STATISTICAL ANALYSIS PLAN

A Phase 3, Multi-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of 0.1% RGN-259 Ophthalmic Solution for the Treatment of Neurotrophic Keratopathy

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Protocol Number: RGN-NK-301/15-110-0006

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Date: 10Sep2019

Version: 1.0

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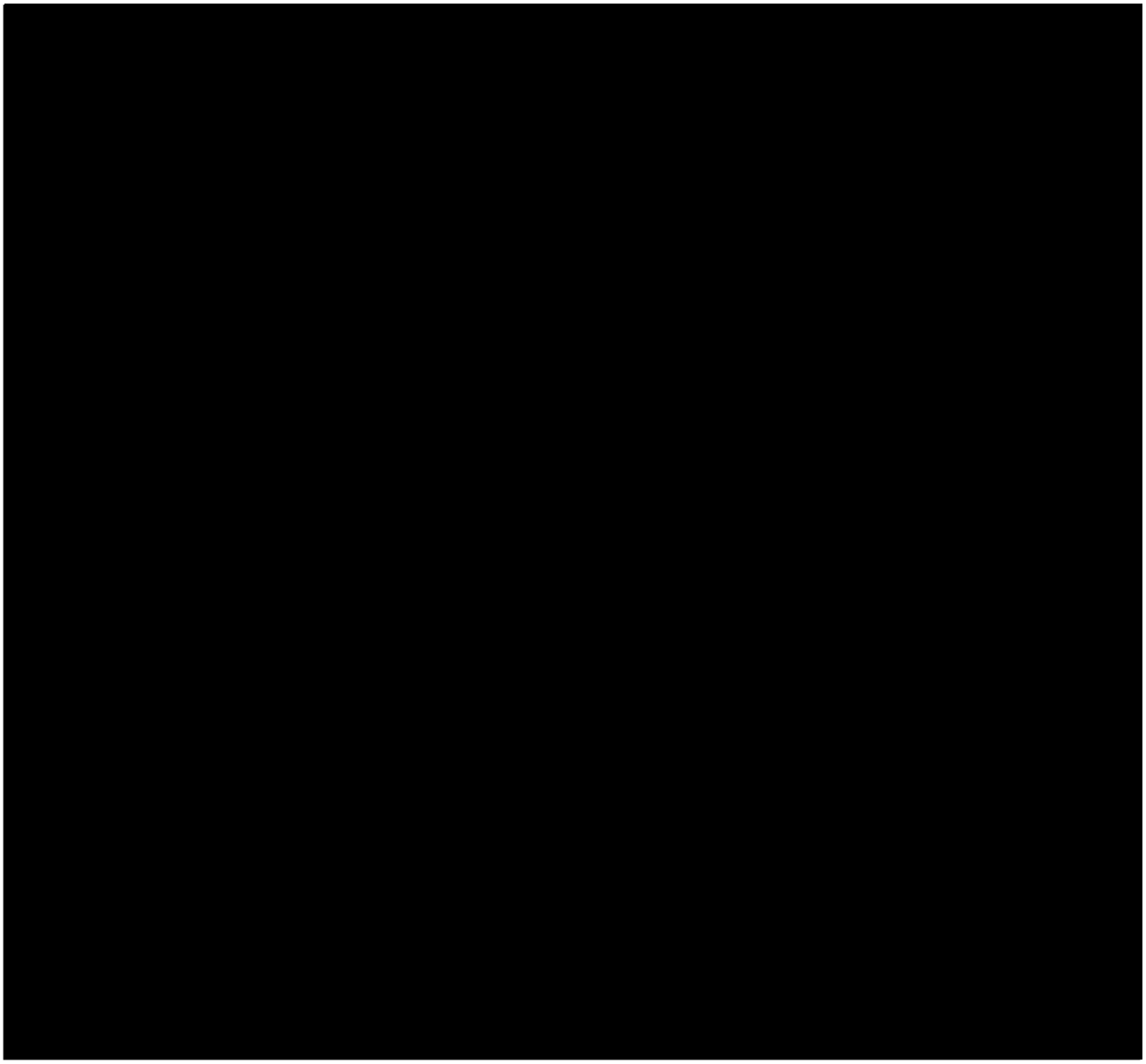
Statistical Analysis Plan Approval



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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
CRF	Case Report Form
CS	Clinically Significant
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NCS	Not clinically significant
NK	Neurotrophic Keratopathy
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFBUT	Tear Film Break-up Time
VA	Visual Acuity
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol RGN-NK-301/15-110-0006, version 5.0 dated 04May2017.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR.

2. Study Objectives

The objective of this study is to compare the safety and efficacy of RGN-259 Ophthalmic Solution to placebo for the treatment of neurotrophic keratopathy (NK).

3. Study Variables

3.1 Primary Variables

The primary efficacy variable is the following:

- [redacted]

3.2 Secondary Variables

The secondary efficacy variables include the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3.3 Safety Variables

The safety variables include the following:

- VA assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale;
- Slit-Lamp Biomicroscopy;
- Cochet-Bonnet;
- Adverse Event (AE) Query;
- Dilated Fundoscopy;
- Intraocular Pressure (IOP).

3.4 Statistical Hypotheses

H_0: There is no difference between study eyes treated with RGN-259 and study eyes treated with placebo, RGN-259 – placebo, in the percentage of study eyes achieving complete healing of epithelial defect at Day 29 (Visit 5).

H_A: There is a difference between study eyes treated with RGN-259 and study eyes treated with placebo, RGN-259 – placebo, in the percentage of study eyes achieving complete healing of epithelial defect at Day 29 (Visit 5).

[redacted]

4. Study Design and Procedures

4.1 General Study Design

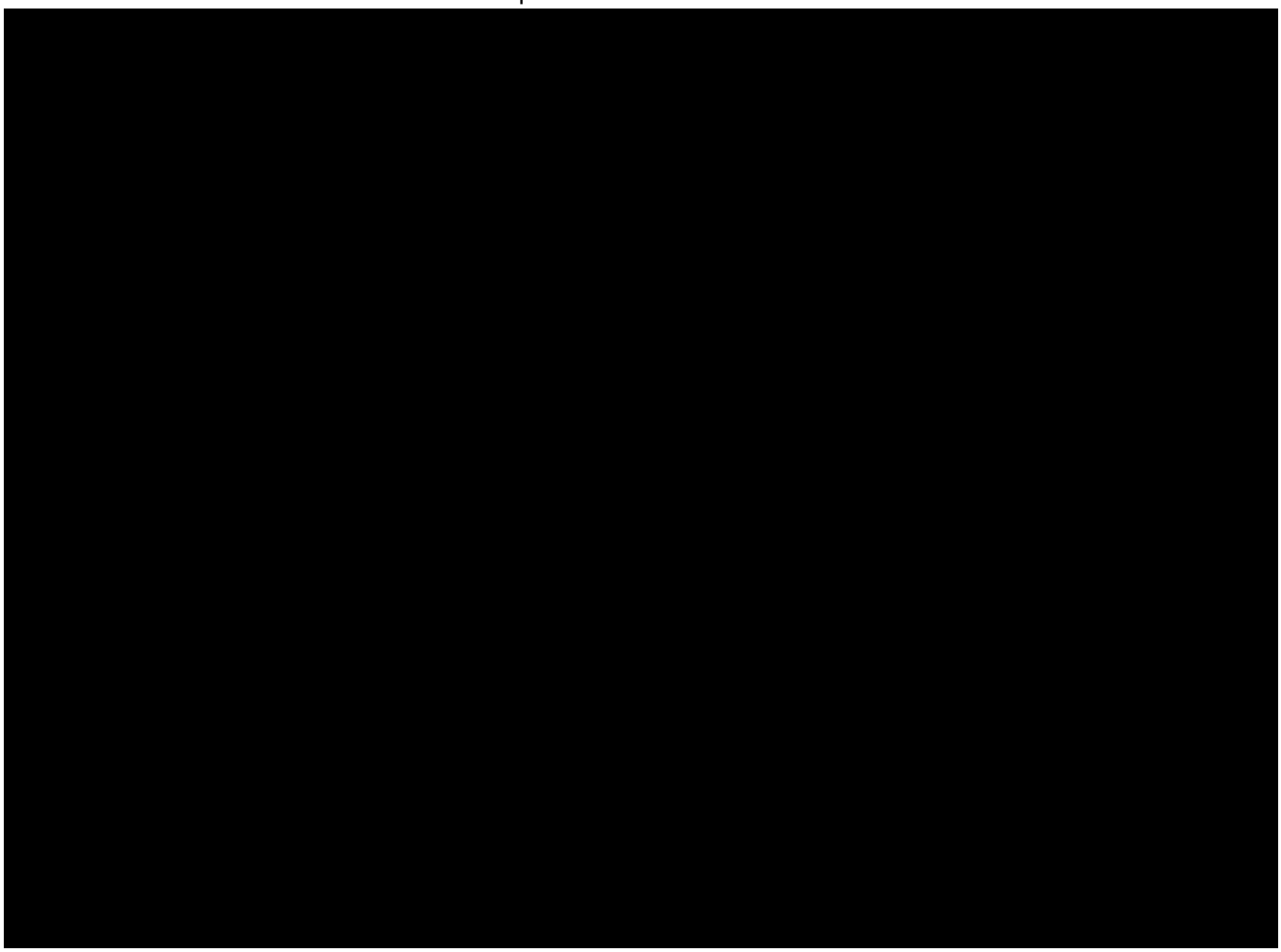
This is a Phase 3, multicenter, randomized, double-masked, placebo controlled safety and efficacy study. It consists of two treatment arms, a 0.1% concentration of RGN-259 ophthalmic solution and placebo ophthalmic solution, [redacted]. There are seven scheduled visits over approximately 6 weeks (43 days), with approximately 100 subjects being screened [redacted]. Visit 1 (Day 1) is the screening visit, as well as the baseline visit for subjects who are eligible for the study. Eligible subjects will be randomized to receive one of the two study treatments. Randomized subjects will then begin using study drug in the affected eye(s) 5 times per day for 28 days.

Study visits will be referred to in all tables and listings as the expected study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. The following table shows the scheduled study visits, their planned study day (Day 1 corresponds to the day of randomization), and the acceptable visit window for each study visit:

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day 1	n/a
Visit 2	Day 8	± 2 Days
Visit 3	Day 15	± 2 Days
Visit 4	Day 22	± 2 Days
Visit 5	Day 29	± 2 Days
Visit 6	Day 36	± 3 Days
Visit 7	Day 43	± 3 Days

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.



4.3 Early Termination of the Study

Due to the rarity of the disease and the roughly 5 year enrollment period at multiple sites the Sponsor has decided to end this phase 3 trial based on the lack of enrollment. Even with the extended enrollment period, only 18 subjects were enrolled and subsequently completed the study. Analyses will be

conducted as originally intended; however, the study is no longer powered to detect statistical differences. See the revised power calculations in section 6.1 of this SAP.

As with other studies of rare diseases this study will focus on clinically meaningful difference. Clinically meaningful results will be assessed by the Sponsor's medical and/or regulatory teams.

5. Study Treatments

The study treatments are 0.1% RGN-259 Ophthalmic Solution and Placebo Ophthalmic Solution (Vehicle).

5.1 Method of Assigning Subjects to Treatment Groups

At Visit 1, subjects who provide written informed consent will be assigned a unique 5-digit screening number, which includes the 2-digit site number plus a unique 3-digit screening number beginning with 001 (e.g., 11001, 11002, 11003, etc.). Screening numbers must be assigned in ascending consecutive order.

If all inclusion and exclusion criteria are met at Visits 1, each qualifying subject will then be assigned a 4-digit randomization number at the end of Visit 1. All randomization numbers will be assigned in strict numerical sequence and no numbers will be skipped or omitted. Assignment of qualified subjects to a treatment group will be accomplished by using a randomization code generated by an independent biostatistician. Investigators and study staff who will conduct the assignment procedure will be masked to the randomization code.

5.2 Masking and Unmasking

This is a double-masked study. Subjects, Investigators and site staff, sponsor and Ora/Statistics & Data Corporation (SDC) study staff are masked to the treatment group assignments for the duration of the study. The randomization schedule was created by an unmasked statistician who is not otherwise involved in the conduct of the study.

Under normal circumstances, the mask should not be broken. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking study drug.

6. Sample Size and Power Considerations

[redacted]

[redacted]

6.1 Revised Power Calculations

Due to the rarity of the disease and the Sponsor's early termination of the study the proposed sample size of 42 will not be attained. [redacted]

7. Data Preparation

All reported study data will be recorded on the electronic case report forms (eCRFs) supplied by SDC using iMedNet™. Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor and Ora in consultation with SDC.

All analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to SDC standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC and Sponsor personnel;
- Protocol deviations have been identified and status defined (major/minor deviations);
- Analysis populations have been determined; and
- Randomized treatment codes have been unmasked.

8. Analysis Populations

8.1 [redacted]

[redacted]

8.2 [redacted]

[redacted]

8.3 Safety

The safety population includes all randomized subjects who have received at least one dose of the investigational medicinal product. The safety population will be analyzed for all safety assessments according to the treatment actually received.

The statistical analysis of safety data will be performed for the safety population. The analysis of baseline and efficacy data will be performed for the ITT population. The primary efficacy analysis will also be performed on the PP population as sensitivity analyses.

9. General Statistical Considerations

9.1 Unit of Analysis

The unit of analysis in this study will be the study eye for all efficacy summaries and any treated eye for ocular safety summaries. In general, NK is unilateral. If a patient presents with bilateral epithelial defects that both meet the entry criteria, the study eye will be defined as the affected eye with the largest affected area, and the other eye will be considered a qualified fellow eye. If both affected eyes have the same affected area, the right eye will be the study eye and the left eye will be considered a qualified fellow eye.

Ocular AEs will be summarized for all eyes and for any treated eye (if at least one subject has bilateral NK in which both eyes are treated), and ocular safety assessments will be analyzed by study eye and both treated eyes (again, if at least one subject has bilateral NK in which both eyes are treated), where the worst safety outcome over both eyes is summarized. Medical history and non-ocular AEs and safety assessments will be presented at the subject level.

9.2 Missing or Inconclusive Data Handling

[redacted]

[redacted]

9.3 Definition of Baseline

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 1 (Day 1).

9.4 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using [redacted] Output will be provided in rich text format (RTF) format for tables and portable document file (PDF) format for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, visit (as applicable), and time point (as applicable) based on all randomized subjects unless otherwise specified.

[redacted]

9.5 Adjustments for Multiplicity

[redacted]

10. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages [redacted]

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

The demographic variables collected in this study include age, sex, race, ethnicity, and iris color. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for the ITT population and Safety populations, separately.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: [redacted]

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, ethnicity and iris color (by study eye).

No statistical inference testing will be performed for the demographic variables. A subject listing that includes all demographic variables will be provided.

11.2 Pretreatment Variables and Baseline Disease Characteristics

[redacted]

12. Medical History, Prior and Concomitant Medications

12.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0.

Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by System Organ Class (SOC) and Preferred Term (PT) using the Safety population. Ocular medical history will be similarly summarized at the subject level. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

Listings of medical history will be generated separately for ocular and non-ocular data.

12.2 Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug Global, B3, March 2019) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical (ATC) 4 classification) and preferred name (drug name).

Concomitant medications are defined as those medications listed as having been taken 1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or 2) at any time following the first administration of study drug. Prior medications are defined as those medications listed as having been taken prior to initiation of study drug administration, but not taken after initiation of study drug administration.

Both ocular and non-ocular concomitant medications will be summarized using the Safety population. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than 1 medication per ATC 4 classification. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group.

Listings of prior and concomitant medications will be generated separately for ocular and non-ocular data.

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

[redacted]

13.2 Treatment Exposure

Treatment exposure will be measured at the subject level; [redacted]

14. Efficacy Analyses

14.1 Primary Analysis

The primary analysis variables will be presented in subject listings by visit and time point.

[redacted]

14.2 Sensitivity Analyses

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

14.3 Secondary Analyses

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively [redacted]

14.3.1 Percentage of Subjects with Complete Healing

The percentage of subjects achieving complete healing of the epithelial defect at Visits [redacted]

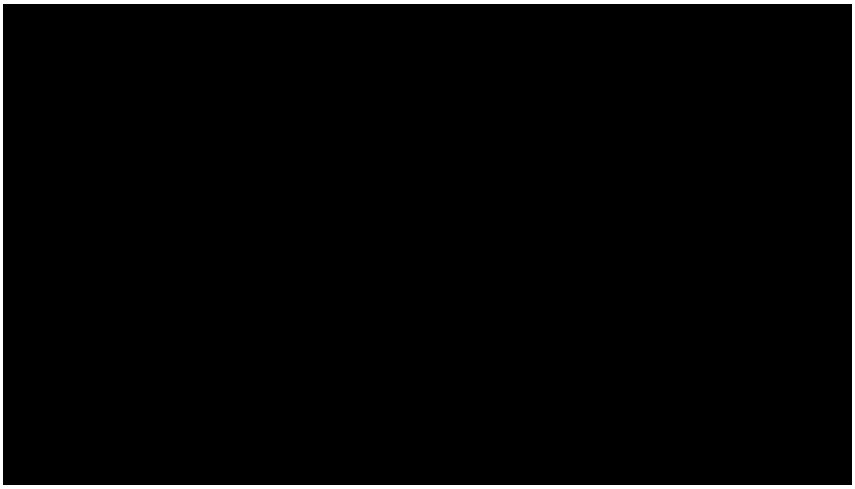
14.3.2 Epithelial Defect Measurement

The epithelial defect will be measured [redacted]

[redacted]

14.3.3 Epithelial Defect Classification

[redacted]



[redacted]

14.3.4 Tear Film Break-Up Time

[redacted]

[redacted]

14.3.6 Visual Acuity (ETDRS)

[redacted]

15. Exploratory Analyses

There are no exploratory analyses in this study.

16. Safety Analyses

All safety analyses will be conducted using the Safety Population.

16.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of an investigational medicinal product (IMP) in humans, whether or not considered IMP-related. An AE can

be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, without any judgment about causality. An AE can arise from any use of the investigational product (e.g. off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning.

Treatment-emergent AEs (TEAEs) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated. As treatment is initiated at Visit 1 in this study, all AEs will be considered TEAEs.

Serious adverse events (SAE) are defined as any event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapability, is a congenital anomaly/birth defect, or is medically significant.

An overall summary will be presented that includes the number of AEs and the number and percentage of subjects who experienced at least one AE, by treatment group. This summary will also include breakdowns of AEs further categorized as ocular (study eye, treated fellow eye, and untreated fellow eye separately) or non-ocular, SAEs, AEs by maximum severity, AEs by maximum relationship, and AEs leading to subject withdrawal.

Additional summaries of AEs will be provided showing the number and percentage of subjects who experienced at least one AE. These summaries will be presented by SOC and PT. Non-ocular AEs will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT. Ocular AEs will be similarly summarized at the subject level for all eyes and treated eyes separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to investigational product or seriousness of the event and should be evaluated according to the following scale:

- Mild: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- Moderate: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- Severe: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

Summaries of AEs by maximal severity will be presented for ocular AEs and non-ocular AEs separately. The number of subjects with any AEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group. To count the number of subjects with any AEs, if a subject has multiple AEs coded to the same PT within the same SOC, the subject will be counted once under the maximal severity.

The relationship of each AE to the study drug should be determined by the investigator using these explanations:

- Definite: When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product and AE;
- Probable: When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable.
- Possible: When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example; due to missing data or insufficient evidence.
- None: When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.
- Unclassified: When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

Only AEs with a relationship of definite, probable, or possible, or with a missing relationship, will be considered as treatment-related AEs.

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- Unexpected: An AE that is not listed in the Investigator's brochure or is not listed at the specificity or severity that has been observed.

- Expected: An AE that is listed in the Investigator's brochure at the specificity and severity that has been observed.
- Not Applicable: Any AE that is unrelated to the study drug.

AEs that are mentioned in the Investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected. AEs that are reported as suspected with respect to relationship to study drug, and are also categorized as unexpected are to be reported directly to Ora, the sponsor, and other authorities as appropriate. Expectedness of the AE will be included in the subject level listings.

As described above, separate summaries will be provided for the following categories of AEs by SOC and PT:

- Ocular AEs in any eye
- Ocular AEs in treated eyes
- Non-ocular AEs
- Treatment-related ocular AEs
- Treatment-related non-ocular AEs
- SAEs

All AEs will be presented in a subject listing. The AEs leading to study treatment discontinuation will be listed separately. In addition, all SAEs will be presented in a separate listing.

16.2 Visual Acuity

[redacted]

16.3 Corneal Sensitivity (Cochet-Bonnet)

[redacted]

16.4 Slit-Lamp Biomicroscopy

[redacted]

16.5 Dilated Fundoscopy

Dilated fundoscopy examinations will be conducted on both eyes [redacted]

16.6 Intraocular Pressure (IOP)

IOP will be measured for both eyes [redacted]

17. Interim Analyses

No interim analyses are planned for this study.

18. Deviations from Protocol-Stated Analyses

No deviations from the protocol specified analyses are currently planned.

19. References

Dunn SP, Heidemann DG, Chow CYC, Crockford D, Turjman N, Angel J, Allan CB, Sosne G. Treatment of Chronic Nonhealing Neurotrophic Corneal Epithelial defects with Thymosin β4. Archives of Ophthalmology 2010b, 128:636-638.

Ratitch, B., Lipkovich, I., and M. O'Kelley. "Combining Analysis Results from Multiply Imputed Categorical Data." PharmaSUG 2013 - Paper SP03.

20. Tables

Tables that will be included in the topline delivery are shown in boldface font.