CLINICAL STUDY PROTOCOL

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate 0.2% Nanoemulsion Eye Drops in Patients with Dry Eye Disease (DED)

Protocol Number:	OCU-310-301
Investigational Product:	OCU310 (Brimonidine Tartrate Ophthalmic Nanoemulsion 0.20%)
Version:	v. 1.0 (12 Aug 2018)
IND Applicant/Product Sponsor:	Ocugen, Inc. 5 Great Valley Parkway, Suite 160 Malvern, PA 19355 USA
Authorized Signatory:	Daniel Jorgensen, MD, MPH Chief Medical Officer Ocugen, Inc. 5 Great Valley Parkway, Suite 160 Malvern, PA 19355 USA Telephone: (484) 328-4702 Fax: 610-644-4005 E-mail: dan.jorgensen@ocugen.com

Table 1. Administrative Structure

Medical Monitor: **(24-hour emergency contact)**	Barbara Wirostko, MD Trial Runners 116 W. Villard Dickinson, ND 58601 Phone: 24-hour contact : 347-453-1521 Email: barbarawirostko@trialrunners.com
Biostatistician:	Steve Crockett, PhD Design and Analysis of Trials Associates, Inc 10053 Border Drive, East Grand Bay, AL 36541 Email: scrocket@iglou.com
Serious Adverse Event Reporting:	Barbara Wirostko, MD Medical Monitor Trial Runners 116 W. Villard Dickinson, ND 58601 Email: barbarawirostko@trialrunners.com Phone: 347-453-1521 General Fax: SAE Fax Number (US): SAE Hot Line Number (US):

INVESTIGATOR'S SIGNATURE

I have received and read the Investigator's brochure for Brimonidine (OCU310). I have read protocol OCU-310-301 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 Investigator

_____

Title of Investigator

_____

Signature of Investigator

_____

Date

SPONSOR'S SIGNATURE

Approved by:

Daniel Jorgensen, MD, MPH Chief Medical Officer Ocugen, Inc.	Date

PROTOCOL REVISION HISTORY

Table 2. Revision History

Version Number	**Version date**	**Summary of Revisions Made**	
		Major	**Administrative**
Version 1.0	12 August 2018		

SYNOPSIS

Protocol Title:

A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate 0.2% Nanoemulsion Eye Drops in Patients with Dry Eye Disease (DED)

Protocol Number:

OCU-310-301

Clinical Phase:

Phase 3

IND Applicant/Product Sponsor:

Ocugen, Inc.
5 Great Valley Parkway, Suite 160
Malvern, PA 19355 USA
Telephone: 484-328-4701
Fax: 610-644-4005

Authorized Signatory:

Daniel Jorgensen, MD, MPH
Chief Medical Officer

Regulatory IND Number:

136132

Indication:

Relief of signs and symptoms of dry eye disease

Investigational Drug:

Brimonidine Tartrate Nanoemulsion 0.20% Ophthalmic Solution (OCU310).

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 Dry Eye Disease (DED)

Primary Efficacy Endpoint(s):

1. Change from baseline to 4 weeks (Day 28) in SANDE score
2. Change from baseline to 4 weeks (Day 28) in Lissamine Green conjunctival staining scores

   Note: This endpoint would be considered in a hierarchical fashion if statistical success is first demonstrated for SANDE at Day 28.

Secondary Efficacy Endpoint(s):

3. Change from baseline to 2 weeks (Day 14) in SANDE score
4. Change from baseline to 2 weeks (Day 14) in Lissamine Green conjunctival staining scores

Note: The above endpoints (Primary and Secondary) will be tested in a fixed sequence (1-4) proceeding to the next endpoint until a p-value >0.05 is found.

Safety Endpoint(s):

- Rate of ocular adverse events (AEs)

Exploratory Endpoint(s):

- Change from baseline to 4 weeks (Day 28) in Lissamine Green corneal staining scores
- Change from baseline to 2 weeks (Day 14) in Lissamine Green corneal staining scores
- Change from baseline to 4 weeks (Day 28) in Schirmers scores
- Change in appearance from baseline to 4 weeks (Day 28) in Validated Bulbar Redness (VBR) scale
- Change in appearance from baseline to 4 weeks (Day 14) in Validated Bulbar Redness (VBR) scale
- Clinical Global Impression (CGI) of change in symptoms from baseline (physician's rating) to 4 weeks (Day 28)
- Subject Global Assessment (SGA) of overall change from baseline (subject's rating) to 4 weeks (Day 28)

Investigational Products
Investigational Drug Dosage:

One drop of Brimonidine Tartrate Nanoemulsion 0.20% administered in each eye, two times a day (bid)

Control Dosage:

One drop of OBS administered in each eye, two times a day (bid)

Inclusion Criteria

Subjects will be eligible for the study if **all** the following criteria are met:

1. Aged 18 years or older.
2. Sign and date informed consent form approved by the IRB
3. History of Dry Eye Disease for ≥6 months
4. Demonstrate the following 2 signs of DED in the same eye at Screening and Baseline (Day 1):
    a. Conjunctival staining at ≥3 (out of a possible score of 6 per eye), and
    b. Schirmer test (with anesthesia) at ≥1 to ≤7mm in 5 minutes
5. Symptomatic evidence of DED by having a global symptom score (Overall SANDE) ≥40 mm at Screening and Baseline (Day 1) visit
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 and who are either abstinent or sexually active on an acceptable method of birth control for at least 4 weeks prior to Visit 1 and throughout the study (i.e., until Day 28), 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 prior to initial dosing:

1. Allergic to brimonidine or any similar products, or excipients of brimonidine or loteprednol
2. Use of contact lenses within 14 days prior to Screening visit or planned use during study
3. Currently receiving brimonidine or other treatment for glaucoma or ocular hypertension or history of glaucoma surgery.
4. Receiving or have received any experimental or investigational drug or device within 30 days prior to Screening visit
5. Intraocular pressure <5 mmHg or >22 mmHg in either eye
6. Active ocular infection or history of ocular herpetic keratitis
7. History of neurotrophic keratitis or ocular neuropathic pain
8. Any history of eyelid surgery or intraocular/ocular surgery within the past 3 months
9. Punctal occlusion within 3 months prior to Screening visit or during study
10. Corneal epithelial defect larger than 1 mm^2 in either eye
11. Have active drug/alcohol dependence or abuse history
12. Are neonates, pregnant/lactating women, children, or others who may be considered vulnerable populations
13. Received corticosteroid-containing eye drops within 14 days prior to Screening visit or planned use during study
14. Any change in systemic corticosteroids/immunosuppressives, cyclosporine ophthalmic emulsion 0.05% (Restasis®), or lifitegrast ophthalmic solution 5% (Xiidra™) within 30 days prior to Screening visit or planned change during study
15. In the opinion of Investigator or Study Coordinator, be unwilling or unable to comply with study protocol or unable to successfully instill eye drops
16. Disease, condition, or disorder that in the judgement of Investigator could confound study assessments or limit compliance to study protocol

Note: Subjects will be permitted to continue all their ocular treatments, including the use of artificial tears, eyelid massage, or warm compresses, if they commit to using the same brand/regimen throughout the study. None of the ocular treatments, whether OTC or prescription (e.g. Restasis or Xiidra) 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.

General Statistical Methods and Types of Analysis

The primary analysis is a test of superiority of topical OCU300 vs OBS drops with a set of ordered endpoints to be tested in a fixed sequence.

Tests will be conducted using two-sided *alpha* = .05 in a fixed sequence.

Unit of Analysis

The unit of analysis for variables measured at the individual eye level will be the study eye. Each subject will have a single eye identified as the study eye as follows: (i) if only 1 eye meets inclusion criteria, this eye will be the study eye and the other eye will be considered the non-qualified fellow eye; (ii) if both eyes meet inclusion criteria, the eye with the higher Lissamine Green conjunctival staining score will be the study eye and the other eye will be considered the qualified fellow eye; (iii) if both eyes have the same Lissamine Green conjunctival staining score, then the eye with the lower Schirmer score will be the study eye and the other eye will be considered the qualified fellow eye; (iv) if both eyes have same Schirmer score, the right eye will be the study eye and the other eye will be considered the qualified fellow eye. Analysis of safety and efficacy variables measured at the eye level will be primarily performed on the study eyes and secondarily on the qualified fellow eyes (for efficacy) and all fellow eyes (for safety).

The unit of analyses for variables measured at the subject level will be the subject.

Power and Sample Size

One-hundred eight subjects in each of the OCU 310 and placebo arms yields 99% power to reject the null hypothesis and conclude superiority of OCU 310 over placebo in the mean change from baseline SANDE score at 4 weeks assuming the mean changes from baseline in OCU 310 and placebo are -20.0 and -3.5 respectively, a common standard deviation of 25.0, and a two-sided alpha = 0.05.

Additionally, 108 study eyes in each of the OCU 310 and placebo arms yields 90% power to reject the null hypothesis and conclude superiority of OCU 310 over placebo in the mean change from baseline Lissamine Green conjunctival staining score in the study eye at 4 weeks assuming the mean changes from baseline in OCU 310 and placebo are -0.4 and 0.2 respectively, a common standard deviation of 1.35, and a two-sided alpha = 0.05. For the secondary endpoints (Day 14), there are not enough data to make a power/sample size statement.

For the primary analysis, with 108 subjects per arm, the study will have approximately 90% power to reject both H_{01} and H_{02}, assuming independence between endpoints (with higher power should the endpoints be positively correlated), and conclude the OCU 310 to be superior to placebo in both the mean change from baseline SANDE score at 4 weeks and the mean change from baseline Lissamine Green conjunctival staining score in the study eye at 4 weeks.

Accounting for 10% subject discontinuations, **240** total subjects will be enrolled (120 per arm).

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. The safety set will be analyzed according to the treatment actually received.

Intent-to-treat (ITT) Population

The ITT set will be the primary analysis set for the efficacy endpoints and will include all randomized subjects who have at least one post-baseline efficacy measurement. The ITT population will be analyzed according to the planned treatment.

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. The PP population will be analyzed according to the treatment actually received.

Hypotheses

The following type of hypothesis will be tested:

H_0: The difference (OCU 310 minus placebo), between subjects treated with the OCU 310 and subjects treated with placebo in the mean change from baseline = 0.

H_A: The difference (OCU 310 minus placebo), between subjects treated with the OCU 310 and subjects treated with placebo in the mean change from baseline ≠ 0, with superiority claimed if the difference < 0.

Fixed sequence testing will be employed to maintain the type I error rate.

General Considerations

Continuous study assessments will be summarized by treatment and visit (as applicable) and change from baseline to each post-baseline visit using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Categorical study assessments will be summarized by treatment and visit (as applicable) using frequency counts and percentages.

Efficacy Analysis

Four endpoints (two primary and two secondary) will be tested in a fixed sequence proceeding to the next endpoint until a p-value >0.05 is found. The analysis of the four outcomes will employ a repeated measures mixed model with mean change from baseline score at the stated time point as the response with baseline score as a covariate and treatment, visit, and their interaction as fixed effects. The least squares mean difference (OCU 310 – placebo) at the stated time point will be tested. The 2-sided p-values and associated 95% confidence intervals will be presented.

The primary efficacy analyses will be conducted on the ITT population. The same set of efficacy analyses will also be performed on the per-protocol population.

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: 12 August 2018

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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
CFR	Code of Federal Regulations
CFS	Corneal fluorescein staining
CGI	Clinical Global Impression
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel test
CRF	Case report form
DBP	Diastolic blood pressure
DED	Dry Eye Disease
ECM	Extracellular matrix
eCRF	Electronic case report form
EDTRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug Application
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LG	Lissamine Green

logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
MMRM	Mixed model of repeated measurements
NEI	National Eye Institute
NIH	National Institute of Health
OBS	Ophthalmic Buffered Saline
ODD	Orphan Drug Designation
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
UAR	Unexpected Adverse Reaction
UCVA	Uncorrected Visual Acuity
USA	United States of America
VAS	Visual Analog Scale
VBR	Validated Bulbar Redness
WHO	World Health Organization
WOCP	Women of child-bearing potential

1 INTRODUCTION

Ocugen Inc. is developing a proprietary novel product (OCU310) consisting of brimonidine tartrate (0.2%) as an ophthalmic nanoemulsion eye drops for the relief of signs and symptoms of Dry Eye Disease (DED). Brimonidine is an imidazoline compound that acts as a specific alpha 2 adrenergic receptor agonist. Brimonidine tartrate ophthalmic solution is currently an FDA approved product and is available at different concentrations and is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

1.1 Dry Eye Disease

Dry eye disease (DED) is a common ocular disorder involving the aberrant production and instability of tear film, which results in damage to the ocular surface and is correlated with symptoms of ocular discomfort. DED is also recognized as keratoconjunctivitis sicca (KCS), sicca syndrome, keratitis sicca, xerophthalmia, dry eye syndrome (DES), dysfunctional tear syndrome (DTS), ocular surface disease (OSD) or dry eye. DED is caused by chronic instability of preocular tear film. Tear film instability can be triggered by insufficient tear production, or by poor tear film quality that results in increased tear evaporation (Phadatare et al 2015). Furthermore, dry eye is typically categorized into two groups:

1) Aqueous tear deficient dry eye disease
2) Evaporative dry eye disease

DED is a result of changes to the lacrimal functional unit (LFU). The LFU is composed of the lacrimal glands, cornea, eyelids, meibomian glands, conjunctiva, goblet cells, and ocular nerves. The LFU is responsible for the sustained production of adequate tear film to consistently lubricate the ocular surface. Structural changes to the LFU can induce tear film instability and insufficiency, which in turn can lead to tear hyperosmolarity. Chronic osmotic stress from tear film can activate stress associated pathways in ocular surface epithelial cells, thereby triggering a pro-inflammatory response that involves a mix of chemokines, cytokines, and matrix metalloproteinases. The subsequent maturation of antigen-presenting cells (APC's) on the ocular surface leads to the migration, activation, and expansion of autoreactive T cell lymphocytes as well as other leukocytic classes in the LFU. The constant recruitment of pro-inflammatory leukocytes onto the ocular surface inflicts epithelium damage in the form of small abrasions and epithelium barrier defects (Pflugfelder et al 2008; Stevenson et al 2012). These abrasions can eventually progress to superficial punctuate keratitis, squamous metaplasia, extracellular matrix deposits, decreased goblet cell differentiation, increased epithelial cell turnover (epitheliopathy), and significant ocular surface nerve damage and neuropathy.

As DED progresses, lacrimal gland obstruction, meibomian gland orifice obstruction, thickened eyelid margins, cloudy, solid, or granular meibum secretion, eyelid telangiectasia, and meibomian gland dysfunction become common clinical features. In advanced cases, dry eye can cause fibrotic thickening of the cornea and conjunctiva, filamentous keratitis, mucoid clumping, trichiasis, symblepharon, keratinization of the eyelids and meibomian glands, corneal and conjunctival erosion and thinning, corneal and conjunctival neovascularization, corneal and conjunctival scarring, corneal ulceration, and corneal perforation. In addition, prolonged ocular surface inflammation can lead to moderate or absolute loss/atrophy of the meibomian glands, lacrimal glands, and conjunctival goblet cells, and subsequently a dramatic reduction in tear film production and the onset of permanent DED (Messmer et al 2015).

DED prevalence increases with age. The most common causes of dry eye are contact lens usage, autoimmune disorders, systemic drug effects, and refractive surgeries, particularly in middle-aged and older adults. DED also occurs in a higher percentage of women than men, especially in women entering menopause or pregnancy; hormone imbalances during menopause or pregnancy can cause lacrimal gland and ocular surface inflammation and tear film abnormalities (Phadatare et al 2015).

1.2 Dry Eye Disease: Clinical Signs and Symptoms

Common signs and symptoms of DED include: eye redness, ocular pain, burning and stinging sensation, foreign body sensation, pruritus, itchy or scratchy eye sensation, tired eyes, enhanced eye pressure, photophobia, painful mucous discharge, and in some cases epiphora. DED typically affects eyes bilaterally. Dry eye can heavily impact visual function especially during visually intensive activities and can overall decrease quality of life. (Phadatare et al 2015; Messmer et al 2015)

1.3 Dry Eye Disease: Diagnostic Testing

Clinicians use several diagnostic tests to diagnose DED and to assess disease severity. These tests fall into two groups: signs (objective) and symptoms (subjective). For DED signs, there are several quantitative tests, including: Schirmer Test, Schirmer I Test, Schirmer II test, tear film breakup time (TBUT), non-invasive tear film breakup time (NITBUT) epithelial staining scores (rose bengal, lissamine green, fluorescein) via slit-lamp examination, tear function index (TFI), tear fluid protein immunoassays, fluorophotometry, meibography, meibometry, meiboscopy, meniscometry, lacrimal gland biopsy, impression cytology, hypolysozyme measurement, hyperosmolarity measurement, and lipid layer analysis, ocular redness scoring, automated blink analysis, and meniscus evaluation utilizing Lipiview II, Keratograph 5M, or OCT equipment (Phadatare et al 2015).

Symptom measurements utilizing physician and/or patient disease scoring include: extensive dry eye questionnaire (DEQ), visual analog scale (VAS), ocular surface disease index (OSDI), national eye institute visual function questionnaire (NEI-VFQ-25), symptom assessment in dry eye questionnaire (SANDE), and standardized patient evaluation of eye dryness questionnaire (SPEED). While most physicians use OSDI as the primary diagnostic questionnaire for dry eye, the SANDE visual analog scale-based questionnaire offers significant advantages, such as simplicity and brevity, while maintaining a high degree of diagnostic accuracy. In addition, in two recent review articles, the SANDE questionnaire showed a significant correlation to OSDI in terms of DED scoring (Amparo, et al, 2015; Saboo, et al, 2015).)

1.4 Dry Eye Disease: Current Management

Typically, clinicians prescribe artificial tear eyedrops and topical corticosteroids for short-term relief of DED. Antibiotics (tetracyclines and macrolides), non-steroidal anti-inflammatory agents, autologous serum drops, omega fatty acids, mucin secretagogues, and anti-inflammatory agents are also used to combat DED symptoms. In addition, prosthetic scleral lenses (i.e. PROSE) that also serve as supplemental tear reservoirs are increasingly being prescribed to enhance ocular surface hydration in patients with chronic DED. Hot eyelid compresses are often utilized to treat meibomian gland dysfunction, a primary driver of evaporative dry eye disease. In advanced cases of DED, punctual plugs can be installed to block tear drainage. In severe cases of dry eye, tarsorrhaphy surgery, tear duct cauterization, or amniotic membrane transplant might be required to reduce tear evaporation (Phadatare et al 2015; Lin et al 2014).

Currently there are only two pharmaceutical agents that are FDA approved for the treatment of dry eye: cylcosporine A ophthalmic emulsion (Restasis®) and lifitegrast ophthalmic solution (Xiidra™). Restasis® 0.05% is a topical immunomodulator indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with

keratoconjunctivitis sicca (Restasis® Prescribing Information). Xiidra™ 5% is a lymphocyte function-associated antigen (LFA-1) antagonist indicated for the treatment of signs and symptoms of dry eye disease (Xiidra™ Prescribing Information). Given the complexity, severity, and frequency of DED, and given the limited modes of action by which these two compounds treat dry eyes, there is a medical need for other dry eye therapies, particularly those with multiple modes of action that target the wider dry eye population and are effective and safe for early relief and long-term daily use.

1.5 Scientific Rationale for Brimonidine Therapy in Dry Eye Disease

As mentioned, brimonidine tartrate is a selective alpha-2 adrenergic receptor agonist and is currently available as an ophthalmic solution at different concentrations and is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

1.5.1 Preclinical Data Supporting Use of Brimonidine in DED

The scientific rationale to establish a medically plausible basis for the use of local brimonidine tartrate for the treatment of DED include the potential following mechanisms:

1. Reduction of ocular surface blood flow: As an alpha agonist, brimonidine tartrate can significantly cause vasoconstriction leading to the reduction of blood flow to the ocular surface, which, in turn, reduces local pressure, edema and inflammation (Piwnica, 2014). In this manner, brimonidine has the potential to reduce redness and inflammation of the ocular surface.
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 directly studied with brimonidine tartrate, activation of alpha 2 receptors (with another alpha 2 agonist) has been shown to suppress the reactivation of T lymphocytes (Felsner, 1995). In addition, 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 by its action on pain receptors (Bradshaw, 1984). As an alpha 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 corneal surface inflammation: In the mouse dry eye model, ocular staining data comparing brimonidine to other treatments showed a reduction in fluorescein staining scores over a 2-week period, indicating an overall decrease in ocular surface inflammation. This effect was further enhanced in OCU300 relative to marketed brimonidine.

In summary, brimonidine, through its ability to vasoconstrict and reduce inflammation, has the potential to reduce redness of the ocular surface. In addition, by attenuating chronic inflammation, brimonidine tartrate allows the ocular surface and tear film producing glands to heal and to avoid further damage from DED. Moreover, brimonidine tartrate can alleviate heightened ocular pain through its analgesic and anti-inflammatory properties, which maximizes tolerability when delivered to the surface of the eye. Finally, brimonidine tartrate is an FDA approved product that has demonstrated a robust safety profile via topical ocular delivery for the chronic treatment of open-angle glaucoma.

In short, brimonidine may address the signs and symptoms of DED through several mechanistic pathways. In contrast, the available treatments for dry eye disease have limited mechanisms of action, and this may explain their inability to completely resolve the signs and symptoms of DED.

1.5.2 Clinical Data Supporting Use of Brimonidine in DED

Brimonidine tartrate is an FDA approved product that has demonstrated a robust safety profile via topical ocular delivery for the treatment of open-angle glaucoma. Brimonidine tartrate 0.2%, which includes the preservative benzalkonium chloride (BAK), is generally safe and well tolerated. Given that preservative-free OCU310 nanoemulsion was not yet available for clinical trials in late 2017, an IND-opening phase 2 proof-of-concept study was conducted, using commercially available brimonidine.

The main objective of the study was to establish whether subjects with DED can tolerate receiving Brimonidine 0.2% eye drops, alone or in combination with loteprednol 0.2%, two times a day for twelve weeks (84 days). The other objective was to investigate the preliminary efficacy of Brimonidine 0.2% topical eye drop solution, alone or in combination with loteprednol 0.2%, in treating DED, and to use this information, if possible, to select the appropriate brimonidine treatment regimen (with or without loteprednol) and the appropriate efficacy endpoints for phase 3 studies. This was a randomized, placebo-controlled, double-blind study, in which 84 subjects were enrolled at three clinical sites. The primary endpoint was tolerability at Day 84, using a visual analog scale (VAS). There were several pre-specified exploratory efficacy endpoints.

In summary, the phase 2 study showed that both brimonidine combination therapy (with loteprednol) and brimonidine monotherapy (without loteprednol) are safe and well tolerated, and both were consistently better than placebo for key exploratory efficacy endpoints, particularly at early post-baseline visits. The most promising symptom endpoint was SANDE, for which both brimonidine regimens (combination and monotherapy), were statistically superior to placebo at the Day 28 visit, and only the monotherapy arm was statistically superior at Day 84, the primary assessment visit. The most promising sign endpoint was Lissamine Green Staining of either the conjunctivae or the cornea, for which both brimonidine regimens (combination and monotherapy) were better than placebo at the Day 84 visit, and the differences bordered on statistical significance. Given the results of this study, and given the mechanism of action of brimonidine, these endpoints have been selected as primary endpoints in phase 3.

Further, based on the results of this study, there is no significant incremental benefit in adding loteprednol to brimonidine, when compared to using brimonidine alone, in treating patients with DED. Given that ocular steroids, such as loteprednol, have their own associated adverse effects, it makes sense to proceed to phase 3 with the brimonidine monotherapy product: brimonidine tartrate 0.2% without loteprednol in a nanoemulsion formulation, also known as OCU310.

1.6 Product Rationale

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). This product was also shown to be safe and tolerable, while demonstrating preliminary efficacy, in a phase 2 proof-of-concept study conducted in 2017.

OCU 310 is a sterile, preservative-free solution of brimonidine tartrate 0.2% in an ophthalmic nanoemulsion. It was developed to provide relief of the signs and symptoms of dry eye disease for topical instillation in the eye. The proposed dose is one drop of OCU310 (0.2% brimonidine tartrate ophthalmic nanoemulsion) twice daily (approximately 12 hours apart) into each eye using a single-use container.

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

In this study, one drop of OCU310 (brimonidine tartrate nanoemulsion 0.2%) will be administered into each eye, two times a day (bid) for 28 days. The brimonidine tartrate concentration (0.2%) is similar to 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 (0.2%). 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 positive tolerability and efficacy signals in a phase 2 study of dry eye disease, 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 310 for the relief of signs and symptoms of dry eye disease.

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 in Patients with Dry Eye Disease (DED)

2.2 Study Endpoints

2.2.1 Primary Endpoints

Two primary efficacy endpoints will be tested:

1. Change from baseline to 4 weeks (Day 28) in SANDE score
2. Change from baseline to 4 weeks (Day 28) in Lissamine Green conjunctival staining scores

   Note: This endpoint would be considered in a hierarchical fashion if statistical success is first demonstrated for SANDE at Day 28 (Section 11).

2.2.2 Secondary Endpoints

3. Change from baseline to 2 weeks (Day 14) in SANDE score
4. Change from baseline to 2 weeks (Day 14) in Lissamine Green conjunctival staining scores

Note: The above endpoints (Primary and Secondary) will be tested in a fixed sequence (1-4) proceeding to the next endpoint until a p-value >0.05 is found (Section 11)

2.2.3 Exploratory Endpoints

- Change from baseline to 4 weeks (Day 28) in Lissamine Green corneal staining scores
- Change from baseline to 2 weeks (Day 14) in Lissamine Green corneal staining scores
- Change from baseline to 4 weeks (Day 28) in Schirmers scores
- Change in appearance from baseline to 4 weeks (Day 28) in Validated Bulbar Redness (VBR) scale
- Change in appearance from baseline to 4 weeks (Day 14) in Validated Bulbar Redness (VBR) scale
- Clinical Global Impression (CGI) of change in symptoms from baseline (physician's rating) to 4 weeks (Day 28)
- Subject Global Assessment (SGA) of overall change from baseline (subject's rating) to 4 weeks (Day 28)

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 centers. Upon meeting the eligibility criteria, enrolled subjects with a history of DED will be randomly assigned in a 1:1 fashion to receive either Brimonidine Nanoemulsion Eye Drops 0.2% investigational product or ophthalmic buffered saline (placebo).

Four study visits are planned: Day -7± 1day (screening visit), Day 1 (randomization), Day 14 ± 3 days, and Day 28 ± 7 days (See Table 4). An informed consent form (ICF) must be obtained from each subject prior to the commencement of any study procedures. All subjects must be given ample time to review the ICF and ask questions regarding the study prior to participation in the study. The subject will be provided a copy of the signed ICF.

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 28 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

Given the long-term safety profile of marketed brimonidine tartrate (0.15%-0.20%), the positive tolerability and efficacy signals in a phase 2 study of dry eye disease, 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 310 for the relief of signs and symptoms of dry eye disease (Section 1.7). The medical need, in part, may be due to the limited mechanisms of action of existing dry eye products (Section 1.5.1).

To support the proposed indication, efficacy in both a sign and a symptom of DED are expected to be demonstrated in phase 3 studies. In phase 2, positive efficacy signals were observed across multiple endpoints, consistent with the hypothesis that brimonidine works through multiple mechanistic pathways. The strongest signals observed for "sign" (Lissamine Green staining of the conjunctivae) and for "symptom" (SANDE score) were selected as primary endpoints in phase 3. Moreover, in phase 2, efficacy signals were observed as early as the first post-baseline study visit (Day 28), which supports the selection of Day 28 as the primary timepoint for endpoint assessments in phase 3.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Number of Subjects

At least 240 participants will be randomly assigned to the study treatment such that approximately 120 evaluable subjects per active arm (OCU310) and 120 per placebo arm (OBS) complete the study (1:1 randomization).

4.2 Subject Inclusion Criteria

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

1. Aged 18 years or older.
2. Sign and date informed consent form approved by the IRB
3. History of Dry Eye Disease for ≥6 months
4. Demonstrate the following 2 signs of DED in the same eye at Screening and Baseline (Day 1):
   a. Conjunctival staining at ≥ 1 (out of a possible score of 6 per eye), and
   b. Schirmer test (with anesthesia) at ≥ 1 to ≤ 7 mm in 5 minutes
5. Symptomatic evidence of DED by having a global symptom score (Overall SANDE) ≥40 mm at Screening and Baseline (Day 1) visit
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 and who are either abstinent or sexually active on an acceptable method of birth control for at least 4 weeks prior to Visit 1 and throughout the study (i.e., until Day 28), 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 or loteprednol

2. Use of contact lenses within 14 days prior to Screening visit or planned use during study
3. Currently receiving brimonidine or other treatment for glaucoma or ocular hypertension or history of glaucoma surgery.
4. Receiving or have received any experimental or investigational drug or device within 30 days prior to Screening visit
5. Intraocular pressure <5 mmHg or >22 mmHg in either eye
6. Active ocular infection or history of ocular herpetic keratitis
7. History of neurotrophic keratitis or ocular neuropathic pain
8. Any history of eyelid surgery or intraocular/ocular surgery within the past 3 months
9. Punctal occlusion within 3 months prior to Screening visit or during study
10. Corneal epithelial defect larger than 1 mm^2 in either eye
11. Have active drug/alcohol dependence or abuse history
12. Are neonates, pregnant/lactating women, children, or others who may be considered vulnerable populations
13. Received corticosteroid-containing eye drops within the past 14 days prior to Screening visit or planned use during study
14. Any change in systemic corticosteroids/immunosuppressives, cyclosporine ophthalmic emulsion 0.05% (Restasis®) or lifitegrast ophthalmic solution 5% (Xiidra™) within 30 days prior to Screening visit or planned change during study
15. In the opinion of Investigator or Study Coordinator, be unwilling or unable to comply with study protocol or unable to successfully instill eye drops
16. Disease, condition, or disorder that in the judgement of Investigator could confound study assessments or limit compliance to study protocol

Note: Subjects will be permitted to continue all their ocular treatments, including the use of artificial tears, eyelid massage, or warm compresses, if they commit to using the same brand/regimen throughout the study. None of the ocular treatments, whether OTC or prescription (e.g. Restasis or Xiidra) 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.

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.

If study medication use has been discontinued, subjects should continue to attend all scheduled visits. A subject will be discontinued from study medication for any of the following reasons:

- Pregnancy
- At the discretion of the Investigator at any time
- At the subject's request (voluntary discontinuation)
- 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 to receive study medication. 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 withdraw from the study outside of any scheduled visit will be encouraged to complete a final study visit at the time of discontinuation. 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.

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 (with explanation)
3. Investigator withdrawal of subject (with explanation and after discussion with MM and Sponsor)
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± 1d (Screening)	Day 1 (Baseline)	Day 14 ± 3d (Week 2)	Day 28 ± 7d (Week 4)
Informed consent	X			
Eligibility criteria	X	X		
Demographic Information	X			
Medical/surgical/ocular history[1]	X	X		
Vitals signs[2]		X	X	X
Review of prior and concomitant medications[3]	X	X	X	X
Urine collection and Pregnancy test (females of childbearing capacity only; hCG dipstick)[4]	X	X		
Visual acuity ([logMar])[5]		X	X	X
Symptom Assessment in Dry eye (SANDE)[6]	X	X	X	X
Ocular redness 100 -point VBR scale via slit lamp[7]		X	X	X
Slit lamp ophthalmic exam	X	X	X	X
Corneal Lissamine green stain[8]		X	X	X
Conjunctival Lissamine green stain[9]	X	X	X	X
Schirmer's test with anesthesia (mm,)[10]	X	X		X
Intraocular pressure[11]	X	X	X	X
Clinical Global Impression (CGI)			X	X
Subject Global Assessment (SGA)			X	X
Randomization		X		
Dispense/Instill Investigative Product[12]		X		
Adverse event surveillance	X	X	X	X
Diary recording and review[13]		X	X	X

1. The ocular history will include any previously diagnosed ophthalmic abnormalities and ocular surgeries (including laser procedures). Ocular history at baseline (day 1) will cover the time from the screening visit.
2. Baseline Vital signs on Day 1 to be completed at least 30 ± 10 mins before dose on Day 1. All othervitals to be completed before ocular assessments on Days 14 and 28.
3. Corticosteroid-containing eye drops are not allowed within 14 days prior to Screening or during the study. Review of prior and concomitant medications and regimens will occur at all study visits. Subjects will be permitted to continue all their ocular treatments, including the use of artificial tears, eyelid massage, or warm compresses if they commit to the same brand/regimen throughout the study. None of the ocular treatments, whether over-the counter or prescription (e.g. Restasis® or Xiidra®) 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.
4. hCG = human chorionic gonadotrophin. A urine pregnancy test is required at screening and baseline (Day 1).. A urine pregnancy test may be performed at any time during study participation if pregnancy is suspected.
5. Subjects should use the most recent correction to attain their best-corrected visual acuity (BCVA).
6. 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 at Screening and on Day 1 prior to first dose (Baseline), Day 14, and Day 28.
7. 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.
8. Corneal lissamine green staining using a solution made from Lissamine Green Ophthalmic Strips. Corneal staining will be graded in 5 zones in each eye. Each zone will be graded from 0 to 3 based on the density of punctate staining (maximum score/eye =15)

9. 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 staining (maximum score/eye = 6).
10. Anesthetize each eye (OS and OD) with a drop of proparacaine. Insert Schirmer strips into lower lid for 5 min.
11. Measure intraocular pressure using Goldman applanation tonometry.
12. 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 the baseline (Day 1) visit for self-administration during the study.
13. Subject diaries must be reviewed by the study staff at each visit prior to the subject's leaving the clinic.

5.2 Study Visits

5.2.1 Unscheduled Study Visits

If an unscheduled visit is necessary to follow an intercurrent event, any untoward findings related to that event should be captured as adverse events and/or as concomitant therapies on source documents and relevant pages of the CRF. If the event meets the requirement for an SAE, please record on the SAE page of the CRF and follow all SAE-related procedures (see Section 10, Adverse Events).

5.2.2 Screening (Day -7 ± 1 day)

An ICF must be obtained from each subject before initiation of any study-related procedures.

The following assessments should be completed at the Screening Visit:

- Informed Consent
- Inclusion and Exclusion criteria check
- Demographic information
- Medical history including prior procedures and conditions
- Ophthalmic history including: date when the DED began, medications used by the subject to treat DED, previous procedures to treat DED.
- Review of prior and concomitant medications: medications used by the subject to treat DED, previous procedures to treat DED; OTC ocular medications; medications for chronic diseases
- Urine collection and dipstick test for pregnancy in women of child bearing capacity
- Symptom Assessment iN Dry Eye (SANDE)
- Slit-lamp ophthalmic exam
- Conjunctival Lissamine Green
- Schirmer's test with anesthesia
- 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 check
    - Note: Eligibility criteria must be fulfilled at both the Screening and Baseline (Day 1) visits. Except for Informed Consent and Demographic Information, all activities at the Screening visit are repeated at the Baseline (Day 1) visit, as detailed below.
- Medical/surgical ocular history (update since Screening visit)
- Review of prior and concomitant medications
- Urine collection and dipstick test for pregnancy in women of child bearing capacity
- Visual Acuity (LogMar)
- Symptom Assessment iN Dry Eye (SANDE)
- Ocular Redness 100-point VBR scale
- Slit-lamp ophthalmic exam
- Corneal Lissamine Green
- Conjunctival Lissamine Green
- Schirmer's test with anesthesia
- Intraocular pressure (IOP)
- Vital signs: body temperature, heart rate, blood pressure, respiratory rate (done at least 30 ± 10 minutes before dose on Day 1)
- 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)
- Make appointment for next visit

5.2.4 Day 14 (± 3 days)

- Review of prior and concomitant medications

- Vital signs: body temperature, heart rate, blood pressure, respiratory rate
- Visual acuity (LogMar)
- Symptom Assessment iN Dry Eye (SANDE)
- Ocular Redness 100-point VBR scale
- Slit-lamp ophthalmic exam
- Corneal lissamine green
- Conjunctival lissamine green
- Intraocular pressure (IOP)
- Clinical Global Impression
- Subject Global Assessment
- Adverse event surveillance
- Diary recording and review

5.2.5 Day 28 (± 7 days)

- Review of prior and concomitant medications
- Vital signs: body temperature, heart rate, blood pressure, respiratory rate
- Visual acuity (LogMar)
- Symptom Assessment iN Dry Eye (SANDE)
- Ocular Redness 100-point VBR scale
- Slit-lamp ophthalmic exam
- 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 recording 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 and Baseline (Day 1) Visits 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 and Baseline (Day 1) Visits, a urine dipstick pregnancy test will be performed for all female subjects of child-bearing potential.

6.4 Efficacy Assessments

6.4.1 Primary Efficacy Assessment

There are two primary efficacy endpoints in this study:

1. Change from baseline to 4 weeks (Day 28) in SANDE score
2. Change from baseline to 4 weeks (Day 28) in Lissamine Green conjunctival staining scores

Note: This endpoint would be considered in a hierarchical fashion if statistical success is first demonstrated for SANDE at Day 28 (Section 11)

6.4.1.1 Symptom Assessment iN Dry Eye (SANDE) at Day 28

The SANDE questionnaire is a short visual analog assessment scale that quantifies both severity and frequency of current dry eye symptoms. The SANDE is comprised of two questions, and each question employs a 100-mm horizontal linear VAS (Figure 2). 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 at Screening, Day 1 prior to first dose, Day 14, and Day 28. 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).

6.4.1.2 Conjunctival Staining Score with Lissamine Green at Day 28

Conjunctival staining with Lissamine Green dye (1%; LG) staining in each eye (OS and OD) will be conducted using the slit lamp at Screening, Day 1 prior to first dose, Day 14, and Day 28. A single drop of 1% Lissamine Green dye will 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. Conjunctival staining will be graded in two zones, as per the methods described in Section 18.3 (Table 6)(Figure 3)(Figure 4).

6.4.2 Secondary Efficacy Assessment

There are two secondary efficacy endpoints in this study:

3. Change from baseline to 2 weeks (Day 14) in SANDE score
4. Change from baseline to 2 weeks (Day 14) in Lissamine Green conjunctival staining scores

Note: The above endpoints (Primary and Secondary) will be tested in a fixed sequence (1-4) proceeding to the next endpoint until a p-value >0.05 is found (Section 11).

6.4.2.1 Symptom Assessment iN Dry Eye (SANDE) at Day 14

See 6.4.1.1 above.

6.4.2.2 Conjunctival Staining Score with Lissamine Green at Day 14

See 6.4.1.2 above.

6.4.3 Exploratory Efficacy Assessments

There are seven exploratory efficacy endpoints in this study:

- Change from baseline to 4 weeks (Day 28) in Lissamine Green corneal staining scores
- Change from baseline to 2 weeks (Day 14) in Lissamine Green corneal staining scores
- Change from baseline to 4 weeks (Day 28) in Schirmers scores
- Change in appearance from baseline to 4 weeks (Day 28) in Validated Bulbar Redness (VBR) scale
- Change in appearance from baseline to 4 weeks (Day 14) in Validated Bulbar Redness (VBR) scale
- Clinical Global Impression (CGI) of change in symptoms from baseline(physician's rating) to 4 weeks (Day 28)
- Subject Global Assessment (SGA) of overall change from baseline (subject'srating) to 4 weeks (Day 28)

6.4.3.1 Corneal Staining Score with Lissamine Green at Day 28

Corneal staining will be graded in 5 zones, as per the methods described in Section 18.3 (Table 6)(Figure 3)(Figure 4).

6.4.3.2 Corneal Staining Score with Lissamine Green at Day 14

Corneal staining will be graded in 5 zones, as per the methods described in Section 18.3 (Table 6)(Figure 3)(Figure 4).

6.4.3.3 Schirmers Test (with anesthesia) at Day 28

A Schirmer's test will be conducted at Screening, Day 1 (prior to first dose), and Day 28 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 the Sponsor will convert to categories based on the number of mm of wetting of the paper after 5 minutes (Ogawa, 2013), 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

6.4.3.4 Validated Bulbar Redness grading scale (VBR) at Day 28

Ocular surface redness (OR; nasal or temporal) will be assessed using the VBR grading scale (Schulze 2007) at Day 1 prior to first dose, Day 14, and Day 28. 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 18.1; Figure 1). 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.

6.4.3.5 Clinical Global Impression (CGI) at Day 28

At Day 14 and Day 28, 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

At Day 14 and Day 28, the subjects will be asked to assess their overall change from baseline. The SGA is assessed as follows (Miller 2010):

Question 1 (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 Day 28 who were able to successfully complete a full 28 days 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 (logMAR)

Monocular and binocular visual acuity will be completed with the subject's best correction vision in place using a logMAR ETDRS chart, at Day 1 prior to the first dose , Day 14, and Day 28. Procedures for BCVA are outlined in Section 18.4 (Figure 5)(Table 7).

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 18.5).

6.5.4 Ophthalmic Examination (Slit Lamp)

Biomicroscopic examination will be completed at each clinic visit (see Section 18.6)(Table 8). The conjunctiva, cornea, anterior chamber, lens and anterior vitreous of each eye will be examined.

6.5.5 Vital Signs

Vital signs will be assessed at the Day 1, Day 14, and Day 28 visits. 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).

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 OCU310 in each eye (OU) approximately every 12 hours. The proposed dosing regimen is twice daily (bid).

7.2 Dose Rationale

OCU310 has a dosage strength of 0.2% brimonidine tartrate applied as a single drop to each eye, twice daily. This dose was selected based on results of the Phase 2 proof-of-concept study and the data available from marketed brimonidine ophthalmic products, accounting for the improved pharmaceutical attributes of an oil-in-water proprietary nanoemulsion of brimonidine tartrate (sterile filtered) formulation compared to the solution formulation. The nanoemulsion formulation, with a pH buffered to maintain the optimum range for ocular delivery, is expected to decrease drainage rate and prolong precorneal residence time, without increasing the drug peak concentration. Based on these pharmaceutical attributes, as well as preliminary clinical data, it is suggested that a 0.2% concentration of brimonidine in the OCU310 ophthalmic nanoemulsion formulation with twice daily application will be able to exert therapeutic effects.

Moreover, the potential protective effect of OCU310 brimonidine tartrate against corneal epithelial damage is assumed to be similar to that of OCU300, which Ocugen is developing for patients with chronic ocular

graft-vs-host disease oGVHD). OCU 300, in comparison to a placebo nanoemulsion, commercially available brimonidine tartrate ophthalmic solution (0.2 %), and marketed products (Restasis ®- Cyclosporine; Xiidra®- Lifitegrast) demonstrated a protective effect in a mouse dry-eye disease model. These results infer that OCU310 could provide better protection for corneal epithelial damage than the reference product brimonidine tartrate ophthalmic solution 0.2 %, and placebo nanoemulsion.

In addition, 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 intra-ocular pressure (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 OCU310 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 “OCU310 Investigational Drug Product” 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 (final visit at Day 28 28 plus 7-day visit window) of eye-dropper vials for self-administration at home. 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 bottles 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

Subjects will be allowed to remain on current concomitant ocular 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, with the exception of corticosteroid containing eyedrops, which are prohibited within 7 days prior to enrollment and during the study. Accordingly, subjects will be permitted to continue all their ocular treatments, including the use of artificial tears, eyelid massage, or warm compresses, , and over-the-counter (OTC) remedies if they commit to using the same brand/regimen throughout the study. None of the ocular treatments, whether OTC, prescription (e.g. Restasis® or Xiidra®) or investigational product should be used within 5 minutes of another ocular treatment during the study. Study medication should not be used within 4 hours prior to any study visit.

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 28 (last study day) in this study.

8.4 Treatment Compliance

Treatment compliance will be documented by way of subject diaries. Subjects will be dispensed diaries at the Day 1 Visit and will be instructed to record portion of day (a.m. or p.m.) during 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 1:1 ratio to OCU310 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 xxxxx 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 personnel 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 Events 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 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: 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 E6 Guidelines for GCP). Any medical condition that is present at the time that the subject is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

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 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 10.1.1.2 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 DED regimen. As noted, a significant change in the over-the-counter DED regimen (e.g., artificial tears, eyelid massage, warm compresses), or in cyclosporine ophthalmic emulsion 0.05% (Restasis®), or lifitegrast ophthalmic solution, 5% (Xiidra®) during the study should be avoided, if possible. In addition, corticosteroid containing eyedrops are prohibited within 14 days prior to enrollment and during the study.

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 Trial Runners/TFS Fax Number: . 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 Associate 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
Dr. Barbara Wirotsko
Trial Runners
116 W. Villard
Dickinson, ND 58601
Phone: 347-453-1521
24-hour contact : 347-453-1521
Email: barbarawirostko@trialrunners.com

SAE Fax Number (US):
SAE Hotline Number (US):

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 Trial Runners/TFS Safety.

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 OCU310 vs OBS drops with a set of ordered endpoints to be tested in a fixed sequence.

Tests will be conducted using two-sided *alpha* = .05 in a fixed sequence.

11.2 Unit of Analysis

The unit of analysis for variables measured at the individual eye level will be the study eye. Each subject will have a single eye identified as the study eye as follows: (i) if only 1 eye meets inclusion criteria, this eye will be the study eye and the other eye will be considered the non-qualified fellow eye; (ii) if both eyes meet inclusion criteria, the eye with the higher Lissamine Green conjunctival staining score will be the study eye and the other eye will be considered the qualified fellow eye; (iii) if both eyes have the same Lissamine Green conjunctival staining score, then the eye with the lower Schirmer score will be the study eye and the other eye will be considered the qualified fellow eye; (iv) if both eyes have same Schirmer score, the right eye will be the study eye and the other eye will be considered the qualified fellow eye. Analysis of safety and efficacy variables measured at the eye level will be primarily performed on the study eyes and secondarily on the qualified fellow eyes (for efficacy) and all fellow eyes (for safety).

The unit of analyses for variables measured at the subject level will be the subject.

11.3 Power and Sample Size Determination

One-hundred eight subjects in each of the OCU 310 and placebo arms yields 99% power to reject H_{01} and conclude superiority of OCU 310 over placebo in the mean change from baseline SANDE score at 4 weeks assuming the mean changes from baseline in OCU 310 and placebo are -20.0 and -3.5 respectively, a common standard deviation of 25.0, and a two-sided alpha = 0.05.

Additionally, 108 study eyes in each of the OCU 310 and placebo arms yields 90% power to reject H_{02} and conclude superiority of OCU 310 over placebo in the mean change from baseline Lissamine Green conjunctival staining score in the study eye at 4 weeks assuming the mean changes from baseline in OCU 310 and placebo are -0.4 and 0.2 respectively, a common standard deviation of 1.35, and a two-sided alpha = 0.05.

For the secondary endpoints, change from baseline in SANDE score at Day 14 and change from baseline in Lissamine Green conjunctival staining scores at Day 14, there are not enough data to make a power/sample size statement.

For the primary analyses, with 108 subjects per arm, the study will have approximately 90% power to reject both H_{01} and H_{02}, assuming independence between endpoints (with higher power should the endpoints be positively correlated), and conclude the OCU 310 to be superior to placebo in both the mean change from baseline SANDE score at 4 weeks and the mean change from baseline Lissamine Green conjunctival staining score in the study eye at 4 weeks.

Accounting for 10% subject discontinuations, **240** total subjects will be enrolled (120 per arm).

Primary and Secondary Efficacy Endpoints (in fixed sequence):

1. Change from baseline to 4 weeks (Day 28) in SANDE score
2. Change from baseline to 4 weeks (Day 28) in Lissamine Green conjunctival staining scores
3. Change from baseline to 2 weeks (Day 14) in SANDE score
4. Change from baseline to 2 weeks (Day 14) in Lissamine Green conjunctival staining scores

These endpoints will be tested in a fixed sequence proceeding to the next endpoint until a p-value >0.05 is found.

Exploratory Endpoint(s):

- Change from baseline to 4 weeks (Day 28) in Lissamine Green corneal staining scores
- Change from baseline to 2 weeks (Day 14) in Lissamine Green corneal staining scores using a standard grading scale, such as NEI or Oxford Schema
- Change from baseline to 4 weeks (Day 28) in Schirmers scores
- Change in appearance from baseline to 4 weeks (Day 28) in Validated Bulbar Redness (VBR) scale
- Change in appearance from baseline to 4 weeks (Day 14) in Validated Bulbar Redness (VBR) scale
- Clinical Global Impression (CGI) of change in symptoms from baseline(physician's rating) to 4 weeks (Day 28)

- Subject Global Assessment (SGA) of overall change from baseline (subject's rating) to 4 weeks (Day 28)

11.4 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. The safety set will be analyzed according to the treatment actually received.

Intent-to-treat (ITT) Population

The ITT set will be the primary analysis set for the efficacy endpoints and will include all randomized subjects who have at least one post-baseline efficacy measurement. The ITT population will be analyzed according to the planned treatment.

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. The PP population will be analyzed according to the treatment actually received. 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 efficacy analyses will be conducted on the ITT population. The same set of efficacy analyses will also be performed on the per-protocol population.

Four endpoints (two primary and two secondary) will be tested in a fixed sequence proceeding to the next endpoint until a p-value >0.05 is found (Section 11.3). The analysis of the four outcomes will employ a repeated measures mixed model with mean change from baseline score at the stated time point as the response with baseline score as a covariate and treatment, visit, and their interaction as fixed effects. The least squares mean difference (OCU 310 – placebo) at the stated time point will be tested. The 2-sided p-values and associated 95% confidence intervals will be presented.

The following type of hypothesis will be tested:

H_{01}: The difference (OCU 310 minus placebo), between subjects treated with the OCU 310 and subjects treated with placebo in the mean change from baseline = 0.

H_{A1}: The difference (OCU 310 minus placebo), between subjects treated with the OCU 310 and subjects treated with placebo in the mean change from baseline ≠ 0, with superiority claimed if the difference < 0.

11.4.2.2 Efficacy Analyses—General Considerations

Efficacy analyses will be conducted primarily on the ITT population. The same set of efficacy analyses will also be performed on per-protocol population. For efficacy endpoints where measurements from both eyes are available, the study eye will be used for the analyses.

For continuous endpoints, the change from baseline will be summarized with descriptive statistics for the values at baseline, values at each post-baseline time point (Day14 and Day 28), 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. Categorical study assessments will be summarized by treatment and visit (as applicable) using frequency counts and percentages.

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 for inflation of type 1 error rate due to multiple hypotheses, the analysis will be conducted in a hierarchical manner.

11.4.3.3 Missing Data

The primary efficacy analyses will be performed using the ITT population, and using a repeated measures model without any imputation for missing observations. Sensitivity analyses using different analysis populations and methods for handling missing data may be further detailed in the Statistical Analysis Plan (SAP).

Secondary analyses will also be based on observed data. Missing data handling techniques for secondary endpoints may also be detailed in the SAP.

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 "Guidance for Industry-E6 Good Clinical Practice: Consolidated Guidance," dated April 1996. This study will also be conducted in accordance with the Declaration of Helsinki (2013).

This study will use (TR/TFS/vendor) 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 (TR/TFS/vendor) 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 should 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 form 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. 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.

17 REFERENCES

Adkins JC, Balfour JA. Brimonidine. A review of its pharmacological properties and clinical potential in the management of open-angle glaucoma and ocular hypertension. Drugs Aging 1998;12(3):225-241.

Ban Y, Ogawa Y, Goto E, Uchino M, Terauchi N, Seki M, et al. Tear function and lipid layer alterations in dry eye patients with chronic graft-*vs*-host disease. Eye (Lond) 2009; 23:202-208.

Ban Y, Ogawa Y, Ibrahim OM, Tatematsu Y, Kamoi M, Uchino M, et al. Morphologic evaluation of meibomian glands in chronic graft-versus-host disease using in vivo laser confocal microscopy. Mol Vis 2011; 17:2533-2543.

Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. Nat Rev Immunol 2012; 12(6):443-458.

Bradshaw CM, Sheridan RD, Szabadi E. Neuronal responses to noradrenaline in the cerebral cortex: evidence against the involvement of alpha 2-adrenoceptors. Br J Pharmacol 1984; 82(2):453-458.

Caraceni A, Cherny N, Fainsinger R, Kaasa S, Poulain P, Radbruch L, et al. Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. J Pain Symptom Manage 2002;23(3):239-255.

Chew SK, Skalicky SE, Goldberg I. Brinzolamide plus brimonidine for the treatment of glaucoma: an update. Expert Opin Pharmacother 2014;15(16):2461-2471.

Curtis LM, Datiles MB, III, Steinberg SM, Mitchell SA, Bishop RJ, Cowen EW, et al. Predictive models for ocular chronic graft-versus-host disease diagnosis and disease activity in transplant clinical practice. Haematologica 2015; 100(9):1228-1236.

Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113(1-2):9-19.

Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94(2):149-158.

Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain 2011;152(10):2399-2404.

Felsner P, Hofer D, Rinner I, Porta S, Korsatko W, Schauenstein K. Adrenergic suppression of peripheral blood T cell reactivity in the rat is due to activation of peripheral alpha 2-receptors. J Neuroimmunol 1995; 57(1-2):27-34.

Genetic and Rare Diseases Information Center. Acute Graft Versus Host Disease. https://rarediseases.info.nih.gov/diseases/6544/acute-graft-versus-host-disease. 2016a. 10-31-2016a.

Genetic and Rare Diseases Information Center. Chronic Graft Versus Host Disease. https://rarediseases.info.nih.gov/diseases/10964/chronic-graft-versus-host-disease. 2016b. 10-31-2016b.

Herrera-Garcia AM, Dominguez-Luis MJ, Arce-Franco M, Armas-Gonzalez E, Alvarez de La RD, Machado JD, et al. Prevention of neutrophil extravasation by alpha2-adrenoceptor-mediated endothelial stabilization. J Immunol 2014; 193(6):3023-3035.

Hong S, Han SH, Kim CY, Kim KY, Song YK, Seong GJ. Brimonidine reduces TGF-beta-induced extracellular matrix synthesis in human Tenon's fibroblasts. BMC Ophthalmol 2015; 15:54.

Katz LJ. Twelve-month evaluation of brimonidine-purite versus brimonidine in patients with glaucoma or ocular hypertension. J Glaucoma 2002;11(2):119-126.

LeBlanc RP. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. Brimonidine Study Group 2. Ophthalmology 1998;105(10):1960-1967.

Lee SJ, Wolff D, Kitko C, Koreth J, Inamoto Y, Jagasia M, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant 2015; 21(6):984-999.

Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. CLAO J. 1995;21: 221–232.

Martin PJ, Lee SJ, Przepiorka D, Horowitz MM, Koreth J, Vogelsang GB, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. The 2014 Clinical Trial Design Working Group Report. Biol Blood Marrow Transplant 2015;21(8):1343-1359.

Melamed S, David R. Ongoing clinical assessment of the safety profile and efficacy of brimonidine compared with timolol: year-three results. Brimonidine Study Group II. Clin Ther 2000;22(1):103-111.

Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD, et al. Minimal clinically important difference for the ocular surface disease index. Arch Ophthalmol 2010; 128(1):94-101.

Mundorf T, Williams R, Whitcup S, Felix C, Batoosingh A. A 3-month comparison of efficacy and safety of brimonidine-purite 0.15% and brimonidine 0.2% in patients with glaucoma or ocular hypertension. J Ocul Pharmacol Ther 2003;19(1):37-44.

Nassar A, Tabbara KF, Aljurf M. Ocular manifestations of graft-versus-host disease. Saudi J Ophthalmol 2013; 27(3):215-222.

Nassiri N, Eslani M, Panahi N, Mehravaran S, Ziaei A, Djalilian AR. Ocular graft versus host disease following allogeneic stem cell transplantation: a review of current knowledge and recommendations. J Ophthalmic Vis Res 2013; 8(4):351-358.

National Organization for Rare Disorders. Graft versus Host Disease. https://rarediseases.org/rare-diseases/graft-versus-host-disease/. 2016. 10-31-2016.

Nguyen QH, McMenemy MG, Realini T, Whitson JT, Goode SM. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. J Ocul Pharmacol Ther 2013;29(3):290-297.

Ogawa Y, Kim SK, Dana R, Clayton J, Jain S, Rosenblatt MI, et al. International Chronic Ocular Graft-vs-Host-Disease (GVHD) Consensus Group: proposed diagnostic criteria for chronic GVHD (Part I). Sci Rep 2013; 3:3419.

Ogawa Y, Shimmura S, Dogru M, Tsubota K. Immune processes and pathogenic fibrosis in ocular chronic graft-versus-host disease and clinical manifestations after allogeneic hematopoietic stem cell transplantation. Cornea 2010; 29 Suppl 1:S68-S77.

Piwnica D, Rosignoli C, de Menonville ST, Alvarez T, Schuppli NM, Roye O, et al. Vasoconstriction and anti-inflammatory properties of the selective alpha-adrenergic receptor agonist brimonidine. J Dermatol Sci 2014; 75(1):49-54.

Rahman MQ, Ramaesh K, Montgomery DM. Brimonidine for glaucoma. Expert Opin Drug Saf 2010;9(3):483-491.

Romero-Sandoval A, Eisenach JC. Clonidine reduces hypersensitivity and alters the balance of pro- and anti-inflammatory leukocytes after local injection at the site of inflammatory neuritis. Brain Behav Immun 2007; 21(5):569-580.

Romero-Sandoval EA, McCall C, Eisenach JC. Alpha2-adrenoceptor stimulation transforms immune responses in neuritis and blocks neuritis-induced pain. J Neurosci 2005; 25(39):8988-8994.

Satitpitakul V, Kheirkhah A, Crnej A, Hamrah P, Dana R. Determinants of ocular pain severity in patients with dry eye disease. Am J Ophthalmol 2017;179:198-204.

Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. Surv Ophthalmol 1996;41 Suppl 1:S27-37.

Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. Arch Ophthalmol 1997;115(7):847-852.

Shikari H, Amparo F, Saboo U, Dana R. Onset of ocular graft-versus-host disease symptoms after allogeneic hematopoietic stem cell transplantation. Cornea 2015; 34(3):243-247.

Sun YC, Chai X, Inamoto Y, Pidala J, Martin PJ, Flowers ME, et al. Impact of ocular chronic graft-versus-host disease on quality of life. Biol Blood Marrow Transplant 2015; 21(9):1687-1691.

Wang Y, Ogawa Y, Dogru M, Tatematsu Y, Uchino M, Kamoi M, et al. Baseline profiles of ocular surface and tear dynamics after allogeneic hematopoietic stem cell transplantation in patients with or without chronic GVHD-related dry eye. Bone Marrow Transplant 2010; 45(6):1077-1083.

Westeneng AC, Hettinga Y, Lokhorst H, Verdonck L, van DS, Rothova A. Ocular graft-versus-host disease after allogeneic stem cell transplantation. Cornea 2010; 29(7):758-763.

18 APPENDICES

18.1 Appendix 1. Validated Bulbar Redness Grading Scales (VBR)

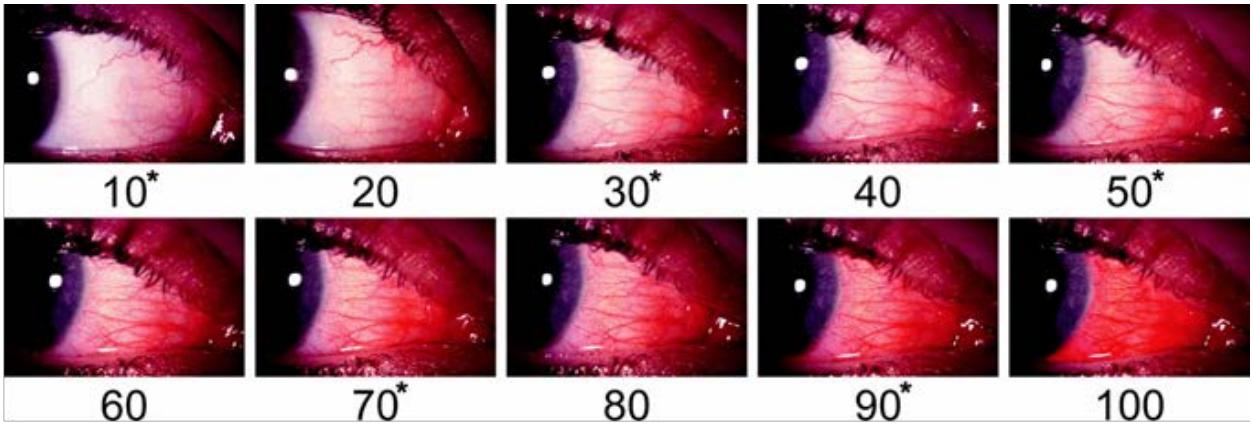
To evaluate ocular redness, the same physician (PI) must assess the subject at all examinations, and under consistent illumination. Examinations must be completed by a slit lamp at 10X magnification using direct diffuse illumination (slit fully opened, angled at 30°- 50° approximately; at half illumination 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 1). 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 1. Validated Bulbar Redness Scale



Source: Shulze, 2007

This manner of testing with increments of 10 as 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 retest.

The above scale will be measured at Screening and at each study visit: Baseline (prior to first dose), Day 14± 3d, and Day 28 ± 7d.

18.2 Appendix 2. Symptom Assessment iN Dry Eye (SANDE)

Administer the questionnaire at Screening, Day 1 (prior to dosing), and again at Day 14 ± 3d, and Day 28 ± 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 current dry eye symptoms (Figure 2).

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 2. 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**

18.3 Appendix 3. 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.

18.3.1 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.

18.3.2 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.

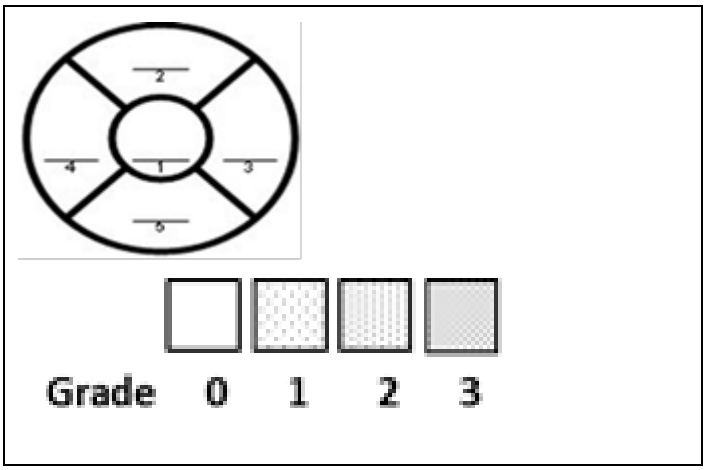
Ocular surface staining is recorded 1-2 minutes after dye instillation (within 4 minutes) as the staining fades variably after 4 minutes. After slightly pulling down the lower eye lid of the patient, Lissamine Green dye will be released into the lower conjunctival sac. The right eye will be evaluated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

18.3.3 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 3 and 4. The dots are ordered on a log scale.

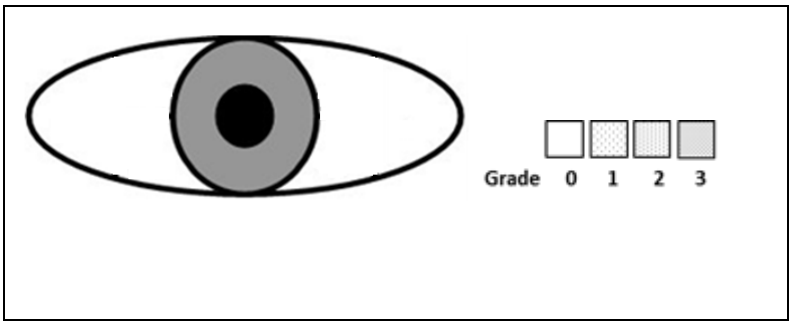
Figure 3. Lissamine Green Corneal Staining Pattern and Grade (NEI Scale)



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 4). 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 4. 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 6.

Table 6. 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: Screening (conjunctival staining only), Day 1 Baseline (prior to first dose), Day 14 ± 3d, and Day 28 ± 7d.

18.4 Appendix 4. LogMAR Visual Acuity

18.4.1 Visual Acuity Testing

It is essential that a standard procedure be used to obtain VA measurements. The VA measurements should be obtained by a qualified ophthalmologist, optometrist or trained ophthalmic technician using the **standard ETDRS charts with light box that will be supplied by the Sponsor**. The right eye (OD) should be tested first

18.4.2 Standard ETDRS Visual Acuity Protocol

The ETDRS visual acuity charts 1 and 2 are used for standardized measurement of visual acuity. Acuity testing of all subjects, regardless of visual acuity, begins at four meters. Two ETDRS Visual Acuity Charts are used for the measurement of visual acuity, each with a different letter sequence. The right eye will always be tested with Chart 1 and the left eye with Chart 2. Each clinic will have/use an ETDRS light box for the ETDRS visual acuity charts during any study acuity testing if the EVA is non-functional. The light box should be hung on the wall or placed on a stand at a height such that the top of the 3rd row of letters (0.8 LogMAR) is 49 $\pm$ 2 inches (124.5 $\pm$ 5.1 cm) from the floor. The distance from the outer canthus of the subject's eye to the front of the ETDRS chart should be 4.0 meters and should be measured with a tape measure, tautly held, or a rigid measuring stick.

To maintain the ETDRS charts in good condition, vision examiners are advised to slide the charts into the front slot of the light box, rather than bending the charts, when changing charts in the front compartment of the light box. To maintain the high contrast of the white background the ETDRS charts, examiners should refrain from touching the front of the charts with their fingers, pens, pencils, etc. If the ETDRS charts become permanently damaged or yellowed, they should be replaced. The ETDRS vision testing equipment (illuminator cabinet, floor stand with casters, Original Series ETDRS charts, and replacement tubes with aluminum sleeves) can be ordered from **Precision Vision, 944 First Avenue, La Salle, IL, 61301, 800-772-9211 (phone).**

18.4.3 Illumination of Visual Acuity Charts and Room

Room lighting should be uniform between the subject and the light box.

The two 20-watt (Cool Daylight) fluorescent tubes in the ETDRS light box must be changed annually; a sticker must be affixed to the side or back of the light box with the date that the bulbs were changed. Cool Daylight (20-watt) fluorescent tubes can be purchased from a local hardware store. When changing the fluorescent tubes, the aluminum fenestrated sleeves must be saved and centered on the new light tubes with the opening of the sleeves pointing towards the back of the light box. If the aluminum sleeves are discarded, they must be replaced. (**Precision Vision, 944 First Avenue, La Salle, IL, 61301, 800-772-9211 (phone)**. Furthermore, when changing the fluorescent light tubes, the new tubes must be "burned in" (i.e., left on continuously for 4 days or 96 hours) before using the ETDRS light box.

18.4.4 Uncorrected (UCVA) and Best-Corrected VA (BCVA)

For BCVA, the subject will be fitted with a half eye trial frame provided by the Sponsor, containing the manifest subjective refraction result, adjusted for optical infinity.

18.4.5 Recording and Scoring VA

Using the Sponsor supplied recording/scoring sheet, an example of which is shown below, the tester will **CIRCLE ALL CORRECT RESPONSES, PUT AN "X" THROUGH THE MISSED LETTERS, AND INSTRUCT THE SUBJECT TO FINISH READING THE ENTIRE LINE.**

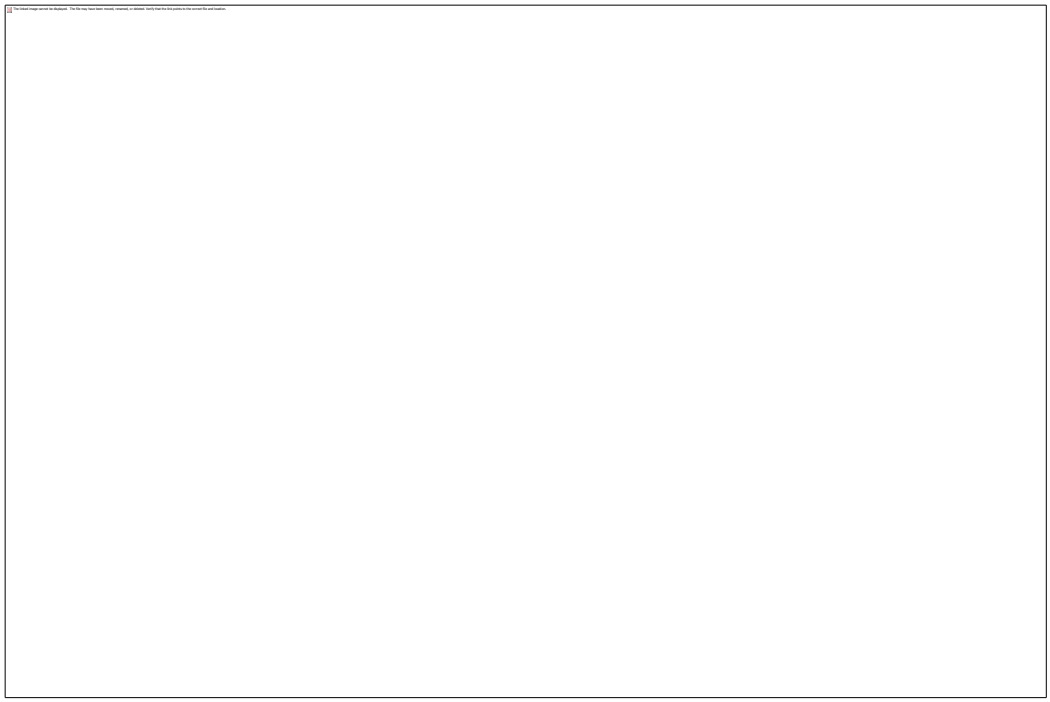
THE SPONSOR-SUPPLIED SCORING SHEET MUST BE KEPT IN THE SUBJECT SOURCE RECORD.

Each line on the ETDRS chart has 5 letters and the number of CORRECT letters will be recorded on the recording/scoring sheet in the far-right box on the corresponding line. The lines will then be added up and the "TOTAL" number of letters correctly identified will be recorded on the recording/scoring sheet. The "TOTAL" is the number that will be entered onto the CRF. For subjects who are unable to see ANY letters, or for subjects whose best VA could be recorded as finger count, hand movement, light perception or no light perception, a score of "0" will be recorded on both the source document and on the CRF.

Example:

> For instance, all lines were read correctly through line 7, line 8 had 2 correct responses, and VA testing was completed. The total letters correctly identified would be 17 and it would be recorded in the space marked "TOTAL" (see Figure 5)

Figure 5. Visual Acuity logMAR



18.4.6 Calculating LogMar from VA Score

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and including in the last line read. This total sum represents the logMAR visual acuity for that eye.

In the example above: Subject correctly reads 5 of 5 letters on the 0.7 line, and 2 of 5 letters on the 0.6 line (see Table 7 below). The correct logMar is 0.66

Table 7. Calculation of logMAR from Visual Acuity Worksheet

Base logMar (The last line in which a letter is read correctly)	0.6
N (total number of letters incorrect on line 0.6 as well as 0.7)	3
N x T (T = 0.02)	0.06
Base logMAR + (N x T)	0.6 + 0.06
logMAR VA	0.66

Instruct the subject to read the ENTIRE top line, from left to right, to the end of that line, even if letters are missed. Circle correct responses and place an "X" through incorrect responses. Have the subject continue to read each ENTIRE line down the chart, from left to right, until they miss 3 or more letters on one line (even with guessing); or they read the entire chart.

NOTE: The ENTIRE line must be attempted (even with guessing) even if letters are missed, as the subject will get credit for all correct letters on that line.

The above scale will be measured at Baseline (Day 1, prior to first dose), Day 14 ± 3d, and Day 28 ± 7d.

18.5 Appendix 5. Intraocular Pressure (IOP)

Intraocular Pressure (IOP) will be measured in both eyes. IOP will be measured at Screening and at each study visit: Day 1 (prior to first dose), Day 14 ± 3d, and Day 28 ± 7d.

18.5.1 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.

18.5.2 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.

18.6 Appendix 6. 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 8:

Table 8. 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

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

Abnormal CS

Abnormal NCS</td></tr>
</table>

*CS = clinically significant; NCS = not clinically significant

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

A. Individual Clinical Study Information

One new clinical study was undertaken during this reporting period (August 2018 to July 2019). The study has been completed.

Title: *A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate 0.2% Nanoemulsion Eye Drops in Patients with Dry Eye Disease (DED)*

	Phase 3
Name and Address of the Clinical Centre	There were 19 study sites, all in US: Chicago Cornea Consultants; Abrams Eye Center; Advanced Laser Vision & Surgical Institute; Aesthetic Eye Care Institute/David Wirta, MD and Associates; Apex Eye, Apex Eye Clinical Research; Toyos Clinic; Cornea Consultants of Albany: Heart of America Eye Care, P.A.; Midtown Eye Physicians & Associates; Kannarr Eye Care; Martel Medical Eye Group; Ophthalmology Associates; Rand Eye Institute; Revolution Research, Inc; Lake Travis Eye and Laser Center; Scott and Christie Eyecare Associates; Shettle Eye Research, Inc.; Total Eye Care; The Eye Institute of Utah. For names of Investigators and site addresses, see Appendix 16.1.4 of CSR
Name and Address of the Clinical Data Management Centre	**CONTRACT RESEARCH ORGANISATION (CRO)** Name: TFS Address: Consell de Cent, 334-336 ES-08009 Barcelona, Spain Phone: +34 931850200 Fax: +34 931850257 **CLINICAL DATA MANAGER (TFS)** Name: Eric Fritz

	Address: 212 Carnegie Center Suite 208, Princeton, NJ 08540 Phone: +1 609-455-9219 E-mail: Eric.Fritz@tfscro.com
Name and Address of the Bio-analytical Laboratory	NA
Name and Address of the Clinical Laboratory	Not Applicable (No clinical specimens were required in this study)

The details of studies completed in 2018-19 are provided below.

Title of Study: *A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate 0.2% Nanoemulsion Eye Drops in Patients with Dry Eye Disease (DED)*

Protocol No.: OCU-310-301

US IND Number: 136132

Investigational Product: Brimonidine Tartrate Nanoemulsion, 0.2% Ophthalmic Solution (OCU310).

Control: Placebo (Ophthalmic Buffered Saline; OBS, pH 6-8)

Purpose of study: To evaluate the safety, tolerability and efficacy of Brimonidine Nanoemulsion eye drops (OCU 310) in subjects with Dry Eye Disease (DED)

Research subject population: Men and women ≥ 18 years of age with a history of DED for at least 6 months who:

Demonstrate the following 2 signs of DED in the same eye at screening and baseline (Day 1):

- Conjunctival staining of ≥3 (out of a possible score of 6 per eye)
- Schirmer's test (with anesthesia) of ≥1 to ≤7 mm in 5 minutes

Symptomatic evidence of DED by having a global symptom score (overall SANDE) of ≥40 mm at screening and baseline (Day 1)

Current status of study: Completed

Total number of subjects initially planned for inclusion in the study: 240 subjects in a 1:1 randomization (120 per study arm).

Total number of subjects entered into the study to date and demographics: 252 subjects in a 1:1 randomization (126 per study arm).

The age (central tendency), gender and race are given in **Table 1**below.

Table 1. Demographic characteristics – Randomized set

		OCU 310 (N=126)	Placebo (N=126)	Total (N=252)
Age (years)	n[a]	126	126	252
	Mean (SD)	61.7 (11.8)	62.1 (11.6)	61.9 (11.7)
	Median	63.0	63.0	63.0
	Min, Max	27, 85	24, 85	24, 85
Gender n (%)	n[a]	126	126	252
	Male	20 (15.9)	21 (16.7)	41 (16.3)
	Female	106 (84.1)	105 (83.3)	211 (83.7)
Race n (%)	n[a]	126	126	252
	White	101 (80.2)	111 (88.1)	212 (84.1)
	Black or African American	19 (15.1)	11 (8.7)	30 (11.9)
	Asian	4 (3.2)	3 (2.4)	7 (2.8)
	American Indian or Alaska Native	1 (0.8)	0 (0.0)	1 (0.4)
	Multiple[b]	1 (0.8)	1 (0.8)	2 (0.8)
Ethnicity n (%)	n[a]	126	126	252
	Hispanic or Latino	12 (9.5)	11 (8.7)	23 (9.1)
	Not Hispanic or Latino	114 (90.5)	115 (91.3)	229 (90.9)

Source: Table 14.1.4 (Clinical Study Report)

a Number of subjects with non-missing data.

b One subject filled in both Asian and Black or African American and one subject filled in both White and Black or African American in CRF

CRF: Case report form; Max: Maximum; Min: Minimum; SD: Standard deviation

- Number of subjects whose participation in the study was completed as planned:
- Of the 252 randomized subjects, 249 completed the study (123 in the OCU 310 group and 126 in the Placebo group).
- Number of subjects who dropped out of the study early for any reason:
- Only 3 subjects, all randomized to the OCU 310 group, withdrew from the study. Specifically, Subjects 305-015 and 322-0009 were lost to follow-up after baseline and were excluded from the ITT and PP populations, and Subject 314-008 discontinued the study due to two AEs and was included in the ITT but excluded from the PP population.

- Pharmacokinetic (PK) Results: Not applicable (N/A). No clinical specimens were required in this study

Brief description of final or interim study results:

NOTE: *Efficacy data will be presented in this section (Section A), while safety data will be presented in the following section (Section B: Summary Investigational Drug Information).*

Synopsis of the Clinical Study Report (CSR) is included with this IND Annual Report in Exhibit I.

Full clinical study report with Appendices will be submitted later as an information amendment to the IND.

INFORMED CONSENT
And AUTHORIZATION to be a RESEARCH SUBJECT FORM

Sponsor / Study Title:	**Ocugen, Inc. / "**A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate 0.2% Nanoemulsion Eye Drops in Patients with Dry Eye Disease (DED)**"**
Protocol Number:	**OCU-310-301**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Additional Contact(s): (Study Staff)	**«AdditionalStaffMemberContacts»**
Address:	**«PiLocations»**

The study doctor wants to know if you would like to be part of a research study. This form describes the study to help you decide whether you want to participate. This form will tell you what you will have to do during the study and the risks and benefits of the study. If you have any questions about, or do not understand something in this form, you should ask the study doctor. Do not sign and date this form unless the study doctor or study staff has answered your questions and you decide that you want to be part of this study. When you have completed reading this form, if you would like to take part in this study, you will sign the form on the last page, initial and date each page, and hand it back to your study doctor. You should also remember that being in this study does not replace your regular medical care.

WHAT IS THIS STUDY ABOUT?

You are invited to take part in a research study because your medical history indicates you have Dry Eye Disease (DED). This study is being done to see how safe and effective an investigational product is in the treatment of your eye disease.

By participating in this study, you will be helping the study Sponsor evaluate a new therapy for this condition. This investigational drug is an eye drop containing Brimonidine, a drug that has already been approved by the FDA for use in patients with glaucoma, but in the form of a nano-emulsion, which increases the time that the eye drop can stay on the surface of your eye. Early studies in animals and humans indicate that brimonidine nano-emulsion, also known as OCU310, can relieve the signs and symptoms of DED. This eye drop is being studied to see if it can help you better manage your DED symptoms, which may include ocular pain or discomfort, and DED signs, which may include redness.

Your study doctor can explain how this investigational drug is intended to work. Your medical history will be reviewed, and you will receive certain standard eye tests to assess the severity of your DED. You must be honest with the study doctor about your medical health history or it may not be safe to participate in the study.

This is a randomized, double-masked study. This means that you will be randomly assigned to receive either OCU310 or PLACEBO (inactive substance) study drug. Neither you nor the study doctor will know to which study drug you have been assigned. The study is designed in a way that you have a 50/50 chance of being assigned OCU310.

HOW DO I KNOW IF I CAN BE IN THIS STUDY?

The first part of the study is called a Screening visit. You will be required to read, sign and date this INFORMED CONSENT and AUTHORIZATION to be a RESEARCH SUBJECT before the Screening visit can begin. The Screening visit will occur 7 days prior to the first day of the study (Day 1). During the Screening visit, the study doctor will decide if you qualify to be in the study based on a list of criteria that he/she will discuss with you. Your selection in part will be determined by your age, the condition of your current DED, your medical history, health status, your current medications, and your ability to participate in all visits and follow-up exams. You cannot be in this study if you are in another research study or if you have been in any other research study in the last 30 days. You cannot be in this study if you are pregnant, or plan on becoming pregnant. A urine test will be performed to check for pregnancy.

Following your completion of the Screening visit you will be informed of whether you have met the eligibility criteria to participate in this study, at which time you can decide again whether to participate or not participate.

HOW MANY SUBJECTS IN TOTAL WILL BE ENROLLED AT HOW MANY STUDY CENTERS?

Approximately two hundred and forty (240) subjects will be enrolled in this study. This study will be conducted at approximately 15 US clinical sites/centers.

WHAT WILL HAPPEN DURING THIS STUDY?

The study will involve 4 visits over a period of 5 weeks. The length of each visit will likely take 2 to 4 hours.

Subject Responsibilities:

While participating in this research study, your responsibilities are to:

- Be willing and able to follow the study directions and procedures.
- Tell the study staff about any side effects or problems.
- Ask questions as you think of them.
- Tell the investigator or the study staff if you change your mind about staying in the study.
- Administer your study in drug in both eyes, 2 times a day approximately 12 hours apart.
- Maintain your same lifestyle and routine such as work, exercise and recreation activities, and diet. Do not take any new, or change any of your current, eye treatments, vitamins, herbs or supplements during the study without first discussing with your study doctor.
- Attend all study visits
- Remain in the clinic for at least 2 to 3 hours after your first drop of study medication

Before the first examination, or before any information can be requested of you, you will have a thorough discussion with your doctor about this study. Following a careful discussion, you will be asked

to sign this INFORMED CONSENT and AUTHORIZATION to be a RESEARCH SUBJECT form. Your decision to be a candidate participant and the signing of this FORM are totally voluntary and up to you. If you agree to be a candidate participant and sign this FORM, the four (4) study visits will involve the following:

Screening Visit:
Before the study starts, you will be asked to sign and date this consent form, give your health history, and tell study staff if you have taken any over-the-counter or prescription medicines, vitamins, probiotics, herbs or nutritional supplements, or eye-drops. Your screening examination visit will last approximately 2 to 3 hours and must occur 7 days prior to the actual start of the study. The study doctor will do some tests to find out if you can be in the study. These tests are often used in the eye clinic and include:

- *Informed Consent*
- *Eligibility Criteria*
- *Demographic Information*
- *Medical/Surgical/Ocular History*
- *Review of Prior and Concomitant Medications*
- *Urine Collection and Pregnancy Test (if applicable)*
- *Symptom Assessment in Dry Eye (SANDE)*
- *Slit Lamp Ophthalmic Exam*
- *Conjunctival Lissamine Green Stain*
- *Schirmer's Test with Anesthesia (mm)*
- *Intraocular Pressure*
- *Adverse Event Surveillance*

Baseline (Day 1) Visit: During this exam, your current medications and changes in your medical history will be discussed and you will receive several routine eye tests. If you continue to meet study inclusion criteria you will be given a 28-35 day supply of the study drug and your subject diary. You will be instructed on how to administer your first dose of study drug in the clinic, and the staff will instruct you on proper methods to place a single drop in each eye, how to record use of the eye drops in your diary, storage of your study drugs, and timing of your daily doses.

Before the first dose of medication is given in the clinic, the study doctor will do some tests. These tests include:

- *Eligibility Criteria*
- *Medical/Surgical/Ocular History*
- *Vital Signs*
- *Review of Prior and Concomitant Medications*
- *Urine Collection and Pregnancy Test*
- *Visual Acuity (logMar)*
- *Symptom Assessment in Dry Eye (SANDE)*
- *Ocular Redness 100-point VBR Scale via Slit Lamp*
- *Slit Lamp Opthalmic Exam*
- *Corneal Lissamine Green Stain*
- *Conjunctival Lissamine Green Stain*
- *Schirmer's Test with Anesthesia (mm)*

- *Intraocular Pressure*
- *Randomization*
- *Dispense/Instill IP*
- *Adverse Event Surveillance*
- *Diary Recording and Review*

There is the possibility that during your screening and baseline (Day 1) visits (Day 1) visit that your study doctor could decide that you are ineligible to participate further in the study for a variety of reasons. If this happens, you will be dismissed from the study.

Study Day 14 Visit: This visit occurs approximately 14 days after your first dose of the study drug and lasts 2- 4 hours. During this visit, you will bring your diary to the clinic and it will be reviewed by the clinic staff. The study doctor will do some tests to find out how you are progressing in the study. These tests include:

- Vital Signs
- *Review of Prior and Concomitant Medications*
- *Visual Acuity (logMar)*
- *Symptom Assessment in Dry Eye (SANDE)*
- *Ocular Redness 100-point VBR Scale via Slit Lamp*
- *Slit Lamp Ophthalmic Exam*
- *Corneal Lissamine Green Stain*
- *Conjunctival Lissamine Green Stain*
- *Intraocular Pressure*
- *Clinical Global Impression (CGI)*
- *Subject Global Assessment (SGA)*
- *Adverse Event Surveillance*
- *Diary Recording and Review*

At the end of this visit you will continue to use the initial study drug that was supplied at the Day 1 Visit. You will continue to record your use of your eye drops in your diary.

Study Day 28 Visit: This visit occurs approximately 28 days after your first dose of the study drug and lasts 2- 4 hours. The assessments are the same as the Day 14 Visit, except there is one more test, the Schirmer's test. During this visit, you will bring your diary to the clinic and it will be reviewed by the clinic staff. Your current medications, daily dose diary and changes in your medical history will be reviewed. Your doctor will conduct tests to see how well you have progressed in the study. These tests include:

- Vital Signs
- *Review of Prior and Concomitant Medications*
- *Visual Acuity (LogMar)*
- *Symptom Assessment in Dry Eye (SANDE)*
- *Ocular Redness 100-point VBR Scale via Slit Lamp*
- *Slit Lamp Ophthalmic Exam*
- *Corneal Lissamine Green Stain*
- *Conjunctival Lissamine Green Stain*
- *Schirmer's Test with Anesthesia (mm)*
- *Intraocular Pressure*
- *Clinical Global Impression (CGI)*

- *Subject Global Assessment (SGA)*
- *Adverse Event Surveillance*
- *Diary Recording and Review*

At the end of the visit you will be DISMISSED from the study.

ARE THERE RISKS TO ME IF I AM IN THIS STUDY?

Any time you are enrolled in a clinical study, there may be risks, discomfort, and side effects that are not yet known.

As mentioned earlier, this is a randomized, double-masked study. This means that you will be randomly assigned to receive either OCU310 or PLACEBO study drug. Neither you nor the study doctor will know to which study medication you have been assigned. The study is designed in a way that you have a 50/50 chance of being assigned OCU310. Neither treatment (OCU310 or Placebo) has a preservative.

The **placebo** in this study is called "ophthalmic buffered saline" or OBS. This is similar to "normal saline eye drops" or "normal saline solution". Normal saline is another name for the kind of saltwater found in your body, including tear drops. Some brands of "artificial tears" contain normal saline. Therefore, some subjects receiving OBS in this study may experience some temporary relief from their DED symptoms. OBS is safe and widely used and no side effects are expected. Like most eye drops, there may be some temporary blurring of vision immediately after application, so wait until the blurring clears before operating your vehicle or heavy machinery.

The **active drug** in this study is "Brimonidine Nanoemulsion" or OCU310. You are encouraged to discuss the safety aspects of Brimonidine Nanoemulsion (OCU310) eye drops with your doctor.

Brimonidine is currently approved for use as a treatment for glaucoma. The FDA approval for brimonidine (Alphagan and Alphagan-P) includes data from three clinical studies in a total of 1214 subjects. Additional safety information is available from 300 peer-reviewed articles involving 13,983 subjects. In summary**,** brimonidine tartrate ophthalmic solution of up to 0.2% is considered safe, based on the long history of chronic use and data available in the published literature.

In clinical studies on its use for treating glaucoma, the following possible side effects have been reported in the approved product label:

- 10-30% of subjects experienced (in order of frequency):
    - Dry mouth,
    - Red eyes,
    - Burning/stinging in eyes,
    - Headache,
    - Blurring,
    - Eye allergic reactions.
- 3-9% of subjects experienced (in order of frequency):
    - Corneal staining,
    - Sensitivity to light,
    - Eyelid redness,
    - Eye pain/irritation.

Less commonly, some of the following conditions have been reported:

- Swelling of the eyelid with associated burning and dryness of the eye.
- Swelling of the eyelid along with pink eye. The symptoms of pink eye include a reddening of the whites of the eyes, itchy eyes, and thick discharge around the eye, often after sleep.

Because approved brimonidine (e.g., Alphagan and Alphagan-P) has a preservative, it is possible that some of the adverse events listed above are caused by the preservative. Of course, should you have any questions about changes in your health and/or vision, you should contact the study doctor or study staff immediately. Please tell the study doctor or study staff right away if you experience any changes in your normal routine. Also, please tell them if you experience any other problems with your health or the way you feel during the study

WHAT ARE THE POTENTIAL RISKS AND THEIR LIKELIHOOD FROM USING THIS NEW STUDY DRUG?

You and your study doctor will discuss the potential risks and likelihood of these risks from the use of this new study drug. This new drug, OCU310, has "brimonidine" as its active ingredient, so the adverse events listed above could potentially occur. Because the new drug, OCUI310, does not have a preservative, there will be no adverse events related to preservative.

The Sponsor has also uncovered the following risks that have been described with eyedrops, in general, when used for DED:

- Skin rash on the eyelids
- Pink eye
- Fungal infection from incorrect use of the eye drop

ARE THERE RISKS IF I AM PREGNANT DURING THE STUDY?

Because the effect of this study medication on babies is unknown, you may not participate if you are a woman who is pregnant or planning to become pregnant. You may not participate if breast feeding. Please inform your study doctor immediately if you become pregnant during the study. If you do become pregnant the sponsor will want to follow you to term or termination to collect information about your pregnancy and birth. If you are a female who is able to become pregnant you are required to use an acceptable method of birth control (oral contraceptive pills, birth control implants/shots or patches, barrier methods) throughout the study.

WILL BEING IN THIS STUDY HELP ME?

This new eye drop therapy may help you better manage your DED symptoms, such as eye pain, or signs, such as redness, but there is no guarantee that this will occur. Although being a research subject in this study may or may not help you personally, information from this study will help the study Sponsor, study doctors and researchers come up with new tests or therapies to help others in the future.

NEW FINDINGS:

If the study doctor learns any new information about the study treatment or your condition that might change your mind about continuing in the study, the study doctor or study staff will tell you about it.

WILL I GET PAID?

You will be paid up to a total of $xx.xx if you complete this study. You will be paid for the visits you complete according to the following schedule:

- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid _____ after each visit

If you have any questions regarding your compensation for participation, please contact the study staff.

WILL I GET PAYMENT IF THE SPONSOR INVENTS NEW TESTS OR THERAPIES?

No. If the Sponsor invents new tests or therapies as a result of this study, you will not receive any money for these tests or therapies. The Sponsor will own any new tests or therapies that are developed using the data from this study.

WHAT IF I GET HURT OR SICK WHILE I AM IN THIS STUDY?

If you become ill or are physically injured as a result of participation in this study, please contact the study doctor right away. The study doctor will treat you or refer you for treatment.

The reasonable costs of such treatment beyond that provided by your insurance will be covered by the sponsor, Ocugen:

- If you followed instructions,
- If the injury is related to the study drug or to properly performed study procedures that are not part of your usual medical care,
- If the injury is not the result of the natural course of any underlying disease and/or pre-existing disease process present prior to the proper administration of the study drug.

In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsor or involved institutions from their legal and professional responsibilities.

You do not give up any of your legal rights by signing this form.

Be aware that your health care payer/insurer might not cover the costs of study-related injuries or illnesses

DO I HAVE TO BE IN THIS STUDY?

Your decision to be in this study is totally voluntary. You do not have to be in this study if you don't want to, and you can change your mind at any time. If you decide to withdraw before your eye(s) are treated then you don't have to have your eye(s) examined. If you withdraw from the study after your eye(s) have been treated, for your safety, you will be asked to come in for a follow-up visit. If you decide not to participate or decide to participate and then later change your mind, there will be no penalty to you, and you won't lose any benefits to which you are otherwise entitled. Your regular medical care at this study center will not change if you decide not to be in the study or withdraw from it after you have agreed to participate.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact**:**

Study Subject Adviser

- By **mail:**
- or call **toll free**:
- or by **email**:

Please reference the following number when contacting the Study Subject Adviser: XXXXXXX.

ARE THERE OTHER ALTERNATIVE TREATMENTS TO HELP TREAT THE SYMPTOMS OF DED?

The US FDA has approved treatment for DED. Other current treatments include Restasis, Xiidra, punctal plugs, and combinations thereof. There are also over-the-counter eyedrops, often called "artificial tears". You should talk with the study doctor about other treatments that might help you.

WHO IS PAYING FOR THIS STUDY?

The Sponsor, Ocugen, Inc. is paying for this study.

WILL IT COST ANYTHING TO BE IN THIS STUDY?

You will not be charged for your participation in this study. All study-related procedures and tests, as well as study drug, will be given to you free of charge during the time you will be participating in this study.

While you are in the study, if you need to get regular medical care, you (and/or your health care payer) will still have to pay for the costs of your regular medical care that are not a part of this study.

WILL INFORMATION ABOUT ME BEING IN THIS STUDY BE USED AND SHARED?

Yes, selectively as follows:

- **Mandatory www.ClinicalTrials.gov Reporting:** A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You are free to search this Web site at any time.

- **Confidentiality and Protected Health Information (PHI):** Protected health information (PHI) includes identifying information and any information about your health. Research personnel who are conducting the study may have access to your PHI. People other than those doing the study may look at both medical charts and study records. These include agencies, your study doctor, departments and committees that make rules and policy about how research is done, and the sponsors of this study. Some specific examples include the US FDA, the Office for Human Research Protections, the Institutional Review Board, the institution's Office of Research Compliance, and the Clinical Trials Office. Ocugen the company that will pay for this study also will have the right to look at your records. In addition, records can be opened by court order or produced in response to a subpoena or a request for production of documents. We will keep any records that we produce private to the extent we are required to do so by law. We will use a study number rather than your name on study records where we can. Your name and other facts that might point to you will not appear when we present this study or publish its results.

If you are or have been a patient at one of the study sites, then you will have a medical record at that site. Your medical records and the study records will be maintained separately. If you are not, and never have been, a patient at any of the study sites, then no medical record will be created at that site for you just because you are participating in a research study.

We will put a copy of your signed Informed Consent Form for the Research Study and your signed HIPAA Authorization form into any medical record that you may have with any of the research sites. Laboratory results and other test results obtained as part of this study may be placed in your medical records, if they exist, at the research site.

DO YOU WANT TO BE IN THIS STUDY?

You have read this form, and you have been able to ask questions about this study. The study doctor or study staff has talked with you about this study. They have answered all your questions. You voluntarily agree to be in this study. By signing this form, you have not given up any of your legal rights as a research participant. I understand there will be no penalty to me for making this decision.

SIGNATURE--ORIGINAL STUDY

Subject's Signature: _____

_____
Subject's PRINTED NAME (*as above)

Date(dd/mmm/yyyy)/Time: _____

Signature of Person Obtaining Consent: _____

Person Obtaining Consent – PRINTED NAME: (*as above): _____

Date(dd/mmm/yyyy)/Time: _____

AUTHORIZATION TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION

If you decide to be in this study, the study doctor and research team will use and share health data about you to conduct the study. Health data may include:

- Your name
- Address
- Phone number
- Date of birth
- Medical history
- Information from your study visits, including all test results

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

For this study, the research team may share health data about you with authorized users. Authorized users may include

- Representatives of Ocugen, Inc.
- Representatives of XXXX (an Institutional Review Board, or IRB, that reviews this study).
- The Food and Drug Administration (FDA) and other US federal and state agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.
- Governmental agencies of other countries.
- Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study.
- Other research doctors and medical centers participating in this research, if applicable.
- A data safety monitoring board which oversees this research, if applicable.

Your health data will be used to conduct and oversee the research, including for instance:

- To see if the study drug works and is safe.
- To compare the study drug to other drugs.
- For other research activities related to the study drug.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the study doctor at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____

Printed Name of Subject

_____ _____

Signature of Subject Date

_____

Printed Name of the Person Obtaining the Authorization

_____ _____

Signature of the Person Obtaining the Authorization Date

EFFICACY RESULTS:

Demographic and Baseline Information

Demographic and other baseline characteristics were comparable between the OCU 310 and placebo groups. Demographic and baseline characteristics were well balanced between the two treatment groups. Briefly, overall mean (SD) age was 62 (12) year, and the majority of subjects were females (84%), and Caucasian (84%). Overall mean time since first DED diagnosis was 5 years. Compliance to the study treatment was ≥ 80%-≤ 100% for the majority (99%) of subjects, and the median number of received doses was the same in the two treatment groups (55).

Primary Efficacy Endpoints

Change from baseline to Day 28 in SANDE score

In the ITT set, both study treatments resulted in a reduction (i.e. improvement) from baseline to Day 28 in SANDE overall, and in frequency of symptoms and severity of symptoms scores. None of the comparisons of OCU 310 vs. placebo were statistically significant, with estimated mean differences between the two treatments (OCU 310 - placebo) of -0.8 mm (p= 0.739) for the overall score, -2.7 mm (p= 0.297) for the frequency of symptoms score, and 0.7 mm (p= 0.803) for the severity of symptoms score. Results were confirmed in the PP set and, overall, in the subgroups (ITT set) analysis for the SANDE overall score with improver subjects, non-improver subjects, as well as subjects with SANDE ≥ 60 at baseline, SANDE ≥ median at baseline, VBR ≥ 40 at baseline, VBR ≥ 50 at baseline and VBR ≥ median at baseline.

Change from baseline to Day 28 in lissamine green total conjunctival staining scores

In the ITT set, both study treatments resulted in a reduction (i.e. improvement) from baseline to Day 28 in lissamine green total conjunctival staining scores in both the study eye and qualified fellow eye. For the study eye, the comparison OCU 310 vs. placebo was not statistically significant, with an estimated mean difference between the two treatments (OCU 310 - placebo) of 0.26 (p= 0.097). Results were confirmed in the PP set, and in the subgroups (ITT set) of improver and non-improver subjects.

Secondary and Exploratory Efficacy Endpoints

None of the secondary or exploratory endpoints demonstrated a statistically significant difference in OCU310 vs. control, except for the Validated Bulbar Redness scale (VBR).

With OCU 310, VBR scores (overall area) for the study eye and the qualified fellow eye decreased

(i.e. improved) from Baseline. With placebo, mean VBR scores (overall area) remained stable at all time points. In the ITT set, mean reductions from baseline in VBR score (overall area) were greater with OCU 310 than with placebo at both Day 14 and Day 28, with estimated mean differences between treatments (OCU 310 - placebo) of -2.8 (p= 0.006) and -2.6 (p= 0.020), respectively. These results were confirmed in the PP set and, in the subgroups, (ITT set) of subjects with SANDE ≥ 60 at baseline, VBR ≥ 40 at baseline and VBR ≥ median at baseline.

CONCLUSIONS:

This study showed that OCU 310 is generally safe and well-tolerated, though it did not meet its co-primary endpoints for DED symptom and sign. Importantly, OCU 310 was better than placebo in reducing ocular redness, an exploratory sign endpoint, at both Day 14 and Day 28.

B. Summary Investigational Drug Information

1. Safety Data Summary

Only one clinical study (OCU310-301) has been conducted thus far using the investigational drug (OCU310):

Title of Study: *A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate 0.2% Nanoemulsion Eye Drops in Patients with Dry Eye Disease (DED)*

This study has been completed.

SAFETY RESULTS:

Brief Summary of Adverse Events

All AEs were reported after the first dose of study treatment and therefore, all AEs were TEAEs (**Table 2**). Forty TEAEs (39 unique TEAEs) were reported in 34 (14%) subjects. In the OCU 310 group, 27 TEAEs were reported in 23 (18%) subjects while 12 TEAEs were reported in 11 (8.7%)

subjects in the placebo group. Regarding treatment related TEAEs, 15 TEAEs were reported in 12 (9.5%) subjects in the OCU 310 group and 5 TEAEs were reported in 4 (3.2%) subjects in the placebo group. TEAEs leading to study treatment discontinuation were reported only in the OCU 310 group, 2 TEAEs in 1 (0.8%) subject. The majority of TEAEs reported during the study treatment were of mild nature, and none were of severe nature. There were no serious TEAEs, including TEAEs leading to death.

Table 2 Summary of AEs – Safety set

	OCU 310 (n=126)	Placebo (n=126)	Total (n=252)
Number of AEs	27	13	40
Number of unique AEs[a]	27	12	39
Number of subjects with at least one AE	23 (18.3%)	11 (8.7%)	34 (13.5%)
Number of AEs leading to death	0	0	0
Number of SAEs[b]	0	0	0
Number of unique SAEs[a]	0	0	0
Number of subjects with at least one SAE	0	0	0
Number of TEAEs	27	13	40
Number of unique TEAEs	27	12	39
Number of subjects with at least one TEAE	23 (18.3%)	11 (8.7%)	34 (13.5%)
Number of AEs where action taken is Drug discontinued	2	0	2
Number of subjects with at least one AE where action taken is Drug discontinued	1 (0.8%)	0	1 (0.4%)
Number of related AEs[c]	15	5	20
Number of subjects with at least one related AE[c]	12 (9.5%)	4 (3.2%)	16 (6.3%)

Source: Table 14.3.1.1 (Clinical Study Report)

[a] Unique adverse event = adverse event of a certain PT, counted only once within each subject

[b] Including deaths

[c] Adverse event with Relationship to study drug 'Definitely Related' or 'Possibly Related'

AE: Adverse event; PT: Preferred term; SAE: Serious adverse event; TEAE: Treatment-emergent adverse event

As expected, the most common ocular SOC reported during the study treatment was eye disorders, 17 events in 13 subjects (5.2%). Eye irritation (SOC: eye disorders) and instillation site irritation (SOC: general disorders and administration site conditions) were the most common ocular TEAEs, 4 events in 4 subjects (1.6%) in each TEAE. Amongst the non-ocular TEAEs, the most common SOC reported was infections and infestations, 8 events in 8 subjects (3.2%). Three events of sinusitis were reported in 3 subjects (1.2%) (**Table 3**).

Table 3 TEAEs by SOC and PT – Safety set

	Ocular TEAEs				Non-ocular TEAEs					
	OCU 310 (n=126)		Placebo (n=126)		OCU 310 (n=126)		Placebo (n=126)		Total (n=252)	
SOC PT[a]	No. (%) subjects	No. events[b]	No. (%) subjects	No. events[b]	No. (%) subjects	No. events[b]	No. (%) subjects	No. events[b]	No. (%) subjects	No. events[b]
Blood and lymphatic system disorders					1 (0.8%)	1			1 (0.4%)	1
Anemia					1 (0.8%)	1			1 (0.4%)	1
Eye disorders	8 (6.3%)	11	5 (4.0%)	6					13 (5.2%)	17
Conjunctival hemorrhages			1 (0.8%)	1					1 (0.4%)	1
Corneal disorder	1 (0.8%)	1							1 (0.4%)	1
Dry eye	2 (1.6%)	2							2 (0.8%)	2
Episcleritis	1 (0.8%)	1							1 (0.4%)	1
Eye irritation	3 (2.4%)	3	1 (0.8%)	1					4 (1.6%)	4
Eye pruritus	1 (0.8%)	1	1 (0.8%)	1					2 (0.8%)	2
Lacrimation increased	1 (0.8%)	1	1 (0.8%)	1					2 (0.8%)	2
Photophobia	1 (0.8%)	1							1 (0.4%)	1
Vision blurred	1 (0.8%)	1	2 (1.6%)	2					3 (1.2%)	3
Gastrointestinal disorders					2 (1.6%)	2			2 (0.8%)	2
Dry mouth					1 (0.8%)	1			1 (0.4%)	1
Gastroesophageal reflux disease					1 (0.8%)	1			1 (0.4%)	1
General disorders and administration site conditions	3 (2.4%)	3	1 (0.8%)	1	1 (0.8%)	1			5 (2.0%)	5
Instillation site irritation	3 (2.4%)	3	1 (0.8%)	1					4 (1.6%)	4
Pain					1 (0.8%)	1			1 (0.4%)	1
Immune system disorders					1 (0.8%)	1			1 (0.4%)	1
Rubber sensitivity					1 (0.8%)	1			1 (0.4%)	1
Infections and infestations					4 (3.2%)	4	4 (3.2%)	4	8 (3.2%)	8
Bronchitis					1 (0.8%)	1			1 (0.4%)	1
Gastroenteritis viral							1 (0.8%)	1	1 (0.4%)	1
Pneumonia					1 (0.8%)	1			1 (0.4%)	1
Sinusitis					1 (0.8%)	1	2 (1.6%)	2	3 (1.2%)	3
Upper respiratory tract infection					1 (0.8%)	1	1 (0.8%)	1	2 (0.8%)	2
Musculoskeletal and connective tissue disorders					1 (0.8%)	1			1 (0.4%)	1
Costochondritis					1 (0.8%)	1			1 (0.4%)	1
Nervous system disorders					2 (1.6%)	2			2 (0.8%)	2
Dizziness					1 (0.8%)	1			1 (0.4%)	1
Hypoaesthesia					1 (0.8%)	1			1 (0.4%)	1
Respiratory, thoracic, and mediastinal disorders					1 (0.8%)	1			1 (0.4%)	1

	Ocular TEAEs				Non-ocular TEAEs					
	OCU 310 (n=126)		Placebo (n=126)		OCU 310 (n=126)		Placebo (n=126)		Total (n=252)	
SOC PT[a]	No. (%) subjects	No. events[b]	No. (%) subjects	No. events[b]	No. (%) subjects	No. events[b]	No. (%) subjects	No. events[b]	No. (%) subjects	No. events[b]
Cough					1 (0.8%)	1			1 (0.4%)	1
Skin and subcutaneous tissue disorders							1 (0.8%)	1	1 (0.4%)	1
Rash							1 (0.8%)	1	1 (0.4%)	1

Source: Table 14.3.1.6 (Clinical Study Report)

Subjects are counted once for each PT, and once for each SOC this preferred term belongs to. Thus, one subject can have one or more PT reported under a given SOC. Consequently, the total number of subjects by PT can be higher than the total number of subjects in that specific SOC.

[a]Text from MedDRA version 21.1

[b]AEs are counted once per subject and PT.

AE: Adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred term; SOC: System organ class; TEAE: Treatment-emergent adverse event

Treatment-related TEAEs were reported in 9.5% of subjects in the OCU 310 group and in 3.2% of subjects in the placebo group. In the OCU 310 group, treatment-related TEAEs reported in > 1 subject were of ocular nature: "dry eye" and "instillation site irritation" (in 1.6% and 2.4% of subjects, respectively). In the placebo group, treatment related TEAEs were reported at most in 1 subject.

Most treatment-related TEAEs were of mild intensity (OCU310: 12 out of 15; Placebo: 5 out of 5), and none were severe. Notably, two treatment-related ocular TEAEs of moderate intensity (PTs: lacrimation increased and eye irritation) in the OCU 310 group led to study treatment discontinuation of one subject (Subject 314-008), and accounted for all TEAEs leading to study treatment discontinuation of the study. Both events resolved by the end of the study without corrective treatment.

Overall, no safety concerns were identified in this study.

2. **Summary of all IND Safety Reports submitted during the previous year:**

   No IND safety reports have been submitted during this reporting period.

3. **List of research subjects who died during participation in clinical studies of the investigational drug (i.e., inclusive of all clinical studies conducted under the IND)**

   No subject died during participation in clinical studies of the investigational drug under the IND.

4. **List of research subjects whose participation in clinical studies of the investigational drug was terminated in association with an adverse experience (i.e., inclusive of all**

clinical studies conducted under the IND):

There were no deaths and no Serious Adverse Events (SAEs).

As mentioned, two (2) treatment-related ocular TEAEs of moderate intensity (PTs: lacrimation increased and eye irritation) in the OCU 310 group led to study treatment discontinuation of one subject (Subject 314-008), and accounted for all TEAEs leading to study treatment discontinuation of the study. Both events resolved by the end of the study without corrective treatment.

5. **Description of new information pertinent to understanding the actions of the investigational drug:**

None.

6. **List of preclinical studies (including *in-vitro* and animal studies) completed or in progress during the past year, and a summary of major preclinical findings:**

In IND application, Ocugen submitted result of a GLP-compliant ocular irritation study conducted in rabbits to assess local tolerability of 0.18% brimonidine tartrate formulation (OCU300) to establish overall tolerance of "OCU310"-similar formulation with 0.2% brimonidine tartrate. In addition, data from single and 14-day repeat dose biodistribution and toxicokinetic studies of 0.18% brimonidine tartrate nanoemulsion were included with original IND submission, which provides a comparative outlook of pharmacokinetic and toxicokinetic profile of brimonidine in nanoemulsion formulation. Results for above studies submitted with OCU310 IND application. No additional preclinical study was conducted during reporting period (August 2018 – July 2019).

7. Summary of any significant manufacturing or microbiological changes made during the past year:

No significant manufacturing or microbiological changes are made during the past year. All the stability results for OCU310 Clinical Drug Product Batch and Ophthalmic Buffered Saline (placebo) are satisfactory.

The following stability tables are included in Exhibit II:

- OCU310 Clinical Drug Product Batch (18E38) at Long Term Storage Condition (25°C ± 2C/40% RH ± 5%) for 12 months
- OCU310 Clinical Drug Product Batch (18E38) at Accelerated Storage Condition (40°C ± 2C/NMT25% RH) for 12 months
- Ophthalmic Buffered Saline Batch (18CL8) at Long Term Storage Condition (25°C ± 2C/60% RH ± 5%) for 18 months
- Ophthalmic Buffered Saline Batch (18CL8) at Long Term Storage Condition (25°C ± 2C/40% RH ± 5%) for 18 months
- Ophthalmic Buffered Saline Batch (18CL8) at Accelerated Storage Condition (40°C ± 2°C/NMT25% RH) for 6 months

C. General investigational plan

1. Rationale for the investigational drug or the research study (studies):

The proposed studies are conducted to support the submission of 505(b) (2) New Drug Application for OCU310. This Annual Report covers the only clinical study the Sponsor has conducted thus far using OCU310:

A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate 0.2% Nanoemulsion Eye Drops in Patients with Dry Eye Disease (DED)

Currently, the only FDA-approved pharmaceutical agents for the treatment of DED are Restasis®, Cequa™ and Xiidra®. Given the complexity, severity and frequency of DED, and the limited modes of action by which these three products treat DED, there is a medical need for other DED therapies, particularly those with multiple modes of action that target the wider DED population and are effective and safe for early relief and long-term daily use.

Brimonidine tartrate ophthalmic solution 0.2% is an FDA-approved product that has demonstrated a robust safety profile via topical ocular delivery in subjects with open-angle glaucoma or ocular hypertension, with a low occurrence of adverse events (AEs). It was also shown to be safe and tolerable, while demonstrating preliminary efficacy, in a Phase 2 proof-of-concept study in subjects with DED conducted in 2017.

OCU 310 is a sterile, preservative-free solution of brimonidine tartrate 0.2% in an ophthalmic nanoemulsion. It was developed for topical instillation in the eye to provide relief of the signs and symptoms of DED. To support the proposed indication, efficacy in both a sign and a symptom of DED are expected to be demonstrated in phase 3 studies. In the above-mentioned Phase 2 study of DED, positive efficacy signals were observed across multiple endpoints, consistent with the hypothesis that brimonidine works through multiple mechanistic pathways.

The present study is further supported by the long-term safety profile of marketed brimonidine tartrate, the tolerability of brimonidine 0.2% in the Phase 2 study of DED and the added pharmaceutical benefits of the preservative-free nanoemulsion.

2. Indication(s) to be studied:

Relief of signs and symptoms of dry eye disease

3. General approach to be followed in evaluating the investigational drug:

The General Investigational Plan for evaluating the investigational drug remains same as submitted in the original IND submission.

4. Types of clinical studies to be conducted in the following year:

The clinical studies proposed to be conducted are as follows:

None

5. Estimated number of patients or subjects who will be administered the investigational drug under these studies during the following year:

Number of subjects: None

6. Anticipated significant risks of study participation:

OCU310 was safe and well tolerated in the above-mentioned phase 3 study. No additional OCU310 studies are planned in the upcoming year. If a future OCU310 study is conducted, Ocugen does not anticipate any significant risks to the subjects enrolling in that study, based on the prior history of the drug and known clinical experience.

D. Investigator Brochure Revisions

The Investigator's Brochure is the same as the one submitted in the IND. No revision planned at this time and if any revisions are made, will be submitted at subsequent annual status update.

E. Protocol Modifications

None

F. Foreign Market Developments

None.

G. Outstanding business with respect to IND

None.

CONFIDENTIAL

CLINICAL STUDY REPORT

SYNOPSIS

A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate 0.2% Nanoemulsion Eye Drops in Patients with Dry Eye Disease (DED)

Study code:	OCU-310-301	Study development phase:	Phase 3
IND number:	136132	Investigational medicinal product:	OCU 310 (Brimonidine Tartrate Ophthalmic Nanoemulsion 0.20%)
Indication:	Relief of signs and symptoms of dry eye disease		
First subject first visit:	December 4th, 2018	Last subject last visit:	February 25th, 2019
Version:	Final	Date:	January 24th, 2020

This study was performed in compliance with Good Clinical Practice (ICH E6).

2 SYNOPSIS

Name of the Sponsor/Company: Ocugen, Inc. **Name of Finished Product:** OCU 310 **Name of Active Ingredient:** Brimonidine tartrate 0.2%	**Individual Study Table Referring to Module 5 of the Dossier** **Volume:** **Page:** **Study No.:**	**(For National Authority Use only)**
STUDY CODE: OCU-310-301		
TITLE OF STUDY: A Phase 3 Randomized, Placebo-Controlled, Double-Masked, Multicenter, Safety and Efficacy Study of Brimonidine Tartrate 0.2% Nanoemulsion Eye Drops in Patients with Dry Eye Disease (DED)		
INVESTIGATORS: Dr. Parag Majmudar, Dr. Marc Abrams, Dr. William Lipsky, Dr. David Wirta, Dr. Robert Benza, Dr. Karen Klugo, Dr. Melissa Toyos, Dr. Robert Schultze, Dr. Brenda Edwards, Dr. Emelike Agomo, Dr. Shane Kannarr, Dr. Joseph Martel, Dr. Ranjan Malhotra, Dr. William Rand, Dr. Kyle Rhodes, Dr. Daniel Zimmer, Dr. Lee Shettle, Dr. David Evans, Dr. Darcy Wolsey.		
STUDY SITES: Chicago Cornea Consultants, Abrams Eye Center, Advanced Laser Vision & Surgical Institute, Aesthetic Eye Care Institute/David Wirta, MD and Associates, Apex Eye, Apex Eye Clinical Research, Toyos Clinic, Cornea Consultants of Albany, Heart of America Eye Care, P.A., Midtown Eye Physicans & Associates, Kannarr Eye Care, Martel Medical Eye Group, Ophthalmology Associates, Rand Eye Institute, Revolution Research, Inc ; Lake Travis Eye and Laser Center, Scott and Christie Eyecare Associates, Shettle Eye Research, Inc., Total Eye Care, The Eye Institute of Utah.		
PUBLICATION (REFERENCE): Not applicable at the date of this report		
STUDY PERIOD (YEARS): Date of first subject first visit: December 4th, 2018 Date of last subject last visit: February 25th, 2019		
PHASE OF DEVELOPMENT: Phase 3		
OBJECTIVES: The primary objective of this study was to evaluate the safety, tolerability and efficacy of Brimonidine Nanoemulsion eye drops (OCU 310) in subjects with DED. **Endpoints:** Primary and secondary endpoints were evaluated in a hierarchical fashion Two primary efficacy endpoints were to be tested: 1. Change from baseline to 4 weeks (Day 28) in Symptom Assessment iN Dry Eye (SANDE) score 2. Change from baseline to 4 weeks (Day 28) in lissamine green conjunctival staining scores Four secondary efficacy endpoints were also to be tested: 3. Change from baseline to 2 weeks (Day 14) in SANDE score 4. Change from baseline to 2 weeks (Day 14) in lissamine green conjunctival staining scores 5. Change from baseline to 4 weeks (Day 28) in lissamine green corneal staining scores 6. Change from baseline to 2 weeks (Day 14) in lissamine green corneal staining scores		

Name of the Sponsor/Company: Ocugen, Inc.	**Individual Study Table Referring to Module 5 of the Dossier** **Volume:** **Page:** **Study No.:**	**(For National Authority Use only)**
Name of Finished Product: OCU 310		
Name of Active Ingredient: Brimonidine tartrate 0.2%		

Exploratory efficacy endpoints:

- Change from baseline to 4 weeks (Day 28) in Schirmer's scores
- Change in appearance from baseline to 4 weeks (Day 28) on the Validated Bulbar Redness (VBR) scale
- Change in appearance from baseline to 2 weeks (Day 14) on the VBR scale
- Clinical Global Impression (CGI) of change in symptoms from baseline (physician's rating) to 4 weeks (Day 28)
- Subject Global Assessment (SGA) of overall change from baseline (subject's rating) to 4 weeks (Day 28)
- Change from baseline to 2 weeks (Day 14) and 4 weeks (Day 28) in temporal bulbar lissamine green conjunctival staining scores
- Change from baseline to 2 weeks (Day 14) and 4 weeks (Day 28) in nasal bulbar lissamine green conjunctival staining scores

Safety endpoints:

- Vital Signs (systolic and diastolic blood pressure, temperature, pulse and respiration rates)
- Best Corrected Visual Acuity
- Ophthalmic Examination (Slit Lamp)
- Intraocular Pressure (IOP)
- Rate of serious adverse events (SAEs), adverse events (AEs) and treatment-emergent adverse event (TEAEs) (ocular/non-ocular)

METHODOLOGY:

This was a randomized, placebo-controlled, double-masked, multicenter phase 3 study in the United States. Upon meeting the eligibility criteria, enrolled subjects with a history of DED were randomly assigned in a 1:1 fashion to receive either OCU 310 (brimonidine tartrate 0.2% nanoemulsion eye drops) or ophthalmic buffered saline (placebo).

Four study visits were planned: Day -7 ±1 day (screening visit), Day 1 (randomization/baseline), Day 14 ± 3 days and Day 28 ± 7 days. An attempt was to be made to schedule subject visits for approximately the same time during the day. Signed informed consent was obtained from each subject prior to the commencement of any study procedures.

Subjects received the first dose of medication on Day 1 at the study site. Study treatment was dispensed to subjects on Day 1 for self-administration during the study.

Subjects were provided with diaries to record twice daily dosing. Doses were to be administered approximately 12 hours apart. In addition, subjects were asked to make note of any missed doses together with the reason for missing the dose.

Name of the Sponsor/Company: Ocugen, Inc.	**Individual Study Table Referring to Module 5 of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: OCU 310		
Name of Active Ingredient: Brimonidine tartrate 0.2%	**Volume:** **Page:** **Study No.:**	

NUMBER OF SUBJECTS (planned and analysed):

	OCU 310	Placebo	Total
No. planned:	120	120	240
No. screened:			401
No. randomized and treated:	126	126	252
Males/females:	20 (16%)/106 (84%)	21 (17%)/105 (83%)	41 (16%)/211 (84%)
Mean age (range), years:	62 (28)	62 (25)	62 (25)
No. analyzed for efficacy (ITT/PP):	124/123	124/124	248/247
No. analyzed for safety:	126	126	252
No. who completed the study:	123	126	249

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

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

1) Aged 18 years or older
2) Sign and date informed consent form approved by the institutional review board (IRB)
3) History of DED for ≥6 months
4) Demonstrate the following 2 signs of DED in the same eye at screening and baseline (Day 1):
    a) Conjunctival staining of ≥3 (out of a possible score of 6 per eye)
    b) Schirmer's test (with anesthesia) of ≥1 to ≤7 mm in 5 minutes
5) Symptomatic evidence of DED by having a global symptom score (overall SANDE) of ≥40 mm at screening and baseline (Day 1)
6) Intraocular pressure (IOP) ≥5 mmHg and ≤22 mmHg in each eye
7) Women who satisfied one of the following:
    a) Were women of child-bearing potential (WOCP) who were not pregnant or lactating and who were either abstinent or sexually active on an acceptable method of birth control for at least 4 weeks prior to Visit 1 and throughout the study (i.e., until Day 28)
    b) Were post-menopausal or had undergone a sterilization procedure

The subjects did not meet any of the following criteria:

1. Allergic to brimonidine or any similar products, or excipients of brimonidine
2. Use of contact lenses within 14 days prior to the screening visit or planned use during the study
3. Currently receiving brimonidine or other treatment for glaucoma or ocular hypertension or history of glaucoma surgery.
4. Receiving or have received any experimental or investigational drug or device within 30 days prior to the screening visit
5. IOP <5 mmHg or >22 mmHg in either eye
6. Active ocular infection or history of ocular herpetic keratitis
7. History of neurotrophic keratitis or ocular neuropathic pain
8. Any history of eyelid surgery or intraocular/ocular surgery within the past 3 months

Name of the Sponsor/Company: Ocugen, Inc.	**Individual Study Table Referring to Module 5 of the Dossier** **Volume:** **Page:** **Study No.:**	**(For National Authority Use only)**
Name of Finished Product: OCU 310		
Name of Active Ingredient: Brimonidine tartrate 0.2%		

9. Punctal occlusion within 3 months prior to the screening visit or during the study
10. Corneal epithelial defect larger than 1 mm^2 in either eye
11. Have active drug/alcohol dependence or abuse history
12. Are neonates, pregnant/lactating women, children, or others who could be considered vulnerable populations
13. Received corticosteroid-containing eye drops within the past 14 days prior to the screening visit or planned use during the study
14. Any change in systemic corticosteroids/immunosuppressives, cyclosporine A 0.05% ophthalmic emulsion (Restasis®), cyclosporine 0.09% ophthalmic solution (Cequa™) or lifitegrast 5% ophthalmic solution (Xiidra®) within 30 days prior to the screening visit or planned change during study
15. In the opinion of the Investigator or Study Coordinator, unwilling or unable to comply with the study protocol or unable to successfully instill eye drops
16. Disease, condition or disorder that in the judgement of the Investigator could confound study assessments or limit compliance with the study protocol

Note: Subjects were permitted to continue all their current ocular treatments, including the use of artificial tears, eyelid massage or warm compresses, if they committed to using the same brand/regimen throughout the study. No ocular treatment, including Restasis®, Cequa™, Xiidra® and study treatment, was to be used within 5 minutes of another ocular treatment during the study. Study treatment was not to be used within 2 hours prior to any study visit.

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

OCU 310, one drop per eye every ~12 hours (i.e. twice daily dosing). OCU 310 contains 0.2% brimonidine tartrate. It was self-administered by participating subjects using an eye dropper. Batch numbers were 18R0040 and 18R0054. Average drop size was 35µL (typical range: 20-70 µL).

DURATION OF TREATMENT: 28 days

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Placebo eye drops containing ophthalmic buffered saline (OBS), one drop per eye every ~12 hours (i.e. twice daily dosing). Placebo eye drops were self-administered by participating subjects using an eye dropper. Batch numbers were 18R0040 and 18R0054. Drop size of reference therapy presumed to be similar to that of test product, given identical dosing vials and near equivalent drop density.

CRITERIA FOR EVALUATION:

EFFICACY:

- SANDE score
- Lissamine green conjunctival and corneal staining score
- Schirmer's score
- VBR scale
- CGI
- SGA

SAFETY:

- AEs (from the time of informed consent completion through the completion of the study)
- Monocular visual acuity (Early Treatment Diabetic Retinopathy Study chart)
- IOP (Goldmann applanation tonometry)
- Slit Lamp examination of the conjunctiva, cornea, anterior chamber, lens and anterior vitreous

Name of the Sponsor/Company: Ocugen, Inc.	Individual Study Table Referring to Module 5 of the Dossier Volume: Page: Study No.:	(For National Authority Use only)
Name of Finished Product: OCU 310		
Name of Active Ingredient: Brimonidine tartrate 0.2%		

- Vital signs: diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR), respiratory rate and body temperature (forehead)

STATISTICAL METHODS:

The following analysis sets were defined:

- Randomized set: All randomized subjects who previously signed the informed consent.
- Safety set: All subjects in the Randomized set who received at least one dose of the Investigational Medicinal Product.
- Intention-To-Treat (ITT) set: All subjects in the Safety set with at least one post-baseline efficacy measurement.
- Per protocol (PP) set: All subjects in the ITT set who fulfilled the study protocol requirements with no major deviations that may affect study results.

Unit of Analysis

The unit of analysis for variables measured at the individual eye level was the study eye. Each subject had a single eye identified as the study eye as follows: (i) if only 1 eye met inclusion criteria, this eye was the study eye and the other eye was considered the non-qualified fellow eye; (ii) if both eyes met inclusion criteria, the eye with the higher lissamine green conjunctival staining score was the study eye and the other eye was considered the qualified fellow eye; (iii) if both eyes had the same lissamine green conjunctival staining score, then the eye with the lower Schirmer's score was the study eye and the other eye was considered the qualified fellow eye; (iv) if both eyes had same Schirmer's score, the right eye was the study eye and the other eye was considered the qualified fellow eye.

Analysis of primary and secondary endpoints

The analysis of the six primary/secondary outcomes employed a Mixed Model for Repeated Measurements (MMRM) with mean change from baseline score (Day 28 for Primary, Day 28 and 14 for Secondary) as the response (dependent variable) with baseline value as a covariate and treatment, visit, and treatment-by-visit interaction as fixed effects (independent variables).

The treatment comparisons (OCU 310 vs. Placebo) were carried out by means of the contrasts on the treatment factor by visit effect in SAS® Software, using proc mixed. Treatment effects were estimated by means of Least Square Means and 95% confidence interval (CI). Differences between treatments were estimated and resulting 2-sided p-values and associated 95% CI were presented.

Primary and Secondary efficacy analyses were conducted primarily on the ITT set and repeated in the PP set for sensitivity purposes. For efficacy endpoints where measurements from both eyes were available, the study eye was used for the analyses.

Results of all primary and secondary analyses are graphically displayed as Forest Plots.

Sites with low enrollment were collapsed into pseudo sites for the primary efficacy analysis. Sites with the smallest number of enrolled subjects were combined until a minimum of 10 subjects per pseudo site was achieved, with the restriction that no pseudo site created by pooling exceeded the average number of subjects in the set of original sites with 10 or more subjects enrolled.

For key efficacy endpoints (SANDE, lissamine green conjunctival staining, CGI and SGA) two sub-groups were compared: Improvers vs. Non-Improvers. While all subjects enrolled were to satisfy eligibility criteria at both Screening and Baseline Visits, some study-eligible subjects (Improvers) may have clinically improved from the Screening Visit to the Baseline Visit, and this may dilute the overall treatment effect.

Name of the Sponsor/Company: Ocugen, Inc.	Individual Study Table Referring to Module 5 of the Dossier Volume: Page: Study No.:	(For National Authority Use only)
Name of Finished Product: OCU 310		
Name of Active Ingredient: Brimonidine tartrate 0.2%		

The definitions of Improver and Non-Improver were pre-specified in the Statistical Analysis Plan.

Post hoc subgroup analyses were also done, based on several baseline cut-off values for SANDE and VBR

Analysis of exploratory endpoints

- Changes from baseline to Day 28 in Schirmer's score were summarized descriptively. A shift table was presented as well.
- Changes from baseline to Day 14 and Day 28 in VBR scale were summarized descriptively, analyzed in both the ITT and PP sets, and graphically displayed as a Forest plots.
- Change from baseline to Day 14 and Day 28 in temporal bulbar and and nasal bulbar lissamine green conjunctival staining scores were presented in shift tables.
- Changes in CGI and SGA from baseline to Day 14 and Day 28 were summarized descriptively.

For CGI and SGA, results were also collapsed into two categories (Responder vs. Non-Responder).

Other efficacy analyses

Time to improvement was investigated graphically through Kaplan-Meier curves.

Post hoc subgroup analyses for three key endpoints (SANDE, VBR and SGA) were also done, based on the following cut-off values: SANDE ≥60 at baseline, SANDE ≥median at baseline, VBR ≥40 at baseline, VBR ≥50 at baseline and VBR ≥median at baseline)

Safety analyses

Most safety data were summarized descriptively.

SUMMARY AND CONCLUSIONS:

EFFICACY RESULTS:

Demographic and other baseline characteristics were comparable between the OCU 310 and placebo groups. Demographic and baseline characteristics were well balanced between the two treatment groups. Briefly, overall mean (SD) age was 62 (12) year, and the majority of subjects were females (84%), and Caucasian (84%). Overall mean time since first DED diagnosis was 5 years. Compliance to the study treatment was ≥ 80%-≤ 100% for the majority (99%) of subjects, and the median number of received doses was the same in the two treatment groups (55).

Primary efficacy endpoints

Change from baseline to Day 28 in SANDE score

In the ITT set, both study treatments resulted in a reduction (i.e. improvement) from baseline to Day 28 in SANDE overall, and in frequency of symptoms and severity of symptoms scores. None of the comparisons of OCU 310 vs. placebo were statistically significant, with estimated mean differences between the two treatments (OCU 310 - placebo) of -0.8 mm (p= 0.739) for the overall score, -2.7 mm (p= 0.297) for the frequency of symptoms score, and 0.7 mm (p= 0.803) for the severity of symptoms score. Results were confirmed in the PP set and, overall, in the subgroups (ITT set) analysis for the SANDE overall score with improver subjects, non-improver subjects, as well as subjects with SANDE ≥ 60 at baseline, SANDE ≥ median at baseline, VBR ≥ 40 at baseline, VBR ≥ 50 at baseline and VBR ≥ median at baseline.

Name of the Sponsor/Company: Ocugen, Inc.	Individual Study Table Referring to Module 5 of the Dossier Volume: Page: Study No.:	(For National Authority Use only)
Name of Finished Product: OCU 310		
Name of Active Ingredient: Brimonidine tartrate 0.2%		

Change from baseline to Day 28 in lissamine green total conjunctival staining scores

In the ITT set, both study treatments resulted in a reduction (i.e. improvement) from baseline to Day 28 in lissamine green total conjunctival staining scores in both the study eye and qualified fellow eye. For the study eye, the comparison OCU 310 vs. placebo was not statistically significant, with an estimated mean difference between the two treatments (OCU 310 - placebo) of 0.26 (p= 0.097). Results were confirmed in the PP set, and in the subgroups (ITT set) of improver and non-improver subjects.

Secondary efficacy endpoints

Change from baseline to Day 14 in SANDE score

In the ITT set, both study treatments resulted in a reduction from baseline to Day 14 in SANDE overall, and in frequency of symptoms and severity of symptoms scores. None of the comparisons of OCU 310 vs. placebo were statistically significant, with estimated mean differences between the two treatments (OCU 310 - placebo) of 2.4 (p= 0.257) for the overall score, 2.8 (p= 0.210) for the frequency of symptoms score, and 2.1 (p= 0.354) for the severity of symptoms score. Results were confirmed in the PP set and in the subgroups (ITT set) of subjects with SANDE ≥ 60 at baseline, SANDE ≥ median at baseline, VBR ≥ 40 at baseline, VBR ≥ 50 at baseline and VBR ≥ median at baseline.

Change from baseline to Day 14 in lissamine green total conjunctival staining scores

In the ITT set, both study treatments resulted in a reduction from baseline to Day 14 in lissamine green total conjunctival staining scores in both the study eye and qualified fellow eye. For the study eye, the comparison OCU 310 vs. placebo favored placebo, with an estimated mean difference between the two treatments (OCU 310 - placebo) of 0.29 (p = 0.034). Results were confirmed in the PP set.

Change from baseline to Day 14 and Day 28 in lissamine green total corneal staining scores

In the ITT set, both study treatments resulted in a reduction from baseline to Day 14 and Day 28 in lissamine green total corneal staining scores in both the study eye and qualified fellow eye at Day 14 and Day 28. For the study eye, the comparison OCU 310 vs. placebo favored placebo at Day 14, with an estimated mean difference between the two treatments (OCU 310 - placebo) of 0.6 (p= 0.016). At Day 28, the comparison OCU 310 vs. placebo was not statistically significant, with an estimated mean difference between the two treatments of 0.53 in favor of placebo (p= 0.063). Results were confirmed in the PP set.

Exploratory efficacy endpoints

Schirmer's score

Both study treatments resulted in an increase (i.e. improvement) of Schirmer's score at Day 28. Mean (SD) changes from baseline was 1.9 (3.9) mm for OCU 310 and 2.5 (4.5) mm for the placebo group in the study eye, and for the qualified fellow eye was 1.6 (4.2) and 1.5 (3.0), respectively.

Most study eyes and qualified fellow eyes had severe Schirmer's score at baseline. Overall, the proportion of eyes with scores that improved from baseline were similar between groups in both the study eye and the qualified fellow eyes. Similarly, the proportion of study eyes and qualified fellow eyes

Name of the Sponsor/Company: Ocugen, Inc.	Individual Study Table Referring to Module 5 of the Dossier Volume: Page: Study No.:	(For National Authority Use only)
Name of Finished Product: OCU 310		
Name of Active Ingredient: Brimonidine tartrate 0.2%		

that deteriorated from baseline was similar in the two treatment groups in both study eye and qualified fellow eye. In a *post hoc* analysis on 124 study eyes (ITT), 14 (11%) of OCU310 subjects and 20 (16%) of placebo subjects went from having a Schirmer's score ≤10 mm at baseline to a Schirmer's score >10 mm (tear production) at Day 28.

VBR scale

With OCU 310, VBR scores (overall area) for the study eye and the qualified fellow eye decreased (i.e. improved) from baseline. With placebo, mean VBR scores (overall area) remained stable at all time points. Results obtained for VBR scores for the nasal and temporal areas confirmed those obtained for the overall area in both the study eye and qualified fellow eye. In the ITT set, mean reductions from baseline in VBR score (overall area) were greater with OCU 310 than with placebo at both Day 14 and Day 28, with estimated mean differences between treatments (OCU 310 - placebo) of -2.8 (p= 0.006) and -2.6 (p= 0.020), respectively. These results were confirmed in the PP set and in the subgroups (ITT set) of subjects with SANDE ≥ 60 at baseline, VBR ≥ 40 at baseline and VBR ≥ median at baseline. For the subgroups of subjects with SANDE ≥ median at baseline and VBR ≥ 50 at baseline non-significant differences were observed between groups at either time points.

Temporal bulbar and nasal bulbar lissamine green conjunctival staining scores

Temporal bulbar lissamine green conjunctival staining scores

Overall, the number of study eyes and qualified fellow eyes that improved from baseline to Day 14 and Day 28 were similar with OCU 310 and with placebo. Similarly, deteriorations from baseline were similar between groups.

Nasal bulbar lissamine green conjunctival staining scores

Improvements from baseline to Day 14 were observed in a similar number of study eyes with OCU 310 and placebo and in a smaller number of qualified fellow eyes with OCU 310 than with placebo (19% vs. 34%). Improvements from baseline to Day 28 were observed in a similar number of study and qualified fellow eyes.

The number of study eyes and qualified fellow eyes that deteriorated from baseline to Day 14 were similar between OCU 310 and placebo groups. Deterioration from baseline to Day 28 was similar between OCU 310 and placebo groups in qualified fellow eyes but greater with OCU 310 than with placebo at Day 28 in the study eyes (15% vs. 7%).

CGI scale

Responder analysis (dichotomized)

Although a higher percentage of CGI responders relative to Baseline was observed in the placebo arm at Day 14 (46% vs. 39%), the percentage was identical at Day 28 (48% vs. 48%). The proportion of subjects worsening from baseline was higher in OCU 310 than in placebo at Day 14 (20% vs. 8.1%), but more similar at Day 28 (13% vs. 4.8%, respectively).

Name of the Sponsor/Company: Ocugen, Inc.	Individual Study Table Referring to Module 5 of the Dossier Volume: Page: Study No.:	(For National Authority Use only)
Name of Finished Product: OCU 310		
Name of Active Ingredient: Brimonidine tartrate 0.2%		

Subgroup Analysis

This analysis was also performed in non-improver and improver subjects and the results are similar to the responder analysis. For the subgroup of non-improvers, the percentage of subjects with an improvement in CGI from Baseline to Day 14 was higher for the placebo arm (51%) than for the OCU310 arm (39%). However, by Day 28, the percentage was identical (48% vs. 48% respectively).

SGA scale

Responder analysis (dichotomized)

At Day 14 the percentage of SGA responders relative to Baseline was slightly higher for the placebo arm (45%) than for the OCU310 arm (42%). However, by Day 28, there is a higher percentage of SGA responders in the OCU310 arm (50%) relative to the placebo arm (44%).

Subgroup analysis

This analysis was also performed in non-improver and improver subjects and the results are similar to the responder analysis. For the subgroup of non-improvers, the percentage of subjects with an improvement in SGA from Baseline to Day 14 was higher for the placebo arm (47%) than for the OCU310 arm (43%). However, by Day 28, there was a higher percentage of OCU310 subjects with improvement relative to Baseline (54%) vs. placebo (43%).

The SANDE, VBR and SGA analyses in subgroups of subjects (SANDE ≥60 at baseline, SANDE ≥median at baseline, VBR ≥40 at baseline, VBR ≥50 at baseline and VBR ≥median at baseline) were also consistent with those obtained in the ITT set.

Multicenter Studies

The pooling analysis, whereby data from 6 low-enrolling sites were combined into 1 pseudo sites, did not change the interpretation of the efficacy data.

SAFETY RESULTS:

Subjects in the two treatment groups received a similar median number of doses of study treatment in the OCU 310 and placebo groups; 55 doses.

TEAEs

Overall, a total of 40 TEAEs (39 unique TEAEs) were reported in 34 (14%) subjects. In the OCU 310 group 27 TEAEs were reported in 18% of subjects while 12 TEAEs were reported in 8.7% subjects in the placebo group. The majority of TEAEs reported during the study treatment were of mild nature, and none were of severe nature. There were no serious TEAEs, including TEAEs leading to death.

As expected, the most common TEAEs were of ocular nature and were reported equally between groups. Amongst ocular TEAEs, those reported in >1 subject in any group were dry eye, eye irritation, vision blurred and instillation site irritation. Among the non-ocular TEAEs, sinusitis was the only one reported in >1 subject.

Name of the Sponsor/Company: Ocugen, Inc.	Individual Study Table Referring to Module 5 of the Dossier Volume: Page: Study No.:	(For National Authority Use only)
Name of Finished Product: OCU 310		
Name of Active Ingredient: Brimonidine tartrate 0.2%		

Treatment related TEAEs were reported in 9.5% of subjects in the OCU 310 group and in 3.2% of subjects in the placebo group. In the OCU 310 group, treatment related TEAEs reported in > 1 subject were of ocular nature: “dry eye” and “instillation site irritation” (in 1.6% and 2.4% of subjects, respectively). In the placebo group, treatment related TEAEs were reported at most in 1 subject.

Notably, two treatment related ocular TEAEs of moderate intensity (PTs: lacrimation increased and eye irritation) in the OCU 310 group led to study treatment discontinuation of one subject, and accounted for all TEAEs leading to study treatment discontinuation of the study. Both events resolved by the end of the study without corrective treatment.

Vital signs

Mean changes from baseline in SBP, DBP, HR, respiratory rate and body temperature were minimal at both Day 14 and Day 28 in both treatment groups. Vital signs were considered as normal or non-significant abnormal by Investigators.

Best corrected visual acuity

Overall, mean best corrected visual acuity of the study eye, qualified fellow eye and non-qualified fellow eye were stable at all time points, with very small and similar mean changes from baseline in both treatment groups.

Intraocular pressure (IOP)

IOP decreased from baseline in both groups at Day 14 and Day 28, with mean changes greater with OCU 310 than with placebo at both time points for the study eye, qualified fellow eye and non-qualified fellow eye. The comparison of OCU 310 vs. placebo for change in IOP from baseline favored OCU 310 at both Day 14 and Day 28, with estimated mean differences between the two treatments (OCU 310 - placebo) of -0.752 mmHg (p= 0.003) at Day 14 and -0.515 mmHg (p= 0.040) at Day 28. Of note, no subject had an IOP measurement outside of the normal range.

Ophthalmic examination

Clinically significant abnormalities were observed for the study eye and qualified fellow eye only for the area “tear film” and were reported in 3 and 2 subjects in the OCU 310 and placebo groups, respectively, from the Baseline visit

CONCLUSIONS:

This study showed that OCU 310 is generally safe and well-tolerated, though it did not meet its co-primary endpoints for DED symptom and sign. Importantly, OCU 310 was better than placebo in reducing ocular redness, an exploratory sign endpoint, at both Day 14 and Day 28. In addition, a numerical, but not statistical, improvement was noted at Day 28 in SGA, an exploratory symptom endpoint, for OCU 310 relative to placebo.

Exhibit II

Stability Data for OCU310 Clinical Drug Product Batch (18E38) at Long Term Storage Condition (25°C ± 2°C/40%RH ± 5%RH)

Test	Acceptance Criteria	Test Method	Time Points (M)			
			0	2	3	6
Appearance of Product	White-to-yellowish or brownish cloudy emulsion	ATM-1095	Yellowish cloudy emulsion	Yellowish cloudy emulsion	Yellowish cloudy emulsion	Yellowish cloudy emulsion
Assay (HPLC)	80 – 120% of label claim	ATM-1704	100%	100%	100%	100%
Impurities (HPLC)	Impurity A: NMT 1.0% Each Impurity: NMT 1.0% Total Impurities (known and unknown): NMT 5.0%	ATM-1705	Imp. A: Not detected RRT 0.82: 0.09% Total: 0.1%	Imp A: Not detected RRT 0.83: 0.06% Total: 0.1%	Imp A: Not detected RRT 0.83: 0.05% Total: 0.1%	Imp A: Not detected RRT 0.75: <0.05% (LOQ) RRT 0.83: 0.07% RRT 1.25:< 0.05% (LOQ) RRT 1.31: <0.05% (LOQ) Total: 0.1%
pH	6.0 – 7.0	USP <791>	6.6	6.6	6.5	6.2
Globule Size (Mastersizer 3000)	Mean Dv (50): NMT 0.150 µm; Dv (10) and Dv (90): For information only	ATM-1707	Dv (10): 0.0256 µm Dv (50): 0.0585 µm Dv (90): 0.128 µm	Dv (10): 0.0220 µm Dv (50): 0.0539 µm Dv (90): 0.128 µm	Dv (10): 0.0245 µm Dv (50): 0.0551 µm Dv (90): 0.120 µm	Dv (10): 0.0222 µm Dv (50): 0.0538 µm Dv (90): 0.126 µm
Particulate Matter (Visual)	Uniform emulsion free from visible particulate matter	USP <790>	Uniform emulsion free from particulate matter	Uniform emulsion free from particulate matter	Uniform emulsion free from particulate matter	Uniform emulsion free from particulate matter
Sterility	Meets compendial requirements	USP <71>	Meets compendial requirements	Not tested per protocol	Not tested per protocol	Not tested per protocol
Bacterial Endotoxin	≤ 10 EU/mL	USP <85>	< 0.5 EU/mL	Not tested per protocol	Not tested per protocol	Not tested per protocol

Stability Data for OCU310 Clinical Drug Product Batch (18E38) at Long Term Storage Condition (25°C ± 2°C/40%RH ± 5%RH) (continued)

Test	Acceptance Criteria	Test Method	Time Points (M)			
			9	12		
Appearance of Product	White-to-yellowish or brownish cloudy emulsion	ATM-1095	Yellowish cloudy emulsion	Yellowish cloudy emulsion		
Assay (HPLC)	80 – 120% of label claim	ATM-1704	100%	101%		
Impurities (HPLC)	Impurity A: NMT 1.0% Each Impurity: NMT 1.0% Total Impurities (known and unknown): NMT 5.0%	ATM-1705	Imp A: <0.05% (LOQ) RRT 0.75: <0.05% (LOQ) RRT 0.83: 0.06% IAQ[1]: <0.05% (LOQ) RRT 1.31: <0.05% (LOQ) Total: 0.1%	Imp A: <0.05% (LOQ) RRT 0.75: <0.05% (LOQ) RRT 0.83: 0.07% RRT 1.31:0.06% Total: 0.1%		
pH	6.0 – 7.0	USP <791>	6.5	6.6		
Globule Size (Mastersizer 3000)	Mean Dv (50): NMT 0.150 µm; Dv (10) and Dv (90): For information only	ATM-1707	Dv (10): 0.0280 µm Dv (50): 0.0535 µm Dv (90): 0.0991 µm	Dv (10): 0.0256 µm Dv (50): 0.0548 µm Dv (90): 0.113 µm		
Particulate Matter (Visual)	Uniform emulsion free from visible particulate matter	USP <790>	Uniform emulsion free from particulate matter	Uniform emulsion free from particulate matter		
Sterility	Meets compendial requirements	USP <71>	Not tested per protocol	Meets compendial requirements		
Bacterial Endotoxin	≤ 10 EU/mL	USP <85>	Not tested per protocol	<0.5 EU/ml		

[1] 6-(2-Imidazolin-2-ylamino) quinoxaline

Stability Data for OCU310 Clinical Drug Product Batch (18E38) at Accelerated Storage Condition (40°C ± 2°C/NMT 25%RH)

Test	Acceptance Criteria	Test Method	Time Points (M)		
			0	2	3
Appearance of Product	White-to-yellowish or brownish cloudy emulsion	ATM-1095	Yellowish cloudy emulsion	Yellowish cloudy emulsion	Yellowish cloudy emulsion
Assay (HPLC)	80 – 120% of label claim	ATM-1704	100%	100%	100%
Impurities (HPLC)	Impurity A: NMT 1.0% Each Impurity: NMT 1.0% Total Impurities (known and unknown): NMT 5.0%	ATM-1705	Imp A: Not detected RRT 0.82: 0.09% Total: 0.1%	Imp A: Not detected RRT 0.83: 0.08% RRT 1.31: 0.09% Total: 0.2%	Imp A: Not detected RRT 0.83: 0.06% RRT 1.31: 0.12% Total: 0.2%
pH	6.0 – 7.0	USP <791>	6.6	6.6	6.5
Globule Size (Mastersizer 3000)	Mean Dv (50): NMT 0.150 µm; Dv (10) and Dv (90): For information only	ATM-1707	Dv (10): 0.0256 µm Dv (50): 0.0585 µm Dv (90): 0.128 µm	Dv (10): 0.0216 µm Dv (50): 0.0528 µm Dv (90): 0.126 µm	Dv (10): 0.0243 µm Dv (50): 0.0552 µm Dv (90): 0.121 µm
Particulate Matter (Visual)	Uniform emulsion free from visible particulate matter	USP <790>	Uniform emulsion free from particulate matter	Uniform emulsion free from particulate matter	Uniform emulsion free from particulate matter
Sterility	Meets compendial requirements	USP <71>	Meets compendial requirements	Not tested per protocol	Not tested per protocol
Bacterial Endotoxin	≤ 10 EU/mL	USP <85>	<0.5 EU/ml	Not tested per protocol	Not tested per protocol

Stability Data for OCU310 Clinical Drug Product Batch (18E38) at Accelerated Storage Condition (40°C ± 2°C/NMT 25%RH) –(Continued)

Test	Acceptance Criteria	Test Method	Time Points (M)		
			6	9	12
Appearance of Product	White-to-yellowish or brownish cloudy emulsion	ATM-1095	Yellowish cloudy emulsion	Yellowish cloudy emulsion	Yellowish cloudy emulsion
Assay (HPLC)	80 – 120% of label claim	ATM-1704	101%	96%	97%
Impurities (HPLC)	Impurity A: NMT 1.0% Each Impurity: NMT 1.0% Total Impurities (known and unknown): NMT 5.0%	ATM-1705	Imp A: 0.08% RRT 0.75: <0.05%(LOQ) RRT 0.83: 0.08% IAQ[1]: <0.05% (LOQ) RRT 1.25: 0.06% RRT 1.31: 0.18% RRT 2.15: <0.05% (LOQ) RRT 2.36: <0.05% (LOQ) Total: 0.4%	Imp A: 0.15% RRT 0.75: 0.07% RRT 0.83: 0.08% RRT 1.16: <0.05%(LOQ) RRT 1.25: 0.08% RRT 1.31: 0.21% RRT 1.38: <0.05%(LOQ) RRT 2.15: <0.05% (LOQ) RRT 2.36: 0.05% Total: 0.6%	Imp A: 0.24% RRT 0.75: 0.08% RRT 0.83: 0.09% RRT 1.25: 0.08% RRT 1.31: 0.23% RRT 2.05: <0.05%(LOQ) RRT 2.15: <0.05% (LOQ) RRT 2.36: 0.08% Total: 0.8%
pH	6.0 – 7.0	USP <791>	6.3	6.4	6.4
Globule Size (Mastersizer 3000)	Mean Dv (50): NMT 0.150 µm; Dv (10) and Dv (90): For information only	ATM-1707	Dv (10): 0.0202 µm Dv (50): 0.0475 µm Dv (90): 0.112 µm	Dv (10): 0.0235 µm Dv (50): 0.0550 µm Dv (90): 0.124 µm	Dv (10): 0.0247 µm Dv (50): 0.0553 µm Dv (90): 0.120 µm
Particulate Matter (Visual)	Uniform emulsion free from visible particulate matter	USP <790>	Uniform emulsion free from particulate matter	Uniform emulsion free from particulate matter	Uniform emulsion free from particulate matter
Sterility	Meets compendial requirements	USP <71>	Not tested per protocol	Not tested per protocol	Meets compendial requirements
Bacterial Endotoxin	≤ 10 EU/mL	USP <85>	Not tested per protocol	Not tested per protocol	< 0.5 EU/ml

[1] 6-(2-Imidazolin-2-ylamino) quinoxaline

Stability Data for Ophthalmic Buffered Saline (18CL8) at Long Term Storage Condition (25°C ± 2°C/60%RH ± 5% RH)

Test	Acceptance Criteria	Test Method	Time Points (M)						
			0	1	3	6	9	12	18
Appearance	Clear, Colorless Solution	TRC-SOP-1032	Pass	Pass	Pass	Pass	Pass	Pass	Pass
pH	6.0 – 8.0	USP <791>	7.0	6.9	7.0	7.0	6.9	6.9	6.9
Assay for Sodium Chloride	90.0 – 110.0% of Label Claim	USP Monograph	101.7%	101.8%	100.9%	100.9%	101.1%	101.7%	100.5%
Sterility	No growth after 14 days	USP <71>	Pass	Not tested per protocol	Not tested per protocol	Not tested per protocol	Not tested per protocol	Pass	Not tested per protocol
Particulate Matter	NMT 50 particles/mL ≥ 10 µm NMT 5 particles/mL ≥ 25 µm NMT 2 particles/mL ≥ 50 µm	USP <789>	1 particle/mL ≥ 10 µm 0 particle/mL ≥ 25 µm 0 particle/mL ≥ 50 µm	Not tested per protocol	Not tested per protocol	Not tested per protocol	Not tested per protocol	19 particles/mL ≥ 10 µm 0 particle/mL ≥ 25 µm 0 particle/mL ≥ 50 µm	Not tested per protocol

Stability Data for Ophthalmic Buffered Saline (18CL8) at Long Term Storage Condition (25°C ± 2°C/40%RH ± 5% RH)

Test	Acceptance Criteria	Test Method	Time Points (M)						
			0	1	3	6	9	12	18
Appearance	Clear, Colorless Solution	TRC-SOP-1032	Pass	Pass	Pass	Pass	Pass	Pass	Pass
pH	6.0 – 8.0	USP <791>	7.0	6.9	7.0	6.9	6.8	6.9	6.9
Assay for Sodium Chloride	90.0 – 110.0% of Label Claim	USP Monograph	101.7%	101.9%	101.3%	100.9%	101.8%	101.4%	102.2%
Sterility	No growth after 14 days	USP <71>	Pass	Not tested per protocol	Not tested per protocol	Not tested per protocol	Not tested per protocol	Pass	Not tested per protocol
Particulate Matter	NMT 50 particles/mL ≥ 10 µm NMT 5 particles/mL ≥ 25 µm NMT 2 particles/mL ≥ 50 µm	USP <789>	1 particle/mL ≥ 10 µm 0 particle/mL ≥ 25 µm 0 particle/mL ≥ 50 µm	Not tested per protocol	Not tested per protocol	Not tested per protocol	Not tested per protocol	28 particles/mL ≥ 10 µm 1 particle/mL ≥ 25 µm 0 particle/mL ≥ 50 µm	Not tested per protocol

Stability Data for Ophthalmic Buffered Saline (18CL8) at Accelerated Storage Condition (40°C ± 2°C/NMT 25%RH)

Test	Acceptance Criteria	Test Method	Time Points (M)			
			0	1	3	6
Appearance	Clear, Colorless Solution	TRC-SOP-1032	Pass	Pass	Pass	Pass
pH	6.0 – 8.0	USP <791>	7.0	6.9	6.9	6.7
Assay for Sodium Chloride	90.0 – 110.0% of Label Claim	USP Monograph	101.7%	101.5%	102.2%	102.8%
Sterility	No growth after 14 days	USP <71>	Pass	Not tested per protocol	Not tested per protocol	Pass
Particulate Matter	NMT 50 particles/mL ≥ 10 µm NMT 5 particles/mL ≥ 25 µm NMT 2 particles/mL ≥ 50 µm	USP <789>	1 particle/mL ≥ 10 µm 0 particle/mL ≥ 25 µm 0 particle/mL ≥ 50 µm	Not tested per protocol	Not tested per protocol	6 particles/mL ≥ 10 µm 0 particle/mL ≥ 25 µm 0 particle/mL ≥ 50 µm