STATISTICAL ANALYSIS PLAN

Document Title:	OCU-300-301 Statistical Analysis Plan
Study Title:	A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate Nanoemulsion Eye Drops in Patients with ocular Graft-vs-Host Disease (oGVHD)
Protocol Number:	OCU-300-301 (25May2018) and Amendment 1(15 Sep2018)
Study Phase	Phase III
Product Name:	OCU300 (Brimonidine Tartrate Ophthalmic Nanoemulsion 0.18%)
Sponsor:	**Ocugen, Inc**. 5 Great Valley Parkway, Suite 160 Malvern, PA 19355 USA
Prepared by	Brightech International LLC 285 Davidson Avenue, Suite 504 Somerset, NJ 08873, USA

REVISION HISTORY

Version 1.0	August 23, 2018
Version 2.0	January, 2020
Version 2.1	May, 2020, updated the list of TFLs for interim analysis in Appendix .

Signature

I have carefully read this statistical analysis plan and agree to the described methods and proceedings.

Authorized Signatory:

[redacted], **Ocugen, Inc.**

[redacted]		
Name	Signature	Date

Designated CRO Authorized Representative, Brightech International LLC, Project Biostatistician

Name	Signature	Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABREVIATIONS

Table 1. List of Abbreviations

Abbreviation or specialist term	Explanation
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AEI	Adverse events of interest
ATC	Anatomic-Therapeutic-Chemical
BCVA	Best corrected visual acuity
BID	Twice daily
CD34+	Transmembrane phosphoglycoprotein; protein encoded by the CD34 gene
CFR	Code of Federal Regulations
CFS	Corneal fluorescein staining
CGI	Clinical Global Impression
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel test
CRF	Case report form
DBP	Diastolic blood pressure
ECM	Extracellular matrix
eCRF	Electronic case report form
EDTRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FGF2	Fibroblast growth factor
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GVHD	Graft-vs-Host Disease
HR	Heart rate

Abbreviation or specialist term	Explanation
ICD	Informed consent document
ICH	International Conference on Harmonization
IND	Investigational New Drug Application
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LG	Lissamine Green
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
MMRM	Mixed model of repeated measurements
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NEI	National Eye Institute
NIH	National Institute of Health
OBS	Ophthalmic Buffered Saline
OD	Right eye
ODD	Orphan Drug Designation
ODS	Ocular Discomfort Score
oGVHD	Ocular Graft-vs-Host Disease
OR	Ocular surface redness
OS	Left eye
OSDI	Ocular Surface Disease Index
OTC	Over-the-counter
OU	Both eyes
PI	Principal Investigator
PP	Per-protocol
PRO	Patient-reported outcomes
QSR	Quality System Regulations
SAE	Serious adverse event

Abbreviation or specialist term	Explanation
SANDE	Symptom Assessment iN Dry Eye
SAP	Statistical Analysis Plan
SAR	Suspected adverse reaction
SBP	Systolic blood pressure
SD	Standard deviation
SGA	Subject Global Assessment
SOP	Standard Operating Procedure
SUSAR	Serious and unexpected suspected adverse reaction
TEAE	Treatment-emergent adverse event
TGF-β	Transformed growth factor-beta
UAR	Unexpected Adverse Reaction
UCVA	Uncorrected Visual Acuity
USA	United States of America
VAS	Visual Analog Scale
VBR	Validated Bulbar Redness
WHO	World Health Organization
WOCP	Women of child-bearing potential

1. INTRODUCTION

This SAP is a detailed technical extension of the clinical Study Protocol and follows the principles of the International Conference on Harmonization (ICH) guidelines E3, E6 and E9 and the relevant Working Instructions (WIs) and Standard Operating Procedures (SOPs).

The purpose of the SAP is to ensure the appropriate analysis of the study data by using pre-specified statistical approaches to the analysis prior to the database lock.

Any further changes to the protocol or CRF may necessitate updates to the SAP. This SAP was written as a separate document, completed after finalizing the protocol, and prior to locking and unblinding the clinical datasets. This SAP includes a more technical and detailed elaboration of the statistical analyses stated in the protocol.

The statistical analyses will be conducted using the SAS® software version 9.4 or later

2. STUDY DESIGN

2.1. Overall Study Design

This will be a randomized, placebo-controlled, double-masked, multicenter phase 3 study in the United States conducted in approximately 15 centers. Upon meeting the eligibility criteria, enrolled subjects with a diagnosis of definite oGVHD will be randomly assigned in a 2:1 (test: control) fashion to receive either Brimonidine Nanoemulsion Eye Drops 0.18% investigational product (test) or ophthalmic buffered saline (placebo).

Up to 5 study visits are planned: including a screening period (Day -7 to 0), and four on-therapy visits at Day 1, Day 28 ± 7 days (Week 4), Day 56 ± 7 days (Week 8), and Day 84 ± 7 days (Week 12) (See Table 2).

Subjects will receive the first dose of medication on Day 1 at the study site. Study medication will be dispensed to subjects at each study visit (except the Day 84 visit) for self-administration during the study, beginning with the Day1 Visit.

Subjects will be provided with diaries to record twice daily dosing. Doses should be administered approximately 12 hours apart.

2.2. Study Objectives

The primary objective of this study is to evaluate the safety, tolerability, and efficacy of Brimonidine Nanoemulsion Eye Drops for the treatment of ocular redness and ocular discomfort in patients with ocular oGVHD.

2.3. Study Endpoints

2.3.1 Co-primary Endpoints

Two primary efficacy endpoints will be tested:

- Ocular Redness based on a 100-point Validated Bulbar Redness (VBR) scale measuring change in appearance from baseline (pre-dose) to Day 84
- Ocular discomfort based on a 10-point Visual Analog Scale (VAS) measuring change in intensity from baseline (pre-dose) to Day 84

2.3.2 Secondary Endpoints

Change in Symptom Assessment iN Dry Eye (SANDE) questionnaire scores from baseline to Day 84

2.3.3 Exploratory Endpoints

- Change from baseline in Validated Bulbar Redness (VBR) score at Days 28 and 56
- Change from baseline in Ocular Discomfort Score at Days 28 and 56
- Change from baseline in OSDI at 12 weeks (Day 84)
- Change from baseline in corneal fluorescein staining at 12 weeks (Day 84)
- Change from baseline in corneal lissamine green (LG) staining at 12 weeks (Day 84)
- Change from baseline in conjunctival lissamine green (LG) staining at 12 weeks (Day 84)
- Change from baseline in tear secretion as measured by Schirmer's test
- Clinical global impression of change in signs and symptoms from baseline (physician's rating)
- Subject global assessment of overall change from baseline (subject's rating)

3 STUDY SCHEDULE

The study schedule can be found on Table 2

Table 2. Study of Schedule of Events

	Screening and Baseline Visit*		**Dosing and Evaluation**		
Visit number					
Day (Time)	Day –7 to Day –0	Day 1 (Baseline)	Day 28 ± 7d (Week 4)	Day 56 ± 7d (Week 8)	Day 84 ± 7d (Week 12)
Informed consent	X				
Eligibility criteria	X	X			
Demographic Information	X				
Medical/surgical/ocular history[1]	X				
Body weight and height[2]		X			
Vital signs (body temperature, heart rate, blood pressure, respiratory rate)[3]		X	X	X	X
Review of prior and concomitant medications[4]	X	X	X	X	X
Urine collection and Pregnancy test (females of childbearing capacity only; hCG dipstick)[5]	X	X	X	X	X

	Ocular Discomfort 10-point VAS[6]	X	X	X	X	X
	OSDI; ocular surface disease index (points)[7]	X	X	X	X	X
	Visual acuity[8]		X	X	X	X
	Symptom Assessment in Dry eye (SANDE)[9]		X	X	X	X
	Ocular redness 100 -point VBR scale via slit lamp[10]	X	X	X	X	X
	Conjunctival Injection (points)[11]	X				
	Slit lamp ophthalmic exam	X	X	X	X	X
	Corneal fluorescein stain (CFS; points)[12]	X				
	Corneal fluorescein stain (NEI scale)[13]		X	X	X	X
	Corneal Lissamine green[14]		X	X	X	X
	Conjunctival Lissamine green stain[15]		X	X	X	X
	Schirmer's test with anesthesia (mm, points)[16]	X	X	X	X	X
	Intraocular pressure[17]	X	X	X	X	X
	Clinical Global Impression (CGI)			X	X	X
	Subject Global Assessment (SGA)			X	X	X
Randomization			X			
Dispense/Instill Investigative Product			X[18]	X	X	
Adverse event surveillance		X	X	X	X	X
Diary recording and review[19]			X	X	X	X

*Maximum 7-day screening period prior to randomization. Duplication of assessments during this period is not required; however, results of some assessments (e.g. corneal fluorescein staining) will be used for both screening and baseline purposes.

1. The ocular history will include any previously diagnosed ophthalmic abnormalities and ocular surgeries (including laser procedures).
2. BMI to be auto-calculated from weight and height using the BMI formula; BMI= (Weight in pounds/ (Height in inches X Height in inches)) x 703
3. Baseline Vital signs on Day 1 to be completed at least 30 ± 10 mins before dose on Day 1. All other vitals to be completed before ocular assessments on Days 28, 56, and 84
4. Review of prior and concomitant medications and regimens will occur at all study visits. Corticosteroid-containing eye drops are not allowed within 14 days prior to Screening or during the study. Subjects will be permitted to continue all their current ocular treatments, including the use of artificial tears, eyelid massage, punctal plugs, or warmcompresses, if they commit to using the same brand/regimen throughout the study. None of the ocular treatments, whether OTC or prescription (e.g. Restasis® ,Xiidra® or Cequa®) or study medication should be used within 5 minutes of another ocular treatment during the study. Study medication should not be used within 2 hours prior to any study visit. If a punctal plug is lost during the study, it may be replaced.
5. hCG = human chorionic gonadotrophin. A urine pregnancy test is required at screening. A urine pregnancy test may be performed at any time during study participation if pregnancy is suspected.
6. To evaluate intensity of Ocular Discomfort, patients will be asked to rate their worst ocular pain/discomfort in the preceding 24 hours using a 10-point scale ranging from "None" (score 0 to "Unbearable/Excruciating" (score 10).

7. OSDI will be completed at all visits and is assessed on a scale of 0 to 100, with higher scores representing greater disability. In determining subject eligibility, 0-3 points will be assessed based on the score. (Ogawa, 2013)
8. Subjects should use the most recent correction to attain their best-corrected visual acuity (BCVA).
9. The SANDE questionnaire measures symptom frequency ("rarely" to "all of the time") and symptom severity ("very mild" to "very severe.") on a visual analogue scale (VAS). Subjects will complete this scale on Day 1 prior to first dose (Baseline), Day 28, Day 56, and Day 84.
10. Injection in the bulbar conjunctiva (nasal and temporal; OS and OD) of the subject's eyes will be evaluated via slit-lamp examination and compared to the reference images in the VBR and graded accordingly. The same grader should assess each time at the slit lamp and use identical lighting conditions.
11. In determining subject eligibility, conjunctival injection grading of each eye, OS and OD, will be assessed, with Grade 0 = none [0 points]; Grade 1 = mild/moderate injection [1 point]; and Grade 2 = severe injection [2 points]. (Ogawa, 2013)
12. In determining subject eligibility, corneal fluorescein stain (CFS) grading of each eye, OS and OD, will be assessed, with Grade 0 = no staining [0 points], Grade 1 = minimal staining [1 point], Grade 2 = mild/moderate staining [2 points], Grade 3 = severe staining [3 points] (Ogawa, 2013)
13. Each eye (OS and OD) CFS=corneal fluorescein stain grading. Corneal staining will be graded in 5 zones in each eye using the NEI scale. Each zone will be graded from 0 to 3 based on the density of punctate staining (maximum score/eye =15)
14. Corneal lissamine green staining using a solution made from Lissamine Green Ophthalmic Strips. Corneal staining will be graded in 5 zones in each eye using the NEI scale. Each zone will be graded from 0 to 3 based on the density of punctate staining (maximum score/eye =15)
15. Conjunctiva lissamine green staining will be performed using a solution made from Lissamine Green Ophthalmic Strips. 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 using the NEI scale (maximum score/eye = 6).
16. Anesthetize each eye (OS and OD) with a drop of proparacaine. Insert Schirmer strips into lower lid for 5 min. If tearing exceeds 15 mm [0 points]; 11-15 min [1 point]; 6-10 mm [2 points]; ≤5 mm [3 points] (Ogawa, 2013).
17. Measure intraocular pressure using Goldman applanation tonometry.
18. Subjects will receive the first dose of medication on Day 1 at the study site and will instill the dose into both eyes before leaving the clinic, with oversight/training by site staff. Study medication will be dispensed to subjects at each study visit (except the Day 84 visit) for self-administration during the study.
19. Subject diaries must be reviewed by the study staff at each visit prior to the subject leaving the clinic.

4 STATISTICAL ANALYSIS PLAN

4.1 General Statistical Methods and Types of Analysis

In general, continuous variables will be presented as the number of non-missing values, mean, standard deviation, median, minimum, maximum, and quartiles. For categorical variables, descriptive statistics will include counts and percentages per category. Confidence intervals (CI) will be computed when appropriate, usually as 95% intervals.

In general, data will not be imputed with the exception of the primary and key secondary efficacy endpoints.

4.2 Power and Sample Size

The sample size is calculated based on limited data ([redacted], May 24, 2017) on OSDI/SGA (as proxy endpoints to ocular discomfort), and ocular redness score (as a proxy endpoint for VBR). With a two-sided alpha of 0.05, a sample size of 60 patients in a 2:1 randomization (40 in OCU300, 20 in control) would provide more than 90% power to detect a difference of 0.47 (SD 0.39) in the mean difference in change from baseline in the validated bulbar redness score (VBR). This sample size provides about 85% of power to detect a clinically meaningful difference in ocular discomfort as measured by the ocular discomfort score (ODS).

4.3 Analysis Populations

Safety Analysis Population

The safety set will be the primary analysis set for the safety endpoints and will include all subjects who have signed informed consent forms, were randomized into the study, and who took at least one dose of study drug.

Intent-to-treat (ITT) Population

The ITT set will be the primary analysis set for the efficacy endpoints and will include all randomized subjects.

Per-protocol (PP) Population

The PP population set will be tested to confirm the robustness of the primary analysis and will include all ITT subjects who have no major protocol violations.

4.4 Unit of Analysis

For eye-specific assessments (e.g., ocular redness), the unit of analysis for the efficacy measures will be the average of study-eligible eyes in each subject. Efficacy measures will be summarized using the average value between the two eyes within a subject and within a visit. For subject-level assessments (e.g. ocular discomfort), the unit of analysis for the efficacy measures will be the subject. Safety analyses will be performed on each eye separately (OD and OS) with the exception of adverse events, which will be presented at the subject level, where ocular adverse events will be considered as occurring if either eye had the adverse event. Safety measures captured at the subject level will be summarized at the subject level.

4.5 Definition of Baseline Value

The last non-missing value prior to the first dose, or the last non-missing value prior to the randomization date if the subject was randomized but not treated, is considered the baseline value.

4.6 Patient Disposition

The number of subjects screened (who signed informed consent form), number of screen failures and number of subjects who were randomized, who were treated, will be summarized.

The number of subjects who completed study, who early discontinued from study after randomization will be summarized by treatment. The percentages will be calculated with the number of randomized subjects as denominator. The reasons for early discontinuation from the study will also be summarized.

4.7 Patient Characteristics

Demographic and baseline disease characteristics will be summarized by treatment and listed for the Intent-to-Treat, Safety, and Per-Protocol populations separately.

4.8 Concomitant Therapy

The concomitant medications will be summarized by treatment for the ITT Population. The concomitant therapies will be mapped using the World Health Organization (WHO) DRUG dictionary will be further classified using Anatomic-Therapeutic-Chemical (ATC) codes for reporting purposes.

4.9 Efficacy Analysis

4.5.1 Primary Efficacy Analyses

The primary evaluation of efficacy will be a co-primary endpoint of and bulbar redness as measured by VBR and ocular discomfort as measured by the ODS after 14 weeks dosing (Day 84). The primary efficacy analysis will be performed on the Intent-to-Treat population.

The following two sets of hypotheses will be tested as the primary hypotheses of the study.

Hypothesis

The statistical hypotheses for the primary endpoint of the mean change from baseline bulbar redness score (VBR) at 14 weeks (Day 84) are as follows:

H_{01}: The difference (OCU 300 minus placebo), between study eyes treated with the OCU 300 and study eyes treated with placebo (OBS) in the mean change from baseline VBR score at 14 weeks (Day 84) = 0.

H_{A1}: The difference (OCU 300 minus placebo), between study eyes treated with the OCU 300 and study eyes treated with placebo in the mean change from baseline VBR score at 14 weeks (Day 84) ≠ 0.

The statistical hypotheses for the primary endpoint of the mean change from baseline ocular discomfort score (ODS) at 14 weeks (Day 84) are as follows:

H_{02}: The difference (OCU 300 minus placebo), between subjects treated with the OCU 300 and subjects treated with placebo (OBS) in the mean change from baseline ODS at 14 weeks (Day 84) = 0.

H_{A2}: The difference (OCU 300 minus placebo), between subjects treated with the OCU 300 and subjects treated with placebo (OBS) in the mean change from baseline ODS at 84 weeks (Day 84) ≠ 0.

To control family-wise type I error, the primary endpoints will be tested with the Hochberg procedure:

- If the p-values for both VBR and ODS are less or equal to 0.05, then both null hypotheses will be rejected, and alternative hypotheses claimed;
- If the p-value for either parameter VBR or ODS is greater than 0.05, then a p-value of 0.025 will be required to reject the null hypothesis for the test on the other parameter;

The primary efficacy analyses will be conducted on the ITT population and the comparison will be made based on the randomized treatment. The same set of efficacy analyses will also be performed on the per-protocol population. For efficacy endpoints where measurements from both eyes are available, a single mean will be calculated for the analyses. For continuous endpoints, the change from baseline will be summarized with descriptive statistics for the values at baseline, values at each time point (Days 28, 56 and 84), and for the change from baseline at each time point for the set of patients who have data at both the baseline and the time point being assessed. The percent change from baseline may also be summarized in a similar manner.

Primary and key secondary continuous endpoints will be analyzed using a mixed model of repeated measurements (MMRM) under a missing at random (MAR) assumption. The model will use an unstructured covariance matrix and include treatment, visit, and visit-by-treatment interaction as fixed terms. From this model, the by-visit results will be presented.

The SAS code for the analysis will be:

```
proc mixed;
    class subject treatment visit;
          model Y  = baseline treatment visit
                       treatment*visit;
          repeated time /  sub = subject type = un;
          lsmeans treatment*visit /slice=visit  cl ;
          estimate 'treatment difference at visit' treatment -1 1
                                                  treatment * visit  0  0  0  0   -1 1
                                                                     0  0 -1 1    0   0
                                                                    -1 1  0  0     0  0/cl;
run;
```

4.5.2 Secondary Efficacy Analysis

Change in Symptom Assessment iN Dry Eye (SANDE) questionnaire scores from baseline to Day 84.

This variable will be analyzed using a mixed model of repeated measurements (MMRM) under a missing at random (MAR) assumption, similar to the analysis for the primary endpoints.

4.5.3 Exploratory Efficacy Analysis

The following exploratory efficacy variables will be analyzed to compare OCU 300 versus control. Continuous variables will be analyzed using a mixed model of repeated measurements (MMRM) under a missing at random (MAR) assumption, similar to the analysis for the primary endpoints. CMH tests will be performed on categorical variables:

- Change from baseline in Validated Bulbar Redness (VBR) score at Days 28 , 56 and 84
- Change from baseline in Ocular Discomfort Score at Days 28 , 56 and 84
- Change from baseline in OSDI at Days 28, 56 and at 12 weeks (Day 84)
- Change from baseline in corneal fluorescein staining at Days 28, 56 and at 12 weeks (Day 84)

- Change from baseline in corneal lissamine green (LG) staining at Days 28, 56 and at 12 weeks (Day 84)
- Change from baseline in conjunctival lissamine green (LG) staining at Days 28, 56 and at 12 weeks (Day 84)
- Change from baseline in tear secretion as measured by Schirmer's test at Days 28 , 56 and 84
- Clinical global impression of change in signs and symptoms from baseline (physician's rating) at Days 28 , 56 and 84
- Subject global assessment of overall change from baseline (subject's rating) at Days 28 , 56 and 84

4.5.4 Missing Data

Primary and key secondary continuous endpoints will be analyzed using a mixed model of repeated measurements (MMRM) under a missing at random (MAR) assumption. A sensitivity analysis using pattern-mixture model with control- based pattern imputation will be performed to compare with the results of the primary analysis.

Exploratory analyses will be based on observed data. Missing data will not be imputed.

4.5.5 Sensitivity Analysis

A sensitivity analysis using pattern-mixture model with control- based pattern imputation (as described by B. Ratitch, M. O'Kelly, 2011) will be performed to compare with the results of the primary analysis. Multiple (100) imputations will be performed (using proc mi, in SAS) and the analyzed using proc mixed). The results will be combined (using proc mianalyze in SAS) using Rubin's method (Rubin, 1987).

4.5.6 Categorical Variable Analysis

For categoric endpoints, such as the severity scores, the analysis will be performed by using the Cochran–Mantel–Haenszel test (CMH) method controlling for baseline scores. The null hypothesis for categorical endpoints is that there is no association between the treatment assignment and the outcomes for each category, the alternative hypothesis is that there is association

The typical SAS code will be

```
proc freq data=indata;
 tables Treatment*Response / cmh;
  run;
```

4.6 Interim Analysis and Sample Size Re-Estimation

Since the sample size is calculated using indirect information, a sample size re-estimation is planned at an interim analysis when data from 50% of patients are available. If the conditional power is less than 90%, the sample size will be increased to provide sufficient power. To control type I error, a two-sided alpha of 0.0002 (0.0001 one-sided) will be spent at the interim analysis, and the two-sided alpha for the final analysis will be 0.0498 (one-sided 0.0249). If sample size is modified, the final critical value of 0.0498 will be adjusted to control type I error.

Table 3. Critical Values for Interim Analysis

Time	Critical value	Nominal alpha	Cumulative alpha
0.5	3.7190	0.0001	0.0001
1	1.9617	0.0249	0.025

If the sample size is modified, the final critical value will be adjusted according to Gao, Ware, Mehta (2008) to control type I error. The final analysis will be based on Gao, Liu, Mehta (2013).

The planed analyses for interim analysis are listed in the Appendix.

4.7 Safety Analysis

All subjects who enter the study will be assessed for safety. Safety analyses will be performed on the Safety set. Safety parameters include ocular examinations, vital signs, AEs, and slit lamp examinations. Safety data will be reported for all patients that have signed informed consent forms.

Clinically significant negative changes from baseline will be analyzed as adverse events.

4.7.1 Adverse Events

An AE is defined as any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (ICH E6 Guidelines for GCP). Any medical condition that is present at the time that the subject is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class (SOC), by system organ class and preferred term (PT) , by system organ class, preferred term and maximal severity, by system organ class, preferred term and strongest relationship, and by system organ class preferred term, maximal severity, and strongest relationship. Separate summaries will be performed for ocular and non-ocular AEs. The treatment groups will be compared with respect to safety endpoints descriptively. No inferential comparison will be conducted.

The following AE summaries will be presented in tables:

- An overall summary of the AEs, including the number and percentage of patients reporting AE, the number and percentage of patients with AE possibly related or related to study treatment, number and percentage of patients reporting serious AE, the number and percentage of patients with serious AE possibly related or related to study treatment, the number and percentage of patients discontinuing

treatment due to AE, the number and percentage of patients' death due to AE, presented by treatment group.

- A breakdown of the number and percentage of patients reporting TEAEs, categorized by system organ class (SOC) and preferred term (PT), presented by treatment group.
- A breakdown of the number and percentage of patients reporting TEAEs, categorized by SOC and PT, presented by treatment group and severity.
- Number and percentage of patients reporting TEAEs, leading to treatment discontinuation, categorized by SOC and PT, presented by treatment group. Patients' TEAEs leading to treatment discontinuation will also be listed.
- Patients with TEAEs possibly related or related to study treatment, categorized by SOC and PT, presented by treatment group.
- Patients with TEAEs possibly related or related to study treatment, categorized by SOC and PT, presented by treatment group and severity.
- Number and percentage of patients reporting Serious AEs (SAEs), categorized by SOC and PT, presented by treatment group.
- Number and percentage of patients reporting Serious AEs (SAEs), categorized by SOC and PT, presented by treatment group and severity.

4.7.2 Ophthalmic Exam Findings

Number and percentage of subjects with normal, abnormal, clinically significant abnormal and non-clinically significant ophthalmic exam findings will be summarized by visit by treatment group.

4.7.3 Vital Signs

Descriptive statistics of patients' vital signs by treatment group and scheduled study visit will be summarized including number of patients, mean, standard deviation, median and range.

Individual values of vital signs will be listed.

4.8 Study drug administration

Study drug dosing record, missed doses of study drug together with the reason for the missed dosage will be listed.

4.9 Pharmacokinetic Analyses

None in this study

4.10 Visit Windows

Visit windows will be as described in the protocol: screening period (Day -7 to 0), Day 1, Day 28 ± 7 days (Week 4), Day 56 ± 7 days (Week 8), and Day 84 ± 7 days (Week 12). All data collected during study follow-up will be displayed and analyzed according to the actual visit data in the CRF. Assessments taken outside of windows described in the protocol will be displayed according to the CRF assessment recorded by the Investigator.

5. Appendix

The planned tables, figures and listings for interim analysis are listed below:

No.	Category	Title	Population
1	Table	Subject disposition and analysis population	All subjects screened
2	Table	Subject disposition and analysis population	Randomized Subjects of Study Disposition
3	Table	Subject disposition status by study site	All subjects screened
4	Table	Baseline demographics	SAF
5	Table	Baseline demographics	ITT Subjects of Study Disposition
6	Table	Baseline disease characteristics	SAF
7	Table	Baseline disease characteristics	ITT Subjects of Study Disposition
8	Table	Previous medications	ITT
9	Table	Concomitant medications	ITT
10	Table	Study-eligible Eye Validated Bulbar Redness Score- Summary Statistics, and MMRM Analyses of Change from Baseline	ITT Subjects of Study Disposition
11	Table	Ocular discomfort - Summary Statistics, and MMRM Analyses of Change from Baseline	ITT Subjects of Study Disposition
12	Table	Symptom Assessment iN Dry Eye (SANDE) - Summary Statistics, and MMRM Analyses of Change from Baseline	ITT Subjects of Study Disposition
13	Table	Overall Summary of Adverse Events	SAF
14	Table	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Ocular AE	SAF
15	Table	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Non-ocular AE	SAF
16	Table	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity -Ocular AE	SAF
17	Table	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity - Non-ocular AE	SAF
18	Table	Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term -Ocular AE	SAF
19	Table	Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term -Non-ocular AE	SAF
20	Table	Treatment-Emergent Adverse Events Related or Probably Related to Study Treatment by System Organ Class and Preferred Term -Ocular AE	SAF
21	Table	Treatment-Emergent Adverse Events Related or Probably Related to Study Treatment by System Organ Class and Preferred Term -Non-ocular AE	SAF

No.	Category	Title	Population
22	Table	Treatment-Emergent Adverse Events Related or Probably Related to Study Treatment by System Organ Class, Preferred Term and Sevirity -Ocular AE	SAF
23	Table	Treatment-Emergent Adverse Events Related or Probably Related to Study Treatment by System Organ Class, Preferred Term and Sevirity -ocular AE	SAF
24	Table	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term-Ocular AE	SAF
25	Table	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term-Non-ocular AE	SAF
26	Table	Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Severity-Ocular AE	SAF
27	Table	Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Severity-Non-ocular AE	SAF
28	Table	Treatment-Emergent Serious Adverse Events Related or Probably Related to Study Treatment by System Organ Class and Preferred Term-Ocular AE	SAF
29	Table	Treatment-Emergent Serious Adverse Events Related or Probably Related to Study Treatment by System Organ Class and Preferred Term-Non-ocular AE	SAF
30	Table	Treatment-Emergent Adverse Events with Fatal Outcome-Ocular AE	SAF
31	Table	Treatment-Emergent Adverse Events with Fatal Outcome-Non-ocular AE	SAF
32	Table	Treatment-Emergent Adverse Events Related or Probably Related to Study Treatment with Fatal Outcome-Ocular AE	SAF
33	Table	Treatment-Emergent Adverse Events Related or Probably Related to Study Treatment with Fatal Outcome-Non-ocular AE	SAF
34	Figure	Study-eligible Eye Validated Bulbar Redness Score – LS Mean of Change from Baseline	ITT Subjects of Study Disposition
35	Figure	Ocular discomfort – LS Mean of Change from Baseline	ITT Subjects of Study Disposition
36	Figure	Symptom Assessment iN Dry Eye (SANDE) – LS Mean of Change from Baseline	ITT Subjects of Study Disposition
37	Listing	Subject disposition	Randomized patients
38	Listing	Screen failures and withdrawals prior to randomization	Non-randomized subjects
39	Listing	Analysis populations and reasons for exclusion	Randomized patients
40	Listing	Demographics	ITT
41	Listing	Diagnosis of Definite oGVHD	ITT
42	Listing	Previous and concomitant medications	ITT
43	Listing	Validated Bulbar Redness	ITT
44	Listing	Ocular Discomfort	ITT
45	Listing	Symptom Assessment iN Dry Eye (SANDE)	ITT
46	Listing	Listing of non-treatment-emergent ocular adverse events	SAF

No.	Category	Title	Population
47	Listing	Listing of non-treatment-emergent non-ocular adverse events	SAF
48	Listing	Listing of treatment-emergent ocular adverse events	SAF
49	Listing	Listing of treatment-emergent non-ocular adverse events	SAF
50	Listing	Listing of treatment-emergent serious ocular adverse events	SAF
51	Listing	Listing of treatment-emergent serious non-ocular adverse events	SAF

Note: SAF = Safety Population; ITT = Intent-to-treat Population.

Study disposition: a subject has either “Yes” or “No” for the header question “Did the subject complete the study?” on the “Study Completion” CRF page.

REFERENCES

- Ratitch, B., O'Kelly M.: Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures , 2011. PharmaSUG2011 - Paper SP04. 2011. https://pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP04.pdf
- Rubin, D.B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, Inc.
- Gao, P. , Ware, J.H. , Mehta, C., (2008), Sample size re-estimation for adaptive sequential designs. Journal of Biopharmaceutical Statistics, 18: 1184–1196, 2008
- Gao,P., Liu, L.Y., and Mehta C. (2013). Exact inference for adaptive group sequential designs . Statistics in Medicine . 32 3991–4005, 2013