1.0 TITLE PAGE

Clinical Study Protocol

A Multi-Center, Double-Masked, Randomized, Active-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of Brimonidine Tartrate Ophthalmic Solution 0.025% Preservative-Free Formulation with Lumify® 0.025% in Adult Subjects with Ocular Redness

Protocol # 908

Developmental phase of study: 3

Version: 2.0

Date: 27 OCT 2021

Sponsor

Bausch & Lomb, Incorporated
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

This clinical investigation is being conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and with Good Clinical Practice (GCP), as required by the US Code of Federal Regulations applicable to clinical studies (21CFR Parts 11, 50, 54, 56 and [312]; 42 USC 282(j); International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline E6(R2): GCP and E2A: Safety Data Management and applicable local regulations, including the archiving of essential documents.

Revision Chronology:
[Final, Original v1.0] - [23 NOV 2020]
[Amendment 1, v2.0] - [27 OCT 2021]

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This protocol contains confidential information about a product provided by Bausch & Lomb, Incorporated. This information is provided for the exclusive use of the investigators participating in this study. Nothing herein may be disclosed to any person or party without prior written approval of Bausch & Lomb, Incorporated.

SPONSOR APPROVAL PAGE

A Multi-Center, Double-Masked, Randomized, Active-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of Brimonidine Tartrate Ophthalmic Solution 0.025% Preservative- Free Formulation with Lumify® 0.025% in Adult Subjects with Ocular Redness

PROTOCOL # 908

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06-DEC-2021
Date

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INVESTIGATOR STATEMENT OF AGREEMENT

A MULTI-CENTER, DOUBLE-MASKED, RANDOMIZED, ACTIVE-CONTROLLED, PARALLEL-GROUP STUDY COMPARING THE EFFICACY AND SAFETY OF BRIMONIDINE TARTRATE OPHTHALMIC SOLUTION 0.025% PRESERVATIVE-FREE FORMULATION WITH LUMIFY® 0.025% IN ADULT SUBJECTS WITH OCULAR REDNESS

PROTOCOL

STUDY # 908

I have read the attached protocol and I agree that it contains all information necessary to conduct this study as described and agree to abide by all provisions set forth therein.

I agree to conduct this study properly, ethically, and safely in accordance with internationally recognized code of good clinical practices (ICH GCP), as required by applicable local laws and regulations. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and the Sponsor. I will obtain written informed consent (and, if applicable, assent for children) from each study subject prior to performing any study specific procedures which are not my routine standard of care.

I understand that my signature/e-signature on a case report form (CRF)/electronic case report form (eCRF) indicates that the data therein has been reviewed and accepted by me.

I understand that this document and related information is subject to confidentiality terms found in my signed Confidentiality or Clinical Services Agreement. I agree to protect the confidentiality of my patients, as required by all local privacy regulations, when allowing the Sponsor of this clinical investigation, and/or relevant regulatory authorities and IRB/ECs, direct access to my medical records for study subjects.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by the Sponsor that is necessary for the proper conduct of this study. I will discuss this material with them to ensure that they are fully informed about the test article and all study related procedures and required documentation.

_____	_____
Principal Investigator, Printed Name	Date
_____	_____
Signature	Site Number

Upon signing, provide a copy of this page to the Sponsor and retain a copy for your files.

PERSONNEL AND FACILITIES

NOTE: The information on this page is subject to change. All changes will be provided under separate cover.

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2.0 SYNOPSIS

Bausch & Lomb, Incorporated Study # 908	
Title:	**A Multi-Center, Double-Masked, Randomized, Active-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of Brimonidine Tartrate Ophthalmic Solution 0.025% Preservative-Free Formulation with Lumify® 0.025% in Adult Subjects with Ocular Redness**
Phase of study:	**Phase 3**
Number of study centers and subjects:	Approximately 386 subjects will be enrolled in this study at 6 sites.
Location:	United States
Planned study period:	Approximately 21 weeks
Objective(s):	**Primary Objective:** To demonstrate that the efficacy of brimonidine tartrate ophthalmic solution preservative-free formulation (BTOS-PF) 0.025% is non-inferior to Lumify® 0.025% for treating ocular redness in a population of adult subjects. **Secondary Objective(s):** To compare the safety of BTOS-PF 0.025% with Lumify® 0.025%.
Study design:	Multi-center, double-masked, randomized, active-controlled, parallel-group, efficacy and safety study
Study duration:	Approximately 5 weeks
Subject population:	Healthy adult (≥ 18 years of age) subjects with ocular redness
Inclusion criteria:	Subjects MUST: 1. Be at least 18 years of age at the time of Informed Consent signing of either gender and any race or ethnicity; 2. Provide written informed consent and sign the HIPAA form; 3. Be willing and able to follow all instructions and attend all study visits; 4. Have a history of vasoconstrictor (redness relief drops) use within the last 6 months, or a desire to use OTC vasoconstrictors for redness relief; 5. Be able to self-administer eye drops satisfactorily or have a subject's care provider at home[1] routinely available for this purpose; 6. (If female and of childbearing potential) agree to have urine pregnancy testing performed at Visit 1 (must be negative) and at exit visit; must not be lactating; and must agree to use at least 1

[1] If a care provider or surrogate will be used to administer eye drops, then he/she must be present at Visit 1 to administer eye drops in-office.

Bausch & Lomb, Incorporated Study # 908	
	medically acceptable form of birth control[2] throughout the study duration and for at least 14 days prior to the first dose of study drug (Visit 1) and for 1 month after the last dose of investigational drug. Note: Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) and have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy); 7. (If male and with female partner of childbearing potential) must use at least 1 medically acceptable form of birth control[3]; 8. A calculated best-corrected (if necessary) visual acuity of 0.3 logMAR or better in each eye, as measured using an ETDRS chart; 9. At Visit 1 (Baseline), show a baseline redness score >1 unit (ie, greater than 1 unit) in both eyes on a 0 to 4 unit scale as scored by the Investigator using the Investigator Ocular Redness Scale; 10. Have stable ocular health (defined as no ocular conditions requiring therapy or surgical intervention during the study).
Exclusion criteria:	Subjects MUST NOT: 1. Have known contraindications or sensitivity to the use of any of the investigational drug(s) or their components, or any other medications required by the protocol; 2. Have had ocular surgical intervention within 3 months prior to screening or during the study and/or a history of refractive surgery within the past 6 months; 3. Have the presence of an active ocular infection (bacterial, viral, or fungal) or positive history of an ocular herpetic infection at any visit; 4. Use any of the following disallowed medications during the period indicated prior to screening and for the duration of the study: - All topical ophthalmic agents including artificial tear products, eye whiteners (e.g., vasoconstrictors), ocular decongestants, ocular antihistamines, ocular corticosteroids, dilating drops, (excluding dilated ophthalmoscopy exam at Visit 1) and contact lenses: 5 days - Systemic antihistamines or decongestants: 7 days

[2] Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject), spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of male partner at least 3 months prior to the first dose of investigational drug (Visit 1).

[3] Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject) or vasectomy at least 3 months prior to the first dose of study drug (Visit 1). Without a vasectomy, must use condoms with spermicidal foam/gel/film/cream/suppository at least 14 days prior to the first dose of investigational drug (Visit 1) and for 1 month after the last dose of the investigational drug (Visit 3).

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	- Systemic corticosteroids or cancer chemotherapy, and/or any other systemic medications which the investigator feels may confound study data, or interfere with subject's study participation: 14 days 5. Have prior (within 7 days of beginning investigational drug) or currently active significant illness that could compromise participation, in the opinion of the investigator; 6. Have prior (within 30 days of beginning investigational drug) or anticipated concurrent use of an investigational drug or device during the study period; 7. Have an ocular or systemic condition or a situation which, in the investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation; 8. Have planned surgery (ocular or systemic) during the trial period or within 30 days after the study period; 9. Be currently breast feeding or planning to breast feed during the study period or is a female who is currently pregnant, is planning a pregnancy, or has a positive urine pregnancy test at Visit 1; 10. Have a diagnosis of ocular hypertension or glaucoma at screening; 11. Have symptoms that, in the opinion of the investigator, may be associated with COVID-19 or in the last 14 days came into contact with someone diagnosed with COVID-19.
Investigational product, dose & mode of administration:	Investigational Product: Brimonidine tartrate ophthalmic solution 0.025% preservative-free formulation Brimonidine tartrate ophthalmic solution preservative-free formulation (BTOS-PF) contains 0.025% of the active brimonidine tartrate, purified water, boric acid, sodium borate decahydrate, potassium chloride, calcium chloride dihydrate, glycerin, sodium chloride, and pH adjusted with hydrochloric acid and sodium hydroxide. Dosage/Dose Regimen: Subjects will be randomly assigned at Visit 1 to receive 1 of the following treatments four times a day (QID) bilaterally: Brimonidine tartrate ophthalmic solution 0.025%, preservative-free formulation (N= 193) • Lumify® (brimonidine tartrate ophthalmic solution 0.025%) (N= 193) • Randomization is at a ratio of 1:1 (investigational product:comparator). Subjects will instill 1 drop of the assigned investigational drug in each eye QID approximately 4 hours apart for up to 4 consecutive weeks.
Duration of treatment:	4 weeks
Comparator treatment :	Comparator Product: Lumify® (brimonidine tartrate ophthalmic solution 0.025%) Lumify® contains 0.025% of the active brimonidine tartrate, purified water, benzalkonium chloride, boric acid, sodium borate decahydrate,

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	potassium chloride, calcium chloride dihydrate, glycerin, sodium chloride, and pH adjusted with hydrochloric acid and sodium hydroxide.
Study procedures:	Summary of Visit Schedule: Screening Visit (Day -28 to Day 1) • Informed Consent/HIPAA • Demographic Data and Medical/Medication/Ocular History Visit 1 (Baseline; Day 1): • Enrollment • Urine Pregnancy Test (for females of childbearing potential) • Pre-instillation ocular redness assessment • In-office investigational drug instillation • Drop comfort/descriptor assessment • Ocular redness assessment at 1 (+0.5), 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), 240(+15), 360(+15), and 480(+15) minutes post-instillation • Safety assessments (AEs, vital signs, physical examination, visual acuity, slit lamp biomicroscopy, intraocular pressure [IOP], and ophthalmoscopy) Visit 2 (Day 15 ± 2 days): • Pre-instillation ocular redness assessment • In-office investigational drug instillation • Ocular redness assessment at approximately 1 and 5 minutes post-instillation • Safety assessment (AEs, vital signs, visual acuity, and slit lamp biomicroscopy) Visit 3 (Day 29 + 2 days): • Pre-instillation ocular redness assessment • In-office investigational drug instillation • Ocular redness assessment at approximately 1 and 5 minutes post-instillation • Safety assessment (AEs, vital signs, physical examination, visual acuity, slit lamp biomicroscopy, IOP, and ophthalmoscopy) Visit 4 (Day 36 + 1 day): • In-office ocular redness rebound assessment • Urine Pregnancy Test (for females of childbearing potential) • Safety assessment (AEs, visual acuity, and slit lamp biomicroscopy) • Study Exit
Criteria for Evaluation:	Primary Efficacy Endpoint:

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	Ocular redness score evaluated by the investigator prior to investigational drug instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1 Secondary Efficacy Endpoints: Secondary efficacy endpoints will be evaluated hierarchically, as follows: 1. Change from pre-instillation ocular redness score evaluated by the investigator at 1 (+0.5) minute after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1; 2. Change from pre-instillation ocular redness score evaluated by the investigator (0-4 unit scale, allowing half unit increments) at: i. 1 minute after investigational drug instillation at Visit 2 ii. 5 minutes after investigational drug instillation at Visit 2 iii. 1 minute after investigational drug instillation at Visit 3 iv. 5 minutes after investigational drug instillation at Visit 3 3. Change from pre-instillation ocular redness score evaluated by the investigator at 360 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1; and 4. Change from pre-instillation ocular redness score evaluated by the investigator at 480 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1. 5. Ocular redness score evaluated by the subject as captured in subjects' dosing diary throughout the treatment period (0-4 unit scale, NOT allowing half unit increments). Tolerability Measures: • Drop comfort assessment (0-10 unit scale) assessed upon instillation, at 30 seconds, and at 1 minute post-instillation at Visit 1 • Drop comfort descriptor questionnaire assessed at 3 minutes post-instillation at Visit 1 Safety Measures: • Ocular and non-ocular adverse events, vital signs, and ophthalmic examination at each visit • Ocular Rebound defined as: o Increase of at least 1 unit in mean ocular redness score evaluated by the Investigator at Visit 4 (0-4 unit scale, allowing half unit increments) compared to pre-instillation score at Visit 1, or o Increase of at least 1 unit in mean ocular redness score evaluated by the subject as captured in subject dosing diaries in the follow-up period, after dosing has ceased (0-4 unit scale, NOT allowing half unit increments) compared to diary day 1 (pre-dose morning assessment).
Sample Size	386 Subjects

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Statistical methods:	Quantitative variables, including demographics at baseline, will be summarized descriptively using number of subjects (n), mean, median, standard deviation, minimum, and maximum. Qualitative variables will be summarized using counts and percentages. BTOS-PF 0.025% will be compared to Lumify® 0.025% for the primary efficacy parameter of ocular redness as evaluated by the investigator (post-instillation assessments) for each of eight times at Visit 1 using two-sided 95% confidence intervals around the difference between means (Test minus Standard) constructed as for 2-sample t-tests. If the upper confidence limit does not exceed 0.22 points at any time point, then the null hypothesis will be rejected in favor of the alternative hypothesis and the Test formulation will be statistically successful in this endpoint. The primary analyses will be performed on the Intent-to-Treat (ITT) population without imputation if all eight Visit 1 post-instillation time points have missing data for the primary endpoint for less than 5% of subjects, and sensitivity analysis will be performed on the Primary Per-Protocol (PPP) population without imputation. If there is at least one Visit 1 time point for which at least 5% of subjects have missing data for the primary endpoint, then the primary analysis will be performed on the ITT population with an imputation strategy accounting for the reason for missing (e.g. intercurrent events), and sensitivity analyses will be performed on the PPP utilizing the same imputation strategy, as well as on the ITT and PPP populations without imputation. Secondary efficacy analyses will be based on the ITT population with an imputation strategy accounting for the reason for missing (e.g. intercurrent events) if at least 5% of subjects have missing data for that endpoint. A non-inferiority margin of 0.22 units will be used to evaluate the secondary efficacy endpoints of investigator-rated redness and a non-inferiority margin of 1.0 units will be used to evaluate the secondary efficacy endpoint of subject-rated redness. The secondary efficacy parameter of ocular redness as recorded in the subject diaries will be analyzed using a generalized linear model accounting for repeated measures. Daily averages will be used for each subject. The change from pre-instillation at each visit and/or time point will also be compared using 2-sample t-tests. Additionally, a responder analysis will compare the percentage of subjects with total clearing (redness scores of 0) in the 2 treatment groups for each post-instillation time point at each visit. BTOS-PF 0.025% will also be compared to Lumify® 0.025% for the tolerability parameter of drop comfort using 2-sample t-tests for each assessment time point. The tolerability parameter will be analyzed using the safety population. The results for the drop comfort descriptor questionnaire will be summarized descriptively by treatment group. All safety parameters will be analyzed using the safety population. Safety of BTOS-PF 0.025% compared to Lumify® 0.025% will be assessed by the review of all of the safety parameters. The number of subjects reporting an adverse event (AE) during the study as well as the number of AEs will be presented. The number of subjects and events for treatment-emergent adverse events (TEAEs) will be tabulated by MedDRA System Organ Class and by preferred term within each System Organ Class for each treatment and overall using the most recently available version of MedDRA. The number of subjects reporting

Bausch & Lomb, Incorporated Study # 908	
	TEAEs will also be summarized by relationship to investigational drug as well as severity. Serious adverse events (SAEs) additionally will be summarized. The results of the slit lamp biomicroscopy, IOP, visual acuity, and vital signs will be summarized using descriptive statistics by treatment group and visit. Change from baseline will also be presented in the same manner. The ocular rebound evaluated by the investigator (at Visit 4) and by the subject (between Visit 3 – Visit 4) will be summarized separately using descriptive statistics by treatment.

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4.0 LIST OF ABBREVIATIONS

Abbreviation /Acronym	Term
AE	Adverse Event
AR	adrenergic receptor
BCVA	Best-Corrected Visual Acuity
B&L	Bausch & Lomb
BTOS	brimonidine tartrate ophthalmic solution
BPM	Beats per Minute
CFR	Code of Federal Regulations
cGCPs	Good Clinical Practices
CRA	Clinical Research Associate
CRO	Clinical Research Organization
DHHS	Department of Health and Human Services
ERC	Ethics Review Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
ETDRS	Early Treatment of Diabetic Retinopathy Study
ET	Early Termination
FDA	United States Food and Drug Administration
GCPs	Good Clinical Practice
HEENT	Heart, eye, ears, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational new drug application
IOP	Intraocular Pressure
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent to Treat
IWRS	Interactive Web Response System
LBs	Pounds
LogMAR	Logarithm of Minimum Angle of Resolution
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
OTC	Over-the-counter

PF	Preservative Free
PP	Per Protocol
QID	Four Times Daily
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
VA	Visual Acuity
WHO	World Health Organization

5.0 INTRODUCTION

Ocular redness is one of the most common ophthalmic conditions and can be caused by inflammation of almost any part of the eye, the lacrimal glands, the eyelids, or by a defective tear film. The most common cause of ocular redness is an inflammation in the conjunctiva, which can be caused by allergies, exposure to environmental irritants, or as a reaction to infectious agents (e.g., bacteria or virus). Vasoconstriction of arteriolar capillary beds, and/or venular networks, provides beneficial relief of vascular-induced tissue congestion. Topical vasoconstrictors used to treat congestion in the eye (ocular redness) or nose are highly efficacious, but tachyphylaxis (tolerance or loss of effectiveness) and rebound congestion are common and restrict long term use. The rebound congestion is thought to be related to generalized ischemia and secondary release of an inflammatory cascade brought about by vasoconstriction.

Current over-the-counter vasoconstrictors are either α1-adrenergic receptor (AR) specific or have a mixed affinity for both α1-ARs and α2-ARs. There is mounting evidence that vasoconstrictor side effects, including tachyphylaxis and rebound redness observed with the current non-selective, mixed α1- and α2-AR agonists used to treat ocular redness, are due to action at the α1-ARs.

Brimonidine is a third generation α2-AR agonist introduced in 1996. Brimonidine has a very high selectivity for α2-ARs, and is used, under prescription, for the treatment of increased intraocular pressure (IOP) in glaucoma patients. The mechanism of action is two-fold: a reduction of aqueous humor flow and increased uveoscleral outflow (Toris, 1995). Brimonidine tartrate developed for treatment of IOP was first approved under the brand name Alphagan® at concentrations of 0.2% and 0.5%. Both concentrations have since been discontinued. These were not discontinued for safety or efficacy reasons. Brimonidine tartrate for treatment of IOP is currently sold as Alphagan P® at concentrations of 0.15% and 0.1%.

Recently, Bausch & Lomb (B&L) developed a low dose (0.025%) brimonidine tartrate ophthalmic solution which was approved by FDA in December of 2017 under the brand name Lumify®. Lumify® is sold over-the-counter for relief of ocular redness due to minor irritations. Lumify® has been demonstrated as an effective treatment of eye redness while minimizing the side effects of tachyphylaxis (tolerance or loss of effectiveness) or rebound congestion commonly associated with other products currently on the market for redness relief.

For some patients, frequent exposure of the ocular surface to the preservative benzalkonium chloride (BAK) can induce or exacerbate existing ocular irritation, burning/stinging, itching, dryness, and redness (Gomes, 2017; Walsh, 2019). A preservative-free formulation of Lumify® would potentially offer a less-irritating ocular decongestant option to patients with ocular redness with no apparent underlying cause. B&L has developed a preservative-free formulation of brimonidine tartrate ophthalmic solution 0.025%, which contains all of the same components as Lumify® with the exception of BAK, with the goal to improve the irritation occasionally reported with frequent use of BAK-preserved eye drops while maintaining the redness-relieving effect of the active brimonidine tartrate.

6.0 STUDY OBJECTIVES AND PURPOSE

The Primary Objective is to demonstrate that the efficacy of brimonidine tartrate ophthalmic solution preservative-free formulation (BTOS-PF) 0.025% is non-inferior to Lumify® 0.025% for treating ocular redness in a population of adult subjects.

The Secondary Objective is to compare the safety of BTOS-PF 0.025% with Lumify® 0.025%.

7.0 INVESTIGATOR AND STUDY ADMINISTRATIVE PROCEDURES

- The study will be conducted at up to six investigative sites located in the United States.
- The study will be conducted by Principal Investigators who are determined by the Sponsor to be suitably qualified by training and experience to conduct this study in compliance with all applicable GCPs and Federal or Local Laws and Regulations. Sub-Investigators will be identified on the Statement of Investigator Agreement Form/ Form FDA 1572.
- Approximately 386 subjects will be enrolled at up to six investigative sites. Each investigative site is expected to enroll approximately 65 subjects. In the event that the selected site does not meet full enrollment, the Sponsor may decide to add additional site(s) to satisfy the enrollment requirements of the study.

8.0 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan Description

This is a multi-center, double-masked, randomized, active-controlled, parallel-group, efficacy and safety study that will enroll 386 subjects at up to six clinical sites. Subjects with ocular redness will be randomized to receive either brimonidine tartrate ophthalmic solution 0.025%, preservative-free formulation, or Lumify® (brimonidine tartrate ophthalmic solution 0.025%). Subjects will be treated with study drug for approximately 4 weeks.

Five visits will take place during this study: Screening Visit (Day -28 to 1), Visit 1 (Baseline; Day 1), Visit 2 (Day 15 ± 2 days), Visit 3 (Day 29 + 2 days), and Visit 4 (Study Exit; Day 36 + 1 day). Efficacy assessments will be performed at Visits 1, 2, and 3. Tolerability assessments will be performed at Visit 1. Safety assessments will be performed at all visits.

Efficacy assessments include ocular redness evaluated by the investigator in-office and ocular redness evaluated by the subject as captured in subjects' dosing diary. Tolerability assessments include drop comfort assessment and drop comfort descriptor questionnaire, both evaluated by the subject. Safety assessments include adverse events, vital signs, BCVA, IOP, dilated ophthalmoscopy, biomicroscopy, and ocular rebound.

9.0 SELECTION OF STUDY POPULATION AND WITHDRAWAL OF SUBJECTS

A total of up to 386 subjects at up to six clinical sites in the United States with ocular redness will be enrolled in this clinical investigation.

9.1 Subject Inclusion Criteria

A subject will be eligible for inclusion in this study if he/she meets all of the following criteria:

Subjects MUST:

1. Be at least 18 years of age at the time of Informed Consent signing of either gender and any race or ethnicity;
2. Provide written informed consent and sign the HIPAA form;
3. Be willing and able to follow all instructions and attend all study visits;
4. Have a history of vasoconstrictor (redness relief drops) use within the last 6 months, or a desire to use OTC vasoconstrictors for redness relief;
5. Be able to self-administer eye drops satisfactorily or have a subject's care provider at home[1] routinely available for this purpose;
6. (If female and of childbearing potential) agree to have urine pregnancy testing performed at Visit-1(must be negative) and at exit visit; must not be lactating; and must agree to use at least 1 medically acceptable form of birth control[2] throughout the study duration and for at least 14 days prior to the first dose of study drug (Visit 1) and for 1 month after the last dose of investigational drug. Note: Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy);
7. (If male and with female partner of childbearing potential) must use at least 1 medically acceptable form of birth control[3]
8. A calculated best-corrected (if necessary) visual acuity of 0.3 logMAR or better in each eye, as measured using an ETDRS chart;
9. At Visit 1 (Baseline), show a baseline redness score >1 unit (ie, greater than 1 unit) in both eyes on a 0 to 4 unit scale as scored by the Investigator using the Investigator Ocular Redness Scale;
10. Have stable ocular health (defined as no ocular conditions requiring therapy or surgical intervention during the study).

[1] If a care provider or surrogate will be used to administer eye drops, then he/she must be present at Visit 1 to administer eye drops in-office.

[2] Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject), spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of male partner at least 3 months prior to the first dose of investigational drug (Visit 1).

[3] Acceptable forms of birth control are true abstinence (when this is in line with the preferred and usual lifestyle of the subject) or vasectomy at least 3 months prior to the first dose of study drug (Visit 1).Without a vasectomy, must use condoms with spermicidal foam/gel/film/cream/suppository at least 14 days prior to the first dose of investigational drug (Visit 1) and for 1 month after the last dose of the investigational drug (Visit 3).

9.2 Subject Exclusion Criteria

A subject will be ineligible for inclusion in this study if he/she meets any of the following criteria:

Subjects MAY NOT:

1. Have known contraindications or sensitivity to the use of any of the investigational drug(s) or their components, or any other medications required by the protocol;
2. Have had ocular surgical intervention within 3 months prior to screening or during the study and/or a history of refractive surgery within the past 6 months;
3. Have the presence of an active ocular infection (bacterial, viral, or fungal) or positive history of an ocular herpetic infection at any visit;
4. Use any of the following disallowed medications during the period indicated prior to screening and for the duration of the study:
   - All topical ophthalmic agents including artificial tear products, eye whiteners (e.g., vasoconstrictors), ocular decongestants, ocular antihistamines, ocular corticosteroids, dilating drops (excluding dilated ophthalmoscopy exam at Visit 1), and contact lenses: 5 days
   - Systemic antihistamines or decongestants: 7 days
   - Systemic corticosteroids or cancer chemotherapy, and/or any other systemic medications which the investigator feels may confound study data, or interfere with subject's study participation: 14 days
5. Have prior (within 7 days of beginning investigational drug) or currently active significant illness that could compromise participation, in the opinion of the investigator;
6. Have prior (within 30 days of beginning investigational drug) or anticipated concurrent use of an investigational drug or device during the study period;
7. Have an ocular or systemic condition or a situation which, in the investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation;
8. Have planned surgery (ocular or systemic) during the trial period or within 30 days after the study period;
9. Be currently breast feeding or planning to breast feed during the study period or is a female who is currently pregnant, is planning a pregnancy, or has a positive urine pregnancy test at Visit 1;

10. Have a diagnosis of ocular hypertension or glaucoma at screening;
11. Have symptoms that, in the opinion of the investigator, may be associated with COVID-19 or in the last 14 days came into contact with someone diagnosed with COVID-19.

9.3 Subject Discontinuation / Withdrawal Criteria

A subject MUST be discontinued prior to the final study visit for any of the following reasons:

- Voluntary withdrawal: All subjects are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice. No constraints will be placed on ordinary subject management, and subjects, when appropriate, will be placed on other conventional therapy upon request or whenever clinically necessary as determined by their physician.
- Death: Complete SAE form
- Subject becomes pregnant: Subject will discontinue study drug immediately, but will be followed to term. Complete pregnancy and SAE forms if applicable and report to the same contacts using the same reporting procedure for an SAE under Section 11.4.6.
- If any adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject as determined by the Investigator. Complete AE form.
- Lost to Follow-Up: See Section 9.4 below.
- Lack of Efficacy: Subject requires alternate treatment for ocular redness and the risk of continuing the subject in the study outweighs the benefit as determined by the investigator.
- Study Terminated by Sponsor: An indication that a clinical study was stopped by its Sponsor.

A subject MAY be discontinued (at the discretion of the Investigator, Sponsor, and/or the IRB/IEC) prior to the final study visit for several reasons, including, but not limited to:

- Serious adverse event (SAE) occurring during the course of the study that precludes continued treatment or follow-up
- Significant non-compliance with study requirements (Protocol Violation): Contact the Sponsor or designee before making decision.
- When concomitant therapy likely to interfere with the results of the study is reported, or required by the subject (the investigator will report all such information on the source documents/electronic case report forms (eCRFs) and decide, in accordance with the sponsor, whether the subject is to be withdrawn)

Prior to discontinuing a subject, every effort should be made to contact the subject, schedule a final study visit, obtain as much follow-up data as possible, and to retrieve all study materials. Adverse events will be followed as described in section 12.4. Subject withdrawals will be documented clearly on the source document and applicable eCRF.

The assessments scheduled for Visit 3 should be performed at this early termination visit.

Notification of subject withdrawals will be made to the Sponsor.

9.4 Lost to Follow-up

Subjects who do not return for their scheduled visits as defined by the visit window and cannot be contacted, may be considered lost to follow-up. Attempts to contact the subjects should include at least 2 phone calls, emails and/or text messages and a certified letter. All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable eCRFs will be completed. For subjects that are lost to follow-up, the date of early termination will be the date of the last attended clinic visit and the date of last dose will be the date of the last in-office instillation.

10.0 TREATMENT PLAN

10.1 Study Duration

The estimated time of study duration, from the start of enrollment to completion of the end of study (EOS) assessments for the final subject is approximately 21 weeks. For each subject, the estimated time on study medication, from baseline to end of treatment (EOT) visit is 4 weeks.

10.2 Methods of Assigning Subjects to Treatment Groups

At Visit 1, approximately 386 subjects will be randomly assigned at a ratio of 1:1 to the following treatments:

- Brimonidine tartrate ophthalmic solution 0.025%, preservative-free formulation (BTOS-PF) (N = 193)
- Lumify® (brimonidine tartrate ophthalmic solution 0.025%) (N= 193)

10.3 Description of Test Article(s)/Treatment(s)

The test article, BTOS-PF, contains 0.025% of the active brimonidine tartrate, purified water, boric acid, sodium borate decahydrate, potassium chloride, calcium chloride dihydrate, glycerin, sodium chloride, and pH adjusted with hydrochloric acid and sodium hydroxide.

The dosing regimen for BTOS-PF 0.025% is 4 times per day (QID) approximately 4 hours apart for a duration of 4 weeks.

10.4 Description of Comparator / Product(s)/Treatment(s)

The comparator product, Lumify®, contains 0.025% of the active brimonidine tartrate, purified water, benzalkonium chloride, boric acid, sodium borate decahydrate, potassium chloride, calcium chloride dihydrate, glycerin, sodium chloride, and pH adjusted with hydrochloric acid and sodium hydroxide.

The dosing regimen for Lumify® is QID approximately 4 hours apart for a duration of 4 weeks.

10.5 Instructions For Use and Administration

Study drug will be provided as a study kit (carton). Each study kit will contain pouches that each hold 5 single-use vials. One single-use vial will be used to dose both eyes 1 time. Subjects will instill 1 drop of the assigned investigational drug in each eye QID approximately 4 hours apart. Subjects should dispose of the single-use vial in the provided zip-lock bag after instillation of 1 drop in both eyes. Subjects should not use any remaining solution in the vial for a subsequent dose.

10.6 Other Materials

- Clarity HCG will be used for pregnancy tests.
- Fluress® ocular anesthetic agent (fluorescein sodium and benoxinate hydrochloride ophthalmic solution USP) will be used for the intraocular pressure (Section 18.3)
- Dilating drops will be used for dilated ophthalmoscopy (Section 18.4)

10.7 Masking/Unmasking or Blinding/Unblinding

Subjects will be assigned to treatments based on a randomization schedule. The Investigator, site staff, subject, CRO, and Sponsor personnel involved in the monitoring or conduct of the study will be masked to the treatment assignments. The randomization list will be produced prior to study enrollment by a statistician not otherwise involved in the trial.

Due to differences in test article and comparator, there will be an Unmasked Designee who will be responsible for the handling of study kits and activities surrounding the use of study kits.

Each site must have a unmasked Designee that will be responsible for:

- all study kit dispensation and accountability,
- daily diary dosing education/review,
- all discussions with study subjects related to study kit

This unmasked designee shall not participate in any other trial procedures and not report this information to other staff. Subjects will be instructed to administer the study drug out of the sight of the Investigator or site staff other than the unmasked designee. Subjects will be instructed not to show or discuss the properties of the assigned study drug to the Investigator or site staff other than the unmasked designee, unless instructed to do so.

When the management of a subject's condition requires knowledge of the treatment assignment, the investigator, or designee, will obtain the trial treatment assignment from the Interactive-Web Response System (IWRS). If possible, the medical emergency should be discussed with the medical monitor prior to obtaining the treatment assignment, or as soon after as.

The Investigator must record the date, time, and reason for unmasking the study drug treatment in the source documentation.

10.8 Randomization Method

Each subject who signs an informed consent form will be assigned a unique Subject number in the IWRS. Once a subject meets all qualification criteria at Visit 1, he/she will be randomized to brimonidine tartrate ophthalmic solution 0.025%, preservative free formulation or Lumify® (brimonidine tartrate ophthalmic solution 0.025% in a 1:1 ratio. Subject numbers will be assigned in a sequential order starting at the lowest number available. No numbers will be skipped or omitted. Subject numbers will be created (in the following format, 3-digit site number plus 3-digit subject number) in the IWRS. Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across the IWRS treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

A trained unmasked Designee will be instructed to dispense the appropriate kit that corresponds to the assigned subject number according to the randomization list.

10.9 Prior and Prohibited Concomitant Medications or Therapy

All therapies and medications administered 30 days prior to screening and through study exit must be recorded in the source documentation and in the appropriate section of the eCRF.

10.10 Treatment Compliance

Any subject who does not follow instructions to a degree that, in the Sponsor or Investigator's opinion, jeopardizes the subject's well-being or the validity of the study, **may** be discontinued.

10.11 Protocol Deviations and Violations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. Deviations usually have an impact on individual subjects or a small group of subjects and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is non-adherence to the protocol that results in a significant, additional risk to the subject; when the subject or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria), and the subject was enrolled without prior sponsor approval; or when there is non-adherence to FDA regulations and/or ICH GCP guideline.

The investigator may implement a deviation from the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation, as well as the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB/IEC for review and approval. It should also be submitted to the sponsor for agreement, and to the regulatory authorities, if required.

The date of and reason for deviations will be documented in all cases. Significant protocol deviations impacting the safety of the subject or the integrity of the study must be reported by the Investigator to the IRB/EC immediately. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB/EC.

Protocol assessments will continue until the end of the study, unless the protocol deviations put the subject at risk or the subject's condition requires that he/she be discontinued from the study.

11.0 STUDY DRUG MATERIALS AND MANAGEMENT

11.1 Name of Investigational Products

- Brimonidine tartrate ophthalmic solution 0.025%, preservative-free formulation
- Lumify® (brimonidine tartrate ophthalmic solution 0.025%)

11.1.1 Packaging and Labeling

The investigational materials will be packaged and labeled in a manner consistent with thestudy design. They will be labelled according to the regulatory requirements and in compliance with the Code of Federal Regulations 21 part 312, section 312.6. The labels for the investigational materials will contain but not limited to the following:

- Protocol number
- Kit number
- Contents
- Investigational new drug statement
- Storage conditions
- Name and address of the sponsor

11.1.2 Storage Requirements / Handling and Disposal of Study Drug

Study drug will be supplied to the investigator by the Sponsor and must be stored in a controlled-access, environmentally controlled area as per the label. The investigational product must be kept in an appropriate, secure area (e.g., locked cabinet, or other contained space).

There are no special procedures required for preparing the study drug for this trial. Study material are stored at the recommended storage conditions 15° - 25° C (59-77° F).

All used, unused and returned product must be returned to the Sponsor at the address below. It will be at the Sponsor's permission to allow disposal of product at the site as per site destruction procedures. Site is to contact sponsor for permission on material disposal on site. Instructions will be provided by the Sponsor regarding final disposition of all study drug in compliance with applicable regulations.

Bausch + Lomb
1400 N Goodman St.
Clinical Trial Materials / A56
Rochester, NY 14609

11.1.3 Treatment Replacement

Any additional or replacement (in the case of loss or damage) of study kits must be ordered through the randomization system.

11.1.4 Study Drug Accountability

The Investigator will be responsible for keeping current and accurate records of the amount of study received and dispensed, and its disposition. The drug must be stored under the appropriate conditions in a secure area and is to be dispensed only to subjects enrolled in the study, in accordance with the conditions specified in this protocol. During the course of the study, the Investigator must maintain an inventory of all drug dispensed to or returned by the subject, including subject numbers and visit numbers.

At time points throughout the study and/or upon completion of the study, the Sponsor/Sponsor's representative will review and verify the Investigator's accountability records. Following verification, and as directed by the Sponsor, all used, unused and returned product must be returned to the Sponsor at the address noted above in Section 11.1.2 (handling and disposal of study drug), or with the Sponsor's permission, disposed of at the site in an appropriate manner. Instructions will be provided by the Sponsor regarding final disposition of all study drug in compliance with applicable regulations.

11.2 Efficacy and Safety Variables

11.2.1 Primary Efficacy Variables

- Ocular redness score evaluated by the investigator prior to investigational drug instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1

11.2.2 Secondary Efficacy Variables

Secondary efficacy endpoints will be evaluated hierarchically, as follows:

1. Change from pre-instillation ocular redness score evaluated by the investigator at 1 (+0.5) minute after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1;
2. Change from pre-instillation ocular redness score evaluated by the investigator (0-4 unit scale, allowing half unit increments)at:
    i. 1 minute after investigational drug instillation at Visit 2
    ii. 5 minutes after investigational drug instillation at Visit 2
    iii. 1 minute after investigational drug instillation at Visit 3
    iv. 5 minutes after investigational drug instillation at Visit 3

3. Change from pre-instillation ocular redness score evaluated by the investigator at 360 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1; and
4. Change from pre-instillation ocular redness score evaluated by the investigator at 480 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1.
5. Ocular redness score evaluated by the subject as captured in subjects' dosing diary throughout the treatment period (0-4 unit scale, NOT allowing half unit increments).

11.2.3 Safety Variables

- Ocular and non-ocular adverse events, vital signs, and ophthalmic examination at each visit
- Ocular Rebound defined as:
  - Increase of at least 1 unit in mean ocular redness score evaluated by the Investigator at Visit 4 (0-4 unit scale, allowing half unit increments) compared to pre-instillation score at Visit 1, or
  - Increase of at least 1 unit in mean ocular redness score evaluated by the subject as captured in subject dosing diaries in the follow-up period, after dosing has ceased (0-4 unit scale, NOT allowing half unit increments) compared to diary day 1 (pre-dose morning assessment).

11.2.4 Tolerability Variables

- Drop comfort assessment (0-10 unit scale) assessed upon instillation, at 30 seconds, and at 1 minute post-instillation at Visit 1
- Drop comfort descriptor questionnaire assessed at 3 minutes post-instillation at Visit 1

12.0 STUDY METHODS, PROCEDURES AND EVALUATIONS

12.1 Study Visits

Refer to Appendix A for a schedule of visits and parameters and Appendix B for methods of clinical evaluation.

12.1.1 Screening Visit (Day -28 to Day 1)

Following identification of a potential subject, the Investigator (or designee) will explain the purpose of the study, procedures, risks/benefits, and subject responsibilities to the potential subject. The subject's willingness and ability to meet the follow-up requirements of the study will be determined. If the subject chooses to participate in the investigation, written informed consent will be obtained. The subject and the person obtaining written consent, will sign and date the IRB/EC-approved ICF, at which point the subject is considered part of the study population. The original signed document will be retained in the subject records, and a copy will be provided to the subject. In addition, the applicable privacy regulation requirements must be met.

- *Informed Consent/HIPAA:* Prior to any changes in a subject's medical treatment and/or study visit procedures, the study will be discussed with each subject, and subjects wishing to participate must give written informed consent and sign a HIPAA form. The informed consent process will be captured in the subject's source documentation.

  Prior to randomization at Visit 1, if it is determined the subject did not in fact meet certain criteria, the subject will be a screen failure. The subject may be brought back at a later date to re-attempt the screening process. Subject will be considered a new subject when re-attempting the screening process. The subject will sign the informed consent again and a new subject number will be assigned.

- *Demographic Data and Medical/Medication/Ocular History:* Collect and record all demographic data, medical history, any medications and any underlying condition(s). Current underlying conditions, including those that began within the last 30 days, which resolved before screening must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within the 30 days prior to screening.

  Medical/medication history and inclusion/exclusion review may be performed at the time of Screening Visit and confirmed at Visit 1.

If there is no washout period, the Screening Visit and Visit 1 can occur on the same day.

12.1.2 Visit 1 (Baseline; Day 1)

- *Update Medication History:* Collect and record any changes or new medications that may have started or that require follow-up from the last visit. If a subject uses a disallowed medication, that subject will be exited from the study.
- *Urine Pregnancy Test[1] (for females of childbearing potential):* Women of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an adequate method of contraception and associated footnotes in order to be enrolled.
- *Best Corrected Visual Acuity at Distance Utilizing an ETDRS Chart:*

  Subjects must have a score of 0.3 logMAR or better in each eye in order to qualify (see Appendix A).

- *Slit Lamp Biomicroscopy:* A slit lamp exam will be performed to exclude subjects with disallowed ocular conditions (see Appendix A).
- *Ocular Redness Assessment:* Redness will be assessed by the investigator using the 0-4 Investigator Ocular Redness Scale (see Appendix A).
- *Intraocular Pressure:* Intraocular pressure will be measured (see Appendix A). It is recommended that subjects should wait a minimum of 10 minutes after instillation of Fluress® before instilling investigational drug.

[1] See section for reporting pregnancies and follow-up (enrolled subjects only).

- *Physical Exam including vital signs (see Appendix A).*
- *Dilated Ophthalmoscopy:* A dilated ophthalmoscopy will be performed by the investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology (see Appendix A).
- *Review of Applicable Inclusion/Exclusion Criteria*: The investigator will verify the trained study technician's review of inclusion/exclusion criteria.
- *Enrollment/Randomization*: Qualifying subjects will be assigned a unique subject number and randomized through IWRS to receive either brimonidine tartrate ophthalmic solution 0.025% preservative free or Lumify®. An unmasked designee will distribute the appropriate study kit.
- *Investigational Drug Dispensation and Instillation*: Drug dispensation of one kit for self-administered dosing until Visit 2. An unmasked designee will observe the subject (or subject's care provider; if applicable) instill investigational drug according to the directions for use. The investigational drug kit number and the time of instillation will be recorded.
- *Drop Comfort Assessment:* Drop comfort will be assessed immediately upon instillation, at 30 seconds, and at 1 minute post-instillation (0 – 10 scale).
- *Drop Comfort Descriptor Questionnaire:* The subject will select 3 descriptor terms for drop comfort at 3 minutes post-instillation.
- *Post-Instillation Ocular Redness Assessment:* Redness will be assessed by the investigator at 1(+0.5), 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), 240(+15), 360 (+15), and 480(+15) minutes after investigational drug instillation using the 0-4 Investigator Ocular Redness Scale.
- *Slit Lamp Biomicroscopy* (Post-Instillation)
- *Investigational Drug and Dosing/Redness Diary Dispensation:* Enrolled subjects (or subject's care provider, if applicable) will be instructed to instill 1 drop of investigational drug in each eye, 4 times daily for approximately 4 weeks beginning the next morning. Subjects will be instructed on how to complete their daily diary and ocular redness assessments using the photographic scale provided.

  Subjects will be instructed to record the time of dosing in the diary.

  Subjects will be instructed NOT to dose within 3.5 hours of arrival on the day of their next scheduled study visit (Visit 2). They will also be instructed to bring both used/unused investigational drug and their daily diary to the next visit (Visit 2) for a compliance check.
- *Adverse Event Query*
- *Schedule Visit 2*

12.1.3 Visit 2 (Day 15 ± 2 days)

- *Investigational Drug and Dosing/Redness Diary Review and Collection*:

Unmasked designee will collect study kit (used and unused investigational material) dispensed at Visit 1. The dosing diary will be collected and reviewed for compliance and to address any queries.

- *Update Medication History:* Collect and record any changes or new medications that may have started or that require follow-up from the last visit. If a subject uses a disallowed medication, that subject will be exited from the study.
- *Adverse Event Query*
- *Best Corrected Visual Acuity at Distance Utilizing an ETDRS Chart:* A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1 will be considered an adverse event.
- *Vital Signs (without body weight)*
- *Slit Lamp Biomicroscopy*
- *Ocular Redness Assessment:* Redness will be assessed at Visit 2 by the investigator using the 0-4 Investigator Ocular Redness Scale.
- *Post-Instillation Ocular Redness Assessment:* Redness will be assessed by the investigator approximately 1 and 5 minutes after investigational drug instillation using the 0-4 Investigator Ocular Redness Scale.
- *Slit Lamp Biomicroscopy* (Post instillation)
- *Investigational Drug and Dosing/Redness Diary Dispensation:* Enrolled subjects (or subject's care provider, if applicable) will be instructed to continue their at-home dosing QID, approximately every 4 hours. Subjects will be instructed to continue to complete their daily diary and ocular redness assessments using the provided photographic scale as instructed.

  Subjects will continue to record the time of dosing in the diary.

  Subjects will be instructed NOT to dose within 3.5 hours of arrival on the day of their next scheduled study visit (Visit 3). They will also be instructed to bring both used/unused investigational drug and their daily diary to the next visit (Visit 3) for a compliance check.
- *Schedule for Visit 3*

12.1.4 Visit 3 (Day 29 + 2 days)

- *Collection of Study Drug kit & Diary*

  Unmasked designee will collect study kit (used and unused investigational material) dispensed at Visit 2. Dosing diary will be collected and reviewed for compliance and to address any queries.
- *Update Medication History*
- *Adverse Event Query*

- *Best Corrected Distance Visual Acuity Utilizing an ETDRS Chart:*
  A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1 will be considered an adverse event.
- *Slit Lamp Biomicroscopy*
- *Ocular Redness Assessment:* Redness will be assessed as at Visit 3 by the investigator using the 0-4 Investigator Ocular Redness Scale.
- *Investigational Drug Instillation*: An unmasked designee will instill investigational drug according to the directions for use. The investigational drug kit number and the time of instillation will be recorded.
- *Post-Instillation Ocular Redness Assessment:* Redness will be assessed by the investigator approximately 1 and 5 minutes post investigational drug instillation using the 0-4 Investigator Ocular Redness Scale.
- *Slit Lamp Biomicroscopy* (Post-Instillation)
- *Intraocular Pressure*
- *Physical Exam including Vital Signs*
- *Dilated Ophthalmoscopy:* A dilated ophthalmoscopy will be performed by the investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology (see Appendix A).
- *Redness Diary Dispensation:* Subjects will be instructed to complete ocular redness assessments QID with intervals of approximately 4 hours up until the night before their next visit (Visit 4) using the photographic scale provided. They will also be instructed to bring their diary to their next visit (Visit 4).
- *Schedule for Visit 4*

12.1.5 Visit 4 (Day 36 + 1 day)

- *Update Medication History*
- *Adverse Event Query*
- *Diary Collection*: The redness diary will be collected and reviewed to address any queries.
- *Urine Pregnancy Test (for females of childbearing potential)*
- *Best Corrected Visual Acuity at Distance Utilizing an ETDRS Chart:*
  A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from Visit 1 will be considered an adverse event.
- *Slit Lamp Biomicroscopy*
- *Ocular Redness Assessment:* Redness will be assessed as at Visit 4 by the investigator using the 0-4 Investigator Ocular Redness Scale.
- *Exit:* Subjects will be exited from the study.

12.1.6 Unscheduled Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional exams should be fully documented in the source documents and on Unscheduled Visit eCRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range, are not considered Unscheduled Visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit eCRF.

If a subject is seen for multiple visits during a given visit timeframe, the data from the visit that is intended to meet the protocol requirements for the scheduled visit should be captured on the visit eCRF. Where such a determination cannot be made, the first visit within the scheduled visit interval will be used for completion of the protocol required scheduled visit eCRF. Data from any additional visits within a scheduled visit interval will be captured on an Unscheduled Visit eCRF.

12.1.7 Missed Visits

If a subject misses any scheduled follow-up visit and cannot be seen prior to the start of the visit range for the next scheduled follow-up visit, the visit is considered missed.

12.2 Post-Study Follow-up

If a subject requires further follow-up of ongoing AEs upon discontinuation or completion of the study, the Investigator should schedule post-study follow-up visits, as necessary.

12.3 Study Completion

The Sponsor will notify the CRO when to contact the IRB/EC to inform them that the study is complete.

12.3.1 Early Study Termination

If during the study it becomes evident to the Sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the Investigator(s), IRB/EC, and FDA, as applicable. The Sponsor will instruct the Investigators to stop dispensing study materials/treatment and the Sponsor will arrange for study closeout visits for each site.

12.4 Adverse Events

12.4.1 Definition of Adverse Event

Definition of Adverse Event/ (AE):

An adverse event is any untoward medical occurrence in a subject participating in a clinical study, which does not necessarily have a causal relationship with the study product/procedure. Therefore, an adverse event includes:

- Any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease onset, that occurs at any time between the signing of the ICF and

study exit, without any judgement about causality (i.e., whether or not it is considered to be related to the study product)

- Exacerbation, worsening, or progression of a pre-existing illness, including an increase in severity, frequency, and/or duration of a pre-existing episodic event or condition
- Events occurring from drug overdose (accidental or intentional), drug abuse or misuse, drug hypersensitivity, drug extravasation, drug interactions, drug dependency, events occurring from drug withdrawal and medication errors
- A condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study

A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first dose of study drug, or that worsened following administration of study drug.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) as event terms; the condition that led to the procedure is the AE if it meets the definition of an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery; and social and/or convenience admissions).

Symptoms associated with disease, which are consistent with the subject's usual clinical course; unless the subject experiences worsening of their symptom(s) or the symptom(s) meet the criteria for an SAE.

12.4.2 General Guidelines for Reporting Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the course of the study. Throughout the study, efforts will be made by the investigator to remain alert to possible AEs. The period of observation for collection of AEs extends from the time the subject gives informed consent until the last study visit or discontinuation from the study. The first concern will always be the safety of the subject, and appropriate medical intervention will be made.

The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject at each study visit. Each AE which appears to be independent of any prior event will be reported separately.

All AEs occurring after the subject signs the informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered drug-related. All AEs, whether in response to a query, observed by the study site personnel, or reported spontaneously by the subject, will be recorded. Any AEs deemed related to treatment reported or observed at the final study/treatment visit will be followed until stabilization or resolution (or up to 30 days after final study visit).

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Tolerability signs and symptoms that result in the subject's requiring a

concomitant therapy, interruption of treatment, or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset date and end date
- Maximum intensity (severity)
- Seriousness
- Action taken regarding study drug
- Corrective treatment/therapy, if given
- Outcome
- Resolution

The investigator will also provide an assessment of the causal relationship to the study drug (for pre-treatment AEs, causality is "not related").

All AEs must be reported regardless of whether the AEs are considered drug-related.

In order to ensure the safety of the subjects, the investigator should take appropriate measures to follow all subjects with adverse events until clinical recovery is complete, progression has been stabilized, the subject is lost to follow-up, or until death. This may result in the need for observations to continue beyond the last planned protocol specified visit, and additional investigations may be requested by the monitoring team. Refer to Section 12.2 for follow-up of AEs following study exit.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs only if:

- the result is clinically significant
- the subject is symptomatic
- the subject requires either corrective treatment or consultation
- the lab result, vital sign, or ECG abnormality leads to study drug discontinuation or dose modification
- the event fulfills a criterion for an SAE

In addition, the investigator's assessment of causality will be recorded.

Vital sign abnormalities are to be recorded as AEs only if they are clinically significant (for example: are symptomatic, requiring corrective treatment, leading to discontinuation or fulfilling a seriousness criterion).

12.4.3 Serious Adverse Events

An AE is considered "serious" if it meets at least one of the following criteria. The event:

- Results in death
- Is life threatening (places the subject at immediate risk of death)

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not

refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: The term "hospitalization" refers to admission to a hospital as an in-patient for more than 24 hours. Therefore, an adverse event would meet the SAE criterion of "requires hospitalization" only if the event necessitated admission to a health care facility for longer than 24 hours. Elective hospitalization for an intervention that was already planned before inclusion of the subject in the study, hospitalization solely for the purpose of diagnostic tests (even if related to an AE), hospital admission for social circumstances, and admission to a day-care facility may not constitute sufficient grounds to be considered an SAE.

  Cases in which subjects are retained in the emergency room for more than 24 hours but not admitted for medical care should be evaluated individually, because the criterion "otherwise medically significant" may apply (see below).

- Results in persistent or significant disability/incapacity

  NOTE: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance (e.g., uncomplicated headache, influenza, or sprained ankle) that may transiently interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered otherwise medically significant, as determined by the PI or medically qualified sub-investigator

  NOTE: The term "medically significant" refers to important medical events that may not immediately be life threatening or result in death or hospitalization, but, based upon appropriate medical judgment, they jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the definition of an SAE.

  Examples of such medically significant events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Spontaneous abortion, elective abortion and ectopic pregnancy will be considered SAEs and must be reported to the sponsor within 24 hours of awareness of the event.

Subjects will be withdrawn from the study if an SAE is identified and thought to be related to the study drug.

The investigator is responsible for the reporting of all SAEs.

Within 24 hours following the investigator's knowledge of an SAE, the investigator must:

- Report the SAE to the sponsor/designee.

  All SAEs occurring between screening and 30 days after the last administered dose of study drug (inclusive) must be reported to the sponsor/designee, independent of the circumstance or suspected cause, and regardless of the relationship to the study drug or protocol, within 24 hours from the time the event was reported to the investigator. For events occurring beyond the 30-day period after the last application of study drug, or for any timeframe greater than 30 days deemed medically significant, only SAEs considered related to the study drug should be reported promptly to the sponsor.
  If the subject dies during participation in the study or during recognized follow-up period, and if cause of death is not available within the 24-hour reporting period, "death" must be reported as an SAE term to meet the timelines. Cause of death must be actively queried and submitted as a follow-up report.
- Fax or email a completed Serious Adverse Event Report to the following designee:

  Sponsor Contact:

  [redacted]

  Include copies of all confirmatory examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the subject's identity is protected (personal identifiers are redacted), and the date and subject identifier in the clinical trial (i.e., subject number) are clearly visible on every page/copy of source document provided to the sponsor. For laboratory results, include the laboratory normal ranges.

- Investigators should not wait to receive additional information before notifying the sponsor of an SAE. If only limited information is initially available, follow-up reports are required.

Within 48 hours following the investigator's knowledge of an SAE, the investigator must:

- Enter the information related to the SAE in the appropriate sections of the eCRF.
- Send notification of the SAE to the monitoring team after investigator approval of the eCRF

All further data updates should be recorded in the CRF within one working day of knowledge of this additional information. Send notification of the updated SAE information to the monitoring team after investigator approval of the eCRF.

Additional documentation (e.g., laboratory data, concomitant medication, subject status, etc.), should be sent by fax or e-mail to the monitoring team within one working day of knowledge of this information. Care should be taken to ensure that the subject's identity is protected (personal identifiers are redacted) and the date and subject identifier in the

clinical trial (i.e., subject number) are clearly visible on every page/copy of source document that is provided to the monitoring team. For laboratory results, include the laboratory normal ranges.

After the EOS visit, the investigator does not need to actively monitor subjects for new SAEs. However, if the investigator becomes aware of a new or previously unreported serious adverse event within 30 days after the last investigational drug instillation, the event should be reported to the sponsor/designee within 24 hours of learning of the event. If the investigator becomes aware of a new or previously unreported SAE after 30 days from the last investigational drug instillation, only SAEs considered related to the study drug should be reported to the sponsor within 24 hours of the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial SAE Report Form cases for the purposes of expedited reporting.

12.4.4 Assessment of Severity of Adverse Events

The severity of an AE will be graded as follows:

Mild	Awareness of a sign or symptom but is easily tolerated, requires no treatment, and does not interfere with subject's daily activities
Moderate	Low level of concern to the subject and may interfere with daily activities but can be relieved by simple therapeutic care.
Severe	Interrupts the subject's daily activity and requires systemic therapy or other treatment

12.4.5 Assessment of Causality of Adverse Events

The relationship of an AE to the study product will be assessed using the following guidelines, based upon available information:

Related	There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.
Not Related	There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

12.4.6 Expedited Serious Adverse Events

Any suspected unexpected serious adverse event considered related to the study drug may warrant expedited reporting. In addition, any unexpected SAE related to a subject's participation in the study (or related to the conduct of the study), regardless of whether or

not the study drug was administered, will be evaluated by Global Pharmacovigilance and Risk Management to determine if expedited reporting is required. For example, an unexpected, severe SAE that could be associated with the study procedures and could modify the study conduct requires expedited reporting.

Each expedited safety report will routinely include a brief cover memorandum, the completed MedWatch Form FDA 3500A, a clinical analysis of the event with any similar events that have occurred with the product, and any additional pertinent information recommended by the study medical monitor. Once the report is compiled, the study center's investigator must submit the expedited safety report to the local IRB/IEC within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The principal investigator must retain a complete copy of each expedited safety report as it was submitted to the IRB/IEC. It is important that the principal investigator review these expedited reports, as they contain safety information that may be relevant to each of the participating subjects.

12.4.7 Pregnancy

All female subjects of childbearing potential and male subjects with female partners of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of contraceptive failure is minimized. Abstinence is allowed as a birth control method. Before enrolling a female subject of childbearing potential or a male subject with a female partner of childbearing potential, the investigator must review the following information about study participation:

- Informed consent requirement
- Contraceptives in current use

By signing the informed consent form, the investigator or designee asserts that he/she has discussed this information with the subject and provided appropriate counseling. Following the review of this information, the subject must sign the informed consent form to enroll in the study. During the study, all subjects should be instructed to contact the investigator immediately if they suspect that they or their partners might be pregnant (e.g., missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to randomization, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject is considered to be a screen failure, must not continue in the study, and must not receive study drug. If pregnancy is suspected while the subject is receiving study treatment, the study drug must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued, and the subject and neonate will be followed until 30 days after the pregnancy comes to term. A Pregnancy Report form will be submitted to the sponsor, both when pregnancy is confirmed, and 30 days after the delivery date. Information provided on the Pregnancy Report Form must include the outcome of the pregnancy and any complications occurring during the pregnancy or the delivery.

If a subject is withdrawn from the study and is found to be pregnant within 30 days of withdrawal, the subject and neonate will be followed until 30 days after the pregnancy comes to term.

All confirmed pregnancies must be immediately reported to the sponsor/designee and medical monitor on a Pregnancy Report form within 24 hours of the investigator's awareness of the pregnancy. If a pregnancy is associated with an SAE, an SAE report form should also be submitted to the sponsor/designee and medical monitor within 24 hours of the investigator's awareness. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Completed SAE Report Forms and completed Pregnancy Report Forms should be transmitted to the sponsor/designee and the medical monitor using the contact information provided below:

Sponsor contact:

[redacted]

If/when the investigator becomes aware of any new information regarding a pregnancy, the sponsor/designee and medical monitor should be notified of these updates as soon as the new information becomes available. Updates should be documented on a Pregnancy Report Form and sent by fax or email using the contact information provided above. The report should be marked as a follow-up report" and should include the updated status of the pregnancy. The original Pregnancy Report Form is not to be altered.

13.0 STATISTICS

13.1 Assessment of Efficacy

13.1.1 Primary Efficacy

13.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint is

- Ocular redness score evaluated by the investigator prior to investigational drug instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1

BTOS-PF 0.025% will be compared to Lumify® 0.025% for the primary efficacy parameter of ocular redness as evaluated by the investigator (post-instillation assessments) for each of the eight time points at Visit 1 using two-sided 95% confidence intervals around the difference between means (BTOS-PF 0.025% minus Lumify® 0.025%) constructed as for two-sample t-tests with a non-inferiority limit of 0.22 units. The primary analyses will be performed on the Intent-to-Treat (ITT) population without imputation if all eight Visit 1 post-instillation time points have missing data for the primary endpoint for less than 5% of subjects and sensitivity analysis will be performed on the Primary Per-Protocol (PPP) population without imputation. If there is at least one Visit 1 time point for which at least 5% of subjects have missing data for the primary endpoint, then the primary analysis will be performed on the ITT population with an imputation strategy accounting for the reason for missing (e.g. intercurrent events), and sensitivity analyses will be performed on the PPP utilizing the same imputation strategy, as well as on the ITT and PPP populations without imputation. Secondary efficacy analyses will be based on the ITT population with an imputation strategy accounting for the reason for missing (e.g. intercurrent events) if at least 5% of subjects have missing data for that endpoint.

13.1.2 Secondary Efficacy

Secondary efficacy endpoints will be evaluated hierarchically, as follows:

1. Change from pre-instillation ocular redness score evaluated by the investigator at 1 (+0.5) minute after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1;
2. Change from pre-instillation ocular redness score evaluated by the investigator (0-4 unit scale, allowing half unit increments) at:
    i. 1 minute after investigational drug instillation at Visit 2
    ii. 5 minutes after investigational drug instillation at Visit 2
    iii. 1 minute after investigational drug instillation at Visit 3
    iv. 5 minutes after investigational drug instillation at Visit 3

3. Change from pre-instillation ocular redness score evaluated by the investigator at 360 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1; and
4. Change from pre-instillation ocular redness score evaluated by the investigator at 480 (+15) minutes after investigational drug instillation (0-4 unit scale, allowing half unit increments) at Visit 1.
5. Ocular redness score evaluated by the subject as captured in subjects' dosing diary throughout the treatment period (0-4 unit scale, NOT allowing half unit increments).

Secondary efficacy endpoint analyses will be based on the ITT population with imputation of missing data as detailed in Section 13.1.6 for a secondary efficacy endpoint if at least 5% of subjects have missing data for that endpoint. Sensitivity analyses for secondary efficacy analyses will be performed in the same manner as the sensitivity analyses for the primary efficacy analyses with the PPP replaced with the Secondary Per-Protocol (SPP) population.

The change from pre-instillation in investigator-rated redness will be compared between treatment groups utilizing the same methods as in the primary efficacy analyses [i.e. two-sided 95% confidence intervals around the difference between group means (BTOS-PF 0.025% minus Lumify® 0.025%) constructed as for two-sample t-tests for each post-instillation time point at each visit]. Two-sample t-tests will also be performed. BTOS-PF 0.025% will be considered statistically non-inferior to Lumify® 0.025% for the change from pre-instillation in investigator-rated redness at a given time and visit if the upper confidence limit does not exceed 0.22 units.

Ocular redness as recorded in the subject diaries at Visit 2 and Visit 3 will be analyzed using a generalized linear model accounting for repeated measures. Daily averages for each date recorded in subject diaries will be used for each subject. If the upper limit of the 95% confidence around the LS mean difference (BTOS-PF 0.025% minus Lumify® 0.025%) is less than 1 unit, BTOS-PF 0.025% will be declared statistically non-inferior to Lumify® 0.025% for the subject-rated ocular redness assessment.

Statistical inference for the secondary efficacy endpoints will only be performed if the primary efficacy analyses are considered successful (Section 13.1.4). Inference for the secondary efficacy endpoints will proceed hierarchically in the order listed above.

13.1.3 Supportive Efficacy

The supportive efficacy endpoint is:

- Total clearance of ocular redness assessed by the Investigator at each post-instillation time point at each visit.

Subjects with total clearance of ocular redness (redness score of 0 based on investigator assessment) will be summarized using counts and percentages by treatment group for each post-instillation time point at each visit. Treatment comparisons will be made separately for each time point using Pearson's chi-squared test or Fisher's exact test if any of the cell counts are less than five.

13.1.4 Statistical Hypothesis Testing and Control of Multiplicity

At each of eight post-instillation times at Visit 1, the null hypothesis (H_0) is that the difference between the mean redness scores for the Test (μ_T) and Standard (μ_S) formulations is 0.22 points or greater. The alternative hypothesis (H_1) is that the difference is less than 0.22 points.

$$H_0: \mu_T - \mu_S \geq 0.22$$
$$H_1: \mu_T - \mu_S < 0.22$$

The non-inferiority margin is the absolute value of one half of the smallest (in absolute value) upper confidence limit around the difference in redness scores (test minus control) observed over eight post-instillation times (5 to 240 minutes) during each of two placebo-controlled randomized clinical trials (B&L studies 11-100-0015 and 861).

The hypotheses above will be tested for each of the eight post-instillation times at Visit 1 utilizing two-sided 95% confidence intervals around the difference between means (BTOS-PF 0.025% minus Lumify® 0.025%) constructed as for two-sample t-tests. If the upper confidence limit does not exceed 0.22 units at any of the eight time points, then the study will be considered a success and BTOS-PF 0.025% will be considered statistically non-inferior to Lumify® 0.025% for investigator-rated ocular redness.

By requiring that the null hypotheses must be rejected at all eight post-instillation times to demonstrate success for the primary efficacy endpoint, the familywise type I error rate for the primary efficacy hypothesis tests is bounded above by the significance level of each hypothesis test (two-sided $\alpha = 0.05$).

Statistical inference will be performed for the secondary efficacy endpoints only if the primary efficacy endpoints demonstrate non-inferiority and statistical inference for the secondary efficacy endpoints will be performed in a hierarchical manner in the order from the list of endpoints in Section 13.1.2.

13.1.5 General Considerations

Quantitative variables, including demographics at baseline, will be summarized descriptively using number of subjects (n), mean, median, standard deviation, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

Differences between treatment groups will be calculated as BTOS-PF 0.025% minus Lumify® 0.025%.

Baseline values will be defined as the last non-missing measure prior to initiation of study treatment. Change from baseline will be calculated as follow-up measure minus baseline measure.

All efficacy analyses will use a 2-sided alpha = 0.05 test unless otherwise stated and corresponding 2-sided 95% confidence intervals (CIs) will be presented as applicable.

For efficacy, tolerability, and non-ocular safety analyses, the unit of analysis will be the subject. In the cases where assessments are recorded for each eye, the average of the eyes will be used. Adverse events will also be summarized at the subject level; if an AE occurs in either or both eyes, the subject will be counted as having the AE. For other ocular safety analyses, the unit of analysis will be each eye (with summaries showing results for the right

eye (OD) and the left eye (OS) separately), with the exception of ocular rebound which will use the averages from both eyes such that the unit of analysis will be the subject.

Statistical methods will be more fully described in a separate Statistical Analysis Plan.

13.1.6 Missing Efficacy Data Imputations

The primary efficacy analysis will be conducted with intercurrent events handled in the following manners:

1. Withdrawal due to lack of efficacy or adverse events [assumed to be missing not at random (MNAR)]: missing data will be imputed employing single imputation using worst observation carried forward [hypothetical strategy]
2. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events [assumed to be missing at random (MAR)]: missing data will be imputed employing multiple imputation using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology to impute non-monotone missing and using randomized treatment-based regression methodology to impute monotone missing [hypothetical strategy].

Intercurrent events for secondary efficacy analyses will be handled utilizing the same strategy for the primary efficacy analysis, with the following addition:

3. Discontinuation of study drug and non-optimal compliance will be ignored (that is, measured values will be used regardless of compliance or discontinuation of study drug) [treatment policy strategy].

Additional sensitivity analyses will be performed assuming all missing values due to withdrawal of any kind imputed employing:

- Single imputation using worst observation carried forward.
- Multiple imputation using randomized treatment-based regression methodology

Additional sensitivity analyses will also be performed using observed data only.

13.1.7 Sensitivity Efficacy Analyses

If imputation is not performed for the primary efficacy analysis, the analysis will be repeated on the PPP population without imputation. If imputation is required for the primary efficacy analysis, the analysis will be repeated on the PPP population with imputation and on the PPP and ITT populations without imputation as sensitivity analyses.

Sensitivity analyses for secondary efficacy analyses will be performed in the same manner as the sensitivity analyses for the primary efficacy analyses with the PPP replaced with the Secondary Per-Protocol (SPP) population.

13.1.8 Subgroup Analyses

Any planned subgroup analyses will be formally described in the study Statistical Analysis Plan.

13.2 Assessment of Tolerability

The tolerability endpoints are:

- Drop comfort assessment (0-10 unit scale) assessed by subjects immediately upon instillation, at 30 seconds, and at 1 minute post-instillation at Visit 1
- Drop comfort descriptor questionnaire assessed at 3 minutes post-instillation at Visit 1

BTOS-PF 0.025% will be compared to Lumify® 0.025% for the tolerability parameter of drop comfort using two-sample t-tests for each assessment time point. The tolerability parameter will be analyzed using the safety population. The results for the drop comfort descriptor questionnaire will be summarized descriptively by treatment group.

13.3 Assessment of Safety

The following safety variables will be recorded:

- Vital Signs (resting blood pressure and pulse)
- Adverse Events (reported, elicited, and observed)
- Best Corrected Visual Acuity (BCVA) at Distance
- Slit Lamp Biomicroscopy
- Intraocular Pressure (IOP)
- Ocular Rebound defined as:
    - Increase of at least 1 unit in mean ocular redness score evaluated by the Investigator at Visit 4 (0-4 unit scale, allowing half unit increments) compared to pre-instillation score at Visit 1, or
    - Increase of at least 1 unit in mean ocular redness score evaluated by the subject as captured in subject dosing diaries in the follow-up period, after dosing has ceased (0-4 unit scale, NOT allowing half unit increments) compared to diary day 1 (pre-dose morning assessment).

All safety parameters will be analyzed using the safety population. The safety of BTOS-PF 0.025% compared to Lumify® 0.025% will be assessed by the review of all of the safety parameters.

The results of the slit lamp biomicroscopy, IOP, visual acuity, and vital signs will be presented by treatment and visit with numerical summaries. Change from baseline will also be presented in the same manner. The ocular rebound evaluated by the investigator (at Visit 4) and by the subject (between Visit 3 – Visit 4) will be summarized separately using descriptive statistics by treatment. For assessments performed by eye, left eye and right eye will be summarized separately.

13.3.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of treatment-emergent adverse events (TEAEs) will be summarized at the subject level by system organ class and preferred term for all TEAEs, treatment related TEAEs, serious TEAEs, and TEAEs causing premature treatment discontinuation by

treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study medication. Similar summaries will be presented for all TEAEs by maximal severity. Separate summaries will be performed for ocular and non-ocular AEs.

13.3.2 Safety Laboratory Tests

No safety laboratory tests will be conducted for this study.

13.3.3 Vital Sign Measurements

Vital signs as well as changes from baseline in vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

13.3.4 Concomitant Medications

All previous concomitant medications will be classified based on terminology from the WHO Drug Dictionary. Previous therapies and concomitant medications data will be presented in data listings.

13.4 Subject Disposition

Subject disposition will be presented in terms of the numbers and percentages of subjects who completed the study and discontinued from the study. Disposition will be summarized by treatment group and for all subjects.

The number of randomized subjects in each of the analysis populations (ITT, PP, and Safety) will be displayed by treatment.

The number and percentage of subjects who prematurely discontinue from the study and the reasons for study discontinuation will be summarized by treatment group for all subjects.

13.5 Demographics and Baseline Characteristics

Subject demographics including age, sex, ethnicity, race and iris color and baseline characteristics including results of physical exams and ophthalmoscopy will be summarized using the appropriate descriptive statistics.

13.6 Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A tabulation of protocol deviations (including categorizations of major and minor) will be presented.

Important protocol deviations leading to exclusion from the Primary Per-Protocol Population will include the following.

- Ineligibility
- Missing primary endpoint data at any time point of Visit 1
- Out of window primary endpoint data at any time point of Visit 1
- Use of any prohibited medication potentially affecting the primary endpoint at Visit 1

Additional important deviations leading to exclusion from the Primary and Secondary Per-Protocol Populations may be identified prior to unmasking of the treatment assignments.

13.7 Compliance

Subjects will be provided with a dosing/redness diary to document QID dosing. Compliance rates will be summarized using continuous summary statistics and presented by treatment group on the Safety population. In addition, a discrete summary of the compliance rate categories (non-compliant, compliant, and over compliant) will be provided by treatment group.

13.8 Interim Analyses

There are no interim analyses planned for this study.

13.9 Additional Statistical Considerations

13.9.1 Analysis Populations

- *Intent-to-Treat Population*: The intent-to-treat (ITT) population includes all randomized subjects who receive at least one dose of study medication, and complete at least one post instillation ocular redness evaluation at Visit 1. Subjects will be analyzed according to the treatment to which they were randomized.
- *Primary Per-Protocol Population*: The primary per-protocol (PPP) population will include subjects in the ITT who do not have significant protocol deviations likely to affect the primary endpoint analysis. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PPP population will be analyzed as treated.
- *Secondary Per-Protocol Population*: The secondary per-protocol (SPP) population will include subjects in the ITT who do not have significant protocol deviations likely to affect the secondary endpoints and analyses. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the SPP population will be analyzed as treated.
- *Safety Population*: The safety population includes all randomized subjects who received at least 1 dose of study drug. All subjects in the safety population will be analyzed according to the treatment they received. All safety analyses will be based on the safety population.

13.9.2 Sample Size Determination

A sample size of 183 subjects per treatment group will have approximately 90% power to demonstrate non-inferiority of BTOS-PF 0.025% to Lumify® 0.025% at all eight post-instillation times at Visit 1 using a two-sample t-test and assuming a non-inferiority limit of 0.22 units, mean difference of 0 units, and a common standard deviation of 0.50 units. Assuming a 5% dropout rate, 193 subjects will be randomized to each treatment group (386 total subjects).

13.9.3 Multicenter Issues

The study will be conducted at six investigational centers in North America with the intention of pooling the results for analysis. Site specific data summaries for the primary endpoint, however, will be presented.

13.9.4 Multiplicity Issues

The Type I error rate for the primary efficacy analysis will be controlled by requiring the primary efficacy hypotheses test results to be statistically significant for all eight times at Visit 1 to declare success for the primary endpoint. The overall Type I error rate including the primary and secondary efficacy analyses will be controlled by a hierarchical testing structure. Specifically, statistical inference for the secondary efficacy analyses will only be performed if the primary analyses are successful, after which inference for the secondary efficacy endpoints will be performed in a hierarchical manner in the order of the secondary endpoints from Section 13.1.2.

13.9.5 Windowing Rules

The timing of all study visits is relative to Baseline (Day 1).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Monitoring

Sponsor representatives must be allowed to visit all study site locations to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by the Sponsor.

Prior to the start of the study, member(s) of the Sponsor will review the protocol, CRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/Sub-Investigator(s) and relevant study site personnel.

Monitoring visits and telephone consultations will occur as per the monitoring plan, or as necessary, during the course of the investigation to verify the following:

- the rights and well-being of subjects are protected
- the conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs and IRB/EC requirements
- the integrity of the data, including adequate study documentation
- the facilities remain acceptable
- the Investigator and site personnel remains qualified and able to conduct the study
- test article accountability

During the course of the study, if the Sponsor determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor will take action to secure compliance. In addition, the Sponsor may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the Sponsor's actions.

14.2 Source Documentation

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected. Source documentation consists of original subject documents, as well as data and records with information relevant to the subject and his/her participation in the study.

14.3 Case Report Forms

Subject data required by this protocol are to be recorded on eCRFs. The Investigator and his/her study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification and, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries.

A copy of the eCRFs will be retained by the Investigator, who must ensure that it is stored in a secure place.

14.4 Audits and Inspections

The study will be conducted under the sponsorship of B&L in conformation with all appropriate local and federal regulations, as well as ICH guidelines. Interim and end of study audits of raw data, study files, and final report may be conducted by B&L Quality Assurance Department or designee.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. In addition, the sponsor will be responsible for securing agreement from all involved parties to ensure direct access to all study related investigational centers, source data/documents, eCRFs, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

14.5 Data Quality Assurance

During the course of the trial a clinical research associate (CRA) will make routine site visits to review protocol compliance, assess IMP accountability, and ensure the trial is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the trial monitoring (including medical monitoring) will be outlined in a monitoring plan.

Domestic and foreign regulatory authorities, and quality assurance, sponsor and or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out with consideration to data

protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

15.0 ETHICS AND ADMINISTRATIVE ISSUES

15.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP, and in compliance with local regulatory requirements. The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

15.2 Ethics Review

This protocol, proposed informed consent form and other information to subjects, and all appropriate amendments will be properly reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC). A signed and dated notification of the IRB/IEC approval will be provided to the sponsor and investigator prior to study initiation. The name and occupation of the chairman and members of the IRB/IEC will be supplied to the Sponsor. The investigator will provide required progress reports and report all SAEs to the IRB/IEC as required by the IRB/IEC.

The Investigator should ensure that his/her participation in the study, in addition to the protocol, subject recruitment materials (written information or materials including web pages, radio advertisements, television spots or written text developed to encourage subject enrollment) and the ICF to be used in this study are approved by their institution IRB/EC, or if not using their institution's IRB/EC, approved by the reviewing central IRB/EC prior to entering any subjects in the study. Documentation of IRB/EC approval of the study protocol and informed consent must be provided to the Sponsor prior to initiation of the study. In addition, the Investigator must ensure that the reviewing IRB/EC has provided approval for any protocol amendments prior to implementation. If the amendment necessitates a revision to the ICF, the Investigator should ensure the revised form is also submitted to and approved by the Sponsor and the IRB/EC prior to implementation.

15.3 Written Informed Consent

Written informed consent/assent, in accordance with local clinical investigation regulations, must be obtained prior to participation in the study. The investigator or designee will discuss the purpose of the study with each subject, and provide a description of the study drug (including any potential and possible side effects) and the study procedures. Information must be given both in oral and written form. Subject information will be provided in a language understandable to the subject and may not include any language that appears to waive any of the subject‘s legal rights or appears to release the investigator, the sponsor or the institution from liability or negligence.

The investigator will provide the prospective subject sufficient time to consider whether or not to participate, minimizing the possibility of coercion or undue influence and will discuss any questions the subject may have. The investigator will explain to the subject that participation in the study is voluntary and that withdrawal from the study is possible at any time without detriment to care. The consent must include acknowledgment that

medical records and medical data derived from the study may be forwarded to the Sponsor or to responsible local or federal authorities.

No subject can enter the study or have any study related procedures performed before his/her written informed consent has been obtained. The original signed and dated informed consent form will be retained with the study records, and a copy of the signed form will be given to the subject.

An informed consent template will be supplied by the sponsor or designee. Any changes to the informed consent form must be agreed to by the Sponsor or designee prior to submission to the IRB/IEC, and a copy of the approved version must be provided to the sponsor or designee after IRB/IEC approval.

15.4 Subject Data Protection

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that subject demographics (including age at the time of consent), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (i.e., aggregate) form and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study data or the study results.

15.5 Financial Disclosure

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest.

15.6 Investigator Obligations

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice (GCP).

15.7 Changes to the Protocol

The investigators must read the protocol thoroughly and must follow the instructions exactly. Whenever possible, any planned deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate documentation of Sponsor approval prior to effecting the changes agreed upon. Any amendment to the protocol containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB/IEC before it may be implemented. No change in the conduct of the study can be instituted without written approval from the Sponsor.

15.8 Confidentiality/Publication of the Study and Study Results

All the data furnished to the investigator and his/her staff and all data obtained through this protocol will be regarded as confidential and proprietary in nature and will not be disclosed

to any third party, except for the FDA or other regulatory body, without written consent from the Sponsor.

All study data generated as a result of this study will be regarded as confidential, until appropriate analysis and review by the Sponsor or its designee and the Investigator(s) are completed. The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with the Sponsor, and such that confidential or proprietary information is not disclosed.

Prior to publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee, for comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to Sponsor products and activities receive fair, accurate, and reasonable presentation.

16.0 DATA HANDLING AND RECORD KEEPING

16.1 Inspection of Records

Investigators must maintain detailed records on all study subjects who are enrolled in the study or undergo screening. Data will be recorded in the subject's source documents and in applicable study logs provided by the Sponsor. Source documents include subject medical records, hospital charts, clinic charts, investigator subject study files, as well as the results of diagnostic tests (e.g., laboratory tests). All required data should be recorded in the study documentation completely for prompt data review. Upon study completion or at any other time specified by the Sponsor or designee, the appropriate study documents must be submitted.

The investigator must keep accurate separate records (source documentation) of all subject visits, being sure to include all pertinent study related information. At a minimum, this includes the following information:

- A statement indicating that the subject has been enrolled in the study and the subject number
- Date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (e.g., medical history, screening evaluations)
- Dates of all study related visits and results of any evaluations/procedures performed, including who performed each assessment at each visit
- Use of any concurrent medications / therapies during the study
- Documentation of study drug accountability
- Any and all side effects and AEs must be thoroughly documented to conclusion
- Results of any diagnostic tests conducted during the study
- The date the subject exited the study and a statement indicating that the subject completed the study or was discontinued early, including the reason for discontinuation

Notes describing telephone conversations and all electronic mail with the subject or the sponsor (sponsor's designee) concerning the study must be recorded or kept on file. All source documents must be made available to the sponsor and the sponsor's designated monitor upon request.

16.2 Retention of Records

The investigator should properly store and maintain all study records in accordance with sponsor directives. All records relating to the conduct of this study are to be retained by the investigator until notified by the Sponsor in writing that the records may be destroyed.

The investigator will allow representatives of the Sponsor's monitoring team and quality control department, the governing IRB/IEC, the FDA, and other applicable regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's clinic and/or hospital medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness and accuracy of the data being entered onto the eCRF, and compliance with FDA or other regulatory agency regulations.

17.0 REFERENCES

Gomes, JAP, et al. TFOS DEWS II iatrogenic report. *The Ocular Surface.* 2017; 15: 511-538.

Toris, C. B., et al. Effects of brimonidine on aqueous humor dynamics in human eyes. *Arch Ophthalmol* 1995; 113(12): 1514-1517.

Walsh K, Jones L. The use of preservatives in dry eye drops. *Clinical Ophthalmology.* 2019; 13: 1409-1425

18.0 APPENDIX A

18.1 Visual Acuity Procedures

LogMAR Visual Acuity must be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual Acuity should be evaluated at the beginning of each visit in the study (i.e. prior to slit-lamp examination). Visual acuity testing should be done with best (most recent) correction.

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the subject viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only the 'R' charts, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and well-illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

If the subject changes a response (e.g., 'that was a "C" not an "O"') before he has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the subject says he or she cannot read a letter, he or she should be encouraged to guess. If the subject identifies a letter as one of two letters, he or she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

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 included in the last line read. This total sum represents the logMAR visual acuity for that eye.

For example: Subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR = 0.1

N (total number of letters incorrect on line 0.2 as well as 0.1) = 4

N x T (T=0.02) = 0.08

Base logMAR + (N x T) = 0.1 + 0.08

logMAR VA = 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (ie, a subject forgets his glasses), the subject's prescription as documented at Visit 1 should be placed in a trial frame or phoroptor for visual acuity assessment.

18.2 Slit Lamp Biomicroscopy/External Eye Exam Procedures

Slit lamp biomicroscopy will be performed during the study. Observations for the slit lamp biomicroscopy examination will be graded as described below. For 'Lid and Lid Margin' Erythema and 'Conjunctiva' Erythema/Hyperemia parameters, half grade answers (e.g. 0.5, 1.5, 2.5, and 3.5) will be accepted. If necessary, sodium fluorescein will be used to assess corneal epithelial damage.

Lid and Lid Margin

Erythema

None	0=	Normal
Mild	1=	Redness localized to a small region of the lid(s) margin **OR** skin
Moderate	2=	Redness of most or all the lid(s) margin **OR** skin
Severe	3=	Redness of most or all the lid(s) margin **AND** skin
Very Severe	4=	Marked diffuse redness of both lid(s) margin **AND** skin

0.5 unit increments ARE allowed

Swelling

None	0=	Normal
Mild	1=	Localized to a small region of the lid(s)
Moderate	2=	Diffuse, most or all the lid(s) but not prominent/protruding
Severe	3=	Diffuse, most or all of the lid(s) **AND** prominent/protruding
Very Severe	4=	Diffuse **AND** prominent/protruding **AND** eversion of the lid(s)

0.5 unit increments ARE NOT allowed

Conjunctiva (Palpebral and Bulbar)

Erythema/Hyperemia

None	0=	Normal
Mild	1=	Slight localized injection
Moderate	2=	Pink color, confined to palpebral **OR** bulbar conjunctiva
Severe	3=	Red color of the palpebral **AND/OR** bulbar conjunctiva
Very Severe	4=	Marked dark redness of the palpebral **AND/OR** bulbar conjunctiva

0.5 unit increments ARE allowed

Chemosis

None	0=	Normal
Mild	1=	Slight localized swelling
Moderate	2=	Moderate/medium localized swelling or mild diffuse swelling
Severe	3=	Severe diffuse swelling
Very Severe	4=	Very prominent/protruding diffuse swelling

0.5 unit increments ARE NOT allowed

Ora proprietary scales – Not for distribution without permission

Cornea

Edema

None	0=	Transparent and clear
Mild	0.5=	Trace, localized epithelial haze
Moderate	1=	Dull glass appearance that may include fine individual droplets
Severe	2=	Dull glass appearance of epithelium with large number of vacuoles
Very Severe	3=	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Erosion- Evaluated with fluorescein staining, if epithelial damage is noted

None	0=	No epithelial damage
Mild	1=	Slight epithelial damage confined to a small focus
Moderate	2=	Regionally dense epithelial damage (1mm or greater in diameter) with underlying structure moderately visible
Severe	3=	Marked epithelial damage over a large area of the cornea

0.5 unit increments ARE NOT allowed

Endothelial Condition

None	0=	Normal
Mild	1=	Mild endothelial irregularities
Moderate	2=	Moderate striae and/or stromal edema
Severe	3=	Severe striae with stromal edema
Very Severe	4=	Severe striae, stromal thickening, and bullous keratopathy

0.5 unit increments ARE NOT allowed

Lens Pathology

None	0=	No cataract
Mild	1=	Minimal lens opacity
Moderate	2=	Early lens opacity
Severe	3=	Intermediate lens opacity
Very Severe	4=	Advanced lens opacity

0.5 unit increments ARE NOT allowed

Ora proprietary scales – Not for distribution without permission

Anterior Chamber (slit beam=0.3mm wide, 1.0 mm long)

Cells

None	0=	No cells seen
Mild	1=	1-5 cells seen
Moderate	2=	6-15 cells seen
Severe	3=	16-30 cells seen
Very Severe	4=	>30 cells seen

0.5 unit increments ARE NOT allowed

Flare

None	0=	No Tyndall effect
Mild	1=	Tyndall effect barely discernible
Moderate	2=	Tyndall beam in the anterior chamber is moderately intense
Severe	3=	Tyndall beam in the anterior chamber is severely intense
Very Severe	4=	Tyndall beam is very severely intense. The aqueous has a white and milky appearance.

0.5 unit increments ARE NOT allowed

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18.3 Intraocular Pressure

Applanation tonometry, Goldmann tonometer required. Do NOT use non-contact tonometry. It is recommended that Fluress® (fluorescein sodium and benoxinate hydrochloride ophthalmic solution USP) be used as the anesthetic. It is recommended that subjects should wait a minimum of 10 minutes after instillation of Fluress® before instilling investigational drug.

IOP should always be measured/recorded before pupil dilation.

18.4 Dilated Ophthalmoscopy

At Visit 1 (Day 1) and Visit 4 (Day 36+1), a dilated ophthalmoscopy examination will be performed to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology.

Observations will be graded as Normal or Abnormal. Abnormal findings that are clinically significant (as determined by the investigator that may interfere with study parameters or otherwise confound the data) and those that are not clinically significant will be described. An indirect ophthalmoscopy examination should be performed if retinal disease is detected.

- Vitreous: Examination should emphasize the visual axis.
- Retina, Macula, Choroid: Include an observation of the retina and its blood vessels. Eyes should be excluded from the study if active inflammation is present at Visit 1.
- Optic Nerve: Significant damage or cupping to the optic nerve should be noted.

It is recommended that tropicamide 1% ophthalmic solution be used for pupil dilation. The use of cyclopentolate 1% ophthalmic solution is recommended (in adults) as a secondary dilating medication, should the need arise. The use of phenylephrine dilating drops is disallowed in this study.

18.5 Vital Signs

Each subject will have vital signs assessments i.e., body weight (lbs), heart rate (bpm), and blood pressure (mmHg), conducted at Visits 1 and 3 (if enrolled). At Visit 2, vital signs will be collected without body weight. Vital signs are to be conducted by qualified staff member who may be any of the following: a Board-certified Investigator or sub-Investigator, Nurse Practitioner, Registered Nurse, Physician's Assistant, or trained Research Coordinator.

- **Heart Rate (bpm)**

  Heart rate will be measured with the subjects who have been in a resting state (seated) for at least 5 minutes. Pulse will be counted for 30 seconds and multiplied by 2, and recorded in beats per minute.

- **Systolic/ Diastolic Blood Pressure (mmHg)**

  Systolic and diastolic blood pressure should be measured in the same arm each time using a calibrated sphygmomanometer with the subjects who have been in a resting state (seated upright) at least 5 minutes. Blood pressure will be recorded in mm Hg.

18.6 Physical Examination

Each subject will have a physical examination conducted at Visit 1 and at Visit 3 (if enrolled). A physical examination may be conducted by a Board-certified Investigator or sub-Investigator, Nurse Practitioner or Physician's Assistant. The physical examination will also include an assessment of the following:

- General health
- Head, Eyes, Ears, Nose, Throat (HEENT)
- Comments

18.7 Drop Comfort Assessments

Drop Comfort Assessment Scale

Ora Calibra® Drop Comfort Scale (Subject-Reported):

Will be assessed upon instillation, at 30 seconds, and 1 minute post-instillation of the investigational drug, using the following scale for a subject's eyes:

Right Eye:

0 1 2 3 4 5 6 7 8 9 10

very comfortable **very uncomfortable**

Left Eye:

0 1 2 3 4 5 6 7 8 9 10

very comfortable **very uncomfortable**

Ora proprietary scales – Not for distribution without permission

Ora Calibra® Drop Descriptor Query (Subject-Reported):

The subjects will be asked to choose three words that best describe how each eye drop feels in both of his/her eyes approximately 3 minutes post-instillation:

Burning	**Refreshing**
Comfortable	**Smooth**
Cool	**Soothing**
Filmy	**Sticky**
Gentle	**Gritty**
Stinging	**Irritating**

Please write any additional descriptions if not on list

OTHER:_____

18.8 Investigator Evaluated Signs

INVESTIGATOR EVALUATED SIGNS:

Ora Calibra® Ocular Hyperemia Scale

Ocular Redness:

0 =None

1.0 =Mild-Slightly dilated blood vessels; color of vessels is typically pink; can be quadrantal.

2.0 =Moderate-More apparent dilation of blood vessels; vessel color is more intense (redder); involves the majority of the vessel bed

3.0 =Severe-Numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red, may be less red or pink in presence of chemosis, is not quadrantic.

4.0 =Extremely Severe-Large, numerous, dilated blood vessels characterized by unusually severe deep red color, regardless of grade of chemosis, which involves the entire vessel bed.

0.5 unit increments are allowed

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18.9 Subject Dosing and Redness Grading Diaries

Sample Dosing and Redness Grading Diary Instructions:
Visit X Dosing/Redness Diary Instructions

DOSING INSTRUCTIONS

- Please dose **ONE** (1) drop in each eye with the study drops **FOUR** (4) times a day starting the morning after your Visit 1 appointment. Below is an example of a dosing schedule:
    - Dose 1 (8:00AM)
    - Dose 2 approximately 4 hours after Dose 1 (12:00PM)
    - Dose 3 approximately 4 hours after Dose 2 (4:00PM)
    - Dose 4 approximately 4 hours after Dose 3 (8:00PM)

****DO NOT dose any earlier than 3.5 hours after your previous dose****

- Check **YES** if dose was taken or check **NO** if dose was not taken
- Be sure to record what time you took your dose in your diary

DIARY INSTRUCTIONS

- You will need to assess your ocular redness at the following times:
    - Once **BEFORE** Dose 1, and then approximately 2 MINUTES **AFTER** Dose 1
    - Once **BEFORE** Dose 2, and then approximately 2 MINUTES **AFTER** Dose 2
    - Once **BEFORE** Dose 3, and then approximately 2 MINUTES **AFTER** Dose 3
    - Once **BEFORE** Dose 4, and then approximately 2 MINUTES **AFTER** Dose 4
- Be sure to record what time you assessed your ocular redness **after** each dose.
- Please **DO NOT** dose within 3.5 hours of your next appointment (Visit X)

Visit X Appointment

Date: _____

Time: _____

GENERAL INSTRUCTIONS

- Use a **black pen** to fill out your diary. **DO NOT** use white-out or pencil.
- At the top of each page, please fill out your 'Site Number', 'Subject Number', and 'Initials' with the information given to you by the study staff.
- Enter the date for each day, in the following format: DD/MMM/YYYY.
  For example, January 10th, 2012 would be written as 10/JAN/2012.
- If you make an error, draw a **SINGLE LINE** through the error, and then **DATE** and **INITIAL** below the line. Then enter the correct value or score.

ABC 8/9/10

- You should keep your investigational drug at room temperature (15-25° [59-77°F]). Keep the pouches of single-use vials out of sunlight, and do not freeze or refrigerate the investigational drug. Keep away from children.
- Wash your hands thoroughly before using the study drops.
- To prevent contamination, do not touch the tip of the single-use vial to your eye, eyelids, surrounding areas or other surfaces.
- Look up and gently pull down the lower eye lid with one hand. With your other hand, hold the single-use vial upside down over each target eye, and slowly squeeze 1 drop onto the lower surface of each eye. Gently close your eye and allow the drop to be absorbed. **DO NOT** squeeze your eyelids shut.
- Keep un-used vials in the labeled pouch prior to use.
- Used vials should be placed in the supplied 'Used Vials' bag. **DO NOT** re-use the vial even if there is solution left inside.
- You **MUST** bring back your completed dosing diary and used & unused investigational drug with you to your next visit (Visit X).

18.10 Schedule of Visits and Parameters

All study tasks should be performed by qualified study site personnel as indicated on the delegation of authority log under the supervision of the Principal Investigator. Furthermore, the in-office baseline (prior to first drug instillation) assessments at Visit 1 of ocular redness, slit-lamp examination, IOP, and ophthalmoscopy must be performed by an ophthalmologist.

PROCEDURE/ASSESSMENTS	**Screening**[1]	**Visit 1 (Baseline)**	**Visit 2**	**Visit 3**	**Visit 4**
	Day -28 to Day 1	**Day 1**	**Day 15 ± 2**	**Day 29 + 2**	**Day 36 + 1**
Informed consent/HIPAA[2]	X				
Demographics	X				
Medical History	X				
Concomitant Medications	X	X	X	X	X
Urine Pregnancy Test (for females of childbearing potential)[3]		X		X[12]	X
Physical Examination[4]		X		X	
Vital Signs[5]		X	X	X	
BCVA at Distance		X	X	X	X
Slit lamp biomicroscopy[6]		X	X	X	X
Intraocular Pressure (IOP)		X		X	
Dilated Ophthalmoscopy		X		X	
Randomization		X			
In-Office Redness Assessment		X[7]	X[8]	X[8]	X
In-Office Investigational Drug Instillation		X[9]	X[10]	X[10]	
Drop Comfort/Descriptor Assessment[11]		X			
Dispense Investigational Drug and Dosing Diary[10]		X	X		
Collect Investigational Drug and Dosing Diary[10]			X	X	
Dispense Redness Grading Diary				X	
Collect Redness Grading Diary					X
Assessment of adverse events	X	X	X	X	X
Exit					X

[1] If there is no washout period, the Screening Visit and Visit 1 can occur on the same day.
[2] Informed consent must be signed before any study-related procedure can be performed. If washout of a medication is necessary, informed consent must be obtained prior to Visit 1.
[3] Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
[4] Physical examination includes general health, head, eyes, ears, nose, throat (HEENT), and any other comments.
[5] Vital signs (resting blood pressure and pulse) with body weight will be collected at Visits 1 and 3 and without body weight at Visit 2.
[6] Evaluated prior to and post investigational drug instillation at Visits 1, 2, and 3.
[7] Investigator will evaluate ocular redness prior to investigational drug instillation and at 1 (+0.5), 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), 240(+15), 360(+15), and 480(+15) minutes post investigational drug instillation.
[8] Investigator will evaluate ocular redness prior to investigational drug instillation and approximately 1 and 5 minutes post-instillation.
[9] Performed by the subject or subject's caregiver while under the observation of the unmasked designee.
[10] Performed by the unmasked designee.
[11] Subjects will assess comfort upon instillation, at 30 seconds, and at 1 minute post-instillation using 0-10 unit scale for each eye at Visit 1. Subjects also will select comfort descriptor terms from a predetermined list at 3 minutes post-instillation at Visit 1.
[12] Complete urine pregnancy test if visit-3 is early termination visit