CLINICAL STUDY REPORT

Title:	Observational Post-Authorisation Study of Oxervate® (Cenegermin 20 µg/ml) eye drops in the treatment of adult patients with moderate or severe Neurotrophic Keratopathy.
Study Number:	DEV0118
Investigational Product	rhNGF
Indication studied:	Neurotrophic Keratopathy
Phase of the study:	Observational study
Study initiation date:	17 June 2019
Date of early study termination:	10 May 2020
Principal Investigator:	Prof. Alessandro Lambiase
Centre:	Azienda Ospedaliero Universitaria Policlinico Umberto I University La Sapienza Viale del Policlinico, 155 – 00161 Rome, Italy
Sponsor:	Dompé farmaceutici S.p.A. (Dompé) Via Santa Lucia, 6 - 20122 Milan, Italy
Contract Research Organisation:	EVIDILYA (formerly Sprim Advanced Life Sciences) Via Brisa 3, 20123 Milan, Italy
Report Status:	**Final Version 1.0 date: 06/09/2021**

COMPLIANCE STATEMENT

This study was performed in compliance with GCP, including the archiving of the essential documents

REPORT APPROVAL / SIGNATURES

We certify that this study was conducted according to the procedures herein described, according to the clinical protocol (DEV0118) and in compliance with the Declaration of Helsinki and its amendments (64th WMA General Assembly, Fortaleza, Brazil, October 2013) as well as with the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) and applicable regulatory requirements.
This Clinical Study Report represents a true and accurate record of procedures followed and of the results obtained in the Clinical Study (DEV0118).

PRINCIPAL INVESTIGATOR/COORDINATING INVESTIGATOR

_____ ____/____/____
Prof. Alessandro Lambiase Date

SPONSOR STUDY MANAGER

_____ ____/____/____
Mauro P. Ferrari Date

_____ ____/____/____
Marta Marelli Date

CRO PROJECT MANAGER

_____ ____/____/____
Cesare Mutti Date

MEDICAL AFFAIRS DIRECTOR/DEVELOPMENT DIRECTOR

_____ ____/____/____
Flavio Mantelli Date

CSR SYNOPSIS

<table>
<tr><td>Name of Sponsor:
Dompé farmaceutici S.p.a.</td><td rowspan="3">Individual Study Table
Referring to Part of the Dossier
Volume:
Page</td><td rowspan="3"></td></tr>
<tr><td>Name of Study Drug:
Oxervate(R)</td></tr>
<tr><td>NAME OF ACTIVE INGREDIENT:
cenegermin (i.e. recombinant human nerve growth factor, rhNGF)</td></tr>
<tr><td colspan="3">Title of Study: Observational Post-Authorisation Study of Oxervate® (Cenegermin 20 µg/ml) eye drops in the treatment of adult patients with moderate or severe Neurotrophic Keratopathy (NK).</td></tr>
<tr><td colspan="3">Investigators: Seven investigators: 1) Alessandro Lambiase, 2) Augusto Pocobelli, 3) Rita Mencucci, 4) Giorgio Marchini, 5) Pasquale Aragona, 6) Leonardo Mastropasqua, 7) Tommaso Micelli Ferrari</td></tr>
<tr><td colspan="3">Study Centres: Seven participating centres in Italy: 1) Ospedale Umberto I -Policlinico, Rome; 2) Azienda Ospedaliera San Giovanni Addolorata, Rome 3) AOUC Azienda Ospedaliero-Universitaria Careggi, Florence; 4) Ospedale di Borgo Roma, Verona; 5) Azienda Ospedaliera Universitaria G. Martino, Messina; 6) Policlinico SS Annunziata, Chieti; 7) Ente Ecclesiastico Ospedale “Francesco Miulli” di Acquaviva delle Fonti, Bari</td></tr>
<tr><td colspan="3">Publications (reference): NA</td></tr>
<tr><td>Phase of Development:

Observational study</td><td colspan="2">Studied period (years):
Initiation date (date of first patient enrollment): June 17, 2019
Enrolment was interrupted on: April 17, 2020
Early completion date (date of last patient last visit): 08 May 2020</td></tr>
<tr><td colspan="3">Objectives: This no-control, observational study using a long-term product registry aimed at identifying safety and important potential risks.</td></tr>
<tr><td colspan="3">Methodology: Multicentre, prospective, observational registry with observational follow-up period of 12 months after a treatment duration of 8 weeks.</td></tr>
<tr><td colspan="3">Number of patients (planned, included, and analysed): 250 planned, 37 treated, 37 analysed for safety only.</td></tr>
<tr><td colspan="3">Diagnosis and main criteria for inclusion: Patients diagnosed with moderate (persistent</td></tr>
</table>

epithelial defect) or severe (corneal ulcer) NK
***Test product, dose and mode of administration, batch number*:** Oxervate® (cenegermin, i.e. recombinant human nerve growth factor, rhNGF) as commercial drug in sterile, preservative-free multi-dose Type I glass vials, closed with a rubber stopper and an aluminium overseal with a polypropylene flip-off cap, presented in cardboard cartoons.: 20 micrograms/ml/one drop in the conjunctival sac of the affected eye(s), 6 times a day at 2 hourly intervals, starting from the morning and within 12 hours (according to the EU label posology).
Duration of treatment: Treatment to be continued for 8 weeks (according to the EU label posology). Maximum study duration per patient is 60 weeks (approximately 14 months).
Reference therapy, dose and mode of administration: None
Criteria for evaluation: ***Safety assessments***: Recording of any adverse events (AE, SAE, SUSAR, ADR) during the whole observational period (60 weeks) regardless of treatment administration.
Statistical methods: Summary descriptive statistics and rate calculation of demographic data on patients, prior disease data, treatment data, relevant clinical tests and clinical events of medical interest. ***Safety analysis and reporting***: The safety population included any patient who received at least one treatment of Oxervate® regardless of the length of follow-up. Analysis included: incidence of adverse events and serious adverse events. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarised by preferred terms.
Summary - Conclusions: ***Changes in the conduct of the study or planned analyses*** Despite the company made every reasonable effort to conduct the study as planned, it was prematurely terminated on 10 May 2020. The COVID-19 emergency has impacted both on hospital clinical and administrative activities and on monitoring activities of this clinical study. Due to these issues, Dompé deemed appropriate to interrupt the enrolment prematurely. In particular, the enrolment was interrupted on April 17, 2020. Furthermore, the interruption of enrolment was part of a broader decision to discontinue this observational study due to its non-feasibility. Indeed, less than 15% of the global

enrolment target had been reached (37/250 subjects were enrolled).
The main reason was related to the impossibility of activating the study in the other European countries planned in the study protocol (Germany, France, Spain).

The study, as per its nature, was designed to capture data from the Investigator's standard of care procedures therefore involved the collection of data when and if measured by the physician as per normal clinical practice. This study was not dictating any of the measures as mandatory (except for informed consent form). Consequently, because of the few data collected, only patients disposition, baseline characteristics, ocular medical history, prior and concomitant medications, and Treatment Emergent Adverse Events (TEAEs) could be analysed.

Patient disposition and Medical history
There are 37 patients enrolled, all of them in Italy; 36 discontinued the study due to the early study termination and 1 because of death. The enrolled population mean age was of 64.5 years, females accounted for 51.35% of them. The majority (43.24%) was referred into the study by the investigator or by other clinician (16.22%) at the investigational site. Of the 37 enrolled patients, 26 had at least one ocular medical or surgical history recorded. For 34 subjects (91.9% of the enrolled patients) at least one prior and concomitant medication is reported, among them there are 97 reports of ophthalmic topical treatments, either eye drops or gels.

Effectiveness Results
Not applicable due to inadequate collected data. Non-feasibility and COVID-19 emergency led to early termination of the study with subsequent change in planned analysis.

Safety Results:
Seven (18.9%) out of the 37 enrolled patients experienced one TEAE each. Out of the 7 TEAEs, 6 (16.2%, i.e. 6/37) were assessed as serious (PT Fall, verbatim: Accidental fall; PT Cancer surgery (verbatim: Benign colon surgery), PT Road traffic accident, PT Chronic obstructive pulmonary disease (verbatim: Acute COPD exacerbation), PT Corneal graft rejection (verbatim: Corneal rejection in penetrating keratoplasty), and PT Herpes ophthalmic (verbatim: Herpetic keratitis recurrence). None of them were considered related to the Oxervate® study treatment.

There is only one possibly-related event, a non-serious adverse event of "Slight eye

dryness" of mild intensity which occurred at unspecified time after the start of study drug. Because the event is reported as recovering/resolved, without corrective action and no change to the study drug, the relationship to the study drug is questionable. The relevant Preferred Term Dry eye is not listed among the tabulated list of Oxervate® adverse reactions in the SmPC. Therefore, this event of Dry eye is considered unlisted.

One of the 6 non-related SAEs, PT Fall, verbatim "Accidental Fall", resulted in death. An 86-year-old female experienced an accidental fall leading to unreported severe medical condition on the day of her first study drug treatment. The drug was withdrawn on the same day; unreported corrective procedures were instituted but patient died on the same day. It is unknown if autopsy was performed, and no death certificate is available. Based on the few available data and on the old age of the patient, the Company agrees with the reporter about the lack of relationship between the event and subsequent death with Oxervate® treatment.

Conclusions:

There is only one related TEAE reported as "Eye dryness", which is assessed by the Investigator as non-serious and possibly-related. The relevant PT Dry eye is not listed in the approved SmPC, therefore it is considered unlisted.

Even with the limitation of the few patients involved and the collected data, the safety of Oxervate® treatment resulting from this early terminated study is in line with the known profile. No potential risk has been identified.

Date of the report

06 September 2021

Table of content

1. List Of Abbreviations and Definitions Of Terms

Acronym	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
BCDVA	Best Corrected Distance Visual Acuity
CFS	Corneal Fluorescein Staining
CGI	Clinical Global Impressions scale
COPD	Chronic Obstructive Pulmonary Disease
CRO	Clinical Research Organisation
CRF	Case Report Form
DHA	DocosaHexaenoic Acid
EMA	European Medicines Agency
EU	European Union
FDA	(United States) Food and Drug Administration
FO	Fundus Ophthalmoscopy
GPP	Guidelines for Good Pharmacoepidemiology Practices
HCP	Health Care Professional
HSV	Herpes Simplex Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
i.e.	id est – that is
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
ISPE	International Society for Pharmacoepidemiology
IVCM	in Vivo Confocal Microscopy
LASIK	Laser-ASsisted In situ Keratomileusis
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
mNGF	murine Nerve Growth Factor
NGF	Nerve Growth Factor
NK	Neurotrophic Keratopathy
NKQ	Neurotrophic Keratitis Questionnaire

Acronym	Definition
OCT	Optical Coherence Tomography
PED	Persistent Epithelial Defect
PGIC	Patient Global Impression of Change
PRK	PhotoRefractive Keratectomy
PROs	Patient Reported Outcomes
p75NTR	p75 neurotrophin receptor
RGTA	ReGeneraTing Agents
rhNGF	recombinant human Nerve Growth Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Standard Error
SLE	Slit Lamp Examination
SmPC	European Summary of Product Characteristics
SS	Special Situations
ST	Schirmer I Test
Trk A	Tropomyosin receptor kinase A
US	United States
WHO	World Health Organization
WPAI:NK	Work Productivity and Activity Impairment Questionnaire: Neurotrophic Keratopathy

2. Ethics

2.1 Independent Ethics Committee(s)

The study was reviewed by appropriate IEC(s) (see Section 19.5, Appendix 6) consulted and the relevant written approval/favourable opinion was obtained.

2.2 Ethical Conduct of the study

To our knowledge, it is confirmed that the study was performed in accordance with the ethical principles originating from the Declaration of Helsinki *(64th WMA General Assembly, Fortaleza, Brazil, October 2013)*.

2.3 Compliance with Informed Consent Regulations and Relevant Country Regulations

Eligible patients were asked to read and sign ICF before any relevant data recorded in CRF and transmitted to *Dompé* for this study.

2.4 Compliance with IEC Regulations

This study was conducted in accordance with applicable IEC regulations. The Investigators, who participated in the study, obtained approval from a properly constituted IEC prior to initiating the study. *Dompé* had to be notified immediately if the responsible IEC had been disqualified or if proceedings leading to disqualification had begun. Copies of all IEC correspondence with the Investigator were provided to *Dompé.*

2.5 Compliance with Good Pharmacoepidemiology Practice

To ensure the quality and integrity of this research, the conduct of this study was governed by the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines.

2.6 Compliance with Electronic Records; Electronic Signatures Regulations

This study was conducted in compliance with the regulations on electronic records and electronic signature.

3. Subject information and consent

All adult patients who fulfilled the criteria to receive Oxervate® treatment as per authorised SmPC and who needed to be treated were informed of the nature of this observational study and were requested to provide written informed consent before any data were collected.

When a patient had signed the ICF, a unique patient identification number was assigned (e.g. IT01001 (IT for the Country, 01 corresponding to the # of the clinical site and 001 as unique sequential number for each patient). No patient withdrew his/her consent to the study and therefore no unique patient identification number has been re-allocated.

4. Investigator and study administrative structures

4.1 Investigators

There were 30 ophthalmologic centres planned in EU (Italy, Germany, Spain, France) expected to include 8 patients each.

However, due to non-feasibility and COVID-19 Emergency, only 7 centres, all in Italy, could be activated, as shown in the Appendix 1 and here below (Table 1)

Table 1: Investigators/Centres activated in the study.

Centre No.	Town	Investigator	Hospital
01	Rome	Prof. Alessandro Lambiase	Ospedale Umberto I - Policlinico
02	Rome	Dr. Augusto Pocobelli	Azienda Ospedaliera San Giovanni Addolorata

Centre No.	Town	Investigator	Hospital
04	Florence	Prof. Rita Mencucci	AOUC Azienda Ospedaliero-Universitaria Careggi
05	Verona	Prof. Giorgio Marchini	Ospedale di Borgo Roma
06	Messina	Prof. Pasquale Aragona	Azienda Ospedaliera Universitaria G. Martino
07	Chieti	Prof. Leonardo Mastropasqua	Policlinico SS Annunziata
09	Bari	Dr. Tommaso Micelli Ferrari	Ente Ecclesiastico Ospedale "Francesco Miulli" di Acquaviva delle fonti

4.2 Study administrative structure

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Clinical trial supply

Following the regular hospital supply chain, each centre has managed itself the supply of Oxervate® (cenegermin, i.e. recombinant human nerve growth factor, rhNGF) as the commercial drug.

5. Introduction

Neurotrophic keratopathy (NK), also known as neurotrophic keratitis, refers to a condition where corneal epitheliopathy leading to frank epithelial defect with or without stromal ulceration (melting) is associated with reduced or absent corneal sensation. (1,2,3) NK has been classified as a rare/orphan disease (ORPHA137596) affecting 5 individuals or fewer in 10.000. Although there is a paucity of information in literature regarding the prevalence and incidence of NK, a survey of corneal specialists in the EU with expertise in the management of NK found that most NK patients have mild disease, while the estimated prevalence of patients with moderate and severe NK is less than 1/10.000.

Treatment recommendations for NK are based on the severity of the disease and pathology of the underlying process. Mild NK requires discontinuation of all topical medications and the administration of preservative-free artificial tears and anti-inflammatory therapy if case of inflammation. The same therapeutic approaches apply to patients with moderate NK often accompanied by the addition of patching or therapeutic contact lenses, the use of prophylactic antibiotics to prevent the risk of corneal infection. Due to the low likelihood of healing with standard approaches, experimental options such as the topical administration of autologous serum, neurotrophic proteins, Q10 co-enzyme or cacicol 20/RGTA may be offered to patients with moderate NK. Severe NK is corneal ulceration. When a corneal ulcer develops, therapy is aimed at promoting corneal healing and preventing corneal melting or perforation. Surgical procedures at this stage can preserve or restore ocular integrity but at the expense of cosmetic appearance and visual function. In the event of perforation cyanoacrylate tissue adhesive with therapeutic contact lens and/or fibrin glue could represent a therapeutic option. (4,5,6)

Nerve growth factor (NGF) is a polypeptide discovered in the early 1950s by R. Levi Montalcini. NGF, an endogenous protein in man, is essential for the survival and growth of sympathetic and sensory neurons and for differentiation of neurons in the central nervous system. NGF receptors are expressed in the anterior segment of the eye and by the lacrimal gland as well as by posterior segment intraocular tissues. Activation of NGF receptors in the cornea plays a role in the trophism of the cornea epithelial cells. Experimental evidence suggests that NGF affects all tissues of the anterior ocular segment and, thus could play a

pivotal role in the pathophysiology of several ocular anterior segment diseases including NK and dry eye disease. (7,8)

The E coli-derived rhNGF (cenegermin, Oxervate®) was developed for the treatment of ocular diseases. Its efficacy and safety were evaluated in two multicentre, randomised, double masked, vehicle-controlled clinical studies (NGF0212 and NGF0214) in patients with moderate (persisted epithelial defect) or severe (corneal ulcer) neurotropic keratopathy refractory to non-surgical treatments. In both studies patients received Oxervate® or vehicle 6 times daily in the affected eye(s) for 8 weeks and underwent a follow-up period. Corneal healing of the persistent epithelial defect or corneal ulcer (the primary endpoint, defined as the greatest diameter of corneal fluorescein staining <0.5 mm) after 4 and 8 weeks of treatment for patients who received Oxervate® 20 µg/ml or vehicle was observed in the two studies.
Oxervate® was approved for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratopathy in adults by European Medicines Agency (EMA) in July 2017, in Switzerland (Swissmedic) in September 2018, in Canada (Health Canada) in February 2019, in Israel (MoH) in January 2019, in Australia (TGA) in October 2019 and in China (NMPA) in August 2020. While in the United States (US) the Food and Drug Administration (FDA) approved Oxervate® for the treatment of neurotrophic keratopathy in adults and in children (> 2 years old) in August 2018.

A multi-centre case registry was set up to provide information on the utilisation of topical Oxervate® in adult patients with NK in the European Union (EU) under the guidance of the European Summary of Product Characteristics (SmPC). This long-term disease registry aimed at consolidating virtually existing data on all patients diagnosed with moderate and severe NK exposed to Oxervate® in specialised ophthalmologic centres from the participating countries in the EU (Italy, Germany, Spain, France).

6. Study Objectives

The main objectives of this long-term registry/observational study were to provide insight into the utilisation of Oxervate® topical treatment in moderate and severe NK in real-world clinical practice rather than strict conditions imposed by a formal clinical trial. In particular, the primary objectives were:

- to gather understanding in the natural history and clinical aspects of NK,

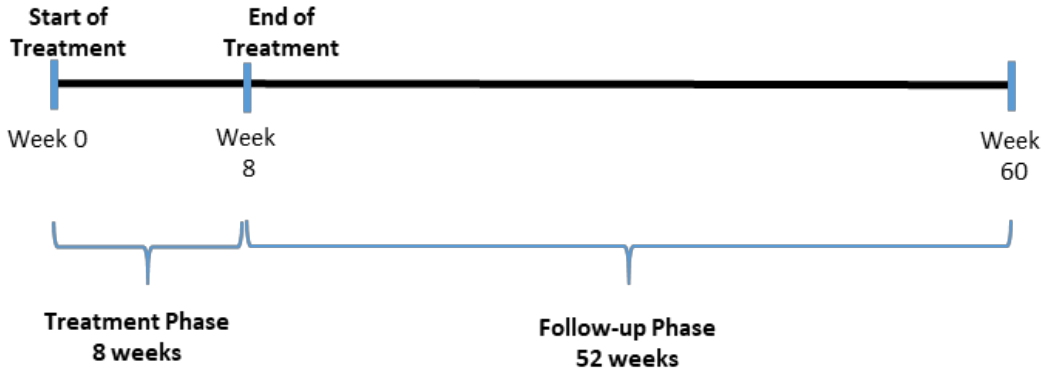
- to describe treatment patterns for adult patients receiving Oxervate® for the cure of moderate and severe NK,
- to identify safety and important potential risks.

7. Investigational Plan

7.1 Overall Study Design and Plan Description

This was a multicentre, prospective, observational study/registry to evaluate the treatment patterns for adult patients receiving Oxervate® for the cure of moderate or severe NK, under conditions of routine medical practice in accordance with the product SmPC. The study was targeting recruitment of 250 patients in ophthalmology clinics throughout selected European Countries (Italy, Germany, Spain, France). As an observational study, all treatment decisions were to be at the discretion of the patient's health-care provider (HCP). There was no control group in this study. All patients who fulfilled the criteria and needed to be treated were informed of the nature of this observational study and were requested to provide written informed consent before any data are collected. All patients were to receive Oxervate® treatment as per authorised SmPC, i.e. 20 micrograms/ml /one drop in the conjunctival sac of the affected eye(s), 6 times a day at 2 hourly intervals, starting from the morning and within 12 hours. "Treatment Phase" was to last 8 weeks, followed by a "Follow-up Phase" of 52 weeks. Patients data collection was to begin at the time of the inclusion in the study and would have to have continued for 14 months after the start of treatment with Oxervate®, whether patients were continuing to receive treatment with Oxervate® or not, as per scheme below. Maximum study duration per patient was 60 weeks (approximately 14 months). The enrolment period was expected to continue for approximately 12 months.

Figure 1. Study phases and duration



The study procedures and timing of clinic visits and the assessments performed at each visit are presented in the below Table 2.

Table 2 : Schedule of Visits and Procedures

Procedure/Data to be recorded	**First Oxervate® treatment (Initial Visit, Day 0)**	**Treatment Phase Visit/s (Week 1–Week 8)**	**Follow-up Visit/s (Week 8-Week60)**
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Demographics and referral	X		
Ocular and Systemic Medical/Surgical History*	X		
Previous and Concomitant Ocular and Systemic Medications, including previous treatment with Oxervate®	X	X	X
BCDVA	X	X	X
Corneal Sensitivity	X	X	X
Schirmer I Test	X	X	X
Slit Lamp Examination	X	X	X
Corneal Fluorescein Staining (CFS)	X	X	X
Corneal Photo with fluorescein (if available)	(X)	(X)	(X)
Optical Coherence Tomography anterior segment (AS-OCT) (if available)	(X)	(X)	(X)
Intraocular Pressure (IOP)	X	X	X
Dilated Fundus Ophthalmoscopy (FO)	X	X	X
In Vivo Confocal Microscopy (IVCM) (if available)	(X)	(X)	(X)
Oxervate® administration dates	X	X	(X)
Determine and record patient's study medication dosing compliance		X	(X)
Patient Reported Outcomes (PROs) **	X	X	(X)
Record AEs	X	X	X

Legend: X =data to be collected if measured by the physician as normal practice for standard of care. This study is not dictating any of these measures as mandatory (except for informed consent form). The study is designed to only capture data from the Investigator's standard of care procedures; (X)=data to be collected only if equipment available, examination performed as per clinical practice and/or if Oxervate® treatment is administered; *=data on medical/surgical treatments taken from NK diagnosis, in the previous 6 months and/or current medical/surgical treatments; **=data to be collected at least at

the end of any Oxervate® treatment cycle (PGIC, NKQ and WPAI:Neurotrophic Keratopathy) and at Initial Visit (NKQ and WPAI:Neurotrophic Keratopathy)

7.2 Discussion of study design

The study design was of non-interventional nature. It was a multicentre, prospective, observational study/registry to collect information on the treatment patterns for adult patients receiving Oxervate® for the cure of moderate or severe NK, under conditions of routine medical practice in accordance with the product's SmPC. As an observational study, all treatment decisions are at the discretion of the patient's health-care provider (HCP) and are not defined or mandated by the study design or protocol.

8. Selection of study population

Approximately 250 adult patients diagnosed with moderate or severe NK were planned to be enrolled at approximately 30 sites in selected European countries (Italy, Germany, Spain, France).

8.1 Inclusion criteria

The following were the requirements for entry into the study:

1. Male or female 18 years of age or older.
2. Diagnosis of moderate (persistent epithelial defect, PED) or severe (corneal ulcer) neurotrophic keratopathy by the Investigator.
3. The prescribing decision has been made to initiate treatment with Oxervate®.
4. Written documentation of informed consent has been obtained in accordance with the relevant Country and local privacy requirements, as applicable.

8.2 Exclusion criteria

The following were the criteria for exclusion from participating in the study:

1. Patients who were contraindicated to Oxervate® treatment as per the European SmPC.
2. Concurrent participation in a clinical trial that dictated treatment or use of an investigational drug.

8.3 Removal of subjects from therapy or assessments

Not applicable.
This is an observational study, all patients treated as per medical practice were to be assessed.

9. Treatments

9.1 Treatment administered

E coli-derived rhNGF (Cenegermin, Oxervate®) developed for the topical treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratopathy was administered as per European approved SmPC: 20 micrograms/ml of cenegermin (i.e. recombinant human nerve growth factor, rhNGF) /one drop in the conjunctival sac of the affected eye(s), 6 times a day at 2 hourly intervals, starting from the morning and within 12 hours. Treatment was to be continued for 8 weeks (according to the EU label posology).

9.2 Identity of investigational product

The investigation product was the commercially available Oxervate®.

Following the regular hospital supply chain, each centre has managed itself the supply of Oxervate® as the commercial drug in sterile, preservative-free multi-dose Type I glass vials, closed with a rubber stopper and an aluminum overseal with a polypropylene flip-off cap, presented in cardboard cartons.

The weekly pack included the following:

- 7 multi-dose vials (each vial contains 1.0 ml of solution)
- 7 vial adapters (i.e. 1 per day), 42 pipettes (i.e. 6 per day), 42 disinfectant wipes (i.e. 6 per day) and a dose recording card
- Extra adapter (1), pipettes (3) and wipes (3) will also be provided as spares.

Once received at the pharmacy, the weekly cartoon containing the vials had to be stored in a freezer at -20 °C ±5 °C. Before administration to the patient, the frozen medicinal product received from the pharmacy should have been thawed for 30 minutes.

An individual multi-dose vial of Oxervate® was to be removed from the fridge for use over the course of a single day. Each opened vial could be stored in the fridge or below 25 °C, but

must have been used within 12 hours. After this period of time the vial contents should have been discarded, irrespective of whether some residual product remained in the vial.

9.3 Methods of assigning subjects to treatment groups

Not Applicable.

9.4 Selection of dose in the study

Treatment was administered at the dosage/dose regimen approved in Europe.

9.5 Selection and timing of dose for each subject

Treatment was administered as per approved SmPC, i.e. 20 micrograms/ml of cenegermin (i.e. recombinant human nerve growth factor, rhNGF) /one drop in the conjunctival sac of the affected eye(s), 6 times a day at 2 hourly intervals, starting from the morning and within 12 hours for 8 weeks.

9.6 Blinding

Not applicable. This is a no-control, observational study.

9.7 Prior and concomitant therapy

Therapy deemed necessary for the patient's welfare was given at the discretion of the Investigator, taking into consideration treatments not recommended and potential interactions reported in the European SmPC. Information related to concomitant medications and procedures were collected and recorded by the Investigator in the CRF. Nevertheless, it was advised to reduce to the minimum the number of concomitant topical ocular medications, and that corneal toxicity by such medications be ruled out before initiating treatment with Oxervate®. Information related to concomitant medications and procedures was collected and recorded by the Investigators in the CRF.

10. Planned Effectiveness and Safety Assessments

10.1 Planned Effectiveness assessments

The following effectiveness variables were planned in protocol sections 6.7.2.2 - 6.7.2.4 to be assessed and analysed.

Ocular examination including (if performed as per clinical practice):

- Assessment of Best Corrected Distance Visual Acuity (BCDVA)
- Assessment of corneal sensitivity as measured by the Cochet-Bonnet esthesiometer
- Slit Lamp Examination (SLE) to assess the eyelid margin, conjunctiva, cornea, anterior chamber, iris and lens
- Corneal Fluorescein Staining (CFS, as per standard practice e.g. NEI scale) following instillation of fluorescein (healing evaluation)
- Corneal photography with fluorescein, only if equipment available and if examination performed as per clinical practice.
- Optical Coherence Tomography of the anterior segment of the eyes (AS-OCT), only if equipment available and if examination performed as per clinical practice.
- Schirmer I test (ST)
- Intraocular pressure (IOP)
- Dilated Fundus Ophthalmoscopy (FO)
- Examination of corneal microscopy by IVCM (In Vivo Confocal Microscopy), only if equipment available and examination performed as per clinical practice.

Treatment Exposure Assessments

- Oxervate® administration dates
- Patient's compliance to Oxervate® treatment (drug utilization) via weekly dose recording card provided with the delivery system
- Adherence to SmPC recommendations by collection of Special situations (SS), which include drug use outside the terms of the authorised conditions, associated or not with a symptom. SS such as misuse, abuse, overdose, occupational exposure, medication errors, use in pregnancy and breastfeeding, lack of drug effect, drug interaction. They had to be recorded on the SS page in the CRF.

Patient Reported Outcomes (PROs) certified translations for each Country involved in the study, self-administration of:

- Patient Global Impression of Change (PGIC) (at least at the end of any Oxervate® treatment cycle)
- Neurotrophic Keratitis Questionnaire (NKQ) (at least at Initial Visit and at the end of any Oxervate® treatment cycle)

- Work Productivity and Activity Impairment Questionnaire: Neurotrophic Keratopathy V2.0 (WPAI:Neurotrophic Keratopathy) (at least at Initial Visit and at the end of any Oxervate® treatment cycle).

10.2 Planned Safety assessments

Per protocol v.2 section 6.3.4 Adverse Events, safety data were to be collected by the Investigator in the CRF from signing the informed consent until the end of the study (end of observational period, i.e. week 60) and included:

- All Treatment Emergent Adverse Events, either non serious and serious, regardless of relationship to treatment, as well as any available associated information including, but not limited to, relevant ophthalmoscopy/ biomicroscopy findings, laboratory, clinical, and other test results. AE data had to be recorded on the AE page in the CRF.
- Special situations (SS), which include drug use outside the terms of the authorised conditions, associated or not with a symptom. SS such as misuse, abuse, overdose, occupational exposure, medication errors, use in pregnancy and breastfeeding, lack of drug effect, drug interaction, associated or not with a symptom.

10.3 Appropriateness of measurements

This was an observational study/registry of an approved drug at an approved dose and dose-schedule for the approved indication and population. All treatment decisions were at the discretion of the patient's health-care provider (HCP) and were not defined or mandated by the study design or protocol. Limitations of this study rests in the observational nature of its design (9) and include the followings:

- No control group, thus conclusions regarding the effectiveness and safety of Oxervate® would allow for comparison with a no-treatment group
- Unmasked, thus conclusions regarding the effectiveness and safety of Oxervate® may be biased as all patients received treatment
- No fixed schedule visits, thus patients could have differential observation and/or missing data collection

The effectiveness and safety variables, as well as treatment compliance/drug utilisation variables were previously used in the two multicentre, randomised, double blind, vehicle-

controlled clinical studies NGF0212 and NGF0214 in patients with moderate or severe neurotropic keratopathy refractory to non-surgical treatments.

11. Data Quality Assurance

Before any patient entered the study, a representative of Evidilya met with the principal investigator and his or her staff to review the procedures to be followed during the study and to train them on recording the data in the eCRFs using the electronic data capture (EDC) system. After the first patient was enrolled, the CRO representative, a monitor, periodically monitored the progress of the study by conducting on-site visits. This clinical research associate (CRA) was also able to review query statuses remotely, possibly warranting more frequent communication with the principal investigator and his or her staff. The principal investigator was to make available to the CRA the eCRFs, source documents, signed ICFs, and all other study-related documents. The principal investigator and his or her staff was responsible for reviewing eCRFs, resolving data queries generated by the CRA via the system, providing missing or corrected data, approving all changes performed on his or her data, and endorsing the patient data within the EDC system. This approval method included applying an electronic signature, a uniquely assigned username and password that together will represent a traditional handwritten signature.

The format and frequency of monitoring was decided by *Dompé* and are described in the monitoring plan.

12. Statistical methods planned in the protocol and determination of sample size

12.1 Statistical and analytical plan

The Statistical Analysis Plan version 1, dated 12 Jan 2021, is attached in Section 19.8 Appendix 8.

No formal hypothesis testing was performed. Continuous variables are summarised by descriptive statistics including: sample size, mean, standard deviation, median, minimum, and maximum. Categorical variables are summarised by frequency and percentage.

Statistical analysis was performed using SAS; the version used as well as further details of the analysis is specified in the statistical analysis plan (see Section 19 Appendix 8).

Summary descriptive statistics and rate calculation are presented for demographic data on patients, prior disease data, referral flow, prior and concomitant treatment data, relevant clinical tests and clinical events of medical interest, and safety data.

The safety population was defined as to include any patient who received at least one treatment of Oxervate® regardless of the length of follow-up.

Safety analysis and reporting was to include the incidence of adverse events and serious adverse events. Adverse events were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarised preferred terms. A summary for treatment-related adverse events was to be done separately.

Treatment exposure was to be summarised in terms of compliance to treatment, but it was not done because of inadequate and insufficient data.

12.2 Determination of sample size

The planned study size was of 250 adult patients diagnosed with moderate or severe NK to be enrolled at approximately 30 sites in selected European countries (Italy, Germany, Spain, France). The sample size was not formally calculated taking into account that NK is a rare disease.

12.3 Analysis of Disease History and Progression

The originally planned analysis of Baseline data and Disease History and Progression are reported in the protocol section 6.7.2.1 Analysis of Disease History and Progression.

Despite the company made every reasonable effort to conduct the study as planned, it was prematurely terminated due to non-feasibility on 10 May 2020.

Following the study interruption and as per SAP document version 1.0, Section 5.5. Changes to the planned analysis (see Section 19 Appendix 8), the limited number of patients enrolled and treated and scarce data provided in the CRF allowed for analysis of the following data only:

- *Subjects Disposition* - Subjects disposition is presented as frequencies (number and percent) of enrolled, treated patients (i.e. Safety Set), patients who discontinued the study early and reasons for discontinuation.

- *Demographics and Baseline Characteristics* - The baseline demographic characteristics are summarised for the Enrolled Set by means of descriptive statistics, as appropriate. The summarised variables include: Age (years). Age is recorded directly in the database and is not calculated separately; Sex (Male, Female); Ethnicity (Hispanic, Latino or Spanish; Not Hispanic, Latino or Spanish; N/A); Race (White; Black or African American; Asian; Native Hawaiian or Other Pacific Islander; American Indian or Alaska Native; N/A; Other); Referral flow (General Practitioner; General Ophthalmologist; Other hospital; Other private clinic; Patient identified by Investigator at investigational site; Patient identified by other clinician at investigational site; Emergency Room at investigational site).
- *Ocular Medical History* - Ocular medical history frequency distributions and percentages are summarised for the Enrolled Set. Counts are given by subject. Subjects experiencing more than one past/concomitant disease event are counted only once within each medical term.

12.4 Analysis of Effectiveness, Treatment Exposure and Patient Reported Outcomes Variables

The originally planned analysis on Effectiveness, Treatment Exposure and Patient reported Outcomes are reported in protocol sections 6.7.2.2 -6.7.2.4. However, despite the company made every reasonable effort to conduct the study as planned, it was prematurely terminated due to non-feasibility. The impossibility to activate all the planned countries and the COVID-19 emergency significantly impacted the recruitment that could not be completed (reached less than 15% of the overall enrolment target). Due to the study interruption and to the limited amount of data collected (i.e. normal clinical practice without any mandatory visit or procedure except for informed consent form), there were no adequate and valid data of Effectiveness, Treatment Exposure, and PROs available for analysis (see section 13 Changes to the conduct of the study or planned analyses and SAP version 1.0, section 5.5).

12.5 Safety Analysis

Only the following analysis could be performed as described in the SAP version 1.0, section 11 Evaluation of safety parameters (see Section 19 Appendix 8):

- Treatment-emergent adverse events (TEAEs), i.e. all events occurring or worsening after the first dose of the IMP.

- Pre-treatment AEs (if reported) and TEAEs are presented separately. Pre-treatment AEs are presented in the listings only.

A summary table of TEAEs, according to their severity and their relationship with the IMP would to be shown as well as two separate tables for TEAEs and SAEs. Details of each AE would also to be presented in listings.

12.6 Subgroup Analyses

Subgroup analyses based on baseline patient characteristics, country or patterns of treatment were not performed because of lack of adequate amount of data for analysis.

13. Changes in the conduct of the study or planned analyses

Despite the company made every reasonable effort to conduct the study as planned, it was prematurely terminated on 10 May 2020.
The COVID-19 emergency has impacted both on hospital clinical and administrative activities and on monitoring activities of this clinical study. Due to these issues, Dompé deemed appropriate to interrupt the enrolment prematurely. In particular, the enrolment was interrupted on April 17, 2020.

Furthermore, the interruption of enrollment was part of a broader decision to discontinue this observational study due to its non-feasibility. Indeed, less than 15% of the global enrolment target had been reached (37/250 subjects were enrolled).

The main reason for discontinue this study was related to the impossibility of activating the study in the other European countries planned in the study protocol (Germany, France, Spain).

The study, as per its nature, was designed to capture data from the Investigator's standard of care procedures therefore involved the collection of data when and if measured by the physician as per normal clinical practice. This study was not dictating any of the measures as mandatory (except for informed consent form).

Due to the study interruption and to the limited amount of data collected, the following changes were implemented in the SAP with respect to the analyses planned in the protocol:

- Enrolled patients were analysed with respect to their demographic characteristics, ocular medical history and prior and concomitant medications.
- No evaluation of disease progression nor treatment exposure was performed.

- No evaluation of the effectiveness parameters, including PROs was performed.
- Safety analysis was based only on all treatment emergent adverse events, including serious treatment emergent adverse events and those leading to deaths, in the Enrolled Set.

14. Study Subjects

14.1 Disposition of subjects

Because of the premature interruption of the study due to non-feasibility and COVID-19 emergency restrictions, out of the 250 planned patients, only 37 patients could be enrolled. All of the patients were enrolled in Italy.

The disposition of subjects by active centre is reported in Appendix 2. The disposition of patients enrolled, treated, those who discontinued and primary reason for end of study is reported in Section 17 of this report, in statistical analysis table 14.1.1. The table below summarises disposition of the enrolled patients (Table 3).

Table 3 - Summary of patients disposition - Enrolled set

	Nr. patients on Oxervate (%)
Enrolled	37
Treated	37 (100)
Discontinued the Study	37 (100)
Primary Reason for End of Study: - Death - Study Terminated by the Sponsor	 1 (2.70) 36 (97.30)

14.2 Protocol deviations

As per SAP v.1 (see Section 19.8 Appendix 8) no analysis of the entry or withdrawal criteria, nor of wrong treatment or incorrect dose was performed.

With respect to the protocol deviation relevant to “intake of excluded concomitant medications”, there are some records of ophthalmic topical agents known to inhibit epithelial healing (including corticosteroids or eye drops containing preservatives such as benzalkonium chloride and cetrimide) in “Prior and concomitant medication” CRF page. However, as data are not adequately confirmed/validated, no analysis on this protocol deviation can be performed.

14.3 Data set analysed

There are 37 subjects enrolled in the study. The Enrolled Set consists of all patients who signed the ICF and were considered eligible for the study. The study, as per its nature, was designed to capture data from the Investigator's standard of care procedures therefore involved the collection of data when and if measured by the physician as per normal clinical practice. This study was not dictating any of the measures as mandatory (except for informed consent form). Consequently, because of the few data collected, no efficacy population is therefore available. All enrolled patients, who received at least one dose of study medication are included in the Safety Set (SAF). All of the 37 enrolled patients contributed to the SAF (Table 4).

Table 4 - Analysis populations

Analysis Sets	**Nr patients per set**
Enrolled Set	37
Safety Set	37 (100%)

14.4 Demographics and other baseline characteristics

The disposition of patients enrolled, treated, those who discontinued and primary reason for end of study is reported in Section 17 of this report, in statistical analysis table 14.1.1.

The mean age of the 37 enrolled patients is of 64.5 years (SD:15.16, range 30-87). Females account for 51.35% of the patients, while males for 48.65%; almost all of them (36/37; 97.30%) are of white race (Table 5).

Only 22.62 % of the enrolled patients was referred to by a general ophthalmologist, while 43.24% were identified by investigator at the investigational site and 16.22% by other clinician at the investigational site (Table 5).

Table 5 - Demographic and Baseline Characteristics - Enrolled Set (Oxevate N=37)

Age (years)	
N	37
Mean (SD)	64.5 (15.16)
Median	67.0
Min, Max	30.87
Sex, N (%)	
Male	18 (48.65)

Table 5 - Demographic and Baseline Characteristics - Enrolled Set (Oxevate N=37)	
Female	19 (51.35)
Ethnicity, N (%)	
Hispanic, Latino or Spanish	5 (13.51)
N/A	4 (10.81)
Not Hispanic, Latino or Spanish	28 (75.68)
Race, N (%)	
Asian	1 (2.70)
White	36/37 (97.30)
Referral flow, N (%)	
Patient identified by Investigator at Investigational site	16 (43.24)
General Ophthalmologist	8 (21.62)
Patient identified by other Clinician at Investigational site	6 (16.22)
Other private Clinic	3 (8.11)
Emergency Room at Investigational site	2 (5.41)
Other Hospital	2 (5.41)

There are 26 subjects out of the 37 enrolled ones with at least one ocular medical or surgical history as follows:

- history of eye disease (verbatim): amblyopia (N=1 record); keratitis (fungal, herpetic, HSV, microbic) (N=5 records); glaucoma (N=2); infection unknown origin, keratoconus, Sjogren disease, ocular trauma, diabetic retinopathy, hemovitreous, high ocular pressure, the latter were all reported once.
- history of ocular surgery (verbatim): cataract and cataract surgery (N= 4 records); dalk for keratoconus (n=2), perforating keratoplasty with or without anterior segment partial synechiolysis (N=2), retinal detachment (N=2) and subsequent surgery ppv23g, endolaser and s620 (N=2), scleral buckling, vitrectomy, oxane 1300 tamponade for retinal detachment (N=2), Oxane 1300 or sylicon oil removal (N=2), anterior chamber wash (N=2), amniotic membrane transplant (N=2), argon laser treatment for retinal tear (N=1), and Descemet membrane endothelial keratoplasty (DMEK) (N=1).

The summary statistical analysis table 14.1.4 displaying ocular medical history is included in section 17 of this report.

The prior and concomitant medications are summarised uncoded in section 17 of this report as displayed in the statistical analysis table 14.1.5. For the 34 subjects (91.9% of the enrolled patients) there is at least one prior and concomitant medication reported, among them there

are 97 reports of ophthalmic topical treatments, either eye drops or gels. Thirty-seven of the 97 reports of ophthalmic treatment, include ophthalmic topical agents known to inhibit epithelial healing, including corticosteroids or eye topical agents containing preservatives such as benzalkonium chloride and cetrimide.

14.5 Measurement of treatment compliance

Due to early termination of the study, given the very limited number of patients enrolled and data collected, measurement of treatment compliance is not feasible, as per SAP document version 1.0, Section 10." Evaluation of Effectiveness Parameters" (see Section 19.8 Appendix 8).

14.6 Efficacy results and tabulations of individual efficacy data

Due to early termination of the study, given the very limited number of patients enrolled and data collected, analysis of the effectiveness could not be done, as per SAP document version 1.0, Section 10." Evaluation of Effectiveness Parameters" (see Section 19.8 Appendix 8).

15. SAFETY EVALUATION

15.1 Adverse Events (AEs)

15.1.1 Brief summary of adverse events

There are no AEs occurring prior to treatment, therefore all adverse events are TEAEs.

Table 6 provides the overall summary frequency of seriousness, relatedness, intensity, action taken, and outcome of the reported Adverse Events.

Table 6 - Summary of the frequency of all the TEAEs by seriousness, relatedness, intensity, action taken and outcome.

(from Statistical Analysis Table 14.3.1 "TEAE Safety Set" and Statistical Analysis Listing 16.2.7.1 "Adverse events"- See Section 17)

	Nr of TEAEs **7**	**Nr of Subjects (% of Safety Set N=37)** **7 (18.9%)**
Seriousness:		
- Serious	6	6 (16.2%)
- Non Serious	1	1 (2.7%)
Relatedness:		
- Related	1	1 (2.7%)

Table 6 - Summary of the frequency of all the TEAEs by seriousness, relatedness, intensity, action taken and outcome.

(from Statistical Analysis Table 14.3.1 "TEAE Safety Set" and Statistical Analysis Listing 16.2.7.1 "Adverse events"- See Section 17)

	Nr of TEAEs **7**	**Nr of Subjects (% of Safety Set N=37)** **7 (18.9%)**
- Not Related	6	6 (16.2%)
Intensity:		
- Mild or Moderate	3	3 (8.1%)
- Severe	2	2 (5.4%)
- Not provided	2	2 (5.4%)
Outcome		
- Not resolved	2	2 (5.4%)
- Not resolved - Fatal	1	1 (2.7%)
- Resolved with sequelae	1	1 (2.7%)
- Recovering /Resolved	3	3 (8.1%)
Action taken as to study treatment		
- Discontinued prior to event	3	3 (8.1%)
- Drug not changed	2	2 (5.4%)
- Drug interrupted	1	1 (2.7%)
- Drug withdrawn	1	1 (2.7%)
Action Taken, Other than study treatment		
- Corrective procedures/medication	5	5 (13.5%)
- No action taken	2	2 (5.4%)

There are 7 TEAEs reported in 7 patients (18.9%) out of the 37 enrolled/treated patients. Of the reported TEAEs, 6 are serious, i.e. 6 SAEs in 6 patients (16.2% of the enrolled patients).

Only one TEAE is considered possibly related to the use of the investigational treatment. It is the non serious event "Slight eye dryness".

Intensity of the SAEs is reported as severe in 2 patients only. All the 6 SAEs are considered unrelated to the use of Oxervate®.

One TEAE resolved with sequelae, 3 were either recovering or resolved, 3 were not resolved, of them one had a fatal outcome (SAE "Accidental fall").

In 3 cases, the study drug was discontinued prior to the event, in 2 cases the study drug treatment was not changed, in 1 case it was interrupted, and in 1 case it was withdrawn.

In 5 cases, corrective procedures or medications were instituted following the TEAE, while in 2 cases there was no corrective action taken.

15.2 Display of Adverse Events

The below summary table (Table 7) displays all TEAEs, their seriousness, relationship, outcome, and action taken with respect to the study drug treatment.

Table 7 - All Treatment Emergent Adverse Events (TEAE) by Event Term, Verbatim, Seriousness, Relatedness, Outcome, and Action taken (from Section 17)

Event Term	**Verbatim**	**Serious / Non Serious**	Related/ Not Related	**Outcome**	**Action taken for IMP**	**Nr ^**
Fall	Accidental fall	Serious	Not Related	Death	Drug withdrawn	1/1
Chronic obstructive pulmonary disease	Acute COPD exacerbation	Serious	Not Related	Recovering/Re-solved	Drug interrupted	1/1
Cancer surgery	Benign colon surgery	Serious	Not Related	Recovering/Re-solved	NA *	1/1
Road traffic accident	Car accident	Serious	Not Related	Not resolved	NA *	1/1
Herpes ophthalmic	Herpetic keratitis recurrence	Serious	Not Related	Not resolved	NA *	1/1
Corneal graft rejection	Corneal rejection in penetrating keratoplasty	Serious	Not Related	Res. with Sequelae	Drug not changed	1/1
Eye dryness	Slight eye dryness	Non-Serious	Related	Recovering/Re-solved	Drug not changed	1/1

Table 7 - All Treatment Emergent Adverse Events (TEAE) by Event Term, Verbatim, Seriousness, Relatedness, Outcome, and Action taken (from Section 17)						
Event Term	**Verbatim**	**Serious / Non Serious**	Related/ Not Related	**Outcome**	**Action taken for IMP**	**Nr ^**
Legenda: ^ Nr of reports /patients * NA = Study drug discontinued prior to event						

The SAE "Accidental fall" lead to drug withdrawal. It is a general disorder, the term of which clearly identifies its accidental nature. This accident had a fatal outcome.

The SAE "Chronic obstructive pulmonary disease" led to drug interruption.

Three SAEs occurred after drug discontinuation, i.e. Cancer surgery occurred more than 2 weeks, Road traffic accident after 2 months, and Herpes ophthalmic about three months after drug discontinuation.

The study drug was not changed after occurrence of "Corneal rejection" and "Eye dryness".

15.2.1 Analysis of Adverse Events

No SUSAR was reported. There is only one AE considered possibly-related by the Investigator, i.e. a non-serious AE of "Slight eye dryness" in Subject IT05_001. It was of mild intensity and occurred one week after the start of study drug.
Because the AE is reported as recovering/resolved without corrective action and no change to the study drug, and because of lack of information about the underlying ocular conditions, the use of contact lenses or of other ocular medications, the relationship to the study drug is possible for the Sponsor.

Nonetheless, the relevant Preferred Term Dry Eye is not listed among the tabulated list of Oxervate® adverse reactions in the SmPC. Therefore, this event with PT Dry eye term is considered unlisted.

There are 6 non-related AEs, all serious as reported below.

- Fall, verbatim "Accidental fall", in Subject IT07_002, causing a severe unreported medical condition which led to drug withdrawal. Notwithstanding the corrective procedures, the event resulted in fatal outcome within one day. This SAE is further discussed in Section 15.3 of this report.

- Chronic obstructive pulmonary disease, verbatim "Acute COPD exacerbation", in Subject IT05-010. The event has a reported duration of 6 days. It caused drug interruption and resolved with corrective procedures. The event was recovering or had resolved at study end.
  COPD probably occurred in a patient at risk of exacerbation and independently from the topical use of Oxervate®. Because of the limited information available, the Sponsor agrees with the Investigator in assessing this SAE as not related to the use of Oxervate®.
- Road traffic accident, verbatim "Car accident" in Subject IT01_001. The event occurred at about 2 months after study drug discontinuation. It is reported of moderate severity and unresolved at study end notwithstanding corrective procedures.
  Whether a medical condition was the cause of the car accident, this is not reported. In addition, there is lack of information about the medical consequence of the car accident. Corrective procedures were taken but the event was not resolved at study end. Considering the time of occurrence, i.e. after discontinuation of the topical administration of the study drug, and the limited information at hand, the Company agrees with the Investigator in assessing this SAE as not related to the use of Oxervate®.
- Cancer surgery, verbatim "Benign colon surgery" in Subject IT01_004. The event occurred more than 2 weeks after study drug treatment was completed. The event was reported as resolved and patient discharged from the hospital 3 weeks after the intervention.
  There probably is a pre-existing condition leading to the surgery. Whether the surgery was planned or unexpected is also not reported. Considering the time of occurrence, i.e. after drug treatment completion, the topical site administration of the study drug, the probable pre-existing condition, and the limited information at hand, the Company agrees with the Investigator in assessing this SAE as not related to the use of Oxervate®.
- Herpes ophthalmic, verbatim "Herpetic keratitis recurrence" in Subject IT04_001. The event occurred about three months after drug discontinuation. It was of moderate intensity; no corrective medication/ procedure was undertaken and it was not resolved at study end.
  Also in this case, there is a predisposing condition. Considering the time of occurrence, i.e. after drug discontinuation, and the limited information at hand, the Company agrees with the Investigator in assessing this SAE as not related to the use of Oxervate®.

- Corneal graft rejection, verbatim "Corneal rejection in penetrating keratoplasty" in Subject IT02_001. It occurred about one month after start of the study drug and lasted for 90 days. Its intensity is reported as severe. The study drug treatment was not changed after start of corneal rejection. It resolved with sequelae without corrective actions reported.
  There is a pre-existing condition known to be at risk of rejection i.e. keratoplasty. The event is reported as resolved with sequelae, as expected after complications of keratoplasty. Based on the resolution with sequelae without corrective actions and no change of study drug regimen, in addition to the scarce information at hand, the Company agrees with the Investigator on the lack of relationship with the use of the study drug, but more likely to the underlying eye surgery.

Considering the topical ophthalmic application of Oxervate®, it is of interest to analyse the TEAEs occurring at the application site, separately. There are 3 TEAEs involving the ocular application site of the IMP and are:

- a serious non-related Corneal graft rejection,
- a serious non-related Herpes ophthalmic,
- a non-serious possibly-related Dry Eye.

The Corneal graft rejection and Herpes ophthalmic occurred in a patient with pre-existing condition known to be at risk of rejection i.e. keratoplasty, and in a patient with possibly a predisposing condition of recurrence. The study drug was not changed after start of corneal rejection, while the study drug had already been discontinued prior to Herpetic keratitis recurrence.
The non-serious, possibly-related TEAE Dry eye is reported as recovering or recovered without corrective action and no change to the study drug treatment. Information on the pre-existing eye condition and possible use of concomitant eye medications is lacking. Based on the above analysis of ocular TEAEs, the safety of the topical ophthalmic application is confirmed.

15.2.2 Listings of adverse events by subject

The listing of the 7 TEAEs is provided in section 17 of this report (Statistical Analysis Listing 16.2.7.1).

The listing of the 6 SAEs is provided in section 17 of this report (Statistical Analysis Listing 16.2.7.2).

The listing of the SAE leading to death is provided in section 17 of this report (Statistical Analysis Listing 16.2.7.3).

15.3 Deaths, other Serious Adverse Events, and other significant events

The 6 of the 7 TEAEs that were assessed as serious, all not-related to the use of Oxervate® are displayed in table 8.

Table 8 - PT and verbatim of Serious Adverse Events in the Subjects with at least one SAE
(N = 6/37; 16.2 %*)

Type of SAEs (PT - verbatim " .. ")	**N (%)**
Fall - "Accidental fall" (Outcome: Death)	1 (2.7)
Chronic obstructive pulmonary disease - "Acute COPD exacerbation"	1 (2.7)
Corneal graft rejection - "Corneal rejection in penetrating keratoplasty"	1 (2.7)
Cancer surgery - "Benign colon surgery"	1 (2.7)
Road traffic accident - "Car accident"	1 (2.7)
Herpes ophthalmic - "Herpetic keratitis recurrence"	1 (2.7)
Note: * The denominator is the number of safety patients (N=37)	

One of the 6 SAEs, verbatim "Accidental Fall", resulted in death. Subject IT07_002, an 86-year-old white Hispanic, Latino or Spanish female experienced an accidental fall leading to unreported severe medical condition one the day of her first Oxervate® treatment. The drug was withdrawn on the same day; unreported corrective procedures were instituted but patient died on the same day. It is unknown if autopsy was performed, and no death certificate is available.

According to the reporter, there is no relationship between the event and Oxervate® treatment. The old age of the patient (86 years) and the lack of information on prior and concurrent diseases, concomitant medications and cause of the accidental fall, lead the

Sponsor to agree with the Investigator's opinion and to consider this event, and the subsequent death, as not related to the use of the study drug.

Description of the other serious, not-related SAEs is provided in section 15.2.3 of this clinical study report.

16. DISCUSSION AND OVERALL CONCLUSIONS

This no-control, observational study using a long-term product registry aimed at collecting data on natural history and clinical aspects of NK, including PROs, on treatment patterns in adult patients receiving Oxervate® for the cure of moderate or severe NK, and to identify safety and important potential risks. It was to provide insight into the utilisation of this topical treatment in real-world clinical practice in qualified ophthalmologic centres from participating countries in EU. Commercial Oxervate® was given to the patients under conditions of routine medical practice and in accordance to the approved SmPC, i.e. at the approved posology of 20 micrograms/ml/one drop in the conjunctival sac of the affected eye(s), 6 times a day at 2 hourly intervals, starting from the morning and within 12 hours. Treatment was to last for 8 weeks. Thereafter, patients were to be followed-up for 52 weeks.

During the recruitment period, the COVID-19 pandemic occurred which impacted both on hospital clinical and administrative activities and on monitoring activities. Therefore, Dompé deemed appropriate to interrupt the enrolment prematurely. In particular, the enrolment was interrupted on April 17, 2020. Furthermore, despite the company made every reasonable effort to conduct the study, the enrolment interruption was part of a broader decision to discontinue this observational study on May 10, 2020 due to its non-feasibility. Indeed, less than 15% of the global enrolment target had been reached (37/250 subjects were enrolled) mainly because of the impossibility to activate all the planned countries.

Consequently, because of very limited data collected (capture of data from the Investigator's standard of care procedures, no visits or measures as mandatory except for informed consent form), the protocol planned analysis were changed in the SAP and only subjects disposition, demographic and baseline characteristics, ocular medical history, prior and concomitant medications, and Adverse Events (AEs) could be analysed.

The safety population only contributes to the analyses and results of this early terminated study. The safety population is defined as to include any patient who received at least one treatment of Oxervate® regardless of the length of follow-up.

There are 37 patients enrolled, all in Italy; 36 discontinued the study because the study was terminated by the Sponsor and 1 because of death. Their mean age was of 64.5 years; females accounted for 51.35% of them. The majority (43.24%) was referred into the study by the investigator or by other clinician (16.22%) at the investigational site. Of the 37 enrolled patients, 26 had at least one ocular medical or surgical history recorded. For 34 subjects (91.9% of the enrolled patients) at least one prior and concomitant medication is reported, among them there are 97 reports of ophthalmic topical treatments, either eye drops or gels.

Seven (18.9%) of the 37 enrolled/treated patients experienced one TEAE each. Six of them (i.e. 16.2% of the enrolled patients) were assessed as serious (PTs Fall, Cancer surgery, Road traffic accident, Chronic obstructive pulmonary disease, Corneal graft rejection, and Herpes ophthalmic). No SUSAR was reported. Indeed, none of them were evaluated by the investigators as related to the use of Oxervate®.

Two not-related SAEs are located at the ocular application site of the IMP and refer to verbatim “Corneal rejection in penetrating keratoplasty” and “Herpetic keratitis recurrence”, both likely linked to the underlying medical/surgical conditions.

The nature of the remaining 4 not-related SAEs (i.e. verbatim “Accidental fall”, “Car accident”, “Benign colon surgery”, and “Acute COPD exacerbation”) is general or more likely due to underlying unreported pre-existing medical conditions or to chance. The SAE “Accidental Fall” resulted in death. Considering the old age, the lack of important information about corrective actions and course of the event, as well as no information about the autopsy, if performed, the Company agrees with the reporter about the lack of relationship between the study treatment and this event and subsequent death. Likewise, based on the available information, the Company agrees with the Investigators’ opinion on the relationship of the other 5 SAEs and considers them not-related.

There is only one possibly-related event, i.e. a non-serious adverse event of “Slight eye dryness” (PT Dry eye), of mild intensity, which occurred at unspecified time after the start of study drug. Because the event is reported as recovering/resolved, without corrective action and no change to the study drug, and because of lack of useful information on the underlying ocular conditions, the use of eye lenses or of other ocular medications, the relationship to the study drug cannot be evaluated. This event term is not listed in the approved SmPC, therefore, it is considered unlisted.

In conclusion, there is only one related TEAE reported. It refers to "Eye dryness", PT Dry eye, which is assessed by the Investigator as non-serious and possibly-related. This event term is not listed in the approved SmPC, therefore, this PT is considered unlisted.

Even with the limitation of the few patients involved and data, the safety of Oxervate® treatment resulting from this early terminated study is in line with the known profile. No potential risk has been identified.

17. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

STATISTICAL ANALYSIS TABLE 14.1.1 SUMMARY OF PATIENTS DISPOSITION
ENROLLED SET

	Oxervate N=37
Enrolled	37
Treated	37 (100.00)
Discontinued the Study	37 (100.00)
Primary Reason of End of Study	
Death	1 (2.70)
Study Terminated by Sponsor	36 (97.30)

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STATISTICAL ANALYSIS TABLE 14.1.1
DEMOGRAPHIC AND BASELINE CHARACTERISTICS - ENROLLED SET

	Oxervate N=37
Age (years)	
n	37
Mean (SD)	64.5 (15.16)
Median	67.0
Min, Max	30, 87
Ethnicity, n (%)	
Hispanic, Latino or Spanish	5 (13.51)
N/A	4 (10.81)
Not Hispanic, Latino or Spanish	28 (75.68)
Sex, n (%)	
Male	18 (48.65)
Female	19 (51.35)
Race	
Asian	1 (2.70)
White	36 (97.30)
Referral flow, n(%)	
Emergency Room at investigational site	2 (5.41)
General Ophthalmologist	8 (21.62)
Other hospital	2 (5.41)
Other private clinic	3 (8.11)
Patient identified by Investigator at investigational site	16 (43.24)
Patient identified by other clinician at investigational site	6 (16.22)

Note 1: The denominator is the number of enrolled patients

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STATISTICAL ANALYSIS TABLE 14.1.4 OCULAR MEDICAL HISTORY
ENROLLED SET

Medication Name	Oxervate N=37
Number of subjects with at least one ocular medical history	26 (70.3)
Amblyopia	1.0 (2.7)
Amniotic membrane transplant	1.0 (2.7)
Anterior chamber wash + air bubble in anterior chamber	1.0 (2.7)
Anterior chamber wash + ppv23g + pdms	1.0 (2.7)
Application of amniotic membrane	1.0 (2.7)
Argon laser treatment on retinal tear	1.0 (2.7)
Cataract	1.0 (2.7)
Cataract surgery	3.0 (8.1)
Dalk	1.0 (2.7)
Dalk for keratoconus	1.0 (2.7)
Diabetic retinopathy	2.0 (5.4)
Dmek	1.0 (2.7)
Emovitreo	1.0 (2.7)
Fungal keratitis	2.0 (5.4)
Glaucoma	4.0 (10.8)
Herpetic keratitis	1.0 (2.7)
High ocular pressure	1.0 (2.7)
Hsv keratitis	2.0 (5.4)

Note 1: The denominator is the number of enrolled patients

STATISTICAL ANALYSIS TABLE 14.1.4 OCULAR MEDICAL HISTORY (Continued)
ENROLLED SET

Medication Name	Oxervate N=37
Infection ndd	1.0 (2.7)
Keratoconus	1.0 (2.7)
Microbic keratitis	1.0 (2.7)
Ocular trauma	1.0 (2.7)
Oxane 1300 oil removal	1.0 (2.7)
Pars plana vitrectomy 23g + endolaser + sf6 20%	1.0 (2.7)
Perforating keratoplasty	1.0 (2.7)
Perforating keratoplasty + anterior segment partial reconstruction with synechiolysis	1.0 (2.7)
Ppv23g + endolaser + densiron for retinal detachment	1.0 (2.7)
Retinal detachment and following surgery ppv23g + endolaser + s620%	1.0 (2.7)
Retinal detatchment	1.0 (2.7)
Scleral buckling + vitrectomy + sylicon oil tamponade	1.0 (2.7)
Scleral buckling, vitrectomy, oxane 1300 tamponade for retinal detachment	1.0 (2.7)
Sjogren disease	1.0 (2.7)
Sylicon oil removal	1.0 (2.7)

Note 1: The denominator is the number of enrolled patients

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STATISTICAL ANALYSIS TABLE 14.1.5 SUMMARY OF PRIOR AND CONCOMITANT MEDICATIONS
SAFETY SET

Medication Name	Oxervate N=37
Number of subjects with at least one concomitant medication	34 (91.9)
0.1% dexamethasone/0.3% netilmicin	3.0 (8.1)
2.0 mg brimonidine tartrat + 6.8 mg timolol maleate	1.0 (2.7)
Acetazolamide	3.0 (8.1)
Acetylsalicylic acid	1.0 (2.7)
Aciclovir	5.0 (13.5)
Acido ialuronico	1.0 (2.7)
Acyclovir 400 mg	1.0 (2.7)
Adenuric	1.0 (2.7)
Allopurinolo	1.0 (2.7)
Amlodipina besilato	1.0 (2.7)
Amlodipine besylate	2.0 (5.4)
Angiotension antagonist	1.0 (2.7)
Armolipid	1.0 (2.7)
Atorvastatin calcium	1.0 (2.7)
Atropine 1%	1.0 (2.7)
Atropine eye drops 1%	1.0 (2.7)
Azarga	1.0 (2.7)
Azatioprina	1.0 (2.7)
Bimatoprost	1.0 (2.7)
Bimatoprost eye drop	1.0 (2.7)

Note 1: The denominator is the number of enrolled patients

STATISTICAL ANALYSIS TABLE 14.1.5 SUMMARY OF PRIOR AND CONCOMITANT MEDICATIONS (Continued)
SAFETY SET

Medication Name	Oxervate N=37
Bimatoprost ophthalmic	1.0 (2.7)
Birth controll pill	1.0 (2.7)
Bisoprolol	2.0 (5.4)
Bisoprololo	1.0 (2.7)
Brimonidine tartrate	2.0 (5.4)
Brinzolamid+timolol	1.0 (2.7)
Bromfenac	1.0 (2.7)
Bromfenac sodium eye drops	1.0 (2.7)
Cacicol	2.0 (5.4)
Calcitriolo	1.0 (2.7)
Calcium channel blocker	1.0 (2.7)
Candesartan cilexetil	1.0 (2.7)
Cardioasa	1.0 (2.7)
Cardioaspirin	1.0 (2.7)
Chloramphenicol 0.5% eye drops	1.0 (2.7)
Ciclolux	1.0 (2.7)
Clopidogrel	1.0 (2.7)
Clopidrogel	1.0 (2.7)
Congescor	2.0 (5.4)
Cortivis coll	1.0 (2.7)
Coumadin	2.0 (5.4)
Crestor	1.0 (2.7)

Note 1: The denominator is the number of enrolled patients

STATISTICAL ANALYSIS TABLE 14.1.5 SUMMARY OF PRIOR AND CONCOMITANT MEDICATIONS (Continued)
SAFETY SET

Medication Name	Oxervate N=37
Dapagliflozin	1.0 (2.7)
Delorazepam	1.0 (2.7)
Deltacortene	1.0 (2.7)
Desametasone + netilmicina	1.0 (2.7)
Dexamethasone	1.0 (2.7)
Dexamethasone (luxazone) eye drops	1.0 (2.7)
Dexamethasone 0.15%	2.0 (5.4)
Dexamono	1.0 (2.7)
Diamox	1.0 (2.7)
Diclofenac sodium eye drops	2.0 (5.4)
Diclofenac sodium ophthalmic solution	1.0 (2.7)
Dorzolamide + timolol eye drops	1.0 (2.7)
Dorzolamide hydrochloride	1.0 (2.7)
Dorzolamide/timolol eye drops	1.0 (2.7)
Doxazosin	1.0 (2.7)
Doxiciclina	1.0 (2.7)
Dutasteride	1.0 (2.7)
Enalapril + idroclorotiazide	1.0 (2.7)
Entresto	1.0 (2.7)
Escitalopram	1.0 (2.7)
Esomeprazolo	1.0 (2.7)
Etacortilen	2.0 (5.4)

Note 1: The denominator is the number of enrolled patients

STATISTICAL ANALYSIS TABLE 14.1.3 SUMMARY OF PRIOR AND CONCOMITANT MEDICATIONS (Continued)
SAFETY SET

Medication Name	Oxervate N=37
Eutirox	1.0 (2.7)
Exocin	1.0 (2.7)
Ezetimibe	1.0 (2.7)
Ferro	1.0 (2.7)
Finasteride	2.0 (5.4)
Folina	1.0 (2.7)
Fulcrosupra	1.0 (2.7)
Furosemide	1.0 (2.7)
Gabapentin	1.0 (2.7)
Genticol	1.0 (2.7)
Glicazide	1.0 (2.7)
Humalog	1.0 (2.7)
Hyalistil preservatine free	1.0 (2.7)
Hyaluronate sodium	1.0 (2.7)
Hyaluronate sodium preservative free	1.0 (2.7)
Hyaluronate sodium/threalose	1.0 (2.7)
Ialuvit coll	2.0 (5.4)
Icross gel	1.0 (2.7)
Idrocortisone preservative free	1.0 (2.7)
Ikervis coll	1.0 (2.7)
Insulin	2.0 (5.4)
Insuline	1.0 (2.7)

Note 1: The denominator is the number of enrolled patients

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STATISTICAL ANALYSIS TABLE 14.1.5 SUMMARY OF PRIOR AND CONCOMITANT MEDICATIONS (Continued)
SAFETY SET

Medication Name	Oxervate N=37
Iodim eye drops â®	1.0 (2.7)
Ismigen vaccine	1.0 (2.7)
Keppra	1.0 (2.7)
Lacrimal sostitution	1.0 (2.7)
Lamotrigina	1.0 (2.7)
Lansoprazole	1.0 (2.7)
Lansoprazolo	2.0 (5.4)
Lantus	2.0 (5.4)
Lasix	3.0 (8.1)
Levothyroxine	1.0 (2.7)
Lisina acetilsalicilato	1.0 (2.7)
Litio carbonato	1.0 (2.7)
Losartan	1.0 (2.7)
Lubricants preservative free	1.0 (2.7)
Lubrificants	1.0 (2.7)
Lumigan	1.0 (2.7)
Luxazone	1.0 (2.7)
Medrol	1.0 (2.7)
Metformin	4.0 (10.8)
Metoclopramide	1.0 (2.7)
Moxifloxacin ophthalmic	1.0 (2.7)
Mycophenolate mofetil	1.0 (2.7)

Note 1: The denominator is the number of enrolled patients

STATISTICAL ANALYSIS TABLE 14.1.5 SUMMARY OF PRIOR AND CONCOMITANT MEDICATIONS (Continued)
SAFETY SET

Medication Name	Oxervate N=37
N-acetylcysteine eye drop	1.0 (2.7)
Natamicina	1.0 (2.7)
Netilmicin	2.0 (5.4)
Netilmicin + dexamethasone	2.0 (5.4)
Netilmicin eye drops	1.0 (2.7)
Netilmicin preservative free	3.0 (8.1)
Netilmicin/dexamethasone	6.0 (16.2)
Netilmicine preservative free	1.0 (2.7)
Nettacin monodose	1.0 (2.7)
Nettacin unidose	1.0 (2.7)
Nexium 40 mg	1.0 (2.7)
Nitroglicerina cerotto	1.0 (2.7)
Novarapid	1.0 (2.7)
Ofloxacin	1.0 (2.7)
Ofloxacin eye drops	2.0 (5.4)
Olmesartan medoxomil + amlodipine	1.0 (2.7)
Olmetec	1.0 (2.7)
Omeprazole	4.0 (10.8)
Oxervate	1.0 (2.7)
Oxigen therapy	1.0 (2.7)
Ozodrop	1.0 (2.7)
Ozodropâ®	1.0 (2.7)

Note 1: The denominator is the number of enrolled patients

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STATISTICAL ANALYSIS TABLE 14.1.5 SUMMARY OF PRIOR AND CONCOMITANT MEDICATIONS (Continued)
SAFETY SET

Medication Name	Oxervate N=37
Paracetamol	1.0 (2.7)
Plaquenil	1.0 (2.7)
Prednisone	3.0 (8.1)
Protective contact lens	1.0 (2.7)
Quetiapina	1.0 (2.7)
Ramipril	1.0 (2.7)
Ranibizumab	1.0 (2.7)
Recugel	1.0 (2.7)
Ribolisin	1.0 (2.7)
Rosuvastatin	1.0 (2.7)
Rosuvastatina sale di calcio	1.0 (2.7)
Sequacor	1.0 (2.7)
Seretide	1.0 (2.7)
Siccafluid	1.0 (2.7)
Sitagliptin	1.0 (2.7)
Spironolactone	1.0 (2.7)
Systane	1.0 (2.7)
Systane ultra coll	1.0 (2.7)
Tamsulosin	1.0 (2.7)
Thealoz duo	2.0 (5.4)
Thealoz gel	3.0 (8.1)
Thealoz gel unidose	1.0 (2.7)

Note 1: The denominator is the number of enrolled patients

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STATISTICAL ANALYSIS TABLE 14.1.5 SUMMARY OF PRIOR AND CONCOMITANT MEDICATIONS (Continued)
SAFETY SET

Medication Name	Oxervate N=37
Timolol eye drops	1.0 (2.7)
Timoptol	1.0 (2.7)
Timoptol 0.5	2.0 (5.4)
Torasemide	1.0 (2.7)
Totalip	1.0 (2.7)
Trealose lubrificant drops	1.0 (2.7)
Trealose preservative free	2.0 (5.4)
Triazolam	1.0 (2.7)
Triscudil	1.0 (2.7)
Ursilon	1.0 (2.7)
Ursodeoxycholic acid	1.0 (2.7)
Virgan	1.0 (2.7)
Visial	1.0 (2.7)
Vitamina a	1.0 (2.7)
Vitapos	1.0 (2.7)
Voriconazolo 1% coll	2.0 (5.4)
Xanternet	2.0 (5.4)
Zelitrex	1.0 (2.7)
Zendipress	1.0 (2.7)
Zgel	1.0 (2.7)
Zofenopril calcium	1.0 (2.7)

Note 1: The denominator is the number of enrolled patients

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STATISTICAL ANALYSIS TABLE 14.3.1 TREATMENT EMERGENT ADVERSE EVENTS
SAFETY SET

	Oxervate N=37
Number of Any TEAE	7
Number of Subjects with Any TEAE (n (%))	7 (18.9)
Number of Related TEAEs	1
Number of Subjects with Related TEAEs (n (%))	1 (2.7)
Number of Mild or Moderate TEAEs	3
Number of Subjects with Mild or Moderate TEAEs (n (%))	3 (8.1)
Number of Severe TEAEs	2
Number of Subjects with Severe TEAEs (n (%))	2 (5.4)
Number of Related Severe TEAEs	0
Number of Subjects with Related Severe TEAEs (n (%))	0 (0.0)
Number of Serious TEAEs	6
Number of Subjects with Serious AEs (n (%))	6 (16.2)
Number of Non-Serious TEAEs	1
Number of Subjects with Non-Serious AEs (n (%))	1 (2.7)
Number of Related Serious TEAEs	0
Number of Subjects with Related Serious AE s (n (%))	0 (0.0)
Number of Related Non-Serious TEAEs	1
Number of Subjects with Related Non-Serious AE s (n (%))	1 (2.7)

Note 1: The denominator is the number of safety patients
Cross-reference: Listing 16.2.7.1, 16.2.7.2, 16.2.7.3

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STATISTICAL ANALYSIS TABLE 14.3.2
TREATMENT EMERGENT ADVERSE EVENTS BY PREFERRED TERM
SAFETY SET

	Oxervate N=37
At least one TEAE	7 (18.9)
Fall	1 (2.7)
Chronic obstructive pulmonary disease	1 (2.7)
Benign colon surgery	1 (2.7)
Road traffic accident	1 (2.7)
Corneal graft rejection	1 (2.7)
Herpes ophthalmic	1 (2.7)
Dry eye	1 (2.7)

Note 1: The denominator is the number of safety patients
Cross-reference: Listing 16.2.7.1

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STATISTICAL ANALYSIS TABLE 14.3.3 SERIOUS TREATMENT EMERGENT ADVERSE EVENTS BY PREFERRED TERM
SAFETY SET

	Oxervate N=37
At least one serious TEAE	6 (16.2)
Fall	1 (2.7)
Chronic obstructive pulmonary disease	1 (2.7)
Cancer surgery	1 (2.7)
Road traffic accident	1 (2.7)
Corneal graft rejection	1 (2.7)
Herpes ophthalmic	1 (2.7)

Note 1: The denominator is the number of safety patients
Cross-reference: Listing 16.2.7.2

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STATISTICAL ANALYSIS LISTING 16.2.7.1 ADVERSE EVENTS
SAFETY SET

Subject ID	Treatment	Start Date	End Date	Duration (days)	Ongoing	AE term	MedDRA PT Term	Serious	Severity
IT01_001	Oxervate	09JAN2020			Yes	Car accident	Road traffic accident	Yes	Moderate
IT01_004	Oxervate	19FEB2020			Yes	Benign colon surgery	Cancer surgery	Yes	
IT02_001	Oxervate	04SEP2019	02DEC2019	90		Corneal rejection in penetrating keratoplasty	Corneal graft rejection	Yes	Severe
IT04_001	Oxervate	02DEC2019			Yes	Herpetic keratitis recurrence	Herpes ophthalmic	Yes	Moderate
IT05_001	Oxervate	28JUN2019			Yes	Slight eye dryness	Dry eye	No	Mild
IT05_010	Oxervate	24JAN2020	29JAN2020	6		Acute copd exacerbation	Chronic obstructive pulmonary disease	Yes	
IT07_002	Oxervate	23MAR2020	23MAR2020	1		Accidental fall	Fall	Yes	Severe

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STATISTICAL ANALYSIS LISTING 16.2.7.1 ADVERSE EVENTS
SAFETY SET

Subject ID	Relationship	Action Taken	Action Taken, Other	Outcome	Death	Date of Death
IT01_001	None	Not applicable (study drug discontinued prior to event)	Corrective procedures	Not Resolved		
IT01_004	None	Not applicable (study drug discontinued prior to event)	Corrective medication	Recovering/Resolved		
IT02_001	None	Drug not changed	None	Resolved with Sequelae		
IT04_001	None	Not applicable (study drug discontinued prior to event)	None	Not Resolved		

STATISTICAL ANALYSIS LISTING 16.2.7.1 ADVERSE EVENTS
SAFETY SET

Subject ID	Treatment	Start Date	End Date	Duration (days)	Ongoing AE term	MedDRA PT Term	Serious	Severity
IT05_001	Possible	Drug not changed			Corrective procedures	Recovering/Resolved		
IT05_010	None	Drug interrupted			Corrective procedures	Recovering/Resolved		
IT07_002	None	Drug withdrawn			Corrective procedures	Not Resolved	Yes	23MAR2020

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LISTING 16.2.7.2 SERIOUS ADVERSE EVENTS
SAFETY SET

Subject ID	Treatment	Start Date	End Date	Duration (days)	Ongoing	AE term	MedDRA PT Term	Serious	Severity
IT01_001	Oxervate	09JAN2020			Yes	Car accident	Road traffic accident	Yes	Moderate
IT01_004	Oxervate	19FEB2020			Yes	Benign colon surgery	Cancer surgery	Yes	
IT02_001	Oxervate	04SEP2019	02DEC2019	90		Corneal rejection in penetrating keratoplasty	Corneal graft rejection	Yes	Severe
IT04_001	Oxervate	02DEC2019			Yes	Herpetic keratitis recurrence	Herpes ophthalmic	Yes	Moderate
IT05_010	Oxervate	24JAN2020	29JAN2020	6		Acute copd exacerbation	Chronic obstructive pulmonary disease	Yes	
IT07_002	Oxervate	23MAR2020	23MAR2020	1		Accidental fall	Fall	Yes	Severe

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STATISTICAL ANALYSIS LISTING 16.2.7.2 SERIOUS ADVERSE EVENTS
SAFETY SET

Subject ID	Relationship	Action Taken	Action Taken, Other	Outcome	Death	Date of Death
IT01_001	None	Not applicable (study drug discontinued prior to event)	Corrective procedures	Not Resolved		
IT01_004	None	Not applicable (study drug discontinued prior to event)	Corrective medication	Recovering/Resolved		
IT02_001	None	Drug not changed	None	Resolved with Sequelae		
IT04_001	None	Not applicable (study drug discontinued prior to event)	None	Not Resolved		
IT05_010	None	Drug interrupted	Corrective procedures	Recovering/Resolved		
IT07_002	None	Drug withdrawn	Corrective procedures	Not Resolved	Yes	23MAR2020

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STATISTICAL ANALYSIS LISTING 16.2.7.3 SERIOUS ADVERSE EVENTS LEADING TO DEATH
SAFETY SET

Subject ID	Treatment	Start Date	End Date	Duration (days)	Ongoing	AE term	MedDRA PT term	Serious	Severity
IT07_002	Oxervate	23MAR2020	23MAR2020	1		Accidental fall	Fall	Yes	Severe

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STATISTICAL ANALYSIS LISTING 16.2.7.3 SERIOUS ADVERSE EVENTS LEADING TO DEATH
SAFETY SET

Subject ID	Relationship	Action Taken	Action Taken, Other	Outcome	Death	Date of Death
IT07_002	None	Drug withdrawn	Corrective procedures	Not Resolved	Yes	23MAR2020

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19. APPENDICES

Appendix 1. List of activated Centres/Sites

Appendix 2. List of activted centres and patients disposition by centre

Appendix 3. Clinical research protocol

Appendix 4. Sample case report form

Appendix 5. Curricula vitae of the Investigators

Appendix 6. List of Ethics Committees

Appendix 7. Audit certificates

Appendix 8. Documentation on Statistical Methods

Appendix 9. Publications referenced in the report.

Appendix 10. Case Report Forms