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Treatment Safety and Efficacy of Pro-ocular™ 1% for Chronic Ocular Graft Following Allogeneic HSCT

Sponsor: **Glia, LLC**

Statistical Analytical Plan

September 18, 2019

STATISTICAL ANALYSIS PLAN

Treatment safety and efficacy using Pro-ocular™ 1% for chronic ocular graft-versus-host disease (GvHD) following allogeneic hematopoietic stem cell transplantation.

Sponsor: Glia, LLC

Protocol Number: oGvHD-1

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Version: 1.0

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SAP Date: **18Sep2019**

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List of Abbreviations

AE	Adverse Event
ADL	Activities of Daily Life
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-corrected Visual Acuity
BMT	Bone marrow transplant
CBC	Complete Blood Count
CI	Confidence Interval
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
DFCI	Dana-Farber Cancer Institute
GvHD	Graft-versus-host disease
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
KCS	Keratoconjunctivitis Sicca
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
NIH	National Institutes of Health
PDF	Portable document format
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SANDE	Symptom Assessment iN Dry Eye
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
VAS	Visual Analog Scale
VCMA	Video Capture Manual Analysis
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol oGvHD-1, version 4.0 dated 07APR2019.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (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 clinical study report.

The planned analyses include:

1. The Primary analysis of the Study Treatment Phase will occur after all subjects have completed or discontinued through Visit 5.

2. The final/secondary analysis of the Cross-over Phase will occur after all subjects who enter the Cross-over Phase have completed or discontinued through Visit 7.

This SAP will be finalized and signed prior to the database lock for the primary analysis.

2. Study Objectives

The primary objective of this study is to evaluate the safety and efficacy of Pro-ocular™ 1% topical gel administered twice daily for 70 days in ameliorating symptoms and signs of chronic ocular graft-versus-host disease (GvHD).

2.1 Study Variables

2.2 Efficacy Variables

The key efficacy variables include the following:

- GLIA Ocular Surface Disease Questionnaire taken at the clinic
- Modified Symptom Assessment iN Dry Eye Questionnaire (SANDE) taken at the clinic

Additional efficacy variables include the following:

- Chronic Ocular GvHD Signs including the following:
  - TearScan Examination
  - Visual acuity with current correction
  - Slit lamp biomicroscopy without staining:

        - Lid Edema, Lid Erythema, Lid Margin Ulceration and Conjunctival Hyperemia are of interest however all ocular regions will be analyzed similarly
    - Corneal and conjunctival fluorescein staining
    - Facial Presentation and Blinks per Minute
- Daily diary GLIA Ocular Surface Disease Questionnaire
- Daily use of eye drops
- National Institutes of Health (NIH) Eye Score

2.3 Safety Variables

The safety variables include the following:

- Incidence and severity of Adverse events (AE)
- Visual acuity
- Slit lamp biomicroscopy
- Undilated fundoscopy examination
- Intraocular pressure (IOP)
- Systemic assessment by bone marrow transplant (BMT) physician at Dana- Farber Cancer Institute (DFCI)

2.4 Other Variables

Other variables include laboratory tests for:

- Complete Blood Count (CBC) with differential
- Metabolic panel
- Other Standard GvHD
- Endocrine panel for the assessment of hypothalamic-pituitary-adrenal axis (HPA) function and for Progesterone to detect whether applied drug product is detected in the blood

2.5 Statistical Hypotheses

The null and alternative hypotheses, based on the primary variables, are as follows:

H_{01}: There is no difference between Pro-ocular™ 1% topical gel and placebo in the change from baseline in ocular symptom scores based on the GLIA Ocular Surface Disease Questionnaire when comparing the worse eye for each symptom.

Ha_1: The change from baseline in ocular symptom scores based on the GLIA Ocular Surface Disease Questionnaire is larger with Pro-ocular™ 1% topical gel than with placebo when comparing the worse eye for each symptom.

H_{02}: There is no difference between Pro-ocular™ 1% topical gel and placebo in the change from baseline in ocular symptom scores based on the modified SANDE Questionnaire when comparing the worse eye for each symptom.

Ha2: The change from baseline in ocular symptom scores based on the modified SANDE Questionnaire is larger with Pro-ocular™ 1% topical gel than with placebo when comparing the worse eye for each symptom.

3. Study Design and Procedures

3.1 General Study Design

This is a Phase 2 randomized, single-center, parallel, double-masked, placebo-controlled study assessing the safety and efficacy and the of Pro-ocular™ 1% topical gel administered twice daily for 70 days in ameliorating symptoms and signs of chronic ocular GvHD.

Thirty-three subjects will be enrolled and randomly assigned in a 2:1 ratio to one of two treatments arms:

- Pro-ocular™ 1% topical gel (22 subjects)
- Placebo (11 subjects)

After a Screening visit to assess eligibility, subjects will enter a double-masked 70-day Study Treatment Phase (Visit 2 – Visit 5). Upon completion of the double-masked phase, subjects who were originally randomized to Placebo will cross-over into an open-label Placebo Cross-over Phase and will receive Pro-ocular 1% topical gel for twice-daily administration over 6 weeks (Visit 5 – Visit 7).

Analyses will be conducted separately for the Study Treatment Phase and the Placebo Cross-over Phase. The analysis of the Study Treatment Phase is the Primary analysis, and the analysis of the Placebo Cross-over Phase is secondary.

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. Listings, tables and figures will include visits and study days in the following format: Visit 1 (Day -14), Visit 2 (Day 1), Pre-Dose, Visit 2 (Day 1), Post-Dose, Visit 3 (Day 14), Visit 4 (Day 42), Visit 5 (Day 70), Visit 6 (Week 3) and Visit 7 (Week 6).

Table 1 shows the scheduled study visits, their planned study day, and the acceptable visit window for each study visit.

Table 1. Study Visit Windows

Study Phase	Scheduled Visit	Planned Study Day	Visit Window
Study Treatment Phase (Double-masked)	Visit 1	Screening/ Day -14	Day -14 to -1
	Visit 2	Baseline/ Day 1, Pre-Dose	N/A
	Visit 2	Day 1, Post Dose	N/A

Study Phase	Scheduled Visit	Planned Study Day	Visit Window
	Visit 3	Week 2/ Day 14	± 2 Day
	Visit 4	Week 6/ Day 42	± 3 Day
	Visit 5	Week 10/ Day 70	± 3 Day
Placebo Cross-over Phase for Subjects on Placebo (Open Label)	Visit 6	Week 13 or Week 3 after active treatment / Day 91	N/A
	Visit 7	Week 16 or Week 6 after active treatment/ Day 112	N/A

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in ***Table 2***.

Table 2. Schedule of Visits and Assessments

Blue = Conducted at DFCI		Study Treatment Phase					Placebo Cross-over Phase	
Black = Conducted at MEEI	Visit 1 (Screening)	Visit 2 Baseline & First Drug Application		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Day -14 to -1	Day 1	Day 1	Day 14±2	Day 42±3	Day 70±3	3 weeks	6 weeks
Procedure		Pre-Dose	30-60 min Post-Dose					
2-digit screening number	X							
Informed consent	X							
Visual acuity (current correction)	X					X		
NIH Eye Score	X					X		X
Facial photo		X				X		X
Slit Lamp Biomicroscopy	X			X	X	X	X	X
Undilated Fundoscopy Exam	X					X		
Corneal and Conjunctival Staining	X			X	X	X	X	X
Intraocular Pressure	X					X		X
Inclusion/Exclusion Criteria	X							
Medical/Ophthalmology history and updates	X	X		X	X	X	X	X
Prior and concomitant medication query	X	X		X	X	X	X	X
Concomitant medications (BMT)	X				X	X		X
Medical History & Physical (BMT)	X							
Demographic data	X							
Video of face & eyes (1 minute)		X	X	X	X	X	X	X
TearScan Examination		X	X	X	X	X	X	X
Urine pregnancy test	X					X		
Modified SANDE Questionnaire	X			X	X	X	X	X
GLIA Ocular Surface Disease Symptoms Questionnaire	X	X	X	X	X	X	X	X
Adverse Event Query			X	X	X	X	X	X

Blue = Conducted at DFCI		Study Treatment Phase					Placebo Cross-over Phase	
Black = Conducted at MEEI	Visit 1 (Screening)	Visit 2 Baseline & First Drug Application		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Day -14 to -1	Day 1	Day 1	Day 14±2	Day 42±3	Day 70±3	3 weeks	6 weeks
Screen Pass/Fail	X							
3-digit random number	X							
BMT systemic evaluation & GvHD assessment	X				X	X		X
Standard GvHD, CBC, and metabolic labs	X				X	X		X
Endocrine panel	X				X	X		X
Daily diary collected				X	X	X	X	X
Study drug collected/ accountability				X	X	X	X	X
Study drug application (in-clinic)		X						
Study Drug Dispensed		X		X	X	X	X	
Daily Diary Dispensed			X	X	X	X	X	

Abbreviations: CBC = Complete Blood Count, DFCI = Dana-Farber Cancer Institute, GvHD = graft-versus-host disease, MEEI = Massachusetts Eye and Ear Infirmary.

4. Study Treatments

The study treatment is approximately 0.07g Pro-ocular™ 1% topical gel applied and massaged into the forehead skin twice daily, morning and before bedtime.

All tables, listings, and figures will refer to the treatments as Pro-ocular and Placebo.

4.1 Method of Assigning Subjects to Treatment Groups

At Visit 1 (Screening), subjects who provide verbal and written informed consent will be assigned a 2-digit Screening number (beginning with 01). Subjects who meet all eligibility criteria will be randomized in a 2:1 assignment ratio to either Pro-ocular™ 1% topical gel or Placebo.

An independent statistician who is not otherwise involved in the trial will generate the complete randomization schedule. The statistician will scramble a list of 3-digit numbers from 201 to 290 using a random number generation scheme so that the random number assignment will not be sequential. The statistician will devise a randomization scheme to provide a 2:1 ratio in a block design of active drug:placebo. The 3-digit randomization number will be assigned in the sequence provided by the randomization statistician. If a randomized subject is discontinued from the study for any reason, their randomization number will not be reassigned.

A unique 5-digit subject ID will be used to identify subjects in all datasets and listings for this study.

This unique 5-digit subject ID consists of the 2-digit Screening number plus the unique 3-digit randomization number. If a subject withdraws during screening or fails screening, then 000 or 999 will be used in lieu of the randomization number.

4.2 Masking and Unmasking

During the Study Treatment Phase of the study (Visit 1 – Visit 5), the subject, Investigator, and study staff will be masked.

For each randomization number, the Sponsor will label each of a set of 11 study drug pouches prominently with the 3-digit randomization code followed by container number.

e.g.

Pouch #1, #2, and #3 will be labeled xxx-1, xxx-2 and xxx-3 for dispensing at Visit 2 Day 1 Baseline.

Pouch #4, 5, 6, and 7 will be labeled xxx-4, -5, -6, and -7 for dispensing at Visit 3 Day 14.

Pouch #8, 9, 10, and 11 will be labeled xxx-8, -9,-10 and -11 for dispensing at Visit 4 Day 42

Open label pouches will be supplied for Visit 5 (3 pouches active), and Visit 6 (3 pouches).

Note: Rarely a tube may fail to pump due to airlock. Therefore an extra tube is provided each time to ensure there will be sufficient product. (Each tube dispenses approximately 24 doses.)

The Sponsor is responsible for emergency unmasking as needed.

For each subject, after the completion of all Visit 5 assessments, the Investigator will unmask the individual subject to determine eligibility for the Placebo Cross-over Phase. If the subject was originally randomized to Placebo, then the subject will enter the Placebo Cross-over Phase. If the subject was originally randomized to Pro-ocular™ 1% topical gel, then the subject's participation in the study will be complete.

5. Sample Size and Power Considerations

This study will randomize 33 subjects (22 to Pro-ocular™ 1% topical gel, and 11 to Placebo).

6. Data Preparation

All study data will be recorded on an Excel file prepared by Glia. The file contains multiple worksheets.

Diary data will be collected from subjects at the protocol specified visits and entered by Ora staff into the Excel file as well. Glia and the Ora data entry specialists will review data to ensure accuracy and cleanliness.

The data will be transferred to SDC and then converted into SAS datasets. After data are converted to SAS, limited electronic edit checks and data review will be performed to ensure data is analyzable.

This study will be locked in 2 phases. The first lock will occur after completion of the Study Treatment Phase, including all data up to Visit 5. This will constitute the Primary database lock. The second database lock will occur after completion of the Placebo Cross-over Phase, including all data up to Visit 7. This will constitute the Final database lock.

When all prerequisites for database lock have been met, including availability of all masked external data, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask

the study. Once the study has been unmasked, unmasked data will be sent to SDC. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

The primary analysis will be carried out after the following have occurred:

- Primary Database lock has occurred, including receipt of all final versions of external vendor data, 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.
- Randomized treatment codes have been unmasked.

The final analysis will be carried out after the following have occurred:

- Final Database lock has occurred, including receipt of all final versions of external vendor data, with written authorization provided by appropriate SDC and Sponsor personnel.

7. Analysis Populations

7.1 Modified Intent-to-Treat

The modified intent-to-treat (ITT) population includes all randomized subjects who received at least 1 application of the study drug. Subjects will be analyzed as randomized.

7.2 Per Protocol

The per protocol (PP) population excludes subjects from the ITT population with significant protocol deviations and any subjects with more than 10% missing data in the Glia Ocular Surface Disease Questionnaire. Protocol deviations will be assessed for inclusion by the clinical team, prior to database lock.

The subjects will be analyzed as randomized. If both treatments groups in the PP population retain ≥ 85% of the subjects from the corresponding treatment group in the ITT population, all analyses using the PP population will not be conducted.

7.3 Safety

All subjects who received at least 1 application of the study drug will be included in the Safety population. Subjects will be analyzed as treated.

8. General Statistical Considerations

8.1 Unit of Analysis

The unit of analysis in this study will be the worse eye at baseline for each ocular sign and symptom efficacy measurement. The other eye will be referred to as the fellow eye. Both eyes will be summarized separately unless stated otherwise. The term, eye type, will refer to worse eye and fellow eye. Additionally all eyes under active treatment will be compared to all eyes under placebo. (Combined eye.)

The eye will be the unit for analysis for safety summaries and both eyes will be summarized as Right Eye (OD) and Left Eye (OS) separately.

Non-ocular AEs, non-ocular medical history, non-ocular concomitant medications, Facial Presentation and Blinks per Minute and NIH eye score will be presented at the subject level.

8.2 Missing or Inconclusive Data Handling

There will be not imputation for missing data.

8.3 Definition of Baseline

For the Study Treatment Phase, baseline is defined as the last measurement prior to the first dose of study medication.

For the Cross-over Phase, baseline is defined as the last measurement prior to the first dose of Pro-ocular™ 1% topical gel, which is expected to start on the day after Visit 5.

8.4 Data Analysis Conventions

The Primary analysis will be performed by Statistics & Data Corporation (SDC) after the Study Treatment Phase is completed and the database has been locked and released for unmasking. An additional analysis will be completed once the Cross-over Phase is completed and the database for that portion is locked. Statistical programming and analyses will be performed using SAS® version 9.4 or higher. Output will be provided in rich text format (RTF) for tables, Excel format for tables and listings, and portable document format (PDF) for figures using landscape orientation for any PDF or RTF. All study data will be listed by subject, treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include counts and percentages. All percentages will be rounded to one decimal place (ie, XX.X%). Differences between active treatment group and placebo will be calculated as active minus placebo and change from baseline will be calculated as follow-up visit minus baseline.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence intervals. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as “<0.0001”; p-values greater than 0.9999 will be presented as “>0.9999.”

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit. Listings will be sorted by treatment group, subject number, visit/time point, and parameter as applicable.

8.5 Adjustments for Multiplicity

The Benjamini-Hochberg procedure will be used to adjust for multiplicity for the primary analysis of the key efficacy variables.

The Benjamini-Hochberg procedure is as follows:

1) Sort the original p-values from smallest to largest
2) Assign ranks to the original p-values smallest to largest
3) Calculate the p-values' adjusted Benjamini-Hochberg critical value as follows:

   Adjusted critical p-value = (rank of original p-value/ number of tests i.e. largest rank)*false discovery rate, or $\alpha = 0.05$.

4) Compare the original p-values to adjusted critical p-values; find the largest original p-value that is ≤ 0.05;
5) Reject the null for any original p-values that is the largest original p-value in 4) or smaller than the p-value in 4).

8.6 Visual Analog Scale Standardization

The Visual Analog Scale (VAS) forms used in this study may have varied in length, ie, the Case Report Form (CRF) scale length may have varied by subject or visit. To ensure consistency across subjects and visits, all VAS scores are standardized to account for these differences. The VAS standardized score will be derived by converting the measure length to a maximum score of VAS_{max} with one decimal place as follows:

Score = Measured Result (mm)* VAS_{max} /CRF Scale Length (mm)

The maximum score for each VAS is discussed in the analysis section.

9. Disposition of Subjects

The number of subjects screened, along with the number and percentage of screen failure subjects, will be summarized for all screened subjects.

The number and percentage of subjects included in each analysis population will be summarized by treatment group and overall for all randomized subjects.

A listing of subjects excluded from the PP population and the reason(s) for exclusion will be provided. Reasons will include screen failure, major protocol violation, and >10% missing data on the Glia Questionnaire.

The number and percentage of subjects who enter, complete, and discontinue the Study Treatment Phase, and the Cross-over Phase will be summarized by treatment group and overall for the ITT population. A listing of discontinued subjects including the date and phase discontinued and the reason for discontinuation will be provided.

A subject listing will be provided for all protocol deviations. The listing will include the date of the deviation, the deviation category, the deviation description, and the classification of whether the deviation was judged to be major or minor in a blinded review.

In addition, subject listings will be provided that include informed consent date, randomized treatment and actual treatment.

10. Demographic Variables and Iris Color

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.

Age will be reported in years and calculated using the following formula:

Age = (Informed Consent Date – Date of Birth) / 365.25, truncated as an integer

Age will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: < 65 years and ≥ 65 years. Age will be reported in years.

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

A subject listing that includes all demographic variables will be provided.

11. Medical History and Concomitant Medications or Devices

11.1 Medical History

Ocular and Non-Ocular medical history will be coded using version 22.0.

Ocular and Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the Safety population. If a subject reports the same PT multiple times within the same SOC, then 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.

11.2 Prior and Concomitant Medications or Devices

Concomitant medications will be coded using WHO ATC/DDD Index 2019, searchable version of the complete Anatomical Therapeutic Chemical (ATC) index with defined daily doses (DDDs) and summarized

to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, then the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (eg, multivitamins), then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of "Uncoded."

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.

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 one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant medications will be generated.

Prior medications are defined as those medications or devices with start and end dates before the first dose of study drug. Prior medications or devices will be listed only.

12. Treatment Exposure and Compliance

The duration of treatment exposure by study phase will be calculated in days.

Duration of treatment exposure during the Study Treatment Phase:

Duration (days) = Date of last dose in Study Treatment Phase minus date of first dose in Study Treatment Phase + 1.

Note that the last dose in the Study Treatment Phase is expected to be the morning of Visit 5.

Duration of treatment exposure during the Placebo Crossover Phase:

Duration (days) = last dose date in Placebo Crossover Phase - first dose date in Placebo Cross-over Phase + 1.

Compliance during the Study Treatment Phase:

Compliance = (total count of time entries for drug application in Study Treatment Phase) x 100 / (treatment durationin for the Study Treatment Phase x 2 applications per day)

Compliance during the Placebo Crossover Phase:

Compliance = (total count of time entries for drug application in Placebo Crossover Phase) x 100 / (treatment durationin for the Placebo Crossover Phase x 2 applications per day)

Note that the first dose in the Placebo Crossover Phase is expected to be the day following Visit 5.

Duration of treatment exposure for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group and study phase using the Safety population. A subject listing of treatment exposure will also be produced.

13. Efficacy Analyses

The efficacy measures in this study are described below. All analyses will be conducted separately for the Study Treatment Phase and the Placebo Cross-over Phase. Where applicable a worse eye at baseline will be determined for each individual sign or symptom. Analyses will include the worse eye and fellow eye separately.

13.1 GLIA Ocular Surface Disease Symptoms Questionnaire, Clinic & Daily Diary

The GLIA Ocular Surface Disease Symptoms Questionnaire will be collected in the clinic at every visit (both pre-dose and post-dose at Visit 2) and will be collected via subject daily diary.

A VAS ranging from None to Most Severe will be used to assess subject's symptom severity, by eye, for the following:

- Ocular discomfort
- Dryness
- Grittiness
- Burning
- Stinging
- Foreign body sensation
- Ocular pain
- Conjunctival redness
- Itching
- Mucus discharge
- Photophobia
- Blurred or cloudy vision
- Air flow sensitivity
- Lid redness
- Lid sticking

Subjects will be asked to rate each symptom by placing a vertical mark on the horizontal line to indicate the level of severity. The result (in mm) will be measured from the left endpoint (None) to the slash marked by subject on the line.

For each symptom, a score is derived by converting the measure length to a maximum score of 10 with one decimal place as follows:

13.1.1 ANALYSIS OF GLIA OCULAR SURFACE DISEASE SYMPTOMS QUESTIONNAIRE COLLECTED IN CLINIC

The primary analysis (Study Treatment Phase):

For each symptom, an analysis of covariance (ANCOVA) will be used to compare change from baseline between Pro-ocular and placebo with adjustments for baseline symptom score (BASELINE), treatment group (TRT), visit (VISIT), and treatment x visit interaction (TRT*VISIT) as the explanatory variable. The least squares (LS) means, LS mean differences, SEs, two-sided 95% CIs for the difference in LS means, and two-sided p-values (unadjusted and Benjamini-Hochberg adjusted p-values) will be reported for the treatment effect at each visit and all visits combined. Model effects will also be displayed.

SAS pseudo-code for this model follows:

```
PROC MIXED data=indata order=internal;
        By EYETYPE;
        class TRT VISIT;
        model CFB = TRT  BASELINE VISIT TRT*VISIT;
        LSMEANS TRT VISIT TRT*VISIT / CL PDIFF;
run;
```

The ITT population will be used as the primary population using LOCF for imputation.

Sensitivity analyses will include the ITT population and PP population using observed cases.

Additional analyses:

For each symptom, an analysis of covariance (ANCOVA) will be used to compare change from baseline between Pro-ocular and placebo with adjustments for baseline symptom score (BASELINE), treatment group (TRT), visit (VISIT), eye type (EYETYPE) and treatment x visit interaction (TRT*VISIT) as the explanatory variable. The least squares (LS) means, LS mean differences, SEs, two-sided 95% CIs for the difference in LS means, and two-sided p-values (unadjusted only) will be reported for the treatment effect at each visit and all visits combined. The model effect will also be displayed.

```
PROC MIXED data=indata order=internal;
        class TRT VISIT;
        model CFB = TRT EYETYPE  BASELINE VISIT TRT*VISIT;
        LSMEANS TRT VISIT EYETYPE  TRT*VISIT / CL PDIFF;
run;
```

The ITT population using only observed cases will be used for this analysis. Both ANCOVA analyses will be truncated at Visit 5 and any data presented after Visit 5 will be summarized with continuous descripted statistics. Continuous descriptive statistics will be used to summarize each symptom score by eye type, visit, and treatment group. Change from baseline will also be summarized. Two sample t-tests will be used to compare Pro-ocular to placebo for the visit score and for the change from baseline.

During the Study Treatment Phase, the changes from baseline will be relative to the Study Treatment Phase baseline. During the Placebo Cross-over Phase, the changes from baseline will be relative to the Placebo Cross-over Phase baseline.

Analyses will be performed on the ITT population using observed cases.

All Symptom scores will be presented in a subject listing.

13.1.2 Analysis of GLIA Ocular Surface Disease Symptoms Questionnaire Collected in Daily Diary

The individual symptoms collected in the diary will be analyzed including all data across the 70-day treatment period, testing for a treatment effect using a generalized linear model that accounts for repeated measures, with an unstructured correlation structure, including terms for diary day. The LS means, LS mean differences, SEs, two-sided 95% CIs for the difference in LS means, and two-sided p-values will be reported. Model effects will be presented.

SAS pseudo-code for this model follows:

```
PROC MIXED data=indata order=internal;
        class TRT;
        model SYMPTOM = TRT  DAY;
        repeated / subject=SUBJ type=UN ;
        random DAY;
        LSMEANS TRT / CL PDIFF;
run;
```

The LS mean (and SE) daily scores will be displayed graphically by treatment group across the 70 days. The mixed effects model analyses will be truncated at Visit 5 and any data presented after Visit 5 will be summarized with continuous descripted statistics.

Individual subject plots will also be presented displaying the subject score by day.

Analyses will be performed on the ITT population using observed cases only.

All Symptom scores collected via diary will be presented in a subject listing.

13.2 Modified SANDE – Symptom Assessment iN Dry Eye Questionnaire

The Modified SANDE – Symptom Assessment iN Dry Eye Questionnaire will be collected at Visit 1 and Visits 3 – 7.

A VAS will be used to assess subject's symptoms, by eye, for the following:

- Frequency of Symptoms
- Severity of Symptoms

First, the subject will be asked to place a vertical line to indicate how often, on average, their eyes feel dry and/or irritated. For frequency, the VAS ranges from Rarely to All the Time.

Second, the subject will be asked to place a vertical line to indicate how severe, on average, they feel their symptoms of dryness and/or irritation are. For severity, the VAS ranges from Very Mild to Very Severe.

The result (in mm) will be measured from the left endpoint to the slash marked by subject on the line.

For each symptom, a score is derived by converting the measure length to a maximum score of 100 with one decimal place as follows:

Score = Measured Result (mm)*100/CRF Scale Length (mm)

The total SANDE score is calculated by multiplying the frequency of symptoms score with the severity of symptoms score and obtaining the square root.

Subjects whose values are all 0 for a given symptom for all visits will not be included in the analysis for that symptom

13.2.1 Analysis of SANDE Questionnaire

The primary and additional analyses for the modify SANDE Questionnaire will be the same as the Glia Ocular Surface Disease Symptoms Questionnaire. Both ANCOVA analyses will be truncated at Visit 5 and any data presented after Visit 5 will be summarized with continuous descripted statistics.

13.3 Daily use of eye drops

The daily use of eye drops (e.g. Restasis®, Xiidra®, artificial tears and/or gels, autologous tears) will be collected via subject diary. For each eye, subjects will record the time drops were used, the type of drops used, as well as the number of times drops are administered per wake-time hours and per sleep-time hours.

For each subject and each eye, the average daily use of artificial tears for each week will be calculated as follows:

Weeks are defined relative to the first day of dosing. For example,

Week 1 Day 1 = first day of dosing;
Week 1 Day 2 = first day of dosing + 1;
Etc.
Week 1 Day 7 = first day of dosing + 7;
Week 2 Day 1 = first day of dosing + 8;
Etc.

The sum of the number of times a subject used artificial tears in a given day will be calculated. The average daily frequency for a given week will be the average of the daily sums for all days associated within the same week.

The average daily use of artificial gels will be calculated the same as for artificial tears.

Average daily use of artificial tears and gels will be summarized using continuous descriptive statistics by week and treatment group for each eye separately. Two sample t-tests will be used to compare Pro-ocular to placebo. Artificial tears and gel usage will be summarized and analyzed separately.

Analyses will be performed on the ITT population using observed data only.

All daily use of eye drops (Restasis®, Xiidra®, artificial tears and/or gels, autologous tears) will be presented in a subject listing.

13.4 National Institutes of Health (NIH) Eye Score

NIH Eye Score will be collected at Visits 1, 5, and 7.

The score ranges from 0 to 3 as follows:

- Score 0: No symptoms
- Score 1: Mild dry eye symptoms not affecting Activities of Daily Life (ADL) (requirement of lubricant eye drops <= 3 x per day)
- Score 2: Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new vision impairment due to keratoconjunctivitis sicca (KCS)
- Score 3: Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS

Continuous descriptive statistics will be used to summarize the eye scores by visit and treatment group. Change from baseline will also be summarized.

Wilcoxon Rank Sum tests will be used to compare Pro-ocular to placebo for the visit score and for the change from baseline. Wilcoxon Rank Sum Tests will be truncated to visit 5 and any data after visit 5 will be summarized with counts and percentages.

During the Study Treatment Phase, the changes from baseline will be relative to the Study Treatment Phase baseline. During the Placebo Cross-over Phase, the changes from baseline will be relative to the Placebo Cross-over Phase baseline.

Analyses will be performed on the ITT population using observed data only.

All NIH Eye Scores will be presented in a subject listing.

13.5 Chronic ocular GvHD Signs

The evaluations included as part of the Chronic ocular GvHD Signs are described below.

13.5.1 TearScan Examination

TearScan examinations will be conducted at Visits 2 – 7 (both pre-dose and post-dose at Visit 2). The TearScan will examine the tear film and lid margin as well as meibum expression.

Tear film will be assessed by eye using a VAS with anchors No Tear Film 0, Tear Film Visible 1, Reliable Tear Film 2, and Copious Tear Film 3.

Red eyelids will be assessed by Yes or No.

Meibomian gland expression will be assessed by eye using a VAS with anchors None, Few, and Many.

For each VAS, the Investigator will mark a vertical slash on the VAS to indicate the level of severity.

The result (in mm) will be measured from the left endpoint to the slash marked by the Investigator on the line.

A score is derived by converting the measure length to a maximum score of 3 with one decimal place as follows:

Score = Measured Result (mm)*3/CRF Scale Length (mm)

Continuous descriptive statistics will be used to summarize the results by eye type, visit and treatment group. Change from baseline will also be summarized.

Two sample t-tests will be used to compare Pro-ocular to placebo for the visit score and for the change from baseline.

During the Study Treatment Phase, the changes from baseline will be relative to the Study Treatment Phase baseline. During the Placebo Cross-over Phase, the changes from baseline will be relative to the Placebo Cross-over Phase baseline.

The number and percentage of subjects with red eye will be presented by eye type, treatment, and visit.

Analyses will be performed on the ITT population using observed data only.

All TearScan results will be presented in a subject listing.

13.5.2 Visual Acuity

Visual acuity in each eye will be measured at Visits 1 and 5 using a Snellen chart, then pinhole test, both distance visual acuity and near visual acuity. Visual acuity is based on the current corrected vision, with correction if wearing glasses, or without correction if not wearing glasses. Snellen scores will be transformed into logMAR scores as follows:

Snellen Base score – 0.02*(number of correct letters from next smaller line) or

Snellen Base score + 0.02*(number of correct letters from previous larger line)

where the Snellen Base score is the logMAR equivalent score defined below in Table 3.

Table 3. Snellen Base Scores and LogMAR Conversions

Snellen Base Score	LogMAR Score
20/200	1.00
20/160	0.90
20/125	0.80
20/100	0.70
20/80	0.60
20/63	0.50
20/50	0.40
20/40	0.30
20/32	0.20
20/25	0.10
20/20	0.00
20/16	-0.10
20/12.5	-0.20
20/10	-0.30

The observed and change from baseline visual acuity will be summarized for each eye (worse eye and fellow eye) using continuous descriptive statistics by visit for each treatment group and for all actively treated subjects. A subject listing of visual acuity will also be produced.

13.5.3 Slit Lamp without Staining

Slit lamp biomicroscopy examinations without staining will be performed at Visit 1 and Visits 3 – 7. The exam will assess the following components, by eye:

- Lids (erythema, edema, lid margin ulceration, lid margin notches, entropion/ ectropion, trichiasis/madarosis, floppy eyelids, hordeolum (stye))
- Conjunctiva (hyperemia, cicatricial changes, pseudomembranes, chalasis)
- Cornea (edema, corneal ulcers, filamentous keratitis, corneal thinning, corneal neovascularization, scars, conjunctival epithelium invasion, limbal thickening)
- Anterior Chamber (cells, flare)
- Lens (status, opacity)

A VAS ranging from None to Most will be used to score each component except for Lens.

The Investigator will mark a vertical slash on the VAS to indicate the level of severity.

The result (in mm), will be measured from left endpoint to the slash marked by the Investigator on the line.

For each component, a score is derived by converting the measure length to a maximum score of 10 with one decimal place as follows:

Score = Measured Result (mm)*10/CRF Scale Length (mm)

The Investigator will classify any abnormal results as Abnormal Clinically Significant (CS), or Abnormal Not Clinically Significant (NCS), including any other pathologies noted by the Investigator.

The Lens status will be classified as Phakic, Pseudophakic or Aphakic. For Phakic lens, the Lens Opacity will be scored as 0, +1, +2, or +3.

All continuous slit-lamp measures will be analysed the same as Glia Ocular Surface Disease Symptoms Questionnaire and the modified SANDE Questionnaire with the following exceptions. Only the ITT populations using observed cases will be performed and no adjustments for multiplicity will be applied.

The abnormal findings will be summarized using counts and percentages for each treatment group at each visit for each eye. Percentages will be based on the number of subjects in each treatment group with responses. Shift tables will also be provided comparing each follow-up visit to baseline.

During the Study Treatment Phase, the changes (or shifts) from baseline will be relative to the Study Treatment Phase baseline. During the Placebo Cross-over Phase, the changes (or shifts) from baseline will be relative to the Placebo Cross-over Phase baseline.

Analyses will be performed on the ITT population using observed data only.

All slit lamp results will be presented in a subject listing.

13.5.4 Corneal and Conjunctival Fluorescein Staining

Corneal and conjunctival examinations with fluorescein staining will be performed at Visit 1 and Visits 3 – 7. The exam will assess the following components, by eye:

- Cornea (inferior, superior, central)
- Conjunctiva (inferior, superior, temporal, nasal)

A VAS ranging from None to Most will be used to score each component.

The Investigator will mark a vertical slash on the VAS to indicate the level of severity.

The result (in mm) will be measured from left endpoint to the slash marked by the Investigator on the line.

For each component, a score is derived by converting the measure length to a maximum score of 10 with one decimal place as follows:

Score = Measured Result (mm)*10/CRF Scale Length (mm)

The Investigator will classify any abnormal results as Normal, Abnormal CS, or Abnormal NCS, including any other pathologies noted by the Investigator.

The corneal sum score will be the sum of scores from the inferior, superior, and central regions. The conjunctival sum score will be the sum of scores from the inferior, superior, temporal, and nasal regions.

Continuous descriptive statistics will be used to summarize each score by visit and treatment group. Change from baseline will also be summarized.

Two sample t-tests will be used to compare Pro-ocular to placebo for the visit score and for the change from baseline.

The abnormal findings will be summarized using counts and percentages for each treatment group at each visit for each eye. Percentages will be based on the number of subjects in each treatment group with responses. Shift tables will also be provided comparing each follow-up visit to baseline.

During the Study Treatment Phase, the changes (or shifts) from baseline will be relative to the Study Treatment Phase baseline. During the Placebo Cross-over Phase, the changes (or shifts) from baseline will be relative to the Placebo Cross-over Phase baseline.

Analyses will be performed on the ITT population using observed data only.

All fluorescein staining results will be presented in a subject listing.

13.5.5 Facial Presentation and Blinks per Minute

The blinks per minute will be measured with Video Capture Manual Analysis (VCMA) at Visits 2 – 7 (both pre-dose and post-dose at Visit 2). A 1-minute video will be captured for each subject while subjects are under normal conditions. The Investigator will count the number of times the subject has complete or incomplete blinks within a 1 minute ± 5 second interval.

The facial presentation score at the start of the session will also be captured (0 = eyes closed, 1 = eyes partially open, 2 = eyes fully open).

Continuous descriptive statistics will be used to summarize the number of blinks by visit and treatment group. Change from baseline will also be summarized.

Two sample t-tests will be used to compare Pro-ocular to placebo for the visit score and for the change from baseline.

Analyses will be performed on the ITT population using observed data only.

All facial presentation and blinks per minute results will be presented in a subject listing.

14. Safety Analyses

All safety analyses will be conducted using the Safety population using observed data only. All analyses will be conducted separately for the Study Treatment Phase and the Placebo Cross-over Phase.

14.1 Adverse Events

All adverse events will be collected, whether potentially related or unrelated to study drug use. Study drug includes the investigational drug under evaluation and placebo given during any stage of the study.

Treatment-emergent adverse events (TEAE) are defined as any event that occurs on or after the day that randomized study treatment is initiated. Adverse events recorded in the CRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

The severity of each AE will be evaluated as Mild, Moderate or Severe.

The relationship of each AE to the study drug will be determined by the Investigator as None, Possibly Related, or Probably Related.

Action taken with study drug will be classified as None, Permanently Discontinued, Temporarily Discontinued, or Other.

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one TEAE, by treatment group. This summary will also include breakdowns of TEAEs further categorized as ocular or non-ocular, treatment-related TEAEs, serious AEs (SAE), and TEAEs leading to early treatment discontinuation.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE by treatment group and over all subjects. Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT. Ocular TEAEs 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. In the summary, SOCs will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Separate summaries will be provided for the following categories of AEs:

- Overall AE Summary
- TEAEs
- TEAEs by Relationship to Study Medication
- Treatment Emergent SAEs

All AEs will be presented in a subject listing.

14.2 Visual Acuity

Visual acuity is discussed in section 13.5.2 for the efficacy analysis. For safety, continuous descriptive statistics will be used to summarize visual acuity by eye and treatment group. Change from baseline will also be summarized. The Safety table will be produced with an additional categorical summary of subjects with logMAR change from baseline ≥0.20 logMAR and both eyes, Right Eye (OD) and Left Eye (OS) will be the unit of analysis.

14.3 Slit-Lamp Biomicroscopy Examination

Slit lamp biomicroscopy examination is discussed in section 13.5.3 for the efficacy analysis. For safety, descriptive statistics will be used to summarize slit-lamp biomicroscopy by eye and treatment group in the Safety population. Right Eye (OD) and Left Eye (OS) will be the unit of analysis. .

14.4 Undilated Fundoscopy Examination

Undilated Fundoscopy examinations will be performed at Visits 1 and 5. The exam will assess the following components, by eye:

- Vitreous Humour
- Optic nerve
- Macula
- Cup to disc ratio (vertical)

The Investigator will classify the results as Normal, Abnormal CS, or Abnormal NCS.
The results will be summarized using counts and percentages for each treatment group at each visit for each eye. Percentages will be based on the number of subjects in each treatment group with responses. Shift tables will also be provided comparing the follow-up visit to baseline.

All undilated fundoscopy will be presented in a subject listing.

14.5 Intraocular Pressure (IOP)

Intraocular Pressure (IOP) will be assessed by applanation tonometry in each eye at Visits 1, 5, and 7. Results will be taken from a single measurement and will be recorded in mmHg.

Continuous descriptive statistics will be used to summarize the IOP by visit, eye and treatment group. Change from baseline will also be summarized.

During the Study Treatment Phase, the changes from baseline will be relative to the Study Treatment Phase baseline. During the Placebo Cross-over Phase, the changes from baseline will be relative to the Placebo Cross-over Phase baseline.

All IOP results will be presented in a subject listing.

14.6 Clinical Laboratory Data

Blood samples for clinical laboratory parameters will be collected at Visits 1, 4, 5, and 7.

Clinical laboratory data includes Complete Blood Count (CBC) with differential, metabolic panel, standard GvHD panel, and an endocrine panel (at Visits 1, 5, and 7 only).

The quantitative variables will be summarized by treatment group with continuous descriptive statistics. The qualitative variables (counts and percentages) will be summarized by treatment group at each visit and time point (where appropriate). Change from baseline will also be summarized by treatment group.

The specific parameters and normal ranges are shown below.

All laboratory results will be presented in a subject listing.

Table 3. Complete Blood Count and Differential Parameters and Normal Ranges

Complete Blood Count Panel Parameter	Normal Range*
WBC	3.81 - 8.94 K/uL
RBC	4.35 - 5.61 M/uL
HGB	12.5 - 16.3 g/dL
HCT	37.1 - 49.5 %
PLT	152 - 440 K/uL
MCV	79.0 - 97.0 fL
MCH	26.2 - 32.0 pg
MCHC	33.3 - 35.7 g/dL
RDW	12.1 - 16.0 %
MPV	7.0 - 10.8 fl
NRBC	0.00 /100 WBCs
ABSOLUTE NRBC	K/uL
NEUTS	46.5 - 82.4 %
EOSINOPHIL	0.1 - 6.0 %
BASOPHIL	0.1 - 1.1 %
LYMPHS	8.5 - 32.7 %
MONOS	5.4 - 14.2 %
ABSOLUTE NEUTS	2.23 - 6.11 K/uL
ABSOLUTE EOS	0.00 - 0.52 K/uL
ABSOLUTE BASO	0.00 - 0.11 K/uL
ABSOLUTE LYMPHS	0.21 - 2.74 K/uL
ABSOLUTE MONOS	0.2 - 0.87 K/uL

*Reference ranges may change at the time of analysis. Any changes to the reference ranges used in the final tables will be approved by the client and will be documented in the clinical summary report.

Table 4. Comprehensive Metabolic Panel Parameters and Normal Ranges

Comprehensive Metabolic Panel Parameter	Normal Range*
SODIUM	135 - 145 mmol/L
POTASSIUM	3.5 - 5.0 mmol/L
CHLORIDE	98 - 108 mmol/L
CO2	23 - 32 mmol/L
BUN	9 - 25 mg/dL
CREATININE	0.7 - 1.3 mg/dL
GLUCOSE	70 - 100 mg/dL
ALBUMIN	3.7 - 5.4 g/dL
TOTAL PROTEIN	6.0 - 8.0 g/dL
CALCIUM	8.8 - 10.5 mg/dL
ALKALINE PHOSPHATASE	36 - 118 U/L
TOTAL BILIRUBIN	0.2 - 1.2 mg/dL
AST	9 - 30 U/L
ALT	7 - 52 U/L
GLOBULIN	2.3 - 4.2 g/dL
EGFR	>59 mL/min/1.73m2
ANION GAP	5 - 17 mmol/L

*Reference ranges may change at the time of analysis. Any changes to the reference ranges used in the final tables will be approved by the client and will be documented in the clinical summary report.

Table 5. Standard GvHD Panel Parameters and Normal Ranges

Standard GvHD Panel Parameter	Normal Range*
TACROLIMUS	3.0 - 15.0 ng/mL
SIROLIMUS	3.0 – 12.0 ng/mL
VITAMIN D Total, 25-OH (D2 and D3) Sunquest Lab, OHDT	20-80 ng/mL
T4 (thyroxine), Total, Serum	11 -19 years: 5.9-13.2 µg/dL Adult (> or =20 years): 4.5-11.7 µg/dL
T4 (thyroxine), Free, Serum	11-19 years: 1.0-1.6 ng/dL Adult (> or =20 years): 0.9-1.7 ng/dL
T3 (triodothyronine), Total, Serum	11-19 years: 91-218 ng/dL Adult (> or =20 years): 80-200 ng/dL
ACTH (adrenocorticotropic hormone), Plasma	7.2-63 pg/mL (a.m. draws)
TSH (thyroid stimulating hormone), Serum	0.27 - 4.20 µIU/mL

*Reference ranges may change at the time of analysis. Any changes to the reference ranges used in the final tables will be approved by the client and will be documented in the clinical summary report.

Table 6. Endocrine Panel Parameters and Normal Ranges

Endocrine Panel Parameter	Normal Range*
DHEA-S (dehydroepiandrosterone sulfate), Serum	18-30 years: 105-728 µg/dL 31-40 years: 57-522 µg/dL 41-50 years: 34-395 µg/dL 51-60 years: 20-299 µg/dL 61-70 years: 12-227 µg/dL > or =71 years: 6.6-162 µg/dL
ESTRADIOL, Serum	Follicular Phase 27-156 pg/mL Mid Cycle Peak 48-314 pg/mL Luteal Phase 33-298 pg/mL Postmenopausal <50 pg/mL
FSH (follicle stimulating hormone), Serum	Male 1.6-8.0 mIU/mL Female Follicular Phase 2.5-10.2 mIU/mL Mid-Cycle Peak 3.1-17.7 mIU/mL Luteal Phase 1.5- 9.1 mIU/mL Postmenopausal 23.0-116.3 mIU/mL
LH (luteinizing hormone), Serum	Male 18-59 Years 1.5-9.3 mIU/mL ≥60 Years 1.6-15.2 mIU/mL Female Follicular Phase 1.9-12.5 mIU/mL Mid-Cycle Peak 8.7-76.3 mIU/mL Luteal Phase 0.5-16.9 mIU/mL Postmenopausal 10.0-54.7 mIU/mL
PTH (Parathyroid Hormone), Serum	15-65 pg/mL

Endocrine Panel Parameter	Normal Range*
PROGESTERONE, Serum	MALES > or =18 year: <0.20 ng/mL FEMALES > or =18 years: -Follicular phase: < or =0.89 ng/mL -Ovulation: < or =12 ng/mL
	-Luteal phase: 1.8-24 ng/mL -Post-menopausal: < or =0.20 ng/mL -Pregnancy - 1st trimester: 11-44 ng/mL - 2nd trimester: 25-83 ng/mL - 3rd trimester: 58-214 ng/mL
TESTOSTERONE, Total and Free, Serum Mayo Clinic test code TGRP	TESTOSTERONE, FREE Males (adult): 20-<25 years: 5.25-20.7 ng/dL 25-<30 years: 5.05-19.8 ng/dL 30-<35 years: 4.85-19.0 ng/dL 35-<40 years: 4.65-18.1 ng/dL 40-<45 years: 4.46-17.1 ng/dL 45-<50 years: 4.26-16.4 ng/dL 50-<55 years: 4.06-15.6 ng/dL 55-<60 years: 3.87-14.7 ng/dL 60-<65 years: 3.67-13.9 ng/dL 65-<70 years: 3.47-13.0 ng/dL 70-<75 years: 3.28-12.2 ng/dL 75-<80 years: 3.08-11.3 ng/dL 80-<85 years: 2.88-10.5 ng/dL 85-<90 years: 2.69-9.61 ng/dL 90-<95 years: 2.49-8.76 ng/dL 95-100+ years: 2.29-7.91 ng/dL Females (adult): 20-<25 years: 0.06-1.08 ng/dL 25-<30 years: 0.06-1.06 ng/dL 30-<35 years: 0.06-1.03 ng/dL 35-<40 years: 0.06-1.00 ng/dL 40-<45 years: 0.06-0.98 ng/dL 45-<50 years: 0.06-0.95 ng/dL 50-<55 years: 0.06-0.92 ng/dL 55-<60 years: 0.06-0.90 ng/dL 60-<65 years: 0.06-0.87 ng/dL 65-<70 years: 0.06-0.84 ng/dL 70-<75 years: 0.06-0.82 ng/dL 75-<80 years: 0.06-0.79 ng/dL 80-<85 years: 0.06-0.76 ng/dL 85-<90 years: 0.06-0.73 ng/dL 90-<95 years: 0.06-0.71 ng/dL 95-100+ years: 0.06-0.68 ng/dL TESTOSTERONE, TOTAL Males 17-18 years: 300-1,200 ng/dL > or =19 years: 240-950 ng/dL Females

Endocrine Panel Parameter	Normal Range*
	17-18 years: 20-75 ng/dL > or =19 years: 8-60 ng/dL

*Reference ranges may change at the time of analysis. Any changes to the reference ranges used in the final tables will be approved by the client and will be documented in the clinical summary report.

15. Interim Analyses

No interim analyses are planned for this study.

16. Changes from Protocol-Stated Analyses

The protocol and SAP call for LOCF imputation and for sensitivity analyses in the Per Protocol population for the key efficacy endpoints. Given there is only 1 early discontinuation and no expected major protocol deviations, the LOCF imputation and Per Protocol population have been removed due to the expected similarity with the ITT Population using only observed data. The protocol calls for t-tests and ANCOVA analyses for ordinal data, It has been decided that the Wilcoxon Rank Sum Test will be sufficient and the t-test and ANCOVA will not be done.

All crossover data collected will be summarized with continuous descriptive statistics or with counts and percentages as appropriate.

Interblink interval may appear in the protocol however all instances of interblink interval have been changed to Facial Presentation and Blinks per Minute

Per the Sponsor an additional ANCOVA model including eye type has been added for the key efficacy variables.

Additional exploratory analyses may be requested after final analyses and may be detailed in the clinical study report.

17. References

None.

18. Revision History

Documentation of revision to the SAP will commence after approval of the final version 1.0.

19. Tables, Listings and Figures

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Listing 16.2.5.6	Corneal and Conjunctival Fluorescein Staining Examination All Subject	All Subjects
Listing 16.2.5.7	Facial Presentation and Blinks per Minute by Video Camera All Subject	All Subjects
Listing 16.2.6	All Adverse Events	All Subjects
Listing 16.2.7.1	Visual Acuity	All Subjects
Listing 16.2.7.2	Slit Lamp Biomicroscopy (SLB) Without Staining All Subject	All Subjects
Listing 16.2.7.3	Intraocular Pressure (IOP)	All Subjects
Listing 16.2.7.4	Undilated Fundoscopy Examination All Subject	All Subjects
Listing 16.2.8.1	Pregnancy Test Results	All Subjects
Listing 16.2.8.2	Laboratory Results - Complete Blood Count	All Subjects
Listing 16.2.8.3	Laboratory Results - Metabolic Panel	All Subjects
Listing 16.2.8.4	Laboratory Results - GvHD Panel	All Subjects
Listing 16.2.8.5	Laboratory Results - Endocrine Panel	All Subjects
Figures	Title	Population
Figure 14.2.1.1	GLIA Ocular Surface Disease Symptoms Questionnaire, in Clinic in the Worse Eye by Symptom	ITT Population
Figure 14.2.1.2	GLIA Ocular Surface Disease Symptoms Questionnaire, Daily Diary in the Worse Eye by Symptom	ITT Population
Figure 14.2.2.1	Modified SANDE - Symptom Assessment iN Dry Eye (SANDE) Questionnaire in the Worse Eye by Symptom	ITT Population