OCUGEN, Inc.

Statistical Analysis Plan
Version: Final 1.1

Protocol No: OCU-310-DED-2017

Date: MAY 23, 2018

A Randomized, Placebo-Controlled, Double-Blind, Multicenter, Proof-of-Concept Study of Brimonidine Eye Drops for the Treatment of Dry Eye Disease (DED)

Study Statistician

Statistical Analysis CRO
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Date (MMM DD, YYYY)

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Date (MMM DD, YYYY)

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REVISION HISTORY

Version	Date	Author	Reasons
1.1	**MAY 23, 2018**	[redacted]	**The below points have been updated/added to the SAP version 1.1 based on client request** **Section 4.3.9: Updated the below text to present line plot mono vs placebo and combo vs placebo separately.** **"**line plot of the vas score will be presented separately for brimonidine mono therapy vs placebo and brimonidine combination therapy vs. placebo by visits for safety and pp population." **Section 4.3.9: Added below text to include forest plot for tolerability VAS score to be displayed with summary table.** "A forest plot of VAS score will be presented along with summary table for placebo and Brimonidine mono and combination therapy treatment groups for baseline and post baseline visits for the safety population."
			Section 4.3.11: Updated/Added the below paragraphs for SANDE "Mean change from baseline plot of frequency of symptoms, severity of symptoms and overall SANDE score without 95% CI will be presented for each three treatment groups and study visit using the ITT population. "A forest plot of overall SANDE VAS score will be presented along with summary table for placebo and Brimonidine mono and combination therapy treatment groups for baseline and post baseline visits for the safety population."
			Section 4.3.11: Updated/Added the below text for Change in corneal and conjunctival staining scores by Lissamine Green dye staining "Mean change from baseline plot of frequency of symptoms, severity of symptoms and overall SANDE score without 95% CI will be presented for each three treatment groups and study visit using the ITT population. A forest plot of overall SANDE VAS score will be presented along with summary table for placebo and Brimonidine mono and combination therapy treatment

groups for baseline and post baseline visits for the safety population.
”

Section 4.3.11: Added the below text for change in keratograph ocular redness score (ORS):

“Also, a subgroup analysis of patients with baseline ORS-Bulbar Redness category score >=1.5 (i.e. Baseline Bulbar Redness score >= 1.5) will be summarized for observed ORS score by treatment arm and by eye (study eye and qualified fellow eye) for the ITT and PP population using descriptive statistics and analysis change from baseline of ORS score by treatment arm and study eye using ITT and PP population in addition with MI for ITT population as described above.”

“Also, a subgroup analysis of patients with baseline ORS-Bulbar Redness category score >=1.5 (i.e. Baseline Bulbar Redness score >= 1.5) or VBR-Overall Score >=25 (i.e. Baseline Total VBR Score >= 25) will be summarized for observed ORS score by treatment arm and by eye (study eye and qualified fellow eye) for the ITT and PP population using descriptive statistics and analysis change from baseline of ORS score by treatment arm and study eye using ITT, ITT (MI) and PP population as described above.”

Section 4.3.11 Updated/added the below text for Change in Validated Bulbar Redness (VBR) grading scale

“Also, a subgroup analysis of patients with baseline VBR-Overall Score >=25 (i.e. Baseline Total VBR Score >=25) will be summarized for observed VBR score by treatment arm and by eye (study eye and qualified fellow eye) for the ITT and PP population using descriptive statistics and analysis change from baseline of VBR score by treatment arm and study eye using ITT, ITT (MI) and PP population as described above.”

A subgroup analysis of patients with baseline VBR-Overall Score >=25 (i.e. Baseline Total VBR Score >= 25) will be summarized for derived overall worsening in VBR scale (category given below) using frequency and percentage by Eye (study eye, qualified fellow eye),

	treatment arm and study visit using the ITT and PP population. "The above described subgroup analysis for worsening in VBR scale will also be summarized for patients with baseline ORS-Bulbar Redness category score >=1.5 (i.e. Baseline Bulbar Redness >=1.5) or VBR-Overall Score >=25 (i.e. Baseline Total VBR Score>=25) using frequency and percentage by Eye (study eye, qualified fellow eye), treatment arm and study visit using the ITT and PP population." "Also, a subgroup analysis of patients with baseline ORS-Bulbar Redness category score >=1.5 (i.e. Baseline Bulbar Redness >=1.5) or VBR-Overall Score >=25 (i.e. Baseline Total VBR Score>=25) will be summarized for observed VBR score by treatment arm and by eye (study eye and qualified fellow eye) for the ITT and PP population using descriptive statistics and analysis change from baseline of VBR score by treatment arm and study eye using ITT, ITT (MI) and PP population as described above."

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BID	Two Times a Day
CGI	Clinical Global Impression
CI	Confidence Intervals
DED	Dry Eye Disease
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MAR	MAgnification Requirement
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
N/A	Not Applicable
NC	Not Computable
NITBUT	Noninvasive Tear Breakup Time
ORS	Ocular Redness Score
PD	Protocol Deviation
PP	Per Protocol
PT	Preferred Terms
SANDE	Symptom Assessment in Dry Eye
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SGA	Subject Global Assessment
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
VBR	Validated Bulbar Redness
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) provides the explicit guidance and describes the planned statistical and data handling methods to be followed during the final reporting and analyses for the study protocol OCU-310-DED-2017.

This SAP should be read in conjunction with the study protocol (OCU-310-DED-2017, Version 2.0 (25OCT2017)) and electronic case report form (eCRF) (OCUGEN_OCU-310-DED-2017, Version Final 4.0 (DEC 01, 2017)).

As per the Clinical Study Protocol OCU-310-DED-2017, Ocugen Inc. is evaluating the use of brimonidine tartrate 0.2% eye drops (with or without loteprednol etabonate 0.2% ophthalmic suspension) for the treatment of Dry Eye Disease (DED). Dry eye disease (DED) is a common ocular disorder involving the aberrant production and stability of tear film, which results in damage to the ocular surface and is correlated with symptoms of ocular discomfort.

2 STUDY DETAILS

2.1 Study Objectives

Objective: To evaluate the tolerability and preliminary efficacy of Brimonidine eye drops (with and without loteprednol ophthalmic suspension) for the treatment of DED.

The main study objective is to establish whether subjects with dry eye disease (DED) can tolerate receiving Brimonidine 0.2% eye drops, alone or in combination with loteprednol 0.2% ophthalmic suspension, two times a day for twelve weeks.

The other objective is to investigate the preliminary efficacy of Brimonidine 0.2% topical eye drop solution, alone or in combination with loteprednol 0.2% ophthalmic suspension, in treating DED.

2.2 Study Design

This will be a randomized, placebo-controlled, double-blind study, in which 90 subjects will be enrolled at up to four clinical sites. Subjects will be randomly assigned to one of three groups, with 30 subjects per group, as follows:

Study Drug Arm #1 (combination therapy): Brimonidine (0.2%) administered as eye drops, followed by loteprednol ophthalmic suspension (0.2%), two times a day (BID) for 12 weeks.

Study Drug Arm #2 (monotherapy): Brimonidine (0.2%) administered as eye drops followed by placebo, two times a day (BID) for 12 weeks.

Control Arm (placebo): Lubricant Eye Drops (sodium carboxymethylcellulose, 0.25%), followed by a second application, two times a day (BID) for 12 weeks.

Enrolled subjects will receive the study treatment for 12 weeks and will be asked to return for a final visit at 15 weeks to evaluate safety and efficacy post-treatment.

All enrolled subjects will receive their first dose of the test medication (Brimonidine 0.2% with or without loteprednol ophthalmic suspension 0.2%), or placebo (sodium carboxymethylcellulose, 0.25%), on study Day 1 in the doctor's office, and will self-administer all subsequent doses.

Subjects will be given diaries to record the approximate time of each dose. In addition, they will be asked to make a note of any missed doses together with the reason for the omission. Subjects will return four weeks later (Day 28) for further study assessments, and thereafter at Day 56 and Day 84 (primary endpoint assessment visit), and finally at Day 105 after three weeks (or 21 days) of no study drug treatment.

Table 1: Schedule of Visits and Procedure

	Day -7 to 0 (Screening*)	Day 1*	Day 28 (+/- 7 days)	Day 56 (+/- 7 days)	Day 84 (+/- 7 days)	Day 105 (+/- 7 days)
Informed consent	X					
Demographics	X					
Medical history	X					
Ocular/Dry Eye History	X					
Symptom Assessment iN Dry Eye (SANDE) questionnaire	X	X	X	X	X	X
Diary Review			X	X	X	
Vital Signs		X			X	X
Visual Acuity (via Snellen)		X	X	X	X	X
Ocular Redness Score (ORS) (via keratography)		X	X	X	X	X
Noninvasive Tear Breakup Time (NITBUT) (via Keratograph)	X	X			X	
Validated Bulbar Redness (VBR) Scale (via Slit Lamp)		X	X	X	X	X
Ophthalmic examination (via Slit lamp)	X	X	X	X	X	X
Lissamine Green staining (Corneal and Conjunctival) (via Slit Lamp)	X	X			X	
Schirmer I test	X	X			X	
Intraocular Pressure (IOP) via Goldmann	X	X	X		X	X
Clinical Global Impression (CGI)			X	X	X	X
Subject Global Assessment (SGA)			X	X	X	X
First study medication		X				
Drug dispensation, with instruction on study medication self-administration		X[a]	X[b]	X[b]		
Adverse Events (AEs)		X[c]	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Tolerability Visual Analogue Scale (VAS)		X[d]	X	X	X	

*Day 1, by definition, is when the first dose of study drug is administered. The Screening Visit and Day 1 Visit may be combined into a single visit; in this case, do not duplicate any of the Screening/Day 1 procedures. Subjects taking steroid-containing eye drops at the Screening Visit must discontinue those drops and wait a full 7 days before attending the Day 1 Visit.

[a] After administration of the first dose of study medication, subjects will be trained on how to self-administer the eyedrops and will be given a 1-month supply [b] If required

[c] AE collection begins after the first dose of study medication on Day 1

[d] Tolerability VAS should be completed after the first dose of study medication on Day 1

2.3 Determination of Sample Size:

Thirty (30) subjects per treatment group and a common standard deviation of 20 mm yields precision (half-width) of the point estimate of pairwise difference (active – placebo) in tolerability of +/- 10.3 mm for a two-sided 95% confidence interval (CI) and +/- 8.6 mm for a two-sided 90% CI. Therefore, if the observed mean difference in tolerability is 5.0 mm, the true mean difference in tolerability will be within (-5.3, 15.3) with 95% confidence and (-3.6, 13.6) with 90% confidence.

Additionally, with a sample size of 30 subjects within a treatment group, adverse events that are not observed will be concluded to occur at a true rate of <10% with 95% confidence within that treatment group. For example, if headache is not seen within the combination treatment group, then with 95% confidence, headache would be concluded to occur at a true rate of <10%.

The sample size was not calculated to have pre-determined power for efficacy in this proof-of-concept study.

2.4 Randomization

This placebo-controlled, double-blind study will have three treatment groups utilizing a 1:1:1 randomization.

One group will receive the study drug combination (brimonidine 0.2% then loteprednol ophthalmic suspension 0.2% separated by 5-10 minutes), one group will receive the study drug alone (brimonidine 0.2%, followed by placebo separated by 5-10 minutes), and the third group will receive placebo (sodium carboxymethylcellulose, 0.25%), x 2 applications separated by 5-10 minutes).

Randomization/treatment assignment will be stratified by site and performed by an unblinded study team member.

2.5 Blinding

This is a placebo-controlled, double-blind study and the study drug will be blinded to both patient and Investigator.

Blinding Process:

The person dispensing medication at the site level will be partially unblinded and does not perform subject assessments.

Any person performing subject assessments at the site level will be blinded. In addition, the person doing assessments will not enter or "sign-off" on EDC until after the final visit and all data were entered, monitored, and cleaned; i.e., just before database lock.

In this study, the randomization was partially masked, as assignment to masked randomization groups A, B or C was recorded in the database.

2.6 STATISTICAL AND DATA ANALYSIS CONSIDERATION

The statistical analyses will be performed by Quartesian Clinical Research, using SAS Version 9.2 (or higher). All tables, figures and listings will be produced in landscape format. In general, all data will be listed by the subject and visit/time point where appropriate.

For measures collected at the individual eye level, the unit of analysis will be the study eye. Each subject will have a single eye identified as the study eye as follows:

(i) if only 1 eye meets inclusion criteria, this eye will be the study eye and the other eye will be considered the non-qualified fellow eye;
(ii) if both eyes meet inclusion criteria, the eye with the higher Ocular Redness Score (ORS) will be the study eye and the other eye will be considered the qualified fellow eye;
(iii) if both eyes have the same Ocular Redness Score (ORS), then the eye with the lower Schirmer I score will be the study eye and the other eye will be considered the qualified fellow eye;
(iv) if both eyes have same Schirmer 1 score, the right eye will be the study eye and the other eye will be considered the qualified fellow eye.

Safety and Efficacy analyses will be primarily performed on the study eyes and secondarily on the qualified fellow eyes (for efficacy) and all fellow eyes (for safety). For measures collected at the subject level, the unit of analysis will be the subject.

Data will be summarized by time-point where appropriate. The total number of subjects in the study group (N) under the stated population will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise stated, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum and 90% CI & 95% CI for tolerability endpoint and exploratory efficacy endpoints In case of $n<2$, where n indicates the number of evaluable subjects at the particular time point, only n, mean, minimum and maximum will be displayed. The statistic "Missing" will also be evaluated by enumerating the number of missing entries/subjects, if any at that visit, and presented along with summary statistic. Display NC if any value is not computable.

Decimal Precision Convention: The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

For categorical variables, counts and percentages will be used. The count [n] indicates the actual number of subjects with non-missing value at particular visit or actual number of subjects with that event or category, which should always be less than or equal to the total number of subjects in the respective study group [N].

M is the number of subjects with non-missing data of a variable at particular visit.

Percentages will be calculated as per applicable summary are listed below:

(i) For non-by visit summary, percentage will be calculated as % = (n/N)*100.
(ii) For by visit summary, percentage will be calculated as % = (n/M)*100 (summary of observed data)
(iii) For by visit summary, percentage will be calculated as % = (n/N)*100 (Summary of data with imputation)

Unless otherwise stated, all percentages will be expressed to one decimal place.

Also the distributions for continuous variables will be examined for normality using Shapiro-Wilk tests and Q-Q plot. If any deviation in the normality assumption is judged, then the data will be analyzed using appropriate non-parametric tests. Results of such tests will be presented in SAS LST file as an appendix to that analysis.

As this is a proof of concept study for which there is no pre-determined power for a specific efficacy endpoint measure, there will be no multiplicity adjustments to account for the testing of the multiple endpoints and for the testing of both the combination arm and monotherapy arms relative to placebo.

The following conventions will be applied to analyses/data presentation:

All dates will be displayed in DDMMMYYYY format.

Unscheduled visit data will be presented in Listings, but not in Tables and Figures with by-visit summaries.

For Listings, data will be presented by Subject, parameter, assessment date in chronological order.

Protocol Deviations:

Both manual and programmable Protocol deviations (PDs) will be summarized. Programmable PDs will be derived programmatically. Additional deviations identified during monitoring will be classified as major or minor and will be included in the study report.

Subjects with major protocol deviations, i.e. deviations deemed to have an impact on treatment evaluation will be excluded from the Per Protocol population. The list of protocol deviations which lead to exclusion of subjects from the PP population will be finalized prior to the first analysis of unmasked data and updated as needed prior to database lock for the final analysis.

Programmable deviations will be defined as follows:

1. Inclusion/Exclusion Criteria Not Met (major)
2. Use of prohibited medication (major). Prohibited medications will be identified through a manual review of prior and concomitant medications taken during the study.
3. Treatment compliance <80% or >120% (major).
4. Missed instillations: subject missed at least one scheduled instillation, but compliance is still within the range 80%-120% (minor).
5. Unblinding (major).
6. Visit out of window: visits occurring outside of protocol specified +/- 7 day range (minor).
7. Missing tolerability assessment at Day 84 visit (major)
8. Missing tolerability assessment at Day 1, Day 28 or Day 54 visit (minor)

Handling of Missing Data:

Missing values for primary tolerability endpoint and exploratory efficacy endpoints will be imputed by using LOCF or Multiple imputation; otherwise subjects missing values for each parameter wise will not be included in the respective analysis. Imputed exploratory efficacy endpoints will be primarily analyzed using ITT population.

Efficacy analyses will be performed using the ITT (primary) and PP (secondarily) populations and will summarize both observed data only and with missing data imputed.

Multiple imputation methods will be used to impute missing data for the exploratory efficacy endpoints, assuming missing completely at random and missing not at random mechanism. Details of the imputation methods to be used are provided in Appendix 1

To handle missing or partial AE and concomitant medication dates, the following rules will be applied.

For partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
    a. If the year matches the year of the dose date, then impute the month and day of the dose date.
    b. Otherwise, assign "January."
3. If the day is unknown, then:
    a. If the month and year match the month and year of the first dose date, then impute the day of the dose date.
    b. Otherwise, assign "01."

For partial end dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign "December."
3. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pretreatment or on/after treatment, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

2. If the start date is missing but the stop date is not missing and is on or after the day of study dose administration, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

3. If the start date is missing but the stop date is not missing and is before the day of study dose and after the date of signed informed consent, then the AE (or medication) is considered to be before treatment (or prior medication).

4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken and medication is considered to be concomitant while the AE is defined by start date.

If the Adverse Event Relationship flag is missing, the relationship for adverse event will be imputed and will be considered as definitely related. If the Adverse Event Severity flag is missing, the severity will be imputed and will be considered as severe.

Treatment Group Labelling in TFLs:

The treatment groups will be labelled as

Study drug Arm-1	Study Drug Arm-2	Control Arm
Brimonidine Combination therapy	Brimonidine Monotherapy	Placebo

2.7 Definition

Baseline: Baseline is defined as the latest non-missing assessment (whether from scheduled or unscheduled) prior to the first dose administration of the study drug, unless otherwise stated.

The **Post-baseline** values are defined as measurements taken after the first administration of study drug.

Change from Baseline: The change from baseline values will be calculated as post baseline value minus the baseline value.

An Adverse Event is any untoward medical occurrence in a subject or clinical investigation in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can be any unfavorable sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, whether considered related or not related to the investigational product.

A Pre-Treatment AE is any AE in a clinical study subject that occurs after he/she signed the Informed Consent Form (ICF) up until the first administration of Investigational Medicinal Product (IMP).

A Treatment Emergent AE (TEAE): TEAE is any AE not present prior to the initiation of IMP administration or any event already present that worsens in either intensity or frequency following exposure to the IMP.

An SAE is any AE that results in death, is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, requires medical or surgical intervention to prevent any of the occurrences noted above.

Unexpected Adverse Event: Any adverse event, the specificity or severity of which is not consistent with the current Package Insert.

3 PRIMARY, SECONDARY AND EXPLORATORY ENDPOINTS

3.1 Primary Tolerability Endpoint

The primary tolerability evaluation parameters are:

- Test Substance Tolerance (Visual Analogue Scale)

Subjects will assess their tolerance to the administration of the study drug, utilizing a Visual Analog Scale (VAS). The VAS is a 100-mm horizontal line with verbal descriptors at either end.

The VAS ratings will be completed after administration of the study drug on Day 1 (post-dose), Day 28, Day 56 and Day 84. Subjects will place a single slash mark across the horizontal line between the end labeled "completely intolerable" (0 mm) and "easily tolerable" (100mm).

3.2 Secondary Endpoints

- N/A

3.3 Exploratory Endpoints

The exploratory study endpoints are:

- Symptom Assessment Questionnaire iN Dry Eye (SANDE)
- Change in corneal and conjunctival staining scores by Lissamine Green dye staining
- Change in tear secretion as measured by Schirmer I test
- Change in Keratograph Ocular Redness Score (ORS)
- Change in Validated Bulbar Redness (VBR) grading scale
- Clinical Global Impression (CGI) of change in symptoms from baseline (physician's rating)
- Subject Global Assessment (SGA) of overall change from baseline (subject's rating)

3.4 Safety Endpoints

The safety endpoints are:

- Treatment emergent adverse events, classified by frequency, severity, and relatedness, from baseline (Day 1) through the last study visit (Day 105).
- Vital signs
- Findings from ophthalmic examinations
- The proportion of subjects at Day 84 who successfully complete (i.e., tolerate) a full twelve weeks (i.e.,84 days) of therapy with topical administration two times per day (BID).

4 STATISTICAL METHODOLOGY

4.1 Analysis Populations

All Subjects: All subjects will include the subjects who signed the informed consent form and who meet all inclusion criteria and none of the exclusion criteria and eligible to be randomized.

Randomized Population: The randomized population will include all subjects who were randomized to treatment.

Safety Population: The safety population will include all randomized subjects who have received at least one dose of study medication. This population will be used to summarize safety variables and will summarize subjects as treated.

Intent-to-Treat Population (ITT): The ITT population will include all randomized subjects who have received at least one dose of study medication. This population will be the primary population for efficacy analyses and will be used to summarize all efficacy variables and will summarize subjects as randomized.

Per-protocol population (PP): The PP population is a subset of the ITT population. The PP population will include those subjects who do not have major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment.

(This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables. If the PP and ITT populations are exactly the same, then additional efficacy analyses on the PP population will not be performed. The PP population will summarize subjects as randomized.)

4.2 Coding Dictionaries Used

Adverse events and Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0

Prior & concomitant medication will be coded using World Health Organization-Drug Reference List (WHO-DRL) (Version: WHO DRUG Enhanced Sep-2016 B2) and by Anatomical Therapeutic Chemical (ATC) level 4.

4.3 Statistical Methods and Data Analysis

4.3.1 Disposition

The number and percentage of subjects who entered the study, and those who completed the study will be presented, together with the number and percentage of subjects who prematurely discontinued from the study along with reasons for study discontinuation. Additionally, subjects included in the Randomized population, Safety Population, Intent-to-treat population and per-protocol population will be summarized by treatment groups using all subjects.

A listing of each subject's analysis population (Randomized Population, Safety Population, Intent-To-Treat population and Per-Protocol population), disposition and reason for discontinuation will be listed.

4.3.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics (gender, ethnicity, race, age [years] will be summarized by treatment groups using descriptive statistics for subjects in the Randomized population, ITT population and PP population. Qualitative variables (Gender, ethnicity, race, Age <65 years vs >=65 years) will be summarized using frequencies while quantitative variables (age) will be summarized using mean, SD, median, minimum, and maximum.

Demographic and baseline data will also be listed using Randomized population. The screening test such as ocular and dry eye history will be listed using All Subjects.

4.3.3 Protocol Deviation

A summary of Protocol Deviations for the Randomized Population will be summarized.

A listing of subjects with protocol deviations (PD) will be provided.

4.3.4 Study Drug Administration and Accountability

Duration of Exposure will be defined as [Date of Last Dose] – [Date of First Dose] + 1

Treatment Compliance (%) will be defined as [Number of Actual Instillations] / [Number of Planned Instillations] * 100%. Treatment Compliance would be categorized as <80%, 80% - 120% and >120%.

Number of Actual Instillations will be counted from the subject diaries and first study drug administration CRF form. For all treatment arms, both instillations will be counted.

Number of Planned Instillations will be 336 (84 days of BID dosing & each dose will have two bottles).

Number of Actual Instillations, Treatment Compliance % and Duration of Exposure will be summarized descriptively by treatment group for the Safety population.

The proportion of subjects at Day 84 who successfully complete a full twelve weeks (i.e.,84 days) of therapy with topical administration two times per day (BID) will be summarized by treatment arm and will be presented as total numbers and percentage.

The subjects are said to be a successful completer if the subject exposure to study drug is ≥77 days.

A listing will be provided for study drug administration information including date and approximate time of dosing (am vs. pm), dose administered from bottles #1 and #2 and any comments regarding doses that were not administered.

Also, a listing of exposure, treatment compliance, drug accountability and diary accountability will be provided for the Safety Population.

4.3.5 Medical and Allergic History

Medical history for the Safety Population will be summarized both by each individual treatment group and for the study overall as the number and percentage of subjects in each system organ class (SOC) and sub-categorized by preferred term (PT). Subjects will be counted only once at the preferred term (PT), only once at the system organ class (SOC), and only once at subject level for the counting of total number of subjects with a medical history term. Counts will be presented in descending frequency of SOC term for the overall column unless otherwise specified.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0

Listings of medical and allergy history events will be provided separately for all Subjects.

4.3.6 Prior and Concomitant Medications

Prior medication will be summarize by treatment groups for Randomized population, whereas concomitant medication will be summarized by treatment group for Safety population.

Prior and Concomitant Medications will be coded using World Health Organization-Drug Reference List (WHO DRUG Enhanced Sep-2016 B2) and will be categorized by preferred name and ATC level 4 class per WHO.

A prior medication is one taken only prior to the first dose of the study drug, i.e. stopped prior to the first dose of the study drug. All other medications are concomitant (including those taken both prior to and continued after the first dose and those started after first dose).

All prior and concomitant medications (ocular and other medications) will be listed for the Safety Population.

4.3.7 Concomitant Non-drug treatment/therapies

The concomitant non-drug treatment and therapy will be listed using all subjects.

4.3.8 Table 2: Summary of Analysis Strategy

Endpoint	Statistical Method / Test	Analysis Population	Missing Data Imputation Approach	Parameters/Variables in the analysis (Stat. test/Model)	Analysis Time point
Primary Safety Endpoint					
Test Substance Tolerance (Visual Analogue Scale)	Pairwise Two Sample t-test	Safety and Per Protocol *ITT (if N differs from Safety)	LOCF	VAS	Day 1, Day 28, Day 56 & Day 84.
Exploratory Endpoint(s)					
Symptom Assessment Questionnaire iN Dry Eye (SANDE)	Pairwise Two Sample t-test	ITT and Per Protocol	Multiple Imputation	Change from baseline SANDE	Baseline, Post baseline assessments: Day 28, Day 56, Day 84 & Day 105.
Change in corneal and conjunctival staining scores by Lissamine Green dye staining	Pairwise Two Sample t-test	ITT and Per Protocol	NA	Change from Baseline Corneal and Conjunctival Staining zone wise and Overall Score	Baseline & Post baseline assessments: Day 84.
Change in tear secretion as measured by Schirmer I test	Pairwise Two Sample t-test	ITT and Per Protocol	NA	Change from baseline in tear secretion as measured by Schirmer I test	Baseline & Post baseline assessments: Day 84.
Change in Keratograph Ocular Redness Score (ORS)	Pairwise Two Sample t-test	ITT and Per Protocol	Multiple Imputation	Change from baseline in Keratograph Ocular Redness Score (ORS)	Baseline, Post baseline assessments: Day 28, Day 56, Day 84 & Day 105).

Endpoint	Statistical Method / Test	Analysis Population	Missing Data Imputation Approach	Parameters/Variables in the analysis (Stat. test/Model)	Analysis Time point
Change in Validated Bulbar Redness (VBR) grading scale	Pairwise Two Sample t-test	ITT and Per Protocol	Multiple Imputation	Change from baseline in Validated Bulbar Redness (VBR) grading scale.	Baseline, Post baseline assessments: Day 28, Day 56, Day 84 & Day 105.
Clinical Global Impression (CGI)	Fisher exact test comparison of proportions	ITT and Per Protocol	LOCF	CGI Categories	Day 28, Day 56, Day 84 & Day 105.
Subject Global Assessment (SGA)	Fisher exact test comparison of proportions	ITT and Per Protocol	LOCF	SGA Categories	Day 28, Day 56, Day 84 & Day 105.
Additional Endpoints					
The proportion of subjects with grade improvement in Tear secretion	Fisher exact test comparison of proportions	ITT & PP	NA	Proportion of subjects with grade improvement of 1,2,3	Day 84
Intraocular pressure (via Goldmann tonometry)	Pairwise Two Sample t-test	Safety and Per Protocol	Multiple Imputation	Change from baseline in Intraocular pressure	Baseline, Post baseline assessments: Day 28, Day 84 & Day 105
Intraocular pressure category	Fisher exact test comparison of proportions	Safety and Per Protocol	NA	Intraocular pressure categories	Baseline, Post baseline assessments: Day 28, Day 84 & Day 105

As per the above table if any data is imputed, the imputed data will be presented in corresponding listing with a flag and footnote. (e.g. * - imputed using LOCF).

4.3.9 Primary Endpoints

Primary tolerability endpoint:

The primary tolerability endpoint will be evaluated from subject responses to the Tolerability Visual Analogue Scale (VAS), which will be collected on day 1 post-dose, day 28, day 56 and day 84. The descriptive statistics will be presented for this VAS by treatment arm and study visit using the Safety and PP population. Treatment groups will be compared at each post dose visit by pairwise two sample t-tests and corresponding p-value along with 90% and 95% Confidence Interval (CI) for mean will be presented. Pairwise comparisons in mean among the three treatment groups (i.e. Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy). This analysis will performed for both Safety and PP Population for observed data (without LOCF) and only for Safety population for imputed data (with LOCF).

Two-sided P-value less than 0.05 would be considered as statistical significance.

Line plot of the VAS score will be presented separately for Brimonidine mono therapy vs placebo and Brimonidine Combination therapy vs. placebo by visits for Safety and PP population.

A forest plot of VAS score will be presented along with summary table for placebo and Brimonidine mono and combination therapy treatment groups for baseline and post baseline visits for the safety population.

If the ITT population "N" differs from Safety Population "N", then the above analysis will be produced for ITT population along with safety and PP population (for both tables and figures).

The listing of the VAS scores for the Safety Population will be provided.

LOCF imputations will be applied to missing assessments at Days 56 and 84. The last available post-Day 1 assessment will be carried forward to impute the missing assessments at later visits. Day 1 assessment will not be carried forward, since Day 1 tolerability assessment is performed immediately after dosing, while on other visits these assessments are performed at least 2 hours after dosing.

4.3.10 Secondary endpoint:

There are no secondary endpoints in this study.

4.3.11 Exploratory endpoint:

The exploratory study endpoints will be analysed using the ITT and PP Population for both for observed and imputed data; If ITT and PP population are same then ITT alone will be used to summarize and plot the exploratory endpoints data.

- Symptom Assessment Questionnaire in Dry Eye (SANDE): The SANDE data will be summarized by treatment group and study visit for the ITT and PP Populations. These data will be summarized using descriptive statistics for the observed values and change from baseline values for "frequency of symptoms", "severity of symptoms" and an overall

SANDE VAS score. The overall SANDE score will be calculated by multiplying the frequency score by the severity score and obtaining the square root.

Change from baseline of Frequency of Symptoms, Severity of Symptoms and Overall SANDE VAS score will be compared between the treatment groups for study eye using the ITT and PP population for observed data (without MI) and only ITT population for imputed data (with MI) at each visit by pairwise two sample t-tests and corresponding p-value along with 90% and 95% Confidence Interval (CI) for mean will be presented. Pairwise comparison in mean among the three treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy)

Two-sided P-value less than 0.05 would be considered as statistical significance.

Mean change from baseline plot of SANDE with 95% CI will be presented for each all three treatment groups and study visit using the ITT and PP populations.

Mean change from baseline plot of frequency of symptoms, severity of symptoms and overall SANDE score without 95% CI will be presented for each three treatment groups and study visit using the ITT population.

A forest plot of overall SANDE VAS score will be presented along with summary table for placebo and Brimonidine mono and combination therapy treatment groups for baseline and post baseline visits for the safety population.

The SANDE will also be listed using the Randomized population.

Subjects with missing values will be imputed using the Multiple Imputation(MI) method. See section 4.7 Appendices for Multiple Imputation methodology.

- **Change in corneal and conjunctival staining scores by Lissamine Green dye staining -** Corneal staining will be graded in 5 eye zones. Each eye zone will be graded from 0 to 3 based on the density of punctate staining (for an overall maximum score =15). Similarly, conjunctiva will be graded for each eye from 0 to 3 based on the density of punctate staining in the nasal-bulbar and temporal-bulbar zones staining (maximum score =6).

  The graded scores for corneal and conjunctiva staining will be summarized by eye zone using the descriptive statistics for observed values and change from baseline values and present by treatment arm, study visit and eye (study eye, qualified fellow eye) for the ITT and PP population.

  Change from baseline of corneal and conjunctival score (by eye zone and overall) will be compared between the treatment groups for study eye using the ITT and PP population at each visit by pairwise two sample t-tests and corresponding p-value along with 90% and 95% Confidence Interval (CI) for mean will be presented. Pairwise comparisons in mean among the three treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy)

Two-sided P-value less than 0.05 would be considered as statistical significance.

Mean change from baseline plot of Lissamine Green dye staining scores (by eye zone and overall) with 95% CI for both corneal and conjunctival staining will be presented for all three treatment groups and study visit for study eye for the ITT and PP populations.

Mean change from baseline plot of Overall Lissamine Green dye staining scores for study eye will be plotted without the 95% CI for the ITT populations.

A forest plot of mean change from baseline of Overall Conjunctival and Overall Corneal Lissamine Green dye score will be presented along with summary table for treatment groups for study eye at baseline and post baseline visits for the ITT population.

The corneal and conjunctival staining scores will also be listed using the Randomized population. Also missing values will not be imputed for corneal and conjunctival staining scores.

- **Change in tear secretion as measured by Schirmer I test** – The data for the change in tear secretion will be summarized by treatment arm and study eye designation (study eye or qualified fellow eye) for the ITT and PP populations. These data will be summarized using descriptive statistics for the observed values and change from baseline values. The Change in tear secretion values are determined from the measured amount of moisture (in mm) collected from the Schirmer procedures.

  Change from baseline of tear secretion will be compared between the treatment groups for study eye using the ITT and PP population by pairwise two sample t-tests and corresponding p-value along with 90% and 95% Confidence Interval (CI) for mean will be presented. Pairwise comparison in mean among the three treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy).

  Two-sided P-value less than 0.05 would be considered as statistical significance.

  Also, the measured moisture in mm will be summarized using frequency and percentage by treatment arm, study visit and by eye (study eye, qualified fellow eye) using the ITT and PP population according to the following categories:

  1. Normal is ≥15 mm.
  2. Mild dry eye is 11-14 mm
  3. Moderate dry eye is 6-10mm
  4. Severe dry eye is ≤5 mm

  The proportion of subjects with 1, 2, 3 grade improvement will be summarized by treatment groups for both ITT and PP population.

The proportion of subject with improvement among treatment groups will be compared using Fisher's exact test for both ITT and PP population.

Also shift table will be provided to compare the category shift from baseline to post baseline visit for the ITT and PP population.

Mean change from baseline plot of tear secretion as measured by Schirmer I test with 95% CI will be presented for all three treatment groups and for study eye using ITT and PP population.

The Change in tear secretion as measured in mm and categorized by grade will also be listed using the Randomized population. Also missing values will not be imputed for tear secretion scores.

- **Change in Keratograph Ocular Redness Score (ORS):** The data for the ORS score (range between 0.0-4.0) will be summarized by treatment arm and study eye (study eye or qualified fellow eye) for the ITT and PP populations. These data will be summarized using the descriptive statistics for observed values and change from baseline values by treatment and by eye (study eye and qualified fellow eye) using the ITT and PP population.

  Change from baseline of ORS score will be compared between the treatment groups for study eye using the ITT and PP population for observed (without MI) and only ITT population for imputed data (with MI) at each visit by pairwise two sample t-tests and corresponding p-value along with 90% and 95% Confidence Interval (CI) for mean will be presented. Pairwise comparison in mean among the three treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy)

  Also, a subgroup analysis of patients with baseline ORS-Bulbar Redness category score >=1.5 (i.e. Baseline Bulbar Redness score >= 1.5), will be summarized for observed ORS score by treatment arm and by eye (study eye and qualified fellow eye) for the ITT and PP population using descriptive statistics and analysis change from baseline of ORS score by treatment arm and study eye using ITT and PP population in addition with MI for ITT population as described above.

  Also, a subgroup analysis of patients with baseline ORS-Bulbar Redness category score >=1.5 (i.e. Baseline Bulbar Redness score >= 1.5) or VBR-Overall Score >=25 (i.e. Baseline Total VBR Score >= 25) will be summarized for observed ORS score by treatment arm and by eye (study eye and qualified fellow eye) for the ITT and PP population using descriptive statistics and analysis change from baseline of ORS score by treatment arm and study eye using ITT, ITT (MI) and PP population as described above.

  Two-sided P-value less than 0.05 would be considered as statistical significance.

  Mean change from baseline plot of the Ocular Redness score with 95% CI will be presented for all three treatment groups and study visit for study eye using ITT and PP population.

The ORS will also be listed using the Randomized population.

Subjects with missing values will be imputed using the Multiple Imputation(MI) method. See section 4.7 Appendices for Multiple Imputation methodology.

- **Change in Noninvasive Tear Breakup Time (NITBUT):** The data for the NITBUT will be summarized by treatment arm and study eye (study eye or qualified fellow eye) for the ITT and PP populations. These data will be summarized using the descriptive statistics for observed values and change from baseline values by treatment and by eye (study eye and qualified fellow eye) using the ITT and PP population.

  Change from baseline of NITBUT will be compared between the treatment groups for study eye using the ITT and PP population by pairwise two sample t-tests and corresponding p-value along with 90% and 95% Confidence Interval (CI) for mean will be presented. Pairwise comparison in mean among the three treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy).

  Mean change from baseline plot of the NITBUT with 95% CI will be presented for all three treatment groups and for study eye using ITT and PP population.

  Also, Non-invasive Tear Breakup Time (NITBUT) will be listed using the Randomized population.

  No imputation will be done for NITBUT.

- **Change in Validated Bulbar Redness (VBR) grading scale:** The VBR will be summarized using descriptive statistics for observed values and change from baseline values for graded scores for the temporal, nasal regions and for overall score by treatment arm, study visit and eye (study eye or qualified fellow eye). The overall score of VBR would be arrived by averaging the Nasal and temporal score.

  Change from baseline of VBR (nasal, temporal and overall VBR score) will be compared between the treatment groups for study eye using the ITT and PP population for observed (without MI) and only ITT population for imputed data (with MI) by pairwise two sample t-tests and corresponding p-value along with 90% and 95% Confidence Interval (CI) for mean will be presented. Pairwise comparison in mean among the three treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy).

  Also, a subgroup analysis of patients with baseline VBR-Overall Score >=25 (i.e. Baseline Total VBR Score >=25) will be summarized for observed VBR score by treatment arm and by eye (study eye and qualified fellow eye) for the ITT and PP population using descriptive statistics and analysis change from baseline of VBR score by treatment arm and study eye using ITT, ITT (MI) and PP population as described above.

Mean change from baseline plot of VBR (nasal, temporal and overall score) with 95% CI will be presented for all three treatment groups and for study eye using ITT and PP population.

Subjects with missing values will be imputed using the Multiple Imputation(MI) method. See section 4.7 Appendices for Multiple Imputation methodology.

The overall improvement/worsening in VBR scale (category given below) will be derived and summarized as frequency and percentage by treatment arm and study visit using the ITT and PP population.

A subgroup analysis of patients with baseline VBR-Overall Score >=25 (i.e. Baseline Total VBR Score >= 25) will be summarized for derived overall worsening in VBR scale (category given below) using frequency and percentage by Eye (study eye, qualified fellow eye), treatment arm and study visit using the ITT and PP population.

The above described subgroup analysis for worsening in VBR scale will also be summarized for patients with baseline ORS-Bulbar Redness category score >=1.5 (i.e. Baseline Bulbar Redness >=1.5) or VBR-Overall Score >=25 (i.e. Baseline Total VBR Score>=25) using frequency and percentage by Eye (study eye, qualified fellow eye), treatment arm and study visit using the ITT and PP population.

Also, a subgroup analysis of patients with baseline ORS-Bulbar Redness category score >=1.5 (i.e. Baseline Bulbar Redness >=1.5) or VBR-Overall Score >=25 (i.e. Baseline Total VBR Score>=25) will be summarized for observed VBR score by treatment arm and by eye (study eye and qualified fellow eye) for the ITT and PP population using descriptive statistics and analysis change from baseline of VBR score by treatment arm and study eye using ITT, ITT (MI) and PP population as described above.

i. **Marked worsening (increase > 40)**
ii. **Moderate worsening (increase >20 and ≤40)**
iii. **Minimal worsening (increase >0 and ≤20)**
iv. **Unchanged (difference of 0)**
v. **Minimal improvement (reduction >0 and ≤20)**
vi. **Moderate improvement (reduction >20 and ≤40)**
vii. **Marked improvement (reduction > 40)**

The VBR and overall improvement/worsening in VBR scale category will also be listed using the Randomized population.

No imputation will be done for overall improvement/worsening in VBR scale response category.

- **Clinical Global Impression (CGI) of change in symptoms from baseline (physician's rating)** – The CGI response category (as response category given below) will be summarized as frequency and percentage by treatment arm and study visit using the ITT and PP population.

I. **Marked worsening**
II. **Moderate worsening**
III. **Minimal worsening**
IV. **Unchanged**
V. **Minimal improvement**
VI. **Moderate improvement**
VII. **Marked improvement**

The proportion of subjects with improvements (Minimal improvement, Moderate improvement, Marked improvement) at the day 84 and 105 will be summarized and compared among pairwise treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy) using Fisher's exact test for ITT and PP population for observed (without LOCF) and ITT population for imputed data (with LOCF).

The CGI response category will also be listed using the Randomized population.

The missing values of post dose CGI score will be imputed using LOCF (Last Observation Carried Forward) method, expect for the first post dose assessment.

- **Subject Global Assessment (SGA) of overall change from baseline (subject's rating)** – The SGA response category (as response category given below) will be summarized as frequency and percentage by treatment arm and study visit using the ITT and PP population.
  i. **Much worse**
  ii. **Worse**
  iii. **About the same**
  iv. **Improved**
  v. **Much improved**

  The proportion of subjects with improvement (Improved and Much Improved) at the day 84 and 105 will be summarized and compared among pairwise treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy) using Fisher's exact test for ITT and PP population for observed (without LOCF) and only ITT population for imputed data (with LOCF).

  The SGA response category will also be listed using the Randomized population.

  The missing values of post dose SGA score will be imputed using LOCF (Last Observation Carried Forward) method, expect for the first post dose assessment.

4.3.12 Safety Endpoints:

Adverse Events:

AEs will be coded to system organ class (SOC) and preferred term (PT) using MedDRA (version 20.0). An overall summary of number and percentage of subjects with at least one AE, TEAE, serious TEAE, treatment-related TEAE, serious treatment-related TEAE, and TEAE leading to treatment discontinuation, TEAE leading to study discontinuation will be presented by treatment arm and also by Ocular (by study eye and fellow eye) and Non-Ocular AEs using safety population.

TEAE will also be summarized using frequency and percentage by overall, AE type (Ocular AE (study eye, fellow eye), Non-Ocular AE) and by treatment with SOC and PT using safety population. Each subject can have AEs of all types. Therefore, the percentage base is the number of subjects in the safety population under each treatment.

Number and percentage of patients with TEAEs will be tabulated by MedDRA system organ class, and preferred term by Treatment. TEAEs (MedDRA system organ class and preferred term) will also be summarized by relationship to study drug (by ocular (study eye, fellow eye) and non-ocular AE), severity grade - mild, moderate or severe (by ocular (study eye, fellow eye) and non-ocular AE). Related events will include those with, possibly related, definitely related captured on the CRF.

In calculating the number of subjects who have TEAEs, if a subject has the same event occur more than once, the TEAE with the highest degree of relatedness (Probable, Possible) and the event with the highest severity (from low to high – Mild, Moderate, Severe) will be summarized. In case of missing relatedness or severity, the highest value will be assumed. A summary table for Death due to TEAE will be summarized. All the above tables will be summarized using safety population.

All adverse events (AEs) reported during the study will be present in a by-subject listing using the All Subjects. Separate by-subject listings will be generated to present Serious TEAEs and AEs leading to discontinuation from the study using safety population.

Vital signs:

Vital signs (systolic and diastolic blood pressure, pulse rate and body temperature) will be summarized using the descriptive statistics for each vital sign measurement and change from baseline by treatment arm and study visit using the safety population. Also overall interpretation of vital signs will be summarized with frequency and percentage using the safety population.

Vital Sign data will be listed by individual time course for each parameter and subject using the safety population.

Findings from ophthalmic examinations (via Slit Lamp):

The ophthalmic examinations such as tear film, eye lids, lashes, bulbar and palpebral conjunctiva, upper and lower lid puncta, cornea, anterior chamber, iris, lens, and anterior vitreous will be summarized by categories such as Normal, Abnormal (NCS) and Abnormal (CS) using frequency and percentage for treatment and by eye using safety population.

A separate listing will be presented for the each of the ophthalmic examination findings noted above using the safety population.

Visual acuity collected in CRF is in US notation i.e. Snellen Numerator and Snellen Denominator. Change from baseline will be derived based on transformed decimal notation and line worsening will be categorised using derived logMAR values.

The Visual acuity derivation of Decimal notation, MAR and logMAR are explained below with example.

Visual acuity values are understood best by the following simple rule. On a Snellen chart we determine the line that the person can just recognize. If that line is twice as large as the reference standard (20/20), we state that that person's MAgnification Requirement (MAR) is 2x. If the MAgnification Requirement is 2x, the visual acuity is 1/2 (20/40). Similarly, if the MAgnification Requirement (MAR) is 5x, the visual acuity is 1/5 (20/100); if MAR = 10, visual acuity = 1/10 (20/200), and so on.

LogMAR = log10 (MAR)

Snellen Chart Lines	US notation	Decimal notation	MAR	LogMAR
Super Normal	20/10	2.0	0.5	-0.3
Super Normal	20/15	1.33	0.75	-0.1
Line 10 (normal vision)	20/20	1.0	1.0	0.0
Line 9	20/25	0.8	1.25	0.1
Line 8	20/30	0.67	1.67	0.2
Line 7	20/40	0.50	2.0	0.3
Line 6	20/50	0.40	2.5	0.4
Line 5	20/60	0.33	3.03	0.5
Line 4	20/70	0.28	3.57	0.6
Line 3	20/80	0.25	4	0.6
Line 2	20/100	0.2	5	0.7
Line 1 (worst vision)	20/200	0.1	10	1

LogMAR values will be rounded to 1-digit precision. 1 line change is defined as increase in LogMAR value by 0.1.

Measurement of visual acuity (via Snellen, with eyeglasses if applicable) data will be summarized by treatment group and by eye at each visit and for change from baseline to each visit using discrete summaries including change from baseline in the number of lines and the proportion of subjects with ≥ 3 line change (worsening) from baseline will be summarized by Eye and Visit.

A listing of visual acuity include Snellen individual measurements and abnormal values (≥ 3 line change from Baseline) will be presented using the safety population.

Intraocular pressure (via Goldmann tonometry) will be summarized for Safety and PP population by treatment group and by eye at each visit and for change from baseline to each visit using descriptive statistics.

Change from baseline of Intraocular pressure will be compared between the treatment groups for study eye using the Safety and PP population for observed (without MI) and only Safety population for imputed data (with MI) at each visit by pairwise two sample t-tests and corresponding p-value along with 90% and

95% Confidence Interval (CI) for mean will be presented. Pairwise comparison in mean among the three treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy) will be assessed.

Two-sided P-value less than 0.05 would be considered as statistical significance.

Clinical significant changes (worsening) from baseline (% change from baseline) in Intraocular Pressure of study eye will be categorised as IOP increase >= 20% vs. Baseline; IOP decrease >= 20% vs. Baseline; and No significant change (change value of -19 to 19%) vs. Baseline; and summarized using frequency and percentage by visits and treatment arm.

Mean change from baseline plot of Intraocular pressure with 95% CI will be presented for all three treatment groups and study visit using the Safety and PP populations.

Subjects with missing values will be imputed using the Multiple Imputation (MI) method. See section 4.7 Appendices for Multiple Imputation methodology.

The Intraocular pressure (category given below) will be derived and summarized as frequency and percentage by treatment arm and study visit for both eyes using the Safety and PP population.

i. Normal (>5 =mmHg or <=22 mmHg)

ii. Abnormal (<5 mmHg or >22 mmHg)

The proportion of subjects with Intraocular pressure category (Normal & Abnormal) at the day 84 and 105 will be summarized and compared among pairwise treatment groups (Brimonidine Monotherapy vs. placebo, Brimonidine Combination therapy vs. placebo, Brimonidine Monotherapy vs. Combination therapy) using Fisher's exact test for Safety and PP.

A listing of Intraocular pressure with category will be presented using the Safety population.

No imputation will be done for Intraocular pressure category.

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4.4 INTERIM ANALYSES AND DATA MONITORING

Interim analysis will be performed by the unblinded team for data through Day 84 for regulatory submission. As a part of this interim analysis, the applicable TLFs for the following end points will be submitted for data up to day 84. As this will be the primary analysis for efficacy, no alpha adjustment will be made.

1. Disposition & Demographics
2. Primary Tolerability Endpoint: Test Substance Tolerance (Visual Analogue Scale).
3. Adverse Events - ocular and non-ocular
4. Intraocular pressure
5. Efficacy endpoints as per Section 3.3
    - Symptom Assessment Questionnaire iN Dry Eye (SANDE)
    - Change in corneal and conjunctival staining scores by Lissamine Green dye staining
    - Change in tear secretion as measured by Schirmer I test
    - Change in Keratograph Ocular Redness Score (ORS)
    - Change in Validated Bulbar Redness (VBR) grading scale
    - Clinical Global Impression (CGI) of change in symptoms from baseline (physician's rating)
    - Subject Global Assessment (SGA) of overall change from baseline (subject's rating)

4.5 CHANGES OF ANALYSIS FROM PROTOCOL

Included a summary and analysis for Change in Noninvasive Tear Breakup Time (NITBUT) along with plot.

Interim analysis for Day 84 will be performed for regulatory submission as per Sponsor request.

4.6 REFERENCES

NA

4.7 APPENDICES

Appendix 1- Multiple Imputation Method for the Exploratory Efficacy Endpoint

The missing data pattern of the exploratory efficacy parameters, SANDE VAS, Keratograph Ocular Redness Score (ORS), Validated Bulbar Redness (VBR) scores, and Intraocular Pressure(IOP) will be analyzed by using the Multiple Imputation (MI) method.

Imputation of missing data will be conducted under a working assumption of Missing Completely At Random (MCAR). Missing Completely At Random means that the missing data mechanism is assumed not to depend on observed or unobserved missing values. These assumptions will be assessed in the sensitivity analyses described later in this Appendix.

Multiple Imputation replaces each missing value with a set of m=5 plausible possibilities. The set of these possibilities represent the uncertainty about the unobserved 'true' value that was imputed. The *imputation model* uses observed data to assist in the prediction of the missing data. Then, the m full datasets (with the imputation) are analyzed by the selected *inferential statistical model* separately. The inference is conducted by combining the m point estimates and their variance into a single test as described below.

The exploratory efficacy endpoints, SANDE VAS Score, Keratograph Ocular Redness Score (ORS), Validated Bulbar Redness (VBR) scores, and Intraocular Pressure(IOP) outcome will then be derived out of their respective imputed data set as follows.

The 5 datasets will be summarized to one data set that includes the exploratory efficacy endpoint score average across all datasets for each patient and each time point separately. On the summarized dataset, a change from baseline will be calculated. Finally, the inferential model of the exploratory efficacy endpoints will be applied according to the SAP section 4.3.11.

At a minimum, the set of covariates that will be incorporated into the imputation model is treatment group.

The MI will be conducted in three steps:

Step I: Imputation of Intermediate Missing Data

```
/**Pseudo code to perform Multiple Imputation, with example of SANDE VAS parameter**/
*Format for visit;
PROC FORMAT;
 VALUE vis 1.5 = 'BL'
 2 = 'DAY 28'
 3= 'Day 56'
 4= 'Day 84'
 5= 'Day 105';
RUN;

*Filter data of SANDE VAS parameter and post baseline scheduled visits;
*Transpose to horizontal structure for the parameter SANDE VAS;
PROC TRANSPOSE DATA=sande OUT=onepersub PREFIX=sande;
      BY subjid trt01p paramcd param;
      ID avisitn;
      VAR aval;
RUN;

* Step 1a: Imputation of Intermediate Missing Data;
proc mi data=onepersub out=outds
        nimpute=5 seed=3102017 /*Seed number was based on protocl ID*/
        minimum = 0 0 0 0 /*This will be based on the range of the analysis variable*/
        maximum =  100 100 100 100 /*This will be based on the range of the analysis variable*/
       ROUND =  0.1 0.1 0.1 0.1; /*This will vary bsaed on the analysis variable*/;
var  sande2 sande3 sande4 sande5;
mcmc chain=multiple impute=monotone; /*To impute the intermediate missing data and
make the remaining missingness as monotone*/
run;
```

Step II: Imputation of Withdrawal Missing Data

```
* Step 1b: Imputation of Withdrawal Missing Data;
proc mi data=outds OUT = outds2
nimpute=1 /*Since we already have the 5 imputations from previous step, imputing only once here*/
minimum =. 0 0 0 0 /*This will be based on the range of the analysis variable*/
maximum = . 100 100 100 100 /*This will be based on the range of the analysis variable*/
ROUND = . 0.1 0.1 0.1 0.1; /*This will vary bsaed on the analysis variable*/
class trt01p;
var trt01p sande2 sande3 sande4 sande5;
monotone reg(sande2 sande3 sande4 sande5/ details);
run;

*Step 2a - transpose back to vertical structure;
PROC TRANSPOSE DATA=outds2 OUT=back;
      BY _imputation_ subjid trt01p paramcd param;
      VAR sande2 sande3 sande4 sande5;
RUN;

*Clean up;
DATA _mi;
      SET back;
      *Rederive avist/avisitn;
      avisitn=INPUT(COMPRESS(_name_, 'sande'), BEST.);
      avisit=PUT(avisitn, VIS.);
      DROP _name_;
RUN;

*Sort for merge with original data;
PROC SORT DATA=_mi;
      BY subjid avisitn aval;
RUN;

*Flag imputed records;
DATA mi (RENAME=(_imputation_=imputeno));
      MERGE _mi(IN=mi) sande (IN=observed KEEP=subjid avisitn aval);
      BY subjid avisitn aval;
      IF mi AND NOT observed THEN dtype='MI';
RUN;
```

Step III: Inference

```
*Sort for analysis step;
PROC SORT DATA=mi;
 BY imputeno avisitn subjid;
RUN;

*Step 2b - Analysis step;
/*ods trace on;*/
PROC TTEST DATA=mi ci=equal;
  class trt01p;
  where trt01p in ("COMBO","MONO"); /*selecting only two for pairwise comparison, for
other comparisons change the values*/
  VAR aval;
  BY imputeno avisitn;
  ODS OUTPUT statistics=diffbyvis2;
RUN;
```

```
/*ods trace off;*/
DATA formianalyze2;
      SET diffbyvis2;
      where upcase(class) eq "DIFF (1-2)";
      keep imputeno avisitn mean stderr;
RUN;

*Step 3 - Pooling step;
PROC SORT DATA=formianalyze2;
      BY avisitn imputeno;
RUN;

ODS OUTPUT PARAMETERESTIMATES=diffestvisi2;
PROC MIANALYZE DATA=formianalyze2;
      BY avisitn;
      MODELEFFECTS mean;
      STDERR stderr;
RUN;
ODS OUTPUT CLOSE;
/****the following estimates to be presented in the outputs based on MI**********/
      *Point estimate, StdErr, Confidence interval, Minimum, Maximum, p-value;
/*******************************************************************************/
```

Step IV: Sensitivity analysis for the exploratory efficacy endpoints

```
*For Sensitivity Analyses, Follow above procedure until step 1a and from Step 1b
onwards till Step 3 follow below code;

* Step 1b: Imputation of Withdrawal Missing Data with MNAR;
proc mi data=outds OUT = outsense
nimpute=1 /*Since we already have the 5 imputations from previous step, imputing only once here*/
minimum =. 0 0 0 0 /*This will be based on the range of the analysis variable*/
maximum = . 100 100 100 100 /*This will be based on the range of the analysis variable*/
ROUND = . 0.1 0.1 0.1 0.1; /*This will vary bsaed on the analysis variable*/
class trt01p;
monotone reg(sande2 sande3 sande4 sande5 /details );
mnar  adjust (sande2  /scale=0.9 );
mnar  adjust (sande3  /scale=0.9 );
mnar  adjust (sande4  /scale=0.9 );
mnar  adjust (sande5  /scale=0.9 );
var trt01p sande2 sande3 sande4 sande5;
run;

PROC SORT DATA= outsense;
      BY _imputation_ subjid trt01p paramcd param;
RUN;



*Step 2a - transpose back to vertical structure;
PROC TRANSPOSE DATA=outsense OUT=back2;
      BY _imputation_ subjid trt01p paramcd param;
      VAR sande2 sande3 sande4 sande5;
RUN;
```

```
*Clean up;
DATA _mi2;
      SET back2;
      *Rederive avist/avisitn;
      avisitn=INPUT(COMPRESS(_name_, 'sande'), BEST.);
      avisit=PUT(avisitn, VIS.);
      DROP _name_;
RUN;

*Sort for merge with original data;
PROC SORT DATA=_mi2;
      BY subjid avisitn aval;
RUN;

*Flag imputed records;
DATA mi2 (RENAME=(_imputation_=imputeno));
      MERGE _mi2(IN=mi) sande (IN=observed KEEP=subjid avisitn aval);
      BY subjid avisitn aval;
      IF mi AND NOT observed THEN dtype='MI';
RUN;

*Sort for analysis step;
PROC SORT DATA=mi2;
 BY imputeno avisitn subjid;
RUN;

*Step 2b - Analysis step;
/*ods trace on;*/
PROC TTEST DATA=mi2 ci=equal;
  class trt01p;
  where trt01p in ("COMBO","MONO"); /*selecting only two for pairwise comparison,
for other comparisons change the values*/
  VAR aval;
  BY imputeno avisitn;
  ODS OUTPUT statistics=diffbyvis3;
RUN;

/*ods trace off;*/
DATA formianalyze3;
      SET diffbyvis3;
      where upcase(class) eq "DIFF (1-2)";
      keep imputeno avisitn mean stderr;
RUN;

*Step 3 - Pooling step;
PROC SORT DATA=formianalyze3;
      BY avisitn imputeno;
RUN;

ODS OUTPUT PARAMETERESTIMATES=diffestvisi3;
PROC MIANALYZE DATA=formianalyze3;
      BY avisitn;
      MODELEFFECTS mean;
      STDERR stderr;
RUN;

ODS OUTPUT CLOSE;
```

```
/****the following estimates to be presented in the outputs based on MI**********/
      *Point estimate, StdErr, Confidence interval, Minimum, Maximum, p-value;
/*******************************************************************************/
```

The results of this sensitivity analysis will then be compared with the results of the MCAR analyses. If the results agree, then one can say that the result is robust for the choice of difference in parameter values. All the results of sensitivity analysis of the efficacy and safety parameters will be presented in the supplemental Tables of the respective parameter analysis. Results (Estimates) from the SAS LST output will be presented in the supplemental table outputs. No formal Table shell is required to report the results of sensitivity analysis.

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