STATISTICAL ANALYSIS PLAN

Protocol No: NGF0122

Protocol Title: A long-term extension study to evaluate the safety and efficacy of OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in patients with Stage 1 Neurotrophic Keratitis who were enrolled in the DEFENDO Study

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AMEMDMENT HISTORY

Version	Replaces	Date	Summary of major changes
1.0	N/A	CCI	Initial version
2.0	1.0	2024-03-22	CCI

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
CCI [redacted]	[redacted]
BCDVA	Best-corrected distance visual acuity
CRC	Central Reading Center
CSR	Clinical study report
eCRF	Electronic case report form
FAS	Full Analysis Set
IDEEL	Impact of Dry Eye on Everyday Life
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
NK	Neurotrophic Keratitis
CCI [redacted]	[redacted]
PED	Persistent Epithelial Defect
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System Organ Class
SPK	Superficial punctate keratitis/keratopathy
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 NGF0122 entitled "A long-term extension study to evaluate the safety and efficacy of OXERVATE® 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution in patients with Stage 1 Neurotrophic Keratitis who were enrolled in the DEFENDO Study", in conjunction with its completed parent study NGF0120. Analyses will be based on integrated data from the two studies unless specifically stated otherwise. 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 protocols. 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

Primary Objective

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

Secondary Objective

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

CCI [redacted]

CCI [redacted]

1.2 Study Design

This clinical study will be a multi-center, open label, long-term follow-up study of the patients who were enrolled in the NGF0120 Study who had Stage 1 NK who were treated with OXERVATE™ 0.002% (20 mcg/mL) cenegermin-bkbj ophthalmic solution. All patients enrolled in the NGF0120 Study who are meeting

inclusion and no exclusion criteria and/or are not lost to follow-up will be eligible for the NGF0122 Long-Term Follow-up Study.

The NGF0120 Study duration was for a total of 34 weeks: a screening period of 2 weeks, followed by enrollment in 8 weeks of OXERVATE™ treatment and an Off-Treatment Follow-Up of 6 months. After completing enrollment in the NGF0120 Study, patients will be invited to enter the NGF0122 Long-Term Follow-up Study (all standard of care are permitted). Two (2) additional long-term follow-up visits will occur at 24- and 30-months to evaluate long-term clinical outcomes. During the NGF0122 Study, the patients may be treated at the physician's discretion. Any concomitant treatment must be documented. If warranted for patient safety, the Investigator may elect to see the patient at an Unscheduled Visit(s) to evaluate the patient.

1.3 Criteria for Evaluations Defined in Protocol

1.3.1 Demographics

The demographic data from the NGF0120 Study was carried forward into the current study.

1.3.2 Concomitant Medications

All medications from the completion of the NGF0120 study until the end of extended follow-up period will be clearly documented on the Concomitant Medications electronic Case Report Form (eCRF) page. Medication entries should be specific to product name (if a combination drug product) and spelled correctly (generic and brand name if available). 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".

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 Superficial Punctate Keratitis/keratopathy (SPK) will be determined at Month 24 and 30 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.

Corneal epithelial healing based on the fluorescein corneal staining images collected at Month 24 and 30 will be graded at a Central Reading Center (CRC) per the Reading Center Charter.

1.3.3.2 Corneal Sensitivity Testing

Corneal Sensitivity will be measured (in cm) using a Cochet Bonnet aesthesiometer at Month 24 and 30.

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) will be recorded at Month 24 and 30.

1.3.3.4 Tear Film Break-Up Time (TFBUT)

Tear film break-up time (second) will be assessed using fluorescein at Month 24 and 30.

1.3.3.5 Schirmer Test (w/o Anesthesia)

Unanesthetized Schirmer's test measures the amount of wetting (mm) at Month 24 and 30.

1.3.3.6 Impact of Dry Eye on Everyday Life (IDEEL)

This 57-item questionnaire assesses dry eye impact at Month 24 and 30, 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: "Satisfaction with Treatment Effectiveness" and "Treatment-Related Bother/Inconvenience".
- 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 Month 24 and 30.

CCI [redacted]

CCI [redacted]

1.3.4 Safety Assessments

1.3.4.1 Adverse events

Adverse Events (AEs) will be collected and recorded for any untoward event since the completion of the NGF0120 Study. 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 Slit Lamp Examination

Slit Lamp Examination will be performed to assess lashes, eyelids, conjunctiva, cornea, lens, sclera, iris, and anterior chamber at Month 24 and 30 based on following categories: Normal, Abnormal Non-Clinically Significant, Abnormal Clinically Significant.

1.3.4.3 External Ocular Examination

The motility of the extraocular muscles and the appearance and function of the eyelids will be assessed at Month 24 and 30, and recorded as: Normal, Abnormal Non-Clinically Significant, Abnormal Clinically Significant.

1.4 Study Data

The study data to be analyzed include data carried over from the NGF0120 study, 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.

Final data from the NGF0120 study will be integrated to the NGF0122 study for analysis as applicable, such as summaries of demographic and baseline characteristics, and change from baseline results.

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 enrolled subjects with data available.

2.1 Study Eye

The study eye designated in the study NGF0120 will be used for this study. It will be clearly identified in the listings when the assessments involve both eyes.

2.2 Study Period, Visit, and Day

The study period, visit, and day will be integrated across the NGF0120 and NGF0122 studies, and will consist of screening, baseline (Day -1), treatment (Week 2, Week 4, Week 8), follow-up (Week 32), extended follow-up Month 24 or Week 96, and extended follow-up Month 30 or Week 120.

A reference date refers to the date of the first study product administration in the study NGF0120. 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.

2.3 Definition of Baseline

In general, the baseline is defined as the last assessment before the first study product administration in the study NGF0120 unless specifically stated otherwise.

2.4 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. All unscheduled visit data will be included in data listings.

2.5 Analysis Population

The full analysis set (FAS) will include all enrolled patients who attended either 24-Month Study Visit, or 30-Month Study Visit, or both. The FAS will be used for both efficacy and safety analyses.

2.6 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.

2.7 Definition of Subgroups

No subgroup analyses are planned.

2.8 Descriptive Summaries

Summary statistics and statistical analyses will 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, 25^{th} and 75^{th} quartiles, 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 subjects / eyes with available data (n) will also be reported.

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.

2.9 Type 1 Error Control for Multiple Tests

Not applicable. This is an exploratory, hypothesis generating study. All efficacy analyses are considered exploratory and all statistical tests will be descriptive in nature with no need for control of type 1 error.

2.10 Handling of Missing Data

The primary efficacy analysis will be based on observed cases (i.e. no missing data imputation).

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 explicitly stated otherwise.

In the descriptive summaries, the number of subjects with missing data will be presented under the “Missing” category. Summary statistics for continuous variables will be calculated only on non-missing values. For categorical variables, missing values will be reported under the “Missing” category but not included in the denominator count when computing percentages. When continuous data will be summarized, only the non-missing values will be evaluated for computing summary statistics. Any exception will be declared.

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 based on the data extracted from the Study NGF0120.

3.4 Etiology of Neurotrophic Keratitis

The etiology of neurotrophic keratitis will be included in a listing.

3.5 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 Medical Dictionary for Regulatory Activities (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.

3.6 Protocol Deviations

All reported protocol deviations will be documented and included in the CSR. All reported protocol deviations and inclusion or exclusion exceptions will be included in a listing.

4 CONCOMITANT MEDICATIONS CCI

All reported medications will be coded using World Health Organization-Drug Dictionary (WHO-DD). For summary of medications, the coded anatomical main

group (ATC) level 1 and ATC level 4 will be sorted by alphabetical order, and generic medication name (Preferred Term) will be sorted by overall descending order of frequency.

Concomitant medications include all medications that a subject used during the study on or after the first administration of the study product.

Summary tables will be prepared for the reported use of all concomitant medications including AT by generic name within ATC level 1 and ATC level 4, and location (ocular vs non-ocular) during the entire extended follow-up period.

Summary tables will be provided for CCI non-ocular medications, which will be determined by medical review of the medications on the final data at the end of study.

5 ANALYSIS OF EFFICACY

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

For continuous efficacy endpoints, descriptive statistics of the observed and change from baseline 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 as well as p values from one-sample t-test and Wilcoxon signed rank test (depending on the distribution of the data) to compare the observed values vs baseline.

For responder/categorical efficacy endpoints, analyses will include percentage of responders/categorized results, and associated exact (Clopper-Pearson) 95% confidence intervals where appropriate as well as p values from a binomial test to assess that responder rates are greater than zero.

- Percentage of patients who had corneal epithelial healing at Week 8 in the DEFENDO Study, who maintain healing at Month 24 and Month 30 of the long-term follow-up

The patients who had corneal epithelial healing at Week 8 and maintain healing at Month 24 and Month 30 will be summarized as a binary goal attainment variable (Yes/No) based on the subset of patients who achieved corneal epithelial healing at Week 8, as determined by the CRC.

- Percentage of patients who did not have corneal epithelial healing at Week 8 in the DEFENDO Study who have a healed corneal epithelium at Month 24 and Month 30 of the long-term follow-up

The patients who did not have corneal epithelial healing at Week 8 and who have corneal epithelial healing at Month 24 and Month 30 will be summarized as a binary goal attainment variable (Yes/No) based on the subset of patients who did not have corneal epithelial healing at Week 8, as determined by the CRC.

- Percentage of patients who achieved an improvement in corneal sensitivity at Week 8 in the DEFENDO Study who still have improvement in corneal sensitivity at Month 24 and Month 30 of the long-term follow-up

The improvement in corneal sensitivity is defined as change from baseline > 0 (cm) of the study eye. The patients who achieved an improvement in corneal sensitivity at Week 8 and still have improvement in corneal sensitivity at Month 24 and Month 30 will be summarized as a binary goal attainment variable (Yes/No) based on the subset of patients who achieved an improvement in corneal sensitivity at Week 8.

- Percentage of patients who did not achieve an improvement in corneal sensitivity at Week 8 in the DEFENDO Study who have improvement in corneal sensitivity at Month 24 and Month 30 of the long-term follow-up

The patients who did not achieve an improvement in corneal sensitivity at Week 8 and who have improvement in corneal sensitivity at Month 24 and Month 30 will be summarized as a binary goal attainment variable (Yes/No) based on the subset of patients who did not achieve an improvement in corneal sensitivity at Week 8.

- Mean change in corneal sensitivity from baseline and Week 8 at Month 24 and Month 30

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.

- Schirmer I change from baseline and Week 8 to Month 24 and Month 30

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

- TFBUT change from baseline and Week 8 to Month 24 and Month 30

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 and Week 8 to Month 24 and Month 30

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 from baseline and Week 8 in BCDVA at Month 24 and Month 30

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

- IDEEL change from baseline and Week 8 at Month 24 and Month 30

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 wellbeing” 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
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 "Satisfaction with Treatment Effectiveness" and 2.b "Treatment-Related Bother/Inconvenience".

2.a Satisfaction with Treatment Effectiveness

Satisfaction with Treatment Effectiveness	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

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

4 questions are included in the Treatment Satisfaction/Happiness scale score. If 50% (2) or fewer of the 4 questions used in the calculation of Treatment Satisfaction/Happiness score have a 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 4 item scores are missing, then the scale score is not calculated and should be missing. Multiplying by 25 transforms 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-Related Bother/Inconvenience

Treatment-Related Bother/Inconvenience	Used in calculation of domain score?
6. I was bothered by how often I had to use dry eye treatments	Yes
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 6, 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

4 questions are included in the Treatment-Related Bother scale score. If 50% (2) or fewer of the 4 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 3 or more of the 4 item scores are missing, then the scale score is not calculated and should be set as 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 and from week 8 of above defined subscores will be summarized as a continuous variable at each visit, and mean changes from baseline and from week 8 of all the subscores will be graphically presented (e.g., radar plot) for each visit.

- EQ-5D-5L change from baseline and Week 8 at Month 24 and Month 30

Change from baseline and from week 8 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 and from week 8 of all the dimension scores will be graphically presented (e.g., radar plot) for each visit.

[redacted]

6 ANALYSIS OF SAFETY

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

6.1 Adverse Events

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. All events in the clinical database regardless of when they occurred will be provided in data listings.

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 AEs 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 during the entire extended follow-up period.

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.

A listing of serious AEs (SAEs) will be also provided.

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

6.2 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 (i.e., baseline, Week 8, Month 24 and Month 30). 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.

6.3 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 (i.e., baseline, Week 8, Month 24 and Month 30). The following parameters will be included: Motility of extraocular muscles, Appearance of eyelids, Specific mechanism.

7 DETERMINATION OF SAMPLE SIZE

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

8 PLANNED INTERIM ANALYSIS

A descriptive interim analysis will be carried out as soon as the last patient is enrolled in the study. The purpose of this analysis will be administrative. Since the study has an exploratory nature and no formal hypothesis test is planned, no adjustment is needed for the final analysis due to the performance of an administrative 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

NGF0122 Study Data Management Plan

Appendix 1: Schedule of Evaluations (from Protocol)

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

Appendix 2 Tables, Listing, and Figures

List of tables

Table Number	Table Title	Analysis Population
14.1.1	Analysis Populations	
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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
CCI		
14.1.6.3	Non-ocular Medications during Extended Follow-up	Full Analysis Set
14.2.1.1	Percentage of Patients who Achieved Epithelial Healing at Week 8 and Had Healed during Extended Follow-up	Full Analysis Set
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	CCI	
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Table Number	Table Title	Analysis Population
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CCI	[redacted]	[redacted]
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