1 CLINICAL STUDY PROTOCOL

Recordati Rare Diseases

Protocol Title: Efficacy, Safety and Pharmacokinetics of 3 Doses of REC 0/0559 Eye Drops for the Treatment of Stage 2 (Moderate) and 3 (Severe) Neurotrophic Keratitis in Adult Patients

Protocol Number: REC0559-B-001

IND Number:	139657
EudraCT Number:	2019-002475-34
Name of Investigational Product:	REC 0/0559
Phase of Development:	2
Indication:	Neurotrophic keratitis
Sponsor:	Recordati Rare Diseases Immeuble le Wilson 70 avenue du Général de Gaulle 92800 Puteaux, France Tel: +33 (0) 1 47 73 64 58
Protocol Version:	Final
Protocol Date:	21 February 2022

PROTOCOL APPROVAL SIGNATURES

Protocol Title: Efficacy, Safety and Pharmacokinetics of 3 Doses of REC 0/0559 Eye Drops for the Treatment of Stage 2 (Moderate) and 3 (Severe) Neurotrophic Keratitis in Adult Patients

Protocol Number: REC0559-B-001

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation guidelines for current Good Clinical Practice and applicable regulatory requirements.

Sponsor Signatory

Dr Céline Plisson
Medical Director
Recordati Rare Diseases

Signature

16 MAR 2022
Date (DD-Mmm-YYYY)

Contract Research Organisation Signatory

Nathalie Castaing,
Project Director
Syneos Health

Signature

18 Mar 2022
Date (DD-Mmm-YYYY)

Medical Monitor

Anna Dudzik, MD
Executive Medical Director, Medical Management and Scientific Services
Syneos Health

Signature

16 MAR 2022
Date (DD-Mmm-YYYY)

Biostatistician

Alessandro Antonellini
Head of Statistics and Data Management
Recordati Rare Diseases

Signature

16 MAR 2022
Date (DD-Mmm-YYYY)

INVESTIGATOR SIGNATURE PAGE

Protocol Title: Efficacy, Safety and Pharmacokinetics of 3 Doses of REC 0/0559 Eye Drops for the Treatment of Stage 2 (Moderate) and 3 (Severe) Neurotrophic Keratitis in Adult Patients

Protocol Number: REC0559-B-001

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol, GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Recordati Rare Diseases including, but not limited to, the current investigator's brochure.
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Recordati Rare Diseases and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Recordati Rare Diseases and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Recordati Rare Diseases study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and study records that include all pertinent observations on each of the site's study patients will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.
- Information developed in this clinical study may be disclosed by Recordati Rare Diseases to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

2 SYNOPSIS

Title of Study:	Efficacy, Safety and Pharmacokinetics (PK) of 3 Doses of REC 0/0559 Eye Drops for the Treatment of Stage 2 (Moderate) and 3 (Severe) Neurotrophic Keratitis (NK) in Adult Patients
Protocol Number:	REC0559-B-001
Investigators/Study Sites:	Approximately 45 study sites in 7 countries in Europe and North America
Phase of Development:	Phase 2
Objectives:	The primary objectives are: • In the first 24 patients, to determine the safety, tolerability and PK profile of REC 0/0559 (MT8) given as 1 drop 4 times a day (QID) of escalating doses up to 50 µg/mL. • To determine the efficacy and safety of MT8 given as 1 drop QID at 5, 25, and 50 µg/mL during 8 weeks and select the dose with the best benefit risk ratio.
Study Endpoints:	**Primary Efficacy Endpoint** The primary endpoint of this study is the percentage of patients achieving complete corneal healing of persistent epithelial defects (PED) or corneal ulcer at Week 8, defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading centre. **Secondary Efficacy Endpoints** The secondary efficacy endpoints are: • Percentage of patients who achieve a 5-, 10-, and 15-letter mean improvement in best corrected distance visual acuity (BCDVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) chart at Week 8 compared to baseline (in all patients and in patients with a central location of the PED or corneal ulcer, respectively). • Percentage of patients achieving complete corneal healing of PED or corneal ulcer at Week 8, defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by the investigator. • Time to complete corneal healing of PED or corneal ulcer defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading. • Time to complete corneal healing of PED or corneal ulcer defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by the investigator. • Percentage of patients having deterioration of the disease at Week 8 (defined as increase in lesion size ≥ 1 mm as assessed by the investigator, or mean decrease in BCDVA by > 5 letters compared to baseline, or progression in lesion depth to corneal melting or perforation, or onset of infection). • Mean change in BCDVA from baseline to Week 8 in all patients and in patients with a central location of the PED or corneal ulcer, respectively. • Percentage of patients with improvement in corneal sensitivity from baseline as measured by Cochet-Bonnet aesthesiometer at Week 8. **Other Efficacy Endpoints** • Percentage of patients achieving complete corneal healing of PED or corneal ulcer at Week 8, defined as the greatest diameter of corneal fluorescein staining in the area of the PED or corneal ulcer < 0.5 mm as assessed by central reading.

<table>
<tr><td></td><td>

Percentage of patients achieving complete corneal healing of PED or corneal ulcer at Week 8, defined as the greatest diameter of corneal fluorescein staining in the area of the PED or corneal ulcer < 0.5 mm as assessed by the investigator.
Percentage of patients achieving complete corneal clearing at Week 8, defined as a score of 0 using the Oxford scale.
Time to at least 50% corneal healing (defined as a ≥ 50% reduction in the greatest diameter of the lesion) as determined by central reading.
Time to at least 50% corneal healing (defined as a ≥ 50% reduction in the greatest diameter of the lesion) as determined by the investigator.
Time to onset of healing (defined as a > 20% reduction in the greatest diameter of the lesion) as determined by central reading.
Time to onset of healing (defined as a > 20% reduction in the greatest diameter of the lesion) as determined by the investigator.

Other Exploratory Endpoints

Change from baseline in Quality of Life (QoL) evaluated using the National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25).
Change from baseline in the overall numerical rating scale (NRS) score for ocular symptoms and tolerability.

</td></tr>
<tr><td>Study Design:</td><td>
This Phase 2, international, multicentre, dose-ranging, double-masked, randomised, parallel-group, vehicle-controlled study is designed to evaluate 3 different doses of REC 0/0559 versus vehicle in patients with Stage 2 and Stage 3 NK.
<table>
<tr><td></td><td>Dose of MT8 per day</td><td>Study drug concentration</td></tr>
<tr><td>Dose 1</td><td>0.5 µg/day</td><td>5 µg/mL MT8 given 1 drop QID</td></tr>
<tr><td>Dose 2</td><td>2.5 µg/day</td><td>25 µg/mL MT8 given 1 drop QID</td></tr>
<tr><td>Dose 3</td><td>5 µg/day</td><td>50 µg/mL MT8 given 1 drop QID</td></tr>
<tr><td>Vehicle</td><td>0 µg/day</td><td>Vehicle given 1 drop QID</td></tr>
</table>
Abbreviations: QID, 4 times a day

Screening procedures (V1a) will be performed on Day -3, Day -2, Day -1, or on Day 1, prior to randomisation. The study will have an initial period of dose escalation followed by a parallel recruitment period. After confirmation of eligibility and signature of informed consent, patients will be randomly assigned to treatment with REC 0/0559 or vehicle on Day 1. Randomisation will be stratified by disease stage (Stage 2, Stage 3) and region (Europe, North America).

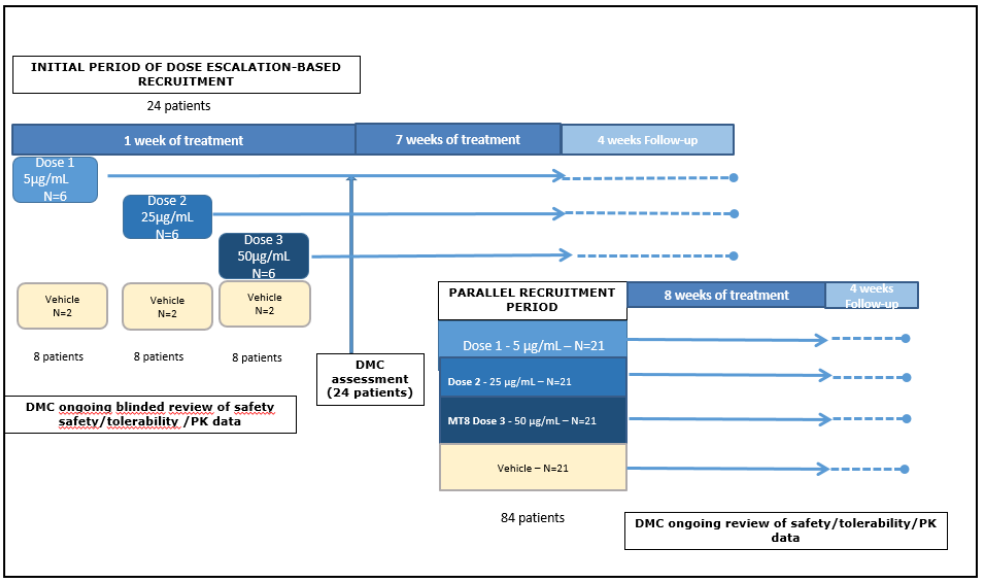
Randomisation of the first 24 patients will be sequential, with cohorts of 8 patients for each dose level randomised in a 3:1 ratio in each cohort (6 patients treated with REC 0/0559 and 2 with vehicle), starting with Dose 1. Patients will be enrolled sequentially in each next highest dose level 7 days after the 8th patient of previous cohort has been enrolled, unless the independent data monitoring committee (DMC) issues a specific recommendation for a change in study conduct. The DMC will receive information related to any non-serious adverse events (AEs) that are considered to be severe and possibly related to the study drug and other AEs of special interest (AESI), to any serious adverse event (SAE), or any serum drug concentration > 10 nM on an ongoing basis.

The initial dose escalation period of the protocol will proceed as follows:

The first 8 patients will receive Dose 1 (5 µg/mL REC 0/0559 administered 1 drop QID) or vehicle.

</td></tr>
</table>

	2. Seven days after the 8th patient has been enrolled at Dose 1, enrolment will start for the next 8 patients who will be treated with Dose 2 (25 µg/mL REC 0/0559 administered 1 drop QID) or vehicle, unless the DMC issues a specific recommendation for study conduct related to the safety information received on an ongoing basis. 3. Seven days after the 8th patient has been enrolled at Dose 2, enrolment will start for the next 8 patients who will be treated with Dose 3 (50 µg/mL REC 0/0559 administered 1 drop QID) or vehicle, unless the DMC issues a specific recommendation for study conduct related to the safety information on an ongoing basis. The DMC will confirm in writing that the enrolment and dose escalation to a next dose level can continue based on the safety data received, if any (AESI, SAE, PK). The DMC can recommend discontinuing the treatment at any time before the formal review of the data from the first 24 patients. Once the 24th patient has been enrolled, enrolment of new patients will be put on hold and the DMC will perform a formal review of all the safety and PK data available before enrolment of new patients is resumed. The treatment of the first 24 patients will continue as planned. The DMC may also recommend discontinuing the 12-lead electrocardiogram (ECG) assessment in the remaining patients (if no significant systemic exposure to the study drug is observed). If no study discontinuation or change in the protocol design is recommended after the formal DMC review of all safety data for the first 24 patients, enrolment will resume and patients will be randomised to all 4 treatment arms in a 1:1:1:1 ratio until approximately 27 patients are enrolled in each arm (approximately 108 patients total). Another formal review of the data by the DMC will be conducted 8 weeks after approximately 50% of patients (54 patients) have been enrolled. During the double-masked treatment period, all patients will administer 1 drop (approximately 25 µL) REC 0/0559 or vehicle in the study eye QID at 4 hour intervals ± 30 minutes (starting in the morning) for 8 weeks. Patients will be followed up for 4 weeks after the end of treatment. At any time during the study, the investigator can discontinue the study drug and initiate a rescue treatment if clinically required (eg, in the case of worsening of disease). In case of study drug discontinuation of any reason, including when a rescue therapy is started, the patient will be asked to stay in the study and perform all the visits and assessments as planned (except in cases where the patient has withdrawn consent for study participation). Patients who discontinue study drug should at least complete the Early Termination and Follow-Up Visits if possible. A central laboratory will be used for haematology, biochemistry, and PK sample analysis. Central reading will be performed for the fluorescein stain test (primary endpoint). In addition, QoL will be evaluated using the NEI VFQ-25. No formal interim analysis is planned for the study. A diagram of the study design is presented below.

	Study Design  Abbreviations: DMC, data monitoring committee; PK, pharmacokinetic.
Selection of Patients:	Main Inclusion Criteria: 1. Have read, understood, and signed the informed consent form (ICF). 2. Be a male or female aged ≥ 18 years at the time of ICF signature. 3. Have Stage 2 moderate (PED) or Stage 3 severe (corneal ulcer) NK involving only 1 eye (study eye) and of at least 2 weeks duration. Patients with Stage 1 NK in the fellow eye can be enrolled. • For the study eye: 4. Have no objective clinical evidence of improvement in the PED or corneal ulceration within the 2 weeks before the Screening Visit despite use of conventional non-surgical treatment (eg, nonpreserved ocular lubricants, nonpreserved topical antibiotics, oral doxycycline, patching, serum tears, and/or therapeutic contact lenses) as determined by the investigator's or referring physician's medical record. 5. Have decreased corneal sensitivity (≤ 4 cm using the Cochet-Bonnet aesthesiometer) within the area of the PED or corneal ulcer and outside of the area of the defect in at least one corneal quadrant. 6. Have a BCDVA score ≤ 75 ETDRS letters in the study eye, due to NK. Main Exclusion Criteria: 1. Have participated in any clinical trial with an investigational drug/device within 2 months before the Screening Visit and throughout the study duration. 2. Have a known hypersensitivity to one of the components of the study drug or procedural medications (eg, fluorescein), including to a compound chemically related to MT8. 3. Have a presence or history of any ocular or systemic disorder or condition that might hinder the efficacy of the study treatment or its evaluation, could possibly interfere with the interpretation of study results, or could be judged by the investigator to be incompatible with the study visit schedule or conduct (eg, progressive or degenerative corneal or retinal conditions, lagophthalmos, uveitis, optic neuritis, poorly controlled diabetes, autoimmune

	disease, systemic infection, neoplastic diseases), or that may compromise the safety of the patient. 4. Have a significant history of alcohol abuse or drug/solvent abuse (within the last 2 years). 5. Be unwilling to comply with any study assessments or procedures. 6. Be a woman who is pregnant, nursing or planning a pregnancy. 7. Be a woman of childbearing potential who is not using a highly effective method of birth control. 8. Be a male patient who is not permanently sterile and who is not willing to use condoms during the study and for 4 weeks after the end of study treatment. For the study eye: 9. Have any active ocular infection (bacterial, viral, fungal or protozoal) or active inflammation not related to NK in the study eye. 10. Have any other ocular disease requiring topical ocular treatment in the study eye during the course of the study treatment period, except for glaucoma if treated by preservative-free eye drop (single-agent treatment, once daily, stable regimen 4 weeks before screening and during the study). 11. Receive topical ophthalmological treatments other than the study drug provided by the study Sponsor and the treatments allowed by the study protocol (eg, preservative-free artificial tears; preservative-free eye drop (single-agent treatment, once daily, stable regimen 4 weeks before screening and during the study) for glaucoma; topical antibiotics; other than tetracycline). 12. Have severe blepharitis and/or severe meibomian gland disease in the study eye. 13. Have severe vision loss in the study eye with no potential for visual improvement in the opinion of the investigator as a result of the study treatment. 14. Have evidence of corneal ulceration/melting involving the posterior third of the corneal stroma, or perforation in the study eye. 15. Have a history of any ocular surgery (including laser or refractive surgical procedures) within 3 months before the Screening Visit in the study eye. An exception to the preceding statement will be allowed if the ocular surgery is considered to be the cause of the Stage 2 or 3 NK. 16. Have a history of corneal transplantation in the study eye performed less than 12 months prior screening.

	17. Have had prior surgical procedures for the treatment of NK (eg, complete tarsorrhaphy, conjunctival flap, etc.) except partial tarsorrhaphy if done more than 6 months prior to screening visit (with investigators assessment documenting that the eye lids are functioning sufficiently to ensure adequate protection of the eye) and amniotic membrane transplantation, if at least 2 weeks after the membrane has disappeared within the area of the PED or corneal ulcer (and at least 6 weeks after the procedure) in the study eye. Patients previously treated with Botox® (Botulinum toxin) injections used to induce pharmacologic blepharoptosis are eligible for enrolment only if the last injection was given at least 3 months before the Screening Visit. 18. Use therapeutic contact lenses or wear contact lenses for refractive correction during the study treatment periods in the eye(s) with NK. 19. Have an anticipated need for punctal occlusion during the study treatment period. Patients with punctal occlusion or punctal plugs inserted before the study are eligible for enrolment provided that the punctal occlusion is maintained during the study. 20. Have an uncontrolled glaucoma at the Screening Visit. Patients suffering from glaucoma requiring ophthalmic drops for topical treatment at the Screening Visit or during the study are not eligible, except if the ophthalmic drops is a preservative-free treatment administered maximum once daily as a single-agent treatment and at a stable regimen 4 weeks before screening and at the same dose during the study. Patients treated with oral intraocular pressure-lowering drugs at the Screening Visit and during the study may be enrolled if their glaucoma status is assessed as stable and controlled. For the fellow eye: 21. Have Stage 2 or 3 NK or perforation. For any eye: 22. Have a history of ocular cancer. 23. Have had prior treatment with Oxervate™ (cenegermin eye drops).
Planned Sample Size:	Approximately 108 enrolled patients (27 per group).
Investigational Therapy:	One drop (approximately 25 µL) of REC 0/0559 ophthalmic solution containing MT8 at the concentration of 5, 25, or 50 µg/mL will be administered 4 times a day in the study eye.
Reference Therapy:	One drop (approximately 25 µL) of ophthalmic solution of the same composition as the study drug without the active substance MT8 will be administered 4 times a day in the study eye.
Treatment Duration:	Each patient will be treated for 8 weeks with study drug. The total length of study participation for each patient will be approximately 12 weeks (Screening, 8-week treatment period, and 4-week follow-up period). The duration of the study will be approximately 18 months from First Patient In to Last Patient Out.
Efficacy:	Efficacy will be evaluated by: • Slit lamp examination/fluorescein staining (lesion size, Oxford scale) • Corneal sensitivity • BCDVA examination
Safety:	Safety assessments include physical examination, ophthalmological examination, vital signs, 12-lead electrocardiogram (ECG), laboratory safety tests, and adverse event (AE) recording (including serious AEs and adverse events of special interest).

Pharmacokinetics:	PK parameters of maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve during a dosage interval (AUCτ) of this study are as follows. For the first 24 patients: • At Day 1: predose, 10, 20, and 40 minutes, and 1, 2, and 4 hours after the first daily administration (last sampling before next dose administration) • At Day 7 (±1 day): predose, 10, 20, and 40 minutes, and 1, 2, and 4 hours after the first daily administration (last sampling before next dose administration) For all patients: • At Day 28 (±2 days) 4 hours postdose but before the next administration • At Day 56 (±3 days), 4 hours postdose
Other Assessments:	Quality of life will be evaluated using the NEI VFQ-25. Ocular symptoms and tolerability will be evaluated using an NRS.
Statistical Methods and Planned Analyses:	**Analysis Populations** Enrolled Population: The enrolled population will include all individuals who sign the ICF. Modified Intent-to-Treat Population: The intent-to-treat (ITT) population will include all patients who are randomised and receive at least 1 drop of study drug, irrespective of any deviation from the protocol or premature discontinuation. The treatment group assignment will be designated according to initial randomisation. The ITT population will serve as the basis for the analysis of efficacy. Safety Population: The safety population will include all randomised patients who receive at least 1 dose of study drug. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety. Per-protocol Population: The per-protocol (PP) population will include all patients in the ITT population for whom no major protocol violations/deviations occurred. **Statistical Analyses** The primary endpoint will be analysed by means of the Cochran-Mantel-Haenszel chi-square test, controlling for disease stage. Hierarchical testing will be performed to account for multiplicity. Benjamini-Hochberg procedure will be applied. The primary analysis will be performed on the ITT population and will consider rescue treatment initiation or randomised treatment discontinuations due to related adverse events as failures, while all the other missing data will be managed according with the last observation carried forward (LOCF) method. A secondary analysis will be performed with the same criteria but including also the data (if available) collected after treatment discontinuation (in this case not considered as failure). As sensitivity analyses, the primary analysis will be repeated on the intent-to-treat population by means of the Cochran-Mantel-Haenszel chi-square test, controlling for disease stage and site (pooled to ensure adequate strata sizes), with missing data imputed as failures, with observed data only and on the PP population. Categorical secondary endpoints will be analysed using the same analysis used for the primary endpoint. Continuous endpoints will be based on an analysis of covariance (ANCOVA) with treatment and sites as main effects and baseline value and disease stage as covariates. Time to event endpoints will be evaluated by means of Kaplan-Meier survival analysis using log-rank test. The Cox's proportional hazard model will be used in order to manage covariates in the proper way. National Eye Institute Visual Functioning Questionnaire-25 scores will be calculated according to the NEI VFQ-25 scoring algorithm (composite score and subscales). An overall NRS score will be calculated as the mean of individual symptoms scores.

3 TABLE OF CONTENTS

1 CLINICAL STUDY PROTOCOL 1
2 SYNOPSIS 4
3 TABLE OF CONTENTS 11
3.1 List of In-text Tables 15
3.2 List of In-text Figures 15
4 LIST OF ABBREVIATIONS 16
5 INTRODUCTION 18
5.1 Background on Neurotrophic Keratitis 18
5.2 Background on MT8 19
5.2.1 Nonclinical Studies 19
5.2.2 Clinical Studies 21
5.3 Study Rationale 21
5.4 Clinical Risks/Benefits of MT8 21
6 STUDY OBJECTIVES AND ENDPOINTS 23
6.1 Study Objectives 23
6.1.1 Primary Objectives 23
6.2 Study Endpoints 23
6.2.1 Primary Efficacy Endpoint 23
6.2.2 Secondary Efficacy Endpoints 23
6.2.3 Other Efficacy Endpoints 24
6.2.4 Other Exploratory Endpoints 24
6.2.5 Safety Assessment 24
6.2.6 Pharmacokinetic Assessment 25
7 INVESTIGATIONAL PLAN 26
7.1 Description of Overall Study Design and Plan 26
7.2 Discussion of Study Design 28
7.3 End of Study 29
7.4 Early Termination of Study 29
8 SELECTION OF STUDY POPULATION 30
8.1 Inclusion Criteria 30
8.2 Exclusion Criteria 31
8.3 Rescreening 33
8.4 Study Withdrawal, Removal, and Replacement of Patients 33

8.4.1 Withdrawal from Study Drug 33
8.4.2 Withdrawal from the Study 34
9 TREATMENTS 35
9.1 Details of Study Treatments 35
9.2 Dosage Schedule 35
9.3 Measures to Minimise Bias: Study Drug Assignment and Masking 36
9.3.1 Method of Study Drug Assignment 36
9.3.2 Masking36
9.4 Dosage Modification 37
9.5 Treatment Accountability and Compliance 37
9.6 Prior and Concomitant Therapy 38
9.6.1 Prior and Concomitant Therapies 38
9.6.2 Rescue Medications 40
10 STUDY PROCEDURES 41
10.1 Informed Consent 45
10.2 Visit 1a (Screening Visit – Day -3 to Day 1) 45
10.3 Visit 1b (Day 1; First Administration of Study Drug) 46
10.4 Visit 2 (Day 3 ±1) 47
10.5 Visit 3 (Day 7 ±1) 47
10.6 Visit 4 (Day 14 ± 2) and Visit 5 (Day 21 ± 2) 48
10.7 Visit 6 (Day 28 ± 2) 48
10.8 Visit 7 (Day 42 ± 3) 49
10.9 Visit 8 (Day 56 ± 3) 50
10.10 Visit 9 (Day 70 ± 7) – Follow-Up Period 50
10.11 Visit 10 (Day 84 ± 7) – Follow-Up Period 51
10.12 Early Termination Visit 51
11 EFFICACY ASSESSMENTS 53
11.1 Slit Lamp Examination/Fluorescein Staining 53
11.1.1 Slit Lamp Examination 53
11.1.2 Fluorescein Staining 53
11.2 Corneal Sensitivity 54
11.3 BCDVA Examination 54
12 SAFETY ASSESSMENTS 55
12.1 Vital Signs 55
12.2 Physical Examination 55
12.3 Electrocardiograms 55

12.4 Ophthalmological Examination 56
12.5 Fundus Examination 56
12.6 Laboratory Assessments 56
12.7 Adverse Events 57
12.7.1 Adverse Events 57
12.7.2 Adverse Events of Special Interest 58
12.7.3 Serious Adverse Events 59
12.7.4 Reporting of Serious Adverse Events and Other Adverse Events Requiring Immediate Reporting 59
12.7.5 Suspected Unexpected Serious Adverse Reactions 60
12.8 Pregnancy 61
12.9 Other Reportable Information 61
13 PHARMACOKINETICS 62
13.1 Pharmacokinetic Sampling 62
13.1.1 Blood Samples 62
13.2 Pharmacokinetic Analytical Methodology 62
14 OTHER ASSESSMENTS 63
14.1 NEI VFQ-25 (Quality of Life) 63
14.2 NRS for Ocular Symptoms and Tolerability 63
14.3 Study Drug Diary 63
15 STATISTICAL ANALYSIS 64
15.1 Determination of Sample Size 64
15.2 Analysis Populations 64
15.3 Efficacy Analysis 65
15.3.1 Analysis of Primary Efficacy Endpoint 65
15.3.2 Analysis of Secondary Efficacy Endpoints 65
15.4 Analysis of Other Exploratory Endpoints 65
15.5 Safety Analysis 66
15.6 Pharmacokinetic Analysis 66
15.7 Interim Analysis 66
15.8 Data Monitoring Committee 66
16 STUDY MANAGEMENT 67
16.1 Approval and Consent 67
16.1.1 Regulatory Guidelines 67
16.1.2 Institutional Review Board/Independent Ethics Committee 67

16.1.3 Informed Consent....67
16.2 Data Handling....67
16.3 Source Documents....68
16.4 Record Retention....69
16.5 Monitoring....69
16.6 Quality Control and Quality Assurance....69
16.7 Protocol Amendment and Protocol Deviation....70
16.7.1 Protocol Amendment....70
16.7.2 Protocol Deviations....70
16.8 Ethical Considerations....70
16.9 Financing and Insurance....70
16.10 Publication Policy/Disclosure of Data....70
17 REFERENCES....72
18 APPENDICES....74
APPENDIX 1.... CONTRACEPTION GUIDELINES 75
APPENDIX 2..... OCULAR SYMPTOMS AND TOLERABILITY NUMERICAL RATING SCALE....77

3.1 List of In-text Tables

Table 1 Classification of NK....18
Table 2. Schedule of Assessments 42
Table 3. Laboratory Assessments....56
Table 4. Classification of Adverse Events by Intensity 58
Table 5. Classification of Adverse Events by Relationship to Study Drug or Study Procedure 58

3.2 List of In-text Figures

Figure 1 Study Design 28

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUCτ	area under the plasma concentration-time curve during a dosage interval (τ)
ANCOVA	analysis of covariance
BCDVA	best corrected distance visual acuity
BDNF	brain derived neurotrophic factor
BFS	blow fill seal
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CNU	corneal neurotrophic ulcer
CRA	clinical research associate
CRO	contract research organisation
CYP	cytochrome P450
DMC	data monitoring committee
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
GCP	Good Clinical Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IND	Investigational New Drug
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	interactive web response system
LOCF	last observation carried forward
MT6	free acid form of MT8
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NGF	nerve growth factor
NK	neurotrophic keratitis/neurotrophic keratopathy
NOAEL	no-observed-adverse-effect level
NRS	numerical rating scale
PBS	phosphate-buffered saline
PED	persistent epithelial defects
PK	pharmacokinetic(s)
QID	four times a day (quater in die)

Abbreviation	Definition
QoL	quality of life
REC 0/0559	the ophthalmic solution of MT8 dissolved in phosphate-buffered saline
rhNGF	recombinant human nerve growth factor
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SPK	superficial punctate keratopathy
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TrkA	tropomyosin receptor kinase A
TrkB	tropomyosin receptor kinase B
WOCBP	women of childbearing potential
US	United States

5 INTRODUCTION

5.1 Background on Neurotrophic Keratitis

Neurotrophic keratitis (NK; also known as neurotrophic keratopathy; ORPHAnet number 137596[1]) is a degenerative corneal condition involving the epithelial layer and the corneal stroma, associated with vascularisation and opacification, which may evolve, through superficial punctate keratopathy (SPK) or persistent epithelial defects (PED), towards corneal ulceration - a severe condition called corneal neurotrophic ulcer (CNU) - and eventually leading to corneal perforation.

The hallmark of NK is corneal hypoaesthesia or anaesthesia that leave the organ susceptible to injury and epithelial breakdown that can lead to ulceration, infection, stromal melting, and perforation, secondary to poor healing. It results from palsy or deficiency of one or more divisions of the trigeminal nerve or its branches, caused by surgery, neoplasia, aneurysm or facial trauma. Other causes include physical or chemical burns, ocular surgery, (herpetic) infections, (ab)use of topical anaesthetics, β-blockers or non-steroidal anti-inflammatory drugs, systemic diseases (ie, diabetes mellitus), corneal dystrophies, congenital diseases (ie, Riley-Day syndrome and Goldenhar-Gorlin syndrome), increasing age, or iatrogenic causes (contact lens wear and ocular surgery).[2-5]

Despite the high number of pathological events leading to impairment of trigeminal corneal innervation, NK is a rare disease (EU/3/14/1400; defined in the European Union [EU] as a disease affecting less than 5 in 10,000 people and in the United States [US] as a disease affecting less than 200,000 people nationwide).[6]

NK is classified (Table 1) by the degree of the corneal tissue damage (based on Mackie classification). Stage 1 (mild) shows slight, non-specific signs and symptoms. Stage 2 (moderate) is characterised by epithelial defects, progressively leading to PED. Stage 3 (severe) is characterised by stromal disruption associated with a CNU that progresses to perforation.

Table 1 Classification of NK

Stage 1	Punctate epithelial staining Decreased tear break up test Rose Bengal staining of inferior palpebral conjunctiva Dellen Gaule spots Stromal scarring
Stage 2	Epithelial defect Stromal swelling Surrounding rim of loose epithelium Rare anterior chamber reaction
Stage 3	Corneal ulcer Stromal lysis Perforation

Abbreviations: NK, neurotrophic keratitis.
Adapted from Semeraro et al., 2014.[3]

Conventional treatment of NK depends on the stage of the disease.[7] In Stage 1 NK, preservative-free tear substitutes are used to maintain lubrication and support the tear film; and topical antibiotics are used prophylactically to prevent superinfection in the presence of epithelial defects. In Stage 2 NK, treatment of PED aims to prevent progression of the corneal lesion to corneal ulcer. Corneal and scleral contact lenses are commonly used, and in unresponsive cases, tarsorrhaphy is recommended, either surgically or temporarily through botulinum A toxin injection.[4] Amniotic membrane transplantation provides a mechanical bandage rich with growth factors and cytokines, and this in combination with tarsorrhaphy has been shown to be useful for promotion the healing of refractory neurotrophic corneal ulcers.[8] In Stage 3 NK, stromal lysis must be prevented and ocular integrity preserved. Topical collagenase inhibitors, such as N-acetylcysteine, tetracycline, or medroxyprogesterone are used to reduce stromal melting. Conjunctival flaps are also an option that provides metabolic and mechanical supply, promotes healing and restores integrity; however, visual function is sacrificed.[9] Small perforations are sometimes treated with cyanoacrylate glue and a soft bandage contact lens or amniotic membrane, however larger defects require keratoplasty.

Despite these treatments, healing response in NK patients remains difficult to obtain and visual outcomes are poor.[10,11]

Experimental models and clinical data have shown that recombinant human nerve growth factor (rhNGF) eye drops were able to induce corneal healing and recovery of sensitivity, to ameliorate tear production and quality, and to modulate inflammatory reaction.[2,12-15] Oxervate™ (cenegermin, recombinant form of human nerve growth factor [NGF]; Dompé Pharmaceuticals) was approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in 2017 and 2018, respectively, for the treatment of NK. However, a number of local tolerability adverse events (AEs) were reported and medical need remains for a well-tolerated, practical, and efficacious local treatment of NK.

Based on these data, MT8, a non-peptidic neurotrophin mimetic compound capable to bind the high-affinity NGF receptor tropomyosin receptor kinase A (TrkA) and the brain derived neurotrophic factor (BDNF) receptor tropomyosin receptor kinase B (TrkB) at nanomolar concentrations, could be of interest in the treatment of NK.

5.2 Background on MT8

The compound MT8 is a non-peptidic neurotrophin mimetic capable of binding TrkA and TrkB at nanomolar concentrations. The drug product REC 0/0559 is an ophthalmic solution and is prepared by dissolving MT8 in a phosphate-buffered saline (PBS) solution. The activity of MT8 (lysine salt) is due to the active form MT6, the free acid form of MT8 present in solution. The methyl ester of MT6, MT2, shows a similar pharmacological profile to MT8.

5.2.1 Nonclinical Studies

The pharmacodynamic activity of the drug substance MT8 was investigated in *in vitro*, *ex vivo*, and *in vivo* studies, including *in vivo*/*ex vivo* models of corneal ulcer in the rabbit.

In vitro experiments with different cell lines of human (HCEP 0.5, HFCEC), bovine (BCE C/D-1b), and rabbit (SIRC) origin showed that MT8 is able to sustain cell proliferation and to prevent cell apoptosis similarly to NGF.

The pharmacodynamic activity of MT8 was investigated *in vivo* in an alcohol-induced corneal dis-epithelialisation model in rabbits and in an experiment conducted in rabbits whose cornea were mechanically scraped. The results collectively indicate that MT8 has significant healing capacity in the corneal epithelium and stroma through promotion of cellular proliferation and inhibition of apoptosis.

MT8 is a selective compound and did not interact significantly with a panel of 45 kinase and 57 recombinant human receptors. MT8 did not induce or inhibit CYP450 enzymes, and it did not bind melanin in vitro.

Metabolism of MT8 was measured in rat, dog and human hepatocytes. MT8 was detected practically unchanged in dog and human hepatocytes and weakly metabolised in rat hepatocytes. In rat hepatocytes, hydroxylation and conjugation with glutathione were the most important metabolic reactions. MT8 does not present a concern for direct phototoxicity, since it does not absorb light within the range of natural sunlight (290 to 700 nm). The pharmacokinetic profile of MT8 in vivo in rat and rabbit following intravenous (IV), subcutaneous (SC), oral, and ocular administration showed a short half-life of about 30 and 10 min, respectively, an oral bioavailability of 45% to 65%, and almost complete bioavailability by SC administration in rats; a lower bioavailability of about 20% was observed in rabbits and about 29% in dogs following ocular administration.

Non-clinical toxicology studies conducted with IV MT8 in rats and in rabbits using ocular administration of 0.01 to 1 mM of MT8 in PBS (single and repeated dose, 3 times per day, up to 28 days) revealed no signs of damage or irritation to the eye; no signs of general toxicity or of systemic effects were noted. Preliminary results of an additional 13-week study in rats by SC route did not show relevant changes that may have suggested systemic toxicity up to 30 mg/kg/day, which could therefore be considered as the no-observed-adverse-effect level (NOAEL). A 13/26-week toxicity study in rabbits after MT8 ocular administration has also been completed. In this study, no systemic or local toxic effects were observed with MT8 ocular dosing up to ~400 µg/day (including by fluorescein staining, ophthalmologic evaluation, and slit lamp examination). No relevant treatment-related histopathological changes of the eye or other organs were noted. The toxicokinetic profile showed an increment of systemic exposure of MT6 (free acid of MT8), which did not increase proportionally with the dose level. Three genotoxicity studies have been completed. MT8 was non-mutagenic in an Ames Assay, did not induce chromosomal aberrations in human lymphocytes, and did not induce micronuclei in polychromatic erythrocytes.

Results of the safety pharmacology central nervous system (CNS) and respiratory study in rats show that MT8 at 0.1, 1 or 20 mg/kg had no effect on respiratory parameters or CNS activity in conscious male rats. There was no significant inhibition of human ether-a-go-go-related gene (hERG) by MT8 with half maximal inhibitory concentration values estimated to be > 30µM, and

no biologically relevant cardiovascular effects were observed with MT8 up to 4.725 mg/kg IV in conscious, telemetered, Beagle dogs.

The cumulative results of these studies demonstrate the safety of REC 0/0559, including when administered up to ~400µg/day by ocular route for up to 6 months or 30 mg/kg/day by SC route for 13 weeks.

Further details of nonclinical studies are in the investigator's brochure (IB).[16]

5.2.2 Clinical Studies

No clinical studies have been conducted by the Sponsor.

In a compassionate use investigator-based program conducted in Italy in 27 patients using the 25 µg/mL concentration 4 times per day, it was reported that most of the patients achieved healing of the corneal ulcer with MT8, with a good tolerability of the treatment.[17]

5.3 Study Rationale

Available nonclinical and clinical data indicate that MT8 could be efficacious in the treatment of patients with NK. The objective of this Phase 2 dose-ranging, double-masked, randomised, parallel-group, vehicle-controlled study is to demonstrate the safety and the efficacy of MT8 in patients with NK and to select the most appropriate dose.

The rationale for the design of the study is discussed in Section 7.2.

5.4 Clinical Risks/Benefits of MT8

The proposed clinical study intends to evaluate the pharmacokinetics (PK), safety and efficacy of REC 0/0559 in patients with NK. REC 0/0559 will be administered at the maximal MT8 dose of 5 µg/day (50 µg/mL concentration administered as 1 drop [(approximately 25 µL]), 4 times a day [QID]) for 8 weeks in this study.

In the 26-week rabbit study where ocular MT8 was administered, no local (including irritation of the conjunctivae, iris or cornea) or systemic toxicity was observed with a NOAEL of 400 µg/day. Based on these data, the safety margin in terms of doses administered is at least 600 fold for the highest dose planned in this clinical study. In addition, a low systemic drug concentration was observed in rabbits after ocular administration (the maximum concentrations after 180 days of treatment remained < 10 ng/ml). Of note, similar preliminary results were obtained the first day of administration of a 800 µg/day ocular dose in dogs. Considering that much lower doses will be administered to patients in this study and the difference in body mass and surface area, very low systemic exposure if any is expected in patients.

No clinical trial has been conducted with REC 0/0559 so far. The drug has been used in a compassionate use program, and though there are limitations of such an exploratory assessment, it was reported that most of the patients achieved corneal healing while no local or systemic AEs were reported.[17]

Based on these data, no specific MT8-related safety concern is expected.

REC 0/0559 is administered as eye drops. Common risks associated with eye drops are eye disorders such as ocular irritation or discomfort, eye or eyelid pain, increased lacrimation and blurred vision. Allergic reactions including of the skin in case of overflow have also been reported.

The drug product is formulated in a phosphate buffer, which has been associated in very rare cases with corneal calcifications in some patients with significantly damaged corneas. However, the EMA considered that the evidence did not warrant a restriction on the use of phosphate buffers in eye drops, with an appropriate notification to prescribers and patients.[18]

Specific study measures will be in place to ensure the safety and well-being of patients. The study will include a dose escalation and extensive safety and PK monitoring of the first 24 patients included. An independent data monitoring committee (DMC) will be set up to monitor patients' safety on an ongoing basis and to authorise enrolment to continue after the first 24 patients. Patients will keep their treatment by preservative-free eye drops and/or topical antibiotics (except tetracycline) as required, and at any time during the study the investigator can initiate a rescue treatment in case of clinical need such as disease worsening. In addition, women of childbearing potential will have urinary pregnancy tests and the use of a highly effective contraception method contraception is required. Men with partners of childbearing potential should use condoms. Finally, experienced and trained personnel will conduct the study procedures including the specific ophthalmologic assessments.

In conclusion, the rationale for the use of MT8 in NK, the available data (in particular the data supporting the very large safety margin) and the study measures planned to be in place collectively support a positive benefit risk ratio.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objectives

The primary objectives are:

- In the first 24 patients, to determine the safety, tolerability and PK profile of REC 0/0559 (MT8) given as 1 drop QID of escalating doses up to 50 µg/mL.
- To determine the efficacy and safety of MT8 given as 1 drop QID at 5, 25, and 50 µg/mL during 8 weeks and select the dose with the best benefit risk ratio.

6.2 Study Endpoints

6.2.1 Primary Efficacy Endpoint

The primary endpoint of this study is the percentage of patients achieving complete corneal healing of PED or corneal ulcer at Week 8, defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading centre.

6.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are described below:

The baseline value is defined as the last available measurement before the first administration of study treatment.

- Percentage of patients who achieve a 5-, 10-, and 15-letter mean improvement in best corrected distance visual acuity (BCDVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) chart at Week 8 compared to baseline (in all patients and in patients with a central location of the PED or corneal ulcer, respectively).
- Percentage of patients achieving complete corneal healing of PED or corneal ulcer at Week 8, defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by the investigator.
- Time to complete corneal healing of PED or corneal ulcer defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading.
- Time to complete corneal healing of PED or corneal ulcer defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by the investigator.
- Percentage of patients having deterioration of the disease at Week 8 (defined as increase in lesion size ≥ 1 mm as assessed by the investigator, or mean decrease in BCDVA by > 5 letters compared to baseline, or progression in lesion depth to corneal melting or perforation, or onset of infection).
- Mean change in BCDVA from baseline to Week 8 in all patients and in patients with a central location of the PED or corneal ulcer, respectively.

- Percentage of patients with improvement in corneal sensitivity from baseline as measured by Cochet-Bonnet aesthesiometer at Week 8.

6.2.3 Other Efficacy Endpoints

- Percentage of patients achieving complete corneal healing of PED or corneal ulcer at Week 8, defined as the greatest diameter of corneal fluorescein staining in the area of the PED or corneal ulcer < 0.5 mm as assessed by central reading.
- Percentage of patients achieving complete corneal healing of PED or corneal ulcer at Week 8, defined as the greatest diameter of corneal fluorescein staining in the area of the PED or corneal ulcer < 0.5 mm as assessed by the investigator.
- Percentage of patients achieving complete corneal clearing at Week 8, defined as a score of 0 using the Oxford scale.
- Time to at least 50% corneal healing (defined as a ≥ 50% reduction in the greatest diameter of the lesion) as determined by central reading.
- Time to at least 50% corneal healing (defined as a ≥ 50% reduction in the greatest diameter of the lesion) as determined by the investigator.
- Time to onset of healing (defined as a > 20% reduction in the greatest diameter of the lesion) as determined by central reading.
- Time to onset of healing (defined as a > 20% reduction in the greatest diameter of the lesion) as determined by the investigator.

6.2.4 Other Exploratory Endpoints

- Change from baseline in Quality of Life (QoL) evaluated using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25).
- Change from baseline in the overall numerical rating scale (NRS) score for ocular symptoms and tolerability.

6.2.5 Safety Assessment

Safety assessments will be conducted for all patients from the Screening Visit (upon the signature of the informed consent form [ICF]) to the end of the study.

Safety assessments include physical examination, ophthalmological examination, vital signs, 12-lead electrocardiogram (ECG), laboratory safety tests, and AE recording (including serious AEs [SAEs] and adverse events special interest [AESI]).

In addition, an independent DMC will be set up and monitor safety data on an ongoing basis during the enrolment of the first 24 patients (they will receive information related to any non-serious AEs that are considered to be severe and possibly related to the study drug, other AESI as defined in Section 12.7.2, any SAEs, or any serum drug concentration > 10 nM) and continue to monitor safety data regularly throughout the study. The DMC may also recommend discontinuing the

12-lead ECG assessment in the remaining patients (if no systemic exposure to the study drug is observed). Details are described in the DMC charter.

6.2.6 **Pharmacokinetic Assessment**

The PK parameters maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve during a dosage interval (AUCτ) of this study are as follows.

For the first 24 patients:

- At Day 1: predose, 10, 20, and 40 minutes, and 1, 2, and 4 hours after the first daily administration (last sampling before next dose administration)
- At Day 7 (±1 day): predose, 10, 20, and 40 minutes, and 1, 2, and 4 hours after the first daily administration (last sampling before next dose administration)

For all patients:

- At Day 28 (±2 days) 4 hours postdose but before the next administration
- At Day 56 (±3 days), 4 hours postdose

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This Phase 2, international, multicentre, dose-ranging, double-masked, randomised, parallel-group, vehicle-controlled study is designed to evaluate 3 different doses of REC 0/0559 versus vehicle in patients with Stage 2 and Stage 3 NK.

	Dose of MT8 per day	Study drug concentration
Dose 1	0.5 µg/day	5 µg/mL MT8 given 1 drop QID
Dose 2	2.5 µg/day	25 µg/mL MT8 given 1 drop QID
Dose 3	5 µg/day	50 µg/mL MT8 given 1 drop QID
Vehicle	0 µg/day	Vehicle given 1 drop QID

Abbreviations: QID, 4 times a day

Screening procedures (V1a) will be performed on Day -3, Day -2, Day -1, or on Day 1, prior to randomisation. The study will have an initial period of dose escalation followed by a parallel recruitment period. After confirmation of eligibility and signature of informed consent, patients will be randomly assigned to treatment with REC 0/0559 or vehicle on Day 1. Randomisation will be stratified by disease stage (Stage 2, Stage 3) and region (Europe, North America).

Randomisation of the first 24 patients will be sequential, with cohorts of 8 patients for each dose level randomised in a 3:1 ratio in each cohort (6 patients treated with REC 0/0559 and 2 with vehicle), starting with Dose 1. Patients will be enrolled sequentially in each next highest dose level 7 days after the 8th patient has been enrolled, unless the independent DMC issues a specific recommendation for a change in study conduct. The DMC will receive information related to any non-serious AEs that are considered to be severe and possibly related to the study drug and other AESI as defined in Section 12.7.2, to any SAE, or any serum drug concentration > 10 nM on an ongoing basis.

The initial dose escalation period of the protocol will proceed as follows:

1. The first 8 patients will receive Dose 1 (5 µg/mL REC 0/0559 administered 1 drop QID) or vehicle.
2. Seven days after the 8th patient has been enrolled at Dose 1, enrolment will start for the next 8 patients who will be treated with Dose 2 (25 µg/mL REC 0/0559 administered 1 drop QID) or vehicle, unless the DMC issues a specific recommendation for study conduct related to the safety information received on an ongoing basis.
3. Seven days after the 8th patient has been enrolled at Dose 2, enrolment will start for the next 8 patients who will be treated with Dose 3 (50 µg/mL REC 0/0559 administered 1

drop QID) or vehicle, unless the DMC issues a specific recommendation for study conduct related to the safety information on an ongoing basis.

The DMC will confirm in writing that the enrolment and dose escalation to a next dose level can continue based on the safety data received, if any (AESI, SAE, PK).

The DMC can recommend discontinuing the treatment at any time before the formal review of the data from the first 24 patients.

Once the 24th patient has been enrolled, enrolment of new patients will be put on hold and the DMC will perform a formal review of all the safety and PK data available before enrolment of new patients is resumed. The treatment of the first 24 patients will continue as planned. The DMC may also recommend discontinuing the 12-lead ECG assessment in the remaining patients (if no significant systemic exposure to the study drug is observed).

If no study discontinuation or change in the protocol design is recommended after the formal DMC review of all safety data for the first 24 patients, enrolment will resume and patients will be randomised to all 4 treatment arms in a 1:1:1:1 ratio until approximately 27 patients are enrolled in each arm (approximately 108 patients total). Another formal review of the data by the DMC will be conducted 8 weeks after approximately 50% of patients (54 patients) have been enrolled.

During the double-masked treatment period, all patients will administer 1 drop (approximately 25 µL) REC 0/0559 or vehicle in the study eye QID at 4 hour intervals ± 30 minutes (starting in the morning) for 8 weeks.

Patients will be followed up for 4 weeks after the end of treatment.

Details related to the DMC are in Section 15.8.

At any time during the study, the investigator can discontinue the study drug and initiate a rescue treatment if clinically required (eg, in the case of worsening of disease).

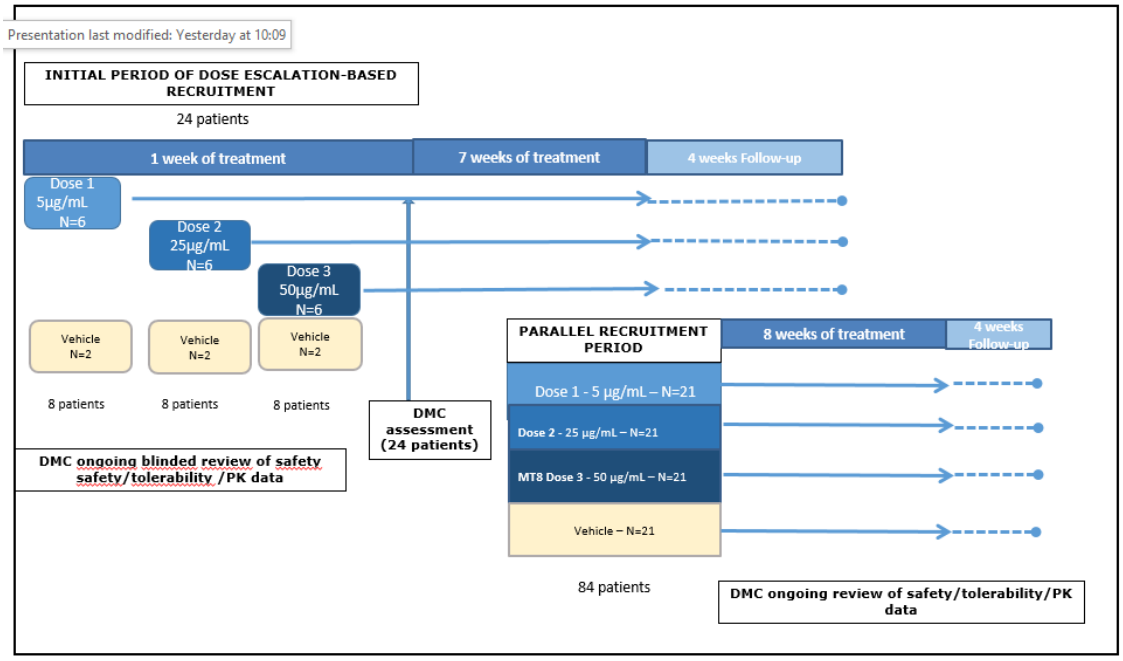
In case of study drug discontinuation for any reason, including when a rescue therapy is started, the patient will be asked to stay in the study and perform all the visits and assessments as planned (except in cases where the patient has withdrawn consent for study participation). Patients who discontinue study drug should at least complete the Early Termination and Follow-up Visits if possible.

Study procedures will be performed according to the schedule in Table 2 and as described in Sections 10, 11 and 12. A central laboratory will be used for haematology, biochemistry, and PK sample analysis. Central reading will be performed for the fluorescein stain test as described in Section 11.1.2. In addition, QoL will be evaluated using the NEI VFQ-25.

No formal interim analysis is planned for the study.

A diagram of the study design is presented in Figure 1.

Figure 1 Study Design



Abbreviations: DMC, data monitoring committee; PK, pharmacokinetic.

7.2 Discussion of Study Design

The objective of this Phase 2 dose-ranging, double-masked, randomised, parallel-group, vehicle-controlled study is to demonstrate the safety and the efficacy of MT8 in patients with NK and to select the most appropriate dose.

Patients will be adults with moderate (Stage 2, PED) to severe (Stage 3, corneal ulcer) NK, affecting one eye and not improved by conventional non-surgical treatment. It is planned to include 108 patients in total (27 per arm).

In this clinical study, REC 0/0559 will be administered at 3 different doses (5, 25, and 50 µg/mL) or vehicle given as 1 drop in the study eye, QID at 4 hour intervals ± 30 minutes starting in the morning for 8 weeks, followed by a 4 week follow-up without treatment.

The study includes a first period of thorough safety and PK analysis in 24 patients involving a DMC to ensure patient safety. Recruitment will be sequential, starting with the lowest dose of REC 0/0559 and then with the next higher doses if the treatment is well tolerated.

The proposed starting dose of 5 µg/mL is derived from the in vivo and in vitro non clinical pharmacological models having shown the pharmacological activity of this low dose of MT8 (10 µM). The intermediate 25 µg/ml dose was shown to be possibly efficacious and well tolerated during the compassionate use of MT8 in 27 patients with NK. The highest dose of 50 µg/mL was chosen to evaluate if efficacy or time to achieve the healing improves.

The administration schedule (QID for 8 weeks) was the same as in the exploratory compassionate use program. An 8-week treatment duration was shown to be appropriate for achieving healing with rhNGF (cenegermin) and MT8 in the compassionate use program. The 4-week follow-up is intended to collect safety data (AEs) as well as clinical and ophthalmological data after study drug discontinuation. Based on the short half-life observed in animal data, elimination of the drug is expected to be rapid.

The primary endpoint will capture complete corneal healing assessed conservatively as no corneal fluorescein staining in the area of the prior PED or corneal ulcer by an independent central reading centre made of experienced and trained readers masked to the treatment group. A separate manual will detail the procedures used for central reading, including clinical picture collection method(s) and definitions for central reading assessment. In addition, the assessment of corneal healing by the investigator will be a secondary endpoint. The assessment of corneal healing using a definition taking into account the lower limit of reliable slit lamp assessment ie, < 0.5 mm lesion staining will be also collected.

7.3 End of Study

A patient will have fulfilled the requirements for study completion if/when the patient has completed all study periods, including End of Treatment or Early Termination Visit and the last Follow-up Visit as indicated in the Schedule of Assessments (Table 2).

The end of the study will be the last patient's last assessment as indicated in the Schedule of Assessments.

After the end of this study, REC0/0559 will not be available to patients. Patients will not be restricted with regard to pursuing available treatments for NK.

7.4 Early Termination of Study

The Sponsor may decide at any time with appropriate notification to prematurely terminate or suspend the participation of a particular clinical trial centre (eg, for lack of subject enrolment or noncompliance with clinical trial protocol, regulations, or Good Clinical Practice [GCP]) or prematurely suspend the clinical trial (eg, for reasons of safety, quality of study drug, regulatory, legal, or other reasons aligned with GCP).

8 SELECTION OF STUDY POPULATION

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Have read, understood, and signed the ICF.
2. Be a male or female aged ≥ 18 years at the time of ICF signature.
3. Have Stage 2 moderate (PED) or Stage 3 severe (corneal ulcer) NK involving only 1 eye (study eye) and of at least 2 weeks duration. Patients with Stage 1 NK in the fellow eye can be enrolled.

- For the study eye:

4. Have no objective clinical evidence of improvement in the PED or corneal ulceration within the 2 weeks before the Screening Visit despite use of conventional non-surgical treatment (eg, nonpreserved ocular lubricants, nonpreserved topical antibiotics, oral doxycycline, patching, serum tears, and/or therapeutic contact lenses) as determined by the investigator's or referring physician's medical record.
5. Have decreased corneal sensitivity (≤ 4 cm using the Cochet-Bonnet aesthesiometer) within the area of the PED or corneal ulcer and outside of the area of the defect in at least one corneal quadrant.
6. Have a BCDVA score ≤ 75 ETDRS letters in the study eye, due to NK.

8.2 Exclusion Criteria

Individuals meeting any of the following criteria at the Screening Visit are ineligible to participate in this study:

1. Have participated in any clinical trial with an investigational drug/device within 2 months before the Screening Visit and throughout the study duration.
2. Have a known hypersensitivity to one of the components of the study drug or procedural medications (eg, fluorescein), including to a compound chemically related to MT8.
3. Have a presence or history of any ocular or systemic disorder or condition that might hinder the efficacy of the study treatment or its evaluation, could possibly interfere with the interpretation of study results, or could be judged by the investigator to be incompatible with the study visit schedule or conduct (eg, progressive or degenerative corneal or retinal conditions, lagophthalmos, uveitis, optic neuritis, poorly controlled diabetes, autoimmune disease, systemic infection, neoplastic diseases), or that may compromise the safety of the patient.
4. Have a significant history of alcohol abuse or drug/solvent abuse (within the last 2 years).
5. Be unwilling to comply with any study assessments or procedures.
6. Be a woman who is pregnant, nursing or planning a pregnancy.
7. Be a woman of childbearing potential who is not using a highly effective method of birth control. For non-sexually active females, true abstinence (when in line with the preferred and usual lifestyle of the subject) may be accepted as an adequate method of birth control; however, if the patient plans to become sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study and for 4 weeks after the end of study treatment.[19] For the definition of childbearing potential and list of highly effective methods of contraception, see APPENDIX 1.
8. Be a male patient who is not permanently sterile and who is not willing to use condoms during the study and for 4 weeks after the end of study treatment. Male patients whose partners are not of childbearing potential are not required to use condoms.

For the study eye:

9. Have any active ocular infection (bacterial, viral, fungal or protozoal) or active inflammation not related to NK in the study eye.
10. Have any other ocular disease requiring topical ocular treatment in the study eye during the course of the study treatment period, except for glaucoma if treated by preservative-free eye drop (single-agent treatment, once daily, stable regimen 4 weeks before screening and during the study).
11. Receive topical ophthalmological treatments other than the study drug provided by the study Sponsor and the treatments allowed by the study protocol (eg, preservative-free artificial tears; preservative-free eye drop (single-agent treatment, once daily, stable regimen 4,weeks before screening and during the study) for glaucoma; topical antibiotics; other than tetracycline; see Section 9.6.1).
12. Have severe blepharitis and/or severe meibomian gland disease in the study eye.

13. Have severe vision loss in the study eye with no potential for visual improvement in the opinion of the investigator as a result of the study treatment.
14. Have evidence of corneal ulceration/melting involving the posterior third of the corneal stroma, or perforation in the study eye.
15. Have a history of any ocular surgery (including laser or refractive surgical procedures) within 3 months before the Screening Visit in the study eye. An exception to the preceding statement will be allowed if the ocular surgery is considered to be the cause of the Stage 2 or 3 NK. Ocular surgery will not be allowed during the study treatment period and elective ocular surgery procedures in the study eye should not be planned during the duration of the study.
16. Have a history of corneal transplantation in the study eye performed less than 12 months prior screening.
17. Have had prior surgical procedures for the treatment of NK (eg, complete tarsorrhaphy, conjunctival flap, etc.) except partial tarsorrhaphy if done more than 6 months prior to screening visit (with investigators assessment documenting that the eye lids are functioning sufficiently to ensure adequate protection of the eye) and amniotic membrane transplantation, if at least 2 weeks after the membrane has disappeared within the area of the PED or corneal ulcer (and at least 6 weeks after the procedure) in the study eye.

    Patients previously treated with Botox® (Botulinum toxin) injections used to induce pharmacologic blepharoptosis are eligible for enrolment only if the last injection was given at least 3 months before the Screening Visit.
18. Use therapeutic contact lenses or wear contact lenses for refractive correction during the study treatment periods in the eye(s) with NK.
19. Have an anticipated need for punctal occlusion during the study treatment period. Patients with punctal occlusion or punctal plugs inserted before the study are eligible for enrolment provided that the punctal occlusion is maintained during the study.
20. Have an uncontrolled glaucoma at the Screening Visit. Patients suffering from glaucoma requiring ophthalmic drops for topical treatment at the Screening Visit or during the study are not eligible, except if the ophthalmic drops is a preservative-free treatment administered maximum once daily as a single-agent treatment and at a stable regimen 4 weeks before screening and at the same dose during the study. Patients treated with oral intraocular pressure-lowering drugs at the Screening Visit and during the study may be enrolled if their glaucoma status is assessed as stable and controlled.

For the fellow eye:

21. Have Stage 2 or 3 NK or perforation.

For any eye:

22. Have a history of ocular cancer.
23. Have had prior treatment with Oxervate (cenegermin eye drops).

8.3 Rescreening

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria (screen failures) may be rescreened once, provided the investigator assesses and documents that the patient's condition(s) may evolve in order to allow enrolment.

8.4 Study Withdrawal, Removal, and Replacement of Patients

Withdrawals will not be replaced (neither withdrawals from study drug, nor withdrawals from the study).

8.4.1 Withdrawal from Study Drug

Patients permanently withdrawn from study drug should not be withdrawn from the study and, apart from study drug administration, should continue all scheduled study visits and procedures until the end of the scheduled treatment period at Day 56/Visit 8 (±3 days) to ensure complete follow-up (except in cases where the patient has withdrawn consent for study participation). The Follow-up Visit should take place 4 weeks after Day 56/Visit 8 (±3 days) regardless the date of definitive study drug discontinuation. If this is not possible, patients will be at least asked to return to the study site as soon as possible to complete the Early Termination and Follow-up Visit assessments as indicated in the Schedule of Assessments (Table 2).

If a patient discontinues study drug for any reason, the study site must immediately notify the medical monitor. The date and the reason for discontinuation must be recorded on the electronic case report form (eCRF).

In the event that a patient discontinues study drug prematurely because of a treatment-emergent adverse event (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilises, or until it is judged by the investigator to no longer be clinically significant.

A patient may be withdrawn from the study drug at any time for reasons including, but not limited to, the following:

- Progressive disease: A rescue treatment may be initiated by the investigator according to clinical judgment as described in Section 9.6.2.
- Unacceptable toxicity or AE
- General or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria (eg, suspected hypersensitivity to the study drug, pregnancy, etc)

Corneal healing is not a reason that study drug should be withdrawn before the end of the 8-week treatment period.

8.4.2 Withdrawal from the Study

Patients may withdraw from the study at any time for any reason without jeopardy or prejudice or compromising their clinical care. However, every effort should be made to adhere to as many study assessments as possible. If a patient indicates that he/she wishes to withdraw from the study, whenever possible, the patient should be seen by the investigator and the procedures for the Early Termination Visit should be performed (refer to Table 2).

A patient may be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Patient withdrawal of consent: At any time, a patient's participation in the study may be terminated at his/her request or on the basis of the investigator's clinical judgment. The reason for patient withdrawal will be noted on the eCRF.
- Patient fails to adhere to the protocol requirements (eg, drug noncompliance, failure to return for study visits).
- Lost to follow-up: The patient did not come for 3 visits, and study personnel were unable to contact the patient for at least 8 weeks.
- Pregnancy, as indicated in Section 12.8
- The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, (S)AEs, and administrative or other reasons. Data for all visits to the point of withdrawal must be recorded in the patient's medical record and in the eCRF.

The data to be collected for patients who withdraw from the study should include:

- Date of withdrawal from the study
- Reason for withdrawal from the study
- Data on assessments conducted (if possible) as part of the Early Termination Visit as described in Table 2
- Data on any (S)AEs present at the time of withdrawal from the study

The investigator will follow patients who are withdrawn from the study as a result of an (S)AE until the event has resolved, subsided, stabilised or until the event is otherwise explained or the patient is lost to follow-up (refer to Section 12.7.4). If withdrawal from the study is a result of a SAE or pregnancy, the SAE/pregnancy will need to be reported and followed up as described in Section 12.7.4 and Section 12.8 respectively.

After study withdrawal, treatment will be decided by the investigator according to clinical judgment and may consist of topical, oral or surgical treatment.

9 TREATMENTS

9.1 Details of Study Treatments

The drug product REC 0/0559 is an ophthalmic solution packaged in single-use blow fill seal (BFS) containers. The solution will be stored at room temperature (below 25°C).

Patients are to use a single BFS container per study drug administration (ie, 4 BFS containers per day).

Three strengths (5, 25, and 50 µg/mL) of ophthalmic solution with MT8 will be prepared, one for each active treatment arm.

For the comparator, an ophthalmic solution of the same composition as the study drug without the active substance MT8 (vehicle) will be used. The vehicle is identical in appearance and packaging to the study drug, and study drugs are labelled in a masked manner.

All study drug will be provided by the Sponsor and will be packaged and labelled in accordance with the principles and the detailed guidelines of Good Manufacturing Practice (GMP) for Medicinal Products. The primary label as well as the secondary container labelling will be in country specific language. Label contents will be compliant with local regulatory requirements. All study drug provided will be stored in a secure locked area with access limited to those authorised by the investigator and under controlled storage conditions described in the product's labelling.

For each patient entering in the study, the investigator will be provided with a set of numbered study drug kits each containing 4 pouches of 10 eye drop solution single dose units (BFS containers) with 0.5 mL each of REC 0/0559 (5, 25, or 50 µg/mL) or vehicle. Each study drug kit will provide treatment for a period of 7 days, and contain treatment for 3 additional days as spare.

9.2 Dosage Schedule

Patients will be directed to administer, by themselves or with assistance from a relative or caregiver, 1 drop of study drug (approximately 25 µL) 4 times a day at 4-hour intervals (± 30 minutes) starting in the morning in the study eye, for the duration of the 8-week double-masked treatment period. If a drop does not reach the eye during study drug administration, a second drop should be administered from the same BFS container.

The total daily dose for the vehicle and 5, 25, and 50 µg/mL arms will therefore be 0, 0.5, 2.5 and 5 µg/day.

On Day 1, the total number of drops administered may be adapted depending on the time of first dose administration (ie, a decreased number of administrations may occur if treatment is started in the afternoon).

On Day 7/Visit 3 (±1 day), the first 24 patients enrolled in the study will be required to take their first daily dose of study drug at the study site.

Administration of any other topical treatments in the eye is required to take place at least 15 minutes before or after REC 0/0559 administration, and it is highly recommended to administer other topical treatments at least 1 hour before or after REC 0/0559 administration.

If clinically required, study drug can be continued, temporarily interrupted, or stopped at the discretion of the investigator, as described in Section 8.4.1. If study drug is interrupted, when medically possible and indicated, study drug should be restarted.

9.3 Measures to Minimise Bias: Study Drug Assignment and Masking

9.3.1 Method of Study Drug Assignment

Patients will be randomly assigned by central randomisation to 1 of the 4 treatment groups. Randomisation will be stratified by disease stage and region. The first 24 patients will be assigned in a 3:1 ratio to active treatment (1 drop QID of either 5, 25, or 50 µg/mL MT8) or vehicle, starting with the 5 µg/mL dose of MT8. Enrolment will proceed sequentially to the next highest dose level unless the DMC recommends a change (that can occur at any time based on ongoing review of the safety, tolerability, and PK data). After a formal DMC review of all safety, tolerability, and PK data in the first 24 patients (6 each assigned to 1 drop QID of 5, 25, and 50 µg/mL MT8, and 6 vehicle), if the DMC does not recommend any change to the dosing schedule, patients will be enrolled in all 4 treatment arms in a 1:1:1:1 ratio.

Randomisation will be performed through an interactive web response system (IWRS) integrated in the eCRF (Randomisation and Trial Supply Management module). The randomisation request, randomisation number allocation, and study drug kit number allocation at selected visits will be performed in the eCRF.

At each site, Subject ID number will be assigned by IWRS to patients who have consented to participate in the study. Data obtained for each patient will be identified with the Subject ID number.

9.3.2 Masking

The study is investigator-masked and patient-masked (investigators and patients will not have knowledge of the treatment or dose received). The Sponsor and study monitor will also be masked during the study. All assessments of efficacy and safety will be performed by a masked investigator (or other qualified, masked study staff member).

The investigator or designee will obtain the study drug kit number from the IWRS for the patient according to the randomisation schedule as indicated in the Schedule of Assessments (Table 2). The allocated study drug will be delivered to the patient in accordance with the pharmacy manual by the pharmacist or designee at the study centre.

No study site personnel, patients, Sponsor personnel, or Sponsor designees will be unmasked to treatment assignment throughout the duration of the study unless unmasking is required. If an investigator becomes unmasked to a given patient's study treatment, that patient will be discontinued from the study drug unless there are ethical reasons for that patient not to be discontinued; approval from the medical monitor must be obtained in such instances.

Any unmasking at the study site level should be done only in an emergency that requires the study treatment to be identified for the medical management of the participant. In the event that emergency unmasking is required for a given patient because of AEs or concerns for the patient's safety, the investigator may break the randomisation code for the patient via the IWRS, by which system the unmasking will be captured. The investigator is responsible for notifying the medical monitor and/or Sponsor of such an event as soon as possible. The unmasking and its cause will also be documented in the eCRF.

9.4 Dosage Modification

Dosage modification is not allowed, as the study is conducted in a double-masked manner. Patients should receive the study drug with the agreed frequency and in the concentration assigned by the randomisation system.

Patients who do not tolerate study drug or experience worsening disease may be withdrawn from study drug as described in Section 8.4.

9.5 Treatment Accountability and Compliance

The investigator will be responsible at the site level for maintenance of records of study drug delivered to the study site, the inventory at the study site, the distribution to and use by each patient, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, batch numbers, expiration dates, in-clinic temperature log, and study drug kit numbers assigned.

At each visit after initiation of treatment, study site personnel will record compliance of the patient with the patient's assigned regimen. Patients will be instructed to bring their unused/partially used/empty containers back for inspection at each study visit and the number of opened BFS containers will be recorded. Patients will also be instructed to fill out a paper diary recording the date and time of study drug administration, which should be brought to the site at each study visit and reviewed with the patient. Patients are to be reminded of the importance of compliance with their assigned regimen, with an emphasis on taking their study drug on schedule and maintaining the prescribed interval between doses.

At each study visit during the treatment period, the patient will have to bring back used and unused BFS as well the diary. At Day 3 (±1 day) Visit, the investigator should review the patient's diary in order to discuss with the patient any issue in compliance so that this is corrected by the Day 7 (±1 day) Visit.

Patient compliance with the treatment will be assessed at each study visit during the treatment period.

Investigators will maintain records that adequately document that the patients were provided with the correct study drug kits and reconcile the products received from the drug dispensing centre. Study drug will not be returned to the Sponsor until accountability has been fully monitored.

Study drug kits must be returned at each visit, as compliance will be assessed by number of opened BFS containers. Noncompliance is defined as taking less than < 80% or more than 120% of study drug during any outpatient evaluation period (visit to visit). Discontinuation of treatment for noncompliance is at the investigator's discretion and is to be noted on the eCRF.

Upon completion or termination of the study, all remaining study drug will be retained according to applicable regulations. Once the retention period has elapsed, any remaining drug will be returned to the Sponsor in the original containers, or destroyed, as directed in writing by the Sponsor.

9.6 Prior and Concomitant Therapy

9.6.1 Prior and Concomitant Therapies

Restricted Prior Therapies

The following prior surgical therapies are restricted in the study eye:

- Prior surgical therapies for NK including but not limited to complete tarsorrhaphy, partial tarsorrhaphy done less than 6 months prior screening, conjunctival flap
- Amniotic membrane transplantation administered less than 6 weeks before the Screening Visit, or if less than 2 weeks have elapsed since the membrane has disappeared within the area of the PED or corneal ulcer
- Any ocular surgery including laser or refractive procedure within 3 months before the Screening Visit (unless the surgery is considered to be the cause of Stage 2 or 3 NK)
- Any history of corneal transplantation performed less than 12 months prior screening

The following prior drug therapies are restricted:

- Prior treatment with botulinum toxin injection to induce pharmacologic blepharoptosis is not allowed for 90 days before the Screening Visit (in study eye)
- Prior treatment with Oxervate (cenegermin eye drops) (in any eye)

Restricted Concomitant Therapies in the Study Eye (Unless Rescue Therapy; See Section 9.6.2)

Restricted surgical therapies in the study eye during the study are:

- Any ocular surgery.
- Surgical treatment of NK including but not limited to tarsorrhaphy, conjunctival flap, or amniotic membrane transplantation.
- Punctal occlusion (eg, plugs) or punctal coagulation applied after the Screening Visit. Patients with punctal occlusion or punctal plugs inserted before the study should have the punctal occlusion maintained during the study.

Use of contact lenses is not allowed during study (either therapeutic contact lenses or contact lenses for refractive correction) and should be stopped at the Screening Visit.

All medications and other treatments taken by the patient during the study, including those treatments initiated before the start of the study, must be recorded on the eCRF.

Medications taken by or administered to the patient for the time period before the Screening Visit will be recorded in the eCRF. Any medications considered necessary for the patient's welfare, and that are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator, except for the treatments noted below which are not allowed during the study:

- Oxervate (cenegermin eye drops)
- Serum tears (should be stopped before the Screening Visit and are not allowed during treatment period)
- Topical ophthalmological treatments other than the study drugs provided by the study Sponsor and those listed below (Allowed Concomitant Therapies) are not allowed during the study including anti-viral topical and tetracycline ophthalmic treatment
- Botox (botulinum toxin) injections for pharmacological blepharoptosis

Allowed Concomitant Therapies

Topical ophthalmological treatments approved to be used during the study are:

- Preservative-free artificial tears (it is recommended to maintain a stable regimen during the study)
- Preservative-free topical antibiotics except topical tetracycline (if preservative-free antibiotic drops are not available, it is highly recommended to administer antibiotic drops with preservatives not more than once daily)
- Preservative-free anti glaucoma eye drop treatment only if administered maximum once daily as a single-agent treatment and at a stable regimen 4 weeks before screening and at the same dose during the study
- If possible, it is recommended to avoid formulations containing phosphate compounds

Administration of any other topical treatments in the eye is recommended to take place at least 1 hour before or after REC 0/0559 administration (and should not be administered less than 15 minutes before or after REC 0/0559).

Preventive anti-viral systemic treatment for herpes simplex virus (oral) is allowed (on a stable basis).

Generally, drugs needed to treat diseases causing NK (eg, diabetes) should be continued as required to ensure an appropriate treatment of the background disease.

COVID-19 vaccines will be considered as a concomitant medication and will be reported in the eCRF as described below.

Any medication or therapy that is taken by or administered to the patient during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

9.6.2 **Rescue Medications**

Anytime during the study, investigator can initiate a rescue treatment if clinically required (eg, if the disease worsens). Study drug should be discontinued. The rescue treatment will be decided by the investigator according to clinical judgment and may consist of topical, oral or surgical treatment. Rescue treatment will not be supplied by the Sponsor.

10 STUDY PROCEDURES

Table 2 outlines the timing of procedures and assessments to be performed throughout the study. Section 12.6 specifies laboratory assessment samples to be obtained.

Assessments and procedures scheduled at a visit where study drug is administered should be performed before administration of study drug unless otherwise indicated in the Schedule of Assessments (Table 2).

Efficacy assessments are described in Section 11 and include slit lamp examination, fluorescein staining, corneal sensitivity, and BCDVA examination.

Safety assessments are described in Section 12 and include vital signs, physical examinations, ECGs, laboratory assessments, AEs, and dilated fundus ophthalmoscopy.

The NEI VFQ-25 will be used to assess QoL. Ocular symptoms and tolerability will be evaluated by NRS.

The investigator may, at his/her discretion, arrange for a patient to have an unscheduled visit/assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of study drug.

Study discontinuation procedures are described in Section 8.4.

Table 2. Schedule of Assessments

	Screening	Treatment Period								Follow-Up Period		ET
Visit at Week	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**6**	**8 End of Treatment Visit**	**10**	**12**	
Study Day **Allowed time window**	**D-3 to D1**	**D1**	**D3 ±1**	**D7 ±1**	**D14 ±2**	**D21 ±2**	**D28 ±2**	**D42 ±3**	**D56 ±3**	**D70 ±7**	**D84 ±7**	
Visit Number	**V1a [a]**	**V1b [a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	
Informed consent	X											
Inclusion/exclusion criteria	X											
Medical history	X											
Demographics	X											
NEI VFQ-25		X					X		X			X
Randomisation		X										
Clinical Evaluations												
Vital signs [b]	X	X [c]	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X [c]	X	X	X	X	X	X	X	X	X	X
Height and weight [d]	X								X			X
12-lead electrocardiogram [e]		X					X		X		X	X
Concomitant medication review	X	X [c]	X	X	X	X	X	X	X	X	X	X
(S)AE reporting	X	X	X	X	X	X	X	X	X	X	X	X
Ocular symptoms and tolerability (NRS)		X	X	X	X	X	X	X	X	X	X	X
Ophthalmological Evaluations												
BCDVA	X			X	X	X	X	X	X	X	X	X
Slit lamp examination	X		X	X	X	X	X	X	X	X	X	X
Corneal photo without fluorescein	X		X	X	X	X	X	X	X	X	X	X
Fluorescein stain test and corneal photo	X		X	X	X	X	X	X	X	X	X	X

	Screening	Treatment Period								Follow-Up Period		
Visit at Week	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**6**	**8 End of Treatment Visit**	**10**	**12**	**ET**
Study Day **Allowed time window**	**D-3 to D1**	**D1**	**D3 ±1**	**D7 ±1**	**D14 ±2**	**D21 ±2**	**D28 ±2**	**D42 ±3**	**D56 ±3**	**D70 ±7**	**D84 ±7**	
Visit Number	**V1a** [a]	**V1b** [a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	
Corneal sensitivity	X								X		X	X
Fundus examination	X			X					X		X	X
Schirmer test	X											
Laboratory Evaluations												
Haematology [f]		X					X		X			X
Biochemistry [g]		X					X		X			X
Urine pregnancy test [h]	X								X		X	X
PK sample		X [i]		X [i]			X [j]		X [j]			
Study Drug												
Dispensation of study drug kits[k]		X		X	X	X	X	X				
Administration of study drug		→										
Collection of used/unused study drug containers				X	X	X	X	X	X[l]			X
Review of study drug diary			X	X	X	X	X	X	X			X
Assess compliance			X	X	X	X	X	X	X			X

Abbreviations: AE, adverse event; BCDVA, best corrected distance visual acuity; ET, early termination; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; NRS, numerical rating scale; PK, pharmacokinetic.

[a] Procedures in Visit 1a may take place on Day -3, Day -2, Day -1 prior to V1b, or on the same day as Visit 1b (Day 1), prior to randomisation. All procedures listed under Visit 1a are to be completed as part of the Screening Visit before initiating Visit 1b procedures.

[b] Vital signs include blood pressure and heart rate.

[c] If Visit 1a and Visit 1b take place on the same day, these procedures do not need to be repeated.

[d] Height will be measured only at Visit 1a.

[e] ECGs will be performed as planned for the first 24 patients. After formal review of data from the first 24 patients, the DMC may decide to discontinue ECG examination for other patients.

[f] Haematology tests will include full and differential blood count, haematocrit, haemoglobin, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, and white blood cell count with differential.

[g] Serum biochemistry tests will include albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen or urea, creatinine, electrolytes (sodium, potassium, chloride, calcium, phosphorus), gamma-glutamyl transpeptidase, glucose, lactate dehydrogenase, total bilirubin, direct bilirubin, total cholesterol, and triglycerides.

[h] Only in women of childbearing potential.

[i] Day 1 and Day 7 (±1 day) PK sampling will be done for the first 24 patients only. On Day 1 and Day 7 (±1 day), PK samples will be obtained predose, and postdose PK samples will be obtained at 10, 20, and 40 minutes, and 1, 2, and 4 hours after the first daily administration (but before the next administration). On Day 7 (±1 day), patients should be instructed not to take their first dose of study drug before the clinic visit, so that the predose PK sample can be obtained.

[j] Trough PK sampling will be done for all patients, at day 28 (±2 days), 4 hours postdose but before the next administration and at Day 56 (±3 days), 4 hours postdose. Patients should administer study drug before the clinic visit and record the time of study drug administration in the study drug diary, so that timing for the PK sampling can be determined.

[k] At visit 1b, provide patient with study drug diary and instruction how to fill it out.

[l] Visit 8 is the last day of study drug administration. After last study assessments belonging to Visit 8, no more study drug administration is allowed.

10.1 Informed Consent

Before performing any study-related procedures, the investigator (or designee) will obtain written informed consent from the patient as described in Section 16.1.3.

An identification number will be assigned via IWRS to each patient who has consented to participate in the study.

In the event that rescreening occurs, the individual is required to sign a new ICF and must be assigned a new identification number.

10.2 Visit 1a (Screening Visit – Day -3 to Day 1)

At the Screening Visit, the patient's eligibility for study participation will be determined by checking all inclusion and exclusion criteria as specified in Section 8.

Medical history will be recorded at the Screening Visit. Investigators should document the occurrence, signs, and symptoms of all prior significant illnesses. Medical conditions ongoing at the time when informed consent is given or at the Screening Visit (Visit 1a) are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 12.7. All changes not present at the Screening Visit or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all patients and include year of birth, sex, ethnic origin (race) and iris colour.

The Screening Visit (Visit 1a) will entail the following evaluations:

- Inclusion/exclusion criteria
- Medical history
- Demographics
- Concomitant medications
- Recording of (S)AEs
- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- Measure height and weight
- Review of concomitant medications
- BCDVA – **both eyes**
- Slit lamp examination – **both eyes**

- Corneal photo without fluorescein **– both eyes**
- Fluorescein stain test and corneal photo– **both eyes**
- Corneal sensitivity – **both eyes**
- Fundus examination – **both eyes**
- Schirmer test without anaesthesia
- Urine pregnancy test (for females of childbearing potential)

10.3 Visit 1b (Day 1; First Administration of Study Drug)

If the patient is considered eligible based on the investigator's assessment at the Screening Visit, the patient should be assigned to study treatment as described in Section 9.3.1 and complete the following procedures. These can take place on the same day as the Screening Visit or up to 3 days after the screening visit:

- Recording of (S)AEs
- Randomisation
- NEI VFQ-25
- Measurement of vital signs (blood pressure and heart rate; only if Visit 1a and Visit 1b are not on the same day)
- Physical examination (only if Visit 1a and Visit 1b are not on the same day)
- 12-lead electrocardiogram
- Review of concomitant medications (only if Visit 1a and Visit 1b are not on the same day)
- Assessment of ocular symptoms and tolerability (NRS)
- Blood sampling for:
    - Haematology
    - Biochemistry
    - PK sample (predose) – only for the first 24 patients enrolled
- Dispensation of study drug kit. Instruct patient to bring back used and unused study drug kit at each visit
- Dispensation of patient diary and provide instruction how to fill it out.
- Administration of study drug – **study eye**
- Blood sampling for PK analysis (postdose at 10 minutes (+/- 5 min), 20 minutes (+/- 10 min), and 40 minutes (+/- 10 min), and 1 hour (+/- 15 min), 2 hour (+/- 20 min), and 4 hour

(+/- 60 min) after the first daily administration [but before the next administration]; only for the first 24 patients enrolled)

10.4 Visit 2 (Day 3 ±1)

The following procedures will be performed:

- Review of concomitant medications
- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- Assessment of ocular symptoms and tolerability (NRS)
- Slit lamp examination – **study eye**
- Corneal photo without fluorescein **– study eye**
- Fluorescein stain test and corneal photo – **study eye**
- Review of study drug diary and compliance assessment
- Recording of (S)AEs

10.5 Visit 3 (Day 7 ±1)

The first 24 patients should be instructed not to take their first dose of study drug before the clinic visit, so that the predose PK sample can be obtained.

The following procedures will be performed:

- Collection of used and unused study drug containers and compliance assessment
- Review of study drug diary
- Recording of (S)AEs
- Review of concomitant medications
- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- Assessment of ocular symptoms and tolerability (NRS)
- BCDVA – **study eye**
- Slit lamp examination – **study eye**
- Corneal photo without fluorescein **– study eye**
- Fluorescein stain test and corneal photo– **study eye**
- Fundus examination – **study eye**

- Blood sample for PK analysis (predose; only for the first 24 patients enrolled)
- Dispensation of study drug kits
- Administration of study drug – **study eye** (only done at the site for the first 24 patients enrolled)
- Blood samples for PK analysis (postdose at 10 minutes (+/- 5 min), 20 minutes (+/- 10 min), and 40 minutes (+/- 10 min), and 1 hour (+/- 15 min), 2 hour (+/- 20 min), and 4 hour (+/- 60 min) after the first daily administration [but before the next administration], only for the first 24 patients enrolled)

10.6 Visit 4 (Day 14 ± 2) and Visit 5 (Day 21 ± 2)

The following procedures will be performed:

- Collection of used and unused study drug containers and compliance assessment
- Review of study drug diary
- Recording of (S)AEs
- Review of concomitant medications
- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- Assessment of ocular symptoms (NRS)
- BCDVA – **study eye**
- Slit lamp examination – **study eye**
- Corneal photo without fluorescein **– study eye**
- Fluorescein stain test and corneal photo – **study eye**
- Dispensation of study drug kits

10.7 Visit 6 (Day 28 ± 2)

Patients should administer study drug before the clinic visit, and record the time of study drug administration in the study drug diary, so that timing for the postdose PK sampling can be determined and timing of ECG recorded.

The following procedures will be performed:

- Collection of used and unused study drug containers and compliance assessment
- Review of study drug diary
- Recording of (S)AEs
- Review of concomitant medications

- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- 12-lead electrocardiogram
- NEI VFQ-25
- Assessment of ocular symptoms (NRS)
- BCDVA – **study eye**
- Slit lamp examination – **study eye**
- Corneal photo without fluorescein **– study eye**
- Fluorescein stain test and corneal photo – **study eye**
- Dispensation of study drug kits
- Blood sampling for:
    - Haematology
    - Biochemistry
    - PK sample (4 hours postdose but before the next administration)

10.8 Visit 7 (Day 42 ± 3)

The following procedures will be performed:

- Collection of used and unused study drug containers and compliance assessment
- Review of study drug diary
- Recording of (S)AEs
- Review of concomitant medications
- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- Assessment of ocular symptoms (NRS)
- BCDVA – **study eye**
- Slit lamp examination – **study eye**
- Corneal photo without fluorescein **– study eye**
- Fluorescein stain test and corneal photo – **study eye**
- Dispensation of study drug kits

10.9 Visit 8 (Day 56 ± 3)

Patients should administer study drug before the clinic visit and record the time of study drug administration in the study drug diary, so that timing for the postdose PK sampling can be determined and timing of ECG recorded. Visit 8 is the last day of study drug administration. After last study assessments belonging to Visit 8, no more study drug administration is allowed.

The following procedures will be performed:

- Collection of used and unused study drug containers and compliance assessment
- Review/collection of study drug diary
- Recording of (S)AEs
- Review of concomitant medications
- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- Measure weight
- 12-lead electrocardiogram
- NEI VFQ-25
- Assessment of ocular symptoms (NRS)
- BCDVA – **both eyes**
- Slit lamp examination – **both eyes**
- Corneal photo without fluorescein **– both eyes**
- Fluorescein stain test and corneal photo – **both eyes**
- Corneal sensitivity – **both eyes**
- Fundus examination – **both eyes**
- Blood sampling for:
    - Haematology
    - Biochemistry
    - PK sample (4 hours postdose)
- Urine pregnancy test (for females of childbearing potential)

10.10 Visit 9 (Day 70 ± 7) – Follow-Up Period

The following procedures will be performed:

- Recording of (S)AEs

- Review of concomitant medications
- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- Assessment of ocular symptoms (NRS)
- BCDVA – **study eye**
- Slit lamp examination – **study eye**
- Corneal photo without fluorescein **– study eye**
- Fluorescein stain test and corneal photo – **study eye**

10.11 Visit 10 (Day 84 ± 7) – Follow-Up Period

The following procedures will be performed:

- Recording of (S)AEs
- Review of concomitant medications
- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- 12-lead ECG
- Assessment of ocular symptoms (NRS)
- BCDVA – **study eye**
- Slit lamp examination – **study eye**
- Corneal photo without fluorescein **– study eye**
- Fluorescein stain test and corneal photo– **study eye**
- Corneal sensitivity – **study eye**
- Fundus examination – **both eyes**
- Urine pregnancy test (for females of childbearing potential)

10.12 Early Termination Visit

The following procedures will be performed:

- Collection of used and unused study drug containers and compliance assessment
- Review/collection of study drug diary
- Recording of (S)AEs
- Review of concomitant medications

- Measurement of vital signs (blood pressure and heart rate)
- Physical examination
- Measure weight
- 12-lead ECG
- NEI VFQ-25
- Assessment of ocular symptoms (NRS)
- BCDVA – **both eyes**
- Slit lamp examination – **both eyes**
- Corneal photo without fluorescein **– both eyes**
- Fluorescein stain test and corneal photo– **both eyes**
- Corneal sensitivity – **both eyes**
- Fundus examination – **both eyes**
- Blood sampling for:
    - Haematology
    - Biochemistry
- Urine pregnancy test (for females of childbearing potential)

11 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 2) outlines the efficacy assessments to be performed throughout the study and their timing.

11.1 Slit Lamp Examination/Fluorescein Staining

11.1.1 Slit Lamp Examination

A slit lamp is an instrument consisting of a biomicroscope and high-intensity light source that can be focused to shine a thin sheet of light into the eye. The slit lamp facilitates an examination of the anterior segment and posterior segment of the human eye, which includes the eyelid, sclera, conjunctiva, cornea, iris, natural crystalline lens, and vitreous body. The slit lamp examination will be performed according to local medical practice and applicable medical standards at the site.

The slit lamp examination must be performed before the instillation of any dilating or anaesthetic eye drops or the fluorescein agent. Slit lamp examination will assess the anterior eye segment general status but in particular will concentrate on corneal abnormalities such as:

- Presence of PED
- Presence of corneal ulcer
- Progression in lesion depth to corneal melting or perforation
- Presence of infection
- Presence of any other condition that may influence subject eligibility or study endpoints
- Corneal photo without fluorescein: A photo of the cornea of the study eye will be taken after slit lamp examination and before the instillation of fluorescein agent by a slit lamp camera focusing on the epithelial defect and using white, diffuse (homogenous) frontal illumination. All sites will be trained for standardisation of the corneal photo without fluorescein and the accompanying manual will be provided.

11.1.2 Fluorescein Staining

Fluorescein allows identification of corneal damage.[4] The use of fluorescein stain, which is taken up by exposed corneal stroma and appears green, helps in defining the surface and margins of the corneal damage. Corneal healing will be defined as no fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading.

After a standard slit lamp examination, fluorescein will be administered to the study eye and an anterior eye segment photograph will be taken. All sites will be trained for standardisation of fluorescein use and the accompanying manual will be provided.

The following assessments and procedures will be performed as part of the fluorescein staining:

- Following the instillation of fluorescein in the study eye the size of the PED or corneal ulcer (length of the greatest dimension and the length of the perpendicular dimension expressed in mm) and the grade (density) of the corneal fluorescein staining outside of the

area of the PED or corneal ulcer using the Oxford scale must be assessed at the slit lamp using a yellow barrier filter and cobalt blue illumination.

- The location of the PED or corneal ulcer will be assessed as central or not.
- Corneal photo with fluorescein: Within 5 minutes after the instillation of the fluorescein a corneal photo of the study eye using a yellow barrier filter and cobalt blue illumination will be taken to document the observed corneal findings.
- Instillation of fluorescein and grading of the corneal staining using the Oxford scale in the fellow eye should be performed after the corneal photo with fluorescein has been completed in the study eye (at the Screening Visit and Visit 8/ET; see Table 2).

11.2 Corneal Sensitivity

The Cochet-Bonnet aesthesiometer will be used to quantify corneal sensitivity. A nylon filament from 0 to 6 cm in length is touched to each quadrant of the cornea to elicit a blink or a patient response. The length of the nylon filament in cm when response is elicited (ie, the resistance) is the quantification of corneal sensitivity.

11.3 BCDVA Examination

Assessment of BCDVA for the study eye and the fellow eye will be done using the ETDRS protocol.[20] Distance visual acuity will be measured with best correction. Qualified study personnel following manifest refraction and using certified visual acuity equipment/lanes will perform the assessment. The BCDVA should precede any examination requiring contact with the study eye. The method of visual acuity assessment should remain consistent throughout a patient's study participation.

The BCDVA examination will start from the distance of 4 meters from the chart. The number of letters correctly read by the patient will be collected. Eyes reading 19 or fewer letters correctly at 4 meters should be tested at a 1 meter distance. If visual acuity is so poor that the patient cannot read any letter from 1 meter then counting fingers, hand motion test, and light perception should be tested.

A detailed description of the ETDRS BCDVA procedure will be provided to sites in form of an accompanying manual.

12 SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, ECG recording, AEs, SAEs, clinical laboratory results [routine haematology and biochemistry], and ophthalmological examination) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 2).

12.1 Vital Signs

Vital signs (heart rate and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments (Table 2). All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study.

Vital sign measurements will be repeated if machine/equipment errors occur. Out-of-range blood pressure or heart rate measurements will be repeated at the investigator's discretion. Any abnormalities detected before signing the ICF or at the Screening Visit should be recorded as part of the patient's medical history. Any confirmed, clinically significant vital sign measurements found during the study must be recorded as an AE.

12.2 Physical Examination

A limited physical examination to verify continued patient eligibility and to follow up regarding any change in medical history will be performed at the visits indicated in the Schedule of Assessments (Table 2). Symptom-driven, limited physical examinations will be performed by a physician as clinically indicated at any study visit. Any abnormalities detected before signing the ICF or at the Screening Visit should be recorded as part of the patient's medical history. Any confirmed, clinically significant physical examination abnormalities found during the study must be recorded as AEs.

Height will be collected at the Screening Visit. Weight will be collected as indicated in the Schedule of Assessments (Table 2).

12.3 Electrocardiograms

A 12-lead, resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 2).

An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if artefacts are present. Any abnormalities detected before signing the ICF or at the Screening Visit should be recorded as part of the patient's medical history. Any confirmed, clinically relevant ECG abnormality found during the study must be recorded as an AE.

ECGs will be performed as described in the Schedule of Assessments in the first 24 patients. After formal review of data from the 24 first patients, the DMC may decide to discontinue ECG examination for other patients (this will be described in the DMC charter).

12.4 Ophthalmological Examination

A full ophthalmic examination, including slit lamp examination of eyelids, lashes, conjunctiva, cornea, lens, iris, and anterior chamber, will be performed in all patients by the investigator. Any abnormalities detected before signing the ICF or at the Screening Visit should be recorded as part of the patient's medical history. Any confirmed, clinically significant abnormality found during the study must be recorded as an AE.

12.5 Fundus Examination

The fundus examination may be performed by binocular indirect ophthalmoscopy, fundus biomicroscopy or wide field fundus. The assessment of the fundus may require use of pupil dilating topical medication. If wide field fundus is used, pupil dilating topical medication may not be used.

The following structures may be assessed during the fundus examination: retina, vitreous, macula, choroid, and optic nerve. Any abnormalities detected before signing the ICF or at the Screening Visit should be recorded as part of the patient's medical history. Any confirmed, clinically significant abnormality found during the study must be recorded as an AE.

12.6 Laboratory Assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 2). Patients should be recommended to fast before laboratory assessments whenever possible.

Table 3. Laboratory Assessments

Haematology	**Serum Chemistry**
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	Albumin ALT ALP AST BUN or urea Creatinine Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose LDH Total bilirubin Direct bilirubin Total cholesterol Triglycerides
Pregnancy test: A urine pregnancy test will be performed on all women of childbearing potential at the Screening Visit, Day 56/Visit 8, Day 84/Visit 10 or Early Termination Visit.	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transpeptidase; Hb, haemoglobin; Hct, haematocrit; LDH, lactate dehydrogenase; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell.

Blood samples will be analysed at a central laboratory facility. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the patient's eCRF and medical record (source document) for that visit.

All clinically significant out-of-range laboratory values at the Screening Visit will be recorded in the medical history form (the investigator should report a diagnosis rather than the laboratory value whenever possible). All clinically significant out-of-range laboratory values after the Screening Visit are to be reported as an AE.

Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention) if this abnormality was not present at the Screening Visit or is assessed as having worsened since the Screening Visit (ie, changed significantly from the Screening Visit). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilise, or are no longer clinically significant.

12.7 Adverse Events

12.7.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at the Screening Visit, worsens during the study, regardless of the suspected cause of the event. All medical conditions (except those related to the indication under study) present at the Screening Visit will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant findings from laboratory assessments, vital signs measurements, ECGs, and other procedures that result in a diagnosis should also be recorded as AEs. Surgical procedures that were planned before the patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient's medical history.

Patients will be instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, seriousness, relationship to study drug, action taken with study drug, treatment of event, and outcome. For ocular AEs, the eye (study eye or fellow eye) must be recorded on the eCRF as well. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent until the last Follow-up Visit. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilises at a level acceptable to the investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in Table 4 and Table 5.

Table 4. Classification of Adverse Events by Intensity

MILD: An AE that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An AE that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An AE that prevents normal everyday activities.

Abbreviation: AE, adverse event.

Table 5. Classification of Adverse Events by Relationship to Study Drug or Study Procedure

UNRELATED: AEs with no reasonable temporal sequence from administration of the study drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.
RELATED: AEs with reasonable temporal sequence from administration of the study drug (including the course after withdrawal of the study drug), or for which possible involvement of the study drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.

Abbreviation: AE, adverse event.

12.7.2 Adverse Events of Special Interest

An AESI (serious or non-serious) is an event of scientific and medical concern specific to the Sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the Sponsor could be appropriate. Such an event might require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, DMC, regulators) might also be warranted.

The following AEs are considered AESI:

1. Corneal calcifications in the study eye, independent of intensity
2. All non-serious AEs that are severe in intensity and considered related to the study drug

Any AESI occurring from the time informed consent is obtained, during the study, or within 4 weeks of stopping study drug must be reported to the Syneos Health Safety and Pharmacovigilance group. Any AESI must be reported within 24 hours of occurrence or when the investigator becomes aware of the event using the process described in Section 12.7.4. Syneos Health will communicate these AESI within one business day to the Sponsor Safety and Medical department.

12.7.3 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect
- is an important medical event (other important medical events that may not be immediately life-threatening or result in death or hospitalisation, based upon appropriate medical judgment, are considered serious AEs [SAEs] if they are thought to jeopardise the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE)

Serious AEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.7.4 Reporting of Serious Adverse Events and Other Adverse Events Requiring Immediate Reporting

An SAE occurring from the time informed consent is obtained, during the study, or within 4 weeks of stopping study drug must be reported to the Syneos Health Safety and Pharmacovigilance group. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of awareness.

The eCRF should be used for SAE reporting, however, notification can also be made using the dedicated fax line or email for the Syneos Health pharmacovigilance group:

Syneos Health Safety and Pharmacovigilance fax number: +1-877-464-7787

Syneos Health Safety and Pharmacovigilance email address: SafetyReporting@SyneosHealth.com

If the investigator contacts the Syneos Health pharmacovigilance group or clinical research associate by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymised photocopies of other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the study drug.

Appropriate remedial measures should be taken to treat the SAE, and the outcome should be recorded in the eCRF. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the aetiology of the problem. The investigator must report all additional follow-up evaluations to the Syneos Health Safety and Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed up until it either resolves, stabilises, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

Syneos Health will determine whether the event meets the criteria for being reportable as a suspected unexpected serious adverse reaction (SUSAR).

12.7.5 **Suspected Unexpected Serious Adverse Reactions**

Adverse events that meet all of the following criteria will be classified as SUSARs and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with information in the Reference Safety Information section of the IB)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study drug

There are no expected AEs for MT8. Each case of AE assessed as related to study drug and fulfilling seriousness criteria will be assumed to be a SUSAR.

The investigator will assess whether an event is causally related to study drug. Syneos Health will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report.

Fatal or life-threatening SUSARs must be reported to the regulatory authorities and the IEC/institutional review boards (IRBs) (where required) within 7 days after the Sponsor or Syneos Health has first knowledge of them, with a follow-up report submitted within a further 8 calendar days, where applicable.

Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor or Syneos Health first has knowledge of them.

Syneos Health is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes.

Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

12.8 Pregnancy

Women of childbearing potential (WOCBP) must have a negative urine pregnancy test at the Screening Visit. Following administration of study drug, any known cases of pregnancy in female patients will be reported until the patient completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to Syneos Health within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow up with the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The investigator should notify Syneos Health of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including anomaly detected in an aborted foetus]), the investigator will follow the procedures for reporting a SAE within 24 hours of awareness. Syneos Health will forward all cases of pregnancy to the Sponsor (Medical and Safety Department) within one business day.

Upon discontinuation from the study, only those procedures that would not expose the patient to undue risk in the investigator's judgment will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor and Syneos Health after delivery.

12.9 Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes the following:

- Overdose of an investigational product with or without an AE. For this study, an overdose is defined as an increase of the intake frequency of the study medication to more than 8 times per day (ie, > 2 × the daily dose specified in the protocol).
- Inadvertent or accidental exposure to an investigational product with or without an AE.
- Medication errors with or without an AE (medication error is an administration of study drug that does not match what was allocated by randomisation, administration of an expired study drug, or administration of a study drug that has not met storage conditions as described in the protocol, and use outside what is foreseen in the protocol, including other storage conditions).
- Misuse, where the medicinal product is intentionally used not in accordance with the protocol.
- Any suspicion of transmission of an infectious agent via an investigational product.

13 PHARMACOKINETICS

13.1 Pharmacokinetic Sampling

13.1.1 Blood Samples

Blood samples for pharmacokinetic (PK) analysis of MT8 levels will be collected at the time points indicated in the Schedule of Assessments (Table 2). The actual date and time of each blood sample collection will be recorded.

Day 1 and Day 7 (±1 day) PK sampling will be done for the first 24 patients only. On Day 1 and Day 7 (±1 day), PK samples will be obtained predose, and postdose PK samples will be obtained at 10, 20, and 40 minutes, and 1, 2, and 4 hours after the first daily administration (and before the next administration).

Trough PK sampling will be done for all patients, 4 hours postdose but before the next administration on Day 28 (±2 days) and 4 hours postdose on Day 56 (±3 days).

Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

13.2 Pharmacokinetic Analytical Methodology

The concentration of study drug will be determined from the plasma samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

The analysis will remain masked to everyone except the PK laboratory, which will provide any exposure > 10 nM to the DMC during the dose escalation phase (first 24 patients).

14 OTHER ASSESSMENTS

14.1 NEI VFQ-25 (Quality of Life)

The NEI VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales (ocular pain; near activities; distance activities; vision specific social functioning, mental health, role difficulties, and dependency; driving; colour vision; and peripheral vision) and one general health item.[21,22] This questionnaire will be administered at all study sites by masked study site personnel (interviewer).

This questionnaire will be presented in its interviewer-administered format in the local language and should be administered in a quiet room by a study-related person qualified to administer this type of questionnaire, preferably before other visit procedures are performed.

14.2 NRS for Ocular Symptoms and Tolerability

The NRS of ocular symptoms and tolerability will use an 11-point scale (see APPENDIX 2). The scale question will be "On average since your last visit how would you rate the following symptoms in your treated eye on the scale 0 to 10, 0 means no symptoms and 10 means the worst possible discomfort. The scale will be administered for each of the following 7 symptoms: foreign body sensation, burning/stinging, itching, ocular pain, sticky feeling, blurred vision, and photophobia."

14.3 Study Drug Diary

Patients will fill out a paper diary recording the date and time of study drug administration. Study staff will provide the diary and instruct patients in how to use the diary. The diary should be brought to the site at each study visit and the study staff should review the diary with the patient to encourage compliance with study drug dosing.

The diary will also be used at Day 28/Visit 6 (±2 days) and Day 56/Visit 8 (±3 days) to determine the timing for PK sampling (see Section 13.1.1 for details).

15 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

Subgroup analyses may be defined and added in the SAP, before the database lock, such as gender, NK grade, region or other based on specific characteristics of the enrolled population.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarised with the number of patients (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of patients for each category by treatment group.

No formal interim analysis is planned.

15.1 Determination of Sample Size

A total of 108 patients will be randomly assigned to 1 of the 3 active treatment arms or the vehicle treatment arm (27 patients per arm). Randomisation will be stratified by disease stage (Stage 2, Stage 3) and region (Europe, North America)

Considering an estimated response rate of 27% for the vehicle treatment arm based on studies conducted in a similar patient population with cenegermin (Oxervate)[23] and with approximately 80% of power and a two-sided alpha 0.05, the sample size of 27 patients per group (including a 15% estimate of dropout rate) should allow analysis to show a difference of at least 45% between the active treatment arms and the vehicle treatment arm.

15.2 Analysis Populations

Enrolled Population

The enrolled population will include all individuals who sign the ICF.

Modified Intent-to-Treat Population

The intent-to-treat (ITT) population will include all patients who are randomised and receive at least 1 drop of study drug, irrespective of any deviation from the protocol or premature discontinuation. The treatment group assignment will be designated according to initial randomisation. The ITT population will serve as the basis for the analysis of efficacy.

Safety Population

The safety population will include all randomised patients who receive at least 1 dose of study drug. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

Per-protocol Population

The per-protocol (PP) population will include all patients in the ITT population for whom no major protocol violations/deviations occurred.

15.3 Efficacy Analysis

15.3.1 Analysis of Primary Efficacy Endpoint

The primary endpoint will be analysed by means of the Cochran-Mantel-Haenszel chi-square test, controlling for disease stage. Hierarchical testing will be performed to account for multiplicity. Benjamini-Hochberg procedure will be applied.

The primary analysis will be performed on the ITT population and will consider rescue treatment initiation or randomised treatment discontinuations due to related AEs as failures, while all the other missing data will be managed according with the last observation carried forward (LOCF) method.

A secondary analysis will be performed with the same criteria but including also the data (if available) collected after treatment discontinuation (in this case not considered as failure).

As sensitivity analyses, the primary analysis will be repeated on the ITT population by means of the Cochran-Mantel-Haenszel chi-square test, controlling for disease stage and site (pooled to ensure adequate strata sizes), with missing data imputed as failures, with observed data only and on the PP population.

15.3.2 Analysis of Secondary Efficacy Endpoints

Categorical secondary endpoints will be analysed using the same analysis used for the primary endpoint.

The analysis of continuous endpoints will be based on an analysis of covariance (ANCOVA) with treatment and site as main effects and baseline value and disease stage as covariates.

Time to event endpoints will be evaluated by means of Kaplan-Meier survival analysis using log-rank test. The Cox's proportional hazard model will be used in order to manage covariates in the proper way.

15.4 Analysis of Other Exploratory Endpoints

Scores for the NEI VFQ-25 will be calculated according to the NEI VFQ-25 scoring algorithm (composite score and subscales).[21,22]

An overall NRS score will be calculated as the mean of individual symptoms scores.

15.5 Safety Analysis

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent AEs (TEAEs; events with onset dates on or after the start of the study drug) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a patient experiences more than one occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. Serious AEs and AEs causing discontinuation will be tabulated. All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Clinical laboratory data and vital signs will be summarised using descriptive statistics, including mean values and mean change from baseline values, as well as numbers of patients with values outside limits of the normal range at each time point.

Summary tables will be provided for concomitant medications initiated during the study period.

15.6 Pharmacokinetic Analysis

The standard PK parameters of peak plasma concentration and area under the curve will be estimated by standard noncompartmental methods. This description could also include single- and multiple-dose parameters, use of WinNonlin program, linear least squares, etc.

15.7 Interim Analysis

No interim analysis is planned.

15.8 Data Monitoring Committee

An independent DMC will be established by the Sponsor to review accumulating safety data at regular intervals throughout the study and monitor overall study conduct. Members will include experts in ophthalmology and biostatistics, who are not participating in this study and do not have an affiliation with the investigators or the Sponsor. The DMC can recommend in writing to the Sponsor whether to continue, modify, or stop the clinical study based on safety considerations. The DMC will review information related to any non-serious AEs that are considered to be severe and possibly related to the study drug and other AESI as defined in Section 12.7.2, to any SAE, or any serum drug concentration more than 10 nM on an ongoing basis in the first 24 patients treated with study drug. A formal review of the data will be conducted 7 days after the 24th patient has been enrolled and the DMC will recommend whether to continue enrolling patients in all treatment arms. The DMC may also recommend discontinuing the 12-lead ECG assessment in the remaining patients (if no significant systemic exposure to the study drug is observed). Another formal review of the safety data by the DMC will be conducted 8 weeks after approximately 50% (54) patients have been enrolled.

The DMC's specific duties as well as statistical monitoring guidelines and procedures and potential stopping rules will be fully described in a DMC charter.

16 STUDY MANAGEMENT

16.1 Approval and Consent

16.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

16.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted independent ethics committee (IEC)/institutional review board (IRB). Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material, patient information sheets, and other patient-facing material.

16.1.3 Informed Consent

For each study patient, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the Principal Investigator (PI) or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

16.2 Data Handling

Clinical data will be captured via the secure, internet-based electronic data capture (EDC) system, provided and managed by the contract research organisation (CRO) Syneos Health for transmission to the Sponsor.

Access to the EDC system will be available to only authorised and trained users via the study's internet web site, where a user unique assigned username and password are required for access.

The clinical data will be entered by the investigator/site staff and will be transmitted directly into the central clinical database. The central laboratory data will be received in electronic format and uploaded electronically. The IWRS data will be directly integrated with the eCRF instead.

Site personnel will be trained during the site initiation visit. A record of the completed training will be archived. The investigator should enter data close to real-time and for the full duration of the clinical study, to ensure Sponsor and CRO have visibility of all data. The eCRF must be kept current to reflect patient status at each phase during the course of the study. The investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded. A complete electronic audit trail will be maintained.

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 16.3.

Data on eCRFs must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which data are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted.

Clinical data will be reviewed by Syneos Health data management/clinical research associate (CRA) staff by way of both manual and electronic edit checks for consistency and completeness. The data review by data management will allow the generation of queries for the clarification of unclear/missing/inconsistent data. The errors found will be assessed by the data manager/CRA of the study and investigators will be involved in resolving them.

Any changes made to data after collection will be made using the EDC system. Electronic case report forms will be considered complete when all missing and/or incorrect data have been resolved.

The process of data entry and data cleaning will start when the study is still in the phase of treatment/follow-up and should be completed soon after the study completion in all patients. After all corrections to the data are made, the database will be “locked” and no data will be changed without adequate documentation.

Copies of the eCRFs together with all data changes made will be supplied to the investigator at the end of the study. The investigator will be responsible for retaining all records pertaining to the study as specified in the appropriate contract (see also Section 16.4). At the end of the study, a copy of the eCRFs and of all SAS datasets will be provided to the Sponsor on electronic support.

The working procedures used will be documented in the Data Management Plan.

16.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of study-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

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, not obscure the original entry, and be explained if necessary.

16.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations of the US, EU relating to the privacy of patient health information. The investigator shall ensure that study patients authorise the use and disclosure of protected health information in accordance with all applicable federal, state, and local laws and regulations and in a form satisfactory to the Sponsor.

16.5 Monitoring

The study will be monitored according to the CRO's monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits will be a combination of on-site and telephone visits and contacts will be made at appropriate times during the study. The Principal Investigator will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

16.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The CRO will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 Protocol Amendment and Protocol Deviation

16.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of patients or the conduct of the study will be classed as administrative (non-substantial) amendments and will be submitted to the IEC/IRB for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

16.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable regulatory authority mandates is a CRO responsibility and will be done according to the local regulations.

16.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; the European Clinical trial Regulation EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

Independent ethics committees/IRBs will review and approve this protocol and the ICF. All patients are required to give written informed consent before participation in the study.

16.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and

intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

17 REFERENCES

1. Neurotrophic keratopathy. Orphanet. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=137596. Updated March 2017. Accessed 20 June 2019.
2. Lambiase A, Rama P, Bonini S, Caprioglio G, Aloe L. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med. 1998;338(17):1174-80.
3. Semeraro F, Forbice E, Romano V, Angi M, Romano MR, Filippelli ME, et al. Neurotrophic keratitis. Ophthalmologica. 2014;231(4):191-7.
4. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014;8:571-9.
5. Mantelli F, Nardella C, Tiberi E, Sacchetti M, Bruscolini A, Lambiase A. Congenital Corneal Anesthesia and Neurotrophic Keratitis: Diagnosis and Management. Biomed Res Int. 2015.
6. EU/3/14/1400: Public summary of opinion on orphan designation: (1S,4R,5R,7S)-3,4-dibenzyl-2-oxo-6,8-dioxa-3-azabyciclo[3.2.1]octane-7- carboxylic acid-L-lysine for the treatment of neurotrophic keratitis
7. Versura P, Giannaccare G, Pellegrini M, Sebstiani S, Campos EC. Neurotrophis keratitis: current challenges and future prospects. Eye Brain. 2018;10:37-45.
8. Khokhar S, Natung T, Sony P, Sharma N, Agarwal N, Vajpayee RB. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. Cornea. 2005;24(6):654-60.
9. Khodadoust A, Quinter AP. Microsurgical approach to the conjunctival flap. Arch Ophthalmol. 2003;121(8):1189-93.
10. Bonini S, Rama P, Olzi D, Lambiase A. Neurotrophic keratitis. Eye (Lond). 2003;17(8):989-95.
11. Kordić R, Kuzman T, Popović-Suić S, Kalauz M, Ćurković T. Neurotrophic Keratopathy: Case Report. Acta clinica Croatica. 2007;46(1-Supplement 1):117-20.
12. Bonini S, Lambiase A, Rama P, Caprioglio G, Aloe L. Topical treatment with nerve growth factor for neurotrophic keratitis. Ophthalmology. 2000;107(7):1351-2.
13. Mauro C, Pietro L, Emilio CC. The use of nerve growth factor in herpetic keratitis: a case report. J Med Case Rep. 2007;1:124.
14. Lambiase A, Coassin M, Sposato V, Micera A, Sacchetti M, Bonini S, et al. NGF topical application in patients with corneal ulcer does not generate circulating NGF antibodies. Pharmacol Res. 2007;56(1):65-9.
15. Tan MH, Bryars J, Moore J. Use of nerve growth factor to treat congenital neurotrophic corneal ulceration. Cornea. 2006;25(3):352-5.
16. REC0559 Investigator's Brochure. Recordati Rare Diseases. Version 1.0 draft (May 2019).
17. Mimetech MT8 Compassionate Use Data Report.
18. EMA/CHMP/753373/2012: Questions and answers on the use of phosphates in eye drops. 2012.
19. Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials.

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed 20 June, 2019.

20. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Arch Ophthalmol. 1985;103:1796-806.
21. Mangione, CM. Version 2000 The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25): NEI VFQ Scoring Algorithm – August 2000.
22. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001;119(7):1050-8.
23. EMA/CHMP/351805/2017: EPAR summary for the public Oxervate. European Medicines Agency. 2017.

18 APPENDICES

APPENDIX 1 describes the contraception guidelines applicable for this study.

APPENDIX 1. CONTRACEPTION GUIDELINES

Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must use at least one highly effective method of contraception during the study and for 4 weeks after the last dose of study drug.

A woman is considered to be a WOCBP (fertile) following menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception are those which have a failure rate of <1% (when implemented consistently and correctly) and include:

- combined (containing oestrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal ligation or occlusion
- vasectomy (provided that the male has a medical assessment of surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk in relation to the duration of the clinical study, in line with the preferred and usual lifestyle of the patient)

All patients will be strongly advised that they (or the female partners of male patients) should not become pregnant while on study drug or for 4 weeks after the last dose. A female patient will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Reference

1. [HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed 20 June, 2019.

APPENDIX 2. OCULAR SYMPTOMS AND TOLERABILITY NUMERICAL RATING SCALE

Ocular Symptoms and Tolerability Numerical Rating Scale

On average, how would you rate the following symptoms in the study eye since your last visit (or in the last week if this is your first visit) on the scale 0 to 10?

0 means no symptoms and 10 means the worst possible discomfort.

1. **Foreign Body Sensation**

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

2. **Burning or Stinging**

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

3. **Itching**

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

4. **Ocular Pain**

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

5. **Sticky Feeling**

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

6. **Blurred Vision**

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

7. **Photophobia**

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**