Statistical Analysis Plan and Shells

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Authors: Sophie C. Jentzsch, Principal Biostatistician
Marieve Gendron, Senior Pharmacokineticist

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I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

Sophie C. Jentzsch, Principal Biostatistician		
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
Natalie Steigerwald, Principal Biostatistician		
Name, Title Senior Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)
Marieve Gendron, Senior Pharmacokineticist		
Name, Title PK Specialist	Signature	Date (DD-Mmm-YYYY)

Recordati Rare Diseases Approval

Alessandro Antonellini, Head of Biometrics		
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
Stefano Biondi, Head of Pre Clinical		
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last observed concentration
AUC_{0-4}	Area under the plasma concentration-time curve from time zero to 4 hours post dose
AUC_{τ}	Area under the plasma concentration-time curve during a dosage interval (τ)
BCDVA	Best Corrected Distance Visual Acuity
BFS	Blow Fill Seal
BLQ	Below Limit of Quantification
C_{max}	Maximum plasma concentration
$C_{max\ ss}$	Maximum plasma concentration at steady-state
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CNU	Corneal Neurotrophic Ulcer
CRF	Case Report Form
C_{trough}	Plasma concentration at trough
CV	Coefficient of Variation
DB	Database
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
HR	Hazard Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat

Abbreviation	Description
IWRS	Interactive Web Response System
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
LSM	Least Squares Mean
MAR	Missing at random
Max	Maximum
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
Min	Minimum
mITT	Modified Intent-to-Treat
MNAR	Missing not at random
MT6	Free acid form of MT8 (active metabolite)
N/A	Not Applicable
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NE	Not Estimable
NK	Neurotrophic Keratitis/Neurotrophic Keratopathy
NRS	Numerical Rating Scale
OC	Observed Cases
OR	Odds Ratio
PD	Protocol Deviation
PDNC	Protocol Deviations and Non Compliances
PED	Persistent Epithelial Defects
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QID	Four times a day (Quater In Die)
QoL	Quality of Life
REC 0/0559	The ophthalmic solution of udonitrectag dissolved in phosphate-buffered saline
SAE	Serious Adverse Event
SAF	Safety Population

Abbreviation	Description
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SPK	Superficial Punctate Keratopathy
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to peak plasma concentration
$T_{max\ ss}$	Time to peak plasma concentration at steady-state
TLF	Table, Listing and Figure
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, listings and figures (TLFs) that include all safety, efficacy and pharmacokinetic (PK) data.

2.2. Timings of Analyses

The primary analysis of safety, efficacy, and pharmacokinetics is planned after the database lock.

An independent data monitoring committee (IDMC) will formally review descriptive summaries of accumulating safety, PK, patient disposition, and limited efficacy data seven days after the 24th patient has been enrolled, and also conduct another formal review after approximately 50% (54) patients have been enrolled. Further description of the IDMC analyses can be found in the current version of both IDMC Statistical Analysis Plan and IDMC charter. An unmasked team from Syneos Health Biostatistics will perform the analyses as described in Section 4.4 of this SAP to maintain the masking of the study.

2.3. Changes from the protocol

The protocol defines the primary endpoint as the capture of complete corneal healing assessed as no corneal fluorescein staining in the area of the prior PED or corneal ulcer by an independent central reading centre. A key secondary endpoint including a more conservative definition assessing the fluorescein staining after 8 weeks of treatment in the area of the initial lesion/ulcer and the persistent staining in the area outside of the lesion/ulcer is also of interest in regards of the post-hoc analysis performed with oxervate™.

Considering the limited number of patients by group, the hierarchical approach has been replaced by a gatekeeping approach.

An estimand framework that is not outlined in the protocol is added to the SAP to follow current standards for submissions. Due to the implementation of the estimand framework in the SAP, the imputation method for missing data post intercurrent event was adapted to the type of intercurrent events.

The protocol specifies (pooled) site as covariate for the primary and secondary efficacy analyses (CMH test, ANCOVA). As the sites are already pooled within region, which is a randomisation stratum, the variable region at randomisation will be used instead of (pooled) site in the models.

3. Study Objectives

3.1. Primary Objective

The primary objectives are:

- In the first 24 patients, to determine the safety, tolerability and PK profile of REC 0/0559 given as 1 drop 4 times a day (QID) of escalating doses up to 50 µg/mL.
- To determine the efficacy and safety of REC 0/0559 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.

4. Study Details/Design

4.1. Brief Description

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 REC 0/0559 in patients with neurotrophic keratitis/neurotrophic keratopathy (NK) and to select the most appropriate dose.

NK 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 patients will be adults with moderate (Stage 2, PED) to severe (Stage 3, corneal ulcer) NK, affecting only one eye and not improved by conventional non-surgical treatment.

In this clinical study, the study drug will be administered as 3 different doses (0.5, 2.5, and 5.0 µg/day) of REC 0/0559 or vehicle given as 1 drop in the study eye, QID at 4-hour intervals (± 30 minutes) starting in the morning for 8 weeks. This treatment period is followed by a 4-week follow-up period. An overview of the study treatment arms and dose levels is provided in Table 1.

Table 1: Study Treatment Arms and Dose Levels of MT8

Arm	Dose of REC 0/0559 per Day	Study Drug Concentration
Dose 1	0.5 µg/day	5 µg/mL REC 0/0559 given 1 drop QID
Dose 2	2.5 µg/day	25 µg/mL REC 0/0559 given 1 drop QID
Dose 3	5.0 µg/day	50 µg/mL REC 0/0559 given 1 drop QID
Vehicle	0.0 µg/day	Vehicle given 1 drop QID

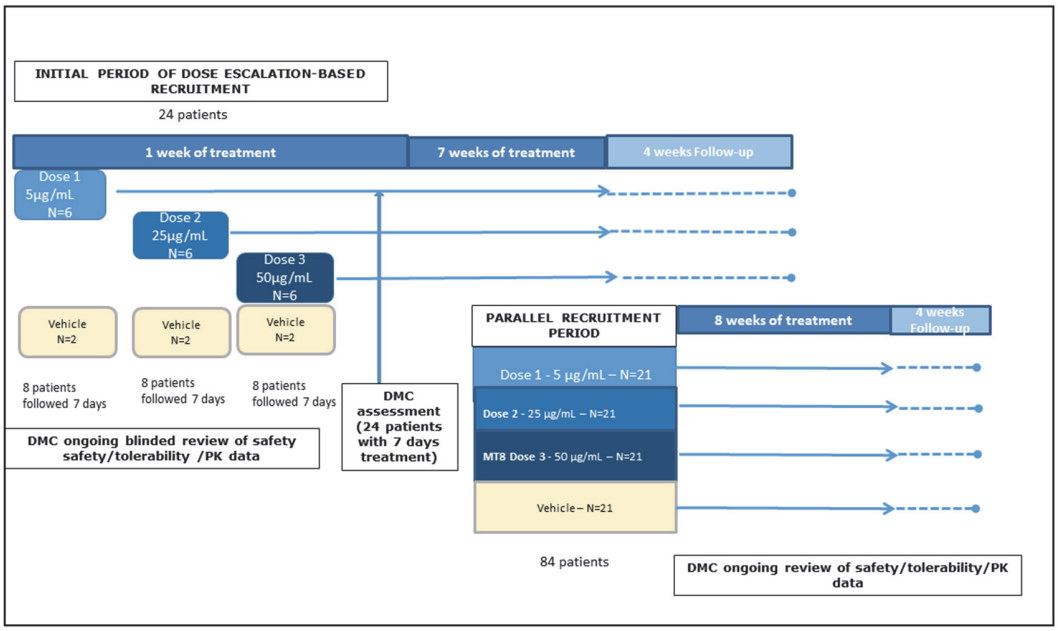
The study will have an initial period of dose escalation followed by a parallel recruitment period (Figure 1). After confirmation of eligibility and signature of informed consent, patients will be randomly assigned to treatment with REC 0/0559 or vehicle on Day 1.

The patients are randomised sequentially to 4 cohorts as described below:

- Cohorts 1 to 3 each include 8 patients for a total of 24 patients (6 randomised to REC 0/0559 and 2 to vehicle per cohort)
- Cohort 4 includes 84 patients (ratio 1:1:1:1, randomised to 1 of 3 doses of REC 0/0559 or vehicle).

Details on the randomisation and masking are in Section 4.4 as well as in the Randomisation Specifications.

Figure 1: Study design



Abbreviations: DMC, data monitoring committee; PK, pharmacokinetic

The 4-week follow-up is intended to collect safety data (AEs) as well as clinical and ophthalmological data after study drug discontinuation.

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, i.e., < 0.5 mm lesion staining, will be also collected.

4.2. Patient Selection

4.2.1. Inclusion Criteria

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

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 (e.g., 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 Best Corrected Distance Visual Acuity (BCDVA) score ≤ 75 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the study eye, due to NK.

4.2.2. 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 (e.g., fluorescein), including to a compound chemically related to REC 0/0559.

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 (e.g., 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 patient) 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. For the definition of childbearing potential and list of highly effective methods of contraception, see the study protocol, 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.

11. Receive topical ophthalmological treatments other than the study drug provided by the study Sponsor and the treatments allowed by the study protocol (e.g., preservative-free artificial tears; 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. 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 (e.g., 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.

18. 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.

19. Use therapeutic contact lenses or wear contact lenses for refractive correction during the study treatment periods in the eye(s) with NK.

20. 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.

21. 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. 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:

22. Have Stage 2 or 3 NK or perforation.

For any eye:

23. Have a history of ocular cancer.

24. Have had prior treatment with Oxervate™ (cenegermin eye drops).

4.3. 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) and with approximately 80% of power and a 2-sided alpha of 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.

4.4. Treatment Assignment and Masking

Treatment 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 REC 0/0559) or vehicle, starting with the 5 µg/mL dose of REC 0/0559. Enrolment will proceed sequentially to the next highest dose level unless the IDMC recommends a change (a change can occur at any time based on ongoing review of the safety, tolerability, and PK data). The IDMC will formally review all safety, tolerability, and PK data in the first 24 patients: 6 each assigned to 0.5 µg/day REC 0/0559 (Cohort 1), 2.5 µg/day REC 0/0559 (Cohort 2), and 5.0 µg/day REC 0/0559 (Cohort 3), and 6 to vehicle (2 patients in each of these cohorts). If the IDMC does not recommend any change to the dosing schedule, the patients in Cohort 4 will be enrolled in all 4 treatment arms in a 1:1:1:1 ratio. The study cohorts as well as the dose levels per cohort and number of patients are detailed in Table 2.

Table 2: Study Cohorts, Dose Levels and Number of Patients

Cohort	Treatment groups	Number of patients
Cohort 1	Dose 1 (0.5 µg/day), Vehicle	8 (REC 0/0559: 6, Vehicle: 2)
Cohort 2	Dose 2 (2.5 µg/day), Vehicle	8 (REC 0/0559: 6, Vehicle: 2)
Cohort 3	Dose 3 (5.0 µg/day), Vehicle	8 (REC 0/0559: 6, Vehicle: 2)
Cohort 4	Dose 1, Dose 2, Dose 3, Vehicle	84 (each arm: 21)

Randomisation will be performed through an interactive web response system (IWRS) integrated in the electronic Case Report Form (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, Patient 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 Patient ID number.

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 Lead Statistician as well as the Lead Statistical Programmer, the Lead SDTM Programmer and any supporting statistical programmers or (senior) reviewing statisticians remain masked until official unmasking after database (DB) lock.

A separate unmasked team of statisticians and statistical programmers to produce and review the outputs (TLFs) for the formal IDMC meetings is in place. All details on the unmasked team and procedures of the creation of the IDMC outputs are included in the Unblinded Team Management Plan as well as the IDMC SAP. The standard processes – if not otherwise detailed in the referenced documents – will be strictly followed according to the Syneos Health Standard Operating Procedure (SOPs).

4.5. Administration of Study Medication

The study drug product REC 0/0559 is an ophthalmic solution packaged in single-use blow fill seal (BFS) containers. For each patient entering in the study, the investigator is 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 provides treatment for a period of 7 days, and contains treatment for 3 additional days as spare.

Patients are 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, 20, 100, and 200 µg/mL (respectively, 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 (i.e., 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.

4.6. Study Procedures and Flowchart

The timing of procedures and assessments to be performed throughout the study are outlined in Table 13 Appendix 1. Assessments and procedures scheduled at a visit where study drug is administered should be performed before administration of study drug unless otherwise indicated.

Efficacy assessments are described in the study protocol, Section 11, and include slit lamp examination, fluorescein staining, corneal sensitivity, and BCDVA examination. The National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) will be used to assess quality of life (QoL) (Mangione 2000,

Mangione et al 2001). Ocular symptoms and tolerability will be evaluated by the numerical rating scale (NRS) (study protocol, Appendix 2).

The pharmacokinetic assessments are described in protocol Section 13, and will be evaluated using an intense PK sampling schedule for the first 24 patients on Day 1 and Day 7. All patients, including first 24 ones, will have trough PK levels sampling at Day 28 and Day 56.

The safety assessments are described in Section 12 of the study protocol, and include vital signs, physical examinations, electrocardiograms (ECGs), laboratory assessments, AEs, ophthalmological and fundus examinations.

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 the study protocol, Section 8.4.

5. Endpoints

5.1. 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.

5.2. Key Secondary Efficacy Endpoint

The key secondary 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 and no persistent staining outside of corneal lesion elsewhere in the cornea (i.e. not changing in shape and/or location at different timepoints) as assessed by an independent central reading centre.

5.3. Secondary Efficacy Endpoints

- Percentage of patients who achieve a 5-, 10-, and 15-letter mean improvement in BCDVA by the 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 compared to baseline 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.

5.4. 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.

5.5. Other Exploratory Endpoints

- Change from baseline in QoL evaluated using the NEI VFQ-25.
- Change from baseline in the overall NRS score for ocular symptoms and tolerability.

5.6. Pharmacokinetic Analyses

For the first 24 patients, the C_{max}, $C_{max\ ss}$, T_{max}, $T_{max\ ss}$, AUC_{0-4} (Day 1), AUC_{τ} (Day 7) and AUC_{0-t} PK parameters will be assessed according to the following sampling schedule :

- On Day 1 and Day 7: predose, 10, 20 and 40 minutes and 1, 2, and 4 hours and 8 hours, if applicable, after the 1st daily administration (last sampling before next dose);
- On Day 1 and Day 7: at 20 minutes and 4 hours after the 2nd daily administration
- On Day 28 and Day 56: at 4 hours postdose and before the next REC 0/0559 administration

For all patients, C_{trough}:

- On Day 28 and Day 56: at 4 hours postdose and before the next REC 0/0559 administration

5.7. Safety Analyses

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

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

6. Analysis Sets

6.1. Enrolled Population

The enrolled population will include all individuals who signed the informed consent form (ICF), including screen failures and patients randomised but not treated. Unless specified otherwise, this set will be used for all patient listings and the summary table of patient disposition.

6.2. Safety Population (SAF)

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.

6.3. Modified Intent-to-Treat Population (mITT)

The modified intent-to-treat 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 mITT population will serve as the basis for the analysis of efficacy.

6.4. Per Protocol (PP) Population

The per-protocol population will include all patients in the mITT population for whom no major protocol violations/deviations occurred. Patients will be analyzed according to randomised treatment.

Criteria for exclusion from the PP population will be determined at the blinded data review meeting (BDRM) shortly before the database lock at the end of the study. All protocol deviations (PDs) will be tracked during the study and reviewed at the BDRM. The BDRM will be performed according to SOP 3911.

6.5. PK Population (PK)

For PK analysis all patients included in the mITT and having at least one plasma concentration of study drug measured will be included. Subjects with insufficient number of PK samples to derive PK parameters may still be used for listing and summary of PK concentrations.

6.6. Protocol Deviations

Major protocol deviations, as determined by a review of the data prior to DB lock, will result in the exclusion of a subject from the PP population. All deviations/scenarios that arise during the BDRM will be documented and reported in the protocol deviations log. The details of handling protocol deviations and non compliances (PDNC) are specified in the PDNC management plan of this study.

6.7. Sub-Populations

At the time of the BDRM sub-populations may be defined based on data availability and will be described in the Blind Data Review and Analysis Sets Report following the decisions of the BDRM before database lock.

7. Estimands

7.1. Estimands for the Primary Efficacy Endpoint

The primary efficacy endpoint is the evaluation of 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, and the population level summary will be the difference in treatment proportions (common risk difference) at Week 8. The primary estimand for the primary efficacy endpoint will be evaluated in the mITT population, which is patients with stage 2 or stage 3 NK as defined by the inclusion/exclusion criteria who received at least one dose of study drug.

Intercurrent events are events occuring after treatment initiation that affect the interpretation of or the existence of the measurements associated with the clinical question of interest. As more than one intercurrent event is possible, Table 3 lists all potential intercurrent events and the strategy to deal with them.

Table 3: Potential intercurrent events for the primary estimand

Intercurrent Event	**Primary estimand: Strategy to Deal With Intercurrent Event Within Analysis**	**Primary estimand: Assessment of Patient**
ICE1: Treatment discontinuation due to treatment-related AE	Composite	Available data observed on or after the occurrence of the ICE will be set to missing and imputed as failure.
ICE2: Treatment discontinuation due to any other reason than treatment-related AE or death	Treatment policy strategy	Available data occurring on or after the ICE will be used for the analysis as observed. Monotone missing data will be imputed using LOCF
ICE3: Prohibited rescue treatments or rescue procedures initiation during the 8 week study treatment administration period	Composite	Available data observed on or after the occurrence of the ICE will be set to missing and imputed as failure.
ICE4: Death	Composite	All monotone missing data will be imputed as failure.

For patients who discontinue treatment due to a treatment-related AE (ICE1), due to strat of prohibited rescue treatments or rescue procedures during the 8 week study treatment administration period or due to death (ICE4) a composite strategy will be applied. All observed data occurring on or after ICE1 and ICE3 will be set to missing and imputed as failure. Prohibited rescue treatment or rescue procedures starting at

or after the visit evaluation will not be considered as ICE for the analysis (Table 3). In case of treatment discontinuation due to death (ICE4) the subsequently missing efficacy assessment will be imputed as failure.

7.1.1. Supplementary Estimands of the Primary Efficacy Endpoint

The primary efficacy endpoint is the evaluation of 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, and the population level summary will be the difference in treatment proportions (common risk difference) at Week 8. The supplemetary estimand for the primary efficacy endpoint will be evaluated in the mITT population, which is patients with stage 2 or stage 3 NK as defined by the inclusion/exclusion criteria who received at least one dose of study drug.

Table 4 lists all potential intercurrent events and the strategy to deal with them.

Table 4: Potential intercurrent events for the supplementary estimand

Intercurrent Event	**Supplementary estimand: Strategy to Deal With Intercurrent Event Within Analysis**	**Supplementary estimand: Assessment of Patient**
ICE1: Treatment discontinuation due to treatment-related AE	Treatment policy strategy	Available data occurring on or after the ICE will be used for the analysis as observed. Any monotone missing data will be imputed under MAR assumption.
ICE2: Treatment discontinuation due to any other reason than treatment-related AE or death	Treatment policy strategy	Available data occurring on or after the ICE will be used for the analysis as observed. Any monotone missing data will be imputed under MAR assumption.
ICE3: Prohibited rescue treatments or rescue procedures initiation during the 8 week study treatment administration period	Treatment policy strategy	Available data occurring after the ICE will be used for the analysis as observed. Any monotone missing data will be imputed under MAR assumption.
ICE4: Death	Composite strategy	All monotone missing data after the occurence of the ICE are imputed as failure.

The approach for the supplementary estimand assumes that for patients discontinuing study treatment because of treatment-related AEs (ICE1), any reason other than treatment-related AEs and death (ICE2) and prohibited rescue treatments or rescue procedures during the planned 8 week study treatment administration period (ICE3) a non-confounded estimate of the treatment effect is provided. Therefore the treatment policy strategy will be applied and any missing assessment of complete corneal fluorescein staining will be imputed by MI assuming missing at random (MAR). Patients will be imputed based on their treatment group and randomization strata (NK stage and region).

In case of treatment discontinuation due to death (ICE4) a composite strategy will be applied where the subsequently missing efficacy assessment will be imputed as failure, regardless of treatment group or randomisation strata.

More details on the multiple imputation approaches are provided in Section 8.3.

7.1.2. First Sensitivity Analysis of the Primary Efficacy Endpoint

The first sensitivity analysis of the primary efficacy endpoint is based on the mITT population but MI for monotone missing data due to ICE2 (treatment discontinuation due to other reasons) assuming MNAR will be implemented. Otherwise the definitions of the intercurrent events and strategies on how to deal with them are the same as for the primary estimand (Table 3).

7.1.3. Second Sensitivity Analysis of the Primary Efficacy Endpoint

The second sensitivity analysis of the primary efficacy endpoint is based on the mITT population but analyses are performed only on observed cases, i.e. no imputations are performed.

7.1.4. Supportive Sensitivity Analysis of the Primary Efficacy Endpoint

The supportive sensitivity analysis of the primary efficacy endpoint is based on the PP population and presentation as per the primary estimand is applied. The definitions of the intercurrent events are the same as for the primary estimand (Table 3).

7.2. Estimands for the Secondary, Other and Exploratory Efficacy Endpoints

The estimands framework for the primary efficacy endpoint will apply for the secondary, other and exploratory efficacy endpoints related to the secondary efficacy objective, other efficacy objectives and other exploratory efficacy objectives, for all visits up to and including Week 8. This includes the definitions of the intercurrent events (Table 3) as well as their imputation methods for all binary endpoints.

For all continuous efficacy endpoints the definitions of the intercurrent events, strategies to handle the intercurrent events and imputation methods are detailed in Table 5.

Table 5: Potential intercurrent events for continuous endpoints

Intercurrent Event	Estimand: Strategy to Deal With Intercurrent Event Within Analysis	Estimand: Assessment of Patient
ICE1: Treatment discontinuation due to treatment-related AE	Hypothetical	Available data occurring on or after the ICE will be not be used for the analysis and set to

		missing. Monotone missing data will be imputed assuming MNAR.
ICE2: Treatment discontinuation due to any other reason than treatment-related AE or death	Treatment policy strategy	Available data occurring on or after the ICE will be used for the analysis as observed. Monotone missing data will be imputed assuming MAR
ICE3: Prohibited rescue treatments or rescue procedures initiation during the 8 week study treatment administration period	Hypothetical	Available data occurring on or after the ICE will be not be used for the analysis and set to missing. Monotone missing data will be imputed assuming MNAR.
ICE4: Death	Composite	Worst-case data imputation, i.e., BCDVA worst value in surviving patients

Patients who discontinue due to treatment-related AEs (ICE1) will be assumed to confound the estimate of the treatment effect and therefore is assumed have a similar outcome over time as the vehicle group under a hypothetical setting. Therefore assessments after treatment discontinuation due to treatment-related AEs will be set to missing (if not already missing) and will be imputed under the MNAR assumption using a control-based pattern approach with vehicle group as reference and randomisation strata (NK stage and region) included.

For patients discontinuing study treatment because of any reason other than treatment-related AEs and death (ICE2), a non-confounded estimate of the treatment effect is provided. Therefore the treatment policy strategy will be applied and any missing assessment will be imputed by MI assuming MAR. Patients will be imputed based on their treatment group and randomization strata (NK stage and region).

For patients who start rescue treatments or rescue procedures during the planned 8 week study treatment administration period used for treatment of NK (ICE3), a confounded estimate of the treatment effect is assumed. Therefore the estimand allows for the assessment of the treatment effect in a hypothetical setting, assuming a similar outcome over time, as expected under vehicle administration. Assessments after the start of the rescue treatments or rescue procedures will be set to missing (if not already missing) and will be imputed under the assumption of MNAR using a control-based pattern approach with the vehicle group as reference and randomisation strata (NK stage and region) included.

In case of treatment discontinuation due to death (ICE4) a composite strategy will be applied where the subsequently missing efficacy assessment will be imputed with the worst value single imputation approach, regardless of treatment group or randomisation strata (NK stage and region).

All time to event efficacy endpoints, definitions of the intercurrent events, strategies to handle the intercurrent events and imputation methods are detailed in Table 6.

Table 6: Potential intercurrent events for time to event endpoints

Intercurrent Event	Estimand: Strategy to Deal With Intercurrent Event Within Analysis	Estimand: Assessment of Patient
ICE1: Treatment discontinuation due to treatment-related AE	Composite	Available data observed on or after the occurrence of the ICE and up to week 8 (day 56) will be set to missing and imputed as failure. The patient will be censored at the end of week 8 (day 56) of the study treatment administration period.
ICE2: Treatment discontinuation due to any other reason than treatment-related AE or death	Treatment policy strategy	Available data occurring on or after the ICE will be used for the analysis as observed. Monotone missing data will be imputed using LOCF up to week 8 (day 56).
ICE3: Prohibited rescue treatments or rescue procedures initiation during the 8 week study treatment administration period	Composite	Available data observed on or after the occurrence of the ICE and up to week 8 (day 56) will be set to missing and imputed as failure. The patient will be censored at the end of week 8 (day 56) of the study treatment administration period.
ICE4: Death	Composite	All monotone missing data up to week 8 (day 56) will be imputed as failure. The patient will be censored at the end of week 8 (day 56) of the study treatment administration period.

Time to event is defined as time from treatment start to event, e.g. complete corneal healing, in days. Patients that do not have an event until end of treatment (Visit 8/Day 56) and, in case of no intercurrent event (ICE), will be censored at their last available assessment date, i.e. Visit 8 or earlier. In case ICE1 (treatment discontinuation due to treatment-related AE), ICE3 (start of rescue treatments/procedures) or ICE4 (treatment discontinuation due to death) occurred during the treatment administration period (up to Visit 8 (Day 56), the composite strategy applies where the observed values after the ICE are set to missing and imputed as failure up to Visit 8 (Day 56). If ICE2 (treatment discontinuation due to any other reasons) occurs during the treatment administration period and up to Visit 8 (Day 56), treatment policy strategy will be applied where LOCF is used to impute any monotone missing data up to Visit 8 (Day 56). The censoring date after the occurrence of an ICE and respective imputation will be the actual assessment date at Visit 8 (Day 56), if available. In case the patient has no efficacy assessment done at Visit 8 (Day 56), the censoring time (days) after the ICE occurrence will be set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol.

8. General Aspects for Statistical Analysis

8.1. General Methods

Statistical methodology and analyses are in accordance with the principles outlined by the International Conference on Harmonization (ICH) E9 guidelines. Statistical analyses will be carried out by using SAS Version 9.4 or higher. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the clinical study report.

Patient listings of all data in the database will be provided, including data collected in the eCRF as well as data transferred electronically (e.g., lab data). All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication, which is designated as Day 1. The listings will be presented based on the respective analysis population set and sorted by cohort, treatment group, patient number, and assessment date and time (if applicable).

Tabulations will be produced for appropriate demographic, baseline, safety, efficacy and PK parameters. For continuous variables, absolute values and change from baseline (if applicable) will be summarised by reporting the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum.

Categorical data will be summarised using number of observations (n), and frequency and percentages (%) of patients. The categories in the summary will follow the logical ordering on the eCRF page, with the 'Other' category displayed after all other pre-specified categories. If the calculation of percentages include patients with missing values, a 'Missing' category is displayed last. The number of patients per treatment group and overall (in a 'Total' column) will be used as the denominator for percentage calculations, unless stated otherwise in the table shell. All percentages will be rounded to one decimal percentages between 0.1% and 100%, inclusive, unless otherwise specified. Percentages equal to 100.0 will be presented as 100% and no percentages will be presented in case of frequencies of zero.

Only scheduled time points will be presented in summary tables. Data from unscheduled time points will be listed only. Tables will be presented by treatment group (and Total if applicable) as presented in Table 7. All header conventions are detailed in Section 16.2.4.

Table 7: Example of study phase and dose level presentation in TLF Shells

REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)	Total (N=xx)

Adverse events, medical history, prior surgeries/procedures and ocular interventions terms will be coded for summarisation using the Medical Dictionary for Regulatory Activities (MedDRA® Version 22.1 or later). Prior and concomitant medications, will be coded using the World Health Organization (WHO) Drug Dictionary (September 2019 version).

8.2. Key Definitions

Baseline and change from baseline:

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

Change from baseline = (post-baseline value – baseline value).

Percentage change from baseline = (change from baseline / baseline value) * 100

Study day:

The study day is calculated relative to the day of first study drug administration, i.e., the first day of study drug administration is designated as Day 1. The day after is Day 2 and so forth until end of study (EOS). The preceding day to Day 1 is designated as Day -1, the day before Day -1 is Day -2, etc.

Calculation of duration

Applicable for adverse events, medical history, and concomitant medication.

If times are available and if the duration is less than 24 hours, the duration will be calculated as (end date/time – start date/time) and presented in hh:mm. If at least 1 time is missing or if the duration is at least 24 hours, it will be calculated as (end date - start date) + 1 and presented in days.

In case of partial/missing start or end date, duration will not be calculated.

8.3. Handling of Missing Data

All missing or partial data will be presented in the patient data listing as they are recorded on the eCRF. In general, partial or completely missing dates will not be imputed.

8.3.1. Handling of Missing or Partial Dates

The following rules apply for medications and procedures to determine if they are concomitant in case of partial or completely missing dates:

In a case where a medication, surgery, or procedure has the day of the start date missing but the start month and year are complete, it will be excluded as being concomitant only if the start month/year is before the month/year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration. If the start day and month are missing but the start year is complete, a medication, surgery or procedure will be excluded as concomitant only if the start year is before the year of study drug administration and if the stop date (either: full date, month and year if missing day, or year if missing month and day) is before study drug administration.

The following rules apply to AEs with partial or completely missing dates to determine if they occurred during the treatment administration study period:

If the start day is missing but the start month and year are complete, an AE is not considered as a treatment-emergent AE (TEAE) only if the start month/year is before the month/year of study drug administration or if the stop date/time is before first treatment administration. If the start day and month are missing but the start year is complete, an AE is not considered as TEAE only if the start year is before the year of treatment administration or if the stop date/time is before first treatment administration. If the start date is completely missing, an AE will be considered as TEAE unless the stop date is before first treatment administration.

For the calculation of time since first NK diagnosis, partial dates are imputed as follows: if only month and year are available, the day = 15 will be assumed. If only year is available, month = 6 and day = 15 will be assumed. In case the imputed date is greater than the date of signed informed consent (IC), then the date of IC will be used as date of first NK diagnosis.

Missing visits or assessments and protocol deviations due to COVID-19 will be summarised and listed (Section 9.2.3).

8.3.2. Handling of Missing Data for the Primary, Secondary, Other and Exploratory Efficacy Endpoints

Missing efficacy assessment data due to intercurrent events will be handled according to the strategies as described in the estimand Section 7. All efficacy analyses using the primary estimand framework for definitions of ICEs and the strategies to deal with them, will be imputed via single value imputation, i.e. as failure/non-responder or LOCF.

For all parameters that need to be imputed using multiple imputation, ranges (minimum and maximum values) and decimal rounding will be specified as applicable. In total 20 imputed datasets will be created per parameter and visit (proc mi).

All intermittent missing efficacy assessment data will be multiple imputed under MAR assumption using a Markov Chain Monte Carlo (MCMC) approach for all endpoints where MI is required.

Once the monotone missing data pattern is obtained the remaining missing values (whether missing due to ICE or not) will be imputed. Missing efficacy assessment data that are missing without the definition of an ICE met, will be multiple imputed under MAR assumption with either a monotone linear regression for continuous parameters or monotone logistic regression for categorical parameters, as applicable. Treatment group and randomisation strata will be included.

For the supplementary estimand strategy and first sensitivity analysis of the primary endpoint as well as for the continuous secondary efficacy endpoints multiple imputation will be applied for missings due to intercurrent events as follows:

- MNAR: multiple imputation will be performed based on the assumption of MNAR with a control-based pattern approach and vehicle as reference group. Randomisation strata will be included. Categorical parameters will be imputed using a monotone logistic regression and continuous parameters will be imputed with monotone linear regression, as applicable.
- MAR: multiple imputation will be used to impute continuous parameters with monotone linear regression and categorical parameters with monotone logistic regression, as applicable. Treatment group and randomisation strata are included.
- Composite strategy: efficacy assessments that are not performed because of treatment discontinuation due to death will be imputed with worst value or failure/non-responder single imputation approach.

After the multiple imputation is completed, any necessary derivations, e.g. calculation of change from baseline, percentage change from baseline or categorisation of responders/non-responders based on an imputed continuous parameter, will be derived. Then the statistical tests as per efficacy endpoint (i.e., CMH test, ANCOVA) will be performed on all 20 imputed datasets per parameter. The ANCOVA results will be summarised directly by Rubin's rules (proc mianalyze) and presented in the summary tables. For the CMH test results the Wilson-Hilferty transformation (Wilson & Hilferty 1931) will be applied before combining the results by Rubin's rules. Odds ratios (OR) based on the 20 imputed datasets will be combined by Rubin's rules with the standard errors calculated based on the confidence intervals (CI) and log-transformation will be applied. Back-transformed results for OR will be presented in the tables.

8.4. Visit Windows

The allowed time windows between visits are detailed in Table 13, Appendix 1.

8.5. Pooling of Centres

For the efficacy endpoint analyses the sites are already pooled by region which is a randomisation stratum.

8.6. Subgroups

Subgroups for additional analyses, such as gender, NK stage, region, or other specific characteristics, may be defined at the time of the BDRM before DB lock and prior to unmasking.

9. Demographic, Other Baseline Characteristics and Medication

9.1. Patient Disposition and Withdrawals

Patient disposition will be summarised by treatment group and overall and will include the following:

- Number of patients screened
- Number of screen failures
- Number (%) of patients treated
- Number (%) of patients by region (at randomisation), country and site
- Number (%) of patients by disease stage (at randomisation)
- Number (%) of patients completing the study
- Number (%) of patients who discontinued treatment and/or study and reason(s) for discontinuation
- Number (%) in each patient population for analysis (the reasons for exclusion from the analysis populations will be listed)

All disposition data will be presented in by-patient listings.

9.2. Demographic and Other Baseline Characteristics

9.2.1. Demographics

Demographics and baseline characteristics will be presented by treatment group and overall. The following variables will be summarised using both continuous and categorical descriptive statistics based on the mITT and PP populations:

- Region (at randomisation)
- Country
- Disease stage (as reported at screening and at randomisation)
- Age (years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Iris color of the study eye
- Weight (kg)
- Height (cm)
- Alcohol status
- Smoking status

Additionally, all demographics and baseline characteristics will be listed for the enrolled population.

9.2.2. Schirmer Test

The Schirmer test is performed only at baseline. All data will be listed.

9.2.3. Protocol Deviations

The number and percentage of patients with a major deviation by type of deviation category will be summarised for the mITT population. Protocol deviations due to COVID-19 will also be presented.

In addition, all major and minor protocol deviations will be provided in a by-patient listing. Also, a by-patient listing will be provided detailing missing visits and assessments due to COVID-19, if applicable.

9.3. Neurotrophic Keratitis Medical History in the Study Eye

Descriptive statistics of NK medical history characteristics in the study eye, including NK stage at screening, time since first diagnosis (weeks), number of episodes/recurrences since first diagnosis, prior treatment or surgical procedures and the underlying cause of NK will be presented by treatment group and overall. All data will be summarised using both continuous and categorical descriptive statistics based on the mITT population.

Time since first diagnosis will be calculated in weeks as:

- Time since first diagnosis = (date of informed consent – date of first diagnosis) / 7

Imputation in case of partial dates for the calculation of the time since first diagnosis will be applied according to Section 8.3.

All NK data for the study eye will be presented in a by-patient listing.

9.4. Other Medical History

Medical history other than NK in the study eye will be coded using MedDRA 22.1. System Organ Class (SOC) and Preferred Term (PT) will be presented alphabetically in a table by treatment group and overall based on the mITT population.
The by-patient listing will display the SOC and PT, sorted by start date as well as SOC and PT alphabetically.

9.5. Medications and Other Interventions

9.5.1. Prior Medication

Prior medication will be coded using the WHO Drug Dictionary, and patient incidence will be summarised and tabulated by Anatomic Therapeutic Class (ATC) Level 2 and Level 3 term and preferred term by treatment group and overall based on the mITT population. Patients will be counted only once for each ATC term or preferred term in the event that they have multiple records of the same ATC term or preferred term in the database. If a prior medication is used to treat an AE, the AE number will be presented in the prior and concomitant medication listing. If the prior medication is related to the medical history, the medical history number will be listed as well. The same applies if the use of prior medication is related to any ocular intervention or surgery or procedure, then the respective event number will be displayed in the listing for reference.

Prior medications will be defined as any medication taken before the date of first treatment administration.

9.5.2. Concomitant Medication

Concomitant medication will be coded using the WHO Drug Dictionary, and patient incidence will be summarised and tabulated by ATC Level 2 and 3 term and preferred term by treatment group and overall based on the mITT population. Patients will be counted only once for each ATC term or preferred term in the event that they have multiple records of the same ATC term or preferred term in the database. If a concomitant medication is used to treat an AE, the AE number will be presented in the prior and concomitant medication listing. If the concomitant medication is related to the medical history, the medical history number will be listed as well. The same applies if the use of concomitant medication is related to any ocular intervention or surgery or procedure then the respective event number will be displayed in the listing for reference.

A concomitant medication is defined as taken between the date of first dose of treatment and the date of last dose of treatment.

Any medication missing both start and stop dates or having a start date prior to the first treatment administration and missing the stop date or having a stop date on or after the last treatment administration and missing start date will be counted as concomitant. If only partial dates are available the approaches described in Section 8.3 are used to determine if a medication is concomitant.

9.5.3. Prior and Concomitant Ocular Interventions

All prior and concomitant ocular interventions will be listed. If the intervention is related to a record of medical history or an AE, then the AE/medical history number will be presented in the listing as well.

Ocular interventions will be summarised using both continuous and categorical descriptive statistics based on the mITT population.

Prior interventions will be defined as any intervention before the date of first treatment administration. A concomitant intervention is defined as conducted between the date of first dose of treatment and the date of last dose of treatment.

Any intervention missing the start date it will be counted as concomitant. If only partial dates are available the approaches described in Section 8.3 are used to determine if an intervention is concomitant.

9.5.4. Prior and Concomitant Surgeries and Procedures (Other Than Ocular)

All prior and concomitant surgeries and procedures will be listed. If they are related to a record of medical history or an AE, then the AE/medical history number will be presented in the listing as well.

Any surgery or procedure will be summarised using both continuous and categorical descriptive statistics based on the mITT population.

Prior surgeries or procedures will be defined as any surgery or procedure before the date of first treatment administration. A concomitant surgery or procedure is defined as conducted between the date of first dose of treatment and the date of last dose of treatment.

Any surgery or procedure missing the start date will be counted as concomitant. If only partial dates are available the approaches described in Section 8.3 are used to determine if a surgery or procedure is concomitant.

9.6. Extent of Exposure

Exposure will be calculated in days as:

- Exposure = date of last treatment administration - date of first treatment administration + 1.

In case the treatment dosing is interrupted by either the patient or investigator, the number of subjects with interruptions will be summarised, and the duration of interruption (days) is calculated and summarised. This interruption duration is also subtracted from the extent of exposure duration.

- Interruption = interruption end date - interruption start date + 1.

Study duration (days) will be obtained as follows:

- Study duration = end of study date - date of informed consent + 1.

All data for study drug dispensation, dosing, and supply accountability will be listed. A summary will be provided for the extent of exposure by treatment group and overall based on the SAF population.

9.7. Treatment Compliance

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. Patient compliance with the treatment will be assessed overall.

Overall 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. Discontinuation of treatment for noncompliance is at the investigator's discretion and is to be noted on the eCRF.

Overall compliance (%) = (Number of used BFS containers) / [4 * (number of BFS to be used based on actual number of days of treatment)] * 100

With actual number of days of treatment calculated as:

Actual number of days = (last treatment administration date) – (first treatment administration date) + 1

Overall compliance will be summarised in a table by treatment group and overall based on the SAF population, and all data will be presented in a by-patient listing.

10. Efficacy

The analysis of all efficacy endpoints will be performed for the mITT population. Tertiary sensitivity analyses of the primary efficacy endpoint will also be performed on the PP population. The vehicle group will be used as reference group for all statistical tests.

All categorical endpoints will be analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by region at randomisation as well as NK stage at randomisation. SAS procedure proc freq will be used.

All time-to-event endpoints will be evaluated by means of Kaplan-Meier (Kaplan & Meier 1958) survival analysis using a log-rank test. The Cox's proportional hazard model is used to estimate the hazard ratios, 95% confidence limits and p-values and includes covariates such as treatment group and randomisation strata, i.e. NK stage and region. SAS procedure proc lifetest will be used for the Kaplan-Meier analysis and proc phreg will be used for the Cox model.

All data from the enrolled patient population will be listed. Screen failures or patients who are not treated will be presented at the end of the listings. All SAS procedures and algorithms will be detailed in the supplemental ADaM results metadata as well as the ADaM specifications and complex algorithem document.

10.1. Primary Efficacy Endpoint and Analysis

10.1.1. Primary Analysis of the Primary 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:

- Complete corneal healing: if the question of no corneal fluorescein staining is reported 'Yes' and the greatest diameter of corneal fluorescein staining < 0.5 mm in the area of the PED/ulcer
- No complete corneal healing: if the question of no corneal fluorescein staining is reported 'No' and the greatest diameter of corneal fluorescein staining < 0.5 mm in the area of the PED/ulcer

The primary analysis will be performed on the mITT population. The estimand framework and handling of intercurrent events will be applied as per Section 7.1. Missing data will be imputed with single value imputation as per Section 8.3.2. The CMH test will be used for the analysis, controlling for randomisation strata, i.e. NK stage and region at Week 8.

Confirmatory analysis will be based on the primary estimand. The study will compare 3 different doses of REC 0/0559 with vehicle, resulting in the need of a multiplicity adjustment. Assuming a treatment effect and considering the limited number of patients per group that might impact in the true percentages for the pairwise comparisons, a gate keeping procedure will be applied allocating initially 4% type one error to the 1. REC 0/0559 5.0 µg/day vs vehicle and 1% type one error to the, 2. REC 0/0559 2.5 µg/day vs vehicle.

- If the 1. REC 0/0559 5.0 µg/day is significant at 4%, the 2. REC 0/0559 2.5 µg/day will be tested at 5% (1%+4%).
- If the 2. REC 0/0559 2.5 µg/day is significant at 1%, the 1. REC 0/0559 5.0 µg/day will be tested at 5% (4%+1%).

If both the doses are significant vs vehicle then the 3. REC 0/0559 0.5 µg/day vs vehicle will be tested at 5% level.

In the table output, the number and percentage of patients who achieved corneal healing at Week 8 and the number and percentage of patients who did not will be presented by randomisation strata for each treatment group. In addition, the risk estimates and difference for response (complete corneal healing) with 95% confidence intervals (CIs) to show the effectiveness in each of the treatment groups will be presented by randomisation strata. In case the cell counts of the 2x2 tables are too small, the exact 95% CIs (Clopper Pearson CI) will be reported if available (Clopper & Pearson 1934). The common risk difference, odds ratio (OR), 95% CI, and the CMH test statistics will be presented.

10.1.2. Supplementary Estimand of the Primary Endpoint

The supplementary estimand of the primary endpoint will be performed according to the estimand framework and definitions of intercurrent events in Section 7.1.1. Missing data will be imputed with MI as per Section 8.3.2.

The same table output will be created as for the primary analysis.

10.1.3. First Sensitivity Analysis of the Primary Endpoint

As first sensitivity analyses, the primary analysis will be performed according to the estimand framework and definitions of intercurrent events in Section 7.1.2. Missing data will be imputed with MI as per Section 8.3.2.

10.1.4. Second Sensitivity Analysis of the Primary Endpoint

As secondary sensitivity analyses, the primary analysis will be repeated for the mITT population with all ICE and true missing data based on observed data only as per Section 7.1.3.

10.1.5. Supportive Sensitivity Analysis of the Primary Endpoint

As supportive sensitivity analyses, the primary analysis will be repeated for the PP population according to the estimand framework and definitions of intercurrent events in Section 7.1.4.

10.2. Key Secondary Efficacy Endpoint and Analyses

The key secondary 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 and no persistent staining outside of corneal lesion elsewhere in the cornea (i.e. not changing in shape and/or location at different timepoints) as assessed by an independent central reading centre:

The analysis will be performed on the mITT population according to the primary estimand framework and ICE definitions of the primary efficacy endpoint (Section 7.2) using the CMH test controlling for randomisation strata at Week 8. Missing data will be imputed with single value imputation as per Section 8.3.2. A similar table output as for the primary efficacy analysis will be provided..

10.3. Secondary Efficacy Endpoints and Analyses

If significance is reached for the three doses on the primary endpoint, the gate keeping procedure used for the primary endpoint will also be used for secondary endpoints (in the hierarchical order as listed in section 5).

10.3.1. Secondary Efficacy Endpoint 1

The percentage of patients who achieve a ≥ 5-, 10-, and 15-letter mean improvement in BCDVA by the ETDRS chart at Week 8 compared to baseline will be summarised for all patients and for patients with a central location of the PED or corneal ulcer.

The analysis will be performed on the mITT population according to the estimand framework and ICE definitions of the binary secondary efficacy endpoints (Section 7.2) using the CMH test controlling for randomisation strata at Week 8. Missing data will be imputed with single value imputation as per Section 8.3.2. A similar table output as for the primary efficacy analysis will be provided by all patients and by only patients with a central location of PED or corneal ulcer.

A descriptive frequency table will present the number and percentage of patients per visit and overall that have reported finger counting, hand motion, light perception or no light perception based on observed data.

10.3.2. Secondary Efficacy Endpoint 2

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 the investigator, will be summarised. The analysis will be performed on the mITT population according to the estimand framework and ICE definitions of the binary secondary efficacy endpoint (Section 7.2) using the CMH test controlling for randomisation strata at Week 8. Missing data will be imputed with single value imputation as per Section 8.3.2. The same table output as for the primary efficacy analysis will be created.

10.3.3. Secondary Efficacy Endpoint 3

The time to complete corneal healing of PED or corneal ulcer is defined as the time from treatment start to no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reader in days. Treatment group and randomisation strata, disease stage and region, are used as covariates. Patients who do not achieve complete corneal healing until end of treatment (V8/D56) are censored at date of V8/D56 or last available assessment date if early terminated in case no intercurrent event (ICE) occurred. The censoring date after the occurrence of an ICE and respective imputation will be the actual assessment date at (V8/D56), if available. In case the patient has no efficacy assessment done at (V8/D56), the censoring time (days) after the ICE occurrence will be set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. The analysis will be performed on the mITT population according to the estimand framework and ICE definitions for the time to event endpoints (Section 7.2). Missing data will be imputed with single value imputation as per Section 8.3.2.

The hazard ratios (HRs) and their 95% Wald CIs and p-values, as well as the estimate and 95% CI for the median, 25% and 75% quartiles of time to complete corneal healing, will be reported in a table; the survival probability for the treatment groups will be plotted in a figure.

10.3.4. Secondary Efficacy Endpoint 4

The time to complete corneal healing of PED or corneal ulcer is defined as the time from treatment start to no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by the investigator in days. Treatment group and randomisation strata, disease stage and region are used as covariates. Patients who do not achieve complete corneal healing until end of treatment (V8/D56) are censored at date of V8/D56 or last available date if early terminated terminated in case no intercurrent event (ICE) occurred. The censoring date after the occurrence of an ICE and respective imputation will be the actual assessment

date at (V8/D56) if available. In case the patient has no efficacy assessment done at (V8/D56), the censoring time (days) after the ICE occurrence will be set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. The analysis will be performed on the mITT population according to the estimand framework and ICE definitions for the time to event endpoints (Section 7.2). Missing data will be imputed with single value imputation as per Section 8.3.2..

The HRs and their 95% Wald CIs and p-values, as well as the estimate and 95% CI for the median, 25% and 75% quartiles of time to complete corneal healing, will be reported in a table; the survival probability for the treatment groups will be plotted in a figure.

10.3.5. Secondary Efficacy Endpoint 5

Deterioration of the disease at Week 8 is defined as an increase in lesion size ≥ 1 mm compared to baseline 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.

The analysis will be performed on the mITT population according to the estimand framework ind ICE definitions of the binary secondary efficacy endpoint (Section 7.2) using the CMH test controlling for randomisation strata at Week 8. Missing data will be imputed with single imputation as per Section 8.3.2. The same table output as for the primary efficacy analysis will be created.

10.3.6. Secondary Efficacy Endpoint 6

An ANCOVA will be performed for the 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 with missing values imputed as per estimand strategies and definitions of intercurrent events for continuous secondary efficacy endpoints as described in Section 7.2. Missing data will be imputed with MI as per Section 8.3.2. The least squares mean (LSM) estimates and 95% CIs of each treatment group as well as the LSM differences, 95% CIs, and p-values from the comparison between the REC 0/0559 groups and vehicle group will be reported separately for all patients and for patients with a central location of PED or corneal ulcer. Descriptive summary of the mean change from baseline at Week 8 based on imputed data will also be presented. In addition, BCDVA values and changes from baseline are summarised descriptively by visit based on observed data only.

10.3.7. Secondary Efficacy Endpoint 7

The percentage of patients at Week 8 with improvement in corneal sensitivity from baseline, as measured by the Cochet-Bonnet aesthesiometer, will be summarised.

The corneal sensitivity is assessed as the mean (cm) of the results of the assessment of the 5 cornea sections (central, superior-nasal, inferior-nasal, superior-temporal, inferior-temporal). The mean is calculated based on all available results at a certain visit. Assessments of cornea locations that are not applicable are disregarded and not included in the calculation of the mean.

The analysis will be performed on the mITT population according to the estimand framework and ICE definitions of the binary secondary efficacy endpoints (Section 7.2) using the CMH test controlling for randomisation strata at Week 8. Missing data will be imputed with single value imputation as per Section 8.3.2. Imputation is performed on the responder/non-responder variable, derived from the mean values calculated from the 5 cornea sections at the respective visits. The same table output will be created as for the primary efficacy analysis.

10.4. Other Efficacy Endpoints and Analyses

10.4.1. Other Efficacy Endpoint 1

The 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 a central reader, will be summarised.

The analysis will be performed on the mITT population according to the estimand framework and ICE definitions of the binary secondary and other efficacy endpoints (Section 7.2) using the CMH test controlling for randomisation strata at Week 8. Missing data will be imputed as per Section 8.3.2. The same table output will be created as for the primary efficacy analysis.

10.4.2. Other Efficacy Endpoint 2

The 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, was summarised.

The analysis will be performed on the mITT population according to the estimand framework and ICE definitions of the binary secondary and other efficacy endpoints (Section 7.2) using the CMH test controlling for randomisation strata at Week 8. Missing data will be imputed as per Section 8.3.2. The same table output will be created as for the primary efficacy analysis.

10.4.3. Other Efficacy Endpoint 3

The percentage of patients achieving complete corneal clearing at Week 8, defined as a score of 0 using the Oxford scale, will be summarised.

The analysis will be performed on the mITT population according to the estimand framework ind ICE definitions of the binary secondary and other efficacy endpoints (Section 7.2) using the CMH test controlling for randomisation strata at Week 8. Missing data will be imputed as per Section 8.3.2. The same table output will be created as for the primary efficacy analysis. In addition the Oxford scale results are summised descriptively by frequency counts by visit based on observed data only.

10.4.4. Other Efficacy Endpoint 4

The time from treatment start to at least 50% corneal healing is defined as a ≥ 50% reduction in the greatest diameter of the lesion as determined by a central reader in days. Treatment group and randomisation strata are used as covariates. Patients who do not achieve at least 50% corneal healing until end of treatment (V8/D56) are censored at date of V8/D56 or last available date if early terminated in case no intercurrent event (ICE) occurred. The censoring date after the occurrence of an ICE and respective imputation will be the actual assessment date at (V8/D56), if available. In case the patient has no efficacy assessment done at (V8/D56), the censoring time (days) after the ICE occurrence will be set to Day 56, which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. The analysis will be performed on the mITT population according to the estimand framework and ICE definitions for the time to event endpoints (Section 7.2). Missing data will be imputed with single value imputation as per Section 8.3.2.

The HRs and their 95% Wald CIs and p-values, as well as the estimate and 95% CI for the median, 25% and 75% quartiles of time to at least 50% corneal healing, will be reported in a table; the survival probability for the treatment groups will be plotted in a figure.

10.4.5. Other Efficacy Endpoint 5

The time from treatment start to at least 50% corneal healing was defined as a ≥ 50% reduction in the greatest diameter of the lesion as determined by the investigator in days. Treatment group and randomisation strata are used as covariates. Patients who do not achieve at least 50% corneal healing until end of treatment (V8/D56) are censored at date of V8/D56 or last available date if early terminated in case no intercurrent event (ICE) occurred. The censoring date after the occurrence of an ICE and respective imputation will be the actual assessment date at (V8/D56), if available. In case the patient has no efficacy assessment done at (V8/D56), the censoring time (days) after the ICE occurrence will be set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. The analysis will be performed on the mITT population according to the estimand framework and ICE definitions for the time to event endpoints (Section 7.2). Missing data will be imputed with single value imputation as per Section 8.3.2.

The HRs and their 95% Wald CIs and p-values, as well as the estimate and 95% CI for the median, 25% and 75% quartiles of time to at least 50% corneal healing, will be reported in a table; the survival probability for the treatment groups will be plotted in a figure.

10.4.6. Other Efficacy Endpoint 6

The time from treatment start to onset of healing was defined as a > 20% reduction in the greatest diameter of the lesion as determined by a central reader in days. Treatment group and randomisation strata are used as covariates. Patients who do not achieve > 20% reduction until end of treatment (V8/D56) are censored at date of V8/D56 or last available date if early terminated in case no intercurrent event (ICE) occurred. The censoring date after the occurrence of an ICE and respective imputation will be the actual assessment date at (V8/D56) if available. In case the patient has no efficacy assessment done at (V8/D56), the censoring time (days) after the ICE occurrence will be set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. The analysis will be performed on the mITT population according to the estimand framework and ICE definitions for the time to event endpoints (Section 7.2). Missing data will be imputed with single value imputation as per Section 8.3.2.

The HRs and their 95% Wald CIs and p-values, as well as the estimate and 95% CI for the median, 25% and 75% quartiles of time to onset of corneal healing, will be reported in a table; the survival probability for the treatment groups will be plotted in a figure.

10.4.7. Other Efficacy Endpoint 7

The time from treatment start to onset of healing was defined as a > 20% reduction in the greatest diameter of the lesion as determined by the investigator in days. Treatment group and randomisation strata are used as covariates. Patients who do not achieve > 20% reduction until end of treatment (V8/D56) are censored at date of V8/D56 or last available date if early terminated in case no intercurrent event (ICE) occurred. The censoring date after the occurrence of an ICE and respective imputation will be the actual assessment date at (V8/D56), if available. In case the patient has no efficacy assessment done at (V8/D56), the censoring time (days) after the ICE occurrence will be set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. The analysis will be performed on the mITT population according to the estimand framework and ICE definitions for the time to event endpoints (Section 7.2). Missing data will be imputed with single value imputation as per Section 8.3.2.

The HRs and their 95% Wald CIs and p-values, as well as the estimate and 95% CI for the median, 25% and 75% quartiles of time to onset of corneal healing, will be reported in a table; the survival probability for the treatment groups will be plotted in a figure.

10.5. Other Exploratory Endpoints and Analyses

10.5.1. Other Exploratory Endpoint 1

The change from baseline in QoL evaluated using the NEI VFQ-25 will be analyzed (Mangione at al. 2001). Scores for the NEI VFQ-25 will be calculated according to the NEI VFQ-25 scoring algorithm document, and the original responses captured in the CRF are recoded according to Table 8. The subscale scores are calculated as the arithmetic mean over the items available in each subscale (Table 9). The composite score is the arithmetic mean over all subscale scores excluding the general health item.

Responses for each item are converted to a scale from 0 to 100, with 0 representing the worst and 100 representing the best visual functioning.

Table 8: Recoding of item responses for calculation of subscale means

Item Numbers	Original Response Category	Recoded
1, 3, 4, 15c *	1 2 3 4 5	100 75 50 25 0
2	1 2 3 4 5 6	100 80 60 40 20 0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a	1 2 3 4 5 6	100 75 50 25 0 Missing #
17, 18, 19, 20, 21, 22, 23, 24, 25	1 2 3 4 5	0 25 50 75 100

*: Item 15c has four-response levels but is expanded to five-levels using item 15b. If 15b = 1 then recode to 15c = 0; if 15b = 2 then 15c = missing; if 15b = 3 then 15c = missing.

#: The original response category 6 indicates problems that are not related to vision and therefore it is recoded as missing.

Table 9: Averaging items to generate subscale scores

Scale	Number of items	Items to be averaged (after recoding per Table 10)
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14

Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Mean scores per subscale are calculated based on non-missing answers devided by the total number of items with non-missing answers. The same is applicable for the composite score.

An ANCOVA will be performed for the change from baseline in composite score data at Week 8. The LSM estimates and 95% CIs of each treatment group, as well as the LSM differences, 95% CIs and p-values from the comparison between the REC 0/0559 groups and the vehicle group, will be reported. Missing values for the composite and subscale scores are imputed according to the estimand framework and definition of ICE of the continuous secondary and other exploratory efficacy endpoints (Section 7.2). Missing data will be imputed with MI as per Section 8.3.2. A summary table will present all values and changes from baseline in composite and subscale scores by visit and treatment group based on observed data only.

10.5.2. Other Exploratory Endpoint 2

The change from baseline in the overall NRS score for ocular symptoms and tolerability will be analyzed. The overall NRS score will be calculated as the arithmetic mean of individual symptoms scores. If more than 3 symptom scores are missing the overall NRS mean score will be set to missing for the respective visit.

An ANCOVA will be performed for the change from baseline in overall NRS score at Week 8. The LSM estimates and 95% CIs of each treatment group, as well as the LSM differences, 95% CIs and p-values from the comparison between the REC 0/0559 groups and vehicle group, will be reported. Missing values for the overall mean NRS score are are imputed according to the estimand framework and definition of ICE of the continuous secondary and other exploratory efficacy endpoints (Section 7.2). Missing data will be imputed with MI as per Section 8.3.2. A summary table will present all values and changes from baseline in each symptom score and overall score by visit and treatment group based on observed data only.

11. Analysis of Pharmacokinetics

The pharmacokinetics of MT6, the active metabolite of REC 0/0559, will be evaluated using an intense PK sampling schedule for the first 24 patients on Day 1 and Day 7. All randomised patients will have trough levels measured at Day 28 and Day 56. All outputs are presented for the patients in the PK population.

11.1. PK Sampling Schedule

Blood samples for the PK analysis of MT6 levels will be collected at the time points indicated below. 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), a predose PK sample will be obtained, and postdose PK samples will be obtained at 10, 20, and 40 minutes, and 1, 2, and 4 hours after the first daily REC 0/0559 administration (before the next REC 0/0559 administration), and at 20 minutes and 4 hours after the second daily REC 0/0559 administration.

On Day 28 (±2 days) and Day 56 (±3 days), trough PK sampling will be done for all patients at 4 hours postdose (before the next REC 0/0559 administration).

11.2. Plasma PK Parameters

For the first 24 patients:

- On Day 1 and Day 7: PK parameters of C_{max}, $C_{max\ ss}$, T_{max}, $T_{max\ ss}$, AUC_{0-4} (Day 1), AUC_{τ} (Day 7) and AUC_{0-t} for the 1st daily administration using an intense PK collection schedule
- On Day 1 and Day 7: plasma levels at 20 minutes and 4 hours after the 2nd daily administration

C_{trough} for all patients:

- On Day 28 and Day 56: trough plasma levels at 4 hours postdose (before the next REC 0/0559 administration)

11.3. Presentation of Concentration Data

11.3.1. Handling of Missing Data

Missing concentration data for all patients who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of AUC and for the individual plasma concentration versus time curves, the following rules will apply:

- On Day 1 and Day 7, all sample concentrations BLQ will be set to zero before the first measurable concentration, otherwise they will be set to missing
- The sampling time of pre-dose samples, collected before the first administration, relative to dosing will also be treated as zero

For plasma concentration summary, the following rules will apply:

- All BLQ values will be set to zero
- No further imputation will be applied to any missing values

11.3.2. Listing and Presentation of Individual PK Data

The actual and nominal sampling times of PK blood sample collection will be listed for each patient and will include the deviation in time from the protocol scheduled time (i.e., nominal time), if applicable.

All measured concentrations will be presented in original units as reported by the bioanalytical laboratory.

- Individual patient plasma concentration data will be listed by dosing regimen (dose level), patient, study visit and time point.
- Individual PK profiles on Day 1 and Day 7 will be presented by nominal times by dose level, if required by randomisation strata

11.3.3. Summary of PK Concentrations by Matrix

The summary of PK concentrations will be presented by dose level (cohort), by randomisation strata disease stage and region, by scheduled time points for each visit using the following descriptive statistics: n, number and % BLQ, arithmetic mean, SD, CV%, minimum, median, maximum.

11.4. PK Parameters Derivation

11.4.1. Handling of the No Reportable Concentration Values

Samples with invalid concentration (due to bioanalytical or clinical issue) will be replaced by “0.00” when it occurs prior to dosing. Otherwise they will be set to missing for tabulation, graphical representation and calculation purposes if it occurs after dosing.

11.4.2. Handling of the Difference between the Scheduled and the Actual Sampling Times

The actual clock time for dosing and each collection time for the PK samples will be recorded. For all sampling times, the actual sampling times relative to dosing will be calculated as the difference between the actual clock time of sampling and the actual clock time of dosing. The actual post-dose sampling times relative to dosing expressed in hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to dosing, which will always be reported as zero (0.000), regardless of the time difference. Scheduled sampling times will be presented in concentration tables individual and mean graphs.

11.4.3. Plasma Pharmacokinetic Parameters

Plasma concentrations from MT6 will be used to calculate the following parameters by standard non-compartmental methods.

On Day 1 and Day 7 (first 24 patients), the following PK parameters will be derived:

- C_{max}: maximum plasma concentration by direct observation from the concentration-time profile (on Day 1)
- T_{max}: Time to peak plasma concentration by direct observation from the concentration-time profile (on Day 1)

- $C_{max\ ss}$: maximum plasma concentration at steady-state by direct observation from the concentration-time profile (on Day 7)
- $T_{max\ ss}$: Time to peak plasma concentration at steady-state by direct observation from the concentration-time profile (on Day 7)
- AUC_{0-4}: area under the plasma concentration-time curve from zero to 4 hours post the 1st daily administration
- AUC_T: area under the plasma concentration-time curve during a dosage interval (4 hours) for the 1st daily administration using linear up log down trapezoidal method (on Day 7)
- AUC_{0-t}: Area under the concentration-time curve from time zero to the last measurable concentration for the 1st daily administration using linear up log down trapezoidal method (on Days 1 and 7)
- C_{trough}: Trough plasma concentration (measured concentration at the end of a dosing interval [taken directly before next administration])

The remaining other plasma levels will only be listed and summarised and not used for any PK parameters calculations.

11.4.4. PK Parameters Summarisation

C_{max}, $C_{max\ ss}$, T_{max}, $T_{max\ ss}$, AUC_{0-4} (Day 1), AUC_T (Day 7) and AUC_{0-t} and C_{trough} will be summarised for Day 1 and Day 7 using arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean, and geometric CV%.

The PK parameters will be summarised by dose level and by randomisation strata disease stage (stage 2 and stage 3) and region (North America and Europe) based on the PK population.

11.5. Planned Statistical Models for PK Parameters and Concentrations

Not applicable.

11.6. Interim Analyses

Not applicable.

11.7. Deviation from Analyses Planned in Protocol

Not applicable.

12. Safety

The population used for safety analyses will be the Safety Population (SAF). Safety will be assessed on the basis of AEs, clinical laboratory data, ECG parameters, physical examinations, further opthalomological examinations, and vital signs.

12.1. Adverse Events

Adverse events will be coded using the MedDRA coding system.

Analyses of AEs will mostly be performed for those events that are treatment-emergent, which is defined as any condition that was not present prior to the first study drug treatment but appeared following treatment.

If the start date of an AE is partially missing, the date will be compared as far as possible with the start date of study treatment. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur during the treatment administration period (worst case approach).

The following general rules to determine if an AE is treatment-emergent will be used:

- If the start day is missing but the start month and year are complete, an AE will be excluded only if the start month/year is before the month/year of treatment administration or if the stop date/time is before first treatment administration.
- If the start day and month are missing but the start year is complete, an AE will be excluded only if the start year is before the year of treatment administration or if the stop date/time is before first treatment administration.
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date is before first treatment administration.

Adverse events are summarised by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given SOC or PT (i.e., the most related occurrence or the most intense occurrence).

An overall AE incidence summary table will be produced and will include:

- The number and percentage of patients reporting at least 1 AE
- The number and percentage of patients reporting at least 1 Ocular AE
- The number and percentage of patients reporting at least 1 Ocular AE on study eye
- The number and percentage of patients reporting at least 1 TEAE
- The number and percentage of patients reporting at least 1 ocular TEAE
- The number and percentage of patients reporting at least 1 TEAE (by maximum intensity)
- The number and percentage of patients reporting at least 1 Serious AE (SAE)
- The number and percentage of patients reporting at least 1 ocular Serious AE (SAE)
- The number and percentage of patients reporting at least 1 serious TEAE
- The number and percentage of patients reporting at least 1 ocular serious TEAE
- The number and percentage of patients reporting at least 1 related TEAE
- The number and percentage of patients reporting at least 1 related serious TEAE
- The number and percentage of patients reporting at least 1 TEAE leading to study drug discontinuation

- The number and percentage of patients reporting at least 1 ocular TEAE leading to study drug discontinuation
- The number and percentage of patients with AEs leading to death
- The number and percentage of patients reporting at least 1 AE of special interest
- The number and percentage of patients reporting at least 1 AE due to overdose
- The number and percentage of patients reporting at least 1 AE onset during the screening period
- The number and percentage of patients reporting at least 1 ocular AE onset during the screening period
- The number and percentage of patients reporting at least 1 AE onset during the treatment administration period
- The number and percentage of patients reporting at least 1 ocular AE onset during the treatment administration period
- The number and percentage of patients reporting at least 1 AE onset during the follow-up period
  The number and percentage of patients reporting at least 1 ocular AE onset during the follow-up period

Tabulations by SOC and PT will be produced for:

- All AEs (overall and by study period: screening, treatment administration and follow-up)
- Ocular AEs, overall and stratified for eye
- TEAEs
- Ocular TEAEs, overall and stratified for eye
- TEAEs by maximum intensity
- Ocular TEAEs by maximum intensity
- SAEs, overall, non-ocular and ocular, stratified for eye
- Serious TEAEs, overall, non-ocular and ocular, stratified for eye
- Related TEAEs (related to study drug and/or study procedure)
- Related serious TEAEs
- TEAEs leading to study drug discontinuation, overall, non-ocular and ocular, stratified for eye
- AEs leading to death
- AEs of special interest
- AEs due to overdose

These will be presented by SOC and PT, sorted by highest frequency within SOC and PT in the Total column. The 'All AEs' table will be presented by study period (overall, screening, treatment administration and follow-up). AEs that span multiple of these periods will only be counted once in the study period of the onset of the AE.

Patient listings will be generated for all AEs, all ocular AEs, all SAEs, TEAEs, AEs of special interest, AEs leading to study drug discontinuation, AEs due to overdose, and deaths.

12.2. Laboratory Evaluations

Baseline values and changes from baseline for each laboratory parameter reported in Table 10 will be descriptively summarised by treatment group and number of patients with values outside limits of the normal range at each time point will be presented. In case of multiple available results per visit and timepoint, the first will be used and esults below the lower limit of quantitation will be set equal to the LLOQ for the descriptive summary tables. All data will be listed as collected.

Table 10: Clinical Laboratory Parameters

Hematology	**Biochemistry**
Red blood cells	Albumin
White blood cells	Alanine aminotransferase
Neutrophils	Aspartate aminotransferase
Lymphocytes	Alkaline phosphatase
Monocytes	Blood urea nitrogen
Eosinophils	Creatinine
Basophils	Sodium
Haematocrit	Potassium
Haemoglobin	Chloride
Mean corpuscular haemoglobin	Calcium
Mean corpuscular haemoglobin concentration	Phosphorus
Mean corpuscular volume	Gamma-glutamyl transpeptidase
Platelet count	Glucose
Other	Lactate dehydrogenase
	Total bilirubin
	Direct bilirubin
	Total cholesterol
	Triglycerides
	Other

12.3. Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate), including the change from baseline, will be presented in a summary table for all treatment groups by visit, and all data (including height and weight) are presented for each patient in a listing.

12.4. ECG

The 12-Lead ECG findings will be presented in a by-patient listing. ECG assessments were only performed in the first 24 patients of cohorts 1 to 3 as the IDMC decision in the first formal meeting was to drop the ECG assessments from the list of scheduled study assessments for all patients enrolled in the cohort 4.

12.5. Physical Examination

All physical examination findings will be presented in a by-patient listing.

12.6. Other Safety

12.6.1. Opthalmological Safety Examination

All findings from the slit lamp examin ation (except from the cornea) of the study eye and the fellow eye will be listed.

12.6.2. Fundus Examination

All data from the fundus examination of the study eye and the fellow eye will be listed.

13. Interim Analyses

No formal interim analysis is planned.

14. Reference List

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15. Programming Considerations

Computer-generated output will adhere to the following specifications. The standard operating procedures (SOPs) of Syneos Health Clinical will be followed in the creation and quality control of all tables, listings and figures.

PK parameters are calculated with Phoenix® WinNonlin® version 8.3.4 (Certara USA, Inc., Princeton, NJ).

15.1. General Considerations

- Every TLF program creates only one output. Macros can be used within multiple TLF programs
- Every TLF program creates one RTF and XML file. If inferential statistical methods are used then also a separate detailed output of the SAS procedures referred to as 'stat output' will be created as well.
- Numbering of TLFs will follow ICH E3 guidance

15.2. Table, Listing, and Figure Format

15.2.1. General

- All TLFs will be produced in landscape format on unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TLFs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ, ≥). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2. Headers

- All output should have the following header at the top left of each page, e.g.:

```
Recordati Rare Diseases Protocol REC0559-B-001 (Syneos Health study number 7001386)
```

```
Draft/Final Run, Date of DB data extract: <date>
```

- All output should have Page n of N at the top or bottom right corner of each page. TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

15.2.3. Display Titles

- Each TLF are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TLFs with related contents. The title is left aligned. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line. Subtitles are displayed left aligned directly beneath the last title tine:

```
Table x.y.z: First Line of Title xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Xxxxxxxxxxxxxxxxxxxx Second Line of Title if Needed (ITT)

Subtitle1: xxxx

Subtitle2: yyy if needed
```

15.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column if applicable. P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be lowest treatment dose first followed by the vehicle and then total column if applicable.

15.2.5. Body of the Data Display

15.2.5.1. General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified

- Whole numbers are central aligned
- Numbers containing fractional portions are center aligned

15.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n (%)
severe	0
moderate	8 (20.5)
mild	3 (79.5)

  Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more digit than the original values, and standard deviations are printed out to 2 more digits than the original values. The minimum and maximum should report the same digits as the original values. For example:

n	XX
Mean (SD)	XXX.X (XX.XX)
Minimum	XXX
Median	XXX.X
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- If in descriptive summary table n = 1 the SD should be presented as “(-)”
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8), 13 (5.4)). The number N of patients in the analysis set for the treatment group who have an observation will be the denominator unless stated in a footnote

otherwise. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Any overall or total scores that are calculated based on scores reported in the CRF, are to be presented with one more decimal than the original scores.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC and within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC2 and ATC3 code), and adverse events (by preferred term) are displayed by highest frequency count within the Total column.
- P-values, estimates or confidence intervals which cannot be estimated are displayed as 'NE' with a footnote 'NE = Not estimable'
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. If calculated otherwise it is described in details in the footnotes or programming notes.
- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Exact confidence intervals are calculated if the number of observations per cell in contingency tables is too small. Otherwise asymptotic CIs will be reported.

15.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups (lowest dose to highest dose and then vehicle), patient number, visit/collection day, and visit/collection time if not specified otherwise in the programming notes.
- Missing data are represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where applicable.

15.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

15.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Patient specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than 10 lines of footnotes are planned, then all footnotes are displeay only on the first page of the output and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source, and/or the dataset (i.e., ‘`Program: myprogram.sas  Listing source: 16.x.y.z`’).

16. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the process of statistical programming for SDTMs, ADaMs and TLF are detailed in the SOPs 3921.01 and 3922.02. Qulaity control is detailed in the SAS Programming and Validation Plan for this study and the purpose and generation of this plan is detailed in SOP 3920.01.

17. Index of Tables

Index of table shells is provided in Section 20.1.

18. Index of Figures

Index of figure shells is provided in Section 20.1.

19. Index of Listings

Index of listing shells is provided in Section 20.2.

20. Shells

20.1. Tables and Figures

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Table 14.1.1.1 Summary of Patient Enrollment and Disposition (Enrolled Set)

	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)	Total (N=xx) n (%)
Patients screened				n	n
Screen failures					n
Patients randomised	n (xx)	n (xx)	n (xx)	n (xx)	
Patients treated	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Region at randomisation					
North America	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Europe	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Country					
Xxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Site					
Xxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage at randomisation					
2 (Moderate)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
3 (Severe)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Patients discontinued treatment	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Adverse Event	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
COVID-19					
Withdrawal by subject	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Death	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Lost to follow-up	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Physician decision	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Protocol Deviation	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Other	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Patients completed treatment	n (xx)	n (xx)	n (xx)	n (xx)	
Patients completed study	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Patients discontinued from study	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Adverse Event					
COVID-19					
Withdrawal by subject	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Death	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)

Lost to follow-up	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Physician decision	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Protocol Deviation	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Other	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)

n: Number of patients with data available, N: Number of randomised patients within treatment group
Note: Percentage is based on number of patients within treatment group (N).
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Percentages are based on N.

Table 14.1.2.1 Summary of Protocol Deviations (mITT)

	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)	Total (N=xx) n (%)
At least one Major Protocol Deviation	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Major Protocol Deviations					
Xxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Xxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Protocol Deviations due to COVID-19	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)

n: Number of patients with data available, N: Number of patients within treatment group
Note: Percentage is based on number of patients within treatment group.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Percentages are based on N.

Table 14.1.2.2 Summary of Study Populations (Enrolled Set)

Analysis Population	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)	Total (N=xx) n (%)
Enrolled Population	n (100)	n (100)	n (100)	n (100)	n (100)
Safety Population (SAF)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Reasons for exclusion rom SAF					
Xxxxxxxxxx xxxxxxxxxxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Xxxxxx xxxxxxxxxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Modified Intent-to-Treat (mITT)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Reasons for exclusion from mITT					
Xxxxxxxxxx xxxxxxxxxxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Xxxxxx xxxxxxxxxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Per Protocol Population (PP)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Sub-populations					
Xxxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Xxxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)

n: Number of patients with data available, N: Number of patients within treatment group
Note: Percentage is based on number of patients within treatment group.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
The Sub-population sets are listed based on the data availability before DB lock according to SAP section 6.6. See section 14 for Format of output in the SAP. Percentages are based on N.

Table 14.1.3.1.1 Summary of Demographic and Baseline Characteristics (mITT)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)	Total (N=xx)
Region at Randomisation, n (%)					
North America	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Europe	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Country, n (%)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Xxxxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…					
Disease stage at Screening, n (%)					
2 (Moderate)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
3 (Severe)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Disease stage at Randomisation, n (%)					
2 (Moderate)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
3 (Severe)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Age (years)					
n	x	x	x	x	x
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx
Sex, n (%)					
Male	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Female	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Childbearing potential, n (%) #					
Yes	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
No	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Race, n (%)					
American Indian or Alaska Native	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Asian	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Black or African American	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Native Hawaiian or other Pacific Islander	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
White	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Other	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Xxxx	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Ethnicity, n (%) *					

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)	Total (N=xx)
Hispanic or Latino	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Not Hispanic or Latino	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Not Reported	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Unknown	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Iris color of the Study Eye, n (%)					
Blue	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Green	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Light Brown	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Dark Brown	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Unable to assess	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Weight (kg)					
n	x	x	x	x	x
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx
Height (cm)					
n	x	x	x	x	x
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx
Alcohol Status, n (%)					
Current	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Former	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Never	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Smoking Status, n (%)					
Current	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Former	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Never	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)

n: Number of patients with data available, N: Number of patients within treatment group, SD: Standard Deviation
#: Percentages are calculated based on only the female patients as denominator
*: Only available for patients from North America
Note: Percentages are based on number of patients within each treatment group.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Percentages are based on N except indicated otherwise by footnote.

Table 14.1.3.1.2 Summary of Demographic and Baseline Characteristics (PP)

Programming Note:
The layout and footnotes are the same as Table 14.1.3.1.1 but based on per-protocol population.

Table 14.1.3.2.1 Summary of Neurotrophic Keratitis (NK) Medical History in the Study Eye (mITT)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)	Total (N=xx)
Disease Stage at Screening, n (%)					
2 (Moderate)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
3 (Severe)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Time Since First Diagnosis (weeks)					
n	x	x	x	x	x
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx
Number of Episodes/Recurrences since First Diagnosis, n (%) [1]					
1	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
2	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Underlying Cause of NK, n (%)					
Herpes simplex	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Main Reason	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Other Cause	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Herpes zoster	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Main Reason	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Other Cause	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Neurosurgical procedure	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Main Reason	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)

n: Number of patients with data available, N: Number of patients within treatment group, SD: Standard Deviation
Note: Percentage is based on number of patients within treatment group.
Note: Time since first diagnosis (weeks) is calculated as ((date of informed consent signature) – (date of first diagnosis)) / 7. If only month and year are available, the day = 15 will be assumed. If only year is available, month = 6 and day = 15 will be assumed. In case the imputed date is greater than the date of signed informed consent (IC), then the date of IC will be used as date of first NK diagnosis.
Note: 'Other cause' for NK only includes CRF responses 'Yes' for each of the underlying causes.
[1]: Free text is assigned to appropriate category of number of episodes as applicable.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Percentages are based on N. Sort the order the underlying cause as listed in the CRF.

Table 14.1.3.3.1 Summary of Other Medical History (Except NK in Study Eye) (mITT)

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)	Total (N=xx) n (%)
Any Other Medical History (Except NK in Study Eye)	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Primary System Organ Class 1	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 1	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 2	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 3	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Primary System Organ Class 2	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 1	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 2	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 3	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 4	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)

n: Number of patients with data available, N: Number of patients within treatment group, NK: Neurotrophic Keratitis
Note: Percentage is based on number of patients within treatment group.
Note: a Patient is only counted oncve per SOC and PT.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Percentages are based on N. Sort by SOC and PT by highest frequency within the Total group. Add MedDRA version instead of place holder <version> in the footnote.

Table 14.1.3.3.2 Summary of Other Ocular Medical History (Except NK in Study Eye) (mITT)

Programming Note:
Use layout from table 14.1.3.3.1. and select only ocular medical history.

See section 15 for Format of output in the SAP. Percentages are based on N. Sort by SOC and PT by highest frequency within the Total group. Add MedDRA version instead of place holder <version> in the footnote.

Table 14.1.3.3.3 Summary of Prior and Concomitant Ocular Interventions (mITT)

Ocular Interventions: <occurrence>

	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)	Total (N=xx) n (%)
Any Ocular Intervention	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Type of Ocular Intervention					
Vitrectomy	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Cataract Surgery	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Reason for Intervention					
Adverse Event	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Medical History	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
NK Rescue	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Worsening of NK	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Other	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Eye					
Study	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Fellow	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Both	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Reason/Intervention resolved?	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Yes	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
No	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)

n: Number of patients with data available, N: Number of patients within treatment group, NK: Neurotrophic Keratitis
Note: Percentage is based on number of patients within treatment group.
Note: A patient is only counted once per ocular intervention.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Percentages are based on N. Present table by 'Overall' (prior and concomitant), 'Prior' and 'Concomitant' in subtitle. Sort intervention type as ordered in CRF.

Table 14.1.4.1 Summary of Prior and Concomitant Medications (mITT)

Medication: <occurrence>

ATC Level 2 ATC Level 3 Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)	Total (N=xx) n (%)
Any Medication	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
ATC Level 2 Term 1	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
ATC Level 3 Term 1	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 1	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 2	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 3	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
ATC Level 2 Term 2	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
ATC Level 3 Term 1	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 1	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 2	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 3	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Preferred Term 4	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
…	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
...					

n: Number of patients with data available, N: Number of patients within treatment group
Note: Percentage is based on number of patients within treatment group.
Note: A patient is only counted once per ATC level and PT.
Note: WHOdd <version> used.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Percentages are based on N. Patients will be counted only once for each ATC or preferred term in the event that they have multiple records of the same ATC or preferred term in the data. Sort by highest frequency by ATC 2 and 3 Level and PT. Present table by 'Overall' (prior and concomitant), 'Prior' and 'Concomitant' medication in subtitle. Add WHOdd version instead of <version> place holder in the footnote.

Table 14.1.4.2 Summary of Prior and Concomitant Surgery and Procedures (Other than Ocular) (mITT)

	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)	Total (N=xx) n (%)
Any Surgery or Procedure	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Prior	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Concomitant	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Reason for Surgery or Procedure					
Adverse Event	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Medical History	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)

n: Number of patients with data available, N: Number of patients within treatment group
Note: Percentage is based on number of patients within treatment group.
Note: A patient is only counted once per surgery or procedure.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Percentages are based on N.

Table 14.1.5.1 Summary of Treatment Compliance (SAF)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)	Total (N=xx)
Overall Compliance, n (%)					
< 80%	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
80% - 120%	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
> 120%	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Overall compliance (%)					
n	x	x	x	x	x
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx

n: Number of patients with data available, N: Number of patients within treatment group, SD: Standard Deviation, BFS: Blow Fill Seal

Note: Percentage is based on number of patients within treatment group.

Note: Overall compliance (%) is calculated based on (the number of used BFS containers) / [4 * (number of BFS containers to be used based on actual days of treatment)] * 100.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Display metrics for each scheduled Visit to Visit interval as well as the overall compliance over all visits at last.

Table 14.2.1.1 Percentage of Patients Achieving Complete Corneal Healing of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region - Central Reading – Primary Estimand (mITT)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Intercurrent events (ICE) up to Week 8, n (%)				
ICE1: Treatment discontinuation due to treatment-related AE	n (xx)	n (xx)	n (xx)	n (xx)
ICE2: Treatment discontinuation due to other reasons	n (xx)	n (xx)	n (xx)	n (xx)
ICE3: Start of rescue treatments/procedures	n (xx)	n (xx)	n (xx)	n (xx)
ICE4: Treatment discontinuation due to death	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage, Region at Randomisation				
2 (Moderate), EU				
Healed (%)	xx.x	xx.x	xx.x	xx.x
Not healed (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for complete corneal healing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), EU				
Healed (%)	xx.x	xx.x	xx.x	xx.x
Not healed (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for complete corneal healing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
2 (Moderate), NA				
Healed (%)	xx.x	xx.x	xx.x	xx.x
Not healed (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for complete corneal healing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), NA				
Healed (%)	xx.x	xx.x	xx.x	xx.x
Not healed (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for complete corneal healing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Odds (OR) controlling for disease stage and region for complete corneal healing				
Healed (%)	xx.x	xx.x	xx.x	xx.x
Not healed (%)	xx.x	xx.x	xx.x	xx.x
Estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Risk Difference				
Estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Cochran-Mantel-Haenszel (CMH) Test				

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Value	x.xx	x.xx	x.xx	
p-value [1]	x.xxx	x.xxx	x.xxx	

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal healing is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading centre.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP.

Table 14.2.1.2 Percentage of Patients achieving Complete Corneal Healing of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region - Central Reading – Supplementary Estimand (mITT)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Intercurrent events (ICE) up to Week 8, n (%)				
ICE1: Treatment discontinuation due to treatment-related AE	n (xx)	n (xx)	n (xx)	n (xx)
ICE2: Treatment discontinuation due to other reasons	n (xx)	n (xx)	n (xx)	n (xx)
ICE3: Start of rescue treatments/procedures	n (xx)	n (xx)	n (xx)	n (xx)
ICE4: Treatment discontinuation due to death	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage, Region at Randomisation				
2 (Moderate), EU				
Mean healed (%)	xx.x	xx.x	xx.x	xx.x
Mean not healed (%)	xx.x	xx.x	xx.x	xx.x
Mean risk difference for complete corneal healing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), EU				
Mean healed (%)	xx.x	xx.x	xx.x	xx.x
Mean not healed (%)	xx.x	xx.x	xx.x	xx.x
Mean risk difference for complete corneal healing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
2 (Moderate), NA				
Mean healed (%)	xx.x	xx.x	xx.x	xx.x
Mean not healed (%)	xx.x	xx.x	xx.x	xx.x
Mean risk difference for complete corneal healing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), NA				
Mean healed (%)	xx.x	xx.x	xx.x	xx.x
Mean not healed (%)	xx.x	xx.x	xx.x	xx.x
Mean risk difference for complete corneal healing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Odds (OR) controlling for disease stage and region for complete corneal healing				
Mean healed (%)	xx.x	xx.x	xx.x	xx.x
Mean not healed (%)	xx.x	xx.x	xx.x	xx.x
Mean estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Risk Difference				
Mean estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Cochran-Mantel-Haenszel (CMH) Test				

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Value	x.xx	x.xx	x.xx	
p-value [1]	x.xxx	x.xxx	x.xxx	

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal healing is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading centre.

Note: Multiple imputation (MI) with a Markov Chain Monte Carlo (MCMC) approach is used for any intermittent missing data. For monotone missingness up to Week 8 after occurrence of ICE1, ICE2 and ICE3, MI is implemented assuming missing at random (MAR). Observed data as collected are used. Unobserved data due to ICE4 is imputed as failure single imputation approach.

Note: The results that are displayed in this table are combined from 20 imputed datasets according to Rubin's rules. For the CMH test the Wilson-Hilferty transformation is applied prior to combining by Rubin's rules. OR results are log-transformed prior to combining by Rubin's rules and back-transformed results are presented.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Programming Note:

The missing data due to ICE1, ICE2 and ICE3 are imputed under MAR assumption and ICE4 as failure single value imputation.

Table 14.2.1.3 Percentage of Patients achieving Complete Corneal Healing of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region - Central Reading – First Sensitivity Analysis (mITT)

Programming Note:
The layout is the same as Table 14.2.1.2 but all data after ICE2 are included assuming missing not at random (MNAR), MI is implemented with a control-based pattern approach (vehicle as reference).

Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal healing is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading centre.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed under MNAR assumption using a control-based pattern approach with vehicle as reference.

Note: The results that are displayed in this table are combined from 20 imputed datasets according to Rubin’s rules. For the CMH test the Wilson-Hilferty transformation is applied prior to combining by Rubin’s rules. OR results are log-transformed prior to combining by Rubin’s rules and back-transformed results are presented.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Table 14.2.1.4 Percentage of Patients achieving Complete Corneal Healing of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region - Central Reading – Second Sensitivity Analysis (mITT)

Programming Note:
The layout is the same as Table 14.2.1.1 but all data after any intercurrent event (ICE1, ICE2, ICE3 and ICE4) are included as observed, no imputation is performed.

Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal healing is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading centre.

Note: All available data after occurrence of any ICE are used as observed, no imputation is performed.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Table 14.2.1.5 Percentage of Patients achieving Complete Corneal Healing of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region - Central Reading – Supportive Sensitivity Analysis (PP)

Programming Note:
The layout is the same as Table 14.2.1.1 but based on the PP population only.

Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal healing is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading centre.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Table 14.2.1.6 Percentage of Patients achieving Complete Corneal Healing of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region - Central Reading – Key Secondary Efficacy Endpoint (mITT)

Programming Note:
The layout is the same as Table 14.2.1.1.

Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal healing of PED or corneal ulcer at Week 8 is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer and no persistent staining outside of corneal lesion elsewhere in the cornea as assessed by an independent central reading centre.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Table 14.2.2.1.1 Percentage of Patients Who Achieved a ≥ 5-, 10- and 15-Letter Improvement in BCDVA at Week 8 Compared to Baseline – Secondary Efficacy Endpoint 1 (mITT)

Location: <location>
Improvement: <letters>

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Intercurrent events (ICE) up to Week 8, n (%)				
ICE1: Treatment discontinuation due to treatment-related AE	n (xx)	n (xx)	n (xx)	n (xx)
ICE2: Treatment discontinuation due to other reasons	n (xx)	n (xx)	n (xx)	n (xx)
ICE3: Start of rescue treatments/procedures	n (xx)	n (xx)	n (xx)	n (xx)
ICE4: Treatment discontinuation due to death	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage, Region at Randomisation				
2 (Moderate), EU				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for <x>-letter improvement in BCDVA	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), EU				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for <x>-letter improvement in BCDVA	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
2 (Moderate), NA				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for <x>-letter improvement in BCDVA	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), NA				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for <x>-letter improvement in BCDVA	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Odds Ratio (OR) controlling for disease stage and region for >= <x>-letter improvement in BCDVA				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Risk Difference				
Estimate	x.xx	x.xx	x.xx	

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Cochran-Mantel-Haenszel (CMH) Test				
Value	x.xx	x.xx	x.xx	
p-value [1]	x.xxx	x.xxx	x.xxx	

n: Number of patients with data available, N: Number of patients within treatment group, BCDVA: Best Corrected Distance Visual Acuity, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP.

Include subtitle 'Location: ' and list 'All' and 'Central PED or central corneal ulcer' for place holder <location>.

Add subtitle for 'Improvement: ' with '>= 5 letters', '>= 10 letters' and '>= 15 letters' instead of the place holder <letters>.

Present by Location and then by Improvement.

Replace <x> in first column with '≥ 5', '≥ 10' or '≥ 15' in accordance with the Improvement subtitle.

Table 14.2.2.1.2 Summary of BCDVA in Patients Who Read 0 Letters Correctly by Visit - Secondary Efficacy Endpoint 1 (mITT)

Visit Result	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)
Baseline	n (xx)	n (xx)	n (xx)	n (xx)
Count fingers	n (xx)	n (xx)	n (xx)	n (xx)
Hand motion	n (xx)	n (xx)	n (xx)	n (xx)
Light perception	n (xx)	n (xx)	n (xx)	n (xx)
No light perception	n (xx)	n (xx)	n (xx)	n (xx)
Visit x	n (xx)	n (xx)	n (xx)	n (xx)
Count fingers	n (xx)	n (xx)	n (xx)	n (xx)
Hand motion	n (xx)	n (xx)	n (xx)	n (xx)
Light perception	n (xx)	n (xx)	n (xx)	n (xx)
No light perception	n (xx)	n (xx)	n (xx)	n (xx)
…				

n: Number of patients with data available, N: Number of patients within treatment group, BCDVA: Best Corrected Distance Visual Acuity
Note: Percentage is based on number of patients within treatment group.
Note: Baseline is the last available value before treatment start.
Note: The results that are displayed in this table are based on observed data only.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Present all scheduled visits.

Table 14.2.2.1.3 Frequency Summary of BCDVA in Patients Who Achieved a ≥ 5-, 10- and 15-Letter Improvement in BCDVA at Week 8 Compared to Baseline - Secondary Efficacy Endpoint 1 (mITT)

Result	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)
Overall >= 5-Letter Improvment				
Improved	n (xx)	n (xx)	n (xx)	n (xx)
Not improved	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage, Region at Randomisation				
2 (Moderate), EU				
Improved	n (xx)	n (xx)	n (xx)	n (xx)
Not improved	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage, Region at Randomisation				
3 (Severe), EU				
Improved	n (xx)	n (xx)	n (xx)	n (xx)
Not improved	n (xx)	n (xx)	n (xx)	n (xx)
…				
Overall >= 10-Letter Improvment				
Improved	n (xx)	n (xx)	n (xx)	n (xx)
Not improved	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage, Region at Randomisation				
2 (Moderate), EU				
Improved	n (xx)	n (xx)	n (xx)	n (xx)
Not improved	n (xx)	n (xx)	n (xx)	n (xx)
…				
Overall >= 15-Letter Improvment				
Improved	n (xx)	n (xx)	n (xx)	n (xx)
Not improved	n (xx)	n (xx)	n (xx)	n (xx)
…				

n: Number of patients with data available, N: Number of patients within treatment group, BCDVA: Best Corrected Visual Acuity
Note: Percentage is based on number of patients within treatment group.
Note: Baseline is the last available value before treatment start.
Note: The results that are displayed in this table are based on observed data only.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Present all scheduled visits.

Table 14.2.2.2.1 Percentage of Patients Achieving Complete Corneal Healing of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region – Investigator Assessment – Secondary Efficacy Endpoint 2 (mITT)

Programming Note:
The layout is the same as Table 14.2.1.1. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal healing is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by the investigator.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Table 14.2.2.2.2 Frequency Summary of Percentage of Patients Achieving Complete Corneal Healing of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region – Investigator Assessment – Secondary Efficacy Endpoint 2 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.1.3 but replace 'improved' with 'healed' and replace with following footnotes:

Note: Complete corneal healing is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by the investigator.

Table 14.2.2.3.1 Time to Complete Corneal Healing of PED or Corneal Ulcer, in days – Central Reading - Secondary Efficacy Endpoint 3 (mITT)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Number of patients with event, n (%)	n (xx)	n (xx)	n (xx)	n (xx)
Number of patients censored, n (%)	n (xx)	n (xx)	n (xx)	n (xx)
25% Quartile [days] (95% CI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Median time to event [days] (95% CI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
75% Quartile [days] (95% CI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Hazard Ratio (95% Wald CI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	
p-value [1]	x.xxx	x.xxx	x.xxx	

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, CI: Confidence Interval

Note: Percentage is based on number of patients within treatment group.

Note: Time from treatment start to complete corneal healing (event) is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading centre in days. Patients that do not have an event until end of treatment (Visit 8/Day 56) and in case no intercurrent event (ICE) occurred, the patient is censored at their last available assessment date. In case ICE1 (treatment discontinuation due to treatment-related AE), ICE3 (start of rescue treatments/procedures) or ICE4 (treatment discontinuation due to death) occurred during the 8 week treatment administration period, the observed values after the ICE are set to missing and imputed as failure up to Week8/Day 56. If ICE2 (treatment discontinuation due to any other reasons) occurs during the treatment administration period, last observation carried forward (LOCF) is used to impute any monotone missing data up to Week 8/Day 56. The censoring date after the occurrence of an ICE and respective imputation is the actual assessment date at Week 8/Day 56, if available. In case the patient has no efficacy assessment done at Week 8/Day 56, the censoring time (days) after the ICE occurrence is set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. Cox's proportional hazard model is used to estimate the hazard ratio, 95% confidence limits and p-values and treatment group and randomisation strata disease stage and region are included as covariates. The 25%, median and 75% quartiles and respective 95% confidence intervals are estimated with the Kaplan-Meier survival analysis method.

[1]: Vehicle group is used as reference. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

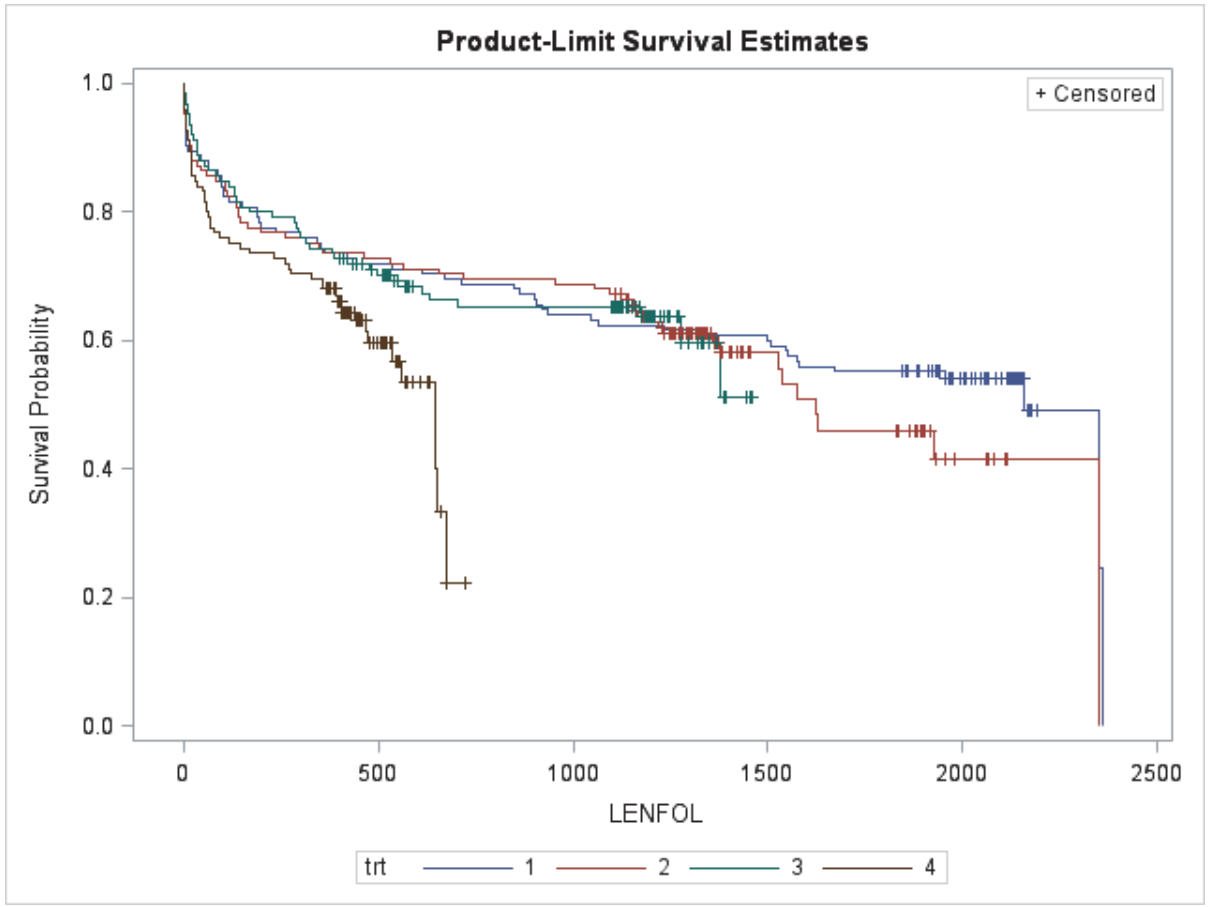
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Present footnotes on first page if needed.

Figure 14.2.2.3.2 Kaplan-Meier Curve of Time to Complete Corneal Healing of PED or Corneal Ulcer, in days – Central Reading – Secondary Efficacy Endpoint 3 (mITT)



PED: Persistent Epithelial Defects

Note: Time from treatment start to complete corneal healing (event) is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by an independent central reading centre in days. Patients that do not have an event until end of treatment (Visit 8/Day 56) and in case no intercurrent event (ICE) occurred, the patient is censored at their last available assessment date. In case ICE1 (treatment discontinuation due to treatment-related AE), ICE3 (start of rescue treatments/procedures) or ICE4 (treatment discontinuation due to death) occurred during the 8 week treatment administration period, the observed values after the ICE are set to missing and imputed as failure up to Day 56. If ICE2 (treatment discontinuation due to any other reasons) occurs during the treatment administration period, last observation carried forward (LOCF) is used to impute any monotone missing data up to

Day 56. The censoring date after the occurrence of an ICE and respective imputation is the actual assessment date at Week 8/Day 56 if available. In case the patient has a no efficacy assessment done at Week 8/Day 56, the censoring time (days) after the ICE occurrence is set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x, Table: 14.2.x.x.1

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

Present 'Time' as label on x-axis and add the respective time unit (e.g. days) to the x-axis label. Present number of subject at risk at each x-axis time point.

Table 14.2.2.4.1 Time to Complete Corneal Healing of PED or Corneal Ulcer, in days – Investigator Assessment – Secondary Efficacy Endpoint 4 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.3.1. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, CI: Confidence Interval

Note: Percentage is based on number of patients within treatment group.

Note: Time from treatment start to complete corneal healing (event) is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by the investigator in days. Patients that do not have an event until end of treatment (Visit 8/Day 56) and in case no intercurrent event (ICE) occurred, the patient is censored at their last available assessment date.In case ICE1 (treatment discontinuation due to treatment-related AE), ICE3 (start of rescue treatments/procedures) or ICE4 (treatment discontinuation due to death) occurred during the treatment administration period, the observed values after the ICE are set to missing and imputed as failure up to Day 56. If ICE2 (treatment discontinuation due to any other reasons) occurs during the treatment administration period, last observation carried forward (LOCF) is used to impute any monotone missing data up to Day 56. The censoring date after the occurrence of an ICE and respective imputation is the actual assessment date at Week 8/Day 56 if available. In case the patient has a no efficacy assessment done at Week 8/Day 56, the censoring time (days) after the ICE occurrence is set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. Cox's proportional hazard model is used to estimate the hazard ratio, 95% confidence limits and p-values and treatment group and randomisation strata disease stage and region are included as covariates. The 25%, median and 75% quartiles and respective 95% confidence intervals are estimated with the Kaplan-Meier survival analysis method.

[1]: Vehicle group is used as reference. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Figure 14.2.2.4.2 Kaplan-Meier Curve of Time to Complete Corneal Healing of PED or Corneal Ulcer, in days – Investigator Assessment – Secondary Efficacy Endpoint 4 (mITT)

Programming Note:
The layout and footnotes are the same as Figure 14.2.2.3.2. except for:

Note: Time from treatment start to complete corneal healing (event) is defined as no corneal fluorescein staining in the area of the PED or corneal ulcer as assessed by the investigator in days.

Table 14.2.2.5.1 Percentage of Patients Having Deterioration of the Disease at Week 8 – Secondary Efficacy Endpoint 5 (mITT)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Intercurrent events (ICE) up to Week 8, n (%)				
ICE1: Treatment discontinuation due to treatment-related AE	n (xx)	n (xx)	n (xx)	n (xx)
ICE2: Treatment discontinuation due to other reasons	n (xx)	n (xx)	n (xx)	n (xx)
ICE3: Start of rescue treatments/procedures	n (xx)	n (xx)	n (xx)	n (xx)
ICE4: Treatment discontinuation due to death	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage, Region at Randomisation				
2 (Moderate), EU				
Deterioration (%)	xx.x	xx.x	xx.x	xx.x
No deterioration (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for deterioration	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), EU				
Deterioration (%)	xx.x	xx.x	xx.x	xx.x
No deterioration (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for deterioration	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
2 (Moderate), NA				
Deterioration (%)	xx.x	xx.x	xx.x	xx.x
No deterioration (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for deterioration	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), NA				
Deterioration (%)	xx.x	xx.x	xx.x	xx.x
No deterioration (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for deterioration	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Odds Ratio (OR) controlling for disease stage and region for deterioration of the disease				
Deterioration (%)	xx.x	xx.x	xx.x	xx.x
No deterioration (%)	xx.x	xx.x	xx.x	xx.x
Estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Risk Difference				
Estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Cochran-Mantel-Haenszel (CMH) Test				
Value	x.xx	x.xx	x.xx	

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
p-value [1]	x.xxx	x.xxx	x.xxx	

n: Number of patients with data available, N: Number of patients within treatment group, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Deterioration of the disease at Week 8 is defined as 1) increase in lesion size by >= 1mm as assessed by the investigator compared to baseline or 2) mean decrease in BCDVA by >= 5 letters compared to baseline or 3) progression in lesion depth to corneal melting, perforation or onset of infection.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Programming Note:

See section 15 for Format of output in the SAP. Present footnotes on first page if needed.

Table 14.2.2.5.2 Frequency Summary of Patients Having Deterioration of the Disease at Week 8 – Secondary Efficacy Endpoint 5 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.1.3 but replace 'improved' with 'deterioration' and replace with following footnotes:

Note: Deterioration of the disease at Week 8 is defined as 1) increase in lesion size by >= 1mm as assessed by the investigator compared to baseline or 2) mean decrease in BCDVA by >= 5 letters compared to baseline or 3) progression in lesion depth to corneal melting, perforation or onset of infection.

Table 14.2.2.6.1 Mean Change in BCDVA from Baseline to Week 8 – Secondary Efficacy Endpoint 6 (mITT)

Location: <location>

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Intercurrent events (ICE) up to Week 8, n (%)				
ICE1: Treatment discontinuation due to treatment-related AE	n (xx)	n (xx)	n (xx)	n (xx)
ICE2: Treatment discontinuation due to other reasons	n (xx)	n (xx)	n (xx)	n (xx)
ICE3: Start of rescue treatments/procedures	n (xx)	n (xx)	n (xx)	n (xx)
ICE4: Treatment discontinuation due to death	n (xx)	n (xx)	n (xx)	n (xx)
Mean change in BCDVA from baseline to week 8				
n	x	x	x	x
Mean (SE)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx
Maximum	xx	xx	xx	xx
LSM estimate	x.xx	x.xx	x.xx	x.xx
95% confidence interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
LSM difference	x.xx	x.xx	x.xx	
95% confidence interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value [1]	x.xxx	x.xxx	x.xxx	

n: Number of patients with data available, N: Number of patients within treatment group, SE: Standard Error, BCDVA: Best Corrected Distance Visual Acuity, LSM: Least Squares Mean

Note: The LSM estimates, LSM differences and 95% confidence intervals as well as the p-values are obtained from an ANCOVA with treatment as main effect and baseline value (last available value before treatment start) and randomisation strata disease stage and region as covariates.

Note: Multiple imputation (MI) with a Markov Chain Monte Carlo (MCMC) approach is used for any intermittent missing data. For monotone missingness up to Week 8 due to ICE1 and ICE3 assuming missing not at random (MNAR), MI is implemented with a control-based pattern approach (vehicle as reference). Observed data as collected will be used for ICE2 and MI under MAR assumption is used for any monotone missing data. Unobserved data due to ICE4 is imputed with a worst value single imputation approach.

Note: The results that are displayed in this table are combined from 20 imputed datasets according to Rubin’s rules.

[1]: Vehicle group is used as reference. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP.

Include subtitle ‘Location: ’ and list ‘All’ and ‘Central PED or central corneal ulcer’ for place holder <location>

Table 14.2.2.6.2 Summary of Change from Baseline in BCDVA by Visit – Secondary Efficacy Endpoint 6 (mITT)

Location: <location>
Eye: <eye>

	REC 0/0559 0.5 µg/day (N=xx)		REC 0/0559 2.5 µg/day (N=xx)		REC 0/0559 5.0 µg/day (N=xx)		Vehicle (N=xx)	
	Value	Change from baseline	Value	Change from baseline	Value	Change from baseline	Value	Change from baseline
Screening								
n	x		x		x		x	
Mean (SD)	xx.x (x.xx)		xx.x (x.xx)		xx.x (x.xx)		xx.x (x.xx)	
Minimum	xx		xx		xx		xx	
Median	xx.x		xx.x		xx.x		xx.x	
Maximum	xx		xx		xx		xx	
Baseline								
n	x		x		x		x	
Mean (SD)	xx.x (x.xx)		xx.x (x.xx)		xx.x (x.xx)		xx.x (x.xx)	
Minimum	xx		xx		xx		xx	
Median	xx.x		xx.x		xx.x		xx.x	
Maximum	xx		xx		xx		xx	
Visit x								
n	x	x	x	x	x	X	x	x
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	xx	Xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx	Xx	xx	xx
Visit y								
n	x	x	x	x	x	X	x	x
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	xx	Xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx	xx	xx	xx
Visit z								
…	…	…	…	…	…	…	…	…

n: Number of patients with data available, N: Number of patients within treatment group, SD: Standard Deviation, BCDVA: Best Corrected Distance Visual Acuity
Note: Baseline is the last available value before treatment start.
Note: The results that are displayed in this table are based on observed data only.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP.

Table 14.2.2.7.1 Percentage of Patients with Improvement in Corneal Sensitivity from Baseline as Measured by Cochet-Bonnet Aesthesiometer at Week 8 – Secondary Efficacy Endpoint 7 (mITT)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Intercurrent events (ICE) up to Week 8, n (%)				
ICE1: Treatment discontinuation due to treatment-related AE	n (xx)	n (xx)	n (xx)	n (xx)
ICE2: Treatment discontinuation due to other reasons	n (xx)	n (xx)	n (xx)	n (xx)
ICE3: Start of rescue treatments/procedures	n (xx)	n (xx)	n (xx)	n (xx)
ICE4: Treatment discontinuation due to death	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage, Region at Randomisation				
2 (Moderate), EU				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for improvement	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), EU				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for improvement	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
2 (Moderate), NA				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for improvement	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), NA				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for improvement	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Odds Ratio (OR) controlling for disease stage and region for improvement in corneal sensitivity				
Improved (%)	xx.x	xx.x	xx.x	xx.x
Not improved (%)	xx.x	xx.x	xx.x	xx.x
Estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Risk Difference				
Estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Cochran-Mantel-Haenszel (CMH) Test				

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Value	x.xx	x.xx	x.xx	
p-value [1]	x.xxx	x.xxx	x.xxx	

n: Number of patients with data available, N: Number of patients within treatment group, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Improvement of corneal sensitivity from baseline is measured by the Cochet-Bonnet aesthesiometer. The mean (cm) of the results of the assessment of the 5 cornea sections (central, superior-nasal, inferior-nasal, superior-temporal, inferior-temporal) is calculated based on all available results at a certain visit. Assessments of cornea locations that are not applicable are disregarded and not included in the calculation of the mean.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Programming Note:

See section 15 for Format of output in the SAP. Present footnotes on first page if needed.

Table 14.2.2.7.2 Frequency Summary of Patients with Improvement in Corneal Sensitivity from Baseline as Measured by Cochet-Bonnet Aesthesiometer at Week 8 – Secondary Efficacy Endpoint 7 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.1.3.

Table 14.2.3.1.1 Percentage of Patients Achieving Complete Corneal Healing (<0.5 mm) of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region - Central Reading – Other Efficacy Endpoint 1 (mITT)

Programming Note:
The layout is the same as Table 14.2.1.1. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal healing is defined as the greatest diameter of corneal fluorescein staining in the area of the PED or corneal ulcer < 0.5 mm as assessed by an independent central reading centre.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Table 14.2.3.1.2 Frequency Summary of Patients Achieving Complete Corneal Healing (<0.5 mm) of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region - Central Reading – Other Efficacy Endpoint 1 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.1.3 but replace 'improved' with 'healed' and replace with following footnotes:

Note: Complete corneal healing is defined as the greatest diameter of corneal fluorescein staining in the area of the PED or corneal ulcer < 0.5 mm as assessed by an independent central reading centre.

Table 14.2.3.2.1 Percentage of Patients Achieving Complete Corneal Healing (<0.5 mm) of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region – Investigator Assessment – Other Efficacy Endpoint 2 (mITT)

Programming Note:
The layout is the same as Table 14.2.1.1. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal healing is 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.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Table 14.2.3.2.2 Frequency Summary of Patients Achieving Complete Corneal Healing (<0.5 mm) of PED or Corneal Ulcer at Week 8 controlling for Disease Stage and Region – Investigator Assessment – Other Efficacy Endpoint 2 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.1.3 but replace 'improved' with 'healed' and replace with following footnotes:

Note: Complete corneal healing is 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.

Table 14.2.3.3.1 Percentage of Patients Achieving Complete Corneal Clearing at Week 8 assessed with the Oxford Scale – Other Efficacy Endpoint 3 (mITT)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Intercurrent events (ICE) up to Week 8, n (%)				
ICE1: Treatment discontinuation due to treatment-related AE	n (xx)	n (xx)	n (xx)	n (xx)
ICE2: Treatment discontinuation due to other reasons	n (xx)	n (xx)	n (xx)	n (xx)
ICE3: Start of rescue treatments/procedures	n (xx)	n (xx)	n (xx)	n (xx)
ICE4: Treatment discontinuation due to death	n (xx)	n (xx)	n (xx)	n (xx)
Disease Stage, Region at Randomisation				
2 (Moderate), EU				
Cleared (%)	xx.x	xx.x	xx.x	xx.x
Not cleared (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for completed corneal clearing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), EU				
Cleared (%)	xx.x	xx.x	xx.x	xx.x
Not cleared (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for completed corneal clearing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
2 (Moderate), NA				
Cleared (%)	xx.x	xx.x	xx.x	xx.x
Not cleared (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for completed corneal clearing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
3 (Severe), NA				
Cleared (%)	xx.x	xx.x	xx.x	xx.x
Not cleared (%)	xx.x	xx.x	xx.x	xx.x
Risk difference for completed corneal clearing	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Odds Ratio (OR) controlling for disease stage and region for complete corneal healing				
Cleared (%)	xx.x	xx.x	xx.x	xx.x
Not cleared (%)	xx.x	xx.x	xx.x	xx.x
Estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Common Risk Difference				
Estimate	x.xx	x.xx	x.xx	
95% Confidence Interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
Cochran-Mantel-Haenszel (CMH) Test				

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Value	x.xx	x.xx	x.xx	
p-value [1]	x.xxx	x.xxx	x.xxx	

n: Number of patients with data available, N: Number of patients within treatment group, NA: North America, EU: Europe, AE: Adverse Event

Note: Percentage is based on number of patients within treatment group.

Note: Complete corneal clearing is defined as a score of 0 using the Oxford scale.

Note: Occurrence of ICE1, ICE3 and ICE4 are considered as failure at Week 8. Observed data as collected are used for ICE2 and monotone missing values are imputed using last observation carried forward (LOCF) up to Week 8.

[1]: Vehicle group is used as reference for the risk differences, OR and CMH test. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Programming Note:

See section 15 for Format of output in the SAP. Present footnotes on first page if needed.

Table 14.2.3.3.2 Summary of the Oxford Scale Grades by Visit - Other Efficacy Endpoint 3 (mITT)

Visit Oxford Scale Score	REC 0/0559 0.5 µg/day (N=xx) n (%)	REC 0/0559 2.5 µg/day (N=xx) n (%)	REC 0/0559 5.0 µg/day (N=xx) n (%)	Vehicle (N=xx) n (%)
Baseline				
0	n (xx)	n (xx)	n (xx)	n (xx)
1	n (xx)	n (xx)	n (xx)	n (xx)
2	n (xx)	n (xx)	n (xx)	n (xx)
3	n (xx)	n (xx)	n (xx)	n (xx)
4	n (xx)	n (xx)	n (xx)	n (xx)
5	n (xx)	n (xx)	n (xx)	n (xx)
Visit x				
0	n (xx)	n (xx)	n (xx)	n (xx)
1	n (xx)	n (xx)	n (xx)	n (xx)
2	n (xx)	n (xx)	n (xx)	n (xx)
3	n (xx)	n (xx)	n (xx)	n (xx)
4	n (xx)	n (xx)	n (xx)	n (xx)
5	n (xx)	n (xx)	n (xx)	n (xx)
…				

n: Number of patients with data available, N: Number of patients within treatment group
Note: Percentage is based on number of patients within treatment group.
Note: Baseline is the last available value before treatment start.
Note: The results that are displayed in this table are based on observed data only.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 14 for Format of output in the SAP. Percentages are based on N.

Table 14.2.3.4.1 Time to at Least 50% Corneal Healing of PED or Corneal Ulcer – Central Reading – Other Efficacy Endpoint 4 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.3.1. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, CI: Confidence Interval

Note: Percentage is based on number of patients within treatment group.

Note: Time to 50% corneal healing (event) is defined as a ≥ 50% reduction in the greatest diameter of the lesion as determined by a central reader. Patients that do not have an event until end of treatment (Visit 8/Day 56) and in case no intercurrent event (ICE) occurred, the patient is censored at their last available assessment date. In case ICE1 (treatment discontinuation due to treatment-related AE), ICE3 (start of rescue treatments/procedures) or ICE4 (treatment discontinuation due to death) occurred during the treatment administration period, the observed values after the ICE are set to missing and imputed as failure up to Day 56. If ICE2 (treatment discontinuation due to any other reasons) occurs during the treatment administration period, last observation carried forward (LOCF) is used to impute any monotone missing data up to Day 56. The censoring date after the occurrence of an ICE and respective imputation is the actual assessment date at Week 8/Day 56 if available. In case the patient has a no efficacy assessment done at Week 8/Day 56, the censoring time (days) after the ICE occurrence is set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. Cox's proportional hazard model is used to estimate the hazard ratio, 95% confidence limits and p-values and treatment group and randomisation strata (disease stage and region) are included as covariates. The 25%, median and 75% quartiles and respective 95% confidence intervals are estimated with the Kaplan-Meier survival analysis method.

[1]: Vehicle group is used as reference. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Figure 14.2.3.4.2 Kaplan-Meier Curve of Time to at Least 50% Corneal Healing of PED or Corneal Ulcer – Central Reading – Other Efficacy Endpoint 4 (mITT)

Programming Note:
The layout and footnotes are the same as Figure 14.2.2.3.2 except for:

Note: Time to 50% corneal healing (event) is defined as a ≥ 50% reduction in the greatest diameter of the lesion as determined by a central reader.

Table 14.2.3.5.1 Time to at Least 50% Corneal Healing of PED or Corneal Ulcer – Investigator Assessment – Other Efficacy Endpoint 5 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.3.1. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, CI: Confidence Interval

Note: Percentage is based on number of patients within treatment group.

Note: Time to 50% corneal healing (event) is defined as a ≥ 50% reduction in the greatest diameter of the lesion as determined by the investigator. Patients that do not have an event until end of treatment (Visit 8/Day 56) and in case no intercurrent event (ICE) occurred, the patient is censored at their last available assessment date. In case ICE1 (treatment discontinuation due to treatment-related AE), ICE3 (start of rescue treatments/procedures) or ICE4 (treatment discontinuation due to death) occurred during the treatment administration period, the observed values after the ICE are set to missing and imputed as failure up to Day 56. If ICE2 (treatment discontinuation due to any other reasons) occurs during the treatment administration period, last observation carried forward (LOCF) is used to impute any monotone missing data up to Day 56. The censoring date after the occurrence of an ICE and respective imputation is the actual assessment date at Week 8/Day 56 if available. In case the patient has a no efficacy assessment done at Week 8/Day 56, the censoring time (days) after the ICE occurrence is set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. Cox's proportional hazard model is used to estimate the hazard ratio, 95% confidence limits and p-values and treatment group and randomisation strata (disease stage and region) are included as covariates. The 25%, median and 75% quartiles and respective 95% confidence intervals are estimated with the Kaplan-Meier survival analysis method.

[1]: Vehicle group is used as reference. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Figure 14.2.3.5.2 Kaplan-Meier Curve of Time to at Least 50% Corneal Healing of PED or Corneal Ulcer – Investigator Assessment – Other Efficacy Endpoint 5 (mITT)

Programming Note:
The layout and footnotes are the same as Figure 14.2.2.3.2 except for:

Note: Time to 50% corneal healing (event) is defined as a ≥ 50% reduction in the greatest diameter of the lesion as determined by the investigator.

Table 14.2.3.6.1 Time to Onset of Corneal Healing of PED or Corneal Ulcer – Central Reading – Other Efficacy Endpoint 6 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.3.1. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, CI: Confidence Interval

Note: Percentage is based on number of patients within treatment group.

Note: Time to onset of healing (event) is defined as a > 20% reduction in the greatest diameter of the lesion as determined by a central reading centre. Patients that do not have an event until end of treatment (Visit 8/Day 56) and in case no intercurrent event (ICE) occurred, the patient is censored at their last available assessment date. In case ICE1 (treatment discontinuation due to treatment-related AE), ICE3 (start of rescue treatments/procedures) or ICE4 (treatment discontinuation due to death) occurred during the treatment administration period, the observed values after the ICE are set to missing and imputed as failure up to Day 56. If ICE2 (treatment discontinuation due to any other reasons) occurs during the treatment administration period, last observation carried forward (LOCF) is used to impute any monotone missing data up to Day 56. The censoring date after the occurrence of an ICE and respective imputation is the actual assessment date at Week 8/Day 56 if available. In case the patient has a no efficacy assessment done at Week 8/Day 56, the censoring time (days) after the ICE occurrence is set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. Cox's proportional hazard model is used to estimate the hazard ratio, 95% confidence limits and p-values and treatment group and randomisation strata (disease stage and region) are included as covariates. The 25%, median and 75% quartiles and respective 95% confidence intervals are estimated with the Kaplan-Meier survival analysis method.

[1]: Vehicle group is used as reference. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Figure 14.2.3.6.2 Kaplan-Meier Curve of Time to Onset of Corneal Healing of PED or Corneal Ulcer – Central Reading – Other Efficacy Endpoint 6 (mITT)

Programming Note:
The layout and footnotes are the same as Figure 14.2.2.3.2 except for:

Note: Time to onset of healing (event) is defined as a > 20% reduction in the greatest diameter of the lesion as determined by a central reading centre.

Table 14.2.3.7.1 Time to Onset of Corneal Healing of PED or Corneal Ulcer – Investigator Assessment – Other Efficacy Endpoint 7 (mITT)

Programming Note:
The layout is the same as Table 14.2.2.3.1. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, PED: Persistent Epithelial Defects, CI: Confidence Interval

Note: Percentage is based on number of patients within treatment group.

Note: Time to onset of healing (event) is defined as a > 20% reduction in the greatest diameter of the lesion as determined by the investigator. Patients that do not have an event until end of treatment (Visit 8/Day 56) and in case no intercurrent event (ICE) occurred, the patient is censored at their last available assessment date. In case ICE1 (treatment discontinuation due to treatment-related AE), ICE3 (start of rescue treatments/procedures) or ICE4 (treatment discontinuation due to death) occurred during the treatment administration period, the observed values after the ICE are set to missing and imputed as failure up to Day 56. If ICE2 (treatment discontinuation due to any other reasons) occurs during the treatment administration period, last observation carried forward (LOCF) is used to impute any monotone missing data up to Day 56. The censoring date after the occurrence of an ICE and respective imputation is the actual assessment date at Week 8/Day 56 if available. In case the patient has a no efficacy assessment done at Week 8/Day 56, the censoring time (days) after the ICE occurrence is set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol. Cox's proportional hazard model is used to estimate the hazard ratio, 95% confidence limits and p-values and treatment group and randomisation strata (disease stage and region) are included as covariates. The 25%, median and 75% quartiles and respective 95% confidence intervals are estimated with the Kaplan-Meier survival analysis method.

[1]: Vehicle group is used as reference. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Figure 14.2.3.7.2 Kaplan-Meier Curve of Time to Onset of Corneal Healing of PED or Corneal Ulcer – Investigator Assessment – Other Efficacy Endpoint 7 (mITT)

Programming Note:
The layout and footnotes are the same as Figure 14.2.2.3.2 except for:

Note: Time to onset of healing (event) is defined as a > 20% reduction in the greatest diameter of the lesion as determined by the investigator.

Table 14.2.4.1.1 Change from Baseline in NEI VFQ-25 Composite Score at Week 8 – Other Exploratory Endpoint 1 (mITT)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Intercurrent events (ICE) up to Week 8, n (%)				
ICE1: Treatment discontinuation due to treatment-related AE	n (xx)	n (xx)	n (xx)	n (xx)
ICE2: Treatment discontinuation due to other reasons	n (xx)	n (xx)	n (xx)	n (xx)
ICE3: Start of rescue treatments/procedures	n (xx)	n (xx)	n (xx)	n (xx)
ICE4: Treatment discontinuation due to death	n (xx)	n (xx)	n (xx)	n (xx)
Mean change in NEI VFQ-25 Composite Score from baseline to week 8				
n	x	x	x	x
Mean (SE)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx
Maximum	xx	xx	xx	xx
LSM estimate	x.xx	x.xx	x.xx	x.xx
95% confidence interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
LSM difference	x.xx	x.xx	x.xx	
95% confidence interval	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value [1]	x.xxx	x.xxx	x.xxx	

n: Number of patients with data available, N: Number of patients within treatment group, SE: Standard Error, NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25, LSM: Least Squares Mean

Note: The LSM estimates, LSM differences and 95% confidence intervals as well as the p-values are obtained from an ANCOVA with treatment as main effect and baseline value (last available value before treatment start) and randomisation strata (disease stage and region) as covariates.

Note: Multiple imputation (MI) with a Markov Chain Monte Carlo (MCMC) approach is used for any intermittent missing data. For monotone missingness up to Week 8 due to ICE1 and ICE3 assuming missing not at random (MNAR), MI is implemented with a control-based pattern approach (vehicle as reference). Observed data as collected will be used for ICE2 and MI under MAR assumption is used for any monotone missing data. Unobserved data due to ICE4 is imputed with a worst value single imputation approach.

Note: The results that are displayed in this table are combined from 20 imputed datasets according to Rubin’s rules.

[1]: Vehicle group is used as reference. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP.

Table 14.2.4.1.2 Summary and Change from Baseline of the NEI VFQ-25 Subscale and Composite Scores by Visit – Other Exploratory Endpoint 1 (mITT)

Scale score: <subscale>

	REC 0/0559 0.5 µg/day (N=xx)		REC 0/0559 2.5 µg/day (N=xx)		REC 0/0559 5.0 µg/day (N=xx)		Vehicle (N=xx)	
	Value	Change from baseline	Value	Change from baseline	Value	Change from baseline	Value	Change from baseline
Baseline								
n	x		x		x		x	
Mean (SD)	xx.x (x.xx)		xx.x (x.xx)		xx.x (x.xx)		xx.x (x.xx)	
Minimum	xx		xx		xx		xx	
Median	xx.x		xx.x		xx.x		xx.x	
Maximum	xx		xx		xx		xx	
Visit x								
n	x	x	x	X	x	x	x	x
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	Xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx	xx	xx	xx
Visit z								
…	…	…	…	…	…	…	…	…

n: Number of patients with data available, N: Number of patients within treatment group, SD: Standard Deviation, NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25

Note: Baseline is the last available value before treatment start.

Note: The results that are displayed in this table are based on observed data only.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Present in subtitle 'Scale score: ' the subscales e.g. 'General Vision' as in SAP Table 11 as well as the composite score as 'Composite'. Present the subscales in order of Table 11 in SAP and the composite score at last.

Table 14.2.4.2.1 Change from Baseline in the Overall NRS Score for Ocular Symptoms and Tolerability at Week 8 – Other Exploratory Endpoint 2 (mITT)

Programming Note:
The layout is the same as Table 14.2.4.1.1. Present the symptom scores in subtitle. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, SE: Standard Error, NRS: Numerical Rating Scale, LSM: Least Squares Mean

Note: The LSM estimates, LSM differences and 95% confidence intervals as well as the p-values are obtained from an ANCOVA with treatment as main effect and baseline value (last available value before treatment start) and randomisation strata (disease stage and region) as covariates.

Note: Multiple imputation (MI) with a Markov Chain Monte Carlo (MCMC) approach is used for any intermittent missing data. For monotone missingness up to Week 8 due to ICE1 and ICE3 assuming missing not at random (MNAR), MI is implemented with a control-based pattern approach (vehicle as reference). Observed data as collected will be used for ICE2 and MI under MAR assumption is used for any monotone missing data. Unobserved data due to ICE4 is imputed with a worst value single imputation approach.

Note: The results that are displayed in this table are combined from 20 imputed datasets according to Rubin's rules.

[1]: Vehicle group is used as reference. For the confirmatory analysis based on the primary estimand a gate keeping procedure is applied in the following order:

1. REC 0/0559 5.0 µg/day vs vehicle at 0.04 alpha level and if significant, REC 0/0559 2.5 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.
2. REC 0/0559 2.5 µg/day vs vehicle at 0.01 alpha level and if significant, REC 0/0559 5.0 µg/day vs vehicle at 0.05 alpha level. If both tests are significant, REC 0/0559 0.5 µg/day vs vehicle is tested at 0.05 alpha level.

Table 14.2.4.2.2 Summary and Change from Baseline in Each Symptom Score and the Overall NRS Score for Ocular Symptoms and Tolerability by Visit – Other Exploratory Endpoint 2 (mITT)

Programming Note:
The layout is the same as Table 14.2.4.1.2. Following footnotes to be displayed:

n: Number of patients with data available, N: Number of patients within treatment group, SD: Standard Deviation, NRS: Numerical Rating Scale
Note: Baseline is the last available value before treatment start.
Note: The results that are displayed in this table are based on observed data only.

Table 14.2.5.1 Summary of MT6 Plasma Concentrations by Visit and Time Point (PK)

Randomisation strata: <strata>

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Visit 1b, Pre-dose				
n	x	x	x	x
BLQ [n (%)]	x (x.xx)	x (x.xx)	x (x.xx)	x (x.xx)
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
CV%	xx	xx	xx	xx
Minimum	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx
Visit 1b, 10 mins post-dose				
n	x	x	x	x
BLQ [n (%)]	x (x.xx)	x (x.xx)	x (x.xx)	x (x.xx)
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
CV%	xx	xx	xx	xx
Minimum	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx
Visit y				
…	…	…	…	…

n: Number of patients with data available, N: Number of patients within treatment group, BLQ: Below limit of quantification, SD: Standard Deviation, CV: Coefficient of variation

Note: MT6 is the free acid form of the MT8 (REC 0/0559) treatment.

Note: All BLQ values will be set to zero.

Note: Percentage is based on number of patients within treatment group.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

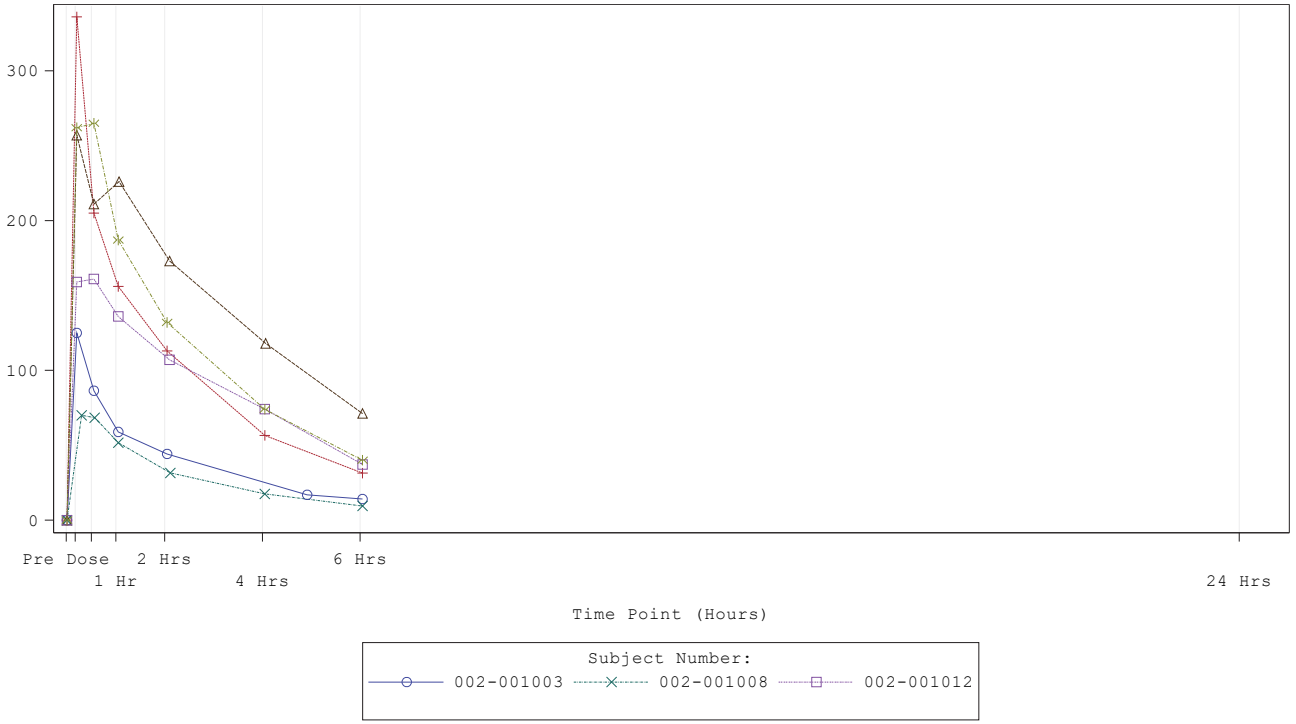
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Display all scheduled visits and time points. Repeat pages per randomisation strata and add subtitle 'Randomisation strata: <strata>' to each page for 'Overall', 'Disease stage 2 (moderate)', 'Disease stage 3 (severe)', 'Region North America' and 'Region Europe'.

Figure 14.2.5.2 Individual and mean MT6 plasma concentrations vs time profile by Visit (PK)

Randomisation strata: <strata>, Treatment group: <treatment>, Visit: <visit>



Note: MT6 is the free acid form of the MT8 (REC 0/0559) treatment.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
Display timepoints on x-axis according to visit schedule. Add subtitles 'Randomisation strata: ', 'Treatment group: ' and 'Visit: 'to each page to present all individual plasma concentration and mean plasma concentration by disease stage ('Overall', 'Disease stage 2 (moderate)', 'Disease stage 3 (severe)', 'Region North America' and 'Region Europe'), treatment group and per day. Mean is calculated based on data available within each randomisation stratum and treatment groups per visit. Patient IDs and Mean are explained in the legend of the figure. Mean will be presented as a solid bold line.

Table 14.2.5.3 Summary of MT6 Plasma PK Parameters (PK)

Randomisation strata: <strata>, Parameter: <parameter>

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)
Visit 1b				
n	x	x	x	x
Mean (SD)	x (x.xx)	x (x.xx)	x (x.xx)	x (x.xx)
CV%	xx	xx	xx	xx
Minimum	xx	xx	xx	xx
Median	xx	xx	xx	xx
Maximum	xx.x	xx.x	xx.x	xx.x
Geometric Mean	xx	xx	xx	xx
CV% Geometric Mean	xx	xx	xx	xx
Visit 3				
n	x	x	x	x
Mean (SD)	x (x.xx)	x (x.xx)	x (x.xx)	x (x.xx)
CV%	xx	xx	xx	xx
Minimum	xx	xx	xx	xx
Median	xx	xx	xx	xx
Maximum	xx.x	xx.x	xx.x	xx.x
Geometric Mean	xx	xx	xx	xx
CV% Geometric Mean	xx	xx	xx	xx
…	…	…	…	…

n: Number of patients with data available, N: Number of patients within treatment group, SD: Standard Deviation, CV: Coefficient of variation, AUC_T: Area under the plasma concentration-time curve during the dosage interval (4 hrs) for the first administration, C_{max}: Maximum plasma concentration, $C_{max\ ss}$: Maximum plasma concentration at steady state, T_{max}: Time to peak plasma concentration, $T_{max\ ss}$: Time to peak plasma concentration at steady state, AUC_{0-4} (Day 1): Area under the plasma concentration-time curve from zero to 4 hours post the 1st daily administration, AUC_{0-t}: Area under the concentration-time curve from time zero to the last measurable concentration, C_{trough}: Trough plasma concentration

Note: MT6 is the free acid form of the MT8 (REC 0/0559) treatment.

Note: Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose Visit 1b (Day 1) samples are treated as zero and the sampling time of pre-dose samples relative to dosing are also treated as zero. All BLQ values occurring after Visit 1b (Day 1) are set to ½ lower limit of quantification (LLOQ).

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Display all scheduled visits and time points. Repeat pages per disease stage and add subtitles 'Disease stage: ' and 'Parameter: ' to each page for 'Overall', 'Disease stage 2 (moderate)', 'Disease stage 3 (severe)', 'Region North America' and 'Region Europe' as well as each PK parameter as listed in the footnote.

Table 14.3.1.1 Overall Summary of Adverse Events (SAF)

	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Adverse Event (AE)	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any Ocular Adverse Event	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Study Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Fellow Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Both	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any Treatment-emergent Adverse Event (TEAE)	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any ocular Treatment-emergent Adverse Event (TEAE)	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Study Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Fellow Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Both	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any Treatment-emergent Adverse Event (TEAE) by maximum intensity	n (xx)	n (xx)	n (xx)	n (xx)	n (xx) m
Mild	n (xx)	n (xx)	n (xx)	n (xx)	n (xx) m
Moderate	n (xx)	n (xx)	n (xx)	n (xx)	n (xx) m
Severe	n (xx)	n (xx)	n (xx)	n (xx)	n (xx) m
Any Serious Adverse Event	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any Serious Ocular Adverse Event	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Study Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Fellow Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Both	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any Serious TEAE	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any Serious ocular TEAE	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Study Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Fellow Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Both	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any Related TEAE	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Related to Study Drug	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Related to Study Procedure	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any Related Serious TEAE	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
At least 1 TEAE leading to study drug discontinuation	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

At least 1 ocular TEAE leading to study drug discontinuation	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Study Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Fellow Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Both	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any AE leading to death	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any AE of special interest	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any AE due to overdose	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any AE onset during the screening period	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any ocular AE onset during the screening period	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Study Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Fellow Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Both	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any AE onset during the treatment administration period	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any ocular AE onset during the treatment administration period	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Study Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Fellow Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Both	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any AE onset during the follow-up period	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Any ocular AE onset during the follow-up period	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Study Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Fellow Eye	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Both	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events

Note: Percentage is based on number of patients within treatment group.

Note: AEs of special interest (AESI) are defined as (1) corneal calcifications in the study eye, independent of intensity or (2) all non-serious AEs that are severe in intensity and considered related to the study drug as assessed by the investigator.

Note: If subjects experienced multiple AEs of different intensities, the subjects are counted only once in the respective catogory of the overall maximum intensity.

Note: The screening period is defined as the time from signed informed consent to treatment start date. The treatment administration period is defined from first treatment administration date to last treatment administration date. The follow-up period is defined as the 4 weeks following the last treatment administration date.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once in each category in case more than one AE is present. All events from a patient are counted for m.

Table 14.3.1.1.1 Overall Summary of Ocular Adverse Events (SAF)

Programming Note:
The layout and footnotes are the same as Table 14.3.1.1 based on only ocular events.

Table 14.3.1.2 Summary of Adverse Events by System Organ Class and Preferred Term (SAF)

Study period: <period>

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Adverse Event	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events

Note: Percentage is based on number of patients within treatment group.

Note: The screening period is defined as the time from signed informed consent to treatment start date. The treatment administration period is defined from first treatment administration date to last treatment administration date. The follow-up period is defined as the 4 weeks following the last treatment administration date.

Note: MedDRA <version> used for coding.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>. Present by study period in subtitles: 'Study period: ' 'Overall', 'Screening', 'Treatment administration' and 'Follow-up'. AEs spanning over multiple study periods are only counted once in the study period of the AE onset.

Table 14.3.1.3 Summary of Ocular Adverse Events by System Organ Class and Preferred Term (SAF)

Location: <eye>

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Ocular Adverse Event	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>. Add subtitle 'Location: ' and display table by 'Overall', 'Study Eye', 'Fellow Eye' and 'Both'.

Table 14.3.1.4 Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term (SAF)

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Treatment-emergent Adverse Event	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>.

Table 14.3.1.4.1 Summary of ocular Treatment-emergent Adverse Events by System Organ Class and Preferred Term (SAF)

Programming Note:
The layout and footnotes are the same as Table 14.3.1.4 based on only ocular events. Add subtitle 'Location: ' and display table by 'Overall', 'Study Eye', 'Fellow Eye' and 'Both'.

Table 14.3.1.5 Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term by Maximum Intensity (SAF)

		Maximum Intensity			
Treatment	System Organ Class Preferred Term (MedDRA <version>)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
REC 0/0559 0.5 µg/day (N=xx)	Any Adverse Event	n (xx)	n (xx)	n (xx)	n (xx)
	System Organ Class 1	n (xx)	n (xx)	n (xx)	n (xx)
	Preferred Term 1	n (xx)	n (xx)	n (xx)	n (xx)
	Preferred Term 2	n (xx)	n (xx)	n (xx)	n (xx)
	Preferred Term 3	n (xx)	n (xx)	n (xx)	n (xx)
	Preferred Term 4	n (xx)	n (xx)	n (xx)	n (xx)
	Preferred Term 5	n (xx)	n (xx)	n (xx)	n (xx)
	Preferred Term 6	n (xx)	n (xx)	n (xx)	n (xx)
	…	n (xx)	n (xx)	n (xx)	n (xx)
	…				
REC 0/0559 2.5 µg/day (N=xx)	Any Adverse Event	n (xx)	n (xx)	n (xx)	n (xx)
	System Organ Class 1	n (xx)	n (xx)	n (xx)	n (xx)
	Preferred Term 1	n (xx)	n (xx)	n (xx)	n (xx)
	Preferred Term 2	n (xx)	n (xx)	n (xx)	n (xx)
	…	n (xx)	n (xx)	n (xx)	n (xx)
	…				
…					

n: Number of patients with data available, N: Number of patients within treatment group
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present in. Only the AE with the highest intensity is counted per SOC and PT. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>.

Table 14.3.1.5.1 Summary of ocular Treatment-emergent Adverse Events by System Organ Class and Preferred Term by Maximum Intensity (SAF)

Programming Note:
The layout and footnotes are the same as Table 14.3.1.5 based on only ocular events. Add subtitle 'Location: ' and display table by 'Overall', 'Study Eye', 'Fellow Eye' and 'Both'.

Table 14.3.1.6 Summary of Serious Adverse Events (SAE) by System Organ Class and Preferred Term (SAF)

Location: <location>

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Serious Adverse Event	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>. Add subtitle 'Location: ' and display table by 'Overall', 'Non-ocular', 'Ocular: Overall', 'Ocular: Study Eye', 'Ocular: Fellow Eye' and 'Ocular: Both' in this order.

Table 14.3.1.7 Summary of Serious Treatment-emergent Adverse Events (TEAE) by System Organ Class and Preferred Term (SAF)

Location: <location>

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Serious TEAE	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>. Add subtitle 'Location: ' and display table by 'Overall', 'Non-ocular', 'Ocular: Overall', 'Ocular: Study Eye', 'Ocular: Fellow Eye' and 'Ocular: Both' in this order.

Table 14.3.1.8 Summary of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term (SAF)

Relationship: <relationship>

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Related TEAE	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>. Add subtitle 'Relationship: ' and display table by 'Overall', 'Study Treatment' and 'Study Procedure'.

Table 14.3.1.9 Summary of Related Serious Treatment-emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term (SAF)

Relationship: <relationship>

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Related Serious TEAE	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>. Add subtitle 'Relationship: ' and display table by 'Overall', 'Study Treatment' and 'Study Procedure'.

Table 14.3.1.10 Summary of Treatment-emergent Adverse Events (TEAEs) That Led to Study Drug Discontinuation by System Organ Class and Preferred Term (SAF)

Location: <location>

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any TEAE that led to study drug discontinuation	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>. Add subtitle 'Location: ' and display table by 'Overall', 'Non-ocular', 'Ocular: Overall', 'Ocular: Study Eye', 'Ocular: Fellow Eye' and 'Ocular: Both' in this order.

Table 14.3.1.11 Summary of Adverse Events That Led to Death by System Organ Class and Preferred Term (SAF)

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Adverse Event that led to death	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>.

Table 14.3.1.12 Summary of Adverse Events of Special Interest (AESIs) by System Organ Class and Preferred Term (SAF)

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Adverse Event of Special Interest	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events

Note: Percentage is based on number of patients within treatment group.

Note: AEs of special interest (AESI) are defined as (1) corneal calcifications in the study eye, independent of intensity or (2) all non-serious AEs that are severe in intensity and considered related to the study drug as assessed by the investigator.

Note: MedDRA <version> used for coding.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>.

Table 14.3.1.13 Summary of Adverse Events due to Overdose by System Organ Class and Preferred Term (SAF)

System Organ Class Preferred Term	REC 0/0559 0.5 µg/day (N=xx) n (%) m	REC 0/0559 2.5 µg/day (N=xx) n (%) m	REC 0/0559 5.0 µg/day (N=xx) n (%) m	Vehicle (N=xx) n (%) m	Total (N=xx) n (%) m
Any Adverse Event due to Overdose	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
System Organ Class 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 1	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 2	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 3	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
Preferred Term 4	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m
…	n (xx) m	n (xx) m	n (xx) m	n (xx) m	n (xx) m

n: Number of patients with data available, N: Number of patients within treatment group, m: Number of events
Note: Percentage is based on number of patients within treatment group.
Note: MedDRA <version> used for coding.
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. All patients are only counted once for n in case more than one AE is present. All events from a patient are counted for m. Sort SOC and PT by highest frequency in the Total column. Add the MedDRA version to footnote instead of place holder <version>.

Table 14.3.2.1 Deaths - Listing (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	AE Nr.	System Organ Class/ Preferred Term	Date of Death (Study Day)	Ocular? / Eye	TEAE/ SAE/ AESI/ OD	Relationship to Study Drug/ to Other Study Procedure	Severity/ Action Taken/ Treatment required	Serious Criteria
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	1	Xxxxxx/ Yyyyy	ddMMMyyyy (XX)	Yes/ Left *	Yes/ Yes/ Yes/ No	Unrelated/ Related	Severe/ Discontinued/ Medication	Life-threatening, Other serious medically important event
Xxxxxx/ yyyy/ NA/ 3/ Zzzzz	1	Xxxxxxxxx/ Yyyy	ddMMMyyyy hh:mm	No	Yes/ No/ Yes/ No	Related/ Unrelated	Moderate/ None/ Other action: xxx	N/A
…								

AE: Adverse Event, TEAE: Treatment-emergent Adverse Event, SAE: Serious Adverse Event, AESI: Adverse Event of Special Interest, OD: Overdose
$: Stage 2 = Moderate, Stage 3 = Severe
*: Study eye
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. In case of ocular AE present in the study eye it will be flagged with '*'. Present time of death if available.

Table 14.3.2.2 Serious Adverse Events - Listing (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	AE Nr.	System Organ Class/ Preferred Term	Start Date (Study Day) and Time/ Stop Date (Study Day) and Time/ Duration	Ocular? / Eye	TEAE/ SAE/ AESI/ OD	Relationship to Study Drug/ to Other Study Procedure	Severity/ Action Taken/ Outcome/ Treatment required/ Withdrawn from Study	Serious Criteria
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	1	Xxxxxx/ Yyyyy	ddMMMyyyy (XX) hh:mm/ ddMMMyyyy (XX) hh:mm/ 3 days	Yes/ Left *	Yes/ Yes/ Yes/ No	Unrelated/ Related	Severe/ Discontinued/ Recovered/Resolved / Medication/ Yes	Life-threatening, Other serious medically important event
Xxxxxx/ yyyy/ NA/ 3/ Zzzzz	1	Xxxxxxxxx/ Yyyy	ddMMMyyyy hh:mm/ Ongoing	No	Yes/ Yes/ No/ Yes	Related/ Unrelated	Moderate/ None/ Not Recovered/Not Resolved/ Other action: xxx/ No	Requires or prolongs hospitalization
…								

AE: Adverse Event, TEAE: Treatment-emergent Adverse Event, SAE: Serious Adverse Event, AESI: Adverse Event of Special Interest, OD: Overdose

$: Stage 2 = Moderate, Stage 3 = Severe

*: Study eye

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe

Note: Duration is calculated as (End date and time – Start date and time) if time available and within 24 hours then presented in hours. If the Duration is > 24 hours then present in days. In case only date is present Duration is calculated as (End date – Start date) + 1 and presented in days.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. In case of ocular AE present in the study eye it will be flagged with '*'.

Table 14.3.2.3 Treatment-emergent Adverse Events - Listing (Enrolled Set)

Programming Note:
The layout and footnotes are the same as Table 14.3.2.2.

Table 14.3.2.4 Adverse Events That Led to Study Drug Discontinuation - Listing (Enrolled Set)

Programming Note:
The layout and footnotes are the same as Table 14.3.2.2.

Table 14.3.2.5 Adverse Events of Special Interest - Listing (Enrolled Set)

Programming Note:
The layout and footnotes are the same as Table 14.3.2.2.

Table 14.3.2.6 Adverse Events due to Overdose - Listing (Enrolled Set)

Programming Note:
The layout and footnotes are the same as Table 14.3.2.2.

Table 14.3.4.1.1.1 Summary and Change from Baseline of Hematology Parameters by Visit (SAF)

Parameter: <parameter>

	REC 0/0559 0.5 µg/day (N=xx)		REC 0/0559 2.5 µg/day (N=xx)		REC 0/0559 5.0 µg/day (N=xx)		Vehicle (N=xx)	
	Value	Change from baseline	Value	Change from baseline	Value	Change from baseline	Value	Change from baseline
Baseline								
n [n*]	x [x]		x [x]		x [x]		x [x]	
Mean (SD)	xx.x (x.xx)		xx.x (x.xx)		xx.x (x.xx)		xx.x (x.xx)	
Minimum	xx		xx		xx		xx	
Median	xx.x		xx.x		xx.x		xx.x	
Maximum	xx		xx		xx		xx	
Visit x								
n [n*]	x [x]	x [x]	x [x]	x [x]	x [x]	x [x]	x [x]	x [x]
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx	xx	xx	xx
Visit y								
n [n*]	x [x]	x [x]	x [x]	x [x]	x [x]	x [x]	x [x]	x [x]
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	xx	xx	xx	xx
Visit z								
…	…	…	…	…	…	…	…	…

n: Number of patients with data available, n*: Number of patients outside of normal range, N: Number of patients within treatment group, SD: Standard Deviation

Note: Baseline is the last available value before treatment start.

Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Display all scheduled visits. Repeat pages per parameter and add subtitle 'Parameter: <parameter>' to each page for the parameters ordered as on the CRF.

Table 14.3.4.1.2.1 Summary and Change from Baseline of Biochemistry Parameters by Visit (SAF)

Programming Note:
The layout and footnotes are the same as Table 14.3.4.1.1.1.

Table 14.3.4.2.1 Summary and Change from Baseline of Vital Signs by Visit (SAF)

Programming Note:
The layout and footnotes are the same as Table 14.3.4.1.1.1. Parameters are: Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg) and Heart Rate (beats/min).

Table 14.3.4.5.1 Summary of Extent of Exposure (SAF)

	REC 0/0559 0.5 µg/day (N=xx)	REC 0/0559 2.5 µg/day (N=xx)	REC 0/0559 5.0 µg/day (N=xx)	Vehicle (N=xx)	Total (N=xx)
Duration of Exposure (days)					
n	x	x	x	x	X
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	Xx	xx	xx	xx	Xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	Xx	xx	xx	xx	Xx
Study Duration (days)					
n	x	x	x	x	X
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	Xx	xx	xx	xx	Xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	Xx	xx	xx	xx	Xx
Interruptions, n (%)					
By Investigator	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
By Patient	n (xx)	n (xx)	n (xx)	n (xx)	n (xx)
Duration of Interruption (days)					
n	x	x	x	x	X
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Minimum	xx	xx	xx	xx	Xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx	xx	xx	xx	Xx

n: Number of patients with data available, N: Number of patients within treatment group, SD: Standard Deviation
Note: Percentage is based on number of patients within treatment group.
Note: Duration of exposure (days) = (date of last treatment administration - date of first treatment administration) + 1.
Note: Study duration (days) = (end of study date - date of informed consent) + 1.
Note: Duration of Interruption (days) = (interruption end date – interruption start date) + 1.
Note: In case the treatment dosing was interrupted for a patient, the duration of interruption (days) is subtracted from the duration of exposure (days).
Analysis dataset: ADxx.SAS7BDAT; Data Source: Listing 16.2.x
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP.

20.2. Listings

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Listing 16.2.1.1 Patient Disposition (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Informed Consent Date/ Date of PK Informed Consent *	Randomisation Date/ Randomisation Number	Treatment Start Date/Time	Treatment Termination Date (Study Day)/ Primary Reason/ Continued Schedule	Completed Study per Protocol?/ Protocol Version	Study Completion or Discontinuation Date (Study Day)/ Status
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	ddmmmyyyy/ ddmmmyyyy	ddmmmyyyy/ xxxxx	ddmmmyyyy/ hh:mm	ddmmmyyyy (xx)/ Withdrawal by Subject/ No further visits	No/ 1.0	ddmmmyyyy (xx)/ Withdrawal by Subject
Xxxxxx/ yyyy/ NA/ 3/ Zzzzz	ddmmmyyyy/ ddmmmyyyy	ddmmmyyyy/ xxxxx	ddmmmyyyy/ hh:mm	ddmmmyyyy (xx)/ Completed	Yes/ 2.0	ddmmmyyyy (xx)/ Completed
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	ddmmmyyyy/ ddmmmyyyy	ddmmmyyyy/ xxxxx	ddmmmyyyy/ hh:mm	ddmmmyyyy (xx)/ Adverse Event/ Follow up visits only	No/ 1.1	ddmmmyyyy (xx)/ Adverse Event: xx
Xxxxxx/ yyyy/ NA/ 3/ Zzzzz	ddmmmyyyy	ddmmmyyyy/ xxxxx	ddmmmyyyy/ hh:mm	ddmmmyyyy (xx)/ Other: xxxx	No/ 2.0	ddmmmyyyy (xxx)/ Other: xxxx

$: Stage 2 = Moderate, Stage 3 = Severe
*: Only applicable for first 24 randomised patients
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
Display 'Adverse Event: xx' where xx is the AE number in case the patient discontinued due to an adverse event. If study discontinuation status is 'Other' specify reason xxxx as 'Other: xxxx'. If patient discontinued treatment add Continued Schedule information. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.2.1 Protocol Deviations (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	End of Treatment Status	Date of Deviation (Study Day)	Protocol Deviation	Protocol Deviation Term	Category
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	Completed	ddmmmyyyy (xx)	Inclusion or Exclusion Criteria	Xxxxxxxxxxxxxxx	Major
		ddmmmyyyy (xx)	Visit Window		Minor
Xxxxxx/ yyyy/ NA/ 3/ Zzzzz	Adverse Event	ddmmmyyyy (xx)	Study Procedure	Xxxxxxxxxxxxxxx	Major
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	Other: xxx	ddmmmyyyy (xx)	Dosing	Xxxxxxxxxxxxxxx Xxxxxxxxxxxxxxx	Major
Xxxxxx/ yyyy/ NA/ 3/ Zzzzz	Completed	ddmmmyyyy (xx)	Visit Window	Xxxxxxxxxxxxxxx	Minor

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
Sort listing by treatment group (lowest MT8 to highest and then Vehicle) and patient ID. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.2.2 Missing Visits and Assessments due to COVID-19 (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	End of Treatment Status	Visit	Missing Assessment	Reason
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	Completed	Visit x	All	Patient not able to come to site due to COVID-19
		Visit y	Vital Signs	Covid-19 related
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	Other: xxx	Visit y	Physical Examination	Due to COVID-19
Xxxxxx/ yyyy/ NA/ 3/ Zzzzz	Completed	Visit z	Spirometry	Not performed because of covid-19

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
Sort listing by treatment group (lowest MT8 to highest and then Vehicle) and patient ID. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. All missing assessments of a visit are listed separately. If a visit is missed completely so that no assessments are available, list the term 'All'.

Listing 16.2.3.1 Inclusion/Exclusion (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Failed Criterion	Description	Protocol Version */ Additional Version Information
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	INCL03	Xxxxxxxxxxxxxxxxxxx	1.0/ -
Xxxxx	EXCL02	Xxxxxxxxxxxxxxx	2.0/ xxxx xxxxxxxx

*: Protocol version under which the patient failed the inclusion or met the exclusion criteria
$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Only patients with failed inclusion or exclusion criteria are listed. If a patient is treated display information of treatment group and randomisation strata.

Listing 16.2.3.2 Analysis Populations (Enrolled Set)

				Sub-populations		
Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Safety Set (SAF)/ Reason for Exclusion	Modified Intention to Treat Set (mITT)/ Reason for Exclusion	Per-Protocol Set (PP)/ Reason for Exclusion	xxxxxxx	yyyyyyy	zzzzzzzz
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	Yes	No/ xxxxxxx xxxxx	No/ xxxxxx	zzz	www	www
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	Yes	Yes	Yes	zzz	www	www
Xxxxxx/ yyyy/ NA/ 2/ zzzzzz	Yes	Yes	Yes	zzz	www	www
Xxxxxx/ yyyy/ EU/ 2/ zzzzzz	Yes	Yes	Yes	zzz	www	www
Xxxxxx/ yyyy/ EU/ 3/ zzzzzz	Yes	Yes	Yes	zzz	www	www
Xxxxxx/ yyyy/ NA/ 3/ zzzzzz	Yes	Yes	Yes	zzz	www	www

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
Additional Sub-populations are based on the availability of data and will be defined before DB Lock. They are detailed in the SAP section 5. Include only sub-populations that have data available at the end of the study Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.4.1 Demographics (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Previous Patient ID if re-screened	Year of Birth/ Age (years) §	Sex	Childbearing potential?	Race/ Ethnicity #	Iris color	Weight (kg)	Height (cm)	Alcohol status	Smoking status
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Left	N/A	yyyy/ xx	Male	N/A	White/ Not Hispanic or Latino	Blue	xx.x	xxx.x	Current	Former
Xxxxx/ REC 0/0559 0.5 µg/day/ EU/ 3/ Left	xxxxxx	yyyy/ xx	Female	Yes	African American	Light Brown	xx.x	xxx.x	Never	Former
Xxxxx/ yyyy/ zz/ v/ uuuuuu	N/A	yyyy/ xx	Male	N/A	Native Hawaiian or other Pacific Islander	Dark Brown	xx.x	xxx.x	-	Current
Xxxxx/ yyyy/ zz/ v/ uuuuuu	N/A	yyyy/ xx	Male	N/A	Other: xxxx	Blue	xx.x	xxx.x	Former	Never
Xxxxx/ yyyy/ zz/ v/ uuuuuu	N/A	yyyy/ xx	Female	No	American Indian or Alaska Native	Blue	xx.x	xxx.x	Never	-

$: 2 = Moderate, 3 = Severe

§: At screening: derived using 01-Jan-<birth year> and date of informed consent

#: Available for patients from NA only

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe

Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest MT8 to highest and then Vehicle) and patient ID. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.4.2 Medical History Other Than NK in Study Eye (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Medical History Number	System Organ Class/ Preferred Term Verbatim	Start Date/ Stop Date/ Duration	Ocular condition/ Eye
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	1	Xxxxxx/ Yyyyy/ XXXXX	ddMMMyyyy/ ddMMMyyyy/ 3 days	Yes/ Right *
	2	Xxxxxx/ Yyyyy/ xxxxxxx	ddMMMyyyy/ ddMMMyyyy/ 5 days	No
Xxxxx/ yyyy/ zz/ v/ uuuuuu	1	Xxxxxxxxx/ Yyyy/ Xxxxxxxxxxx xxxxx	ddMMMyyyy/ Ongoing	No
…				

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
*: Study eye
Note: MedDRA version <version> is used.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, start date, SOC and PT. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. In case an end date is missing and/or the event is ongoing the term 'Ongoing' will be presented. In case of ocular condition present in the study eye it will be flagged with '*'. Insert MedDRA version in footnote <version> place holder.

Listing 16.2.4.3 Neurotrophic Keratitis (NK) Medical History in Study Eye (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Date of first Diagnosis/ Time since first Diagnosis (weeks)	Disease stage at Screening	Current Episode the first?/ Number of Episodes	Main underlying Cause of NK	Other underlying Causes	History of NK surgical or procedural Treatment?/ History of NK Drug Treatment?/ Any other Treatment
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Ddmmmyyyy/ xx	2 (Moderate)	Yes	Herpes simplex	Other: xxxxx, Ocular surgery: xxxx	Yes/ Yes/ Xxxxxxxx
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy/ xx	3 (Severe)	No/ 3	Herpes zoster	Neurosurgical procedure: xxxxx, Ocular surgery: xxxx	Yes/ No/ -
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy/ xx	2 (Moderate)	Yes	Neurosurgical procedure: xxxxx	Herpes zoster	Yes/ No/ -
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy/ xx	2 (Moderate)	Yes	Ocular surgery: xxxxx	Herpes zoster	Yes/ No/ -
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy/ xx	3 (Severe)	Yes	Herpes simplex	No	No/ No/ xxxxxxx
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy/ xx	2 (Moderate)	No/ -	Other: xxxx	Other: xxxxxx	No/ Yes/ xxxxx

$: Stage 2 = Moderate, Stage 3 = Severe

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe

Note: Time since first diagnosis (weeks) is calculated as ((date of informed consent signature) – (date of first diagnosis)) / 7. If only month and year are available, the day = 15 will be assumed. If only year is available, month = 6 and day = 15 will be assumed. In case the imputed date is greater than the date of signed informed consent (IC), then the date of IC will be used as date of first NK diagnosis.

Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest MT8 to highest and then Vehicle) and patient ID. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. In case multiple underlying causes are available then they are all listed and separated by commas. If no other underlying causes (that are not the main cause) are available as captured in the CRF then display 'No'.

Listing 16.2.4.4 Prior and Concomitant Medication (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	ATC Level 2/ ATC Level 3/ Preferred Term Medication	Start Date/ Stop Date/ Duration	Prior or Concomitant	Dose (unit)/ Dose Form/ Frequency/ Route	Ophthalmic?/ Eye	Reason
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Xxxxxx/ Yyyyy/ Xxxx/ wwwwwwwwwww	ddMMMyyyy/ ddMMMyyyy/ 3 days	Prior	100 (mg)/ Tablet/ QH/ Oral	No	Medical History: xx, yy
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Xxxxxxxxx/ Yyyy/ Xxxxxx/ wwwwwwww	ddMMMyyyy/ Ongoing	Concomitant	5 mL/ Suspension/ BID/ Intraocular	Yes/ Right *	Rescue Treatment for NK: Other: xxxx
…						

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
*: Study eye
Note: WhoDD version <version> is used.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, ATC level and PT. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. In case an end date is missing and/or the medication is ongoing the term 'Ongoing' will be presented. Reasons will be concatenated by '/'. In case of multiple events per reason e.g. Adverse Events present as 'Adverse Event: ' and then list and separate the event numbers by ','. In case ophthalmic medication is taken for the study eye it will be flagged with '*'. Insert WhoDD version in place holder <version> in footnote.

Listing 16.2.4.5 Prior and Concomitant Ocular Interventions (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	OI Nr.	Type of Ocular Intervention/ System Organ Class/ Preferred Term/ Description	Date of Intervention (Study day)	Prior or Concomitant	Resolved?	Eye	Reason
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	1	Vitrectomy/ Xxxxxx/ Yyyyyyyyy/ Wwwwwwwwwww/	ddMMMyyyy	Prior	Yes	Both	Medical History: xx, yy
	2	Xxxxxxxx/ yyyyy/ Yyyyyyyyy/ Wwwwwwwwwww/	ddMMMyyyy	Prior	No	Left *	Medical History: xx
Xxxxx/ yyyy/ zz/ v/ uuuuuu	1	Other Laser/ xxxxx/ Yyyyyyyyy/ Wwwwwwwwwww/	ddMMMyyyy	Concomitant	No	Right	Adverse Event: xx/ Rescue Treatment for NK: Other: xxxx
…							

OI: Ocular Intervention
$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
*: Study eye
Note: MedDRA version <version> is used.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, start date and type. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. Reasons will be concatenated by '/'. In case of multiple events per reason e.g. Adverse Events present as 'Adverse Event: ' and then list and separate the event numbers by ','. Insert MedDRA version in footnote <version> place holder.

Listing 16.2.4.6 Prior and Concomitant Surgery and Procedures (Other than Ocular) (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Surgery/ Procedure Number	System Organ Class/ Preferred Term/ Surgery/Procedure	Date of Surgery/Procedure	Prior or Concomitant	Reason
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	1	Xxxxxxxxxxx xxxxx/ Yyyyyyyy/ zzzzzzzzzzzzzzzzzz	ddMMMyyyy	Prior	Medical History: xx, yy
Xxxxx/ yyyy/ zz/ v/ uuuuuu	1	xxxxxxxx/ Yyyyyyyy/ zzzzzzzzzzzzzzzzzz	ddMMMyyyy	Concomitant	Adverse Event: xx
…					

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: MedDRA version <version> is used.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, start date and procedure. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. Reasons will be concatenated by '/'. In case of multiple events per reason e.g. Adverse Events present as 'Adverse Event: ' and then list and separate the event numbers by ','. Insert MedDRA version in footnote <version> place holder.

Listing 16.2.4.7 Schirmer Test (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Date of Measurement	Right Eye Result (mm)/Reason Not Done	Left Eye Result (mm)/Reason Not Done
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	ddmmmyyyy	Xxx	Xxxx
Xxxxx/ yyyy/ zz/ v/ uuuuuu	ddmmmyyyy	Xxxxxxxxxxxxxx x xxx xxxxxxxx	Xxxxx

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, start date and procedure. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.5.1.1 Study Drug Dosing (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Date and Time of first Dose/ Date and Time of last Dose/ Duration	Interrupted/ Decided by	Interruption Start Date/ Interruption End Date/ Duration	Numbers of doses missed
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Ddmmmyyyy hh:mm/ DDmmmyyyy hh:mm/ X days	Yes/ Investigator	Ddmmmyyyy/ DDmmmyyyy/ X days	Xxx
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy hh:mm/ DDmmmyyyy hh:mm/ X days	No	N/A	N/A
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy hh:mm/ DDmmmyyyy hh:mm/ X days	No	N/A	N/A
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy hh:mm/ DDmmmyyyy hh:mm/ X days	No	N/A	N/A

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Duration of exposure (days) = (date of last treatment administration - date of first treatment administration) + 1.
Note: Duration of Interruption (days) = (interruption end date – interruption start date) + 1.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID and visit.

Listing 16.2.5.1.2 Study Drug Dispensation and Compliance (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Visit	Date of Dispensation	Kit Numbers/ Reason Not Done	Date of Previous Visit	Numbers of used BFS	Comment	Expected number of used BFS/ Overall Compliance (%)
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Visit x	Ddmmmyyyy	Xxx, yyy	N/A	Xxx	Xxxxxxx	
	Visit y	Ddmmmyyyy	Xxxxxxxxxxxxx	Ddmmmyyyy	Xxx	-	
	…	Ddmmmyyyy	Xxx	Ddmmmyyyy	Xxx	-	xx.x
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Visit x	Ddmmmyyyy	Xxx	N/A	Xxx	-	
	Visit y	Ddmmmyyyy	Xxx	Ddmmmyyyy	Xxx	-	
	…	Ddmmmyyyy	Xxx	Ddmmmyyyy	Xxx	-	xx.x

BFS: Blow Fill Seals

$: Stage 2 = Moderate, Stage 3 = Severe

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe

Note: Overall compliance (%) is calculated as (Number of used BFS containers) / [4 * (number of BFS to be used based on actual number of days of treatment)] * 100. Non-compliance is defined as < 80% or > 120% overall compliance.

Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID and visit.

Listing 16.2.5.1.3 Patient Supply Accountability (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Visit	Kit ID/ Lot ID/ Date of Expiry	Kit Type (unit)	Quantity Dispensed (Kits)/ IP Units Dispensed (BFS)	Item Status/ Date Returned	Condition/ Quantity of returned Kit	IP Units unused (BFS)	Comment
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Visit x	Xxxx/ yyyyy/ ddmmmyyyy	Xxxx (yyyy)	Xx/ yyy	Returned/ ddmmmyyyy	Good/ xxx	Xxx	-
	…	Xxxx/ yyyyy/ ddmmmyyyy	Xxxx (yyyy)	Xx/ yyy	Returned/ ddmmmyyyy	Good/ xxx	Xxx	-
		Xxxx/ yyyyy/ ddmmmyyyy	Xxxx (yyyy)	Xx/ yyy	Returned/ ddmmmyyyy	Damaged/ xxx	Xxx	-
		Xxxx/ yyyyy/ ddmmmyyyy	Xxxx (yyyy)	Xx/ yyy	Returned/ ddmmmyyyy	Unopened/ xxx	Xxx	-
		…	Xxxx (yyyy)	Xx/ yyy	Returned/ ddmmmyyyy	Good/ xxx	Xxx	-
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Visit x	Xxxx/ yyyyy/ ddmmmyyyy	Xxxx (yyyy)	Xx/ yyy	Not Returned	N/A	N/A	xxxxx
	…	…	Xxxx (yyyy)	Xx/ yyy	Returned/ ddmmmyyyy	Good/ xxx	xxx	-

IP: Investigational Product, BFS: Blow Fill Seals
$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest MT8 to highest and then Vehicle) and patient ID and visit.

Listing 16.2.5.2.1 MT6 plasma concentrations (PK)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Study Drug Administration Date and Time (Study Day)	Visit	Scheduled Time Point	Sample Collected?	Collection Date and Time (Study Day)	Deviation in Sample Collection Time (min) (Actual Time – Planned Time)	Concentration (ng/mL)
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Ddmmmyyyy hh:mm (xx)	Visit 1b	Pre-dose	Yes	Ddmmmyyyy hh:mm (xx)	N/A	BLQ
			10 min post-dose	Yes	Ddmmmyyyy hh:mm (xx)	3	Xxx
			20 min post-dose	No	-	-	-
			…				
	Ddmmmyyyy hh:mm (xx)	Visit 3	Pre-dose	Yes	Ddmmmyyyy hh:mm (xx)	N/A	BLQ
			10 min post-dose	Yes	Ddmmmyyyy hh:mm (xx)	4	Xxx
			20 min post-dose	Yes	Ddmmmyyyy hh:mm (xx)	2	xxx
			…				
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy hh:mm (xx)	Visit 1b	Pre-dose	Yes	Ddmmmyyyy hh:mm (xx)	N/A	BLQ
			10 min post-dose	Yes	Ddmmmyyyy hh:mm (xx)	3	Xxx
			20 min post-dose	Yes	Ddmmmyyyy hh:mm (xx)-	0	xxx
…							

BLQ: Below limit of quantification
$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID and by visit and time point.

Listing 16.2.5.2.2 MT6 plasma PK parameters (PK)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Study Drug Administration Date and Time (Study Day)	Timepoint	AUC_{0-4} (h*ng/mL)/ AUC_T (h*ng/mL)	C_{max} (ng/mL)/ $C_{max\ ss}$ (ng/mL)	AUC_{0-t} (h*ng/mL)	T_{max}/ $T_{max\ ss}$	C_{trough}
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Ddmmmyyyy hh:mm (xx)	x	xx	xxx	xxx	xxx	xxx
	Ddmmmyyyy hh:mm (xx)	x	xxx	xxx	xxx	xxx	xxx
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Ddmmmyyyy hh:mm (xx)	x	xx	xx	xx	xx	xx
…							

AUC_T: Area under the plasma concentration-time curve during the dosage interval (4 hrs) for the first administration, C_{max}: Maximum plasma concentration, $C_{max\ ss}$: Maximum plasma concentration at steady state, T_{max}: Time to peak plasma concentration, $T_{max\ ss}$: Time to peak plasma concentration at steady state, AUC_{0-4} (Day 1): Area under the plasma concentration-time curve from zero to 4 hours post the 1st daily administration, AUC_{0-t}: Area under the concentration-time curve from time zero to the last measurable concentration, C_{trough}: Trough plasma concentration$: Stage 2 = Moderate, Stage 3 = Severe

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe

Note: Study Day 1 is the first day of study treatment.

Note: Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose Visit 1b (Day 1) samples are treated as zero and the sampling time of pre-dose samples relative to dosing are also treated as zero. All BLQ values occurring after Visit 1b (Day 1) are set to ½ lower limit of quantification (LLOQ).

Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID and by visit and time point.

Listing 16.2.6.1 Grading Form for Corneal Images – Central Reading (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Visit	Date of Examination (Study Day)	Examination	Result
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Visit x	Ddmmmyyyy (xx)	Complete corneal healing (no fluorescein staining)	No
			Complete corneal healing (<0.5 mm fluorescein staining)	No
			White to white diameter (pixel)	xxxx
			Maximum dimension of lesion (pixel)	xxx
			Maximum dimension of lesion (%) *	xx
			Maximum dimension of lesion (%) (derived) *	xx
			Reduction (%) of greatest diameter from Visit 1a (derived)	xxx.xx
			> 20% Reduction of greatest diameter from Visit 1a (derived)	Yes
			>= 50% Reduction of greatest diameter from Visit 1a (derived)	Yes
			Area of cornea (pixels)	xxxxxxx
			Area of lesion (pixels)	xxxxxx
			Percentage (%) of corneal surface affected	xx
			Percentage (%) of corneal surface affected (derived)	xx
			Is there staining elsewhere on the cornea?	Yes – Not Persistent
			Comment	-
	Visit y	Ddmmmyyyy (xx)	Complete corneal healing (no fluorescein staining)	Yes
	…		Complete corneal healing (<0.5 mm fluorescein staining)	Yes
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Visit x	Ddmmmyyyy (xx)	Complete corneal healing (no fluorescein staining)	No
			Complete corneal healing (<0.5 mm fluorescein staining)	No
			…	
	Visit y	Ddmmmyyyy (xx)	Complete corneal healing (no fluorescein staining)	No
	…			

*: Percentage of corneal diameter
$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, visit, start date and examination as ordered on the CRF. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.6.2 Slit Lamp Cornea and Fluorescein Test – Investigator Assessment (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Eye	Visit	Date of Assessment (Study Day)	Test	Assessment	Result/Reason Not Done
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Study	Visit x	Ddmmmyyyy (xx)	Fluorescein	PED or corneal ulcer present?	Yes
					Type: Location	PED: Involve the central cornea, Involve inferior-nasal
					Length of the greatest dimension (mm)	xxx
					Length of the greatest perpendicular dimension (mm)	xxx
					Complete corneal healing (no fluorescein staining)	No
					Complete corneal healing (<0.5 mm fluorescein staining)	Yes
					Oxford scale grade	1
					Reduction (%) of greatest diameter from Visit 1a *	xxx
					> 20% Reduction of greatest diameter from Visit 1a #	No
					>= 50% Reduction of greatest diameter from Visit 1a #	No
				Slit Lamp	Cornea	Dellen, Infection Stromal swelling
		Visit y …	Ddmmmyyyy (xx)	Fluorescein	PED or corneal ulcer present?	Yes
					Type: Location	PED: Involve the central cornea, Involve inferior-nasal
					…	
				Slit Lamp	Cornea	Infection
	Fellow	Visit x	Ddmmmyyyy (xx)	Fluorescein	NK present?	No
				Slit Lamp	Cornea	Dellen
		Visit y	Ddmmmyyyy (xx)	Fluorescein	NK present?/ Stage	Yes/ 1
					Oxford scale grade	3
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Study	Visit x	Ddmmmyyyy (xx)	Fluorescein	PED or corneal ulcer present?	Yes

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Eye	Visit	Date of Assessment (Study Day)	Test	Assessment	Result/Reason Not Done
					Type: Location	Corneal Ulcer: Involve the central cornea
		…			…	

PED = Persistent Epithelial Defects, NK = Neurotrophic Keratitis
*: Reduction is calculated as (greatest diameter [mm] at visit) / (greatest diameter [mm] at Visit 1a) * 100
#: > 20% and >= 50% reduction (Yes/No) is derived based on assessment 'Reduction (%) of greatest diameter from Visit 1a'
$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Study Day 1 is the first day of study treatment.
Note: Examination of the fellow eye is scheduled only at screening (V1a) and end of treatment (V8/EoT).
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, eye (display first study eye then fellow eye), visit, start date and test and assessments as ordered on the CRF. Add derived endpoints for Reduction of greatest diameter at the end of Fluorescein Test results for each visit. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. If multiple slit lamp results for the cornea separate by comma in the Results column.

Listing 16.2.6.3 Best Corrected Distance Visual Acuity (BCDVA) (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Eye	Visit	Date of Assessment (Study Day)	Assessment	Result
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Study	Visit x	Ddmmmyyyy (xx)	ETDRS Letter Score (4m)	xxx
				ETDRS Letter Score (1m)	xx
				Total ETDRS Letter Score (derived)	xxxx
				Difference of Total ETDRS Letter Score to Visit 1a (derived)	xxx
				If zero (0) letters read correctly at 1m indicate best visual acuity	Hand motion
		Visit y	Ddmmmyyyy (xx)	ETDRS Letter Score (4m)	xxx
		…		Total ETDRS Letter Score (derived)	xxxx
				Difference of Total ETDRS Letter Score to Visit 1a (derived)	xxx
	Fellow	Visit x	Ddmmmyyyy (xx)	ETDRS Letter Score (4m)	xxx
				…	
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Study	Visit x	Ddmmmyyyy (xx)	ETDRS Letter Score (4m)	xxx
				Total ETDRS Letter Score (derived)	xxxx
				…	

ETDRS: Early Treatment Diabetic Retinopathy Study
$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, eye (study eye first, then fellow eye), visit, start date and Assessment as ordered on the CRF. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.6.4 Time to Event Endpoints (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Endpoint	Occurrence of ICE/ Date (Study Day)	Treatment Start Date	Event/Censoring Date (Study Day)	Duration (days)
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Complete corneal healing (no fluorescein staining) – central reading	N/A	Ddmmmyyyy	Ddmmmyyyy	xxx
	Complete corneal healing (no fluorescein staining) – investigator	N/A	Ddmmmyyyy	Ddmmmyyyy	xxx
	Time to at least 50% corneal healing – central reading	N/A	Ddmmmyyyy	Ddmmmyyyy	xxx
	Time to at least 50% corneal healing – investigator	N/A	Ddmmmyyyy	Ddmmmyyyy	xxx
	Time to onset (> 20%) of corneal healing – central reading	N/A	Ddmmmyyyy	Ddmmmyyyy *	xxx
	Time to onset (> 20%) of corneal healing – investigator	N/A	Ddmmmyyyy	Ddmmmyyyy *	xxx
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Complete corneal healing (no fluorescein staining) – central reading	ICE3/ Ddmmmyyyy (xx)	Ddmmmyyyy	-	xxx §
	Complete corneal healing (no fluorescein staining) – investigator assessment	ICE3/ Ddmmmyyyy (xx)	Ddmmmyyyy	-	xxx §
	Time to at least 50% corneal healing – central reading	ICE3/ Ddmmmyyyy (xx)	Ddmmmyyyy	-	xxx §
	Time to at least 50% corneal healing – investigator assessment	ICE3/ Ddmmmyyyy (xx)	Ddmmmyyyy	-	xxx §
	…	ICE3/ Ddmmmyyyy (xx)	Ddmmmyyyy	-	xxx §
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Complete corneal healing (no fluorescein staining) – central reading	ICE1/ Ddmmmyyyy (xx)	Ddmmmyyyy	Ddmmmyyy #	xxx
	Complete corneal healing (no fluorescein staining) – investigator assessment	ICE1/ Ddmmmyyyy (xx)	Ddmmmyyyy	Ddmmmyyy #	xxx
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Complete corneal healing (no fluorescein staining) – central reading	N/A	Ddmmmyyyy	Ddmmmyyyy *	xxx
…					

*: Event, #: Censored at available Week 8 assessment date, §: Set to Day 56 as last scheduled efficacy assessment date as planned per protocol if no assessment date at Week 8 is available

$: Stage 2 = Moderate, Stage 3 = Severe

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe, ICE = Intercurrent Event, LOCF = Last Observation Carried Forward, ICE1: Treatment discontinuation due to treatment-related AE, ICE2: Treatment discontinuation due to other reasons, ICE3: Start of rescue treatments/procedures, ICE4: Treatment discontinuation due to death

Note: Study Day 1 is the first day of study treatment.

Note: In case no event occurred the patient is censored at their last available assessment date up to Week 8. In case ICE1, ICE2 or ICE4 occurred during the treatment administration period, the observed values after the ICE are set to missing and imputed as failure up to

Week 8/Day 56. If ICE2 occured during the treatment administration period, LOCF will be used to impute any monotone missing data up to Week 8/Day 56. The censoring date after the occurrence of an ICE and respective imputation is the actual assessment date at Week 8/Day 56 if available. In case the patient has a no efficacy assessment done at Week 8/Day 56, the censoring time (days) after the ICE occurrence is set to Day 56 which is the last scheduled efficacy assessment day in the 8 week treatment administration period as planned per protocol.

Note: Duration (days) is calculated as (event or censoring date) – (treatment start date) + 1.

Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID and Endpoint as listed. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. Add '*' to the Event/Censoring Date column if a patient had an event.

Listing 16.2.6.5 Corneal Sensitivity (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Eye	Visit	Date of Assessment (Study Day)	Location	Result (cm)/Reason Not Done
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Study	Visit x	Ddmmmyyyy (xx)	Central *	6.0
				Superior-nasal GLOBAL score*	0.5
		Visit y	Ddmmmyyyy (xx)	Central *	5.0
		…			
	Fellow	Visit x	Ddmmmyyyy (xx)	Inferior-nasal	0.5
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Study	Visit x	Ddmmmyyyy (xx)	Inferior-temporal *	4.5
		…		Superior-temporal	0.5
…					

*: PED or corneal ulcer main location (only applicable for study eye)
$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID and eye (study eye first, then fellow eye), visit and location as ordered on the CRF. If a patient is treated but not randomised then sort these patients at the end of the listing. Add '*' to the location to indicate the main location in the study eye.

Listing 16.2.6.6 Quality of Life NEI VFQ-25 (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Visit	Subscale	Item Number	Item Label	Response	Score *
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Visit x	General Health	1	In general, would you say your overall health is	Good	50
				General Health Subscale Score	N/A	50
		General Vision	2	At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor, or are you completely blind?	Fair	60
				General Vision Subscale Score	N/A	60
		Ocular Pain	4	How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)?	Mild	75
			19	How often does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing?	None of the time	100
				Ocular Pain Subscale Score	N/A	87.5
	…	…				
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Visit x	General Health		In general, would you say your overall health is	Fair	25
…						

NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25

*: The score of each item is coded according to the NEI VFQ-25 manual. The subscale scores are the arithmetic mean over the responses of all items within a subscale at the respective visit. The composite score is the arithmetic mean over the subscale scores (excluding General Health).

$: Stage 2 = Moderate, Stage 3 = Severe

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe

Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, visit, subscale and items as ordered in the CRF. At last display each subscale score and composite score at the end of a

visit. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.6.7 Ocular Symptoms and Tolerability Assessed with the NRS (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Visit	Symptom	Result *	Reason Not Done
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Visit x	Foreign body sensation	5	N/A
		Burning/stinging	2	N/A
		Itching	1	N/A
		Ocular pain	6	N/A
		Sticky feeling	4	N/A
		Blurred vision	7	N/A
		Photophobia	7	N/A
		Overall NRS Score	4.6	N/A
	…			
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Visit x	All	-	Xxxxxxxxxxxxxx
	Visit y	Foreign body sensation	8	N/A
…				

NRS: Numeric Rating Scale

*: The symptom is rated on a scale from 0 to 10 (0 means no symptoms and 10 means the worst possible discomfort). The overall NRS score is calculated as the arithmetic mean over the results of the single symptoms at the respective visit. If more than 3 symptom scores are missing the overall NRS mean score will be set to missing for the respective visit.

$: Stage 2 = Moderate, Stage 3 = Severe

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe

Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, visit and symptom as ordered in the CRF. At last display each overall NRS score at the end of a visit. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.6.8 Corneal Photo with and without Fluorescein (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Eye	Visit	Date of Assessment (Study Day)	Type
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Study	Visit x	Ddmmmyyyy (xx)	Without fluorescein
		Visit y	Ddmmmyyyy (xx)	With fluorescein
	Fellow	Visit x	Ddmmmyyyy (xx)	Without fluorescein
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Study	Visit x	Ddmmmyyyy (xx)	Without fluorescein
…				

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, eye (first study eye, then fellow eye), visit and date and type as ordered in the CRF. Present only available data. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.6.9 Intercurrent Events (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Intercurrent Event (ICE)	Date of ICE (Study Day)	Primary Estimand Strategy */ Data handling after ICE	First Sensitivity of Primary Estimand Strategy/ Data handling after ICE	Secondary Sensitivity of Primary Estimand Strategy/ Data handling after ICE	Tertiary Sensitivity of Primary Estimand Strategy/ Data handling after ICE
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	ICE1: Treatment discontinuation due to treatment-related AE	Ddmmmyyyy (xx)	Hypothetical/ MI MNAR	Hypothetical/ Single value imputation as non-responder/failure	Treatment policy/ As observed	Hypothetical/ MI MNAR
Xxxxx/ yyyy/ zz/ v/ uuuuuu	ICE3: Start of prohibited/rescue medication intake	Ddmmmyyyy (xx)	Hypothetical/ MI MNAR	Hypothetical/ Single value imputation as non-responder/failure	Treatment policy/ As observed	Hypothetical/ MI MNAR
Xxxxx/ yyyy/ zz/ v/ uuuuuu	ICE2: Treatment discontinuation due to other reasons	Ddmmmyyyy (xx)	Treatment policy/ As observed	Treatment policy/ As observed	Treatment policy/ As observed	Treatment policy/ As observed
Xxxxx/ yyyy/ zz/ v/ uuuuuu	ICE4: Treatment discontinuation due to death	Ddmmmyyyy (xx)	Composite/ Return to baseline	Treatment policy/ As observed	Treatment policy/ As observed	Composite/ Return to baseline
…						

MI: Multiple Imputation, MAR: Missing at Random, MNAR: Missing not at Random

*: Also applied to secondary efficacy endpoints, other efficacy endpoints and exploratory endpoints if applicable

$: Stage 2 = Moderate, Stage 3 = Severe

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe

Note: True monotone missing values not due to ICE are imputed with a MI MAR approach and intermittent missing values are imputed with a MI MCMC approach for the Primary Estimand Strategy as well as the Tertiary Sensitivity of the Primary Estimand and Secondary Efficacy Endpoints, Other Efficacy Endpoints and Exploratory Efficacy Endpoints if applicable.

Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, eye (first study eye, then fellow eye), visit and date and type as ordered in the CRF. Present only available data.

Listing 16.2.7.1 Adverse Events (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	AE Nr.	System Organ Class/ Preferred Term Verbatim	Start Date (Study Day) and Time/ Stop Date (Study Day) and Time/ Duration	Ocular?/ Eye	TEAE/ SAE/ AESI/ OD	Relationship to Study Drug/ to Other Study Procedure	Severity/ Action Taken/ Outcome/ Treatment required/ Withdrawn from Study	Serious Criteria
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	1	Xxxxxx/ Yyyyy	ddMMMyyyy (xx) hh:mm/ ddMMMyyyy (xx) hh:mm/ 3 days	Yes/ Left *	Yes/ Yes/ Yes/ No	Unrelated/ Related	Severe/ Discontinued/ Recovered/Resolved/ Medication/ Yes	Life-threatening, Other serious medically important event
Xxxxx/ yyyy/ zz/ v/ uuuuuu	1	Xxxxxxxxx/ Yyyy	ddMMMyyyy (xx) hh:mm/ Ongoing	No	Yes/ Yes/ Yes/ Yes	Related/ Unrelated	Moderate/ None/ Not Recovered/Not Resolved/ Other action: xxx/ No	Requires or prolongs hospitalization
…								

AE: Adverse Event, TEAE: Treatment-emergent Adverse Event, SAE: Serious Adverse Event, AESI: Adverse Event of Special Interest, OD: Overdose

*: Study eye

$: Stage 2 = Moderate, Stage 3 = Severe

Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe

Note: Duration is calculated as (End date and time – Start date and time) if time available and within 24 hours then presented in hours. If the Duration is > 24 hours then present in days. In case only date is present Duration is calculated as (End date – Start date) + 1 and presented in days.

Analysis dataset: ADxx.SAS7BDAT;

Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:

Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, start date, SOC and PT. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. In case an end date is missing and/or the AE is ongoing the term 'Ongoing' will be presented. Serious Criteria will be listed separated by ','. In case of ocular AE present in the study eye it will be flagged with '*'.

Listing 16.2.7.2 All Ocular Adverse Events (Enrolled Set)

Programming Note:
The layout and footnotes are the same as Listing 16.2.7.1.

Listing 16.2.8.1.1 Laboratory Assessment - Hematology (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Test Name (unit)	Visit	Collection Date (Study Day)	Result/Reason Not Done	Flag	Normal Range	Clinical Significance
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Hemoglobin (unit)	Visit x	ddmmmyyyy (xx)	xxx	H	xx-xxx	Yes
		Visit y	ddmmmyyyy (xx)	xxx	L	xx-xxx	No
		…	ddmmmyyyy (xx)	Yyyyyyyyy yyyyyyyy y yyyy	-	-	-
			ddmmmyyyy (xx)	xxx	N	xx-xxx	No
			ddmmmyyyy (xx)	xxx	L	xx-xxx	No
			ddmmmyyyy (xx)	xxx	L	xx-xxx	No
			ddmmmyyyy (xx)	xxx	L	xx-xxx	No
			ddmmmyyyy (xx)	xxx	N/A	xx-xxx	N/A
			ddmmmyyyy (xx)	xxx	N/A	xx-xxx	N/A
	Hematocrit (unit)	Visit x	ddmmmyyyy (xx)	xxx	H	xx-xxx	No
		Visit y	ddmmmyyyy (xx)	xxx	H	xx-xxx	No
		…	ddmmmyyyy (xx)	xxx	N/A	xx-xxx	N/A
			ddmmmyyyy (xx)	xxx	N/A	xx-xxx	N/A
			ddmmmyyyy (xx)	xxx	N/A	xx-xxx	N/A
			ddmmmyyyy (xx)	-	-	-	-
			ddmmmyyyy (xx)	xxx	N/A	xx-xxx	N/A
			ddmmmyyyy (xx)	xxx	N/A	xx-xxx	N/A
			ddmmmyyyy (xx)	xxx	N/A	xx-xxx	N/A
			ddmmmyyyy (xx)	xxx	N/A	xx-xxx	N/A
	Red Blood Cells (unit)	Visit x	ddmmmyyyy (xx)	xxx	H	xx-xxx	Yes
		…					

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe, H = High, L = Low, N = Normal
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest MT8 to highest and then Vehicle) and patient ID, test name and visit. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing. Display all available visits including unscheduled where abnormal clinically significant values are present.

Listing 16.2.8.1.2 Laboratory Assessment - Biochemistry (Enrolled Set)

Programming Note:
The layout and footnotes are the same as Listing 16.2.8.1.1

Listing 16.2.8.1.3 Pregnancy Test (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Visit	Date of Pregnancy Test (Study Day)	Result	Reason Not Done
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Visit x	ddmmmyyyy (xx)	xxx	N/A
	Visit y	ddmmmyyyy (xx)	xxx	N/A
	Visit x	ddmmmyyyy (xx)	xxx	N/A
	Visit y	ddmmmyyyy (xx)	xxx	N/A
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Visit x	ddmmmyyyy (xx)	-	Xxxxx

Note: - = unknown or not evaluated, N/A = not applicable
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID and visit. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.8.2.1 Vital Signs (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Parameter (SI unit)	Visit	Assessment Date (Study Day)	Result	Reason Not Done
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Systolic Blood Pressure (mmHg)	Visit x	Ddmmmyyyy (xx)	xxx	N/A
		Visit y	Ddmmmyyyy (xx)	xxx	N/A
		Visit z	Ddmmmyyyy (xx)	-	Xxxxxxxxxxx
		…	Ddmmmyyyy (xx)	xxx	N/A
	Diastolic Blood Pressure (mmHg)	Visit x	Ddmmmyyyy (xx)	xxx	N/A
		Visit y	Ddmmmyyyy (xx)	xxx	N/A
		Visit z	Ddmmmyyyy (xx)	-	Xxxxxxxxx
		…	Ddmmmyyyy (xx)	xxx	N/A
	Heart Rate (beats/min)	Visit x	Ddmmmyyyy (xx)	Xxx	N/A
		Visit y	Ddmmmyyyy (xx)	Xxx	N/A
		Visit z	Ddmmmyyyy (xx)	Xxx	N/A
		Visit v	Ddmmmyyyy (xx)	-	Xxxxxxxxxxxxxxxx
		…	Ddmmmyyyy (xx)	xxx	N/A
	Weight (kg)	Visit x	Ddmmmyyyy (xx)	xxx	N/A
		…	Ddmmmyyyy (xx)	xxx	N/A
	Height (cm)	Visit x	Ddmmmyyyy (xx)	xxx	N/A
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Systolic Blood Pressure (mmHg)	Visit x	Ddmmmyyyy (xx)	xxx	N/A
		Visit y	Ddmmmyyyy (xx)	xxx	N/A
		Visit z	Ddmmmyyyy (xx)	xxx	N/A
		…	Ddmmmyyyy (xx)	xxx	N/A

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, parameter (order as collected in CRF) and visit. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.8.2.2 Electrocardiogram (ECG) (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Visit	Assessment Date and Time (Study Day)	Any abnormal clinically significant findings?/ Any new abnormal clinically significant findings since last visit?	Reason Not Done
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Visit x	Ddmmmyyyy hh:mm (xx)	No/ No	N/A
	Visit y	Ddmmmyyyy hh:mm (xx)	Yes: xxxxxxxxxx/ Yes: xxxxxxxxxxxx xxxxxx	N/A
	Visit z	Ddmmmyyyy hh:mm (xx)	No/ No	N/A
	…	Ddmmmyyyy hh:mm (xx)	No/ No	N/A
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Visit x	Ddmmmyyyy hh:mm (xx)	No/ No	N/A
	Visit y	Ddmmmyyyy hh:mm (xx)	Yes: xxxxxxxxxx/ No	N/A
	Visit z	Ddmmmyyyy hh:mm (xx)	-	Xxxxxxxxxxxx
	…	Ddmmmyyyy hh:mm (xx)	Yes: xxxxxxxxxxxxxxxxxx/ Yes: xxxxxxxxxxxxxx	N/A

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID and visit. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.8.2.3 Physical Examination (Enrolled Set)

Programming Note:
The layout and footnotes are the same as Listing 16.2.8.2.2 but display in column 3 only 'Assessment Date (Study Day)' without the time portion.

Listing 16.2.8.2.4 Slit Lamp Examination Safety Assessment - except the Cornea (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Eye	Visit	Assessment Date (Study Day)	Any abnormal clinically significant findings?/ Any new abnormal clinically significant findings since last visit?	Reason Not Done
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Study	Visit x	Ddmmmyyyy (xx)	No/ No	N/A
		Visit y	Ddmmmyyyy (xx)	Yes/ Yes	N/A
		Visit z	Ddmmmyyyy (xx)	No/ No	N/A
		…	Ddmmmyyyy (xx)	No/ No	N/A
	Fellow	Visit x	Ddmmmyyyy (xx)	No/ No	N/A
		…	Ddmmmyyyy (xx)	No/ No	N/A
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Study	Visit x	Ddmmmyyyy (xx)	No/ No	N/A
		Visit y	Ddmmmyyyy (xx)	Yes/ No	N/A
		Visit z	Ddmmmyyyy (xx)	-	Xxxxxxxxxxxx
		…	Ddmmmyyyy (xx)	Yes/ Yes	N/A

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, Eye (first study then fellow eye) and visit. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

Listing 16.2.8.2.5 Fundus Examination (Enrolled Set)

Patient ID/ Treatment group/ Region/ Disease stage $/ Study eye	Eye	Visit	Assessment Date (Study Day)	Pupil Dilated?	Eye Part	Any clinically significant Abnormalities?	Reason Not Done
Xxxxx/ REC 0/0559 0.5 µg/day/ NA/ 2/ Right	Study	Visit x	Ddmmmyyyy (xx)	Yes	Macula	No	N/A
		Visit y	Ddmmmyyyy (xx)	Yes	Optic Nerve	Yes: xxxxxxxxxxx	N/A
		Visit z	Ddmmmyyyy (xx)	Yes	Retina	Yes: xxxxxxxxx	N/A
		…	Ddmmmyyyy (xx)	No	Retina	No	N/A
	Fellow	Visit x	Ddmmmyyyy (xx)	Yes	Choroid	No	N/A
		…	Ddmmmyyyy (xx)	Yes	Retina	No	N/A
Xxxxx/ yyyy/ zz/ v/ uuuuuu	Study	Visit x	Ddmmmyyyy (xx)	No	Vitreous Body	Yes: xxx xxxxxxxx	N/A
		Visit y	Ddmmmyyyy (xx)	Yes	Retina	No	N/A
		Visit z	Ddmmmyyyy (xx)	Yes	Macula	No	N/A
		…	Ddmmmyyyy (xx)	-	-	-	Xxxxxxxxxxxxx

$: Stage 2 = Moderate, Stage 3 = Severe
Note: - = unknown or not evaluated, N/A = not applicable, NA = North America, EU = Europe
Note: Study Day 1 is the first day of study treatment.
Analysis dataset: ADxx.SAS7BDAT;
Date/time of run: ddmmmyyyy:hh:mm <program name>

Programming Note:
See section 15 for Format of output in the SAP. Sort listing by treatment group (lowest REC 0/0559 to highest and then Vehicle) and patient ID, Eye (first study then fellow eye) and visit. If a patient is not treated or a screen failure display 'Not Treated' or 'Screen Failure' in first column as Treatment group and sort these patients at the end of the listing.

21. Appendices

21.1. Appendix 1

Table 11: 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 between 2 visits	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 between 2 visits**	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		X		X	X	X	X	X				
Administration of study drug		→										
Collection of used study drug containers				X	X	X	X	X	X			X
Review of study drug diary			X	X	X	X	X	X	X			X
Assess compliance				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 between 2 visits**	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	

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 over 4 days (Day -3 to Day 1), or on the same day (Day 1) as Visit 1b. 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 IDMC 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 REC 0/0559 administration (and before the next REC 0/0559 administration), and at 20 minutes and 4 hours after the second daily REC 0/0559 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, 4 hours postdose and before the next REC 0/0559 administration on Day 28 (±2 days) and Day 56 (±3 days). 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.