study having a related relationship to study drug will be considered as an ADR.

Adverse Event of Special Interest (AESI)

Not applicable.

- **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 SAE and reported to Dompé.

Dompé considers cancer and abortion (spontaneous or non-spontaneous) as SAEs, 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 of the suspected medicinal product. 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 unexpected serious adverse reaction

A suspected unexpected serious 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.

9.2 MONITORING FOR ADVERSE EVENTS

At each Follow Up visit, after the patient 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 patient'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 patient'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.

9.3 RECORDING

AEs will be collected and recorded for any untoward event that occurs in a patient from the time he or she signed the ICF in the DEFENDO Study until completing the DEFENDO Long-Term Follow-up Study. Thus, any untoward medical occurrences or unfavorable and unintended signs, symptoms, or diseases that occur during the post treatment period (i.e., during the long-term follow up) should 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; (related/unrelated)
- Action(s) taken
- Outcome

Medical conditions/diseases, or cancer related signs/symptoms present before starting study treatment should have been documented in the medical history section of the CRF during the DEFENDO Study; these conditions are considered AEs only if they increase either in frequency or severity during the DEFENDO Long-Term Follow-up Study.

9.3.1 Follow-Up of Patients with Adverse Events

The Investigator is responsible for adequate and safe medical care of patients during the Study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the Study. 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 the patient 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., patient or Investigator is unable to provide additional information, or the patient is lost to follow up), unless patient has withdrawn his/her consent.

9.3.2 Relationship of AEs to a Medicinal Product

The Investigator will assess the possible relationship between the AE and the investigational medication used in the DEFENDO Study and any treatment received, including Oxervate as standard of care, in this DEFENDO Long-Term Follow-up Study, according to the criteria in the below table.

Relationship of the Adverse Event to the Medicinal Product

Unrelated	No reasonable possibility that the administration of the Medicinal Product caused the event, no temporal relationship between the Medicinal Product and event onset, or an alternate etiology has been established.
Related	It is known to occur with the Medicinal Product, is a reasonable possibility that the Study Product caused the AE, or there is a temporal relationship between the Medicinal Product and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the Medicinal Product and the AE.

9.3.3 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]).

9.4 SERIOUS ADVERSE EVENT REPORTING

9.4.1 Reporting Procedure for Investigators to PPD and Dompé Global Pharmacovigilance, Safety, and Surveillance

The Investigator must report all SAEs, regardless of presumed causal relationship, to PPD PPD Dompé Global Pharmacovigilance, Safety, and Surveillance (GPS2), by e-mail (preferred) or fax within 24 hours of learning of the event.

SAE reporting should be sent to:

- SAE Email address:
  - PPD
  - PPD
- PPD

In case of failure of/lack of access to email, or fax, the event should be reported using the SAE hotline telephone number: PPD

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. In the SAE form, the Investigator shall clearly report any other concomitant medicinal product administered at the time of the SAE onset and shall assess the causal relationship (related or unrelated) of the SAE in respect to Oxervate treatment (that occurred during the previous DEFENDO Study) and any other concomitant medicinal product.

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 SAE, 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 International Conference on Harmonization (ICH) E2A provisions, although the Investigator does not usually need to actively monitor patients for AEs once the study 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 – including the long-term follow-up (whether study completion or withdrawal), the SAE should be reported by the Investigator to the DompéPPD 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.

9.4.2 Conditions that should not be reported as SAEs

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 DEFENDO Long-Term Follow-up 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:

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

9.4.3 Reporting Procedure to IRB/IEC and to Regulatory Authorities and Notification to NDA or BLA holder

SUSAR determined to be related to treatment with Oxervate 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.

Dompé is also the BLA holder of Oxervate, therefore as Sponsor, Dompé must also submit safety information from the clinical study as prescribed by the relevant post-marketing safety reporting requirements (e.g., under Code of Federal Regulations (CFR) §§ 600.80). If the results of an investigation show that an ADR 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 PPD 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 Investigational New Drug (IND) safety report of any suspected adverse reaction that is both serious and unexpected and of potential serious risks, from clinical studies 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 the FDA in an IND safety report of potential serious risks, from clinical studies 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 AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the AE.

- 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.

When SAEs are determined to be related to treatment with other medicinal products administered during the DEFENDO Long-Term Follow-up Study, the Sponsor will also forward the report to the NDA or BLA holder, manufacturer, packer, or distributor of the marketed drug.

9.4.4 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, as applicable.

9.5 ADVERSE EVENTS CAUSING TREATMENT DISCONTINUATION

If a patient is withdrawn from the study because 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.

9.6 UNMASKING

This is a single arm study with no active treatment with no provisions for masking.

10 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).

10.1 SAMPLE SIZE

The sample size for this study is not based on hypothesis-testing and power considerations but is determined by the number of patients from the DEFENDO Study who will rollover to the DEFENDO Long-Term Follow-up Study. The DEFENDO Study enrolled a total of 37 patients.

10.2 PATIENT POPULATION

Analysis Sets

The Full Analysis Set (FAS) will consist of all patients who are enrolled (with signed and dated IC) in DEFENDO Long-Term Follow-up Study. The FAS population will be used for presenting efficacy and safety results.

10.3 STATISTICAL METHODOLOGY

Statistical analysis will be performed by the clinical research organization (CRO) appointed by Dompé.

Appropriate descriptive statistics will be produced by treatment arms according to the nature of the variable. For continuous data, number of observations, mean, standard deviation, median and range (minimum and maximum) and 95% confidence intervals will be presented. For categorical data, frequency distributions and percentages with exact 95% confidence intervals will be presented.

Unless otherwise specified, the significance level used for statistical testing (for descriptive purposes) will be 0.05 and two-sided tests will be used. All patient data collected on the CRF will be listed by patient and center.

10.3.1 Demographic and baseline characteristics

Baseline demographic and background variables will be summarized based upon the data originally collected in the DEFENDO Study. The number of patients who enroll in the DEFENDO Long-Term Follow-up Study and the number and percentage of patients who reach 24 months and month 30 of the long-term follow-up will be presented along with the frequency and percentage of patients who withdraw.

10.3.2 Analysis of efficacy variables

Efficacy endpoints will be analyzed at each available time point by appropriate inferential tests versus baseline and/or week 8. All tests will be descriptive in nature, no formal hypothesis test will be conducted.

10.3.3 Analysis of safety variables

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. Slit-Lamp and External Ocular Examination results will be summarized at each available time point.

10.3.4 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.

10.3.5 Changes to the statistical plan

The SAP will be issued before database lock with more technical and detailed elaboration of the principal features of statistical analyses. Additional post-hoc analysis may be produced according to the results obtained. Any deviations from the original statistical plan (including unplanned analyses) will be documented in the Clinical Study Report.

11 ETHICAL CONSIDERATIONS

11.1 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.

11.2 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

United States

Approval by the IRB before the start of the study will be the responsibility of the 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 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 SAEs or other significant safety findings. The study protocol, 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.

11.3 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 Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP) and any local regulations.

11.4 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 and 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. Patients will keep the same Patient Identification (PID) as the DEFENDO Study.

11.5 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, patients will be identified ONLY by the assigned patient number. If patient names are included on copies of documents submitted to PPD the names will be obliterated or masked, and the assigned patient number added to the document.

11.6 COMPENSATION FOR MEDICINE-INDUCED INJURY AND INDEMNIFICATION

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

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 ICF.

12 DATA HANDLING AND RECORD KEEPING

12.1 CASE REPORT FORMS

All data relating to the study will be recorded on CRFs to be provided PPD through the Electronic Data Capture (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.

12.2 DATA MANAGEMENT

A dedicated data integration program will be used to integrate relevant information from the DEFENDO Study EDC to the DEFENDO Long-Term Follow-up Study EDC. 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 DompéPPD 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 study records that include all pertinent observations on each of the site's study 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.

13 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 Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP) and any local regulations.

13.1 MONITORING AND QUALITY ASSURANCE

During the study a Clinical Research Associate (CRA) will make routine site visits to review protocol compliance and ensure the study 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 patient confidentiality. Further details of the study 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 patient confidentiality to the extent that local, state, and federal laws apply.

13.2 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 study.

13.3 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.

13.4 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/IEC 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.

13.5 DISCONTINUATION OF THE STUDY

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

13.6 STUDY REPORT AND PUBLICATIONS

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

Following the last patient's visit at 30 months of long-term follow-up after completing 8-weeks of treatment in the DEFENDO Study, the database will be locked, and a clinical study report will be written by the Sponsor or its designee.

14 REFERENCES

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15 APPENDICES

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15.1 APPENDIX 1- SPONSOR APPROVAL PAGE

Dompé Protocol NGF0122 DEFENDO Long-Term Follow-up Study

Sponsor Medical Expert: PPD

PPD Dompé CMO

Sponsor Clinical Trial Manager: PPD

PPD Dompé Trial Manager

Sponsor Study Responsible PPD

PPD Dompé Head of Medical Affairs

15.2 APPENDIX 2- INVESTIGATOR'S SIGNATURE PAGE

Investigator's Statement

I have read study protocol *NGF0122* DEFENDO Long-Term Follow-up Study Version No. 2.0 dated 29Sep2022 and agree to conduct the study as outlined in the protocol, and in accordance with the Declaration of Helsinki, ICH-GCP and any local regulations, being responsible for personally supervise the study conduct and ensure study staff complies with protocol requirement.

Name of Principal Investigator (block letters):_____

Signature: _____ Date: _____

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15.3 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 breastmilk. 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.**

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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 P P .

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.

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.

PPD

For more information, go to www.oxervate.com or call PPD

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

15.4 APPENDIX 4- MACKIE CLASSIFICATION

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