CLINICAL STUDY PROTOCOL

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
Investigational:	OCU300 (Brimonidine Tartrate Ophthalmic Nanoemulsion 0.18%)
Version:	Amendment 1 (07 Dec 2018)
IND Applicant/Product Sponsor:	Ocugen, Inc. 5 Great Valley Parkway, Suite 160 Malvern, PA 19355 USA
Authorized Signatory:	[redacted] Ocugen, Inc. 5 Great Valley Parkway, Suite 160 Malvern, PA 19355 USA Telephone: [redacted] Fax: [redacted] E-mail: [redacted]

Table 1. Administrative Structure

Medical Monitor: **(24-hour emergency contact)**	[redacted] [redacted] - Office [redacted] – Cellular 24-hour contact: [redacted] Email: [redacted]
Biostatistician:	[redacted] Brightech International LLC 285 Davidson Ave., Suite 504 Somerset, NJ 08873 Email: [redacted]
Serious Adverse Event Reporting:	[redacted] [redacted] G2 BioPharma Services, Inc. 3637 Brunswick Pike Princeton, NJ 08540 Email: [redacted] Phone: [redacted] SAE Fax Number (US): [redacted] SAE Hot Line Number (US): [redacted]

PRINCIPAL INVESTIGATOR'S SIGNATURE

I have received and read the Investigator's Brochure for Brimonidine. I have read protocol OCU-300-301 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Principal Investigator

_____

Title of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

SPONSOR'S SIGNATURE

Approved by:

[redacted]

Ocugen, Inc.

01 November 2019
Date

PROTOCOL REVISION HISTORY

Table 2. Revision History

Version Number	Version date	Summary of Revisions Made	
		Major	**Administrative**
Version 1.0	25 May 2018		
Amendment 1	07 Dec 2018	The Diagnosis of Definite oGVHD using the International Chronic Ocular GVHD Consensus Group revised diagnostic criteria was adapted for use in this protocol (Appendix 1, Section 18.1) The Diagnosis of Definite oGVHD, using the International Chronic Ocular GVHD Consensus Group revised diagnostic criteria language has been clarified to indicate "in at least one eye". The protocol schedule of events was updated to clarify that screening procedures that are also to be done at the baseline D1 visit do not need to be duplicated if the screening visit and baseline D1 visit occur on the same day. "Change from baseline in corneal lissamine green (LG) staining at 12 weeks (Day 84)" added as exploratory endpoint. "Received corticosteroid-containing eye drops within 14 days prior to Screening visit or planned use during study" has been added to exclusion criteria. "Validated Bulbar Redness score ≥ 40" inclusion criteria language has been updated to indicate in both eyes	All page numbers have been updated to reflect the updated protocol. The list of abbreviations was updated to include additional items. The sponsor medical monitor and corresponding contact information were updated. The sponsor safety representative and corresponding contact information were updated. The previously listed medical writer and corresponding contact information were removed from the protocol.

		Use of contact lenses exclusion criteria has been updated to exclude use within 14 days of screening visit and any time during the study. For subject-level assessments (e.g. ocular discomfort), the unit of analysis for the efficacy measures will be the subject ITT population simplified to "all randomized subjects" Section 4.5 was updated to include additional information regarding which assessments are to be completed at the subject early termination/discontinuation visit. Exclusion #2 was updated to exclude all Glaucoma management treatments. The study procedure schedule/schedule of events was updated to show that a review of prior and concomitant medications will take place at all in-clinic visits. The study procedure schedule/schedule of events was updated to show that a urine pregnancy test will be collected at all in-clinic visits. Section 18.9 (Appendix 9) Visual Acuity was simplified	

Synopsis

Protocol 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
Clinical Phase: Phase 3
IND Applicant/Product Sponsor: Ocugen, Inc. 5 Great Valley Parkway, Suite 160 Malvern, PA 19355 USA Telephone: [redacted] Fax: [redacted]
Authorized Signatory: [redacted]
Regulatory IND Number: 136917
Indication: Treatment of ocular redness and ocular discomfort in patients with oGVHD
Investigational Drug: Brimonidine Tartrate Nanoemulsion 0.18% Ophthalmic Solution (OCU300).
Control: Placebo (ophthalmic buffered saline; OBS, pH 6-8)
Primary Objective(s): • To evaluate the safety, tolerability, and efficacy of Brimonidine Nanoemulsion Eye Drops in Patients with ocular Graft-vs-Host Disease (oGVHD)
Primary Efficacy Endpoint(s): • Ocular redness based on a 100-point Validated Bulbar Redness (VBR) scale measuring change in appearance from baseline to Day 84 • Ocular discomfort based on a 10-point Visual Analog Scale (VAS) measuring change in intensity from baseline to Day 84

Secondary Efficacy Endpoint(s):

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

Safety Endpoint(s):

- Rate of ocular adverse events (AEs)

Exploratory Endpoint(s):

- Change from baseline in in Validated Bulbar Redness (VBR) score at Days 28 and 56
- Change from baseline in 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)

Investigational Products
Investigational Drug Dosage:

One drop of Brimonidine Tartrate Nanoemulsion 0.18% administered in each eye, two times/day (bid)

Control Dosage:
One drop of ophthalmic buffered saline administered in each eye, two times/day (bid)

Study Population
Inclusion Criteria:

Subjects must meet **all** the following criteria to participate in the study:

1. Men and women ≥ 18 years of age
2. Diagnosis of 'definite' oGVHD using the International Chronic Ocular GVHD Consensus Group revised diagnostic criteria (see Appendix I) in at least one eye
3. Ocular Discomfort Score ≥ 3
4. Validated Bulbar Redness score ≥ 40 in both eyes
5. Subjects who are capable and willing to provide informed consent and follow study instructions
6. Intraocular pressure (IOP) ≥5 mmHg and ≤22 mmHg in each eye
7. Women who satisfy one of the following:
    a) Are of child-bearing potential (WOCP) who are not pregnant or lactating at the screening visit; and who are either abstinent or sexually active on an acceptable method of birth control (oral contraceptive pills, birth control implants/shots or patches, barrier methods) for at least 4 weeks prior to baseline visit (Day 1) and throughout the study, Or
    b) Are post-menopausal or have undergone a sterilization procedure

Exclusion Criteria:

Subjects will not be eligible for the study if **any** of the following criteria are met:

1. Allergic to brimonidine or any similar products, or excipients of brimonidine
2. Currently receiving brimonidine or other treatment for glaucoma
3. Receiving or have received any experimental or investigational drug or device within 30 days prior to Screening visit
4. Use of contact lenses within 14 days prior to Screening visit or planned use during study
5. Active ocular infection or ocular allergies
6. Any history of eyelid surgery or ocular surgery within the past 3 months
7. Corneal epithelial defect larger than 1 mm^2 in either eye
8. Received corticosteroid-containing eye drops within 14 days prior to Screening visit or planned use during study
9. Any change in systemic corticosteroids/immunosuppressives, topical ocular antibiotics, cyclosporine ophthalmic emulsion 0.05% (Restasis®), cyclosporine ophthalmic solution 0.09% (Cequa™), lifitegrast ophthalmic solution 5% (Xiidra®), or autologous serum tears within 30 days prior to Screening visit or planned change during study

Note: 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.

General Statistical Methods and Types of Analysis

The primary analysis is a test of superiority of topical OCU300 vs OBS drops with co-primary endpoints. Tests will be conducted using two-sided *alpha* = .05.

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.

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). 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 will be spent at the interim analysis, and the two-sided alpha for the final analysis will be 0.0498. If sample size is modified, the final critical value of 0.0498 will be adjusted to control type I error. The details of the interim analysis will be provided in the Statistical Analysis Plan (SAP).

Analysis Populations

Safety 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 deviations.

Hypothesis and Power

Because there are two co-primary endpoints, a composite hypothesis testing framework will be defined as following:

Hypothesis

The statistical hypotheses for the primary endpoint of the mean change from baseline bulbar redness score (VBR) at 12 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 12 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 (OBS) in the mean change from baseline VBR score at 12 weeks (Day 84) ≠ 0.

The statistical hypotheses for the primary endpoint of the mean change from baseline ocular discomfort score (ODS) at 12 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 12 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 12 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;

In general, continuous variables will be presented as 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.

Efficacy Analysis

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. A sensitivity analysis using pattern-mixture model with control- based pattern imputation will be performed to compare with the results of the primary 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 an association.

Safety Analysis

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.

Full details of the statistical analysis method used for the primary and secondary endpoints will be described in the Statistical Analysis Plan (SAP).

Date of Protocol: 15 September, 2018

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LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Table 3. Abbreviations

Abbreviation or specialist term	Explanation
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AEI	Adverse events of interest
BCVA	Best corrected visual acuity
BID	Twice daily
BPM	Beats Per Minute
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
CRO	Contract Research Organization
DBP	Diastolic blood pressure
ECM	Extracellular matrix
eCRF	Electronic case report form
ETDRS	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
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
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
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
VA	Visual Acuity
VBR	Validated Bulbar Redness
WHO	World Health Organization
WOCP	Women of child-bearing potential

1 INTRODUCTION

1.1 Ocular Graft vs Host Disease

Graft-vs-Host Disease (GVHD) is an autoimmune disorder that can occur in patients receiving allogeneic or, in rare instances, autologous hematopoietic stem cell transplantation (allo-HSCT and auto-HSCT) (Blazar 2012). Both acute GVHD and chronic GVHD are recognized as rare diseases (Genetic and Rare Diseases Information Center 2016a; Genetic and Rare Diseases Information Center 2016b; National Organization for Rare Disorders 2016). It is estimated that 60%-90% of GVHD patients experience oGVHD symptoms (Curtis 2015, Nassiri 2013, Shikari 2015; Sun 2015).

Ocular GVHD (oGVHD) is characterized as a chronic autoimmune ocular disorder in patients who suffer from GVHD. Pathologically, the disease is driven by the invasion of HSCT derived leukocytes onto the ocular surface of HSCT recipients, fibrosis, and excessive production of extracellular matrix (ECM) proteins. The donor leukocytes subsequently launch an autoimmune assault on the tear producing glands, cornea, conjunctiva, and eyelid of the eye, resulting in decreased tear production. Dry eye, pain and redness can develop any time from a few weeks up to 100 months after transplantation, and the median time is usually around 6 months (Nassiri 2013). In the chronic setting, oGVHD is commonly associated with severe dry eye symptoms including visual hazing, reduction in visual acuity, photophobia, excessive ocular redness (caused by hyperemia and telangiectasia), foreign body sensation, heightened ocular pain, and corneal perforation, melting, and ulceration (Curtis 2015; Westeneng 2010). The lack of tear film secretion from the damaged tear glands induces severe thinning, fibrosis, opacification, and atrophy of the ocular surface, particularly in the conjunctiva and cornea (Ban 2009; Ban 2011; Ogawa 2010; Wang 2010). Punctuate keratopathy, filamentous keratitis, and high tear film osmolarity are also common signs of oGVHD (Nassar 2013; Wang 2010). Other notable oGVHD signs/symptoms in chronic patients include: severe eyelid inflammation (hyperemia and telangiectasia), severe blepharitis, lagophthalmos, eyelid dermatitis/perioribital hyperpigmentation, ectropion, poliosis, madarosis, and vitiligo (Nassar 2013). If left untreated, oGVHD can cause significant vision loss and irreparable damage to the aforementioned tissues.

1.2 Product Rationale

OCU 300 is a sterile, preservative-free solution of brimonidine tartrate 0.18% in an ophthalmic nanoemulsion. It was developed to treat the signs and symptoms associated with oGVHD as defined by the International Chronic Ocular GVHD Consensus Group revised diagnostic criteria (see Appendix I) .

There is currently no FDA approved drug product for the treatment of oGVHD. Therefore, there is a significant clinical need for oGVHD treatment options that can be administered as topical ophthalmic formulations.

Brimonidine tartrate ophthalmic solution, 0.2% is an FDA approved product that has demonstrated a robust safety profile via topical ocular delivery in patients with open-angle glaucoma or ocular hypertension, with low occurrence of adverse events (AEs). Brimonidine tartrate, the active component in OCU300, is an alpha-adrenergic receptor agonist that also mediates autoimmune leukocyte inflammation and down-regulates fibrosis formation, which are hallmarks of oGVHD (Piwnica, 2014).

1.3 Trial Rationale

OCU-300 may provide a clinical benefit to patients with oGVHD. The scientific rationale to establish a medically plausible basis for the use of OCU300 for the treatment of oGVHD include the following potential mechanisms:

1. Reduction of ocular surface blood flow: As an α agonist, brimonidine tartrate can significantly cause vasoconstriction leading to the reduction of blood flow to the ocular surface by reducing local pressure, edema, and inflammation (Piwnica 2014).
2. Disruption of leukocyte extravasation to the ocular tissue: brimonidine can inhibit the infiltration of activated leukocytes by modulating endothelial cell activity (Herrera-Garcia 2014).
3. Suppression of leukocytes activation: Although inhibition of T lymphocytes has not been studied with brimonidine tartrate, activation of α2 receptors (with another α2 agonist) has been shown to suppress the reactivation of T lymphocytes (Felsner 1995). However, induction of neutrophil apoptosis with brimonidine has been reported in acute inflammation (Herrera-Garcia 2014).
4. Analgesic properties: Brimonidine antagonizes or suppresses the excitatory response of phenylephrine and noradrenaline (Bradshaw 1984). As an α agonist, brimonidine may attenuate pro-inflammatory cytokine release from leukocytes, which in turn attenuates neuritis-induced pain (Romero-Sandoval 2007; Romero-Sandoval 2005).
5. Reduction of fibrosis and suppression of excessive ECM formation: Fibrosis in oGVHD is characterized by an excessive number of CD34+ fibroblasts, excessive fibrosis, and over accumulation of ECM in the lacrimal glands leading to the dysfunction of this exocrine gland (Ogawa 2010). Brimonidine has been shown to attenuate the TGF-β1-induced production of ECM proteins, which in turn leads to the decrease in the synthesis of fibronectin and collagens in human fibroblasts (Hong 2015).

By attenuating autoimmune activity and inflammation, brimonidine tartrate helps the ocular surface and tear film producing glands to avoid further atrophy and to heal from damage sustained during an HSCT pre-conditioning regimen. In addition, brimonidine tartrate can alleviate elevated ocular pain through its analgesic and anti-inflammatory properties. This, in turn, makes the drug highly tolerable when administered directly to the ocular surface.

1.4 Summary of Known and Potential Risks and Benefits to Human Subjects

In this study, one drop of OCU300 (brimonidine tartrate nanoemulsion 0.18%) will be administered into each eye, two times a day (bid) for 84 days. The brimonidine tartrate concentration (0.18%) is less than the concentration of the currently marketed brimonidine tartrate (0.2%) used for chronic dosing in glaucoma patients.

Several studies have reported the overall safety and efficacy of marketed brimonidine 0.2% and 0.15% after 1, 3, and 4 years. (Katz 2002, Mundorf 2003, Adkins 1998, Chew 2014, Melamed 2000, LeBlanc 1998, Schuman 1996, Schuman 1997, Nguyen 2013, Rahman 2010) Based on the current evidence, related serious adverse events are not expected with the dose in the current study (0.18%). One study demonstrated a reduction in adverse effects with brimonidine 0.15%, relative to 0.2% (Katz 2002), but another has shown no difference between brimonidine 0.2% and 0.15% (Mundorf 2003). The most common systemic side effects include dysgeusia, fatigue, eye pain, dry mouth, and headache (Adkins 1998, Chew 2014, Melamed 2000, LeBlanc 1998, Schuman 1997). The incidence of blepharitis and blepharoconjunctivitis has been reported in 9.0 – 12.7% of patients (Schuman 1997, Katz 1999, Schuman

1996), follicular conjunctivitis in 7.8 – 12.7% of patients (Schuman 1997, Katz 1999), and conjunctival hyperemia in 5.0 - 30.3% of patients (Nguyen 2013, Rahman 2010).

Given the long-term safety profile of marketed brimonidine tartrate (0.15%-0.20%), the added benefits of a preservative-free nanoemulsion, and the high medical need in this patient population, the risk/benefit profile supports the use of OCU 300 for the relief treatment of ocular redness and ocular discomfort in patients with oGVHD.

2 STUDY DESIGN

2.1 Study Objectives

2.1.1 Primary Objective(s)

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.

2.2 Study Endpoints

2.2.1 Co-primary Efficacy Endpoints

Two primary efficacy endpoints will be tested:

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

2.2.2 Secondary Efficacy Endpoints

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

2.2.3 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 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This will be a randomized, placebo-controlled, double-masked, multicenter phase 3 study in the United States conducted in approximately 15-20 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 4 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 1). An informed consent document (ICD) must be obtained from each subject prior to the commencement of any study procedures. All subjects must be given ample time to review the ICD and ask questions regarding the study prior to participation in the study. The subject will be provided a copy of the signed ICD.

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. In addition, subjects will be asked to make note of any missed doses together with the reason for the missed dosage. The intent is to capture missed doses, per se, rather than a shifted dosing schedule.

3.2 Rationale for the Study Design

oGVHD is an orphan disease with no ophthalmic drug products approved for its treatment. There is a significant therapeutic need for an oGVHD ophthalmic formulation that mediates autoimmune leukocyte inflammation and fibrosis, with low occurrence of long-term ocular AEs. An Orphan Drug Designation (ODD) was granted for brimonidine tartrate for the treatment of oGVHD (Designation request #16-5640) on 03 August 2017.

The criteria for evaluation, study assessments, and follow-up period are consistent with the standard of care for the treatment of oGVHD. The National Institutes of Health (NIH) suggests using patient-reported outcomes (PRO) for the response of oGVHD to treatments (Martin 2015, Lee 2015). Therefore, ocular discomfort (a measure of ocular pain), a subjective score, and ocular redness, an objective score, are the co-primary endpoints. Additional subjective scores, SANDE and SGA, will also be evaluated.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Number of Subjects

At least 60 participants will be randomly assigned to the study treatment such that approximately 40 evaluable subjects per active arm (OCU300) and 20 per placebo arm (OBS) complete the study (2:1 randomization).

4.2 Subject Inclusion Criteria

Subjects must meet **all** the following inclusion criteria to be eligible to enroll in the clinical trial:

1. Men or women ≥ 18 years of age
2. Diagnosis of "definite oGVHD" in at least one eye

   The diagnosis of 'definite' oGVHD will be made using the International Chronic Ocular GVHD Consensus Group Revised Diagnostic criteria. The Consensus Group Severity Scale is based on the cumulative grading of 4 individual scores (See Appendix I):

   - Schirmer's Test (tear film secretion levels)
   - Corneal staining score
   - Conjunctival Injection
   - OSDI score

3. Ocular Discomfort Score ≥ 3
4. Validated Bulbar Redness score ≥ 40 in both eyes
5. Subjects who are capable and willing to provide informed consent and follow study instructions
6. Intraocular pressure (IOP) ≥ 5 mmHg and ≤ 22 mmHg in each eye
7. Women who satisfy one of the following:
   a) Are of child-bearing potential (WOCP) who are not pregnant or lactating at the screening visit; and who are either abstinent or sexually active on an acceptable method of birth control (oral contraceptive pills, birth control implants/shots or patches, barrier methods) for at least 4 weeks prior to baseline visit (Day 1) and throughout the study, OR
   b) Are post-menopausal or have undergone a sterilization procedure

4.3 Subject Exclusion Criteria

The presence of **any** of the following exclusion criteria excludes a subject from study enrollment:

1. Allergic to brimonidine or any similar products, or excipients of brimonidine
2. Currently receiving brimonidine or other treatment for glaucoma.
3. Receiving or have received any experimental or investigational drug or device within 30 days prior to screening visit.
4. Use of contact lenses within 14 days prior to Screening visit or planned use during the study.
5. Active ocular infection or ocular allergies
6. Any history of eyelid surgery or ocular surgery within the past 3 months
7. Corneal epithelial defect larger than 1 mm^2 in either eye
8. Received corticosteroid-containing eye drops within 14 days prior to Screening visit or

planned use during the study.

9. Any change in systemic corticosteroids/immunosuppressive, topic ocular antibiotics, cyclosporine ophthalmic emulsion 0.05% (Restasis®), cyclosporine ophthalmic solution 0.09% (Cequa™), lifitegrast ophthalmic solution 5% (Xiidra®), or autologous serum tears within 30 days prior to Screening visit or planned change during study.

Note: 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.

4.4 Randomization Criteria

Not applicable.

4.5 Subject Withdrawal Criteria

Subjects may withdraw consent at any time for any reason without effect on subsequent care. Subjects will be encouraged to adhere to the protocol and complete all required assessments prior to exiting the study. A subject will be discontinued from the study for any of the following reasons:

- Pregnancy
- At the discretion of the Investigator at any time
- At the subject's request (voluntary withdrawal)
- Occurrence of a treatment-emergent adverse event (TEAE) or considerable worsening of an AE that, in the opinion of the Investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the subject if he/she continues in the study. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
- Progression of disease that, in the opinion of the Investigator, precludes further study drug treatment
- Lack of tolerability to the study drug

Subject participation in the study is purely voluntary. Subjects who are discontinued outside of any scheduled visit will be encouraged to return to the clinic to complete a final study visit, which will consist of all day 84 assessments. Subjects who are discontinued during a scheduled visit will be encouraged to complete all unique assessments for that study visit at the time of discontinuation, including the completion of the Validated Bulbar Redness Scale (VBR), the Visual Analog Scale (VAS), and the Symptom Assessment iN Dry Eye (SANDE) Questionnaire. Subjects who discontinue following study drug administration will not be replaced.

The reason for study withdrawal is to be documented in the subject's source documents and CRFs, as follows:

1. Adverse event
2. Subject voluntary withdrawal
3. Investigator withdrawal of subject
4. Lost-to follow-up
5. Study termination
6. Other (with explanation)

4.6 Study Termination

This study may be terminated at any time if, in the opinion of the Investigator or the Sponsor, continuation of the study represents a significant medical risk to participating subjects. Appropriate consultation between the Sponsor and Investigator must take place prior to termination of the study.

5 STUDY SCHEDULE AND PROCEDURES

5.1 Study Schedule

The study schedule can be found in Table 4. Detailed information on study assessments is provided in Section 6.

Table 4. Study 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 Exam	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.

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5.2 Study Visits

5.2.1 Unscheduled Study Visits

Unscheduled visits may be completed between the scheduled follow-up periods, at the Investigator’s discretion, or if subjects experience AEs that necessitate an unscheduled visit. Subsequent unscheduled visits may be necessary following the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of subjects during the study. Case report forms (CRFs) should be completed for each unscheduled visit.

5.2.2 Screening

There is a maximum 7-day period for completing all screening tests prior to randomization. Therefore, the Screening Visit and Day 1 Visit may be combined into a single visit lasting up to 7 days. In this case, there is no need to duplicate any of the Screening/Day 1 procedures. An ICD must be obtained from each subject before initiation of any study-related procedures.

The following procedures and assessments should be completed at the Screening Visit:

- Informed Consent
- Diagnosis of definite chronic oGVHD using points for Schirmer’s, CFS, OSDI, Conjunctival injection (see Appendix 1)(Table 6)(Table 7)(Table 11)
- Inclusion and Exclusion criteria check
- Demographic information including: birth date, gender, race, and ethnic origin

- Medical history including prior procedures and conditions
- Ophthalmic history including: date when the oGVHD began, medications used by the subject to treat oGVHD, previous procedures to treat oGVHD.
- Review of prior and concomitant medications: medications used by the subject to treat oGVHD, previous procedures to treat oGVHD; OTC medications; medications for chronic diseases
- Urine collection and dipstick test for pregnancy in women of child bearing capacity
- Ocular Discomfort 10-point VAS
- Ocular surface disease index (OSDI) (severity points, for diagnosis of oGVHD)
- Ocular Redness 100-point VBR scale
- Conjunctival injection (severity points, for diagnosis of oGVHD)
- Slit-lamp ophthalmic exam
- Corneal fluorescein (CFS) (severity points, for diagnosis of oGVHD)
- Schirmer's test with anesthesia (severity points, for diagnosis of oGVHD)
- Intraocular pressure (IOP)
- Adverse event surveillance

5.2.3 Day 1 (Baseline, Randomization, and First Treatment Visit)

Baseline: The following should be completed prior to the first dose

- Inclusion and Exclusion criteria confirmation
- Body weight (pounds) and height (inches)
- Vital Signs: body temperature, heart rate, blood pressure, respiratory rate (measured after the subject has been sitting for approximately 3-5 minutes)
- Urine collection and dipstick test for pregnancy in women of child bearing capacity
- Review of prior and concomitant medications
- Ocular Discomfort 10-point VAS
- Ocular surface disease index (OSDI)
- Visual Acuity
- Symptom Assessment iN Dry Eye (SANDE)
- Ocular Redness 100-point VBR scale
- Slit-lamp ophthalmic exam
- Corneal fluorescein(CFS) (NEI scale)
- Corneal lissamine green
- Conjunctival lissamine green

- Schirmer's test with anesthesia
- Intraocular pressure (IOP)
- Randomization
- Instill investigative product (Instruct subject on how to self-administer the study eye drops and when to take the next dose)

Post-Dose: The following assessments should be completed during / after administration of the first dose:

- Dispense the investigational product kit (provide the subject with a sufficient supply to last for approximately 4 weeks, to take home)
- Post-dose evaluation for any adverse effects
- Provide subject with a study diary (study staff should instruct the patient on use and responsibility for the study diary) and record first dose.
- Make appointment for next visit

5.2.4 Day 28 (± 7 days)

- Vital Signs: body temperature, heart rate, blood pressure, respiratory rate (measured after the subject has been sitting for approximately 3-5 minutes)
- Urine collection and dipstick test for Pregnancy in women of child bearing capacity
- Review of prior and concomitant medications
- Ocular Discomfort 10-point VAS
- Ocular surface disease index (OSDI)
- Visual acuity
- Symptom Assessment iN Dry Eye (SANDE)
- Ocular Redness 100-point VBR scale
- Slit-lamp ophthalmic exam
- Corneal fluorescein (CFS) (NEI scale)
- Corneal lissamine green
- Conjunctival lissamine green
- Schirmer's test with anesthesia
- Intraocular pressure (IOP)
- Clinical Global Impression
- Subject Global Assessment
- Collect used investigative products
- Dispense investigative product kit

- Adverse event surveillance
- Diary collection and review

5.2.5 Day 56 (± 7 days)

- Vital Signs: body temperature, heart rate, blood pressure, respiratory rate (measured after the subject has been sitting for approximately 3-5 minutes)
- Urine collection and dipstick test for pregnancy in women of child bearing capacity
- Review of prior and concomitant medications
- Ocular Discomfort 10-point VAS
- Ocular surface disease index (OSDI)
- Visual acuity
- Symptom Assessment iN Dry Eye (SANDE)
- Ocular Redness 100-point VBR scale
- Slit-lamp ophthalmic exam
- Corneal fluorescein (CFS) (NEI scale)
- Corneal lissamine green
- Conjunctival lissamine green
- Schirmer's test with anesthesia
- Intraocular pressure (IOP)
- Clinical Global Impression
- Subject Global Assessment
- Collect used investigative products
- Dispense investigative product kit
- Adverse event surveillance
- Diary collection and review

5.2.6 Day 84 (± 7 days)

- Vital Signs: body temperature, heart rate, blood pressure, respiratory rate (measured after the subject has been sitting for approximately 3-5 minutes)
- Urine collection and dipstick test for pregnancy in women of child bearing capacity
- Ocular Discomfort 10-point VAS
- OSDI
- Visual acuity

- Symptom Assessment iN Dry Eye (SANDE)
- Ocular Redness 100-point VBR scale
- Slit lamp ophthalmic exam
- Corneal fluorescein (CFS) (NEI scale)
- Corneal lissamine green
- Conjunctival lissamine green
- Schirmer's test with anesthesia
- Intraocular pressure (IOP)
- Clinical Global Impression
- Subject Global Assessment
- Collect used investigative products
- Adverse event surveillance
- Diary collection and review

6 ASSESSMENTS

6.1 Demographic/Ocular and Medical History

Information relating to the subject's sex, age, race, height, and weight will be recorded at the Screening Visit on the appropriate case report form (CRF) page. Ocular and medical history of each subject will be collected at the Screening Visit and recorded on the appropriate CRF.

6.2 Prior & Concomitant Medications/Therapies

All prior and concomitant medications/therapies taken by subjects within 30 days prior to enrollment and throughout the study must be recorded on the appropriate CRFs.

6.3 Pregnancy Screen

At the Screening Visit, a urine dipstick pregnancy test will be performed for all female subjects of child-bearing potential. Additionally, a urine pregnancy test may be performed at any time during study participation if pregnancy is suspected.

6.4 Efficacy Assessments

6.4.1 Primary Efficacy Assessment

There are two co-primary efficacy endpoints.

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

6.4.1.1 Validated Bulbar Redness (VBR) grading scale

Ocular surface redness (OR; nasal or temporal) will be assessed using the VBR grading scale (Schulze 2007). The VBR consists of a set of ten images illustrating different degrees of OR, ranging from normal to severe, and each image is assigned a value in an order of ascending severity (see Section 18.3; Figure 2). The VBR will be completed at each clinic visit. The bulbar conjunctival injection of the subject's eye (nasal and temporal) will be examined via slit-lamp examination and compared to the reference images in the VBR and graded accordingly. To maintain uniformity, the same physician (PI) will perform the VBR assessments for each subject, and under constant illumination conditions.

6.4.1.2 Ocular Discomfort (VAS)

Symptom scales often measure both intensity and frequency. In this study, the intensity of ocular discomfort in oGVHD has been selected as a co-primary endpoint and this will be reflected in the visual analogue scale. The term ocular discomfort is meant to capture the ocular surface pain and discomfort experienced by oGVHD patients, often described as "pain", "burning", "grittiness", and "photophobia", or a combination thereof. Because the ocular discomfort associated with oGVHD is chronic in nature, the

frequency of episodic pain will not be captured by the pain VAS. (see Section 18.2, Figure 1) Ocular discomfort (VAS) will be assessed at each clinic visit.

6.4.2 Secondary Efficacy Assessment

6.4.2.1 Symptom Assessment iN Dry Eye (SANDE)

The SANDE questionnaire is a short visual analog assessment scale that quantifies both severity and frequency of dry eye symptoms. The SANDE is comprised of two questions, and each question employs a 100-mm horizontal linear VAS (Figure 3). The measurement of symptom frequency ranges from "rarely" to "all of the time," and the symptom severity from "very mild" to "very severe." Subjects will complete this scale on Day 1 prior to first dose (Baseline), Day 28, Day 56, and Day 84. Data collected from the SANDE questionnaire will be calculated by multiplying the frequency score by the severity score and obtaining the square root. The result is the Overall SANDE score (see Section 18.4).

6.4.3 Exploratory Efficacy Assessments

6.4.3.1 Ocular Surface Disease Index (OSDI)

The OSDI© is a validated and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function (Figure 4). The OSDI will be completed at each clinic visit and is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease (see Section 18.5). The OSDI will be used as part of the Chronic Ocular GVHD Consensus Group criteria for diagnosing oGVHD (Ogawa, 2013). The OSDI will be completed at all follow-up visits.

6.4.3.2 Corneal Staining Score with Fluorescein

Staining of the corneas in each eye (OS and OD) will be conducted using the slit lamp at each clinic visit. At Screening, central corneal fluorescence staining (CFS) will be evaluated as per the methods described in Ogawa, 2013and adapted for this trial (Table 9)(Table 10). (See section 18.7), and for baseline and subsequent measurements, the NEI scale will be used.

6.4.3.3 Corneal and Conjunctival Staining Score with Lissamine Green

Corneal and conjunctival staining with Lissamine Green dye (1%; LG) staining in each eye (OS and OD) will be conducted using the slit lamp on Day 1 prior to first dose (Baseline), Day 28, Day 56, and Day 84 and evaluated using the NEI scale. A single drop of 1% Lissamine Green dye will be applied to the inferior conjunctival fornix of both eyes. The conjunctivae will be examined with the slit lamp at ×10 magnification, using a neutral-density filter, graded in two zones. Corneal staining will be graded in 5 zones, as per the methods described in Section 18.6 (Table 8)(Figure 5)(Figure 6).

6.4.3.4 Schirmer's test

At each clinic visit, a Schirmer's test will be conducted to access tear production. After instilling one drop of a topical anesthetic (e.g., proparacaine) to each eye, wait approximately 30 seconds, then blot the inferior cul-de-sac with a tissue. The test is conducted by application of standardized Schirmer strips over the lower lid margin, toward the temporal angle of the lids in both eye as possible. The subject should be instructed to keep her/his eyelids closed during the test. Strips should remain in place in both eyes for 5

min, or until completely saturated with tears. After 5 min, wetting of the strips will be measured using the millimeter scale on each strip.

The study site will capture the actual measurement in millimeters (mm) and, at the Screening visit, the Sponsor will convert to categories consistent with the chronic oGVHD Consensus Group criteria (Appendix 1; Ogawa, 2013), based on the number of mm of wetting of the paper after 5 minutes, as follows:

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

6.4.3.5 Clinical Global Impression (CGI)

At Day 28, Day 56, and Day 84, the PI will use their clinical evaluation (all signs and symptoms taken together) to provide a global assessment of the subjects' change in symptoms and signs. The CGI is assessed as follows (Miller 2010):

Question (to physician): In general, compared with the subjects' symptoms and signs at baseline, how would you characterize his/her overall signs and symptoms now?

The responses will be categorized on a 7-point scale as follows:

- Marked worsening
- Moderate worsening
- Minimal worsening
- Unchanged
- Minimal improvement
- Moderate improvement
- Marked improvement

6.4.3.6 Subject Global Assessment (SGA)

At Day 28, Day 56, and Day 84, the subjects will be asked to assess their overall change from baseline. The SGA is assessed as follows (Miller 2010):

Question (to subject): Compared with your first visit, how are your eye symptoms now?

The responses will be categorized on a 5-point scale as follows:

- Much worse
- Worse
- About the same
- Improved
- Much improved

6.5 Safety Assessments

All subjects who enter the study will be assessed for safety. Safety will be monitored by observation of and direct inquiry regarding AEs at each visit. Safety assessments include vital signs, recording of adverse events, as well as ophthalmic exam findings. All ocular and non-ocular adverse events will be assessed for severity and relationship to the investigational product. The following analyses will be performed:

- The proportion of subjects at week 12 who were able to successfully complete a full 12 weeks of therapy with topical ophthalmic administration
- All adverse events reported, whether deemed related to treatment or not
- Clinically significant changes in vital signs or ophthalmic examinations from baseline

6.5.1 Adverse Events

All AEs will be collected from the time of informed consent completion through the completion of the study for each subject. Details regarding AE definitions, collection, recording, and reporting are found in Section 10.1.

6.5.2 Visual Acuity

Monocular visual acuity will be completed with the subject's best correction vision in place using standard of care ETDRS chart, at Day 1 prior to the first dose (Baseline), Day 28, Day 56, and Day 84. Procedures for BCVA are outlined in Section 18.9 (Figure 7)(Table 12).

6.5.3 IOP - Goldmann Applanation

IOP will be assessed in both eyes, at each clinic visit, using the Goldmann applanation tonometry method (see Section 18.10).

6.5.4 Ophthalmic Examination (Slit Lamp)

Biomicroscopic examination will be completed at each clinic visit (see Section 18.11)(Table 13). The conjunctiva, cornea, anterior chamber, lens and anterior vitreous of each eye will be examined.

6.5.5 Vital Signs

Diastolic and systolic blood pressure (DBP/SBP) and heart rate (HR) will be assessed via oscillometer method using an automated sphygmomanometer. At each visit, 3 consecutive readings (at least 2 minutes apart) will be taken by the study staff and recorded in the subject's source documents. The average DBP and SBP will be documented in the CRFs. Subjects should be comfortably seated for 5 minutes prior to blood pressure readings. Study staff must take care to select the appropriate cuff size for each subject. Heart rate will be assessed for at least 1 minute and recorded as beats per minute (bpm), and body temperature (forehead) will be recorded in degrees Celsius (˚C) at Day 1, Day 28, Day 56, and Day 84 by the study staff.

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

7 INVESTIGATIONAL DRUG INFORMATION AND MANAGEMENT

7.1 Investigational Drug Dose Regimen

The proposed dose is one drop of OCU300 in each eye (OU) every 12 hours. The proposed dosing regimen is twice daily (bid).

7.2 Dose Rationale

Brimonidine 0.2% is currently used topically as eye drops, 2-3 times a day, for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

OCU300 has a dosage strength of 0.18% brimonidine tartrate in a preservative-free nanoemulsion and is applied as a single drop to each eye, twice daily. This proposed dose of OCU300 is selected based on data available from the listed drug (LD) and associated Alphagan® ophthalmic products. The emulsion formulation, with a pH buffered to maintain the optimum range for ocular delivery, is expected to prolong the precorneal residence time, and increase aqueous humor drug levels. Based on these pharmaceutical attributes as well as preliminary clinical data, it is suggested that a 0.18% concentration of brimonidine in the proposed OCU300 ophthalmic emulsion formulation with twice-daily application will be able to exert therapeutic effects. The potential protective effect of OCU300 brimonidine tartrate (0.18%) against corneal epithelial damage in comparison to a placebo nanoemulsion and a marketed product was demonstrated in a mouse dry-eye disease model, supporting the selection of OCU300 proposed dose (Arumugham 2018). These results infer that OCU300 provided better protection for corneal epithelial damage than the reference product Restasis® and Placebo (vehicle).

Moreover, brimonidine tartrate solution is considered safe based on the long history of over 20 years for ophthalmic chronic use (Allergan 2010; Serle 1996). Brimonidine tartrate 0.2% is currently used topically as eye drops, 3 times a day, for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. The brimonidine tartrate concentration (0.2%) and frequency of administration > bid may provide a greater exposure, and hence, a greater probability of adverse events, than the proposed OCU300 dosing regimen.

7.3 Investigational Drug Packaging and Labeling

All investigational drugs used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures (SOPs) of Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization (ICH) guidelines for GCP, guidelines for Quality System Regulations (QSR), and applicable regulations.

To maintain the double-masking, the investigational product and placebo will be provided in packaging that will be similar in appearance and labeling. A label with “OCU300 Brimonidine Tartrate Ophthalmic Nanoemolusion 0.18% or Placebo”, or similar language, will be affixed to each pouch containing eye dropper vials and will include the appropriate instructions for storage. The label will also include a statement that the drug is for investigational use.

7.4 Investigational Drug Storage

The study drug will be stored in a designated and secure area, with access given to only authorized study personnel. The recommended storage temperature is 15°-25° C/ 59°-77°F. Other storage conditions will be observed as per the labeling instructions of the study drug.

7.5 Investigational Drug Preparation

Not applicable. The study drugs will be supplied in a form that is ready for instillation in the eye.

7.6 Investigational Drug Administration

At the first treatment visit on Day1, the first study medication dose will be administered by the patient under the supervision of the study staff, after which the patient will be given a 35-day supply (28 days between visits plus 7-day visit window) of eye-dropper vials for self-administration at home. A similar supply will be given to the patient upon completion of the Day 28 and Day 56 visits. At the site level, drug dispensation should only be performed by the pharmacist or designee, and not by the PI or other personnel involved in patient assessments.

Subjects will be instructed on the use of the study medication, for each eye, as follows:

Instructions for Drug Use:

1. Wash your hands thoroughly with soap and water.
2. Remove the vial from its pouch.
3. Check the dropper tip to make sure that it is not chipped or cracked.
4. Avoid touching the dropper tip against your eye or anything else – eye drops and droppers must be kept clean.
5. While tilting your head back, pull down the lower lid of your eye with your index finger to form a pocket.
6. Hold the dropper (tip down) with the other hand, as close to the eye as possible without touching it.
7. While looking up, gently squeeze the dropper so that a single drop falls into the pocket made by the lower eyelid. Remove your index finger from the lower eyelid.
8. Close your eye for 2 to 3 minutes and tip your head down as though looking at the floor. Try not to blink or squeeze your eyelids.
9. Place your finger on the tear duct and apply gentle pressure.
10. Repeat the above listed steps for eye #2.
11. This sequence of steps should be followed twice a day; once in the morning and once in the evening (approximately 12 hours apart).

7.7 Investigational Drug Accountability

The investigational products will be shipped to each Investigative site by the Sponsor's designee. The PI is responsible for the receiving, handling, and reconciliation of the received study drug to shipment records. Any discrepancy should be documented, and the appropriate individual at the Sponsor or designee must be notified immediately. Dispensing of the study medication to subjects must be accounted for and properly documented in the subject or the site's records. Subjects will be instructed to return all dosing vials, used or unused, to the site at each post-baseline visit, for which compliance will be assessed by the Investigator or designee, utilizing the subject's dose diary. The investigational product(s) must only be dispensed to subjects participating in this study by the pharmacist or designee, and not by the PI

or other personnel involved in patient assessments. A Drug Accountability Log will be kept at the clinical site.

7.8 Investigational Drug Handling and Disposal

At the completion of the study, all unused investigational products will be returned by the Investigator to the Sponsor or designee. Any discrepancies or missing study drug bottle/vials will be investigated, resolved, and documented as appropriate.

8 TREATMENT OF SUBJECTS

8.1 Rescue Medication

Subjects will be monitored by the PI at each study visit for any worsening of ocular conditions or other AEs. Any clinical worsening of the subject's condition will be evaluated and properly treated as based on the Investigator's clinical judgment. Treatment may involve use of other medications and/or discontinuation of study drug.

8.2 Prohibited Medications or Treatment

Corticosteroid-containing eye drops are not permitted within 14 days prior to Screening or during the study. Subjects will be allowed to remain on current concomitant therapies during the study, given that no changes are made to the dose and frequency of the medication within 30 days prior to enrollment and throughout the study.

Specifically, 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.

Any changes in concomitant medication from the previous visit should be assessed by the Investigator for AEs and documented as appropriate.

8.3 Other Study Restrictions

The use of scleral contacts is restricted from Day 1 (baseline) to Day 84 (last study day) in this study.

8.4 Treatment Compliance

Treatment compliance will be documented with subject diaries. Subjects will be dispensed diaries at the Day 1 Visit and will be instructed to record the time(s) (a.m. or p.m.) at which bid dosing occurred. Subject diaries must be reviewed by the study staff at each visit prior to the subjects' leaving the clinic.

9 RANDOMIZATION AND MASKING PROCEDURES

9.1 Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who meet study entry criteria will be randomly assigned in a 2:1 ratio to OCU300 or placebo. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central Interactive Web Response System (IWRS) as subjects are entered into the study, with a goal of maintaining balance across the overall study and not necessarily within a study site.

The randomization schedule will be prepared by Brightech International, LLC (Somerset, NJ) before the start of the study. No one involved in the conduct of the study will have access to the randomization schedule before official unmasking of treatment assignment. No subject will be randomized into this study more than once.

9.2 Masking and Unmasking of Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the study, including data management and statistics, will be masked to treatment assignment except for a specified partially unmasked staff member from the designated packaging vendor who will do the package labeling. This person will know the scramble kit numbers and associated drug groups. The partially unmasked study personnel will not otherwise participate in study procedures or data analysis prior to unmasking the study data to all study related personnel.

Study personnel will endeavor to safeguard the integrity of the study masking to minimize bias in the conduct of the study. Treatment unmasking is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unmasking will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. Unmasking should be discussed in advance with the Medical Monitor, if possible.

9.3 Emergency Unmasking

For emergency unmasking, study personnel will use the IWRS. Access to the IWRS unmasking module requires a special password that may be obtained from the medical monitor or other designated team member. If the investigator is not able to discuss treatment unmasking in advance, then he/she must notify the medical monitor as soon as possible about the unmasking incident *without revealing the subject's treatment assignment*. The investigator or designee must record the date and reason for study discontinuation on the appropriate CRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unmasking the subject's treatment assignment.

If treatment assignment is unmasked for an individual subject, study personnel will be notified of that subject's treatment assignment without unmasking the treatment assignments for the remaining subjects in the study. Thus, the overall study mask will not be compromised. If a subject's treatment assignment is unmasked, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

10 ADVERSE EVENTS

10.1 Adverse and Serious Adverse Events

This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with Title 21 Code of Federal Regulations (CFR) 312, ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and ICH Guideline E-6(R2): Guidelines for Good Clinical Practice.

Adverse events will be recorded from the time of informed consent completion, throughout the study, and at early termination; AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The Investigator is responsible for the detection and documentation of AEs, regardless of treatment group or suspected causal relationship to the investigational product. For all AEs, the Investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE, requiring immediate notification to the Sponsor or its designated representative.

10.1.1 Definitions of Adverse Events

10.1.1.1 Adverse Event (AE)

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 E6R2 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.

10.1.1.2 Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes (21 CFR 312.32(a)):

- Death: A death that occurs during the study or that comes to the attention of the Investigator during the protocol-defined follow-up period must be reported to the Sponsor whether it is considered treatment related or not.
- A life-threatening event: An AE or suspected adverse reaction (SAR) is considered "life-threatening" if, in the view of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- In-patient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent

one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of investigational product dependency or abuse.

- Congenital anomaly or birth defect.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to the Sponsor, as described in Section 10.1.5.

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization are considered serious. Any hospitalization except observational admissions of less than 24 hours meets these criteria. This category also includes transfer within the hospital to an acute/intensive care unit (e.g., from a standard of care unit to an acute/intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g. caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24-hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Protocol-specified admission (e.g. for a procedure required by the study protocol)
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject.
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis attack that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

10.1.1.3 Adverse Drug Reaction (ADR) and Suspected Adverse Reaction (SAR)

An adverse drug reaction (ADR) refers to any AE caused by a drug.

Suspected adverse reaction (SAR) refers to any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than an ADR (21 CFR 312.32(a)).

10.1.1.4 Unexpected Adverse Reaction (UAR)

The Sponsor is responsible for assessing AEs for expectedness. With regards to reporting to the FDA, an AE is considered "unexpected" when its nature (specificity), severity, or rate of occurrence is not consistent with applicable product information as described in the safety information provided in the protocol/package insert/Investigator's brochure/prescribing information for brimonidine tartrate. "Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the Investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)).

10.1.1.5 Adverse Events of Interest (AEIs)

Not applicable.

10.1.2 Severity of AEs/SAEs

The study site will grade the severity of AEs experienced by study participants according to the criteria set forth in the National Cancer Institute's *Common Terminology Criteria for Adverse Events Version 5.0*. This document (referred to herein as the "NCI-CTCAE manual") provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of AEs. Please refer to the NCI-CTCAE manual for the desired event and specific grading for that event.

If the event is not listed in the NCI-CTCAE manual, please refer to the following standards in the NCI-CTCAE manual:

- Grade 1 = mild; asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated
- Grade 2 = moderate minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living (ADL), e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money
- Grade 3 = severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g. bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- Grade 4 = life-threatening consequences; urgent intervention indicated
- Grade 5 = death related to AE

For additional information and a printable version of the NCI-CTCAE manual, go to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

The study site will grade the clinical severity of AEs experienced by study participants as either:

- Mild: Causes no limitation of usual activities
- Moderate: Causes some limitation of usual activities
- Severe: Prevents or severely limits usual activities

Note: The terms serious and severe are not synonymous. Serious criteria as defined in Section 10.1.5.2 above serve as a guide for defining regulatory reporting obligations. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache); the event itself, however, may be of relatively minor medical significance. This is not the same as serious, which is based on patient/adverse outcome. Therefore, an AE of severe headache might not be considered serious, but a moderate infection for which a subject is hospitalized should be reported as an SAE.

10.1.3 Relationship to Investigational Drug Treatment

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE and must be provided for all AEs (serious and non-serious).

The Sponsor's determination of attribution will be used for reporting to the appropriate health authorities. The relation of an AE to study participation will be determined using the descriptors and definitions provided in Table 5.

Table 5. Attribution of Adverse Events

Unrelated	The AE is clearly/most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention or concomitant therapy, or the delay between administration and the onset of the AE is incompatible with a causal relation, or the AE started before administration (screening phase). Therefore, there is not a reasonable possibility that the AE was caused by the investigational drug.
Possibly Related	The adverse event follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and the possibility that drug involvement cannot be excluded, e.g. existence of similar reports attributable to the suspected drug, its analog or its pharmacological effect. However, other factors such as underlying disease, concomitant drugs, or concurrent treatment are presumable
Related	There is a reasonable possibility that the AE was caused by the investigational drug. The expression "reasonable possibility" is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship (21 CFR 312.32(a)).

The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. Any AE that is suspected to be related to the investigational product will be classified as an ADR.

10.1.4 Collecting and Recording Adverse Events

10.1.4.1 Period of Collection

All AEs will be collected from the time of informed consent through the subject's final study visit. All AEs and SAEs should be treated as medically appropriate and followed until event resolution.

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the

investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE CRF with the status noted.

10.1.4.2 Methods of Collection

Adverse events may be collected as follows:

- Observing the participant
- Questioning the participant in an unbiased and non-leading manner
- Receiving an unsolicited complaint from the participant

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the Investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk. Note: In this study, there are no planned laboratory evaluations.

10.1.4.3 Recording Method

10.1.4.3.1 Adverse Events

All AEs occurring during this clinical study will be recorded by the Investigator on the appropriate CRF in precise medical terms, along with the date and time of onset and the date and time of resolution. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should combine signs and symptoms into a single term that constitutes a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to study drug. The severity of the AE and its relationship to the study drug will be assessed by the Investigator.

The Investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes. If any medication is administered in response to the AE, this medication should be noted on the concomitant medication CRF as a concomitant medication administered. If possible, medications administered in response to an AE would not constitute a change in the patient's ongoing oGVHD regimen or confound the assessment of the patient's signs or symptoms of oGVHD..

The action taken, and the outcome must also be recorded. The Investigator will follow a non-serious AE until resolution, stabilization of the Follow-up Visit. The Investigator will follow an SAE (regardless of relationship to study drug until the event resolves, stabilizes, or becomes non-serious. The terms of AE resolution (i.e., recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, fatal, unknown) should also be recorded.

10.1.4.3.2 Serious Adverse Events

Serious adverse events will be recorded on the AE CRF and on the SAE CRF, and health authorities will be notified as outlined in Section 10.1.5.2.

10.1.5 Reporting Adverse Events

10.1.5.1 Reporting SAEs to the Sponsor

The following process for reporting an SAE ensures compliance with 21 CFR 312 and ICH guidelines. After learning that a participant has experienced an SAE, the Investigator or designee is responsible for reporting the SAE to the Sponsor, regardless of relationship or expectedness, within 24 hours of becoming aware of the event. The initial SAE report should include as much information as possible, but at a minimum must include the following:

- Reporter
- Subject ID
- Study product or intervention
- Serious AE term
- Relationship to study medication(s)
- Reason why the event is serious

Supplemental CRF pages should be current at the time of SAE reporting: medical history, concomitant medications, demographics, study drug administration, and death, as applicable.

Unavailable details of the event should not delay submission of the known information. As additional details become available, the SAE CRF should be updated and re-submitted.

All SAEs, regardless of relationship to the study treatment, must be reported to the Sponsor (or designee) within 24 hours of the Investigators' becoming aware of the event. An initial written SAE report should be faxed to G2 BioPharma SAE Fax Number [redacted]. This instruction pertains to initial SAE reports and to any follow-up reports.

The SAE report should provide a detailed description of the SAE and supporting medical documents should be included with the report. Follow-up SAE reports must be submitted by the Investigator as new information becomes available.

The Safety Project Manager will forward the SAE reports and documents to the Medical Monitor and the Sponsor for review.

For additional information regarding SAE reporting, contact:

Medical Monitor
[redacted]

[redacted]
[redacted] - Office
[redacted] – Cellular
Email: [redacted]
24-Hour Contact: [redacted]

G2 BioPharma Safety Project Manager
[redacted]

G2 BioPharma Services, Inc.
3637 Brunswick Pike
Princeton, NJ 08540
Email: [redacted]
Phone: [redacted]

SAE Hotline Number (US): [redacted]
The SAE Hotline is available 24/7 to report an SAE when unable to successfully fax an SAE Report or for reporting after normal business hours (Monday-Friday 8:00 AM to 5:00 PM (CST). For all SAE Hotline calls, the investigator and site personnel must also follow-up with the Safety Associate by phone or email and ensure the SAE Report is received by G2 BioPharma Services.

10.1.5.2 Reporting Serious Adverse Events to FDA

The Sponsor will report Investigational New Drug (IND) Safety Reports to the FDA and Investigators, in accordance with the FDA regulations detailed in the 21 CFR 312.32.

After the SAE has been reported by the site Investigator and assessed by the IND Sponsor, there are 2 options for the IND Sponsor to report an event to the appropriate health authorities:

Standard reporting (report in the IND annual report) is required. This option applies if the AE is classified as one of the following:

- Serious, SAR per the definitions section (Section 10.1.1)
- Serious and not an SAR per the definitions section (Section 10.1.1)

Expedited reporting is required. This option applies if the AE/safety finding is classified as one of the following:

- Serious and unexpected suspected adverse reaction (SUSAR) per the definitions section (Section 10.1.1)

The Sponsor must report any SAR that is both serious and unexpected. The Sponsor must report AE as an SAR only if there is evidence to suggest a causal relationship between the study product and the AE, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with the product treatment (e.g. bradycardia, iritis).
- One or more occurrences of an event that is not commonly associated with product treatment but is otherwise uncommon in the population exposed to the product.
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of investigational product therapy) that indicates those events occur more frequently in the treatment group than in a concurrent or historical control group.

- Any safety findings from other studies: The Sponsor must report any findings from other epidemiological studies, pooled analysis of multiple studies, or clinical or nonclinical studies that suggest a significant risk in humans exposed to the investigational product that would result in a safety-related change in the protocol, informed consent, Investigator's brochure, or other aspects of the overall conduct of the study.

These events, which require unmasking, must be reported by the Sponsor to the appropriate health authorities within 15 calendar days; fatal or life-threatening events must be reported within 7 calendar days.

10.1.6 Reporting Pregnancy

During the study, all subjects should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the subject will be withdrawn from the study and followed until the pregnancy comes to term.

The Investigator is responsible for reporting all available pregnancy information on the Pregnancy Questionnaire Form (provided by the Sponsor) within 24 hours of becoming aware of the event, although pregnancy itself if not considered an AE. Study treatment must be discontinued immediately in the event of a pregnancy. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Monitoring of the participant should continue until the conclusion of the pregnancy. The Investigator is responsible for reporting the outcome of the pregnancy and the health of the newborn on the Pregnancy Outcome Form (provided by the Sponsor) as it becomes available. Partner pregnancies of a male subject do not need to be reported.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 10.1.5. If the pregnancy results in a congenital abnormality or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the Investigator suspects is related to the *in-utero* exposure to the study treatment should also be reported.

11 STATISTICAL ANALYSIS PLAN

11.1 General Statistical Methods and Types of Analysis

The primary analysis is a test of superiority of topical OCU300 vs OBS eyedrops with co-primary endpoints. Tests will be conducted using two-sided *alpha* = .05.

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.

11.2 Power and Sample Size Determination

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). 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 will be spent at the interim analysis, and the two-sided alpha for the final analysis will be 0.0498. If sample size is modified, the final critical value of 0.0498 will be adjusted to control type I error. The details of the interim analysis will be provided in the Statistical Analysis Plan (SAP).

Primary Efficacy Endpoint(s):

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

Secondary Efficacy Endpoint(s):

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

Exploratory Endpoint(s):

- Change from baseline in in Validated Bulbar Redness (VBR) score at Days 28 and 56
- Change from baseline in 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 (Oxford scale) 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)

11.3 Analysis Populations

The analysis populations are defined as follows:

- The safety population is defined as all subjects all subjects who have signed informed consent were randomized into the study and took at least one dose of study drug.
- The intent-to-treat (ITT) population is defined as all randomized subjects.
- The per-protocol (PP) population is defined as all ITT subjects who have no major protocol deviations. The PP population will be identified prior to database lock and treatment unmasking.

11.4 Efficacy and Safety Analyses

11.4.1 Background and Demographic Characteristics

Demographics and baseline characteristics including sex, age, race, height, weight, and ocular and medical history will be summarized for the safety population overall and for the ITT population by treatment group.

11.4.2 Efficacy Analyses

11.4.2.1 Primary Efficacy Analyses

The primary evaluation of efficacy will be a co-primary endpoint of bulbar redness as measured by VBR and ocular discomfort as measured by the ODS after 12 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 12 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 12 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 12 weeks (Day 84) ≠ 0.

The statistical hypotheses for the primary endpoint of the mean change from baseline ocular discomfort score (ODS) at 12 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 12 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 12 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;

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.

11.4.2.2 Efficacy Analyses—General Considerations

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 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. 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. A sensitivity analysis using pattern-mixture model with control- based pattern imputation will be performed to compare with the results of the primary 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 an association.

11.4.2.3 Safety Analyses

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 documents.

11.4.2.4 Adverse Events

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, by system organ class and preferred term, 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.

11.4.2.5 Concomitant Medications and Concomitant Therapies

Concomitant medications will be coded using the most recent version of World Health Organization (WHO)-Drug and summarized by treatment group.

11.4.2.6 Pharmacokinetic Analyses

None in this study

11.4.3 Other Statistical Considerations

11.4.3.1 Significance Levels

Tests will be conducted using two-sided *alpha* = .05.

11.4.3.2 Multiple Comparisons

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

11.4.3.3 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.

11.4.3.4 Visit Windows

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.

12 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1 Study Monitoring

According to ICH GCP guidelines, the Sponsor of the study is responsible for ensuring the proper conduct of the study regarding protocol adherence and validity of data recorded on the CRFs. The Sponsor is responsible for assigning the study monitor(s) to this study. The study monitor's duties are to aid the Investigator and the CRO in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the Investigator of the regulatory necessity for study-related monitoring, audits, IRB(s) review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the Investigator all regulations applicable to the clinical evaluation of an investigational drug as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the CRFs and source documentation throughout the study to protect the rights of the subjects; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the clinical monitoring plan.

The Sponsor requires that the Investigator prepare and maintain adequate and accurate records for each subject treated with the investigational drug. Source documents such as any hospital, clinic, or office charts and the signed informed consent forms are to be included in the Investigator's files with the subject's study records.

Study data will be captured on paper source documents and ultimately electronic case files Study site personnel will record CRF data from source documents. Subjects will record selected study assessments directly into the CRF. If any data are first recorded onto documents such as laboratory reports, these documents will be considered source.

12.2 Data Collection and Management

This study will be conducted in compliance with the ICH document E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1). This study will also be conducted in accordance with the Declaration of Helsinki (2013).

This study will use Brightech International's Clinical Information Management Suite (CIMS) for data collection and data management. The Investigator is responsible for ensuring that all sections of each CRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform 100% source document verification to ensure there are no inconsistencies between the CRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the clinical monitoring plan.

At intervals throughout the study and upon completion, data will be exported from the database into SAS datasets.

Data management will be coordinated by the data managers of Brightech International in accordance with their SOPs for data management and a formal study data management plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using the World Health Organization – Drug Reference List.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from the Sponsor, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for these periodic inspections/audits.

14 ETHICS

14.1 Ethics Review

The Investigator will not start this study, nor will investigational devices be shipped to the Investigator's site, before providing the Sponsor with evidence of the IRB(s) approval. The Investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects. The Investigator will not make any changes in the research without the IRB(s) approval, except where necessary to eliminate apparent immediate hazards to the subjects. The Investigator will provide progress reports to the IRB(s) as required by the IRB(s). The Investigator will provide a final report to the IRB(s) after completion of participation in the study.

14.2 Ethical Conduct of the Study

The Investigator is to conduct the study in accordance with this protocol, the Declaration of Helsinki, and ICH GCP guidelines. The Investigator and Sponsor will sign the protocol and study contract to confirm agreement. The Investigator will not implement any amendment (deviation or changes of the protocol) without agreement by the Sponsor and the IRB(s) approval/information, except where necessary to eliminate immediate hazards to study subjects or when changes involve only logistical or administrative aspects of the study.

14.3 Written Informed Consent

14.3.1 Subject Information and Informed Consent

The informed consent document will be approved by the IRB that is appropriate for each study site. The Investigator is responsible for ensuring that the subject fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible. Verbal consent will be accepted for subjects who are unable to read or write. No subject should be obliged to participate in the study. Subjects, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to

participate in the study or withdrawal from the study at any stage is without any prejudice to the subject's subsequent care. Subjects must be allowed sufficient time to decide whether they wish to participate.

The subject must be made aware of and give consent to direct access to his/her source medical records by study monitors, auditors, the IRB(s), and regulatory authorities. The subject should be informed that such access will not violate subject confidentiality or any applicable regulations. The subject should also be informed that he/she is authorizing such access by signing the informed consent form.

Each subject will be given a signed copy of the informed consent form to keep for his/her records.

14.3.2 Provision of New and Important Information Influencing Subject's Consent and Revision of the Written Information

When any new and important information that may be relevant to the subject's consent is obtained, the Investigator and Sponsor will consult with each other on how to deal with the information. When the Sponsor and a responsible Investigator judge it necessary, the Investigator must immediately provide the subjects with such information, revise the written information and other explanatory documents based on the new information, and obtain approval from the IRB(s). In this instance, the Investigator should also immediately inform subjects currently participating in the clinical study of such information, confirm their intention to continue participation, re-explain the study to them using the revised written information and other explanatory documents, and obtain written consent to continue participation based on their voluntary decision.

14.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being. Each subject will be asked to complete a form allowing the Investigator to notify the subject's primary health care provider of his/her participation in this study.

15 ADMINISTRATIVE PROCEDURES

15.1 Publications of the Clinical Study

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to the Sponsor.

15.2 Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the Investigator after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the Investigator and Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

No deviation from the protocol or investigational plan will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the sponsor, and the regulatory authorities (e.g., FDA) or the IRB(s) if applicable, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Sponsor and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

No waivers to inclusion/exclusion criteria will be granted; subjects need to meet all criteria, exactly as specified, to be enrolled. Additionally, prospective deviations from the protocol or investigational plan are not permitted except to protect the life or physical well-being of a subject in an emergency. Deviations that occur unintentionally or are the result of action by the subject must be documented and reported to the Study Sponsor and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

16 DATA HANDLING AND RECORD KEEPING

16.1 Inspection of Records

The Sponsor, their designee(s), the IRB(s), or regulatory authorities will be allowed to conduct site visits to the investigational facilities for monitoring or inspecting any aspect of the study. The Investigator agrees to allow the Sponsor, their designee(s), the IRB(s), or regulatory authorities to inspect the investigational drug storage area, investigational drug stocks, investigational drug records, subject charts and study source documents, and other records relative to study conduct.

16.2 Retention of Records

The principal Investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

16.3 Sample Retention

No blood or tissue samples will be obtained during this study.

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18 APPENDICES

18.1 Appendix 1 Diagnosis of Definite oGVHD

The diagnosis of 'definite' oGVHD shall be made using the International Chronic Ocular GVHD Consensus Group revised diagnostic criteria. The Consensus Group Severity Scale is based on the cumulative grading of 4 individual scores (see Table 6):

1. Schirmer's Test,
2. Corneal staining score,
3. Conjunctival Injection, and
4. OSDI score.

Assign a severity score from 0 to 3 to each of the assessments below, except for conjunctival injection, which should be scored from 0 to 2 points. The sum of the 4 severity scores (in points) gives a total, or aggregate, score for each eye.

Table 6. International Chronic Ocular GVHD Consensus Group Severity Scale for oGVHD

Severity score (points)	Schirmer's test (mm)	CFS* (Grade)	OSDI (Score)	Conjunctival Injection (Description)
0	>15	None (Grade 0)	<13	None
1	11-15	Minimal (Grade 1)	13-22	Mild/Moderate
2	6-10	Mild/Moderate (Grade 2)	23-32	Severe
3	≤5	Severe (Grade 3)	≥33	

CFS = Corneal fluorescein staining, OSDI = Ocular Surface Disease Index
Source: Table adapted from Ogawa, 2013; *For CFS, see appendix 18.7

Based on the aggregate score and the presence or absence of systemic GVHD, a diagnosis of oGVHD will be made for each eye. For example, in the presence of systemic GVHD, aggregate score 0-3 indicates absence of oGVHD (i.e., "none"), aggregate score 4-5 indicates "probable" oGVHD, and aggregate score >6 indicates "definite" oGVHD. In the absence of systemic GVHD, aggregate score 0–5 indicates absence of oGVHD (i.e., "none"), aggregate score 6–7 indicates "probable" oGVHD, and aggregate score ≥ 8 indicates "definite" oGVHD. (see Table 7)

Table 7. Diagnosis of Chronic oGVHD

Systemic GVHD	No oGVHD (points*)	Probable oGVHD (points*)	Definite oGVHD (points*)
Absent	0-5	6-7	≥8
Present	0-3	4-5	≥6

GVHD = graft versus host disease
Source: Adapted from Ogawa 2013. Refer to Appendix 18.7
* Points are aggregate severity scores from 4 diagnostic tests (see Table 6 above).

The above assessment will be measured independently on each eye at the Screening visit. Subjects who meet the diagnosis of "definite oGVHD" in at least one eye satisfy Inclusion Criterion #2.

18.2 Appendix 2 Ocular Discomfort Scale

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)". This type of severity scale has been validated as an assessment of pain intensity in multiple populations. Moreover, it has been recommended as the primary endpoint for use in clinical trials for chronic pain (Ferreira-Valente et al. 2011; Dworkin et al. 2005; Farrar et al. 2001; Caraceni et al. 2002; Satitpitakul et al. 2017).

The 10-point scale will be used as a co-primary endpoint in this study . The scale is illustrated below (Figure 1):

The subject will be asked to mark a single line on the scale that best corresponds to their answer for the following question about their pain over the past 24 hours.

"**On a scale from 0-10, what was the intensity of your Ocular Discomfort, at its worst, over the past 24 hours?"**

Figure 1. Ocular Discomfort Scale

The above scale will be measured at Screening and each study visit: Baseline (prior to first dose), Day 28 ± 7d, Day 56 ± 7d, and Day 84 ± 7d.

Baseline and screening assessments may be combined as long as the window between the Baseline and Screening visit is fewer than 7 days. When the visits are combined, only one (1) Baseline (before dosing) assessment is required.

18.3 Appendix 3 Validated Bulbar Redness Grading Scales (VBR)

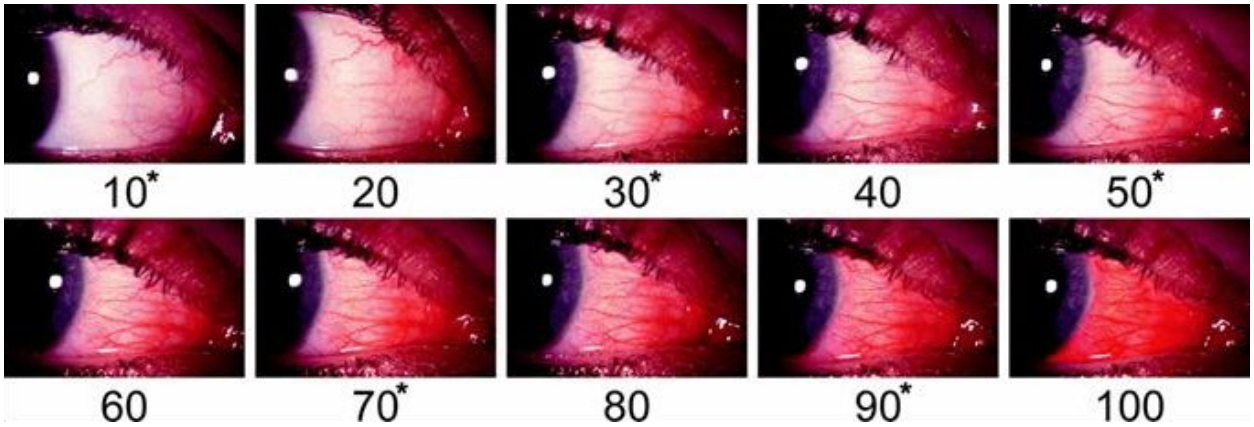
To evaluate ocular redness, the same physician (PI) must assess the subject at all examinations, and under consistent illumination. Examinations must be completed by a slit lamp at 10X magnification using direct diffuse illumination (slit fully opened, angled at 30°- 50° approximately; at half illumination intensity with rheostat set to maximum voltage).

A set of colored reference images will be provided at high resolution (with one image per page) (Figure 2). To maintain the integrity of the original image, the photos should not be photocopied or reproduced in any way by site personnel. Multiple sets of images will be provided to each site, corresponding with the number of examination rooms. If a set of images is lost or damaged, a new one will be supplied to the site.

During the examination, ask the subject to look at nasal or temporal fixation marks while the temporal or nasal bulbar conjunctivae, respectively are examined by the physician. Compare the physician's assessment of the bulbar conjunctival injection of the subject's eye (nasal and temporal) to the reference images in the VBR, and grade accordingly in the subject's source documents and CRFs.

Using the 10-picture photographic grading scale select a number (e.g. 10, 20,… 80, 90, or 100) that best approximates but does not overestimate the average level of bulbar redness observed in each eye (OD, OS). There is no image representing an absolute grade 0, because the bulbar conjunctiva usually exhibits some level of redness. Therefore, a white eye would be scored as a 10.

Figure 2. Validated Bulbar Redness Scale



Source: Shulze, 2007

This manner of testing with increments of 10 was chosen because this assessment yields a slightly higher level of repeatability than continuous scales (e.g. 1, 1.1, 1.2…9.8, 9.9, 10) and a strong linear association between test and re-test.

The above scale will be measured at Screening and at each study visit: Baseline (prior to first dose), Day 28 ± 7d, Day 56 ± 7d, and Day 84 ± 7d.

Baseline and screening assessments may be combined as long as the window between the Baseline and Screening visit is fewer than 7 days. When the visits are combined, only one (1) Baseline (before dosing) assessment is required.

18.4 Appendix 4 Symptom Assessment iN Dry Eye (SANDE)

Administer the questionnaire at Baseline on Day 1 (prior to dosing), and again at all subsequent clinic visits; Day 28 ± 7d, Day 56 ± 7d, and Day 84 ± 7d.

At each visit, ask the subject to place a mark on each of the "frequency" and "severity" lines below based on the extent of their symptoms (Figure 3).

Measure the locations of the marks made by the subject in millimeters, from left to right on the 100 mm horizontal lines; record the results in the subject's source documents and CRFs.

The overall SANDE score will be calculated by multiplying the frequency score by the severity score and obtaining the square root (Amparo, 2015; Saboo, 2015).

Figure 3. SANDE Questionnaire

SANDE Questionnaire

PLEASE COMPLETE THE FOLLOWING QUESTIONS REGARDING THE FREQUENCY AND SEVERITY OF YOUR DRY EYE SYMPTOMS.

1. Frequency of symptoms:
Please place an 'X' on the line to indicate how often, on average, your eyes feel **dry and/or irritated:**

Rarely ——————————————— **All the time**

2. Severity of symptoms:
Please place an 'X' on the line to indicate how severe, on average, you feel your symptoms of **dryness and/or irritation**:

Very Mild ——————————————— **Very Severe**

18.5 Appendix 5 Ocular Surface Disease Index (OSDI)

Figure 4. OSDI Questionnaire

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

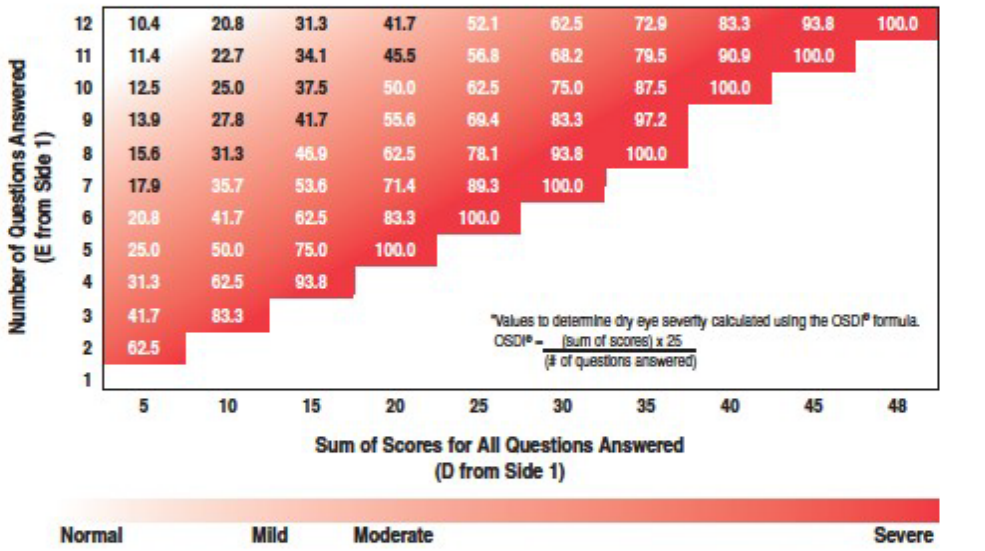
Please turn over the questionnaire to calculate the patient's final OSDI® score.

Evaluating the OSDI® Score[1]

The OSDI® is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI® is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



Patient's Name: _____ Date: _____

How long has the patient experienced dry eye disease? _____

Eye Care Professional's Comments: _____

1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

Encourage subjects **to answer all questions**.

The OSDI score will be calculated = [(SUM of scores) x 25]/Number of Questions answered

The above scale will be measured at Screening and at each study visit: Baseline (prior to first dose), Day 28 ± 7d, Day 56 ± 7d, and Day 84 ± 7d. *At Screening, the OSDI score (range, 0-100) is converted to a "severity score" (range, 0-3) to aid in the diagnosis of oGVHD (Appendix 1).*

Baseline and screening assessments may be combined as long as the window between the Baseline and Screening visit is fewer than 7 days. When the visits are combined, only one (1) Baseline (before dosing) assessment is required.

18.6 Appendix 6. Ocular Surface Staining: Lissamine Green

Lissamine Green dye (approximately 5 µL of 1% solution) will be applied over the surface of both eyes. A solution shall be made from Lissamine Green Ophthalmic Strips.

18.6.1 Lissamine Solution

Materials Supplied:

1. Lissamine Green (LG) Ophthalmic Strips (NDC 17238-920-11) impregnated with 1.5 mg of LG/strip
2. Sterile Saline (0.9 %) solution (supplied as syringe filled normal saline)
3. Sterile microfuge tubes (1.5 mL)
4. Sterile pipette tips (5 µL (microliter) and 200 µL volume dispensing)
5. Fixed Volume Pipettes (5 µL and 200 µL)

Lissamine Green Ophthalmic Strips (NDC 17238-920-11) impregnated with 1.5 mg of LG dye will be used to prepare LG solution. Dispense saline (about 0.5 to I mL) from the pre-filled syringe to an empty sterile microfuge tube. From the microfuge tube, dispense 200 µL of saline solution to an empty microfuge tube using 200 µL pipette. Dip 2 LG strips into the microfuge tube containing 200 µL of saline. Make sure the impregnated portion of the LG is immersed in the saline solution and leave for 5 minutes at room temperature for the LG dye to dissolve from strips and enter in the saline solution.

Afterwards, discard the strips and use the LG solution for staining. Mix the LG solution by finger tapping the bottom of the tube.

18.6.2 Instillation of Lissamine Green

Take out 5 µL of LG solution from microfuge tube using 5 µL fixed volume pipette attached with sterile tip and apply in the lower conjunctival cul-de-sac (inferior conjunctival fornix) by pulling the lower lid to make a pocket and instilling the dye. Instruct the subject to blink 5 times and avoid closing eyelids tightly or squeezing eyelids after dye instillation and ask to move the eyes in all directions (left, right, up and down) while blinking gently to spread the dye.

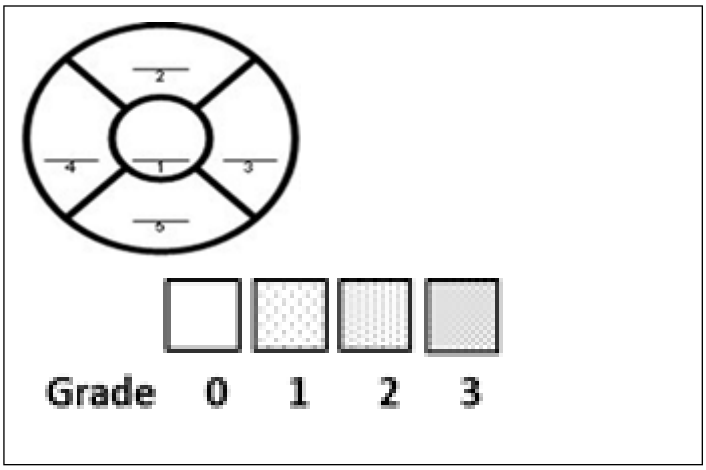
Ocular surface staining is recorded 1-2 minutes after dye instillation (within 4 minutes) as the staining fades variably after 4 minutes. After slightly pulling down the lower eye lid of the patient, Lissamine Green dye will be released into the lower conjunctival sac. The right eye will be evaluated first, and the process will be repeated in the left eye.

18.6.3 Evaluating Lissamine Green Staining

Using the slit lamp (white light of moderate intensity and a Hoya 25A red barrier filter or Kodak Wratten 92 filter), corneal and conjunctival staining will be graded using the grading system described below modified from the NEI Scale (Lempe 1995).

The scoring pattern is represented below in Figures 5 and 6. The dots are ordered on a log scale.

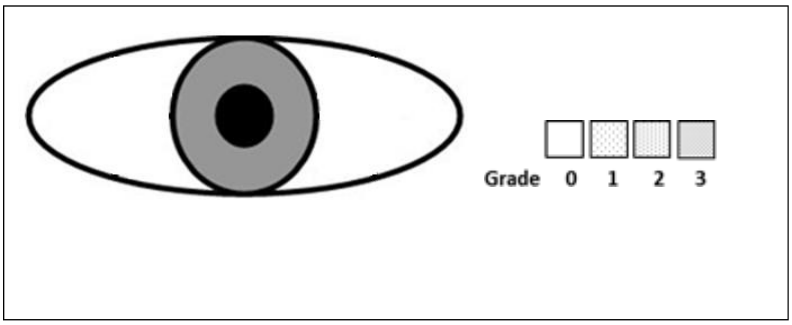
Figure 5. Lissamine Green Corneal Staining Pattern and Grade (NEI Scale)



Corneal staining will be graded in 5 zones (Central (3mm), Superior, Inferior, Nasal, and Temporal). Each zone will be graded from 0 to 3 based on the density of punctate staining (maximum score = 15).

Similarly, the 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) (Figure 6). Instruct the subject to look toward the midline (nasally) to grade the temporal zone. Likewise, instruct the subject to look temporally to grade the nasal conjunctiva.

Figure 6. Lissamine Green Conjunctival Staining Pattern and Grade (NEI Scale)



Because Lissamine Green dye can fade variably within 4-5 minutes, results should be recorded within approximately 1-2 minutes of application to the eye surface. Scoring is demonstrated in Table 8.

Table 8. Corneal and Conjunctival Lissamine Green Scoring

Lissamine Green Staining	Grade	Zones	Maximum Score/Eye (all zones)
Cornea	0-3	Central (3mm) Superior Inferior Nasal Temporal	15 OD 15 OS
Conjunctiva	0-3	Nasal bulbar Temporal bulbar	6 OS 6 OD

The above staining/scale will be measured at each study visit: Day 1 Baseline (prior to first dose), Day 28 ± 7d, Day 56 ± 7d, and Day 84 ± 7d.

18.7 Appendix 7 Ocular Surface Staining: Fluorescein

Fluorescein dye (approximately 5 µL of 1% solution) will be applied over the surface of both eyes to assess corneal fluorescein staining. A Wratten #12 yellow filter may be used to enhance the ability to grade staining.

18.7.1 Fluorescein solution

The examiner will instill 5 µL of 1% sodium fluorescein solution or Fluorescein Ophthalmic Strips may be used into the inferior conjunctival cul-de-sac of each eye. If the strips will be used:

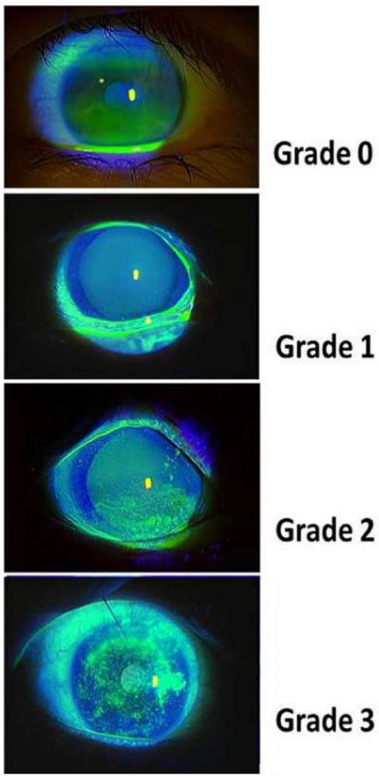
1) Place a drop of saline onto the strip.
2) When the drop has saturated the impregnated tip, shake the excess into a waste bin with a sharp flick.
3) Pull down the right lower lid and tap the strip onto the lower tarsal conjunctiva.

To achieve maximum fluorescence, the examiner should wait approximately 2-3 minutes after instillation before performing the evaluation. The left eye is evaluated after the right eye.

18.7.2 Corneal Fluorescein Staining (CFS) with Severity Points

This assessment shall be conducted at Screening in each eye as part of the definitive diagnosis for oGVHD (see Appendix 1). A Wratten #12 yellow filter may be used to enhance the ability to grade staining at the slit lamp. Scoring is indicated in Table 9.

Table 9. Corneal Fluorescein Staining (CFS) with Severity Points

Severity Points/eye *	Description and Grade	Slit Lamp Micrograph of CFS grading scale
0	None ; Grade 0	
1	Minimal staining; Grade 1	
2	Mild/moderate staining; Grade 2	
3	Severe staining; Grade 3	

Source: Ogawa, 2013

*Corneal fluorescein severity points are added to severity points of three other tests to get oGVHD aggregate score for each eye; the aggregate, in turn, is used to diagnose/classify oGVHD in each eye (Ogawa, 2013) (Refer to appendix 18.1)

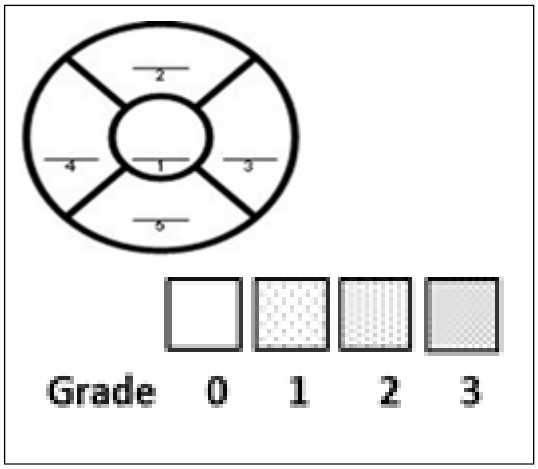
18.7.3 Corneal Fluorescein Staining <u>without</u> Severity Points (NEI scale)

This assessment shall be used at each study visit: Baseline (prior to first dose), Day 28 ± 7d, Day 56 ± 7d, and Day 84 ± 7d. Each eye shall be graded separately. At baseline this assessment (see Table 10) should be performed before the Schirmer's test with anesthetic and after the slit lamp examination.

Only the cornea will be evaluated. Corneal staining will be graded in 5 zones (Central (3mm), Superior, Inferior, Nasal, Temporal). Each zone will be graded from 0 to 3 based on the density of punctate staining (maximum score/eye =15).

Each eye (OS and OD) will be graded according to the NEI Scale.

Table 10. Corneal Fluorescein Scoring (NEI Scale)

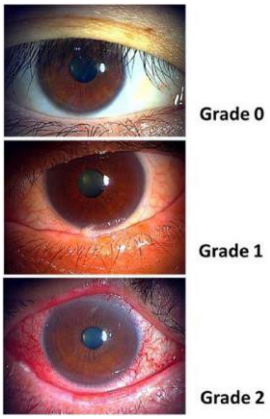
Grade	Staining Pattern	Description (Investigators impression)
0		No staining normal, negative slit lamp findings
1		Minimal staining; mild superficial stippling
2		Mild/moderate staining; punctate staining including superficial abrasion of the cornea
3		Severe-very severe staining; abrasion or corneal erosion

Source: Lemp MA. 1995

18.8 Appendix 8. Conjunctival Injection with Severity Points

To determining subject eligibility, conjunctival injection grading of each eye, OS and OD, will be assessed at the Screening visit. The assessment will be used as part of the definitive diagnosis for oGVHD (see Appendix 1). Scoring is demonstrated below in Table 11.

Table 11. Conjunctival Injection Scoring

Conjunctival Injection	**Severity points/eye***	**Slit Lamp Micrograph of CFS grading scale**
None	**0**	
Mild/moderate injection	**1**	
Severe injection	**2**	

Source: Ogawa, 2013

*Conjunctival injection severity points are added to severity points of three other tests to get oGVHD aggregate score for each eye; the aggregate, in turn, is used to diagnose/classify oGVHD in each eye (Ogawa, 2013)

18.9 Appendix 9. Visual Acuity

18.9.1 Visual Acuity Testing

18.9.1.1 Best-Corrected Visual Acuity (BCVA)

In this study, visual acuity is a safety (not efficacy) endpoint. For BCVA, please use your local ETDRS standard of care for testing. The Snellen equivalent should be recorded in the CRF for each eye.

18.10 Appendix 10. Intraocular Pressure (IOP)

Intraocular Pressure (IOP) will be measured in both eyes. IOP will be measured at Screening and at each study visit: Baseline (prior to first dose), Day 28 ± 7d, Day 56 ± 7d, and Day 84 ± 7d.

18.10.1 Calibration of Tonometer

The Goldmann tonometer shall be used for IOP measurements. The tonometer must be calibrated before first use and calibration will be checked by the Investigator prior to measuring IOP for each subject, with the weight system at 0, 2, and 6 grams as supplied by the manufacturer. When the calibration steps provide readings within ± 0.5 mmHg of the target value for each weight, the tonometer is considered adequately calibrated. The investigator must maintain written documentation (e.g., unit model or serial number, calibration date, name/initial of person performing calibration, indication of pass or fail) of the calibration of each tonometer throughout the study period.

18.10.2 IOP Measurement

IOP will be taken as follows:

1. Anaesthetize the selected eye of the subject.
2. Stain with sodium fluorescein.

   NOTE – step may be combined by using an anesthetic to which sodium fluorescein has already been added.
3. Set the tonometer drum to a force corresponding to an IOP of 10 mmHg. Wherever possible, do not touch the eyelid with the fingers to open the palpebral aperture. If the palpebral aperture is not wide enough to allow the tonometer cone to make contact, instruct the subject to open their eyes wider.
4. Direct the subject to view a distance fixation point.

   NOTE – If distance fixation cannot be maintained and ***near fixation is used, this fact should be recorded****.*
5. Measure the IOP for the mean of the ocular pulse and remove the tonometer from the eye.
6. Repeat steps if the measurement was not valid due to the following reasons;
   - The patient felt a sensation
   - The eyelid was touched
   - The fluorescein ring was too broad or too small
   - Any other circumstances suggesting that the measurement may have been inaccurate
7. If there is any evidence that the anesthetic is no longer fully effective, then re-administer anesthetic.
8. Record the IOP, as the mean of 3 valid measures. Measure and record means for OS and OD.

18.11 Appendix 11. Slit-Lamp Examination

Slit-lamp ophthalmic examination will be performed at each clinic visit. The subject should be seated with their chin and forehead rested against the chin rest and head support during the examination. Fluorescein dye should be instilled into the ocular cul-de-sac to facilitate the examination. The lid, lashes, tear film, conjunctiva, sclera, cornea, anterior chamber, iris, lens, and anterior vitreous of the eye will be examined and graded as follows in Table 13:

Table 12. Evaluation of Slit-Lamp Assessments

Assessment	Observation	Evaluation
External Eyelid Examination	• Eyelid position and character, • Lashes, lacrimal apparatus and tear function; • Globe position; and • Pertinent facial features	Normal Abnormal (CS, not CS)
Iris	• Pigmentation • Atrophy/erosion, peaking • Other	Normal Abnormal (CS, not CS)
Cornea	• No Edema / Edema • Staining • Erosion • Fluorescein staining	Normal: None Abnormal CS Abnormal NCS

Assessment	Observation			Evaluation
Anterior Chamber Cells	**Grade**	**Aqueous Cells** Per 1x1 mm slit	**Global evaluation**	
	0	< 1 cell	Normal	
	0.5+	1-5 cells seen in 45 seconds or 1 minute	Abnormal (CS/NCS)	
	1+	6-15 cells seen at once		
	2+	16-25 cells scattered throughout beam		
	3+	26-50 (Dense scattering of cells; too many to count)		
	4+	> 50 or hypopyon		
	Grade	**Flare (Slit Beam)** Per 1x1 mm slit	**Global evaluation**	
	0	None; Optically empty, compared bilaterally	Normal	
	1+	Faint haze (any appreciable light in slit beam) or not equal bilaterally	Abnormal CS/NCS	
	2+	Moderate: but iris details are clear through slit beam		
	3+	Marked: iris and lens details hazy		
	4+	Severe dense haze: obvious plasmoid aqueous or fibrin present in anterior chamber		
Posterior Segment	Vitreous, Retina, Macular, Blood Vessels, Optic Nerve			Normal: None Abnormal CS Abnormal NCS

*CS = clinically significant; NCS = not clinically significant

For any abnormal case, the investigator will determine whether it is clinically significant or not.