STATISTICAL ANALYSIS PLAN

for

An 8-week, multicenter, open label, prospective study with 24 weeks of follow-up to evaluate safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in patients with Stage 1 Neurotrophic Keratitis (NK) (DEFENDO)

Protocol No: NGF0120

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AMEMDMENT HISTORY

None

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AT	Artificial tears
BCDVA	Best-corrected distance visual acuity
CSR	Clinical study report
eCRF	Electronic case report form
ENRL	Enrolled Population
FAS	Full Analysis Set
FCS	Fluorescein Corneal Staining
FTS	Full Treated Set
ICF	Informed consent form
IDEEL	Impact of Dry Eye on Everyday Life
IOP	Intraocular Pressure
logMAR	Logarithm of the Minimum Angle of Resolution
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
NK	Neurotrophic Keratitis
OCT	Optical Coherence Tomography
OD	Right eye
OS	Left eye
OU	Both eyes
PED	Persistent Epithelial Defect
PT	Preferred Term
SAE	Serious adverse event
SAF	Safety Population
SAP	Statistical analysis plan
SCRN	Screened Population
SD	Standard deviation
SOC	System Organ Class
SPK	Superficial punctate keratitis/keratopathy
TEAE	Treatment-emergent AEs
TFBUT	Tear film break-up time
TFLs	Tables, Figures, and Listings
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the final statistical analysis for subject information, safety data, and efficacy data to be performed for the study entitled “An 8-week, multicenter, open label, prospective study with 24 weeks of follow-up to evaluate safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in patients with Stage 1 Neurotrophic Keratitis (NK)” (Version No.0.4–FINAL 04May2021). Mock shells are also produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to finalized SAP. The SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations identified in the protocol. If the final clinical study report (CSR) contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the CSR.

1.1 Study Objectives

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

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

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

The additional objectives (site-specific) are to evaluate the change from baseline at week 8 and week 24 in confocal microscopy and anterior segment Optical Coherence Tomography (OCT).

1.2 Study Design

This clinical study will be a multi-center, open label, prospective study of 8 weeks of treatment with 24 weeks of follow-up to evaluate the safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution administered as one drop in the affected eye(s), 6 times per day at 2-hour intervals, for eight weeks in patients with Stage 1 NK. The study population will comprise of both female and male subjects. A total of 35 evaluable subjects (those patients completing 8 weeks of Oxervate™) aged $\geqslant$ 18 years will be enrolled in approximately 5 sites within the United States.

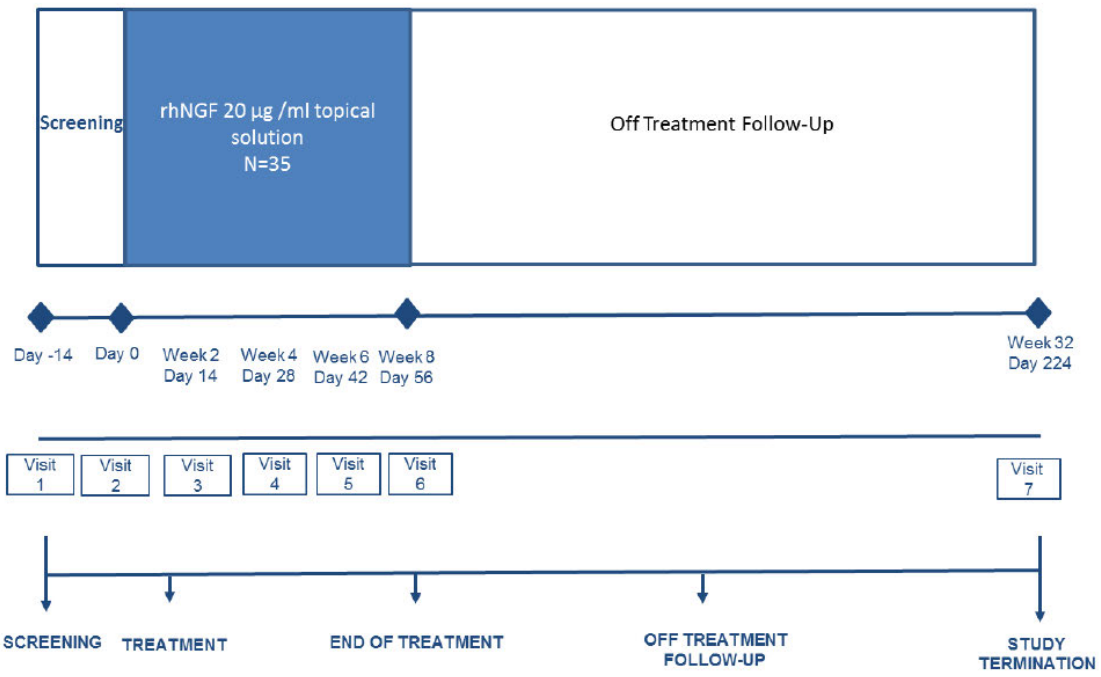
All patients will attend the following clinic visits in the following sequence:

- Screening (Visit 1/Day -14)
- Baseline and First Study Product Pick-Up (Visit 2/Day 0)

- Product Pick-Up (Visit 3/Week 2)
- Treatment Assessment and Study Product Pick-Up (Visit 4/Week 4)
- Product Pick-Up (Visit 5/Week 6)
- End of 8-week Treatment (Visit 6/Week 8)
- Follow-Up and Final Study Visit (Visit 7/Week 32)

The trial structure for subjects is shown in Figure 1.

Figure 1 Study Schematic



The study will be a total of 34 weeks in duration: a screening (washout) period of 2 weeks, followed by 8 weeks of treatment and a 24-week follow-up period. At the end of the screening period (at Visit 2), patients meeting the entry criteria for this study will be assigned to treatment with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution which will be known as Study Product beginning the morning following Visit 2. On Day 0 (baseline visit-Visit 2) and at Visit 3, Visit 4, and Visit 5, the study personnel will give to the Subject the b-weekly kit containing 2 weeks of the study product and delivery kits.

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

Ocular assessments should be conducted by the same assessor throughout a subject's participation period to reduce observer variability. All efficacy

assessments will be carried out consistently either in the morning or the afternoon (preferred time window is ±2 hours) throughout all study visits to minimize intra-subject diurnal variability. The detailed schedule of evaluations is included in the Appendix 1.

1.3 Criteria for Evaluations Defined in Protocol

1.3.1 Demographics and Background Characteristics

Demographic information including date of birth, gender, ethnicity, race, as well as iris color and date of informed consent will be recorded.

Medical history and ocular medical history will be documented and recorded at screening.

1.3.2 Treatment of Subjects

1.3.2.1 Concomitant Medications

All medications (including over-the-counter drugs, systemic medications, herbal products, vitamins, and antacids) should be documented at screening. Additionally, all medications taken within 14 days of study treatment Visit 2 and throughout the study will be clearly documented on the Concomitant Medications eCRF page. Medication entries should be specific to product name (if a combination drug product) and spelled correctly. The dose, unit, frequency, route of administration, start date, discontinuation date, and indication should also be recorded. For medications administered only one time, the frequency column may reflect "once".

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

1.3.2.2 Rescue Therapy

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

During the 24 weeks post treatment, for patients completely healed, no treatment is allowed except for commercially available AT provided by the Sponsor, administered at the physician’s discretion. The use of AT will be tracked via a daily dosing diary. Patients not completely healed and who don’t meet criteria for premature discontinuation will also be followed up but any treatment is allowed at the discretion of the physician, with the exception of additional Oxervate™.

1.3.2.3 Study Drug Administration

The subject will receive a total of 56 OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution vials per treated eye over the 8-week duration of the study product treatment, 1 OXERVATE™ 0.002% (20 mcg/mL)

cenegermin-bkbj ophthalmic solution vial to be used per day. The patient will pick up Study Product from the Investigator's office and bring back used vials for reconciliation at the subsequent study visit. Patients will be instructed to self-administer the study product one drop in the affected eye(s) six times a day at 2 hour intervals starting on the day after Visit 2 (Day 0-Baseline and First Study product Pick Up) of the treatment period. On Day 1, the patient will start the first dose. The patient should not start therapy on the same day as Day 0/Visit 2. The Study Product will be dosed one drop (- 0.70 µg/35 µl of cenegermin-bkbj 0.002% solution) 6 times a day at 2-hour intervals in the affected eye(s) for 8 weeks of treatment.

1.3.2.4 Study Drug Compliance

On Day 0 (baseline visit-Visit 2) and at Visit 3, Visit 4, and Visit 5, the study personnel will give to the Subject the biweekly kit containing two weeks of the study product and delivery kits. At Visits 3, 4, 5 and 6, patients will return the used or unused study boxes/vials to the clinic in the original carton. All Study Product returned by patients should be inventoried same day of return. Inventory will take place at Visits 3, 4, 5 and 6. Any discrepancies and/or deficiencies in study drug accountability must be recorded along with an explanation in the appropriate accountability log.

1.3.3 Efficacy Assessments

1.3.3.1 Fluorescein corneal staining

Following the instillation of fluorescein in the qualifying eye(s) grade (density) of the SPK will be determined at Visit 1, 2, 4, 6, 7 using the NEI (National Eye Institute [NEI]/Industry Workshop 0-15) scale of 0 to 3 for each of the five areas: Zone 1 Central, Zone 2 Superior, Zone 3 Temporal, Zone 4 Nasal, and Zone 5 Inferior.

Epithelial healing, defined as Grade 1 or absence of staining (Grade 0) in a previously qualifying zone, will be determined by the investigators and recorded on eCRF at Visit 4, 6, and 7.

1.3.3.2 Corneal Sensitivity Testing

Corneal Sensitivity will be measured (in cm) using a Cochet Bonnet aesthesiometer at Visit 1, 2, 4, 6, 7

1.3.3.3 Best Corrected Distance Visual Acuity (BCDVA)

The logarithm of the minimal angle of resolution (logMAR) visual acuity score (ranged from -0.3 to 1) and Snellen score (ranged from 20/10 – 20/200) will be recorded at Visit 1, 2, 4, 6, 7.

1.3.3.4 Tear Film Break-Up Time (TFBUT)

Tear film break-up time (sec) will be assessed using fluorescein at Visit 2, 4, 6, 7.

1.3.3.5 Schirmer Test (w/o Anesthesia)

Unanesthetized Schirmer's test measures the amount of wetting (mm) at Visit 2, 4, 6, 7.

1.3.3.6 Impact of Dry Eye on Everyday Life (IDEEL)

This 57-item questionnaire assesses dry eye impact at Visit 2, 4, 6, 7, and constitutes following 3 modules:

- Dry eye Quality of Life (27 questions) comprising three sections: "Daily activities", "Feelings" and "Work".
- Dry eye Treatment satisfaction & Bother (10 questions) comprising two sections: "Treatment – In general" and "Treatment- Eye drop".
- Dry eye Symptom bother (20 questions).

1.3.3.7 EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (Herdman et. al. 2011). This self-administered questionnaire consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) in a scale of 1 (no problems) to 5 (extreme problems) with high score favoring worse as well as the health today score in a scale of 0 (the worst health you can imagine) to 100 (the best health you can imagine) at Visit 2, 4, 6, 7.

1.3.3.8 Anterior Segment Optical Coherence Tomography (OCT) (selected sites)

Anterior segment OCT will be performed at selected sites at Visit 2, 6, 7 to assess epithelial thickness (uM) of central, superior, temporal, nasal, and inferior zones; Stromal Thickness (μM) in the NEI Central Zone, presence/absence of Epithelial surface irregularities, Persistent Epithelial Defect (PED), Scarring of Stroma, Stromal Thinning, Descemet's Membrane Folds, and Corneal Ulceration

1.3.3.9 Confocal microscopy (selected sites)

Confocal microscopy will be performed at selected sites at Visit 2, 6, 7. Structural nerve regeneration (density, length, nerve density, tortuosity) will be assessed by a reading center to be determined.

1.3.4 Safety Assessments

1.3.4.1 Adverse events

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

(start and stop dates), severity, relationship to the study drug, action(s) taken, outcome.

1.3.4.2 Intraocular Pressure

Intraocular Pressure (IOP) measurements (mmHg) will be performed by Goldmann applanation tonometry with a single measurement at visit 1, 2, 6, 7.

1.3.4.3 Slit Lamp Examination

Slit Lamp Examination will be performed to assess lashes, eyelids, conjunctiva, cornea, lens, sclera, iris, and anterior chamber at visit 1, 2, 4, 6, 7 based on following categories: Normal, Abnormal Non-Clinically Significant, Abnormal Clinically Significant.

1.3.4.4 External Ocular Examination

The motility of the extraocular muscles and the appearance and function of the eyelids will be assessed at Visit 1, 2, 4, 6, 7, and recorded as: Normal, Abnormal Non-Clinically Significant, Abnormal Clinically Significant.

1.4 Study Data

The study data to be analyzed include all clinical data captured by eCRF, as well as external data per data transfer agreements. The eCRF database will be locked for the final analyses.

2 GENERAL ANALYSIS DEFINITIONS

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.4 (SAS/STAT 15.1) or higher. Listings for CSR Appendix 16.2 will include, as a minimum, all the subject data points to be used for analyses. Data listings will be provided for all subjects with data available.

2.1 Study Eye

Based on the protocol, the study eye is the eye at Visit 2 having Grade 3 FCS per the NEI scale in the central zone and a decreased corneal sensitivity ($\leqslant$ 4 cm using the Cochet-Bonnet aesthesiometer) in the central zone at both Visit 1 and Visit 2. If both eyes have a qualifying central zone meeting FCS and corneal sensitivity requirements at both Visit 1 and Visit 2, the right eye will be selected as study eye. If both eyes meet the FCS and corneal sensitivity requirements in the central zone, the subject will be treated bilaterally. If only one eye qualifies, but the contralateral eye has FCS in the central zone $\geqslant$2 on NEI scale and the Investigator feels that both eyes would benefit from treatment (i.e. the qualifying eye is abnormal, but does not meet criteria for study) both eyes may be treated with study product. Data will be collected and recorded in the eCRF for both eyes throughout the study. If there is only one qualifying eye/one study eye, only one eye will be treated; however, both eyes will be evaluated, and data will be collected for both eyes.

2.2 Treatment Group

All the analyses will be conducted based on a single treatment group, which is labelled as “cenegermin-bkbj 0.002%”.

2.3 Study Period, Visit, and Day

The overall study consists of initial Screening, a 14-day Washout Period, an 8-week Treatment Period, and a 24-week Follow-up Period.

A reference date refers to the date of the first study product administration. All safety and efficacy assessments at all visits will be assigned a day relative to this date. The relative day will be defined as: visit date – reference date + 1 for visits on or after the reference date, and visit date – reference date for visits before the reference date.

2.4 Definition of Baseline

In general, the baseline is defined as the last assessment before the first study product administration unless specifically stated otherwise. Ocular measurements will use the most recent measurement for each eye.

2.5 Out of Window and Unscheduled Visits

All scheduled assessments after first administration of randomized study product will be used. The protocol defined windows for scheduled visits will not be used in the analyses by visit. Data will be assigned to the scheduled visit closer in time to the scheduled visit. Unscheduled visit data will only be used in an analysis if there is no other available data closer in time to a scheduled visit. Post first dose unscheduled assessments will be taken into account for worst-case determination as applicable. All unscheduled visit data will be included in data listings.

2.6 Analysis Populations

A summary table of number (%) of patients in each analysis population/set will be provided.

2.6.1 Screened Population

The Screened Population will consist of all patients who attended Screening, signed the informed consent form, and were assigned a patient identification number.

2.6.2 Enrolled Population

The Enrolled Population (ENRL) will consist of all patients who signed the informed consent form and attended Visit 2.

2.6.3 Full Analysis Set

The full analysis set (FAS) will include all enrolled patients who received at least one dose of study drug. The FAS will be used also for safety analyses.

2.6.4 Full Treated Set

The full treated set (FTS) will include all enrolled patients who received treatment of study drug through Visit 6.

2.7 Unit of Analysis

In general, the unit of analysis will be study eye (affected eye) for eye-level summary, and subject for subject-level summary. Data for both eyes will be presented in the data listings.

2.8 Definition of Subgroups

No subgroup analyses are planned.

2.9 Descriptive Summaries

Summary statistics and statistical analyses will generally be performed only for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used. For endpoints that are continuous in nature: number of observations, mean, median, minimum and maximum, and standard deviation (SD) values will be presented as descriptive statistics summary for both observed values and change from baseline values at each scheduled visit if applicable. For endpoints that are categorical in nature: frequency counts and percentages will be presented as descriptive statistics summary at each scheduled visit if applicable.

The number of decimal places to display for calculated data will be determined by the original scale of the data. Means and medians will be reported with one (1) additional decimal place. Standard deviation will be reported with two (2) additional decimal places. Minimum and maximum will be reported with the same number of significant digits as the method of capture.

2.10 Type 1 Error Control for Multiple Tests

Not applicable. This is an exploratory, hypothesis generating study. All efficacy analyses are considered exploratory.

2.11 Handling of Missing Data

The primary efficacy analysis will be based on observed cases (i.e. no missing data imputation). Sensitivity analyses will be performed using various missing data imputation approaches as described in Section 5.1.

All analyses unless specified will be conducted on an as observed case basis, that is, no further imputation of missing data will be carried out unless expressly stated otherwise.

Imputation for Missing Concomitant Medication and AE Start and Stop Days:

Missing and/or incomplete dates for concomitant medications and AEs will be imputed for calculating Start/Onset Day and Stop Day only. The Start/Onset Day

and Stop Day may be used for calculating prior or concomitant medications or calculating treatment emergent AEs. Missing and/or incomplete dates will be imputed in a manner that assumes the worst case scenario (i.e. Start/Onset as close as possible to the First Study Treatment Administration and stopped such that it assumed to have lasted for the longest possible duration, taking into account that the Start/Onset date should not be after the Stop date).

Imputation for missing Stop Date:

- For a completely missing stop year (regardless of day or month) the medication/AE will be assumed to be ongoing.
- For a missing stop month (and a medication/AE that is not 'Ongoing') the medication/AE will be assumed to have ended the last available month of that year.
- For a missing stop day (and a medication/AE that is not 'Ongoing') the medication/AE will be assumed to have ended on the last day of the month if the month is available.

Imputation for missing Start/Onset Date:

- For a completely missing Start/Onset date (day, month and year), the Start Day of medication/AE will be considered pre-treatment (i.e. prior) if the stop date or partial stop date concludes the medication/AE was stopped before the first administration of the study product. In all other instances (i.e. inconclusive stop date or Ongoing medication/AE) the Start Day of medication/AE will be assumed to have started at the date of the first administration of the study product (i.e. assumed to be concomitant or treatment emergent as is applicable).
- For a missing start/onset month the medication/AE will be assumed to have started in January of that year, or at the date of first administration of the study product if the start/onset year was the same as the year of first administration of the study product.
- For a missing start/onset day the medication/AE will be assumed to have started on the first day of the month, or at the date of first administration of the study product and the year was the same as the Randomization month and year.

3 SUBJECT INFORMATION

In general, all subject information will be summarized for the FAS Population, unless stated otherwise.

3.1 Disposition Information

Summaries will be provided for number and percentage of completed or discontinued study with the reasons of discontinuation as collected on eCRF.

3.2 Study Visits

The number and percentage of subjects completing each scheduled visit will be tabulated.

3.3 Demographics Characteristics

Descriptive statistics or frequency tabulation will be provided for age, gender, race, and ethnicity.

3.4 Medical and Ocular History and Surgical Procedures

A summary table will be prepared for the medical history/surgical procedure data, and one for ocular history/surgical procedure data. Conditions will be categorized according to MedDRA-coded terms. This table will indicate the number and percentage of subjects who presented with previous history overall and by system organ class (SOC) and preferred term (PT). SOC will be sorted alphabetically and PT within each SOC will be sorted by overall descending order of frequency.

The initial diagnosis of neurotrophic keratitis/keratopathy will be included in a listing.

3.5 Pregnancy Status

The data for urine pregnancy testing will be presented in a listing, for female subjects with childbearing potential only.

3.6 Protocol Deviations

All reported protocol deviations and determined exclusions from any analysis population(s) will be documented and included in the CSR. All reported protocol deviations and inclusion or exclusion exceptions will be included in a listing.

4 TREATMENTS AND MEDICATIONS

In general, all treatment parameters will be summarized for the Full Analysis Set, unless stated otherwise. All reported medications will be coded using World Health Organization-Drug Dictionary (WHO-DD). For summary of medications, the coded generic medication name (Preferred Term) will be sorted by overall descending order of frequency.

4.1 Prior Medications

Prior medications are medications that discontinued prior to receiving the first administration of the study product at Day 1 based on imputed stop day. Summary tables will be prepared for the reported use of all prior medications by generic name and location (ocular vs non-ocular).

4.2 Concomitant Medications

Concomitant medications include all medications that a subject used during the study on or after the first administration of the study product at Day 1. Summary tables will be prepared for the reported use of all concomitant medications by

generic name and location (ocular vs non-ocular), and further classified as On Treatment Period (medications started between the day of first administration of the study product and the day of last administration of the study product), and On Follow-up Period (medications started after the day of last administration of the study product).

4.3 Use of Artificial Tears

Use of artificial tears during the washout period is calculated as days on the use of artificial tears, defined as one plus the difference in days between date of last instillation of artificial tears and the date of first instillation of artificial tears during the washout period. Use of artificial tears will be summarized by descriptive statistics.

4.4 Extent of Exposure to Study Product

Extent of exposure to study product is calculated as days on therapy, defined as one plus the difference in days between date of last instillation of study medication and the date of first instillation of study medication. For subjects for whom the date of last dose is unknown, extent of exposure will be calculated based on the date of last contact. Extent of exposure to study product will be summarized using descriptive statistics.

4.5 Treatment Compliance of Study Product

The overall treatment compliance of study product in the treatment period is calculated as: 100 × The total number of doses / (The total number of days of exposure to study product × 6), where the total number of doses is summed from numbers of daily doses recorded on the Study Product Diary. Overall compliance in the treatment period is categorized as <80%, 80-120%, >120%.

5 ANALYSIS OF EFFICACY

5.1 Primary Efficacy Variable

The primary efficacy variable is the achievement of epithelial healing at Visit 6/Week 8, which is defined as Grade 1 or absence of staining (Grade 0) in the central qualifying zone of study eye via FCS (per NEI scale). The primary efficacy variable will be summarized as a binary goal attainment variable (Yes/No).

The primary analysis will be based on observed cases (i.e. no missing data imputation). As a sensitivity analysis, the last post baseline observation prior to Week 8 will be carried forward for imputing missing data at Week 8. In addition the worst post baseline observation prior to Week 8 will be carried forward for imputing missing data at Week 8 and patients who took any rescue medication prior to Week 8 will be considered as a treatment failure (not epithelial healed) at Week 8.

All summaries and analyses for the primary efficacy variable will be presented for both FAS and FTS populations.

5.2 Secondary Efficacy Variables

All the analyses of secondary efficacy variables will be performed based on the observed cases in the FAS population. No missing data imputation will be considered.

- Percentage of patients who experienced epithelial healing at 4 weeks

The patients who experienced epithelial healing at Visit 4/Week 4 will be determined for study eye similarly as the primary efficacy variable. It will be summarized as a binary goal attainment variable (Yes/No).

- Percentage of patients who achieved epithelial healing at Week 8 and remained healed throughout the follow-up period

The patients who achieved epithelial healing at Week 8 and remained healed throughout the follow-up period will be determined for study eye at Visit 7/Week 32 similarly as the primary efficacy variable. It will be summarized as a binary goal attainment variable (Yes/No) based on the subset of patients who achieved epithelial healing at Week 8, as well as based on the FTS.

- Percentage of patients who experienced complete healing at Week 4 and 8

The patients who experienced complete healing at Week 4 and 8 will be determined for study eye by the investigator and recorded on eCRF. The complete healing is defined as Grade ≤ 1 in the central qualifying zone of study eye via FCS (per NEI scale) and no persistent staining in the non-qualifying zones (excluding the superior zone) defined as the absence (Grade 0) of pathological staining via corneal photography. It will be summarized as a binary goal attainment variable (Yes/No).

- Percentage of patients who achieved complete healing at Week 8 and remained completely healed throughout the follow-up period

The patients who achieved complete healing at Week 8 and remained healed throughout the follow-up period will be determined for study eye at Visit 7/Week 32 by the investigator and recorded on eCRF. It will be summarized as a binary goal attainment variable (Yes/No) based on the subset of patients who achieved complete healing at Week 8, as well as based on the FTS.

- Mean change in corneal sensitivity from baseline at 4, 8, and 32 weeks

The corneal sensitivity (cm) in the NEI zone of the study eye as measured by the Cochet-Bonnet aesthesiometer will be summarized as a continuous variable.

- Percentage of patients that achieve an improvement in corneal sensitivity at 4, 8, and 32 weeks

The improvement in corneal sensitivity, defined as change from baseline > 0 (cm) of the study eye, will be summarized as a binary goal attainment variable (Yes/No).

- Schirmer I change from baseline to weeks 4, 8, and week 32

The Schirmer tear test result (mm) in the study eye will be summarized as a continuous variable.

- TFBUT change from baseline to weeks 4, 8, and week 32

The average TFBUT result (sec) of two repeat measurements in the study eye will be summarized as a continuous variable.

- Mean change in BCDVA from baseline to Week 4, 8, and week 32

The logMAR visual acuity score in the study eye will be summarized as a continuous variable.

- Percentage of patients that achieve a 15-letter gain in BCDVA at 4 and 8 weeks.

The patients that achieve a 15-letter gain in BCDVA at 4 and 8 weeks will be determined based on Week 4 or 8 logMAR – Baseline logMAR $\leqslant$ -0.3. It will be analyzed using a binary goal attainment variable (Yes/No).

- IDEEL change from baseline at week 4, 8, and week 32

Subscores will be derived for the following modules, and will be calculated only if at least 50% of the items of the dimension are completed; otherwise, the scores are missing.

Module 1:

Dry eye impact on daily life (27 questions) comprising 3 QoL domains: 1.a “Daily activities limitations”, 1.b “Emotional well being” and 1.c “Work limitations”. 26 questions will be considered as part of one of these 3 domains. Question 22 will not be considered part of a domain.

1.a: Daily Activities

Daily activities section	**Used in calculation of domain score?**
1. Doing close work in the **morning or afternoon** (such as crossword puzzles, reading, looking at a computer, and/or sewing)	Yes
2. Doing close work in the **evening or at night**	Yes
3. Driving	Yes

4. Being around and/or using scented products (such as cologne or hairspray)	Yes
5. Working on a computer	Yes
6. Going somewhere where there is tobacco smoke or being around someone who smokes	Yes
7. Wearing contact lenses	No
8. Wearing make-up near or on my eyes	No
9. Flying on an airplane	No

Response for questions 1 to 9	Original response code	Item score
I did not do this activity for reasons other than my dry eyes	1	5
None of the time	2	5
A little of the time	3	4
Some of the time	4	3
Most of the time	5	2
All of the time	6	1
I can **no longer** do this activity **due to my dry eyes**	7	0

The response option “I did not do this activity for reasons other than my dry eyes” has a response coded 1 but a scored item value of 5. The original response code is the value to be used for data-entry. The item score is used during the computation of the Daily Activity Limitations Scale Score. Higher item scores are intended to reflect better quality of life (i.e. less limitations on daily activities). Only the first 6 questions are included in the Daily activity Limitations scale score. Questions 7, 8 and 9 are excluded. If 50% (3) or fewer of the 6 questions used in calculating Daily Activity Limitations score have missing item score, then the scale score is calculated by multiplying the mean of the non missing item score by 20. If 4 or more of the 6 item scores are missing then the scale score is not calculated and should be set at missing. Multiplying by 20 transforms the scale score to a 0 to 100 scale, with 0 reflecting the greatest degree of limitations on daily activities measurable by the scale and 100 reflecting the greatest freedom from limitations on daily activities.

1.b Feelings

Feelings	**Used in calculation of domain score?**
10. Irritability	Yes

Feelings	Used in calculation of domain score?
11. Impatience	Yes
12. Feeling sad	Yes
13. Worry that my dry eyes will get worse	Yes
14. Feeling annoyed	Yes
15. Feeling like my eyes do not look nice	Yes
16. Feeling like I have to make adjustments to my life	Yes
17. Feeling different from other people because of my dry eyes	Yes
18. Feeling like I am always aware of my eyes	Yes
19. Feeling older than I really am	Yes
20. Feeling like people look at me and think I am fine when I'm not	Yes
21. Feeling like there is nothing I can do for my dry eyes	No

Response for questions 10 to 21	Original response code	Item score
None of the time	1	4
A little of the time	2	3
Some of the time	3	2
Most of the time	4	1
All of the time	5	0

11 questions are included in the Emotional Well-Being score. Question 21 (IDLEMO12) is excluded from calculation. If 50% (5) or fewer of the 11 questions used in the calculation of Emotional Well-Being score have missing item score, then the scale score is calculated by multiplying the mean of the non missing item scores by 25. If 6 or more of the 11 item scores are missing then the scale score is not calculated and should be set at missing. Multiplying by 25 transforms

the scale score to a 0 to 100 scale, with 0 reflecting the worst level of emotional well-being measurable by the scale and 100 reflecting the best.

1.c Work

Work	Used in calculation of domain score?
22. Are you currently working?	-
23. Feeling distracted	Yes
24. Feeling like I couldn't concentrate	Yes
25. Having to take a break from work	Yes
26. Having to change the way I work (such as the way I read, look at a computer, or work outside)	Yes
27. Having to change my work environment (such as how close I am to an air conditioning or heating vent)	Yes

Response for question 22	Original response code	Item score
Yes	1	1
No	2	0

Response for questions 23 to 27	Original response code	Item score If Response for question 22=0	Item score If Response for question 22=1
None of the time	1	Missing	4
A little of the time	2	Missing	3
Some of the time	3	Missing	2
Most of the time	4	Missing	1
All of the time	5	Missing	0

5 questions are included in the Work Limitations domain. If 50% (2) or fewer of the 5 questions used in the calculation of the Work Limitations score have missing item scores, then the scale score is calculated by multiplying the mean of the non missing item scores by 25. If 3 or more of the 5 item scores are missing then the scale score is not calculated and should be set to missing.
Multiplying by 25 transforms the scale score to a 0 to 100 scale, with 0 reflecting the greatest degree of limitation at work measurable by the scale and 100 reflecting the least limitation at work.

Module 2:

Dry eye Treatment satisfaction & Bother module (10 questions) comprising 2 QoL domains: 2.a “Treatment satisfaction / Happiness” and 2.b “Treatment-related bother”.

2.a Treatment - In general

Treatment in General	**Used in calculation of domain score?**
1. OVER THE LAST TWO WEEKS, how often did you use treatment for your dry eyes?	-
2. I was happy with how quickly my treatments worked	Yes
3. I was happy with how long the effects of my treatments lasted	Yes
4. The treatments I used **completely eliminated** my dry eye symptoms	Yes
5. The treatments I used **relieved most** of my dry eye symptoms	Yes
6. I was bothered by how often I had to use dry eye treatments	Yes

Response for question 1	**Original response code**	**Item score**
None of the time	1	0
A little of the time	2	1
Some of the time	3	2
Most of the time	4	3
All of the time	5	4

Response for questions 2 to 5	**Original response code**	**Item score If Response for question 1 = 0**	**Item score If Response for question 1 > 0 or missing**
None of the time	1	Missing	0
A little of the time	2	Missing	1
Some of the time	3	Missing	2
Most of the time	4	Missing	3
All of the time	5	Missing	4
Response for question 6			
None of the time	1	Missing	4
A little of the time	2	Missing	3
Some of the time	3	Missing	2
Most of the time	4	Missing	1

All of the time	5	Missing	0

5 questions are included in the Treatment Satisfaction/Happiness scale score. If 50% (2) or fewer of the 5 questions used in the calculation of Treatment Satisfaction/Happiness score have missing item score, then the scale score is calculated by multiplying the mean of the non missing item score by 25. If 3 or more of the 5 item scores are missing then the scale score is not calculated and should be missing. Multiplying by 25 transform the scale score to a 0 to 100 scale, with 0 reflecting the lowest level of satisfaction/happiness with treatment measurable by the scale and 100 reflecting the highest level of satisfaction/happiness with treatment.

2.b Treatment- Eye Drops

Treatment- Eye Drops	**Used in calculation of domain score?**
7. Do you ever use eye drops to treat your dry eyes?	-
8. I was bothered by blurriness shortly after using my eye drops	Yes
9. I was embarrassed when I had to use my eye drops	Yes
10. I felt like I could not go anywhere without my eye drops	Yes

Response for question 7	**Original response code**	**Item score**
Yes	1	1
No	2	0

Response for question 8 to 10	**Original response code**	**Item score If Response for question 1 = 0**	**Item score If Response for question 1 > 0**
None of the time	1	Missing	4
A little of the time	2	Missing	3
Some of the time	3	Missing	2
Most of the time	4	Missing	1
All of the time	5	Missing	0

3 questions are included in the Treatment-Related Bother scale score. If 50% (1) or fewer of the 3 questions used in the calculation of Treatment-Related Bother scale score have missing item scores, then the scale score is calculated by multiplying the mean of the non missing item score by 25. If 2 or more of the 3 item scores are missing then the scale score is not calculated and should be set at missing. Multiplying by 25 transforms the scale score to a 0 to 100 scale, with 0 reflecting the greatest degree of treatment related bother measurable by the scale and 100 reflecting the lowest degree of treatment-related bother.

Module 3:

Dry eye Symptom bother (20 questions) comprising a unique domain.

Symptom Bother	Used in calculation of domain score?
1.OVER THE LAST TWO WEEKS, how often did you experience dry eye symptoms?	Yes
2. Eyes that felt gritty or sandy	Yes
3. Felt like I needed to close my eyes even though I was not tired	Yes
4. Burning or stinging eyes	Yes
5. Tired eyes	Yes
6. Blurry vision	Yes
7. Itchy eyes	Yes
8. Irritated eyes	Yes
9. Eyes that felt like they had been scratched by something	Yes
10. Eye dryness	Yes
11. Mucus in, around, or coming out of my eyes	Yes
12. Puffy or swollen eyes	Yes
13. Eye redness	Yes
14. Aching or sore eyes	Yes
15. Felt like something was in my eye	Yes
16. Frequent and/or rapid blinking	Yes
17. Difficulty blinking because of little or no moisture in my eyes	Yes
18. Sensitivity to light, glare, and/or wind	Yes
19. Sensitivity to recirculated air (such as air conditioning and heat)	Yes
20. Headaches associated with dry eye symptoms	Yes

Response for question 1	Original response code	Item score
None of the time	1	0
A little of the time	2	1
Some of the time	3	2
Most of the time	4	3
All of the time	5	4

Response for questions 2 to 20	Original response code	Item score
I did not have this symptom / Not applicable	6	0
Not at all	7	1

Slightly	8	2
Moderately	9	3
Very much	10	4

All questions are included in the Symptom Bother scale score. If 50% (10) or fewer of the 20 questions used in the calculation of Symptom Bother scale score have missing item scores, then the scale score is calculated by multiplying the mean of the non missing item score by 25. If 11 or more of the 20 item scores are missing then the scale score is not calculated and should be set at missing. Multiplying by 25 transforms the scale score to a 0 to 100 scale, with 0 reflecting the greatest degree of treatment related bother measurable by the scale and 100 reflecting the lowest degree of treatment-related bother.

Change from baseline of above-defined subscores will be summarized as a continuous variable at each visit, and mean changes from baseline of all the subscores will be graphically presented (e.g. radar plot) for each visit.

- EQ-5D-5L change from baseline at week 4, 8, and week 32

Change from baseline of each dimension score and overall score of health today will be summarized as a continuous variable at each visit, and mean changes from baseline of all the dimension scores will be graphically presented (e.g. radar plot) for each visit.

5.3 Exploratory Efficacy Variables

All exploratory efficacy analyses will be performed based on the observed cases in the FAS population.

- Frequency of preservative free artificial tears use (drops/day) during the follow up period

The number of doses of artificial tears used by patients during the follow-up period will be based on the number of used vials recorded in the artificial tears accountability log, and will be summarized as a continuous variable.

- Change from baseline structural nerve regeneration per confocal microscopy

The confocal microscopy images will be examined by an external reading center to be determined, and will be summarized as a continuous variable.

- Change from baseline in epithelial thickness per anterior segment OCT

Exploratory analysis of anterior segment OCT data will be and will be summarized as a continuous variable.

5.4 Methods of Efficacy Analysis

Descriptive statistics of the observed and change from baseline of each continuous efficacy endpoint described above will be tabulated by visit where that endpoint is assessed. Where appropriate, the asymptotic 95% confidence intervals of mean change from baseline will be presented.

Analyses for responder/categorical endpoints such as percentage of patients who experience epithelial healing at 4 and 8 weeks, and percentage of patients who remain healed throughout the follow-up period will include percentage of response, and associated exact (Clopper-Pearson) 95% confidence intervals where appropriate.

All efficacy results will be tabulated based on both FAS and FTS as appropriate.

6 ANALYSIS OF SAFETY

All safety parameters will be summarized based on the FAS Population.

6.1 Adverse Events

Adverse events data is collected from the time that informed consent was given, for the duration of the trial on the 'Adverse Events' eCRF page. All events in the clinical database regardless of when they occurred will be provided in data listings. Adverse events will be classified according to the MedDRA to the levels of SOC and PT. SOC will be sorted alphabetically and PT within each SOC will be sorted by overall descending order of frequency.

Pre-treatment AEs are defined as AEs that started during the pre-treatment period (date of informed consent up to the time before the first administration of the study product. Pre-treatment AEs, if any, will be listed only.

Treatment-emergent adverse events (TEAEs) are those with onset after the first dose of study product. Only treatment-emergent events will be summarized.

An overall summary will be presented which gives the number and percentage of subjects that experienced any TEAE, experienced any treatment related TEAE, permanently discontinued treatment due to a TEAE, interrupted treatment due to a TEAE, experienced a serious AE (SAE), and AEs leading to death.

The number and percentage of subjects experiencing one or more events will be tabulated by SOC and PT. In addition, similar tables by SOC and PT will be displayed further by maximum severity, and by closest relationship to treatment. For summary, the TEAEs with relationship to treatment reported as "None" or "Unlikely" are considered "Not Related", and "Possible", "Probable", or "Highly Probable" are considered "Related".

Summary tables will be prepared also for the number and percentage of subjects experiencing one or more events classified as: On Treatment Period (AEs started between the day of first administration of the study product and the day of last administration of the study product), and On Follow-up Period (AEs started after the day of last administration of the study product).

In summary tables for ocular adverse events, AEs occurring in both eyes will be summarized once at the greater severity or closer relationship to study drug.

The number of and percentage of subjects experiencing AEs leading to premature discontinuation from the study will be tabulated and listed.

A listing of serious TEAEs will be also provided.

A glossary listing that shows the verbatim terms assigned to each SOC and PT will be provided.

6.2 Intraocular Pressure

Descriptive statistics of the observed and change from baseline IOP (mmHg) will be summarized as a continuous variable for study eye and treated non-study eye by visit.

6.3 Slit Lamp Examination

Categorical results of slit lamp examination will be summarized for each parameter in a frequency table for study eye and treated non-study eye by visit. Following parameters will be included: Anterior Chamber Cells, Anterior Chamber Flare, Anterior Chamber Other Abnormal Finding, Conjunctiva Edema, Conjunctiva Bulbar Erythema, Conjunctiva Other Abnormal Finding, Cornea Edema, Cornea Endothelial Changes, Cornea Epithelial Changes, Cornea Other Abnormal Finding, Iris, Iris Other Abnormal Finding, Lashes, Lens, Lens Other Abnormal Finding, Eyelid Edema, Eyelid Erythema, Eyelid Other Abnormal Finding, Sclera, Sclera Other Abnormal Finding.

6.4 External Ocular Examination

Categorical results of external ocular examination will be summarized for each parameter in a frequency table for study eye and treated non-study eye by visit. Following parameters will be included: Motility of extraocular muscles, Appearance of eyelids, Specific mechanism.

[redacted]

8 PLANNED INTERIM ANALYSIS

No planned interim analysis.

9 CHANGES FROM PROTOCOL

No changes from protocol are planned.

10 REFERENCES

Impact of Dry Eye on Everyday Life (IDEEL) Questionnaire User Manual, Manual AC6262A version 2, 2 February 2012.

Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011, 20(10):1727-36

Appendix 1: Schedule of Evaluations (from Protocol)

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

Appendix 2 Shells for Tables, Listing, and Figures

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Table Number	Table Title	Analysis Population
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14.1.2	Subject Disposition	Screened
14.1.3	Visit Participation	Full Analysis Set
14.1.4	Demographics	Full Analysis Set
14.1.5.1	Medical History	Full Analysis Set
14.1.5.2	Ocular History	Full Analysis Set
14.1.6.1.1	Ocular Prior Medications	Full Analysis Set
14.1.6.1.2	Non-ocular Prior Medications	Full Analysis Set
14.1.6.2.1	Ocular Concomitant Medications	Full Analysis Set
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14.1.7.1	Treatment Exposure of Study Product	Full Analysis Set
14.1.7.2	Washout Use of Artificial Tears	Full Analysis Set
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14.2.1.1.1	Percentage of Patients who Experienced with Epithelial Healing at 8 weeks	Full Analysis Set
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14.2.1.1.4	Percentage of Patients who Experienced with Epithelial Healing at 8 weeks - WOCF	Full Analysis Set
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